CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

022341Orig1s027

Trade Name: VICTOZA

Generic or Proper Name: liraglutide

Sponsor: Novo Nordisk

Approval Date: August 25, 2017

Indication:

VICTOZA is a glucagon-like peptide-1 (GLP-1) receptor agonist indicated:

- as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus;.

- to reduce the risk of major adverse cardiovascular events in adults with type 2 diabetes mellitus and established cardiovascular disease .

Limitations of Use**:**

- Not for treatment of type 1 diabetes mellitus or diabetic ketoacidosis.
- Has not been studied in combination with prandial insulin.

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APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022341/S-027

SUPPLEMENT APPROVAL

Novo Nordisk Inc.
Attention: Michelle Thompson
Senior Director, Regulatory Affairs
P.O. Box 846
800 Scudders Mill Road
Plainsboro, NJ 08536

Dear Ms. Thompson:

Please refer to your Supplemental New Drug Application (sNDA) dated and received October 25, 2016, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Victoza (liraglutide) injection.

This Prior Approval supplemental new drug application proposes the addition of an indication to reduce the risk of major adverse cardiovascular events in adults with type 2 diabetes mellitus and established cardiovascular disease, and revised labeling to reflect the results of the "Liraglutide Effect and Action in Diabetes: Evaluation of cardiovascular outcome Results" (LEADER) trial.

APPROVAL & LABELING

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text and with the minor editorial revisions listed below:

- Brackets were removed from the dates in the Recent Major Changes section of Highlights.
- The version number and date of issue were updated on the final page of the Prescribing Information.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the prescribing information, Medication Guide, and instructions for use), with the addition of any labeling changes in pending

"Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your application, you are exempt from this requirement.

FULFILLMENT OF POSTMARKETING REQUIREMENT

This supplemental application contained the final report for the following postmarketing requirement listed in the January 25, 2010, approval letter for NDA 022341.

1583-9 A randomized, double-blind, controlled trial evaluating the effect of Victoza (liraglutide [rDNA origin]) injection on the incidence of major adverse cardiovascular events in patients with type 2 diabetes mellitus. This trial must also assess adverse events of interest including the long-term effects of Victoza (liraglutide [rDNA origin]) injection on potential biomarkers of medullary thyroid carcinoma (e.g., serum calcitonin) as well as the long-term effects of Victoza (liraglutide [rDNA origin]) injection on pancreatitis, renal safety, serious hypoglycemia, immunological reactions, and neoplasms.

We have reviewed your submission and conclude that the above requirement was fulfilled.

We remind you that there are postmarketing requirements listed in the January 25, 2010, approval letter that are still open.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Marisa Petruccelli, Regulatory Project Manager, at (240) 402-6147.

Sincerely,

{See appended electronic signature page}

Jean-Marc Guettier, M.D.
Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURES:
Prescribing Information
Medication Guide
Instructions for Use (version approved April 25, 2017)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JEAN-MARC P GUETTIER
08/25/2017

CENTER FOR DRUG EVALUATION AND RESEARCH

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LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use VICTOZA safely and effectively. See full prescribing information for VICTOZA.

VICTOZA® (liraglutide) injection, for subcutaneous use
Initial U.S. Approval: 2010

WARNING: RISK OF THYROID C-CELL TUMORS
See full prescribing information for complete boxed warning.

- **Liraglutide causes thyroid C-cell tumors at clinically relevant exposures in both genders of rats and mice. It is unknown whether VICTOZA causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans, as the human relevance of liraglutide-induced rodent thyroid C-cell tumors has not been determined (5.1, 13.1)**.
- **VICTOZA is contraindicated in patients with a personal or family history of MTC or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Counsel patients regarding the potential risk of MTC and the symptoms of thyroid tumors (4, 5.1).**

----------RECENT MAJOR CHANGES----------
Indications and Usage (1) ---------- 8/2017
Contraindications (4) ---------- 8/2017
Warnings and Precautions (5.2, 5.6, 5.7) ---------- 8/2017

·····INDICATIONS AND USAGE·····
VICTOZA is a glucagon-like peptide-1 (GLP-1) receptor agonist indicated:
- as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (1).
- to reduce the risk of major adverse cardiovascular events in adults with type 2 diabetes mellitus and established cardiovascular disease (1).

Limitations of Use**:**
- Not for treatment of type 1 diabetes mellitus or diabetic ketoacidosis.
- Has not been studied in combination with prandial insulin.

·····DOSAGE AND ADMINISTRATION·····
- Inject subcutaneously in the abdomen, thigh or upper arm (2.1).
- Administer once daily at any time of day, independently of meals (2.2).
- Initiate at 0.6 mg per day for one week then increase to 1 2 mg. Dose can be increased to 1.8 mg for additional glycemic control (2.2).

·····DOSAGE FORMS AND STRENGTHS·····
Injection: 6 mg/mL solution in a pre-filled, multi-dose pen that delivers doses of 0.6 mg, 1.2 mg, or 1.8 mg (3).

·····CONTRAINDICATIONS·····
VICTOZA is contraindicated in patients with a personal or family history of medullary thyroid carcinoma or in patients with Multiple Endocrine Neoplasia syndrome type 2 (4).

VICTOZA is contraindicated in patients with a prior serious hypersensitivity reaction to VICTOZA or any of the product components (4).

·····WARNINGS AND PRECAUTIONS·····
- Thyroid C-cell Tumors: See Boxed Warning (5.1).
- Pancreatitis: Postmarketing reports, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis. Discontinue promptly if pancreatitis is suspected. Do not restart if pancreatitis is confirmed (5.2).
- Never share a VICTOZA pen between patients, even if the needle is changed (5.3).
- Serious Hypoglycemia: When VICTOZA is used with an insulin secretagogue (e.g. a sulfonylurea) or insulin, consider lowering the dose of the insulin secretagogue or insulin to reduce the risk of hypoglycemia (5.4).
- Renal Impairment: Postmarketing, usually in association with nausea, vomiting, diarrhea, or dehydration which may sometimes require hemodialysis. Use caution when initiating or escalating doses of VICTOZA in patients with renal impairment (5.5).
- Hypersensitivity: Postmarketing reports of serious hypersensitivity reactions (e.g., anaphylactic reactions and angioedema). Discontinue VICTOZA and promptly seek medical advice (5.6).
- Acute Gallbladder Disease: If cholelithiasis or cholecystitis are suspected, gallbladder studies are indicated (5.7)

·····ADVERSE REACTIONS·····
- The most common adverse reactions, reported in ≥5% of patients treated with VICTOZA are: nausea, diarrhea, vomiting, decreased appetite, dyspepsia, constipation (6.1).
- Immunogenicity-related events, including urticaria, were more common among VICTOZA-treated patients (0.8%) than among comparator-treated patients (0.4%) in clinical trials (6.2).

To report SUSPECTED ADVERSE REACTIONS, contact Novo Nordisk Inc. at 1-877-484-2869 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
VICTOZA delays gastric emptying. May impact absorption of concomitantly administered oral medications. (7).

·····USE IN SPECIFIC POPULATIONS·····
- Renal Impairment: No dose adjustment recommended (2.4, 8.6, 12.3).
- Pregnancy: Victoza should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus (8.1).

See 17 for PATIENT COUNSELING INFORMATION and FDA-Approved Medication Guide.

Revised: 08/2017

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: RISK OF THYROID C-CELL TUMORS

- **Liraglutide causes dose-dependent and treatment-duration-dependent thyroid C-cell tumors at clinically relevant exposures in both genders of rats and mice. It is unknown whether VICTOZA causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans, as the human relevance of liraglutide-induced rodent thyroid C-cell tumors has not been determined *[see Warnings and Precautions (5.1) and Nonclinical Toxicology (13.1)]*.**
- **VICTOZA is contraindicated in patients with a personal or family history of MTC and in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Counsel patients regarding the potential risk for MTC with the use of VICTOZA and inform them of symptoms of thyroid tumors (e.g. a mass in the neck, dysphagia, dyspnea, persistent hoarseness). Routine monitoring of serum calcitonin or using thyroid ultrasound is of uncertain value for early detection of MTC in patients treated with VICTOZA *[see Contraindications (4) and Warnings and Precautions (5.1)]*.**

1 INDICATIONS AND USAGE

VICTOZA is indicated:

- as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus,
- to reduce the risk of major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke) in adults with type 2 diabetes mellitus and established cardiovascular disease *[see Clinical Studies (14.2)]*.

Limitations of Use**:**

- VICTOZA is not a substitute for insulin. VICTOZA should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis, as it would not be effective in these settings.
- The concurrent use of VICTOZA and prandial insulin has not been studied.

2 DOSAGE AND ADMINISTRATION

2.1 Important Administration Instructions

- Inspect visually prior to each injection. Only use if solution is clear, colorless, and contains no particles.
- Inject VICTOZA subcutaneously in the abdomen, thigh or upper arm. No dose adjustment is needed if changing the injection site and/or timing.
- When using VICTOZA with insulin, administer as separate injections. Never mix.
- It is acceptable to inject VICTOZA and insulin in the same body region but the injections should not be adjacent to each other.

2.2 General Dosing and Administration

- Inject VICTOZA subcutaneously once-daily at any time of day, independently of meals.
- Initiate VICTOZA with a dose of 0.6 mg per day for one week. The 0.6 mg dose is a starting dose intended to reduce gastrointestinal symptoms during initial titration, and is not effective for glycemic control. After one week at 0.6 mg per day, the dose should be increased to 1.2 mg. If the 1.2 mg dose does not result in acceptable glycemic control, the dose can be increased to 1.8 mg. If a dose is

missed, resume the once-daily regimen as prescribed with the next scheduled dose. Do not administer an extra dose or increase in dose to make up for the missed dose.

- If more than 3 days have elapsed since the last VICTOZA dose, reinitiate VICTOZA at 0.6 mg to mitigate any gastrointestinal symptoms associated with reinitiation of treatment. Upon reinitiation, VICTOZA should be titrated at the discretion of the prescriber.

2.3 Concomitant Use with an Insulin Secretagogue (e.g., Sulfonylurea) or with Insulin

When initiating VICTOZA, consider reducing the dose of concomitantly administered insulin secretagogues (such as sulfonylureas) to reduce the risk of hypoglycemia *[see Warnings and Precautions (5.4) and Adverse Reactions (6)]*.

2.4 Dosage in Patients with Renal Impairment

No dose adjustment is recommended for patients with renal impairment.

3 DOSAGE FORMS AND STRENGTHS

Injection: 6 mg/mL solution in a pre-filled, multi-dose pen that delivers doses of 0.6 mg, 1.2 mg, or 1.8 mg.

4 CONTRAINDICATIONS

- **Medullary Thyroid Carcinoma**

VICTOZA is contraindicated in patients with a personal or family history of medullary thyroid carcinoma (MTC) or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2).

- **Hypersensitivity**

VICTOZA is contraindicated in patients with a prior serious hypersensitivity reaction to VICTOZA or to any of the product components. Serious hypersensitivity reactions including anaphylactic reactions and angioedema have been reported with VICTOZA *[see Warnings and Precautions (5.6)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Risk of Thyroid C-cell Tumors

Liraglutide causes dose-dependent and treatment-duration-dependent thyroid C-cell tumors (adenomas and/or carcinomas) at clinically relevant exposures in both genders of rats and mice *[see Nonclinical Toxicology (13.1)]*. Malignant thyroid C-cell carcinomas were detected in rats and mice. It is unknown whether VICTOZA will cause thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans, as the human relevance of liraglutide-induced rodent thyroid C-cell tumors has not been determined.

Cases of MTC in patients treated with VICTOZA have been reported in the postmarketing period; the data in these reports are insufficient to establish or exclude a causal relationship between MTC and VICTOZA use in humans.

VICTOZA is contraindicated in patients with a personal or family history of MTC or in patients with MEN 2. Counsel patients regarding the potential risk for MTC with the use of VICTOZA and inform them of symptoms of thyroid tumors (e.g. a mass in the neck, dysphagia, dyspnea, persistent hoarseness). Routine monitoring of serum calcitonin or using thyroid ultrasound is of uncertain value for early detection of MTC in patients treated with VICTOZA. Such monitoring may increase the risk of unnecessary procedures, due to low test specificity for serum calcitonin and a high background incidence of thyroid disease. Significantly elevated serum calcitonin may indicate MTC and patients with MTC

usually have calcitonin values >50 ng/L. If serum calcitonin is measured and found to be elevated, the patient should be further evaluated. Patients with thyroid nodules noted on physical examination or neck imaging should also be further evaluated.

5.2 Pancreatitis

Based on spontaneous postmarketing reports, acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis, has been observed in patients treated with VICTOZA. After initiation of VICTOZA, observe patients carefully for signs and symptoms of pancreatitis (including persistent severe abdominal pain, sometimes radiating to the back and which may or may not be accompanied by vomiting). If pancreatitis is suspected, VICTOZA should promptly be discontinued and appropriate management should be initiated. If pancreatitis is confirmed, VICTOZA should not be restarted.

In glycemic control trials of VICTOZA, there have been 13 cases of pancreatitis among VICTOZA-treated patients and 1 case in a comparator (glimepiride) treated patient (2.7 vs. 0.5 cases per 1000 patient-years). Nine of the 13 cases with VICTOZA were reported as acute pancreatitis and four were reported as chronic pancreatitis. In one case in a VICTOZA-treated patient, pancreatitis, with necrosis, was observed and led to death; however clinical causality could not be established. Some patients had other risk factors for pancreatitis, such as a history of cholelithiasis or alcohol abuse.

VICTOZA has been studied in a limited number of patients with a history of pancreatitis. It is unknown if patients with a history of pancreatitis are at higher risk for development of pancreatitis on VICTOZA.

5.3 Never Share a VICTOZA Pen Between Patients

VICTOZA pens must never be shared between patients, even if the needle is changed. Pen-sharing poses a risk for transmission of blood-borne pathogens.

5.4 Use with Medications Known to Cause Hypoglycemia

Patients receiving VICTOZA in combination with an insulin secretagogue (e.g., sulfonylurea) or insulin may have an increased risk of hypoglycemia. The risk of hypoglycemia may be lowered by a reduction in the dose of sulfonylurea (or other concomitantly administered insulin secretagogues) or insulin *[see Dosage and Administration (2.2), Adverse Reactions (6.1)]*.

5.5 Renal Impairment

VICTOZA has not been found to be directly nephrotoxic in animal studies or clinical trials.
There have been postmarketing reports of acute renal failure and worsening of chronic renal failure, which may sometimes require hemodialysis in VICTOZA-treated patients *[see Adverse Reactions (6.2)]*. Some of these events were reported in patients without known underlying renal disease. A majority of the reported events occurred in patients who had experienced nausea, vomiting, diarrhea, or dehydration *[see Adverse Reactions (6.1)]*. Some of the reported events occurred in patients receiving one or more medications known to affect renal function or hydration status. Altered renal function has been reversed in many of the reported cases with supportive treatment and discontinuation of potentially causative agents, including VICTOZA. Use caution when initiating or escalating doses of VICTOZA in patients with renal impairment *[see Use in Specific Populations (8.6)]*.

5.6 Hypersensitivity Reactions

There have been postmarketing reports of serious hypersensitivity reactions (e.g., anaphylactic reactions and angioedema) in patients treated with VICTOZA. If a hypersensitivity reaction occurs, discontinue

VICTOZA; treat promptly per standard of care, and monitor until signs and symptoms resolve. Do not use in patients with a previous hypersensitivity reaction to VICTOZA *[see Contraindications (4)]*.

Anaphylaxis and angioedema have been reported with other GLP-1 receptor agonists. Use caution in a patient with a history of anaphylaxis or angioedema with another GLP-receptor agonist because it is unknown whether such patients will be predisposed to these reactions with VICTOZA.

5.7 Acute Gallbladder Disease

In the LEADER trial *[see Clinical Studies (14.2)]*, 3.1% of Victoza-treated patients versus 1.9% of placebo-treated patients reported an acute event of gallbladder disease, such as cholelithiasis or cholecystitis. The majority of events required hospitalization or cholecystectomy. If cholelithiasis is suspected, gallbladder studies and appropriate clinical follow-up are indicated.

6 ADVERSE REACTIONS

The following serious adverse reactions are described below or elsewhere in the prescribing information:

- Risk of Thyroid C-cell Tumors *[see Warnings and Precautions (5.1)]*
- Pancreatitis *[see Warnings and Precautions (5.2)]*
- Use with Medications Known to Cause Hypoglycemia *[see Warnings and Precautions (5.4)]*
- Renal Impairment *[see Warnings and Precautions (5.5)]*
- Hypersensitivity Reactions *[see Warnings and Precautions (5.6)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Common Adverse Reactions

The data in Table 1 are derived from 5 glycemic control, placebo-controlled trials *[see Clinical Studies (14.1)]*. These data reflect exposure of 1673 patients to VICTOZA and a mean duration of exposure to VICTOZA of 37.3 weeks. The mean age of patients was 58 years, 4% were 75 years or older and 54% were male. The population was 79% White, 6% Black or African American, 13% Asian; 4% were of Hispanic or Latino ethnicity. At baseline the population had diabetes for an average of 9.1 years and a mean HbA_{1c} of 8.4%. Baseline estimated renal function was normal or mildly impaired in 88.1% and moderately impaired in 11.9% of the pooled population.

Table 1 shows common adverse reactions, excluding hypoglycemia, associated with the use of VICTOZA. These adverse reactions occurred more commonly on VICTOZA than on placebo and occurred in at least 5% of patients treated with VICTOZA.

Table 1 Adverse reactions reported in ≥ 5% of VICTOZA-treated patients

	Placebo N=661	**Liraglutide 1.2 mg N= 645**	**Liraglutide 1.8 mg N= 1024**
Adverse Reaction	(%)	(%)	(%)
Nausea	5	18	20
Diarrhea	4	10	12
Headache	7	11	10
Nasopharyngitis	8	9	10
Vomiting	2	6	9
Decreased appetite	1	10	9

Dyspepsia	1	4	7
Upper Respiratory Tract Infection	6	7	6
Constipation	1	5	5
Back Pain	3	4	5

Cumulative proportions were calculated combining studies using Cochran-Mantel-Haenszel weights

In an analysis of placebo- and active-controlled trials, the types and frequency of common adverse reactions, excluding hypoglycemia, were similar to those listed in Table 1.

Other Adverse Reactions

Gastrointestinal Adverse Reactions

In the pool of 5 glycemic control, placebo-controlled clinical trials, withdrawals due to gastrointestinal adverse reactions, occurred in 4.3% of VICTOZA-treated patients and 0.5% of placebo-treated patients. Withdrawal due to gastrointestinal adverse events mainly occurred during the first 2-3 months of the trials.

Injection site reactions

Injection site reactions (e.g., injection site rash, erythema) were reported in approximately 2% of VICTOZA-treated patients in the five double-blind, glycemic control trials of at least 26 weeks duration. Less than 0.2% of VICTOZA-treated patients discontinued due to injection site reactions.

Hypoglycemia

Hypoglycemia requiring the assistance of another person in placebo-controlled trials

In 5 glycemic control, placebo-controlled clinical trials of at least 26 weeks duration, hypoglycemia requiring the assistance of another person for treatment occurred in 8 VICTOZA-treated patients (7.5 events per 1000 patient-years). Of these 8 VICTOZA-treated patients, 7 patients were concomitantly using a sulfonylurea.

Table 2 Incidence (%) and Rate (episodes/patient year) of Hypoglycemia in 26-Week Combination Therapy Placebo-controlled Trials

	Placebo Comparator	**VICTOZA Treatment**
Add-on to Metformin	**Placebo + Metformin** (N = 121)	**VICTOZA + Metformin** (N = 724)
Patient not able to self-treat	0	0.1 (0.001)
Patient able to self-treat	2.5 (0.06)	3.6 (0.05)
Add-on to Glimepiride	**Placebo + Glimepiride** (N = 114)	**VICTOZA + Glimepiride** (N = 695)
Patient not able to self-treat	0	0.1 (0.003)
Patient able to self-treat	2.6 (0.17)	7.5 (0.38)
Not classified	0	0.9 (0.05)
Add-on to Metformin + Rosiglitazone	**Placebo + Metformin + Rosiglitazone** (N = 175)	**VICTOZA + Metformin + Rosiglitazone** (N = 355)
Patient not able to self-treat	0	0
Patient able to self-treat	4.6 (0.15)	7.9 (0.49)
Not classified	1.1 (0.03)	0.6 (0.01)

Add-on to Metformin + Glimepiride	**Placebo + Metformin + Glimepiride** (N = 114)	**VICTOZA + Metformin + Glimepiride** (N = 230)
Patient not able to self-treat	0	2.2 (0.06)
Patient able to self-treat	16.7 (0.95)	27.4 (1.16)
Not classified	0	0

"Patient not able to self-treat" is defined as an event requiring the assistance of another person for treatment

Papillary thyroid carcinoma
In glycemic control trials of VICTOZA, there were 7 reported cases of papillary thyroid carcinoma in patients treated with VICTOZA and 1 case in a comparator-treated patient (1.5 vs. 0.5 cases per 1000 patient-years). Most of these papillary thyroid carcinomas were <1 cm in greatest diameter and were diagnosed in surgical pathology specimens after thyroidectomy prompted by findings on protocol-specified screening with serum calcitonin or thyroid ultrasound.

Cholelithiasis and cholecystitis
In glycemic control trials of VICTOZA, the incidence of cholelithiasis was 0.3% in both VICTOZA-treated and placebo-treated patients. The incidence of cholecystitis was 0.2% in both VICTOZA-treated and placebo-treated patients.

In the LEADER trial *[see Clinical Studies (14.2)]*, the incidence of cholelithiasis was 1.5% (3.9 cases per 1000 patient years of observation) in VICTOZA-treated and 1.1% (2.8 cases per 1000 patient years of observation) in placebo-treated patients, both on a background of standard of care. The incidence of acute cholecystitis was 1.1% (2.9 cases per 1000 patient years of observation) n VICTOZA-treated and 0.7% (1.9 cases per 1000 patient years of observation) in placebo-treated patients.

Laboratory Tests
Bilirubin
In the five glycemic control trials of at least 26 weeks duration, mildly elevated serum bilirubin concentrations (elevations to no more than twice the upper limit of the reference range) occurred in 4.0% of VICTOZA-treated patients, 2.1% of placebo-treated patients and 3.5% of active-comparator-treated patients. This finding was not accompanied by abnormalities in other liver tests. The significance of this isolated finding is unknown.

Calcitonin
Calcitonin, a biological marker of MTC, was measured throughout the clinical development program. At the end of the glycemic control trials, adjusted mean serum calcitonin concentrations were higher in VICTOZA-treated patients compared to placebo-treated patients but not compared to patients receiving active comparator. Between group differences in adjusted mean serum calcitonin values were approximately 0.1 ng/L or less. Among patients with pretreatment calcitonin <20 ng/L, calcitonin elevations to >20 ng/L occurred in 0.7% of VICTOZA-treated patients, 0.3% of placebo-treated patients, and 0.5% of active-comparator-treated patients. The clinical significance of these findings is unknown.

Lipase and Amylase
In one glycemic control trial in renal impairment patients, a mean increase of 33% for lipase and 15% for amylase from baseline was observed for VICTOZA-treated patients while placebo-treated patients had a mean decrease in lipase of 3% and a mean increase in amylase of 1%.

In the LEADER trial, serum lipase and amylase were routinely measured. Among VICTOZA-treated patients, 7.9% had a lipase value at any time during treatment of greater than or equal to 3 times the upper limit of normal compared with 4.5% of placebo-treated patients, and 1% of VICTOZA-treated patients had an amylase value at any time during treatment of greater than or equal to 3 times the upper limit of normal versus 0.7% of placebo-treated patients.

The clinical significance of elevations in lipase or amylase with VICTOZA is unknown in the absence of other signs and symptoms of pancreatitis *[see Warnings and Precautions (5.2)]*.

Vital signs
VICTOZA did not have adverse effects on blood pressure. Mean increases from baseline in heart rate of 2 to 3 beats per minute have been observed with VICTOZA compared to placebo.

6.2 Immunogenicity
Consistent with the potentially immunogenic properties of protein and peptide pharmaceuticals, patients treated with VICTOZA may develop anti-liraglutide antibodies. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, the incidence of antibodies to liraglutide cannot be directly compared with the incidence of antibodies of other products.

Approximately 50-70% of VICTOZA-treated patients in five double-blind clinical trials of 26 weeks duration or longer were tested for the presence of anti-liraglutide antibodies at the end of treatment. Low titers (concentrations not requiring dilution of serum) of anti-liraglutide antibodies were detected in 8.6% of these VICTOZA-treated patients. Cross-reacting anti-liraglutide antibodies to native glucagon-like peptide-1 (GLP-1) occurred in 6.9% of the VICTOZA-treated patients in the double-blind 52-week monotherapy trial and in 4.8% of the VICTOZA-treated patients in the double-blind 26-week add-on combination therapy trials. These cross-reacting antibodies were not tested for neutralizing effect against native GLP-1, and thus the potential for clinically significant neutralization of native GLP-1 was not assessed. Antibodies that had a neutralizing effect on liraglutide in an *in vitro* assay occurred in 2.3% of the VICTOZA-treated patients in the double-blind 52-week monotherapy trial and in 1.0% of the VICTOZA-treated patients in the double-blind 26-week add-on combination therapy trials.

Antibody formation was not associated with reduced efficacy of VICTOZA when comparing mean HbA_{1c} of all antibody-positive and all antibody-negative patients. However, the 3 patients with the highest titers of anti-liraglutide antibodies had no reduction in HbA_{1c} with VICTOZA treatment.

In five double-blind glycemic control trials of VICTOZA, events from a composite of adverse events potentially related to immunogenicity (e.g. urticaria, angioedema) occurred among 0.8% of VICTOZA-treated patients and among 0.4% of comparator-treated patients. Urticaria accounted for approximately one-half of the events in this composite for VICTOZA-treated patients. Patients who developed anti-liraglutide antibodies were not more likely to develop events from the immunogenicity events composite than were patients who did not develop anti-liraglutide antibodies.

In the LEADER trial *[see Clinical Studies (14.2)]*, anti-liraglutide antibodies were detected in 11 out of the 1247 (0.9%) VICTOZA-treated patients with antibody measurements.

Of the 11 VICTOZA-treated patients who developed anti-liraglutide antibodies, none were observed to develop neutralizing antibodies to liraglutide, and 5 patients (0.4%) developed cross-reacting antibodies against native GLP-1.

6.3 Post-Marketing Experience

The following additional adverse reactions have been reported during post-approval use of VICTOZA. Because these events are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Medullary thyroid carcinoma *[see Warnings and Precautions (5.1)]*
- Dehydration resulting from nausea, vomiting and diarrhea. *[see Warnings and Precautions (5.5) and Patient Counseling Information (17)]*
- Increased serum creatinine, acute renal failure or worsening of chronic renal failure, sometimes requiring hemodialysis. *[see Warnings and Precautions (5.5) and Patient Counseling Information (17)]*
- Angioedema and anaphylactic reactions. *[see Contraindications (4), Warnings and Precautions (5.6), Patient Counseling Information (17)]*
- Allergic reactions: rash and pruritus
- Acute pancreatitis, hemorrhagic and necrotizing pancreatitis sometimes resulting in death *[see Warnings and Precautions (5.2)]*
- Hepatobiliary disorders: elevations of liver enzymes, hyperbilirubinemia, cholestasis, hepatitis *[see Adverse Reactions (6.1)]*

7 DRUG INTERACTIONS

7.1 Oral Medications

VICTOZA causes a delay of gastric emptying, and thereby has the potential to impact the absorption of concomitantly administered oral medications. In clinical pharmacology trials, VICTOZA did not affect the absorption of the tested orally administered medications to any clinically relevant degree. Nonetheless, caution should be exercised when oral medications are concomitantly administered with VICTOZA.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on animal reproduction studies, there may be risks to the fetus from exposure to VICTOZA during pregnancy. VICTOZA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Animal reproduction studies identified increased adverse developmental outcomes from exposure during pregnancy. Liraglutide exposure was associated with early embryonic deaths and an imbalance in some fetal abnormalities in pregnant rats administered liraglutide during organogenesis at doses that

approximate clinical exposures at the maximum recommended human dose (MRHD) of 1.8 mg/day. In pregnant rabbits administered liraglutide during organogenesis, decreased fetal weight and an increased incidence of major fetal abnormalities were seen at exposures below the human exposures at the MRHD *[see Animal Data]*.

The estimated background risk of major birth defects for women with uncontrolled pre-gestational diabetes (Hemoglobin A_{1C} >7) is 6 to 10%. The major birth defect rate has been reported to be as high as 20 to 25% in women with a Hemoglobin A_{1C} >10. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk

Poorly controlled diabetes in pregnancy increases the maternal risk for diabetic ketoacidosis, pre-eclampsia, spontaneous abortions, preterm delivery, stillbirth and delivery complications due to fetal macrosomia (e.g., perineal injury and lacerations, need for cesarean section, and post-partum hemorrhage). Poorly controlled diabetes increases the fetal risk for neural tube defects, cardiovascular malformations, oral clefts, still birth, macrosomia related morbidity (e.g., brachial plexus injury, hypoxia), and neonatal hyperglycemia.

Animal Data

Female rats given subcutaneous doses of 0.1, 0.25 and 1.0 mg/kg/day liraglutide beginning 2 weeks before mating through gestation day 17 had estimated systemic exposures 0.8-, 3-, and 11-times the human exposure at the MRHD based on plasma AUC comparison. The number of early embryonic deaths in the 1 mg/kg/day group increased slightly. Fetal abnormalities and variations in kidneys and blood vessels, irregular ossification of the skull, and a more complete state of ossification occurred at all doses. Mottled liver and minimally kinked ribs occurred at the highest dose. The incidence of fetal malformations in liraglutide-treated groups exceeding concurrent and historical controls were misshapen oropharynx and/or narrowed opening into larynx at 0.1 mg/kg/day and umbilical hernia at 0.1 and 0.25 mg/kg/day.

Pregnant rabbits given subcutaneous doses of 0.01, 0.025 and 0.05 mg/kg/day liraglutide from gestation day 6 through day 18 inclusive, had estimated systemic exposures less than the human exposure at the MRHD of 1.8 mg/day at all doses, based on plasma AUC. Liraglutide decreased fetal weight and dose-dependently increased the incidence of total major fetal abnormalities at all doses. The incidence of malformations exceeded concurrent and historical controls at 0.01 mg/kg/day (kidneys, scapula), ≥ 0.01 mg/kg/day (eyes, forelimb), 0.025 mg/kg/day (brain, tail and sacral vertebrae, major blood vessels and heart, umbilicus), ≥ 0.025 mg/kg/day (sternum) and at 0.05 mg/kg/day (parietal bones, major blood vessels). Irregular ossification and/or skeletal abnormalities occurred in the skull and jaw, vertebrae and ribs, sternum, pelvis, tail, and scapula; and dose-dependent minor skeletal variations were observed. Visceral abnormalities occurred in blood vessels, lung, liver, and esophagus. Bilobed or bifurcated gallbladder was seen in all treatment groups, but not in the control group.

In pregnant female rats given subcutaneous doses of 0.1, 0.25 and 1.0 mg/kg/day liraglutide from gestation day 6 through weaning or termination of nursing on lactation day 24, estimated systemic exposures were 0.8-, 3-, and 11-times human exposure at the MRHD of 1.8 mg/day, based on plasma AUC. A slight delay in parturition was observed in the majority of treated rats. Group mean body weight of neonatal rats from liraglutide-treated dams was lower than neonatal rats from control group dams.

Bloody scabs and agitated behavior occurred in male rats descended from dams treated with 1 mg/kg/day liraglutide. Group mean body weight from birth to postpartum day 14 trended lower in F_2 generation rats descended from liraglutide-treated rats compared to F_2 generation rats descended from controls, but differences did not reach statistical significance for any group.

8.2 Lactation

Risk Summary

There are no data on the presence of VICTOZA in human milk, the effects on the breastfed infant, or the effects on milk production. Liraglutide was present in milk of lactating rats *[see Data]*.

Developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for VICTOZA and any potential adverse effects on the breastfed infant from VICTOZA or from the underlying maternal condition.

Data

In lactating rats, liraglutide was present unchanged in milk at concentrations approximately 50% of maternal plasma concentrations.

8.4 Pediatric Use

Safety and effectiveness of VICTOZA have not been established in pediatric patients. VICTOZA is not recommended for use in pediatric patients.

8.5 Geriatric Use

In the VICTOZA treatment arms of the glycemic control trials, a total of 832 (19.3%) of the patients were 65 to 74 years of age and 145 (3.4%) were 75 years of age and over. No overall differences in safety or efficacy were observed between these patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

In the VICTOZA treatment arm of the LEADER trial *[see Clinical Studies (14.2)]*, a total of 1738 (37.2%) patients were 65 to 74 years of age, 401 (8.6%) were 75 to 84 years of age, and 17 (0.4%) were 85 years of age or older at baseline. No overall differences in safety or efficacy were observed between these patients and younger patients.

8.6 Renal Impairment

No dose adjustment of VICTOZA is recommended for patients with renal impairment *[see Clinical Pharmacology (12.3)]*. The safety and efficacy of VICTOZA was evaluated in a 26-week clinical study that included patients with moderate renal impairment (eGFR 30 to 60 mL/min/1.73m^2) *[see Clinical Studies (14.1)]*.

In the VICTOZA treatment arm of the LEADER trial *[see Clinical Studies (14.2)]*, 1932 (41.4%) patients had mild renal impairment, 999 (21.4%) patients had moderate renal impairment and 117 (2.5%) patients had severe renal impairment at baseline. No overall differences in safety or efficacy were seen in these patients compared to patients with normal renal function.

There is limited experience with VICTOZA in patients with end stage renal disease. There have been postmarketing reports of acute renal failure and worsening of chronic renal failure, which may sometimes require hemodialysis *[see Warnings and Precautions (5.5) and Adverse Reactions (6.2)]*. Use caution in patients who experience dehydration.

8.7 Hepatic Impairment
There is limited experience in patients with mild, moderate or severe hepatic impairment. Therefore, VICTOZA should be used with caution in this patient population. No dose adjustment of VICTOZA is recommended for patients with hepatic impairment *[see Clinical Pharmacology (12.3)]*.

8.8 Gastroparesis
VICTOZA slows gastric emptying. VICTOZA has not been studied in patients with pre-existing gastroparesis.

10 OVERDOSAGE
Overdoses have been reported in clinical trials and post-marketing use of VICTOZA. Effects have included severe nausea and severe vomiting. In the event of overdosage, appropriate supportive treatment should be initiated according to the patient's clinical signs and symptoms.

11 DESCRIPTION
VICTOZA contains liraglutide, an analog of human GLP-1 and acts as a GLP-1 receptor agonist. The peptide precursor of liraglutide, produced by a process that includes expression of recombinant DNA in *Saccharomyces cerevisiae,* has been engineered to be 97% homologous to native human GLP-1 by substituting arginine for lysine at position 34. Liraglutide is made by attaching a C-16 fatty acid (palmitic acid) with a glutamic acid spacer on the remaining lysine residue at position 26 of the peptide precursor. The molecular formula of liraglutide is $C_{172}H_{265}N_{43}O_{51}$ and the molecular weight is 3751.2 Daltons. The structural formula (Figure 1) is:

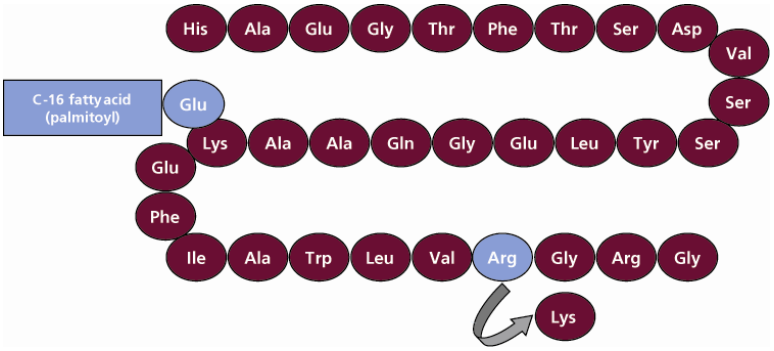


Figure 1 Structural Formula of liraglutide

VICTOZA is a clear, colorless or almost colorless solution. Each 1 mL of VICTOZA solution contains 6 mg of liraglutide and the following inactive ingredients: disodium phosphate dihydrate, 1.42 mg; propylene glycol, 14 mg; phenol, 5.5 mg; and water for injection. Each pre-filled pen contains a 3 mL solution of VICTOZA equivalent to 18 mg liraglutide (free-base, anhydrous).

12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
Liraglutide is an acylated human Glucagon-Like Peptide-1 (GLP-1) receptor agonist with 97% amino acid sequence homology to endogenous human GLP-1(7-37). GLP-1(7-37) represents <20% of total circulating endogenous GLP-1. Like GLP-1(7-37), liraglutide activates the GLP-1 receptor, a membrane-bound cell-surface receptor coupled to adenylyl cyclase by the stimulatory G-protein, Gs, in pancreatic beta cells. Liraglutide increases intracellular cyclic AMP (cAMP) leading to insulin release in the presence of elevated glucose concentrations. This insulin secretion subsides as blood glucose

concentrations decrease and approach euglycemia. Liraglutide also decreases glucagon secretion in a glucose-dependent manner. The mechanism of blood glucose lowering also involves a delay in gastric emptying.

GLP-1(7-37) has a half-life of 1.5-2 minutes due to degradation by the ubiquitous endogenous enzymes, dipeptidyl peptidase IV (DPP-IV) and neutral endopeptidases (NEP). Unlike native GLP-1, liraglutide is stable against metabolic degradation by both peptidases and has a plasma half-life of 13 hours after subcutaneous administration. The pharmacokinetic profile of liraglutide, which makes it suitable for once daily administration, is a result of self-association that delays absorption, plasma protein binding and stability against metabolic degradation by DPP-IV and NEP.

12.2 Pharmacodynamics

VICTOZA's pharmacodynamic profile is consistent with its pharmacokinetic profile observed after single subcutaneous administration as VICTOZA lowered fasting, premeal and postprandial glucose throughout the day *[see Clinical Pharmacology (12.3)]*.

Fasting and postprandial glucose was measured before and up to 5 hours after a standardized meal after treatment to steady state with 0.6, 1.2 and 1.8 mg VICTOZA or placebo. Compared to placebo, the postprandial plasma glucose $AUC_{0\text{-}300min}$ was 35% lower after VICTOZA 1.2 mg and 38% lower after VICTOZA 1.8 mg.

Glucose-dependent insulin secretion

The effect of a single dose of 7.5 mcg/kg (~ 0.7 mg) VICTOZA on insulin secretion rates (ISR) was investigated in 10 patients with type 2 diabetes during graded glucose infusion. In these patients, on average, the ISR response was increased in a glucose-dependent manner (Figure 2).

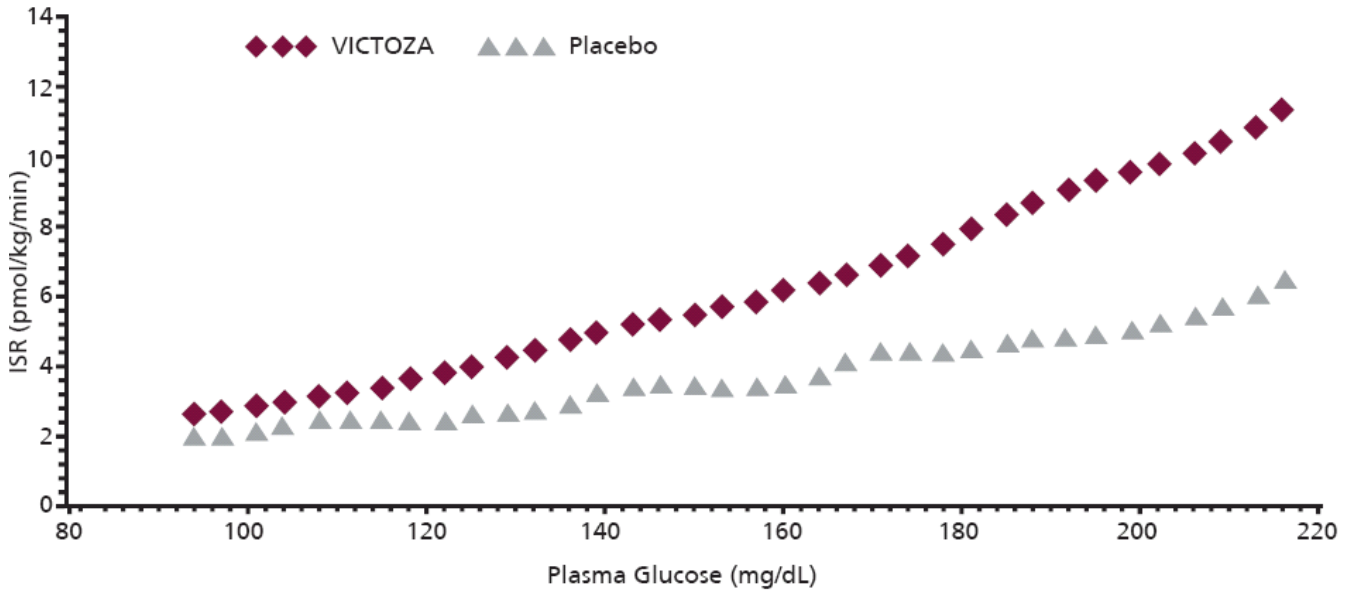


Figure 2 Mean Insulin Secretion Rate (ISR) versus Glucose Concentration Following Single-Dose VICTOZA 7.5 mcg/kg (~ 0.7 mg) or Placebo in Patients with Type 2 Diabetes (N=10) During Graded Glucose Infusion

Glucagon secretion

VICTOZA lowered blood glucose by stimulating insulin secretion and lowering glucagon secretion. A single dose of VICTOZA 7.5 mcg/kg (~ 0.7 mg) did not impair glucagon response to low glucose concentrations.

Gastric emptying
VICTOZA causes a delay of gastric emptying, thereby reducing the rate at which postprandial glucose appears in the circulation.

Cardiac Electrophysiology (QTc)
The effect of VICTOZA on cardiac repolarization was tested in a QTc study. VICTOZA at steady state concentrations with daily doses up to 1.8 mg did not produce QTc prolongation.

12.3 Pharmacokinetics
Absorption - Following subcutaneous administration, maximum concentrations of liraglutide are achieved at 8-12 hours post dosing. The mean peak (C_{max}) and total (AUC) exposures of liraglutide were 35 ng/mL and 960 ng·h/mL, respectively, for a subcutaneous single dose of 0.6 mg. After subcutaneous single dose administrations, C_{max} and AUC of liraglutide increased proportionally over the therapeutic dose range of 0.6 mg to 1.8 mg. At 1.8 mg VICTOZA, the average steady state concentration of liraglutide over 24 hours was approximately 128 ng/mL. $AUC_{0-\infty}$ was equivalent between upper arm and abdomen, and between upper arm and thigh. $AUC_{0-\infty}$ from thigh was 22% lower than that from abdomen. However, liraglutide exposures were considered comparable among these three subcutaneous injection sites. Absolute bioavailability of liraglutide following subcutaneous administration is approximately 55%.

Distribution - The mean apparent volume of distribution after subcutaneous administration of VICTOZA 0.6 mg is approximately 13 L. The mean volume of distribution after intravenous administration of VICTOZA is 0.07 L/kg. Liraglutide is extensively bound to plasma protein (>98%).

Metabolism - During the initial 24 hours following administration of a single [^{3}H]-liraglutide dose to healthy subjects, the major component in plasma was intact liraglutide. Liraglutide is endogenously metabolized in a similar manner to large proteins without a specific organ as a major route of elimination.

Elimination - Following a [^{3}H]-liraglutide dose, intact liraglutide was not detected in urine or feces. Only a minor part of the administered radioactivity was excreted as liraglutide-related metabolites in urine or feces (6% and 5%, respectively). The majority of urine and feces radioactivity was excreted during the first 6-8 days. The mean apparent clearance following subcutaneous administration of a single dose of liraglutide is approximately 1.2 L/h with an elimination half-life of approximately 13 hours, making VICTOZA suitable for once daily administration.

Specific Populations
Elderly - Age had no effect on the pharmacokinetics of VICTOZA based on a pharmacokinetic study in healthy elderly subjects (65 to 83 years) and population pharmacokinetic analyses of patients 18 to 80 years of age *[see Use in Specific Populations (8.5)]*.

Gender - Based on the results of population pharmacokinetic analyses, females have 25% lower weight-adjusted clearance of VICTOZA compared to males. Based on the exposure response data, no dose adjustment is necessary based on gender.

Race and Ethnicity - Race and ethnicity had no effect on the pharmacokinetics of VICTOZA based on the results of population pharmacokinetic analyses that included Caucasian, Black, Asian and Hispanic/Non-Hispanic subjects.

Body Weight - Body weight significantly affects the pharmacokinetics of VICTOZA based on results of population pharmacokinetic analyses. The exposure of liraglutide decreases with an increase in baseline body weight. However, the 1.2 mg and 1.8 mg daily doses of VICTOZA provided adequate systemic exposures over the body weight range of 40 – 160 kg evaluated in the clinical trials. Liraglutide was not studied in patients with body weight >160 kg.

Pediatric - VICTOZA has not been studied in pediatric patients *[see Use in Specific Populations (8.4)]*.

Renal Impairment - The single-dose pharmacokinetics of VICTOZA were evaluated in subjects with varying degrees of renal impairment. Subjects with mild (estimated creatinine clearance 50-80 mL/min) to severe (estimated creatinine clearance <30 mL/min) renal impairment and subjects with end-stage renal disease requiring dialysis were included in the trial. Compared to healthy subjects, liraglutide AUC in mild, moderate, and severe renal impairment and in end-stage renal disease was on average 35%, 19%, 29% and 30% lower, respectively *[see Use in Specific Populations (8.6)]*.

Hepatic Impairment - The single-dose pharmacokinetics of VICTOZA were evaluated in subjects with varying degrees of hepatic impairment. Subjects with mild (Child Pugh score 5-6) to severe (Child Pugh score > 9) hepatic impairment were included in the trial. Compared to healthy subjects, liraglutide AUC in subjects with mild, moderate and severe hepatic impairment was on average 11%, 14% and 42% lower, respectively *[see Use in Specific Populations (8.7)]*.

Drug Interactions
In vitro assessment of drug-drug interactions
VICTOZA has low potential for pharmacokinetic drug-drug interactions related to cytochrome P450 (CYP) and plasma protein binding.

In vivo assessment of drug-drug interactions
The drug-drug interaction studies were performed at steady state with VICTOZA 1.8 mg/day. Before administration of concomitant treatment, subjects underwent a 0.6 mg weekly dose increase to reach the maximum dose of 1.8 mg/day. Administration of the interacting drugs was timed so that C_{max} of VICTOZA (8-12 h) would coincide with the absorption peak of the co-administered drugs.

Digoxin
A single dose of digoxin 1 mg was administered 7 hours after the dose of VICTOZA at steady state. The concomitant administration with VICTOZA resulted in a reduction of digoxin AUC by 16%; C_{max} decreased by 31%. Digoxin median time to maximal concentration (T_{max}) was delayed from 1 h to 1.5 h.

Lisinopril
A single dose of lisinopril 20 mg was administered 5 minutes after the dose of VICTOZA at steady state. The co-administration with VICTOZA resulted in a reduction of lisinopril AUC by 15%; C_{max} decreased by 27%. Lisinopril median T_{max} was delayed from 6 h to 8 h with VICTOZA.

Atorvastatin

VICTOZA did not change the overall exposure (AUC) of atorvastatin following a single dose of atorvastatin 40 mg, administered 5 hours after the dose of VICTOZA at steady state. Atorvastatin C_{max} was decreased by 38% and median T_{max} was delayed from 1 h to 3 h with VICTOZA.

Acetaminophen
VICTOZA did not change the overall exposure (AUC) of acetaminophen following a single dose of acetaminophen 1000 mg, administered 8 hours after the dose of VICTOZA at steady state. Acetaminophen C_{max} was decreased by 31% and median T_{max} was delayed up to 15 minutes.

Griseofulvin
VICTOZA did not change the overall exposure (AUC) of griseofulvin following co-administration of a single dose of griseofulvin 500 mg with VICTOZA at steady state. Griseofulvin C_{max} increased by 37% while median T_{max} did not change.

Oral Contraceptives
A single dose of an oral contraceptive combination product containing 0.03 mg ethinylestradiol and 0.15 mg levonorgestrel was administered under fed conditions and 7 hours after the dose of VICTOZA at steady state. VICTOZA lowered ethinylestradiol and levonorgestrel C_{max} by 12% and 13%, respectively. There was no effect of VICTOZA on the overall exposure (AUC) of ethinylestradiol. VICTOZA increased the levonorgestrel $AUC_{0-\infty}$ by 18%. VICTOZA delayed T_{max} for both ethinylestradiol and levonorgestrel by 1.5 h.

Insulin Detemir
No pharmacokinetic interaction was observed between VICTOZA and insulin detemir when separate subcutaneous injections of insulin detemir 0.5 Unit/kg (single-dose) and VICTOZA 1.8 mg (steady state) were administered in patients with type 2 diabetes.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

A 104-week carcinogenicity study was conducted in male and female CD-1 mice at doses of 0.03, 0.2, 1.0, and 3.0 mg/kg/day liraglutide administered by bolus subcutaneous injection yielding systemic exposures 0.2-, 2-, 10- and 45-times the human exposure, respectively, at the MRHD of 1.8 mg/day based on plasma AUC comparison. A dose-related increase in benign thyroid C-cell adenomas was seen in the 1.0 and the 3.0 mg/kg/day groups with incidences of 13% and 19% in males and 6% and 20% in females, respectively. C-cell adenomas did not occur in control groups or 0.03 and 0.2 mg/kg/day groups. Treatment-related malignant C-cell carcinomas occurred in 3% of females in the 3.0 mg/kg/day group. Thyroid C-cell tumors are rare findings during carcinogenicity testing in mice. A treatment-related increase in fibrosarcomas was seen on the dorsal skin and subcutis, the body surface used for drug injection, in males in the 3 mg/kg/day group. These fibrosarcomas were attributed to the high local concentration of drug near the injection site. The liraglutide concentration in the clinical formulation (6 mg/mL) is 10-times higher than the concentration in the formulation used to administer 3 mg/kg/day liraglutide to mice in the carcinogenicity study (0.6 mg/mL).

A 104-week carcinogenicity study was conducted in male and female Sprague Dawley rats at doses of 0.075, 0.25 and 0.75 mg/kg/day liraglutide administered by bolus subcutaneous injection with exposures 0.5-, 2- and 8-times the human exposure, respectively, resulting from the MRHD based on plasma AUC comparison. A treatment-related increase in benign thyroid C-cell adenomas was seen in males in 0.25 and 0.75 mg/kg/day liraglutide groups with incidences of 12%, 16%, 42%, and 46% and in all female

liraglutide-treated groups with incidences of 10%, 27%, 33%, and 56% in 0 (control), 0.075, 0.25, and 0.75 mg/kg/day groups, respectively. A treatment-related increase in malignant thyroid C-cell carcinomas was observed in all male liraglutide-treated groups with incidences of 2%, 8%, 6%, and 14% and in females at 0.25 and 0.75 mg/kg/day with incidences of 0%, 0%, 4%, and 6% in 0 (control), 0.075, 0.25, and 0.75 mg/kg/day groups, respectively. Thyroid C-cell carcinomas are rare findings during carcinogenicity testing in rats.

Studies in mice demonstrated that liraglutide-induced C-cell proliferation was dependent on the GLP-1 receptor and that liraglutide did not cause activation of the REarranged during Transfection (RET) proto-oncogene in thyroid C-cells.

Human relevance of thyroid C-cell tumors in mice and rats is unknown and has not been determined by clinical studies or nonclinical studies *[see Boxed Warning and Warnings and Precautions (5.1)]*.

Liraglutide was negative with and without metabolic activation in the Ames test for mutagenicity and in a human peripheral blood lymphocyte chromosome aberration test for clastogenicity. Liraglutide was negative in repeat-dose *in vivo* micronucleus tests in rats.
In rat fertility studies using subcutaneous doses of 0.1, 0.25 and 1.0 mg/kg/day liraglutide, males were treated for 4 weeks prior to and throughout mating and females were treated 2 weeks prior to and throughout mating until gestation day 17. No direct adverse effects on male fertility was observed at doses up to 1.0 mg/kg/day, a high dose yielding an estimated systemic exposure 11- times the human exposure at the MRHD, based on plasma AUC. In female rats, an increase in early embryonic deaths occurred at 1.0 mg/kg/day. Reduced body weight gain and food consumption were observed in females at the 1.0 mg/kg/day dose.

14 CLINICAL STUDIES

14.1 Glycemic Control trials in Adults with Type 2 Diabetes Mellitus

In glycemic control trials, VICTOZA has been studied as monotherapy and in combination with one or two oral anti-diabetic medications or basal insulin. VICTOZA was also studied in a cardiovascular outcomes trial (LEADER trial).

In each of the placebo controlled trials, treatment with VICTOZA produced clinically and statistically significant improvements in hemoglobin A_{1c} and fasting plasma glucose (FPG) compared to placebo.

All VICTOZA-treated patients started at 0.6 mg/day. The dose was increased in weekly intervals by 0.6 mg to reach 1.2 mg or 1.8 mg for patients randomized to these higher doses. VICTOZA 0.6 mg is not effective for glycemic control and is intended only as a starting dose to reduce gastrointestinal intolerance *[see Dosage and Administration (2)]*.

Monotherapy

In this 52-week trial, 746 patients were randomized to VICTOZA 1.2 mg, VICTOZA 1.8 mg, or glimepiride 8 mg. Patients who were randomized to glimepiride were initially treated with 2 mg daily for two weeks, increasing to 4 mg daily for another two weeks, and finally increasing to 8 mg daily. Treatment with VICTOZA 1.8 mg and 1.2 mg resulted in a statistically significant reduction in HbA_{1c} compared to glimepiride (Table 3). The percentage of patients who discontinued due to ineffective

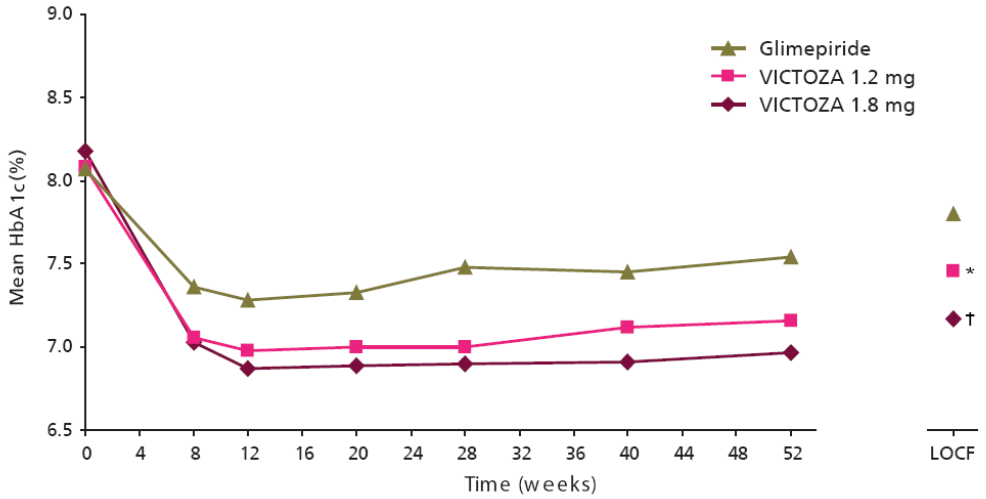
therapy was 3.6% in the VICTOZA 1.8 mg treatment group, 6.0% in the VICTOZA 1.2 mg treatment group, and 10.1% in the glimepiride-treatment group.

The mean age of participants was 53 years, and the mean duration of diabetes was 5 years. Participants were 49.7% male, 77.5% White, 12.6% Black or African American and 35.0% of Hispanic ethnicity. The mean BMI was 33.1 kg/m^2.

Table 3 Results of a 52-week monotherapy trial[a]

	VICTOZA 1.8 mg	VICTOZA 1.2 mg	Glimepiride 8 mg
Intent-to-Treat Population (N)	246	251	248
HbA_{1c} (%) (Mean)			
Baseline	8.2	8.2	8.2
Change from baseline (adjusted mean)[b]	-1.1	-0.8	-0.5
Difference from glimepiride arm (adjusted mean)[b]	-0.6**	-0.3*	
95% Confidence Interval	(-0.8, -0.4)	(-0.5, -0.1)	
Percentage of patients achieving A_{1c} <7%	51	43	28
Fasting Plasma Glucose (mg/dL) (Mean)			
Baseline	172	168	172
Change from baseline (adjusted mean)[b]	-26	-15	-5
Difference from glimepiride arm (adjusted mean)[b]	-20**	-10*	
95% Confidence Interval	(-29, -12)	(-19, -1)	
Body Weight (kg) (Mean)			
Baseline	92.6	92.1	93.3
Change from baseline (adjusted mean)[b]	-2.5	-2.1	+1.1
Difference from glimepiride arm (adjusted mean)[b]	-3.6**	-3.2**	
95% Confidence Interval	(-4.3, -2.9)	(-3.9, -2.5)	

[a]Intent-to-treat population using last observation on study
[b]Least squares mean adjusted for baseline value
*p-value <0.05
**p-value <0.0001



*p-value = 0.0014 for VICTOZA 1.2 mg compared to glimepiride. †p-value < 0.0001 for VICTOZA 1.8 mg compared to glimepiride.
P values derived from change from baseline ANCOVA model.

Figure 3 Mean HbA_{1c} for patients who completed the 52-week trial and for the Last Observation Carried Forward (LOCF, intent-to-treat) data at Week 52 (Monotherapy)

Combination Therapy

Add-on to Metformin

In this 26-week trial, 1091 patients were randomized to VICTOZA 0.6 mg, VICTOZA 1.2 mg, VICTOZA 1.8 mg, placebo, or glimepiride 4 mg (one-half of the maximal approved dose in the United States), all as add-on to metformin. Randomization occurred after a 6-week run-in period consisting of a 3-week initial forced metformin titration period followed by a maintenance period of another 3 weeks. During the titration period, doses of metformin were increased up to 2000 mg/day. Treatment with VICTOZA 1.2 mg and 1.8 mg as add-on to metformin resulted in a significant mean HbA_{1c} reduction relative to placebo add-on to metformin and resulted in a similar mean HbA_{1c} reduction relative to glimepiride 4 mg add-on to metformin (Table 4). The percentage of patients who discontinued due to ineffective therapy was 5.4% in the VICTOZA 1.8 mg + metformin treatment group, 3.3% in the VICTOZA 1.2 mg + metformin treatment group, 23.8% in the placebo + metformin treatment group, and 3.7% in the glimepiride + metformin treated group.

The mean age of participants was 57 years, and the mean duration of diabetes was 7 years. Participants were 58.2% male, 87.1% White and 2.4% Black or African American. The mean BMI was 31.0 kg/m^2.

Table 4 Results of a 26-week trial of VICTOZA as add-on to metformin[a]

	VICTOZA 1.8 mg + Metformin	**VICTOZA 1.2 mg + Metformin**	**Placebo + Metformin**	**Glimepiride 4 mg[†] + Metformin**
Intent-to-Treat Population (N)	242	240	121	242
HbA_{1c} (%) (Mean)				
Baseline	8.4	8.3	8.4	8.4
Change from baseline (adjusted mean)[b]	-1.0	-1.0	+0.1	-1.0
Difference from placebo + metformin arm (adjusted mean)[b]	-1.1**	-1.1**		
95% Confidence Interval	(-1.3, -0.9)	(-1.3, -0.9)		
Difference from glimepiride + metformin arm (adjusted mean)[b]	0.0	0.0		
95% Confidence Interval	(-0.2, 0.2)	(-0.2, 0.2)		
Percentage of patients achieving A_{1c} <7%	42	35	11	36
Fasting Plasma Glucose (mg/dL) (Mean)				
Baseline	181	179	182	180
Change from baseline (adjusted mean)[b]	-30	-30	+7	-24
Difference from placebo + metformin arm (adjusted mean)[b]	-38**	-37**		
95% Confidence Interval	(-48, -27)	(-47, -26)		
Difference from glimepiride + metformin arm (adjusted mean)[b]	-7	-6		
95% Confidence Interval	(-16, 2)	(-15, 3)		
Body Weight (kg) (Mean)				
Baseline	88.0	88.5	91.0	89.0
Change from baseline (adjusted mean)[b]	-2.8	-2.6	-1.5	+1.0
Difference from placebo + metformin arm (adjusted mean)[b]	-1.3*	-1.1*		
95% Confidence Interval	(-2.2, -0.4)	(-2.0, -0.2)		
Difference from glimepiride + metformin arm (adjusted mean)[b]	-3.8**	-3.5**		
95% Confidence Interval	(-4.5, -3.0)	(-4.3, -2.8)		

[a]Intent-to-treat population using last observation on study
[b]Least squares mean adjusted for baseline value
[†] For glimepiride, one-half of the maximal approved United States dose.
*p-value <0.05
**p-value <0.0001

VICTOZA Compared to Sitagliptin, Both as Add-on to Metformin

In this 26–week, open-label trial, 665 patients on a background of metformin ≥1500 mg per day were randomized to VICTOZA 1.2 mg once-daily, VICTOZA 1.8 mg once-daily or sitagliptin 100 mg once-daily, all dosed according to approved labeling. Patients were to continue their current treatment on metformin at a stable, pre-trial dose level and dosing frequency.

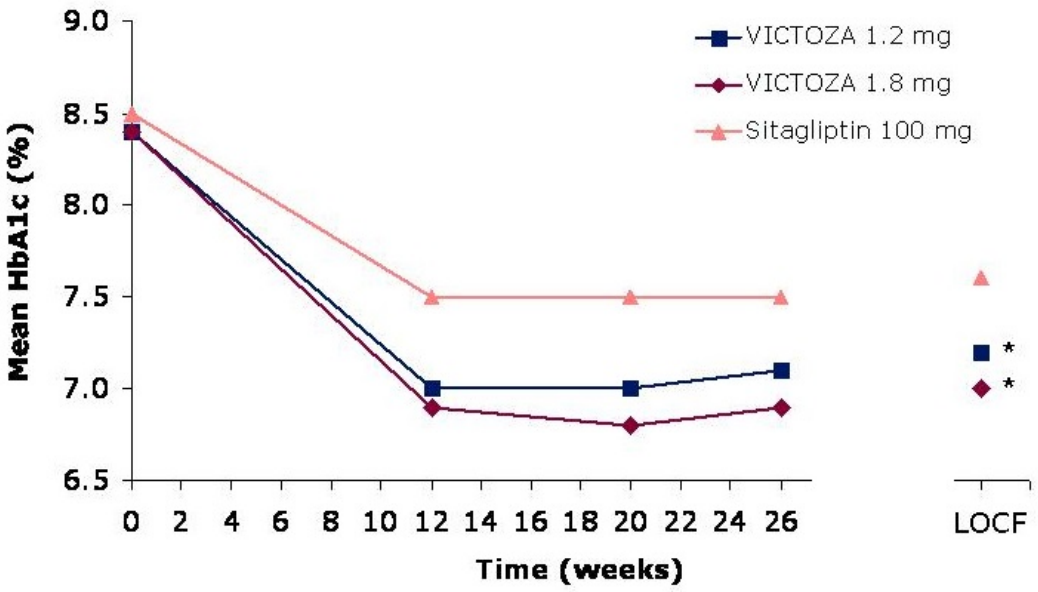
The mean age of participants was 56 years, and the mean duration of diabetes was 6 years. Participants were 52.9% male, 86.6% White, 7.2% Black or African American and 16.2% of Hispanic ethnicity. The mean BMI was 32.8 kg/m^2.

The primary endpoint was the change in HbA_{1c} from baseline to Week 26. Treatment with VICTOZA 1.2 mg and VICTOZA 1.8 mg resulted in statistically significant reductions in HbA_{1c} relative to sitagliptin 100 mg (Table 5). The percentage of patients who discontinued due to ineffective therapy was 3.1% in the VICTOZA 1.2 mg group, 0.5% in the VICTOZA 1.8 mg treatment group, and 4.1% in the sitagliptin 100 mg treatment group. From a mean baseline body weight of 94 kg, there was a mean reduction of 2.7 kg for VICTOZA 1.2 mg, 3.3 kg for VICTOZA 1.8 mg, and 0.8 kg for sitagliptin 100 mg.

Table 5 Results of a 26-week open-label trial of VICTOZA Compared to Sitagliptin (both in combination with metformin)[a]

	VICTOZA 1.8 mg + Metformin	**VICTOZA 1.2 mg + Metformin**	**Sitagliptin 100 mg + Metformin**
Intent-to-Treat Population (N)	218	221	219
HbA_{1c} (%) (Mean)			
Baseline	8.4	8.4	8.5
Change from baseline (adjusted mean)	-1.5	-1.2	-0.9
Difference from sitagliptin arm (adjusted mean) [b]	-0.6**	-0.3**	
95% Confidence Interval	(-0.8, -0.4)	(-0.5, -0.2)	
Percentage of patients achieving A_{1c} <7%	56	44	22
Fasting Plasma Glucose (mg/dL) (Mean)			
Baseline	179	182	180
Change from baseline (adjusted mean)	-39	-34	-15
Difference from sitagliptin arm (adjusted mean) [b]	-24**	-19**	
95% Confidence Interval	(-31, -16)	(-26, -12)	

[a]Intent-to-treat population using last observation on study
[b]Least squares mean adjusted for baseline value
**p-value <0.0001



*p-value <0.0001 for Victoza compared with sitagliptin

P values derived from change from baseline ANCOVA model

Figure 4 Mean HbA_{1c} for patients who completed the 26-week trial and for the Last Observation Carried Forward (LOCF, intent-to-treat) data at Week 26

Combination Therapy with Metformin and Insulin

This 26-week open-label trial enrolled 988 patients with inadequate glycemic control (HbA_{1c} 7-10%) on metformin (≥1500 mg/day) alone or inadequate glycemic control (HbA_{1c} 7-8.5%) on metformin (≥1500 mg/day) and a sulfonylurea. Patients who were on metformin and a sulfonylurea discontinued the sulfonylurea then all patients entered a 12-week run-in period during which they received add-on therapy with VICTOZA titrated to 1.8 mg once-daily. At the end of the run-in period, 498 patients (50%) achieved HbA_{1c} <7% with VICTOZA 1.8 mg and metformin and continued treatment in a non-randomized, observational arm. Another 167 patients (17%) withdrew from the trial during the run-in period with approximately one-half of these patients doing so because of gastrointestinal adverse reactions *[see Adverse Reactions (6.1)]*. The remaining 323 patients with HbA_{1c} ≥7% (33% of those who entered the run-in period) were randomized to 26 weeks of once-daily insulin detemir administered in the evening as add-on therapy (N=162) or to continued, unchanged treatment with VICTOZA 1.8 mg and metformin (N=161). The starting dose of insulin detemir was 10 units/day and the mean dose at the end of the 26-week randomized period was 39 units/day. During the 26 week randomized treatment period, the percentage of patients who discontinued due to ineffective therapy was 11.2% in the group randomized to continued treatment with VICTOZA 1.8 mg and metformin and 1.2% in the group randomized to add-on therapy with insulin detemir.

The mean age of participants was 57 years, and the mean duration of diabetes was 8 years. Participants were 55.7% male, 91.3% White, 5.6% Black or African American and 12.5% of Hispanic ethnicity. The mean BMI was 34.0 kg/m^2.

Treatment with insulin detemir as add-on to VICTOZA 1.8 mg + metformin resulted in statistically significant reductions in HbA_{1c} and FPG compared to continued, unchanged treatment with VICTOZA 1.8 mg + metformin alone (Table 6). From a mean baseline body weight of 96 kg after randomization, there was a mean reduction of 0.3 kg in the patients who received insulin detemir add-on therapy compared to a mean reduction of 1.1 kg in the patients who continued on unchanged treatment with VICTOZA 1.8 mg + metformin alone.

Table 6 Results of a 26-week open label trial of Insulin detemir as add on to VICTOZA + metformin compared to continued treatment with VICTOZA + metformin alone in patients not achieving HbA_{1c} < 7% after 12 weeks of Metformin and VICTOZA[a]

	Insulin detemir + VICTOZA + Metformin	**VICTOZA + Metformin**
Intent-to-Treat Population (N)	162	157
HbA_{1c} (%) (Mean)		
Baseline (week 0)	7.6	7.6
Change from baseline (adjusted mean)	-0.5	0
Difference from VICTOZA + metformin arm (LS mean)[b]	-0.5**	
95% Confidence Interval	(-0.7, -0.4)	
Percentage of patients achieving A_{1c} <7%	43	17
Fasting Plasma Glucose (mg/dL) (Mean)		
Baseline (week 0)	166	159
Change from baseline (adjusted mean)	-39	-7
Difference from VICTOZA + metformin arm (LS mean)[b]	-31**	
95% Confidence Interval	(-39, -23)	

[a]Intent-to-treat population using last observation on study
[b]Least squares mean adjusted for baseline value
**p-value <0.0001

Add-on to Sulfonylurea

In this 26-week trial, 1041 patients were randomized to VICTOZA 0.6 mg, VICTOZA 1.2 mg, VICTOZA 1.8 mg, placebo, or rosiglitazone 4 mg (one-half of the maximal approved dose in the United States), all as add-on to glimepiride. Randomization occurred after a 4-week run-in period consisting of an initial, 2-week, forced-glimepiride titration period followed by a maintenance period of another 2 weeks. During the titration period, doses of glimepiride were increased to 4 mg/day. The doses of glimepiride could be reduced (at the discretion of the investigator) from 4 mg/day to 3 mg/day or 2 mg/day (minimum) after randomization, in the event of unacceptable hypoglycemia or other adverse events.

The mean age of participants was 56 years, and the mean duration of diabetes was 8 years. Participants were 49.4% male, 64.4% White and 2.8% Black or African American. The mean BMI was 29.9 kg/m^2.

Treatment with VICTOZA 1.2 mg and 1.8 mg as add-on to glimepiride resulted in a statistically significant reduction in mean HbA_{1c} compared to placebo add-on to glimepiride (Table 7). The percentage of patients who discontinued due to ineffective therapy was 3.0% in the VICTOZA 1.8 mg + glimepiride treatment group, 3.5% in the VICTOZA 1.2 mg + glimepiride treatment group, 17.5% in the placebo + glimepiride treatment group, and 6.9% in the rosiglitazone + glimepiride treatment group.

Table 7 Results of a 26-week trial of VICTOZA as add-on to sulfonylurea[a]

	VICTOZA 1.8 mg + Glimepiride	VICTOZA 1.2 mg + Glimepiride	Placebo + Glimepiride	Rosiglitazone 4 mg[†] + Glimepiride
Intent-to-Treat Population (N)	234	228	114	231
HbA_{1c} (%) (Mean)				
Baseline	8.5	8.5	8.4	8.4
Change from baseline (adjusted mean)[b]	-1.1	-1.1	+0.2	-0.4
Difference from placebo + glimepiride arm (adjusted mean)[b]	-1.4**	-1.3**		
95% Confidence Interval	(-1.6, -1.1)	(-1.5, -1.1)		
Percentage of patients achieving A_{1c} <7%	42	35	7	22
Fasting Plasma Glucose (mg/dL) (Mean)				
Baseline	174	177	171	179
Change from baseline (adjusted mean)[b]	-29	-28	+18	-16
Difference from placebo + glimepiride arm (adjusted mean)[b]	-47**	-46**		
95% Confidence Interval	(-58, -35)	(-58, -35)		
Body Weight (kg) (Mean)				
Baseline	83.0	80.0	81.9	80.6
Change from baseline (adjusted mean)[b]	-0.2	+0.3	-0.1	+2.1
Difference from placebo + glimepiride arm (adjusted mean)[b]	-0.1	0.4		
95% Confidence Interval	(-0.9, 0.6)	(-0.4, 1.2)		

[a]Intent-to-treat population using last observation on study
[b]Least squares mean adjusted for baseline value
[†] For rosiglitazone, one-half of the maximal approved United States dose.
**p-value <0.0001

Add-on to Metformin and Sulfonylurea

In this 26-week trial, 581 patients were randomized to VICTOZA 1.8 mg, placebo, or insulin glargine, all as add-on to metformin and glimepiride. Randomization took place after a 6-week run-in period consisting of a 3-week forced metformin and glimepiride titration period followed by a maintenance period of another 3 weeks. During the titration period, doses of metformin and glimepiride were to be increased up to 2000 mg/day and 4 mg/day, respectively. After randomization, patients randomized to VICTOZA 1.8 mg underwent a 2 week period of titration with VICTOZA. During the trial, the VICTOZA and metformin doses were fixed, although glimepiride and insulin glargine doses could be adjusted. Patients titrated glargine twice-weekly during the first 8 weeks of treatment based on self-measured fasting plasma glucose on the day of titration. After Week 8, the frequency of insulin glargine titration was left to the discretion of the investigator, but, at a minimum, the glargine dose was to be revised, if necessary, at Weeks 12 and 18. Only 20% of glargine-treated patients achieved the pre-specified target fasting plasma glucose of ≤100 mg/dL. Therefore, optimal titration of the insulin glargine dose was not achieved in most patients.

The mean age of participants was 58 years, and the mean duration of diabetes was 9 years. Participants were 56.5% male, 75.0% White and 3.6% Black or African American. The mean BMI was 30.5 kg/m^2.

Treatment with VICTOZA as add-on to glimepiride and metformin resulted in a statistically significant mean reduction in HbA_{1c} compared to placebo add-on to glimepiride and metformin (Table 8). The percentage of patients who discontinued due to ineffective therapy was 0.9% in the VICTOZA 1.8 mg + metformin + glimepiride treatment group, 0.4% in the insulin glargine + metformin + glimepiride treatment group, and 11.3% in the placebo + metformin + glimepiride treatment group.

Table 8 Results of a 26-week trial of VICTOZA as add-on to metformin and sulfonylurea[a]

	VICTOZA 1.8 mg + Metformin + Glimepiride	Placebo + Metformin + Glimepiride	Insulin glargine[†] + Metformin + Glimepiride
Intent-to-Treat Population (N)	230	114	232
HbA_{1c} (%) (Mean)			
Baseline	8.3	8.3	8.1
Change from baseline (adjusted mean) [b]	-1.3	-0.2	-1.1
Difference from placebo + metformin + glimepiride arm (adjusted mean) [b]	-1.1**		
95% Confidence Interval	(-1.3, -0.9)		
Percentage of patients achieving A_{1c} <7%	53	15	46
Fasting Plasma Glucose (mg/dL) (Mean)			
Baseline	165	170	164
Change from baseline (adjusted mean) [b]	-28	+10	-32
Difference from placebo + metformin + glimepiride arm (adjusted mean) [b]	-38**		
95% Confidence Interval	(-46, -30)		
Body Weight (kg) (Mean)			
Baseline	85.8	85.4	85.2
Change from baseline (adjusted mean) [b]	-1.8	-0.4	1.6
Difference from placebo + metformin + glimepiride arm (adjusted mean) [b]	-1.4*		
95% Confidence Interval	(-2.1, -0.7)		

[a]Intent-to-treat population using last observation on study
[b]Least squares mean adjusted for baseline value
[†] For insulin glargine, optimal titration regimen was not achieved for 80% of patients.
*p-value <0.05
**p-value <0.0001

VICTOZA Compared to Exenatide, Both as Add-on to Metformin and/or Sulfonylurea Therapy

In this 26–week, open-label trial, 464 patients on a background of metformin monotherapy, sulfonylurea monotherapy or a combination of metformin and sulfonylurea were randomized to once daily VICTOZA 1.8 mg or exenatide 10 mcg twice daily. Maximally tolerated doses of background therapy were to remain unchanged for the duration of the trial. Patients randomized to exenatide started on a dose of 5 mcg twice-daily for 4 weeks and then were escalated to 10 mcg twice daily.

The mean age of participants was 57 years, and the mean duration of diabetes was 8 years. Participants were 51.9% male, 91.8% White, 5.4% Black or African American and 12.3% of Hispanic ethnicity. The mean BMI was 32.9 kg/m^2.

Treatment with VICTOZA 1.8 mg resulted in statistically significant reductions in HbA_{1c} and FPG relative to exenatide (Table 9). The percentage of patients who discontinued for ineffective therapy was 0.4% in the VICTOZA treatment group and 0% in the exenatide treatment group. Both treatment groups had a mean decrease from baseline in body weight of approximately 3 kg.

Table 9 Results of a 26-week open-label trial of VICTOZA versus Exenatide (both in combination with metformin and/or sulfonylurea)[a]

	VICTOZA 1.8 mg once daily + metformin and/or sulfonylurea	Exenatide 10 mcg twice daily + metformin and/or sulfonylurea

Intent-to-Treat Population (N)	233	231
HbA_{1c} (%) (Mean)		
Baseline	8.2	8.1
Change from baseline (adjusted mean) [b]	-1.1	-0.8
Difference from exenatide arm (adjusted mean) [b]	-0.3**	
95% Confidence Interval	(-0.5, -0.2)	
Percentage of patients achieving A_{1c} <7%	54	43
Fasting Plasma Glucose (mg/dL) (Mean)		
Baseline	176	171
Change from baseline (adjusted mean) [b]	-29	-11
Difference from exenatide arm (adjusted mean) [b]	-18**	
95% Confidence Interval	(-25, -12)	

[a]Intent-to-treat population using last observation carried forward
[b]Least squares mean adjusted for baseline value
**p-value <0.0001

Add-on to Metformin and Thiazolidinedione

In this 26-week trial, 533 patients were randomized to VICTOZA 1.2 mg, VICTOZA 1.8 mg or placebo, all as add-on to rosiglitazone (8 mg) plus metformin (2000 mg). Patients underwent a 9 week run-in period (3-week forced dose escalation followed by a 6-week dose maintenance phase) with rosiglitazone (starting at 4 mg and increasing to 8 mg/day within 2 weeks) and metformin (starting at 500 mg with increasing weekly increments of 500 mg to a final dose of 2000 mg/day). Only patients who tolerated the final dose of rosiglitazone (8 mg/day) and metformin (2000 mg/day) and completed the 6-week dose maintenance phase were eligible for randomization into the trial.

The mean age of participants was 55 years, and the mean duration of diabetes was 9 years. Participants were 61.6% male, 84.2% White, 10.2% Black or African American and 16.4% of Hispanic ethnicity. The mean BMI was 33.9 kg/m^2.

Treatment with VICTOZA as add-on to metformin and rosiglitazone produced a statistically significant reduction in mean HbA_{1c} compared to placebo add-on to metformin and rosiglitazone (Table 10). The percentage of patients who discontinued due to ineffective therapy was 1.7% in the VICTOZA 1.8 mg + metformin + rosiglitazone treatment group, 1.7% in the VICTOZA 1.2 mg + metformin + rosiglitazone treatment group, and 16.4% in the placebo + metformin + rosiglitazone treatment group.

Table 10 Results of a 26-week trial of VICTOZA as add-on to metformin and thiazolidinedione[a]

	VICTOZA 1.8 mg + Metformin + Rosiglitazone	**VICTOZA 1.2 mg + Metformin + Rosiglitazone**	**Placebo + Metformin + Rosiglitazone**
Intent-to-Treat Population (N)	178	177	175
HbA_{1c} (%) (Mean)			
Baseline	8.6	8.5	8.4
Change from baseline (adjusted mean) [b]	-1.5	-1.5	-0.5
Difference from placebo + metformin + rosiglitazone arm (adjusted mean) [b]	-0.9**	-0.9**	
95% Confidence Interval	(-1.1, -0.8)	(-1.1, -0.8)	
Percentage of patients achieving A_{1c} <7%	54	57	28
Fasting Plasma Glucose (mg/dL) (Mean)			
Baseline	185	181	179
Change from baseline (adjusted mean) [b]	-44	-40	-8

Difference from placebo + metformin + rosiglitazone arm (adjusted mean) [b] 95% Confidence Interval	-36** (-44, -27)	-32** (-41, -23)	
Body Weight (kg) (Mean)			
Baseline Change from baseline (adjusted mean) [b] Difference from placebo + metformin + rosiglitazone arm (adjusted mean) [b] 95% Confidence Interval	94.9 -2.0 -2.6** (-3.4, -1.8)	95.3 -1.0 -1.6** (-2.4, -1.0)	98.5 +0.6

[a]Intent-to-treat population using last observation on study
[b]Least squares mean adjusted for baseline value
**p-value <0.0001

VICTOZA Compared to Placebo Both With or Without metformin and/or Sulfonylurea and/or Pioglitazone and/or Basal or Premix insulin in Patients with Type 2 Diabetes Mellitus and Moderate Renal Impairment

In this 26-week, double-blind, randomized, placebo-controlled, parallel-group trial, 279 patients with moderate renal impairment, as per MDRD formula (eGFR 30−59 mL/min/1.73 m^2), were randomized to VICTOZA or placebo once daily. VICTOZA was added to the patient's stable pre-trial antidiabetic regimen (insulin therapy and/or metformin, pioglitazone, or sulfonylurea). The dose of VICTOZA was escalated according to approved labeling to achieve a dose of 1.8 mg per day. The insulin dose was reduced by 20% at randomization for patients with baseline $HbA_{1c} \leq$ 8% and fixed until liraglutide dose escalation was complete. Dose reduction of insulin and SU was allowed in case of hypoglycemia; up titration of insulin was allowed but not beyond the pre-trial dose.

The mean age of participants was 67 years, and the mean duration of diabetes was 15 years. Participants were 50.5% male, 92.3% White, 6.6% Black or African American, and 7.2% of Hispanic ethnicity. The mean BMI was 33.9 kg/m^2. Approximately half of patients had an eGFR between 30 and <45mL/min/1.73 m^2.

Treatment with VICTOZA resulted in a statistically significant reduction in HbA_{1c} from baseline at Week 26 compared to placebo (see Table 11). 123 patients reached the 1.8 mg dose of VICTOZA.

Table 11 Results of a 26-week trial of VICTOZA compared to placebo in Patients with Renal Impairment[a]

	VICTOZA 1.8 mg + insulin and/or OAD	Placebo + insulin and/or OAD
Intent to Treat Population (N)	140	137
HbA_{1c} (%)		
Baseline (mean) Change from baseline (estimated mean) [b, c] Difference from placebo[b, c] 95% Confidence Interval	8.1 -0.9 -0.6* (-0.8, -0.3)	8.0 -0.4
Proportion achieving HbA_{1c} < 7% [d]	39.3	19.7
FPG (mg/dL)		
Baseline (mean) Change from baseline (estimated mean) [e] Difference from placebo[e] 95% Confidence Interval	171 -22 -12** (-23, -0.8)	167 -10

[a] Intent-to-treat population
[b] Estimated using a mixed model for repeated measurement with treatment, country, stratification groups as factors and baseline as a covariate, all nested within visit. Multiple imputation method modeled "wash out" of the treatment effect for patients having missing data who discontinued treatment.
[c] Early treatment discontinuation, before week 26, occurred in 25% and 22% of VICTOZA and placebo patients, respectively.
[d] Based on the known number of subjects achieving HbA_{1c} < 7%. When applying the multiple imputation method described in b) above, the estimated percents achieving HbA_{1c} < 7% are 47.6% and 24.9% for VICTOZA and placebo, respectively.

[e] Estimated using a mixed model for repeated measurement with treatment, country, stratification groups as factors and baseline as a covariate, all nested within visit.
*p-value <0.0001
**p-value <0.05

14.2 Cardiovascular Outcomes Trial in Patients with Type 2 Diabetes Mellitus and Atherosclerotic Cardiovascular Disease

The LEADER trial (NCT01179048) was a multi-national, multi-center, placebo-controlled, double-blind trial. In this study, 9340 patients with inadequately controlled type 2 diabetes and atherosclerotic cardiovascular disease were randomized to VICTOZA 1.8 mg or placebo for a median duration of 3.5 years. The study compared the risk of major adverse cardiovascular events between VICTOZA and placebo when these were added to, and used concomitantly with, background standard of care treatments for type 2 diabetes. The primary endpoint, MACE, was the time to first occurrence of a three part composite outcome which included; cardiovascular death, non-fatal myocardial infarction and non-fatal stroke.

Patients eligible to enter the trial were; 50 years of age or older and had established, stable, cardiovascular, cerebrovascular, peripheral artery disease, chronic kidney disease or NYHA class II and III heart failure (80% of the enrolled population) or were 60 years of age or older and had other specified risk factors for cardiovascular disease (20% of the enrolled population).

At baseline, demographic and disease characteristics were balanced. The mean age was 64 years and the population was 64.3% male, 77.5% Caucasian, 10.0% Asian, and 8.3% Black. In the study, 12.1% of the population identified as Hispanic or Latino. The mean duration of type 2 diabetes was 12.8 years, the mean HbA1c was 8.7% and the mean BMI was 32.5 kg/m^2. A history of previous myocardial infarction was reported in 31% of randomized individuals, a prior revascularization procedure in 39%, a prior ischemic stroke in 11%, documented symptomatic coronary disease in 9%, documented asymptomatic cardiac ischemia in 26%, and a diagnosis of New York Heart Association (NYHA) class II to III heart failure in 14%. The mean eGFR at baseline was 79 mL/min/1.73 m^2 and 41.8% of patients had mild renal impairment (eGFR 60 to 90 mL/min/1.73m^2), 20.7% had moderate renal impairment (eGFR 30 to 60 mL/min/1.73m^2) and 2.4% of patients had severe renal impairment (eGFR < 30 mL/min/1.73m^2).

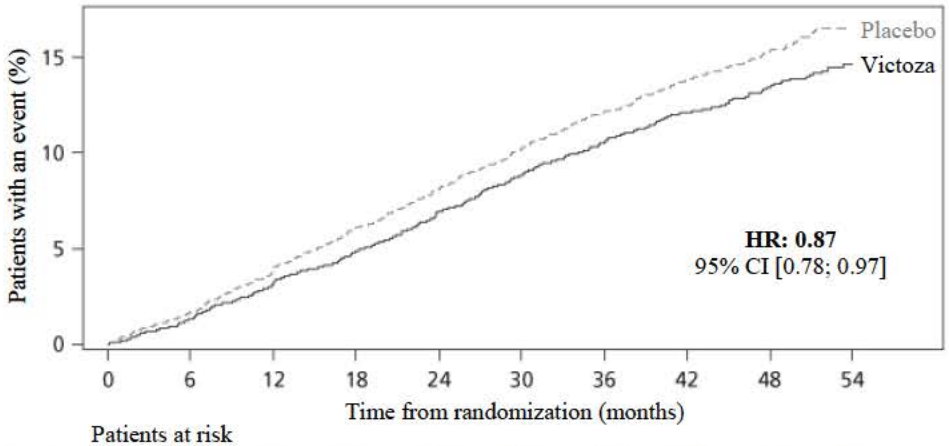
At baseline, patients treated their diabetes with; diet and exercise only (3.9%), oral antidiabetic drugs only (51.5%), oral antidiabetic drugs and insulin (36.7%) or insulin only (7.9%). The most common background antidiabetic drugs used at baseline and in the trial were metformin, sulfonylurea and insulin. Use of DPP-4 inhibitors and other GLP-1 receptor agonists was excluded by protocol and SGLT-2 inhibitors were either not approved or not widely available. At baseline, cardiovascular disease and risk factors were managed with; non-diuretic antihypertensives (92.4%), diuretics (41.8%), statin therapy (72.1%) and platelet aggregation inhibitors (66.8%). During the trial, investigators could modify anti-diabetic and cardiovascular medications to achieve local standard of care treatment targets with respect to blood glucose, lipid, and blood pressure, and manage patients recovering from an acute coronary syndrome or stroke event per local treatment guidelines.

For the primary analysis, a Cox proportional hazards model was used to test for non-inferiority against the pre-specified risk margin of 1.3 for the hazard ratio of MACE and to test for superiority on MACE if non-inferiority was demonstrated. Type 1 error was controlled across multiple tests.

VICTOZA significantly reduced the time to first occurrence of MACE. The estimated hazard ratio (95% CI) for time to first MACE was 0.87 (0.78, 0.97). Refer to Figure 5 and Table 12.

Vital status was available for 99.7% of subjects in the trial. A total of 828 deaths were recorded during the LEADER trial. A majority of the deaths in the trial were categorized as cardiovascular deaths and non-cardiovascular deaths were balanced between the treatment groups (3.5% in patients treated with VICTOZA and 3.6% in patients treated with placebo). The estimated hazard ratio of time to all-cause death for VICTOZA compared to placebo was 0.85 (0.74, 0.97).

Figure 5 Kaplan-Meier: Time to First Occurrence of a MACE in the LEADER Trial (Patients with T2DM and Atherosclerotic CVD)



FAS: full analysis set

Table 12 Treatment Effect for the Primary Composite Endpoint, MACE, and its Components in the LEADER Trial (Patients with T2DM and Atherosclerotic CVD)[a]

	VICTOZA N=4668	Placebo N=4672	Hazard Ratio (95% CI)[b]
Composite of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke (MACE) (time to first occurrence)[c]	608 (13.0%)	694 (14.9%)	0.87 (0.78; 0.97)
Non-fatal myocardial infarction[d]	281 (6.0%)	317 (6.8%)	0.88 (0.75;1.03)
Non-fatal stroke[d]	159 (3.4%)	177 (3.8%)	0.89 (0.72;1.11)
Cardiovascular death[d]	219 (4.7%)	278 (6%)	0.78 (0.66;0.93)

[a]Full analysis set (all randomized patients)
[b]Cox-proportional hazards model with treatment as a factor
[c]p-value for superiority (2-sided) 0.011
[d]Number and percentage of first events

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

VICTOZA is available in the following package sizes containing disposable, pre-filled, multi-dose pens. Each individual pen delivers doses of 0.6 mg, 1.2 mg, or 1.8 mg (6 mg/mL, 3 mL).

2 x VICTOZA pen NDC 0169-4060-12

3 x VICTOZA pen NDC 0169-4060-13

Each VICTOZA pen is for use by a single patient. A VICTOZA pen must never be shared between patients, even if the needle is changed.

16.2 Recommended Storage

Prior to first use, VICTOZA should be stored in a refrigerator between 36ºF to 46ºF (2ºC to 8ºC) (Table 13). Do not store in the freezer or directly adjacent to the refrigerator cooling element. Do not freeze VICTOZA and do not use VICTOZA if it has been frozen.

After initial use of the VICTOZA pen, the pen can be stored for 30 days at controlled room temperature (59°F to 86°F; 15°C to 30°C) or in a refrigerator (36°F to 46°F; 2°C to 8°C). Keep the pen cap on when not in use. VICTOZA should be protected from excessive heat and sunlight. Always remove and safely discard the needle after each injection and store the VICTOZA pen without an injection needle attached. This will reduce the potential for contamination, infection, and leakage while also ensuring dosing accuracy. **Always use a new needle for each injection to prevent contamination.**

Table 13 Recommended Storage Conditions for the VICTOZA Pen

Prior to first use	**After first use**	
Refrigerated 36°F to 46°F (2°C to 8°C)	Room Temperature 59°F to 86°F (15°C to 30°C)	Refrigerated 36°F to 46°F (2°C to 8°C)
Until expiration date	30 days	

17 PATIENT COUNSELING INFORMATION

FDA-Approved Medication Guide

See separate leaflet.

Risk of Thyroid C-cell Tumors

Inform patients that liraglutide causes benign and malignant thyroid C-cell tumors in mice and rats and that the human relevance of this finding has not been determined. Counsel patients to report symptoms of thyroid tumors (e.g., a lump in the neck, hoarseness, dysphagia, or dyspnea) to their physician *[see Boxed Warning and Warnings and Precautions (5.1)]*.

Dehydration and Renal Failure

Advise patients treated with VICTOZA of the potential risk of dehydration due to gastrointestinal adverse reactions and to take precautions to avoid fluid depletion. Inform patients of the potential risk for worsening renal function, which in some cases may require dialysis.

Pancreatitis

Inform patients of the potential risk for pancreatitis. Explain that persistent severe abdominal pain that may radiate to the back and which may or may not be accompanied by vomiting, is the hallmark symptom of acute pancreatitis. Instruct patients to discontinue VICTOZA promptly and contact their physician if persistent severe abdominal pain occurs *[see Warnings and Precautions (5.2)]*.

Acute Gallbladder Disease

Inform patients of the potential risk for cholelithiasis or cholecystitis. Instruct patients to contact their physician if cholelithiasis or cholecystitis is suspected for appropriate clinical follow-up.

Never Share a VICTOZA Pen Between Patients
Advise patients that they must never share a VICTOZA pen with another person, even if the needle is changed, because doing so carries a risk for transmission of blood-borne pathogens.

Hypersensitivity Reactions
Inform patients that serious hypersensitivity reactions have been reported during postmarketing use of VICTOZA. Advise patients on the symptoms of hypersensitivity reactions and instruct them to stop taking VICTOZA and seek medical advice promptly if such symptoms occur *[see Warnings and Precautions (5.6)]*.

Jaundice and Hepatitis
Inform patients that jaundice and hepatitis have been reported during postmarketing use of liraglutide. Instruct patients to contact their physician if they develop jaundice.

Instructions
Advise patients that the most common side effects of VICTOZA are headache, nausea and diarrhea. Nausea is most common when first starting VICTOZA, but decreases over time in the majority of patients and does not typically require discontinuation of VICTOZA.

Inform patients not to take an extra dose of VICTOZA to make up for a missed dose. If a dose is missed, the once-daily regimen should be resumed as prescribed with the next scheduled dose. If more than 3 days have elapsed since the last dose, advise the patient to reinitiate VICTOZA at 0.6 mg to mitigate any gastrointestinal symptoms associated with reinitiation of treatment. VICTOZA should be titrated at the discretion of the prescribing physician *[see Dosage and Administration (2)]*.

Manufactured by:
Novo Nordisk A/S
DK-2880 Bagsvaerd, Denmark

Date of Issue: August 25, 2017
Version: 10

VICTOZA® is a registered trademark of Novo Nordisk A/S.

PATENT Information: http://novonordisk-us.com/patients/products/product-patents.html

For information about VICTOZA contact:
Novo Nordisk Inc.
800 Scudders Mill Road
Plainsboro, NJ 08536

1-877-484-2869

Medication Guide
Victoza® (VIC-tow-za)
(liraglutide) injection, for subcutaneous use

Read this Medication Guide before you start using Victoza and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or your treatment.

What is the most important information I should know about Victoza?

Victoza may cause serious side effects, including:

- **Possible thyroid tumors, including cancer**. Tell your healthcare provider if you get a lump or swelling in your neck, hoarseness, trouble swallowing, or shortness of breath. These may be symptoms of thyroid cancer. In studies with rats and mice, Victoza and medicines that work like Victoza caused thyroid tumors, including thyroid cancer. It is not known if Victoza will cause thyroid tumors or a type of thyroid cancer called medullary thyroid carcinoma (MTC) in people.
- Do not use Victoza if you or any of your family have ever had a type of thyroid cancer called medullary thyroid carcinoma (MTC), or if you have an endocrine system condition called Multiple Endocrine Neoplasia syndrome type 2 (MEN 2).

What is Victoza?

Victoza is an injectable prescription medicine for adults with type 2 diabetes mellitus that:

- along with diet and exercise may improve blood sugar (glucose).
- along with your current treatment for your cardiovascular disease may reduce the risk of major cardiovascular events such as heart attack, stroke or death.

Victoza is not a substitute for insulin and is not for use in people with type 1 diabetes or people with diabetic ketoacidosis.

It is not known if Victoza can be used with mealtime insulin.

It is not known if Victoza is safe and effective for use in children.

Who should not use Victoza?

Do not use Victoza if:

- you or any of your family have ever had a type of thyroid cancer called medullary thyroid carcinoma (MTC) or if you have an endocrine system condition called Multiple Endocrine Neoplasia syndrome type 2 (MEN 2).
- you are allergic to liraglutide or any of the ingredients in Victoza. See the end of this Medication Guide for a complete list of ingredients in Victoza.

What should I tell my healthcare provider before using Victoza?

Before using Victoza, tell your healthcare provider if you have any other medical conditions, including if you:

- have or have had problems with your pancreas, kidneys, or liver.
- have severe problems with your stomach, such as slowed emptying of your stomach (gastroparesis) or problems with digesting food.
- are pregnant or plan to become pregnant. It is not known if Victoza will harm your unborn baby. Tell your healthcare provider if you become pregnant while using Victoza.
- are breastfeeding or plan to breastfeed. It is not known if Victoza passes into your breast milk. You should talk with your healthcare provider about the best way to feed your baby while using Victoza.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Victoza may affect the way some medicines work and some medicines may affect the way Victoza works.

Before using Victoza, talk to your healthcare provider about low blood sugar and how to manage it. Tell your healthcare provider if you are taking other medicines to treat diabetes, including insulin or sulfonylureas.

Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

How should I use Victoza?

- Read the **Instructions for Use** that comes with Victoza.
- Use Victoza exactly as your healthcare provider tells you to.
- **Your healthcare provider should show you how to use Victoza before you use it for the first time.**
- Victoza is injected under the skin (subcutaneously) of your stomach (abdomen), thigh, or upper arm. **Do not** inject Victoza into a muscle (intramuscularly) or vein (intravenously).
- **Use Victoza 1 time each day, at any time of the day.**
- If you miss a dose of Victoza, take the missed dose at the next scheduled dose. **Do not** take 2 doses of Victoza at the same time.
- Victoza may be taken with or without food.

- **Do not** mix insulin and Victoza together in the same injection.
- You may give an injection of Victoza and insulin in the same body area (such as your stomach area), but not right next to each other.
- Change (rotate) your injection site with each injection. **Do not** use the same site for each injection.
- **Do not share your Victoza pen with other people, even if the needle has been changed.** You may give other people a serious infection, or get a serious infection from them.

Your dose of Victoza and other diabetes medicines may need to change because of:

- change in level of physical activity or exercise, weight gain or loss, increased stress, illness, change in diet, or because of other medicines you take.

What are the possible side effects of Victoza?

Victoza may cause serious side effects, including:

- **See "What is the most important information I should know about Victoza?"**
- **inflammation of your pancreas (pancreatitis).** Stop using Victoza and call your healthcare provider right away if you have severe pain in your stomach area (abdomen) that will not go away, with or without vomiting. You may feel the pain from your abdomen to your back.
- **low blood sugar (hypoglycemia).** Your risk for getting low blood sugar may be higher if you use Victoza with another medicine that can cause low blood sugar, such as a sulfonylurea or insulin.

  Signs and symptoms of low blood sugar may include:

  - o dizziness or light-headedness
  - o sweating
  - o confusion or drowsiness
  - o headache
  - o blurred vision
  - o slurred speech
  - o shakiness
  - o fast heartbeat
  - o anxiety, irritability, or mood changes
  - o hunger
  - o weakness
  - o feeling jittery
- **kidney problems (kidney failure).** In people who have kidney problems, diarrhea, nausea, and vomiting may cause a loss of fluids (dehydration) which may cause kidney problems to get worse.
- **serious allergic reactions.** Stop using Victoza and get medical help right away, if you have any symptoms of a serious allergic reaction including:

  - o Swelling of your face, lips, tongue or throat
  - o Problems breathing or swallowing
  - o Severe rash or itching
  - o Fainting or feeling dizzy
  - o Very rapid heartbeat
- **gallbladder problems.** Gallbladder problems have happened in some people who take Victoza. Tell your healthcare provider right away if you get symptoms of gallbladder problems which may include:

  - o pain in the right or middle upper stomach area
  - o fever
  - o nausea and vomiting
  - o your skin or the white part of your eyes turns yellow

The most common side effects of Victoza may include: nausea, diarrhea, vomiting, decreased appetite, indigestion and constipation

Talk to your healthcare provider about any side effect that bothers you or does not go away. These are not all the possible side effects of Victoza.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about the safe and effective use of Victoza.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use Victoza for a condition for which it was not prescribed. Do not give Victoza to other people, even if they have the same symptoms that you have. It may harm them. If you would like more information, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about Victoza that is written for health professionals.

What are the ingredients in Victoza?

Active Ingredient: liraglutide

Inactive Ingredients: disodium phosphate dihydrate, propylene glycol, phenol and water for injection

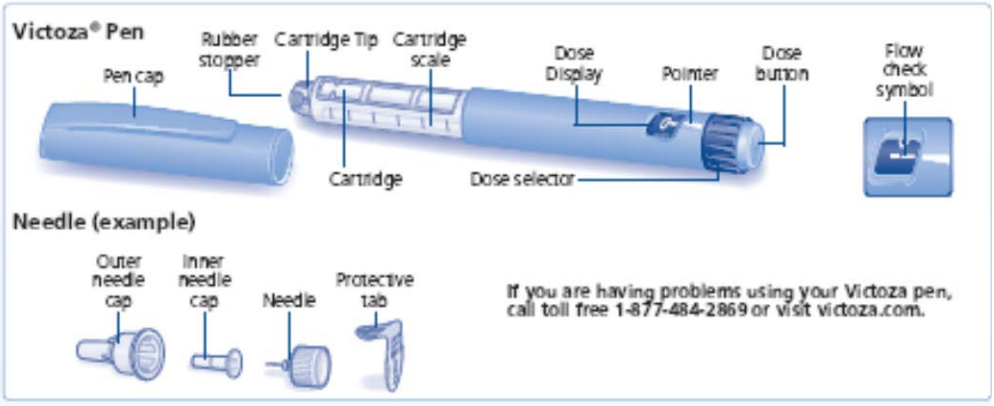
Manufactured by: Novo Nordisk A/S, DK-2880 Bagsvaerd, Denmark *Victoza® is a registered trademark of Novo Nordisk A/S.*

For more information, go to victoza.com or call 1-877-484-2869. PATENT Information: http://novonordisk-us.com/patients/products/product-patents.html

This Medication Guide has been approved by the U.S. Food and Drug Administration. Revised: August 2017

Instructions for Use

Victoza (liraglutide) injection



First read the Medication Guide that comes with your Victoza pen and then read these Patient Instructions for Use for information about how to use your Victoza pen the right way.

These instructions do not take the place of talking with your healthcare provider about your medical condition or your treatment.

Do not share your Victoza Pen with other people, even if the needle has been changed. You may give other people a serious infection, or get a serious infection from them.

Your Victoza pen contains 3 mL of Victoza and will deliver doses of 0.6 mg, 1.2 mg or 1.8 mg. The number of doses that you can take with a Victoza pen depends on the dose of medicine that is prescribed for you. Your healthcare provider will tell you how much Victoza to take.

Victoza pen should be used with Novo Nordisk disposable needles. Talk to your healthcare provider or pharmacist for more information about needles for your Victoza pen.

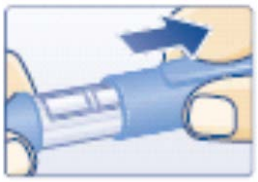
Important Information

- Do not share your Victoza pen with other people, even if the needle has been changed. You may give other people a serious infection, or get a serious infection from them.
- Always use a new needle for each injection. Do not reuse or share your needles with other people. You may give other people a serious infection, or get a serious infection from them.
- Keep your Victoza pen and all medicines out of the reach of children.
- If you drop your Victoza pen, repeat “First Time Use For Each New Pen” (steps A through D).
- Be careful not to bend or damage the needle.
- Do not use the cartridge scale to measure how much Victoza to inject.

- Be careful when handling used needles to avoid needle stick injuries.
- You can use your Victoza pen for up to 30 days after you use it the first time.

First Time Use for Each New Pen

Step A. Check the Pen

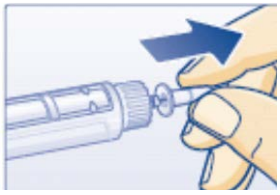


- Take your new Victoza pen out of the refrigerator.
- Wash hands with soap and water before use.
- Check pen label before each use to make sure it is your Victoza pen.
- Pull off pen cap.
- Check Victoza in the cartridge. The liquid should be clear, colorless and free of particles. If not, do not use.
- Wipe the rubber stopper with an alcohol swab.

Step B. Attach the Needle

- Remove protective tab from outer needle cap.
- Push outer needle cap containing the needle straight onto the pen, then screw needle on until secure.

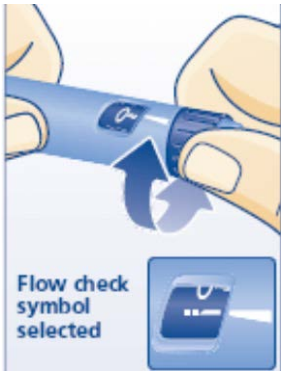
- Pull off outer needle cap. Do not throw away.



- Pull off inner needle cap and throw away. A small drop of liquid may appear. This is normal.

Step C. Dial to the Flow Check Symbol

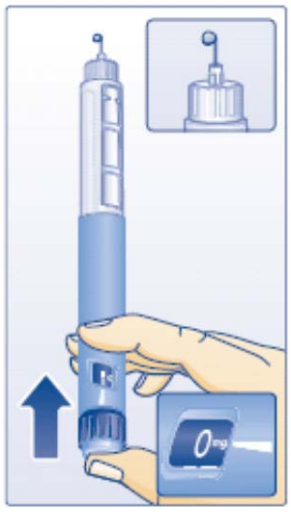
This step is done only ONCE for each new pen and is ONLY required the first time you use a new pen.



- Turn dose selector until flow check symbol (--) lines up with pointer. The flow check symbol does not administer the dose as prescribed by your healthcare provider.
- To select the dose prescribed by your healthcare provider, continue to Step G under “Routine Use”.

Step D. Prepare the Pen

- Hold pen with needle pointing up.
- Tap cartridge gently with your finger a few times to bring any air bubbles to the top of the cartridge.
- Keep needle pointing up and press dose button until 0 mg lines up with pointer. Repeat steps C and D, up to 6 times, until a drop of Victoza appears at the needle tip.

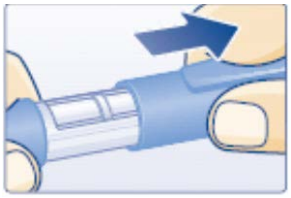


If you still see no drop of Victoza, use a new pen and contact Novo Nordisk at 1-877-484-2869.

Continue to Step G under “Routine Use” →

Routine Use

Step E. Check the Pen



- Take your Victoza pen from where it is stored.
- Wash hands with soap and water before use.
- Check pen label before each use to make sure it is your Victoza pen.

- Pull off pen cap.
- Check Victoza in the cartridge. The liquid should be clear, colorless and free of particles. If not, do not use.
- Wipe the rubber stopper with an alcohol swab.

Step F. Attach the Needle

- Remove protective tab from outer needle cap.
- Push outer needle cap containing the needle straight onto the pen, then screw needle on until secure.
- Pull off outer needle cap. Do not throw away.

- Pull off inner needle cap and throw away. A small drop of liquid may appear. This is normal.

Step G. Dial the Dose

- Victoza pen can give a dose of 0.6 mg (starting dose), 1.2 mg or 1.8 mg. Be sure that you know the dose of Victoza that is prescribed for you.
- Turn the dose selector until your needed dose lines up with the pointer (0.6 mg, 1.2 mg or 1.8 mg).

- You will hear a “click” every time you turn the dose selector. **Do not set the dose by counting the number of clicks you hear.**
- If you select a wrong dose, change it by turning the dose selector

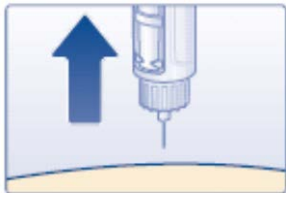
backwards or forwards until the correct dose lines up with the pointer. Be careful not to press the dose button when turning the dose selector. This may cause Victoza to come out.

Step H. Injecting the Dose

- Insert needle into your skin in the stomach, thigh or upper arm. Use the injection technique shown to you by your healthcare provider. **Do not inject Victoza into a vein or muscle.**
- Press down on the center of the dose button to inject until 0 mg lines up with the pointer.
- Be careful not to touch the dose display with your other fingers. This may block the injection.

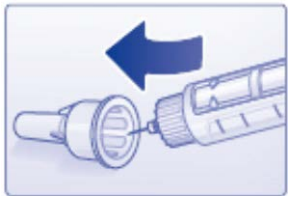
- Keep the dose button pressed down and make sure that you keep the needle under the skin for a full count of 6 seconds to make sure the full dose is injected. Keep your thumb on the injection button until you remove the needle from your skin.
- Change (rotate) your injection sites within the area you choose for each dose. **Do not** use the same injection site for each injection.

Step I. Withdraw Needle



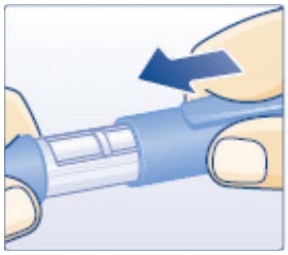
- You may see a drop of Victoza at the needle tip. This is normal and it does not affect the dose you just received. If blood appears after you take the needle out of your skin, apply light pressure, but **do not rub the area**.

Step J. Remove and Dispose of the Needle



- Carefully put the outer needle cap over the needle. Unscrew the needle.
- Safely remove the needle from your Victoza pen after each use.
- Put your used VICTOZA pen and needles in a FDA-cleared sharps disposal container right away after use. Do not throw away (dispose of) loose needles and pens in your household trash.
- If you do not have a FDA-cleared sharps disposal container, you may use a household container that is:
  - made of a heavy-duty plastic
  - can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out
  - upright and stable during use
  - leak-resistant
  - properly labeled to warn of hazardous waste inside the container
- When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used needles and syringes. Do not reuse or share your needles with other people. For more information about the safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: http://www.fda.gov/safesharpsdisposal.
- Do not dispose of your used sharps disposal container in your household trash unless your community guidelines permit this. Do not recycle your used sharps disposal container.

Caring for your Victoza pen



- After removing the needle, put the pen cap on your Victoza pen and store your Victoza pen without the needle attached.
- Do not try to refill your Victoza pen – it is prefilled and is disposable.
- Do not try to repair your pen or pull it apart.
- Keep your Victoza pen away from dust, dirt and liquids.

- If cleaning is needed, wipe the outside of the pen with a clean, damp cloth.

How should I store Victoza?

Before use:

- Store your new, unused Victoza pen in the refrigerator at 36ºF to 46ºF (2ºC to 8ºC).
- If Victoza is stored outside of refrigeration (by mistake) prior to first use, it should be used or thrown away within 30 days.
- Do not freeze Victoza or use Victoza if it has been frozen. Do not store Victoza near the refrigerator cooling element.

Pen in use:

- Store your Victoza pen for 30 days at 59ºF to 86ºF (15ºC to 30ºC), or in a refrigerator at 36ºF to 46ºF (2°C to 8°C).
- When carrying the pen away from home, store the pen at a temperature between 59ºF to 86ºF (15ºC to 30ºC).
- If Victoza has been exposed to temperatures above 86ºF (30°C), it should be thrown away.
- Protect your Victoza pen from heat and sunlight.
- Keep the pen cap on when your Victoza pen is not in use.
- Use a Victoza pen for only 30 days. Throw away a used Victoza pen after 30 days, even if some medicine is left in the pen.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022341Orig1s027

SUMMARY REVIEW

Division Director Memorandum

Date	*See Stamp Date*
From	Jean-Marc Guettier, MDCM
Subject	Division Director Review
NDA/BLA # Supplement#	022341
Applicant	Novo Nordisk Inc.
Date of Submission	10/25/2016
PDUFA Goal Date	08/25/2017
Proprietary Name / Established (USAN) names	Victoza (liraglutide)
Dosage forms / Strength	Injection, for subcutaneous use / 1.8 mg
Proposed Indication(s)	As an adjunct to standard treatment of cardiovascular risk factors to reduce the risk of MACE in adults with T2DM and high cardiovascular risk
Indication Granted	to reduce the risk of MACE in adults with T2DM and established cardiovascular disease
Recommended:	*Approval*

1. Introduction

On 10 October 2016, Novo Nordisk Inc. submitted a supplemental New Drug Application (NDA) for Victoza (liraglutide) pursuant to Section 505(b) (1) of the Federal Food, Drug, and Cosmetic Act. Victoza is a GLP-1 receptor agonist approved on 25 January 2010 as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes.

In this supplement, the applicant seeks to add data from a completed clinical trial entitled, "Liraglutide Effect and Action in Diabetes: Evaluation of cardiovascular outcome Results" or LEADER trial for short. The applicant believes the findings from the LEADER trial support the new claim that Victoza reduces... *the risk of major adverse cardiovascular events in adults with T2DM and high cardiovascular risk.*

2. Background

The LEADER trial was a cardiovascular outcomes trial (CVOT) required by FDA as post-marketing requirement #1583-9 to exclude the possibility that use of liraglutide for the treatment of adults with type 2 diabetes mellitus increased the risk of atherosclerotic cardiovascular disease to unacceptable levels[1]. The trial was also used to address signals of potential serious risks identified in the review of the original NDA. To this end, the PMR specified that data on; biomarkers of medullary thyroid carcinoma, renal safety, pancreatitis, serious hypoglycemia, immunological reactions and neoplasms be systematically collected and reported.

[1] Refer to Guidance for Industry Diabetes Mellitus — Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes
http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm071627.pdf

The results from LEADER have been reviewed in details by Drs. Condarco (Medical Review of Efficacy), Golden (Medical Review of Safety), Sullivan (Medical Review of Thyroid Safety), Hamilton (Statistical Review) and Wang (Statistical Review). Refer to these reviews for details. Dr. Yanoff has summarized the key findings from each of these reviews in her cross-discipline team leader memorandum. My memorandum serves as the decisional summary memorandum for the supplemental application and focuses primarily on whether the data from the LEADER trial are sufficient to support the new cardiovascular benefit claim.

Diabetes and Cardiovascular Disease

Cardiovascular disease is a major cause of morbidity and mortality in patients with diabetes. Large observational studies have demonstrated that diabetes is an independent risk factor for cardiovascular disease and cardiovascular death[2]. Patients with diabetes have an approximately 2-fold higher lifetime risk of atherosclerotic cardiovascular disease and are more likely to die from cardiovascular causes than patients without diabetes.

Hyperglycemia and Cardiovascular Disease

Although observational data suggests an association between hyperglycemia and the excess cardiovascular disease burden observed in patients with type 2 diabetes, to date, no individual, large, prospectively conducted trial has provided conclusive evidence of a beneficial effect of glucose lowering, per se, on cardiovascular outcomes in individuals with type 2 diabetes.

For example, no difference in cardiovascular outcomes between intensive and conventional glucose control groups [between group Hemoglobin A1c (HbA1c) difference; 7.0% versus 7.9% respectively over ~10 years] was observed in patients **with newly diagnosed** type 2 diabetes enrolled United Kingdom Prospective Diabetes Study[3]. In contrast, a strong association between blood pressure reduction and CV risk reduction was observed in UKPDS[4]. In the study, each 10 mm Hg decrease in mean systolic blood pressure was associated with a 15% (12% to 18%, P<0.0001) reduction in the risk of death and an 11% (7% to 14%, P<0.0001) reduction in the risk of myocardial infarction. Better glucose control was also not associated with improvement in cardiovascular outcomes in patients **with long standing diabetes** in the ACCORD trial[5] (Hb1Ac difference; 6.4% versus 7.5% for a median follow-up of 3.4 years), ADVANCE trial[6] (HbA1c difference; 6.5% versus 7.3% for a median follow-up of 5 years) or Veterans Affairs Diabetes trial[7] (HbA1c difference; 6.6% versus 8.4% for a median follow-up of 5.6 years) trials. The ACCORD trial was, in fact, terminated early because intensive glucose control led to a significant increase in cardiovascular and all-cause mortality (i.e., a 35 and 22 percent excess in all cause and cardiovascular death respectively, relative to conventional glucose control).

Multiple reasons have been put forward to explain the neutral and adverse findings. Including the fact that hyperglycemia may be associated with CV risk but is not causally related to it, or that glucose only contributes a small amount to excess risk in the range of HbA1c examined in these trials, or that the duration of follow-up in these studies was insufficient, or that the population in the later studies had

[2] Am J Cardiol. 1974;34(1):29, Circulation 59, No. 1, 1979, Diabetes Care 1993; 16(2):434 and Lancet 2010; 375(9733):2215.
[3] Lancet. 1998;352(9131):837.
[4] BMJ. 2000;321(7258):412.
[5] N Engl J Med 2008; 358:2545-2559
[6] N Engl J Med 2008; 358:2560-2572
[7] N Engl J Med 2009; 360:129-139

disease that was too advanced, that harm (i.e., hypoglycemia) from too aggressive glucose lowering could have outweighed potential benefits gained or that harm from the specific cocktail of drugs used to lower glucose could have outweighed benefits. The actual reason(s) is (are) at present unknown.

Specific Glucose Lowering Drugs and Cardiovascular Disease Benefit

There are 13 broad classes of drugs indicated to improve glucose control in adults with type 2 diabetes mellitus in the United States. These classes differ in the mechanisms by which they lower glucose and many have physiologic effects beyond glucose lowering. Multiple large, randomized controlled trials designed to test the hypothesis that cardiovascular benefit would be conferred by use of a specific glucose lowering drug have failed to demonstrate such a benefit. These trials examined the following specific glucose lowering drugs; pioglitazone[8] (diabetes), aleglitazar (diabetes and prediabetes)[9] nateglinide[10] (prediabetes), insulin glargine[11] (diabetes and prediabetes), saxagliptin[12] (diabetes), sitagliptin[13] (diabetes), and lixisenatide (diabetes)[14]. One drug, Jardiance (empagliflozin), has been shown in an adequate and well-controlled trial[15] to improve cardiovascular mortality in adult individuals with type 2 diabetes with established cardiovascular disease and is indicated for this use. Since publication of the Jardiance findings, liraglutide (the drug in this application) and two other drugs, semaglutide[16] and canagliflozin[17] have been reported to confer a CV benefit. The data in these last two published reports have not been reviewed at this time.

Treatment of Cardiovascular Disease in Diabetes

The approach to the treatment of atherosclerotic cardiovascular disease in diabetes consists in aggressive management of modifiable risk factors. As such, smoking cessation, treatment of hypertension and dyslipidemia and use of aspirin for secondary prevention are the cornerstone of therapy.

3. Clinical/Statistical-Efficacy

The evidence and clinical data submitted to support the cardiovascular benefit claim has been reviewed by Drs. Condarco[18], Hamilton[19] and Yanoff in details. My review will briefly summarize the findings but readers should refer to these reviews for a comprehensive assessment of the evidence.

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[8] Lancet 2005; 366, 1279–1289. In the PROactive study no difference was observed in the primary composite endpoint between placebo and pioglitazone (Hazard Ratio 0.90, 95% CI 0.80-1.02, p=0.095). The most frequent events in the composite endpoint were deaths and the majority of deaths were cardiovascular deaths. No trend suggestive of a benefit was apparent in the mortality assessment (Hazard Ratio 0.96, 95% CI 0.78–1.18). One of the key secondary composite endpoint [non-fatal stroke, non-fatal MI (specifically excluding silent MI) and all cause death] suggested pioglitazone could potentially reduce risk (0.84, 0.72-0.98) but the findings could have been the result of chance. No trials to evaluate the veracity of the hypothesis that pioglitazone could have beneficial effect on the secondary three-point composite endpoint was ever carried out.

[9] *JAMA.* 2014;311(15):1515-1525

[10] N Engl J Med 2010; 362:1463-1476

[11] N Engl J Med 2012; 367:319-328

[12] N Engl J Med 2013; 369:1317-1326

[13] N Engl J Med 2015; 373:232-242

[14] N Engl J Med 2015; 373:2247-2257

[15] N Engl J Med 2015; 373:2117-2128

[16] N Engl J Med 2016; 375:1834-1844

[17] N Engl J Med 2017; 377:644-657

[18] Condarco, T. Clinical Efficacy Review. DARRTS Reference ID: 4124811. July 14, 2017.

[19] Hamilton, K. Statistical Review and Evaluation. DARRTS Reference ID: 4124522. July 17, 2017

The evidence to support the applicant's new claim is provided by the LEADER trial. The LEADER trial was a randomized, double-blind, parallel group, placebo-controlled trial carried out in 9340 adult patients with type 2 diabetes who were inadequately controlled (i.e., HbA1c 7%) on diet and exercise, oral blood glucose-lowering agents or insulin (human neutral protamine Hagedorn, long-acting analog, or premixed) and were at high risk for an ischemic cardiovascular event.

LEADER enrolled a population at high risk for ischemic cardiovascular events. Patients who were at least 50 years old and had a history of; a myocardial infarction, a stroke, a transient ischemic attack, an arterial revascularization event, had known congestive heart failure New York Heart Association class II and III, or chronic renal failure were eligible (~80% of randomized individuals). Patients without such history but who were older than 60 years old and had either; micro-albuminuria or proteinuria, hypertension and left ventricular hypertrophy by electrocardiogram (ECG) or imaging, or an ankle-brachial index <0.9 were also eligible to participate. In addition, the applicant sought to enroll approximately 400 patients with moderate (estimated glomerular filtration rate [eGFR] 30–59 mL/min/1.73 m2 and 200 with severe (eGFR <30 mL/min/1.73 m2) renal impairment (~20% of randomized individuals). Patients with unstable diabetes, atherosclerotic cardiovascular disease, liver disease and renal disease at baseline were excluded from participation. Refer to Table 3 in Dr. Condarco's review for detailed inclusion and exclusion criteria.

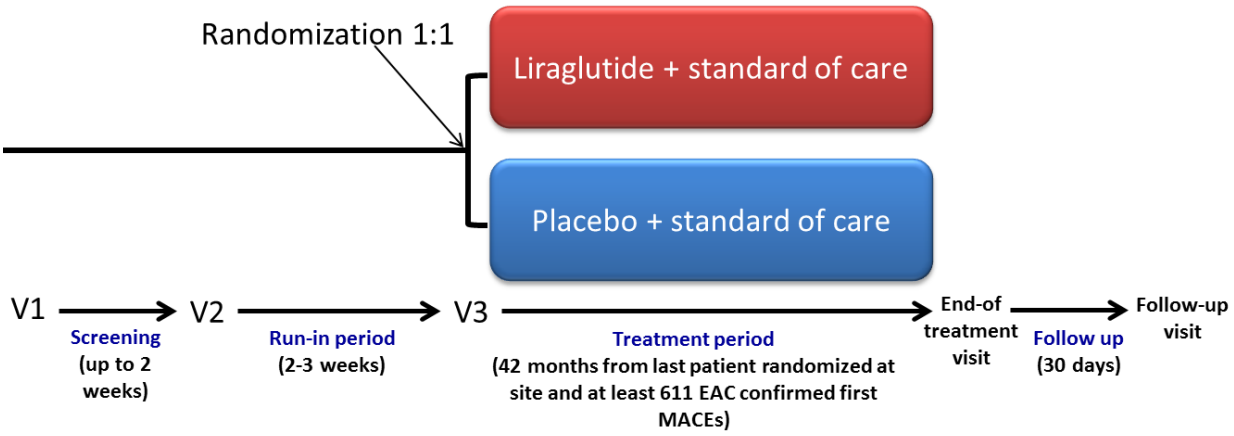
The trial included a screening visit to determine eligibility and obtain informed consent, a two to three week run-in period to identify non-adherent patient (i.e., those performing less than 50% of required placebo injections), a randomization visit, a 42 to 60 months treatment period, a 30 day washout period and a final follow-up visit.

Patients were randomized 1:1 to liraglutide 1.8 mg or placebo. Randomization was stratified by renal function (eGFR at screening <30 or ≥30 ml per minute per 1.73 m^2 of body-surface area). Site visits occurred at months 1, 3, 6, and every 6 months until at minimum the last subject randomized had been in trial for 42 months and 611 major adverse cardiovascular events[20] (MACE) had accrued. The maximum duration of follow-up for any patient was 60 months.

Figure 1 provides a schematic representation of the LEADER trial. Patients in the trial were to receive standard of care treatment for the management of diabetes as background. For patients who did not meet the recommended target for glycemic control (glycated hemoglobin level ≤7% or individualized target at the investigator's discretion) after randomization, the addition of any antihyperglycemic agents except for GLP-1–receptor agonists, DPP-4 inhibitors, or pramlintide was permitted.

[20] Cardiovascular death, Non-fatal myocardial infarction, Non-fatal stroke

Figure 1: Schematic Representation of the LEADER trial (Source: Figure 1 in Dr. Condarco's review)



Abbreviations: EAC: event adjudication committee, MACE: Major adverse cardiovascular event, V1: screening visit, V2 start of run-in period, V3: randomization and start of treatment

Study endpoints (primary efficacy, secondary efficacy and certain safety endpoints) were assessed by Independent Central Adjudication Committees in accordance with the pre-specified study plan. The adjudication committees relied on pre-specified standardized definitions for event adjudications.

The primary endpoint for this trial was the time to first occurrence of a Major Adverse Cardiovascular Event (MACE). A MACE was comprised of either; a positively adjudicated CV death event[21], or a positively adjudicated non-fatal myocardial infarction (including silent MI), or a positively adjudicated non-fatal stroke. Standardized event definitions were used for adjudication. The key secondary endpoint was the time to first occurrence of either a; cardiovascular death, a non-fatal stroke, a non-fatal myocardial infarction, a coronary revascularization event, a hospitalization for unstable angina pectoris event or a hospitalization for heart failure event.

Subjects who completed the trial without having experienced a MACE event were to be censored on the last day of their follow-up (i.e., 30 days after the last planned dose of the investigational product) and subjects who prematurely discontinued the trial without having experienced a MACE event were to be censored on the date of the last contact (i.e., site visit or telephone contact).

The primary analysis population included all randomized patients and patients were evaluated as randomized (i.e., in accordance with the ITT principle). All MACE events confirmed by adjudication with an onset date no later than the follow-up visit (i.e., up to 30 day after drug discontinuation) were considered in the primary analysis. Lost to follow-up status was to be determined at the time of database lock. If a patient's vital status on the date of the follow-up visit remained unknown at database

[21] CV-Death includes; Sudden cardiac death, death due to acute MI, death due to a cerebrovascular event, death due to heart failure, death due to dysrhythmia, death due to pulmonary embolism, death due to a cardiovascular intervention and presumed CV deaths (i.e., deaths not attributed to a category of CV death and not attributed to a non-CV cause).

lock, the patient was to be considered lost to follow up and the subject was censored at the date of last contact.

A Cox regression model with treatment group as a factor was used to estimate risk [i.e., hazard ratio (liraglutide/placebo) and 2-sided 95% confidence interval (CI)]. The first test evaluated whether the risk of MACE in patients receiving liraglutide was increased by 30% or more relative to placebo (i.e., non-inferiority test; the null hypothesis was to be rejected if the upper bound of the 95% CI around the hazard ratio of MACE was less than 1.3). The second test evaluated whether the risk of MACE in patients receiving liraglutide was less than in patients receiving placebo (superiority test; the null hypothesis was to be rejected if the upper bound of the 95% CI around the hazard ratio of MACE was less than 1.0). Type-1 error was controlled across the two pre-specified tests using a hierarchical testing strategy. There were other secondary and exploratory hypotheses tested (refer to Dr. Condarco's review for details).

Exploratory subgroup analyses across multiple pre-specified baseline factors[22] were planned. The effect of the factor of interest (main effect and interaction with treatment) on the time to first MACE was explored for each individual factor considered. Hazard ratios and 2-sided 95% CI for the time to first MACE were calculated for each factor level examined and p-values for the interaction between treatment and the factor were obtained to assess for effect consistency across levels of the factor considered. The applicant had pre-specified that they would evaluate the impact of regional differences on the primary endpoint by including geographical region as a factor in subgroup analyses. For this analysis the applicant had pre-specified that the following levels would be considered; Europe, North America (US, Canada), Asia (China, Taiwan, Korea, India), and the rest of the world (Brazil, Mexico, Australia, South Africa, Turkey, Russian Federation, and the United Arab Emirates). The FDA statistical reviewer performed a post-hoc subgroup analysis by region and defined region into two levels; US versus outside the US. The findings for the subgroup analysis by region will be discussed below.

RESULTS

The trial started on August 31, 2010, subjects were randomized between September 2010 and April 2012 and the last study visit for the last subject occurred on December 17, 2015.

Approximately 12,000 individuals were screened and 9618 participated in the run-in. Screening failures were predominantly due to not meeting HbA1c entry criteria (HbA1c ≥ 7%). A total of 9340 subjects were randomized at 410 study sites (mean ~ 23 subjects/site) across 32 countries in Eastern and Western Europe (35% of randomized subjects) North America (30% of randomized subjects), Asia (8% of randomized subjects), and rest of the world (27% of randomized subjects).

The baseline, demographic characteristics, disease characteristics, and concomitant drugs are shown in tables 11 and 12 of Dr. Condarco's review. Baseline characteristics were for the most part balanced between groups. The majority of participants were male (65%), and White (78%). Black and Asian participants accounted for 8% and 10% of the population respectively. The mean age was 64 years, the mean body mass index was in the obese range (~32 kg/m^2). Mean duration of diabetes at baseline was 13 years and the mean HbA1c at baseline was 8.7%. Anti-diabetic regimen and drug treatment at baseline in the two groups is summarized in the Table below. The trial was carried out predominantly in patients treated at baseline with the most commonly used drugs to treat type 2 diabetes in the United

[22] Refer to Appendix for the full list of pre-specified subgroups.

States [i.e., metformin (76%), and, sulfonylurea (51%) and insulin (46%) alone or in combination]. These drugs were also the most commonly added background drugs in the trial. DPP-4 inhibitors, GLP-1 receptor agonists and SGLT-2 inhibitors were not used in the trial because they were either appropriately excluded by protocol or not approved or widely available at trial start.

Table 1: Antidiabetic Treatment at Baseline

	Liraglutide (N=4668)	**Placebo (N=4672)**
Antidiabetic Treatment Regimens		
Diet and Exercise	194 (4.2)	166 (3.6)
Oral Antidiabetic Drugs Only	2436 (52.2)	2375 (50.8)
Insulin and Oral Antidiabetic Drugs	1677 (35.9)	1754 (37.5)
Insulin Only	361 (7.7)	377 (8.1)
Antidiabetic Medications		
Oral Antidiabetic Drugs (across all regimens)	**4113 (88.1)**	**4129 (88.4)**
Metformin	3540 (75.8)	3604 (77.1)
SU	2370 (50.8)	2363 (50.6)
Alpha glucosidase inhibitors	139 (3.0)	123 (2.6)
TZD	296 (6.3)	279 (6.0)
DPP4 inhibitors	4 (<0.1)	2 (<0.1)
GLP1 receptor agonist	0 (0)	2 (<0.1)
SGLT2 inhibitors	N/A	N/A
Glinides	178 (3.8)	172 (3.7)
Other	0 (0)	1 (<0.1)
Insulin treatment (across all regimens)	**2038 (43.7)**	**2131 (45.6)**
Premix	445 (9.5)	463 (9.9)
Short acting	42 (0.9)	26 (0.6)
Intermediate acting	547 (11.7)	600 (12.8)
Long acting	1041 (22.3)	1077 (23.1)
Other insulins	23 (0.5)	14 (0.3)

Mean eGFR at baseline was 79 mL/min/1.73 m^2 and moderate and severe renal impairment based on eGFR criteria was present in 21% and 2.4% of trial participants respectively. The tables below summarize the cardiovascular disease characteristics by eligibility category across groups at baseline and the cardiovascular medications at baseline.

Table 2: Baseline CVD Characteristics per Trial Eligibility Criteria

	Liraglutide (N=4668)	**Placebo (N=4672)**

Established CVD (age≥50)	3831 (82.1)	3767 (80.6)
Prior myocardial infarction	1464 (31.4)	1400 (30.0)
Prior stroke or transient ischemic attack	730 (15.6)	777 (16.6)
Prior revascularization	1835 (39.3)	1803 (38.6)
>50% stenosis of coronary, carotid, or lower extremity arteries	1188 (25.4)	1191 (25.5)
Documented symptomatic CHD[b]	412 (8.8)	406 (8.7)
Documented asymptomatic cardiac ischemia[c]	1241 (26.6)	1231 (26.3)
Heart failure NYHA II – III	653 (14.0)	652 (14.0)
Chronic kidney disease[d]	1185 (25.4)	1122 (24.0)
CVD risk factors (age≥60)	837 (17.9)	905 (19.4)
Microalbuminuria or proteinuria	501 (10.7)	558 (11.9)
Hypertension and left ventricular hypertrophy	248 (5.3)	251 (5.4)
Left ventricular systolic or diastolic dysfunction	203 (4.3)	191 (4.1)
Ankle-brachial index <0.9	110 (2.4)	116 (2.5)

Table 3: CVD Medications at Baseline

	Liraglutide (N=4668)	**Placebo (N=4672)**
Antihypertensive therapy	**4329 (92.7)**	**4303 (92.1)**
Beta blockers	2652 (56.8)	2529 (54.1)
Calcium channel blockers	1538 (32.9)	1479 (31.7)
ACE inhibitors	2417 (51.8)	2350 (50.3)
Angiotensin receptor blockers	1488 (31.9)	1486 (31.8)
Renin inhibitors	42 (0.9)	40 (0.9)
Others	468 (10.0)	454 (9.7)
Diuretics	**1953 (41.8)**	**1953 (41.8)**
Loop diuretics	824 (17.7)	837 (17.9)
Thiazides	829 (17.8)	788 (16.9)
Thiazide-like diuretics	325 (7.0)	355 (7.6)
Aldosterone antagonists	254 (5.4)	251 (5.4)
Lipid lowering drugs	**3564 (76.3)**	**3515 (75.2)**
Statins	3405 (72.9)	3336 (71.4)
Ezetimibe	165 (3.5)	169 (3.6)
Fibrates	412 (8.8)	432 (9.2)
Niacin	95 (2.0)	95 (2.0)
Other lipid lowering drugs	8 (0.2)	14 (0.3)
Platelet aggregation inhibitors	**3205 (68.7)**	**3121 (66.8)**
Acetylsalicylic acid (ASA)	2977 (63.8)	2899 (62.1)
Clopidogrel, Ticlopidine, Prasugrel, Ticagrelor	720 (15.4)	745 (15.9)

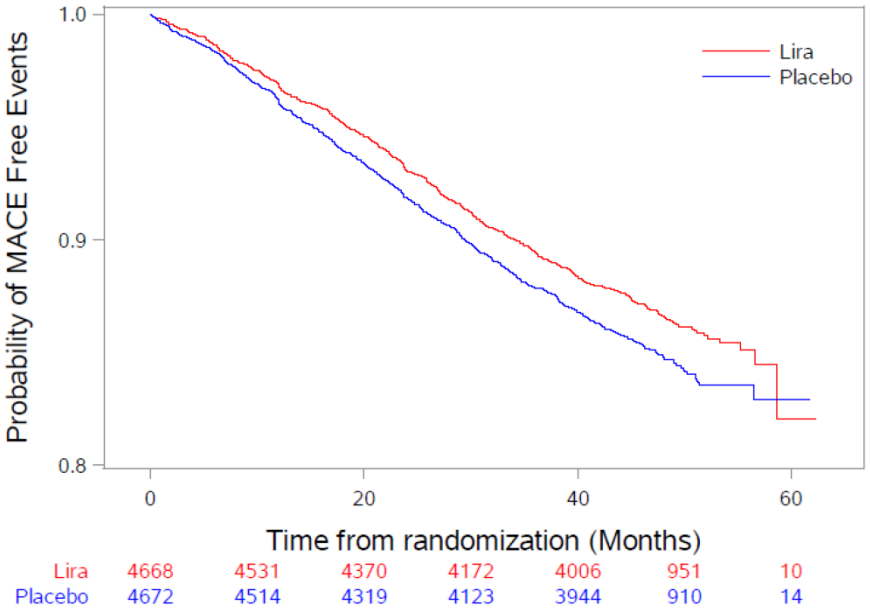
There were 9340 subjects randomized to liraglutide (N=4668) and placebo (N=4672) and all randomized individuals were included in the analysis population. Approximately 80% of all participants were in the trial for 2 years or more, and 70% for 3 years or more. The mean observation time was 3.11 years for liraglutide and 3.04 years for placebo. The median observation time was 3.5 years for liraglutide and placebo.

Overall, there were few missing data in the trial (i.e., 3.2%). Two hundred and ninety patients [139 (3.0%) on liraglutide, and 159 (3.4%) on placebo] discontinued prematurely [i.e., before a MACE events, death or trial closure visit occured]. Follow-up for vital status was essentially complete (99.7%). Vital status was available for all but 29 patients [i.e., 12 (0.25%) on liraglutide and 17 (0.36%) on placebo]. Dr. Hamilton explored the impact of missing data on overall results and concluded that missing data was low and did not raise concerns regarding interpretability of the reported results (refer to Section 5.1 of her review).

The overall trial was positive. Patients who were randomized to liraglutide were observed to have a lower risk of MACE in the LEADER study. A total of 608 patients (13.0%) experienced a first MACE event in the liraglutide arm and 694 patients (14.9%) experienced a first MACE event in the placebo arm. The hazard ratio (95% CI) for MACE estimated using the Cox proportional model was 0.87 (0.78; 0.97) and its associated 2-sided p-value was 0.011. The table and figure below shows the estimate and Kaplan-Meier plot for the time to first MACE in LEADER.

Table 4: Analyses Results (adapted from Table 3 and figure 2 in Dr. Hamilton's review).

	Liraglutide/Placebo	
	HR (95% CI)	**p-value**
MACE	0.87 (0.78, 0.97)	0.011



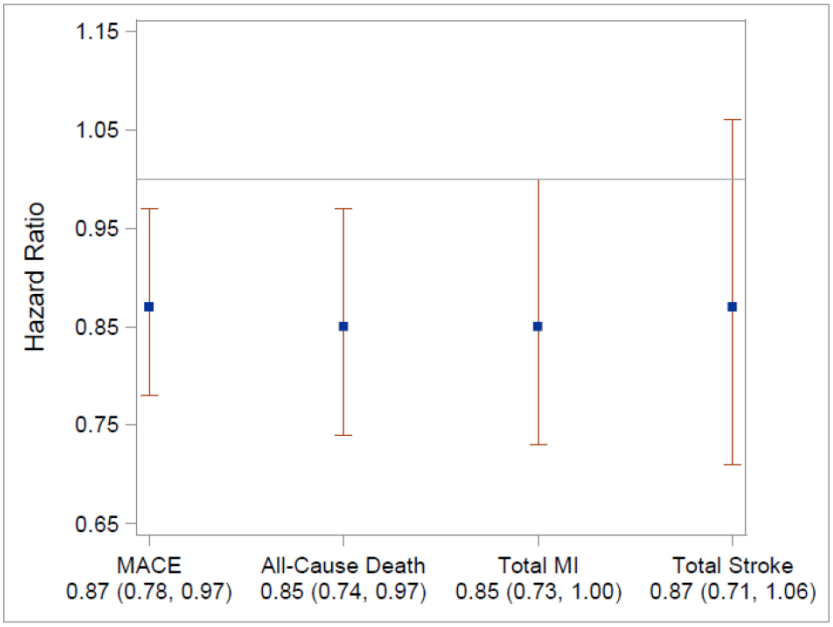
Dr. Condarco examined first MACE according to its constituent components (refer to Table 14 in her review) and Dr. Hamilton examined the proportion of individuals with a first non-fatal MI, first non-fatal stroke or CV death events in the trial (refer to Table 10 in her review). Non-fatal MI made up a majority of MACE events in the trial. All three event types were noted to have risk estimates that numerically favored liraglutide.

The trial had a large number of deaths (i.e., 828) and close to full vital status ascertainment at trial completion (i.e., 99.7% information for all cause death). In an adequate and well-controlled study with full vital status ascertainment, the binary outcome of "all-cause mortality" is arguably the endpoint least subject to biases. In LEADER, nominally significant numerical differences in mortality (i.e., refer to all cause death in figure 7 below) driven entirely by differences in CV deaths (a component of the primary endpoint and overall mortalilty), were observed.

Dr. Hamilton reviewed the individual risk estimates for the time to first CV death, time to first fatal or non-fatal MI and time to first fatal or non-fatal stroke in LEADER. These analyses confirmed that differences on the primary outcome of major adverse cardiovascular events in the LEADER trial were in large part driven by a difference in occurrence of CV deaths between groups [i.e., Hazard Ratio (95% CI) of 0.78 (0.66, 0.93); nominal two-sided p-value=0.007)]. This is shown in the following table and figures adapted from Dr. Hamilton's review (see tables 11, 12 and 13 and figure 7). Given the fact that the trial was adequate and well-controlled, was overall positive on the primary outcome, that the primary outcome included a mortality component, that mortality was close to fully ascertained at trial completion, that a large number of deaths were observed, that the overall mortality results were directionally consistent with the direction of the primary outcome and that the primary analysis results were driven by arguably the most objective and most clinically face-valid component of the composite endpoint [i.e., CV-death; the component that captured survival status], I find the results of the LEADER study to be persuasive. I also believe, given the observed effect on overall mortality, that a "confirmatory" study in the same population would be difficult to justify and conduct on ethical grounds.

	LIRA	**PBO**	**HR (95% CI)**
CV Death	219 (4.7%)	278 (6.0%)	0.78 (0.66, 0.93)
Fatal and Non-fatal MI*	292 (6.3%)	339 (7.3%)	0.85 (0.73, 1.00)
Fatal and Non-fatal Strokes**	173 (3.7%)	199 (4.3%)	0.87 (0.71, 1.06)
*Includes CV Death events attributed to an MI ** Includes CV Death events attributed to a stroke			

Figure 7: MACE and MACE Related Outcomes



Observed Post-Baseline Differences

Post-randomization differences in a number of variables assessed in the trial schedule were noted between patients randomized to Victoza and placebo (i.e., heart rate, HbA1c, systolic blood pressure, background diabetes and cardiovascular medications, body weight and waist circumference). The differences are described in figure 7 of Dr. Condarco's review as well as in text and figures starting on page 99 of the review. Subjects randomized to placebo had greater intensification of their anti-diabetic (mostly insulin) and cardiovascular medications (mostly anti-HTN, diuretics and lipid medications) compared to patients randomized the Victoza across all classes of medications. Patients randomized to Victoza had numerically lower systolic blood pressure, weight and HbA1c than patients randomized to placebo but numerically higher heart rate. There were no within trial differences in lipid parameters between groups.

Observed differences in post-baseline variables are interesting in that they could provide clues to potential reasons why differences in MACE outcomes were observed. Although these findings are hypothesis generating, neither the applicant nor the FDA performed analyses to determine whether, or how, these contributed to the overall results. While robust, retrospective, analyses to evaluate the impact of post-randomization differences on the effect could be envisaged, and may be informative from a scientific standpoint, these would not alter the overall conclusion that Victoza had an effect on a clinically meaningful outcome in the sample population studied. The mechanism or mechanisms by which Victoza impacted the primary MACE outcome was not resolved in the review and to this day remains unknown.

Subgroup Findings

The applicant examined the effect of Victoza on the primary endpoint in a large number of pre-specified subgroups (i.e., 37 pre-specified subgroups in total), most based on baseline characteristics, including demographic, race, region, concomitant illness, CV history, and concomitant drug use. The results for

the 37 pre-specified subgroup analyses are shown in a forest plot in Dr. Condarco's review (see Figure 13). No interactions were observed for sex, age, race, ethnicity, BMI, HbA1c, concomitant anti-diabetic medications or geographical regions (North America, Europe, Asia and Rest of the World).

The p-value for interaction was nominally significant (i.e., below 0.05) for the subgroups examining categories of baseline cardiovascular risk [i.e., > 50 years with established atherosclerotic cardiovascular disease versus > 60 years with CV-risk factors (mostly microalbuminuria)] and categories of baseline renal function (i.e., participants with an eGFR < 60 mL/min/1.73 m2 versus participants with an eGFR ≥ to 60 mL/min/1.73 m^2). The p-value for interaction in both cases was ≥ 0.01 and it is not possible to exclude the possibility that the noted interactions suggesting treatment heterogeneity across these subgroups were simply the result of chance given the large number of subgroups examined.

The hazard ratios for the subgroup analyses examining categories of renal function were directionally consistent with overall results (i.e., both were below unity) and had overlapping 95% CI. This subgroup analyses is not problematic in that it does not call into question the superiority of Victoza over placebo in the two subgroups. This will not be further discussed.

Subgroups based on baseline CV risk factors

The hazard ratios for the applicant's subgroup analyses examining categories of cardiovascular risk factors[23] were directionally opposite (i.e., to the right and left of unity) but had overlapping 95% confidence intervals. The evidence to suggest that the results were truly directionally opposite was relatively weak (i.e., the p-value for interaction was 0.04 which is less strongly suggestive of a true difference compared to a p-value of let's say < 0.001). It is recognized and widely acknowledged by the greater scientific community that caution should be exercised when interpreting subgroup findings as these could be misleading because, in any given trial, variability among subgroups of patients is expected due to chance, and when subgroup sample sizes are small, estimates of effects for subgroups are subject to a large amount of random error. The cardiovascular risk factor subgroup comparison, for example, was lopsided in terms of MACE information provided in each of the subgroup. A lot more information (i.e., 90% of the ~ total 1300 MACE events observed in LEADER) was available to estimate the effect for the > 50 years with established atherosclerotic cardiovascular disease category compared to the > 60 years with CV-risk factors (mostly microalbuminuria) category.

Subgroups based on geographical regions

Recall that an interaction was not identified in the pre-specified subgroup analysis performed by the applicant to examine the consistency of treatment effects across geographical regions (levels examined were; North America, Europe, Asia and Rest of the World). Dr. Hamilton compared the treatment effect observed in the United States [1.03 (0.84, 1.25)] to the treatment effect outside the United States [0.80 (0.70, 92)] in a post-hoc analysis. This analysis revealed the presence of a weak (overlapping 95% CI and p-value 0.048) interaction. The conclusions that can be drawn from this subgroup analysis, if any, are subject to the same limitations as the ones described above for the CV risk factors subgroups.

[23] i.e., 0.83 (0.74, 0.93) for established disease versus 1.20 (0.86, 1.67) for CV risk factors

The applicant examined whether differences in baseline characteristics[24] could explain the apparent US versus non-US interaction. None of the > 30 individual factors examined were found to adequately explain the apparent heterogeneity in treatment effect between the US and non-US. The applicant theorized that differential discontinuation rates between the US and non-US participants (i.e., less duration of exposure to Victoza in the US) may have contributed to the observed difference and provided some analyses which we regard as flawed to support this theory. Dr. Hamilton, in a series of recent additional analyses[25], demonstrated that it was unlikely that differential exposure between the US and ex-US participants could account for the observed difference in effects. Dr. Hamilton in this addendum also performed analyses to estimate the variability of the true underlying treatment effects across regions. This has the purported effect of removing the within group variability caused by random error within a subgroup. These analyses appear to show that within group variability (i.e., random noise) accounted for a majority of the difference observed between the North American subgroup and the other regional subgroups. Based on these analyses the Office of Biostatistics concludes that the best estimate of the liraglutide versus placebo hazard ratio in North America is 0.936 and the difference between 0.936 and 1.01 would be regarded as due to chance (i.e., as the random deviation from the truth).

The Office of Biostatistics[26] states that CV risk factor and regional subgroup findings are likely attributable to chance (i.e., the probability of observing one subgroup with an effect that is directionally opposite is high given the fact that more than 37 subgroups (i.e., pre-specified and post-hoc were examined). They further characterize the CV risk factors and regional subgroup findings as, "marginal evidence that there may be some quantitative but not qualitative difference in observed treatment effect…" In plain English, if the interaction is not due to chance, it is possible that the size of the treatment effect between these subgroups differ (i.e., the mean effect for the overall population may not accurately reflect the effect in each subgroup) but the finding is not consistent with a conclusion that the drug would not be beneficial in one subgroup versus the other.

Subgroup findings were discussed at the June 20th 2017 advisory committee and advisors acknowledged the limitations of subgroup analyses and cautioned against over-interpreting subgroup findings. The majority of advisors, as attested by their voting record and rationale to explain their vote on the second question, did not interpret the US versus non-US subgroup findings as evidence that the effect of Victoza on MACE would not be observed in the United States (refer to the June 20, 2017 EMDAC AC transcript for details).

4. Safety

The LEADER study was also used to address signals of potential serious risks, other than CV-risk, that were identified based on review of the integrated safety data in the original NDA. These issues were listed in the PMR and included: the long-term effects of Victoza (liraglutide [rDNA origin]) injection on potential biomarkers of medullary thyroid carcinoma (e.g., serum calcitonin) as well as the long-term effects of Victoza (liraglutide [rDNA origin]) injection on pancreatitis, renal safety, serious hypoglycemia, immunological reactions, and neoplasms. Drs. Golden, Sullivan, several consultants and Yanoff have reviewed the findings for each of these issues in great details. The reviewers conclude that safety

[24] US patients had slightly higher BMI, slightly lower blood pressure, slightly lower cholesterol, slightly lower eGFR and used slightly more insulin, lipid lowering drugs, and platelet aggregation inhibitors.
[25] Hamilton, K. Statistical Review and Evaluation Addendum. DARRTS Reference ID: 4143443. August 23, 2017
[26] Hamilton, K. Statistical Review and Evaluation. DARRTS Reference ID: 4124522. July 17, 2017

assessments in this trial were comprehensive and well-considered. Use of multiple independent adjudication committees (cardiac, pancreatitis and neoplasms) for certain events of interest allowed for a process that was objective and perhaps less vulnerable to bias. Dr. Golden notes, however, that use of rigid criteria to define certain adverse events (i.e., pancreatitis) for the purpose of adjudication may have resulted in less than comprehensive accounting of these events in the trial (i.e., specificity was increased at the cost of sensitivity) and for these relatively rare events may have led to inaccurate estimates of risk. Overall, the safety findings in LEADER either allay concerns for the above listed issues, or do not drastically change our understanding of potential risks that are already adequately labeled. The one exception was for acute gallbladder events (i.e., gallstone and gallbladder inflammation). This risk was labeled for another liraglutide product (Saxenda) and is now labeled for Victoza based on the data from LEADER. Two issues of particular interest in the trial were medullary thyroid carcinoma (MTC) and pancreatic neoplasm[27]. With regard to MTC and pancreatic safety, Dr. Parola and Yanoff have summarized the new nonclinical data that were not considered in 2010. With regard to MTC, Dr. Sullivan noted that no cases of medullary thyroid carcinoma were noted in subjects randomized to Victoza in LEADER and that biochemistry assessments (i.e., calcitonin) were unrevealing. Dr. Golden and an FDA Oncology consult team independently reviewed the pancreatic cancer information in LEADER and conclude that the nonclinical and LEADER data are too limited to support the existence of a causal association between exposure to Victoza and the risk of pancreatic cancer. Refer to the memoranda by Dr. Golden and Sullivan for a detailed discussion of the safety findings in LEADER and for the recommended regulatory course of action for each of these issues.

5. Advisory Committee Meeting

An Advisory Committee meeting was held on June 20, 2017 to discuss the results of the LEADER study and the proposed new indication refer to t. At that meeting, two voting questions were asked:

For the first voting question (i.e., did the LEADER study satisfy the recommendations laid out in the 2008 Guidance for Industry?), the vote was as follows:

Yes: 19	**No: 0**	**Abstain: 0**

The committee unanimously voted “Yes” and agreed that the LEADER study fulfilled the recommendations laid out in the 2008 Guidance for Industry and demonstrated no increased risk for major adverse cardiovascular events with the use of liraglutide in patients with type 2 diabetes mellitus.

For the second voting question (i.e., Does the LEADER study provide substantial evidence to establish that liraglutide 1.8 mg daily reduces cardiovascular risk in patients with type 2 DM?), the vote was as follows:

Yes: 17	**No: 2**	**Abstain: 0**

The committee members who voted “Yes” found that the results of the LEADER study provided the substantial evidence necessary to establish that Victoza would reduce cardiovascular risk in US patients with type 2 diabetes and established cardiovascular disease. The members who voted yes cited the clinical importance of the primary endpoint used and the consistency of the primary analysis result with

[27] N Engl J Med 2014; 370:794-797

the overall mortality findings to substantiate their vote. These advisors did not put much stock in the subgroup findings stating that these were likely misleading. The two committee members who voted "No" were not comfortable using a single trial to establish the product's effectiveness and remained concerned by the subgroup findings.

6. Pediatrics

Not applicable.

7. Other Relevant Regulatory Issues

There are no other unresolved relevant regulatory issues.

8. Labeling

Victoza will be indicated to reduce the risk of major adverse cardiovascular events in adults with T2DM and established cardiovascular disease. A description of the evidence forming the basis for this new claim will be included in Section 14 of labeling. The Safety sections of labeling were reviewed to ensure accuracy in light of new information from LEADER and to include recent safety labeling changes for the class (e.g., hypersensitivity reactions).

9. Decision/Action/Risk Benefit Assessment

- Regulatory Action

Approval

- Risk Benefit Assessment

In the LEADER study, the applicant established that patients with type 2 diabetes mellitus and cardiovascular disease treated with Victoza were less likely to experience a major adverse cardiovascular events compared to patients receiving standard of care antidiabetic therapies. Patients with clinically manifest cardiovascular disease at baseline made up 80% of the trial population and contributed 90% of the 1300 MACE events. The relative risk reduction for time to first MACE was estimated to be ~13% and the absolute risk reduction 1.9%. Based on these estimates, 53 patients would need to be treated with Victoza to prevent one MACE event. The benefit was consistent across all three of the components of the primary endpoint and was most marked for the endpoint of cardiovascular death. All three components of the primary endpoint were clinically important outcomes.

Results of subgroup analyses were consistent with the overall estimate for most subgroups examined except for two subgroups described above (Refer to Efficacy Section for full subgroup discussion). At most, these analyses suggested that the treatment effects could be smaller in these subgroups [but not neutral or worst harmful]. I do not think anything else can be reliably concluded from these analyses as the probability that these two subgroup findings is misleading is high given the number of subgroups examined. The extent of regional subgroup differences (i.e., US versus non-US) noted in LEADER are similar to those observed in other large cardiovascular outcomes trial (i.e., MERIT-HF, PLATO, and EXAMINE trials) used to support other US regulatory actions. In LEADER, no compelling factor or reason to fully explain the subgroup findings were identified and in the end, the subgroup findings in LEADER

could be due to chance. My approval decision is based on the overall results which I view as the most reliable estimate of whether Victoza will have a beneficial effect on major adverse cardiovascular outcomes in the United States.

The evidentiary standard used by FDA to establish that a new drug is effective under Section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (FDCA) is "substantial evidence" of effectiveness [21 U.S.C. § 355(d)]. Section 505(d) defines substantial evidence as evidence consisting ordinarily of "adequate and well-controlled investigations." FDA has interpreted the plural "investigations" in section 505(d) to mean two or more clinical trials. Replication of trial results is regarded as necessary to rule out chance, bias, and other problems that might undermine the integrity and reliability of trial results. In 1997, Congress amended section 505(d) to authorize FDA to find "substantial evidence" of effectiveness without requiring data from two trials if FDA determines, "*…based on relevant science, that data from one adequate and well-controlled clinical investigation and confirmatory evidence (obtained prior to or after such investigation) are sufficient to establish effectiveness*".

FDA has issued guidance[28] on the characteristics of an adequate and well-controlled trial that could be used to support a determination of effectiveness based on a single trial under section 505(d). One characteristic is that the study is sufficiently large to demonstrate that the effect is not driven by a few clinical sites and that it is consistent across a majority of participating study sites. A second characteristic is that the study demonstrates consistency of the effect across study subsets (subgroups). A third characteristic is that the study design allows for independent confirmation of the effect within the trial (e.g., replication of the effect). A fourth characteristic is that multiple endpoints provide statistically persuasive evidence of a beneficial effect. The fifth characteristic is that the trial show a statistically very persuasive finding.

FDA has relied on only a single adequate and well controlled efficacy study to support approval of a new claim generally only in cases in which a single multicenter study of excellent design provided highly reliable and statistically strong evidence of an important clinical benefit, such as an effect on survival, and where a confirmatory study would have been difficult to conduct on ethical grounds. In the guidance, FDA emphasizes that reliance on data from a single trial to find effectiveness is appropriate only for a drug with an effect on mortality, irreversible morbidity, or a disease with potentially serious outcomes, so that confirmation of the results in an additional trial would be practically or ethically impossible.

I concur with the review team's assessment that the LEADER trial provides the substantial evidence necessary to establish that Victoza reduces major adverse cardiovascular events in patients with type 2 diabetes mellitus and cardiovascular disease for each of the following reasons discussed in details below;

- The trial was large and adequately designed to minimize bias.
- No issues related to trial conduct susceptible to impacting reliability of the primary results were identified in the review.
- The results of the primary analysis were statistically significant and no issues related to the robustness of the results were identified.

[28] http://www.fda.gov/downloads/Drugs/GuidanceCompliance%20RegulatoryInformation/Guidances/UCM078749.pdf+Providing+clinical+evidence+of+effectiveness+for+human+and+bio&client=FDAgov&site=FDAgov&lr=&proxystylesheet=FDAgov&output=xml_no_dtd&ie=UTF-8&access=p&oe=UTF-8.

- The major effect of Victoza on MACE was due to an effect on cardiovascular mortality.
- Vital status was close to fully ascertained in the trial and results for overall mortality based on more than 800 events were consistent with the primary results.
- For the majority of subgroups examined results were consistent with the overall results and for those that were not, the results were not extreme and the probability that these findings occurred by chance, given the number of subgroups examined, is high.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies

No issues were identified that require use of Postmarketing Risk Evaluation and Mitigation Strategies.

- Recommendation for other Postmarketing Requirements and Commitments

This supplemental application contained the final report for postmarketing requirement 1583-9 issued on 1 August 2014 and fulfills this requirement. No new issues were identified in the review of the supplemental application that require issuance of new Postmarketing Requirements and Commitments.

Appendix: Number and Type of Subgroups Examined

1. Sex;
2. Age (<60 years or ≥60 years);
3. Body mass index (≤30 kg/m2 or >30 kg/m2);
4. HbA1c (≤8.3% or >8.3%); Duration of diabetes (≤11 years or >11 years);
5. Region [defined as Europe, North America (US, Canada), Asia (China, Taiwan, Korea, India), and the rest of the world (Brazil, Mexico, Australia, South Africa, Turkey, Russian Federation, UAE)];
6. Race (defined as White, Black or African-American, Asian, or Other);
7. Ethnicity (defined as Hispanic or Latino, Yes or No),
8. Cardiovascular risk groups (defined according to inclusion criteria);
9. Chronic heart failure [New York Heart Association class II–III, Yes or No],
10. Severe renal failure [eGFR at screening < 30 mL/min/1.73 m2 per modification of diet in renal disease (MDRD), Yes or No],
11. Severe and moderate renal failure defined as eGFR at screening < 60 mL/min/1.73 m2 per MDRD (Yes or No);
12. Severe renal failure, defined as eGFR at screening < 30 mL/min/1.73 m2 per Chronic Kidney Disease Epidemiology Collaboration, (Yes or No);
13. Severe and moderate renal failure defined as eGFR at screening < 60 mL/min/1.73 m2 per CKD-EPI (Yes or No);
14. Anti-diabetic medication at baseline (grouped a no concomitant medication, one concomitant oral medication, two or more concomitant oral medications, concomitant treatment with insulin, with or without oral medications)

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/s/

JEAN-MARC P GUETTIER
08/25/2017

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022341Orig1s027

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Summary Review

Date	25 Aug 2017
From	Lisa Yanoff, M.D.
Subject	Cross-Discipline Team Leader Summary Review
NDA/BLA #	022341 Supplement 27
Applicant	Novo Nordisk
Date of Submission	25 Oct 2016
PDUFA Goal Date	25 Aug 2017
Proprietary Name / Established (USAN) names	Victoza/liraglutide injection
Dosage forms / Strength	Solution in a prefilled pen/1.2 mg and 1.8 mg
Proposed Indication(s)	as an adjunct to standard treatment of cardiovascular risk factors to reduce the risk of major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke) in adults with type 2 diabetes mellitus and high cardiovascular risk
Recommended:	Approval

Table of Contents

Introduction

This document contains the CDTL summary review for NDA 022341 Supplement 027, submitted to FDA on 25 Oct 2016 to support a new indication for Victoza (liraglutide injection) as follows: "as an adjunct to standard treatment of cardiovascular risk factors to reduce the risk of major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke) in adults with type 2 diabetes mellitus and high cardiovascular risk" and to satisfy PMR 1583-9 which required a randomized, double-blind, controlled trial evaluating the effect of Victoza (liraglutide) injection on the incidence of major adverse cardiovascular events in subjects with type 2 diabetes mellitus and other safety outcomes.

In this regard, sNDA 027 consisted of results of the LEADER study: "Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results - A long-term, multi-center, international, randomized double-blind, placebo-controlled trial to determine liraglutide effects on cardiovascular events" in addition to two nonclinical studies that were conducted to investigate the mechanism of action of liraglutide's effect on cardiovascular outcomes.

The reader is referred to the multiple discipline reviews for a more detailed discussion of the issues. All reviewers contributing a regulatory action recommendation for this supplement have recommended approval, and other disciplines have not identified any issues precluding approval of this supplemental NDA. This memo and its conclusions rely upon or reference the following documents:

Subject	Author	Date
Clinical Efficacy and CV Safety review	Dr. Tania Condarco	14 Jul 2017
Clinical Non CV Safety review	Dr. Julie Golden	17 Jul 2017
Clinical thyroid safety review	Dr. Shannon Sullivan	22 May 2017
Nonclinical review	Dr. Tony Parola	1 Jun 2017
Office of Clinical Pharmacology (OCP) review	Dr. Jianmeng Chen	14 Jul 2017
Biostatistics review (OB/DBII)	Dr. Kiya Hamilton	17 Jul 2017
OSI Clinical inspection summary	Dr. Cynthia Kleppinger	5 Jul 2017
Division of Medication Error Prevention and Analysis (DMEPA) labeling review	Dr. Ariane Conrad	17 Jan 2017
Office of Prescription Drug Promotion (OPDP) labeling review	Dr. Meena Ramachandra	17 Jul 2017
OPDP and Division of Medical	Dr. Meena Ramachandra and	14 Jul 2017

Policy Programs (DMPP) Patient Labeling review	Aman Sarai	
Oncology consult review	Dr. M. Naomi Horiba	19 May 2017
Ophthalmology consult review	Dr. Wiley Chambers	4 May 2017
Office of Biotechnology Products consult review (immunogenicity)	Dr. Will Hallett	21 Aug 2017
FDA Briefing document for Advisory Committee meeting	Multiple authors	https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM563334.pdf

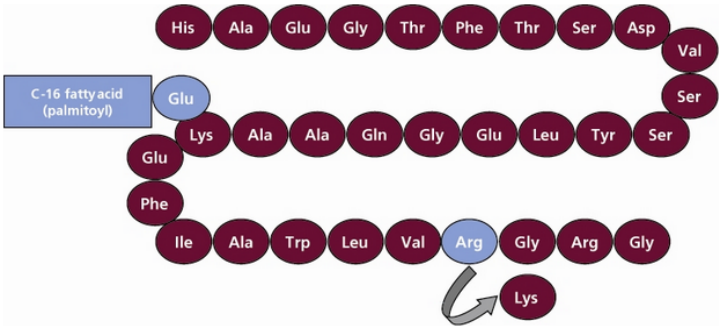
Furthermore, the Endocrinologic and Metabolic Advisory Committee (EMDAC) was convened on June 20, 2017 to discuss this supplemental NDA. A summary of the discussion and vote is included in this review. For details the reader should refer to the official transcript.

Background

Product Information

Liraglutide is a lipidated glucagon-like peptide 1 (GLP-1) analog with prolonged GLP-1 receptor agonist activity after subcutaneous injection (Figure 1, below). Liraglutide (Victoza) was approved as an adjunct to diet and exercise to improve glycemic control in adults with T2DM in January 2010.

Figure 1. Structural formula of liraglutide



Liraglutide decreases glucagon secretion in a glucose dependent manner and activates the GLP-1 receptor resulting in a glucose dependent release of insulin. In addition, liraglutide results in a delay in gastric emptying.

As a single agent, liraglutide (Victoza) is indicated for the treatment of T2DM at doses of 1.2 mg and 1.8 mg once daily; liraglutide (Saxenda) is also indicated for chronic weight management at a dose of 3 mg once daily. Liraglutide is also marketed as a fixed-ratio combination with insulin degludec for the treatment of T2DM under the trade name Xultophy 100/3.6.

Developing Drugs to Treat Type 2 Diabetes and Regulatory History of Victoza (Liraglutide)

Diabetes mellitus affects approximately 29.1 million people (9.3% of the population) in the United States (US), of which 90% to 95% are diagnosed with T2DM.[1] In the US, diabetes is the leading cause of kidney failure, non-traumatic lower limb amputations, and new cases of blindness. Diabetes has been associated with an increase in the risk of cardiovascular disease, cardiovascular death and all-cause mortality,[2,3] with the majority of people with diabetes dying from CV causes.

[1] National diabetes statistics report, 2014. Atlanta GA: Centers for Disease Control and Prevention, 2014 (Accessed February 13, 2015, at http://www.cdc.gov/diabetes/pubs/statsreport14/national-diabetes-report-web.pdf)
[2]Preis SR, Hwang SJ et al. Trends in all-cause and cardiovascular disease mortality among women and men with

The February 2008 draft Guidance for Industry *Diabetes Mellitus: Developing Drugs and Therapeutic Biologics for Treatment and Prevention* states that for efficacy assessment for drugs intended for improvement in glycemic control in patients with diabetes, the preferred primary efficacy endpoint is reduction in HbA1c (generally after six months of treatment).[4] Note that HbA1c is a *surrogate* endpoint supporting a reduced risk of microvascular complications (i.e., nephropathy, neuropathy, and retinopathy) with improved long-term glycemic control. The HbA1c endpoint also reflects a beneficial effect on the immediate clinical consequences of diabetes (hyperglycemia and its associated symptoms). The effect of glucose-lowering therapies on CV risk reduction among patients with T2DM has been less clear, although available data suggests a complex relationship between long-term glycemic control and CV disease. In the United Kingdom Prospective Diabetes Study (UKPDS), subjects originally randomized to intensive glycemic control had long-term reductions in MI and in all-cause mortality after 10 years of follow-up.[5] However, three large, randomized controlled trials (i.e., ACCORD,[6, 7] ADVANCE,[8] and VADT[9]), which enrolled high-CV risk T2DM patient populations (e.g., long-standing T2DM, established CV disease and/or multiple CV risk factors), failed to demonstrate significant reductions in major adverse CV events with intensive glycemic control. More recently, on December 2, 2016, FDA approved a new indication for empagliflozin, a sodium glucose cotransporter 2 (SGLT-2) inhibitor, the reduction of the risk of CV death in patients with established CVD, based on results of a single trial (i.e., the EMPA-REG CVOT). Similar to EMPA-REG, LEADER was originally designed and conducted to evaluate CV safety, but is also proposed in support of a new CV efficacy claim.

The February 2008 draft Guidance recommends phase 3 trial data be available for at least 2,500 subjects exposed to the investigational product, with at least 1,300 to 1,500 of these subjects exposed to the investigational product for 1 year or more and at least 300 to 500 subjects exposed for 18 months or more. Therefore, at the time of approval, there may be limited data to address long latency safety concerns, rare adverse reactions or adverse reactions that may be specific to important subpopulations of intended users.

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and without diabetes mellitus in the Framingham Heart Study, 1950 to 2005.Circulation 2009;119:1728-35.
[3]Sarwar N, Gao P, Seshasai SR, et al. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. Lancet 2010;375:2215-22
[4]Guidance for Industry. Diabetes mellitus: developing drugs and therapeutic biologics for treatment and prevention. Rockville, MD: Food and Drug Administration, February, 2008.
http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidanc es/UCM071624.pdf).
[5] Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med 2008;359:1577-89.
[6]Gerstein HC, Miller ME, Byington RP, et al. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med 2008;358:2545-59
[7]Ismail-Beigi F, Craven T, Banerji MA, et al. Effect of intensive treatment of hyperglycaemia on microvascular outcomes in type 2 diabetes: an analysis of the ACCORD randomised trial. Lancet 2010;376:419-30
[8]Patel A, MacMahon S, Chalmers J, et al. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med 2008;358:2560-72
[9]Duckworth W, Abraira C, Moritz T, et al. Glucose control and vascular complications in veterans with type 2 diabetes. N Engl J Med 2009;360:129-39.

On July 1 and 2, 2008, the EMDAC met to discuss the role of CV risk assessment for antidiabetic medications. This meeting led to the December 2008 issuance of the Guidance for Industry: *Diabetes Mellitus, Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes*[40] ("CV Guidance").

The CV Guidance asks sponsors to do the following during the planning stage of their drug development programs for therapies for T2DM:

- Establish an independent CV endpoints committee to prospectively and blindly adjudicate MACE during phase 2 and 3 clinical trials.
- Ensure that the phase 2 and 3 clinical trials are appropriately designed so that a prespecified meta-analysis of MACE can reliably be performed.
- Enroll patients at increased CV risk, such those experiencing previous CV events and those with renal impairment.

The guidance states that to support approvability from a CV safety standpoint, the sponsor should compare the incidence of MACE with the investigational drug to the incidence of MACE with control and show that the upper bound of the two-sided 95 percent confidence interval for the estimated risk ratio is less than 1.8 with a reassuring point estimate. If this upper bound is between 1.3 and 1.8 and the overall risk-benefit analysis supports approval, then a postmarketing CVOT generally would be needed to definitively show that the upper bound is less than 1.3.

The Victoza (liraglutide) NDA was submitted to FDA prior to the July 2008 EMDAC meeting and prior to issuance of the CV Guidance. Still, FDA asked the Sponsor to provide adequate evidence of CV safety in accordance with the Guidance to support approvability. The approval of Victoza for the treatment of T2DM was based, in part, on results from a pre-marketing meta-analysis of CV adverse events. The Division approach of assessing CV safety was standardized by performing *post hoc* analyses of CV events using Standard MedDRA Queries to define MACE endpoints.

At the April 2, 2009, EMDAC meeting, the committee was asked to vote on whether the Sponsor provided appropriate evidence of CV safety of Victoza. In total, 8 members voted "yes" and 5 members voted "no." Despite the few events identified in the trials, the Division agreed with the EMDAC's majority vote that premarketing trials of Victoza fulfilled the spirit of the CV Guidance and that the analyses provided ruled out unacceptable excess cardiovascular risk relative to comparators. However, panel members cited concerns about the small number of events, the low CV risk of the study population and the adequacy of the *post hoc* analysis, and in general were of the opinion that a postmarketing study to rule out a risk ratio of less than 1.3 should be required.

Therefore, as part of the approval of Victoza, the following postmarketing requirement (PMR) was issued:

> **1583-9**: A randomized, double-blind, controlled trial evaluating the effect of Victoza (liraglutide) injection on the incidence of major adverse cardiovascular events in subjects

with type 2 diabetes mellitus. This trial must also assess adverse events of interest including the long-term effects of Victoza (liraglutide) injection on potential biomarkers of medullary thyroid carcinoma (e.g., serum calcitonin) as well as the long-term effects of Victoza (liraglutide) injection on pancreatitis, renal safety, serious hypoglycemia, immunologic reactions, and neoplasms.

As reflected in the language of PMR 1583-9, FDA identified additional non-CV safety concerns prior to approval. Chief among these concerns were: 1) a potential risk of medullary thyroid carcinoma (MTC), identified in rodent carcinogenicity studies, and 2) risk of pancreatitis, identified in clinical studies of liraglutide and pharmacovigilance data for exenatide, a shorter-acting GLP-1 receptor agonist approved in 2005, and sitagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor approved for the treatment of T2DM in 2006.[10] At time of initial approval, these two risks were addressed both in labeling, and in the requirement for a Risk Evaluation and Mitigation Strategy (REMS). This REMS originally consisted of a Medication Guide, communication plan, and a timetable for submission of assessments of the REMS. These two risks are discussed in further detail below, as are several additional potential safety signals noted during review of the premarketing NDA submission (i.e., renal safety, severe hypoglycemia particularly when used in combination with sulfonylureas, immunogenicity, and other malignancies).

Regarding the potential risk of MTC, FDA and 12 of 13 panel members at the April 2009 public advisory committee meeting concluded that the sponsor did not provide adequate data on the animal thyroid C-cell tumor findings to demonstrate that these findings are not relevant to humans. As a result, the Victoza label includes a boxed warning stating that liraglutide causes dose-dependent and treatment-duration-dependent thyroid C-cell tumors at clinically relevant exposures in both genders of mice and rats, and that the human relevance of liraglutide-induced rodent thyroid C-cell tumors is unknown. Based on C-cell tumorigenicity of liraglutide in rodents, Victoza is contraindicated in patients with a personal or family history of MTC or patients with multiple endocrine neoplasia syndrome type 2 (MEN2) and it is not recommended as first-line therapy for patients with T2DM inadequately controlled on diet and exercise.[10]

Post-marketing reports of acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis, in GLP-1-based therapies have led to warnings regarding pancreatitis in drug labeling for the class. In addition, an imbalance in the incidence of pancreatitis during clinical studies that did not favor liraglutide was observed in premarketing clinical trials for Victoza and Saxenda. Current labeling includes a Warnings and Precautions statement on pancreatitis, which states that treatment with Victoza should be discontinued if pancreatitis is suspected, and not restarted if pancreatitis is confirmed.

At the time of Victoza's initial U.S. approval, data regarding potential pancreatic cancer animal signals with incretin mimetics were emerging. Subsequently, concerns for human pancreatic cancer have also been raised. An FDA perspective published in 2014 concluded that the

[10] Parks M, Rosebraugh C. Weighing Risks and Benefits of Liraglutide — The FDA's Review of a New Antidiabetic Therapy. New England Journal of Medicine 2010;362:774-7.

available data to date did not support a causal association,[11] pancreas safety with liraglutide remains an area of interest, and the LEADER trial was looked to as a potential source of additional data.

Finally, assessment of renal safety, severe hypoglycemia, and immunologic events were specified in the PMR. At the time of Victoza's approval, another GLP-1 product was updating its label due to post-marketing reports of renal impairment associated with gastrointestinal adverse reactions. Similar post-marketing reports were received for liraglutide, and Victoza's label was updated with a renal impairment 'Warning and Precaution' after approval. Severe hypoglycemia – an episode requiring assistance of another person – is a safety concern with virtually all glucose-lowering drugs, including Victoza. Because of concerns for formation of anti-liraglutide antibodies that were not fully characterized at the time of approval, in addition to post-marketing adverse events of hypersensitivity reactions, immunogenicity and immunological reactions were of interest.

On October 25, 2016 Novo Nordisk submitted the LEADER study to NDA 22341 (Victoza) to both fulfill the post-marketing requirement (PMR 1583-9) and to support a new indication of "as an adjunct to standard treatment of cardiovascular risk factors to reduce the risk of major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke) in adults with type 2 diabetes mellitus and high cardiovascular risk."

[11] Egan AG, et al. Pancreatic safety of incretin-based drugs – FDA and EMA assessment. N Engl J Med 2014; 370:794-7.

NONCLINICAL SUMMARY

Mechanism of action of CV effects of liraglutide

This sNDA included reports of 2 nonclinical pharmacology studies evaluating the effects of liraglutide in mouse models of atherosclerosis intended to elucidate the potential mechanism of liraglutide's cardioprotective effect.

Studies submitted:
· Effect on atherosclerotic plaques in ApoE knock-out mice treated with liraglutide (report (b) (4) 140701, non-GLP)
· NN2211: Effect on atherosclerotic plaques in LDL receptor knock-out mice treated with liraglutide (report (b) (4) 141102, non-GLP)

Dr. Parola's review concludes that liraglutide reduced the progression of aortic atherosclerotic plaques induced by a Western diet, but liraglutide did not affect regression of established plaques, but that human relevance of liraglutide-related decreased progression of atherosclerotic plaques in genetically modified mouse models of diet-induced atherosclerosis is confounded by:
1. The absence of effects of liraglutide on established plaques in ApoE KO mice, particularly since established atherosclerotic disease would have been expected to be present in subjects in the liraglutide cardiovascular outcomes, study EX2211-3748.
2. The absence of evidence levels of mRNAs consistent with anti-inflammatory effects are modified by liraglutide in ApoE KO mice under conditions that demonstrate effects of liraglutide on plaque regression.
3. An apparent correspondence between total cholesterol and LDL cholesterol lowering effects and reduced aortic plaque formation and progression in liraglutide-treated Ldlr KO mice compared to minimal total cholesterol and LDL cholesterol effects of liraglutide in humans.

Safety

While not submitted with sNDA 027, previously submitted nonclinical data potentially pertinent to the interpretation of human MTC and pancreatic safety information from LEADER are discussed here. This summary was provided in the nonclinical section of FDA's background materials for the LEADER EMDAC meeting.

Risks of MTC and pancreatitis from liraglutide treatment are attributed to its GLP-1 receptor agonist activity, and these risks are not unique to liraglutide. A boxed warning about the potential risk of MTC is included in the label for products containing long-acting GLP-1 receptor agonists including; liraglutide (Victoza, Saxenda, and Xultophy), dulaglutide (Trulicity), and albiglutide (Tanzeum) and the extended-release formulation of exenatide (Bydureon). The potential risk of MTC was identified from animal carcinogenicity studies and clinical data have been insufficient to definitely exclude a risk to humans. The risk of pancreatitis is another serious risk featured in all product labels for both long-acting and shorter-acting GLP-1 receptor agonists. This risk was identified from clinical data.

To further assess human risks of MTC and pancreatitis, Victoza approval included two nonclinical postmarketing requirements (PMRs) evaluating liraglutide's effects on thyroid C-cells (PMRs 1583-3 and 1583-5) and one evaluating liraglutide's effects on the exocrine pancreas (PMR 1583-4). These were previously reviewed but summarized here for the reader's convenience.

Thyroid C-cell Tumors

The potential risk of liraglutide-related thyroid C-cell tumors in humans was based on carcinogenicity of liraglutide in rodents. Liraglutide causes dose-dependent and treatment-duration-dependent thyroid C-cell tumors at clinically relevant exposures in both genders of mice and rats, and human relevance of liraglutide-induced rodent thyroid C-cell tumors is unknown. The mechanism of liraglutide-induced rodent C-cell tumors is also unknown, but C-cell tumorigenicity of GLP-1 receptor agonists is associated with prolonged GLP-1 receptor activation from long-acting GLP-1 receptor agonists or extended release formulations of shorter-acting GLP-1 receptor agonists. Although mechanistic studies from Novo Nordisk and some published data suggest GLP-1 receptor agonists induce calcitonin secretion and upregulation of calcitonin mRNA in C-cells, C-cell proliferation, and C-cell tumors in rodents, but not in primates, data are insufficient to support a conclusion regarding this potential mechanism. The strongest evidence supporting this mechanism comes from studies in mice showing liraglutide increased plasma calcitonin after the first dose, increased C-cell focal hyperplasia after about 4 weeks of treatment, and induced C-cell tumors after more than 52 weeks of treatment. However, repeat dose toxicity studies and mechanistic studies of liraglutide in rats do not support this mechanism because liraglutide did not persistently increase plasma calcitonin levels above age-related increases, rats less than 8 months old (middle-aged) are insensitive to liraglutide-induced C-cell focal hyperplasia or tumors, and C-cell adenoma induced by 30 weeks of liraglutide treatment initiated when rats were young adults was not preceded by an increased incidence of C-cell focal hyperplasia. Plasma calcitonin was not a biomarker for liraglutide-induced C-cell tumors in rats. Dulaglutide, a long-acting GLP-1 receptor agonist that caused C-cell tumors in rats at clinically relevant exposures in a 2 year carcinogenicity study, induced C-cell focal hyperplasia in rats after 52 weeks of treatment, but without inducing diffuse C-cell hyperplasia and without increasing calcitonin secretion or C-cell mass (Byrd 2015). In rodents, C-cell diffuse hyperplasia is considered a physiologic response while C-cell focal hyperplasia is considered a pre-neoplastic lesion distinguished from C-cell adenoma only by the smaller size of focal hyperplasia. Because of the long latency of liraglutide-induced C-cell tumors in rodents, which occur only after drug exposure for more than 25% of their lifespan, it is unlikely the duration of liraglutide exposure in repeat dose toxicity studies in monkeys or clinical studies in humans will be sufficient to evaluate relevance of liraglutide-induced rodent C-cell tumors to primates.

Victoza approval included two nonclinical postmarketing requirements to further assess human risks of liraglutide-induced rodent C-cell tumors: PMR 1583-3, a 2-year study in mice to determine if 26 weeks of liraglutide treatment (transient exposure) increases the lifetime risk of thyroid C-cell tumors, and PMR 1583-5, a 13-week mouse study to determine if liraglutide-

induced C-cell focal hyperplasia depended on activation of the GLP-1 receptor or REarranged during-Transfection (RET) proto-oncogene.

PMR 1583-3 Evaluating the Lifetime Risk of C-cell Tumors in Mice Transiently Exposed to Liraglutide. This PMR has been considered fulfilled.

In female mice, C-cell focal hyperplasia induced by 9 weeks of liraglutide treatment was not fully reversed after a 15-week recovery period. In a repeat subcutaneous dose study of up to 5 mg/kg/day liraglutide in CD-1 mice treated for up to 9 weeks evaluating reversibility of drug-induced thyroid C-cell focal hyperplasia, C-cell hyperplasia persisted in 31.3% of females treated with the high dose of 5 mg/kg/day liraglutide after a 6-week recovery period and in 6.3% of high dose females after a 15-week recovery period. These results suggested that transient exposure to liraglutide may cause persistent proliferative changes in C-cells of female mice. A potential mechanism for persistent effects from transient GLP-1 receptor agonist exposure was demonstrated for pancreatic beta cells in rats. Intrauterine growth retarded rats develop adult onset insulin resistance and diabetes at 15 to 26 weeks of age, but a short duration of treatment with exenatide during the neonatal period prevents adult-onset diabetes by normalizing pancreatic beta cell proliferation rates and increasing pancreatic beta cell mass via an epigenetic mechanism (Stoffers 2003, Pinney 2011).

To fulfill the requirements of PMR 1583-3, the risk of developing C-cell tumors after transient exposure to liraglutide was assessed in a 104-week study in CD-1 mice exposed to 0 (vehicle), 0.2, 1, or 3 mg/kg/day liraglutide for 26 weeks, approximately 25% of their total lifespan. Three doses of liraglutide were selected based on results from a lifetime carcinogenicity study: 0.2 mg/kg/day, a dose that caused C-cell focal hyperplasia, but not tumors, 1 mg/kg/day, a dose that caused C-cell focal hyperplasia and adenoma, but not carcinoma, and 3 mg/kg/day, a dose that caused C-cell focal hyperplasia, adenoma, and carcinoma. The 26 week treatment duration was expected to cause preneoplastic C-cell focal hyperplasia, but not tumors. At the end of the 26 week treatment period, plasma calcitonin was 6.4- to 14.1-fold higher compared to the vehicle control group in males at ≥0.2 mg/kg/day liraglutide and 3.5- to 4.0-fold higher in females at ≥1 mg/kg/day and the incidence of thyroid C-cell focal hyperplasia was 0%, 4.3%, 8.3%, and 22.7% in males and 0%, 8.3%, 0%, and 31.8% in females in 0, 0.2, 1, and 3 mg/kg/day liraglutide groups, respectively, but C-cell tumors did not occur in any group. By the end of a 78 week recovery period, plasma calcitonin was 1.5- to 1.8-fold higher than the control group in males previously treated with ≥0.2 mg/kg/day liraglutide, but not in females previously treated with liraglutide. The incidence of C-cell focal hyperplasia in males previously treated with 3 mg/kg/day liraglutide (3.8% (3/78)) exceeded the incidence in the concurrent and laboratory historical control groups (2.7% (2/75) and 0% (0/940), respectively), and C-cell focal hyperplasia did not occur in any female group. Benign C-cell adenoma occurred in 1.3% (1/78) females previously treated with 3 mg/kg/day liraglutide, and the incidence in the 3 mg/kg/day recovery group exceeded the incidence in concurrent and historical control groups (0% (0/77) and 0% (0/931), respectively). Despite the rarity of C-cell focal hyperplasia, adenomas, and carcinomas in lifetime carcinogenicity study control groups in CD-1 mice (laboratory historical control incidences of 0%, 0%, and 0% in 940 males, respectively, and 0.2%, 0%, and 0% in 931 females, respectively), a relation between liraglutide and C-cell proliferative lesions occurring

during the 78 week recovery period was confounded by the finding of C-cell focal hyperplasia in 2.7% of control group males. Tertiary review of study results by the Executive Carcinogenicity Assessment Committee in FDA's Center for Drug Evaluation and Research concluded that due to the low incidence of proliferative C-cell lesions in male and female high dose recovery group mice and in concurrent control group male mice, a clear relationship to liraglutide treatment was not established for proliferative C-cell lesions in high dose recovery groups. Results from this study were not published.

PMR 1583-5 Evaluating GLP-1 Receptor and RET Dependence of Liraglutide-Induced C-cell Hyperplasia in Mice

Human relevance of liraglutide-induced rodent thyroid C-cell tumors was not determined by nonclinical or clinical studies prior to approval of Victoza. C-cell proliferative effects of liraglutide in rodents were suspected to be GLP-1 receptor mediated, in part because both exenatide and liraglutide caused rodent C-cell tumors and GLP-1 receptors were localized on C-cells in mice and rats. Although some studies show human C-cells don't express GLP-1 receptors, other studies show they do. In one study using human tissues, GLP-1 receptors were detected in C-cells from 33% of normal thyroid tissue, 91% of MTCs, and all samples of reactive C-cell hyperplasia or C-cell hyperplasia due to germline mutations in RET (Gier 2012). GLP-1 receptors were also detected in 18% of human papillary thyroid cancers (Gier 2012). It is not clear that GLP-1 receptors on C-cells mediate GLP-1 receptor agonist induced proliferation. In vitro in rat MTC 6-23 cells, a C-cell line, liraglutide, exenatide, and GLP-1 increased calcitonin secretion, but not cell proliferation. In humans, activating mutations in the RET proto-oncogene are the most common cause of sporadic and hereditary MTC, a human C-cell tumor. Oncogenic activating mutations in RET resulting in phosphorylation of tyrosine 1062 (Y1062) occur in nearly all hereditary MTCs and in approximately 50% of sporadic MTCs, but the age of onset and clinical aggressiveness of MTC varies with RET genotype. Although liraglutide caused rodent C-cell tumors by a nongenotoxic mechanism, and it is unlikely to cause activating mutations in RET, there were reports that G-protein coupled receptors can modulate RET signaling (Song 2010, Gomes 2009), and potentially affect RET-mediated cell proliferation. Dependence of liraglutide-induced thyroid C-cell focal hyperplasia on the GLP-1 receptor and RET was evaluated in wild-type and genetically engineered GLP-1 receptor-deficient (GLP-1rKO) CD-1 mice.

In a 13-week study evaluating GLP-1 receptor dependence and RET-dependence of liraglutide-induced thyroid C-cell hyperplasia in wild-type and GLP-1rKO mice, liraglutide-induced thyroid C-cell diffuse hyperplasia was GLP-1 receptor dependent because it occurred in liraglutide-treated wild-type mice, but not in liraglutide-treated GLP-1rKO mice. RET was not activated (Y1062 was not phosphorylated) in normal or hyperplastic C-cells in liraglutide-treated wild-type mice. Evaluation of cell signaling pathways potentially downstream from RET activation indicated liraglutide did not activate mitogen activated protein kinase kinases (MEK1/2), but it did activate ribosomal protein S6. Ribosomal protein S6 activation can mediate cell growth or proliferation. Because liraglutide activated ribosomal protein S6 in both normal and hyperplastic C-cells in mice and because C-cell hyperplasia in this study was characterized as diffuse and not focal, a link between liraglutide-induced GLP-1 receptor-mediated ribosomal S6 protein activation and C-cell tumorigenesis was not established. In all previous studies of liraglutide in

mice from the sponsor, liraglutide-induced C-cell hyperplasia was characterized as focal, not diffuse. Results from this study were published (Madsen 2012). This study satisfied the requirements of PMR 1583-5 and supported the following statement added to section "13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility" section of the Victoza label:

> "*Studies in mice demonstrated that liraglutide-induced C-cell proliferation was dependent on the GLP-1 receptor and that liraglutide did not cause activation of the REarranged during Transfection (RET) proto-oncogene in thyroid C-cells*."

Because human relevance of GLP-1 receptor agonist induced rodent thyroid C-cell tumors has not been determined, participation in a MTC Cancer Registry is a post marketing requirement for all manufacturers of long-acting GLP-1 receptor agonists, including Victoza (PMR 1583-7). Approval of Victoza also required Novo Nordisk to conduct a 5 year prospective epidemiological study using a large healthcare claims database to determine the incidence of thyroid cancer among patients with T2DM exposed to Victoza (PMR 1583-6). However, due to the latency of liraglutide-induced thyroid C-cell tumors in rodents, a potential association between liraglutide and thyroid cancer in humans may require long-term epidemiological studies (Andersen 2013).

Pancreatitis and Pancreatic Cancer

The risk of pancreatitis from liraglutide is based on human data, specifically an imbalance in the incidence of pancreatitis during clinical studies that did not favor Victoza, and after approval, spontaneous postmarketing reports. The nonclinical program for Victoza did not identify liraglutide-related adverse effects on the exocrine pancreas. In the nonclinical drug development program for liraglutide using normoglycemic animals, there were no dose or treatment-duration-dependent adverse effects in the pancreas of mice or rats treated for up to 2 years or monkeys treated for up to 1 year. In addition to the concern for GLP-1 receptor agonist-related pancreatitis, acute pancreatitis has the potential to progress to chronic pancreatitis and pancreatic cancer (Andersen 2013).

Victoza approval included a nonclinical postmarketing requirement to further investigate the potential for liraglutide to induce pancreatitis: PMR 1583-4, a 3-month study of the effects of liraglutide on the exocrine pancreas in a rodent model of T2DM.

PMR 1583-4 Evaluating Effects of Liraglutide on Exocrine Pancreas in a Rat Model of T2DM
To fulfill PMR 1583-4, effects of liraglutide on the exocrine pancreas were characterized in a 3-month repeat subcutaneous dose toxicity study of liraglutide in male and female diabetic Zucker Diabetic Fatty (ZDF) *fa/fa* rats, models of T2DM characterized by hyperphagia, obesity, hyperlipidemia, insulin resistance, and fasting hyperglycemia. Both male and female ZDF *fa/fa* rats are homozygous recessive for mutations resulting in a defective leptin receptor, but males and females differ in dietary requirements to induce diabetes. Male ZDF *fa/fa* rats become diabetic on a normal rodent diet while female ZDF *fa/fa* rats only become diabetic on a high fat diet. In this study, males were maintained on a normal rodent diet while females were fed a high fat diet for at least 6 weeks prior to switching to a normal rodent diet during week 4 of the study

to minimize mortality due to prolonged consumption of the high fat diet. Liraglutide was pharmacologically active in diabetic ZDF *fa/fa* rats, decreasing food and water consumption, decreasing body weight gain, lowering non-fasting plasma glucose, and lowering HbA1c in males and females. Increased pancreas beta cell mass in liraglutide-treated diabetic females, but not in liraglutide-treated diabetic males, was consistent with greater glucose lowering efficacy in females. Increased beta cell mass in liraglutide-treated females was attributed to improved cell survival and/or increased cell size because it occurred in the absence of increased beta cell proliferation. Liraglutide had no adverse effects on the exocrine pancreas of diabetic ZDF *fa/fa* rats. At several time points during the 12-week treatment period, liraglutide increased plasma amylase in male and female diabetic rats, but without increasing plasma lipase or plasma triglycerides and without evidence of treatment-related macroscopic or microscopic pathology findings in the exocrine pancreas. In diabetic male rats, liraglutide had no effect on pancreas weight. In diabetic females, liraglutide significantly decreased pancreas weight, but decreased pancreas weight lacked correlative adverse findings in the exocrine or endocrine pancreas. Liraglutide did not affect exocrine cell mass (acinar cells or ductal) or exocrine cell proliferation in diabetic male or female rats. Results of this study were published (Vrang 2012).

Other Assessments of the Effects of Incretin-based Drugs on the Exocrine Pancreas
Marketed incretin-based drugs include DPP-4 inhibitors and GLP-1 receptor agonists. To evaluate models for identifying pancreatic toxicity of incretin-based drugs, FDA independently conducted studies in ZDF rats, C57Bl/6 mice fed a high fat diet, and chemically-induced pancreatitis in mice. Sitagliptin, a DPP-4 inhibitor, or exenatide, a GLP-1 receptor agonist, had no adverse effects on pancreas in ZDF rats or chemically induced pancreatitis in mice. In male C57BL/6 mice, exocrine pancreatic injury induced by 6 weeks of treatment with sitagliptin or exenatide included acinar cell injury (autophagy, apoptosis, necrosis, and atrophy), vascular injury, interstitial edema and inflammation, fat necrosis, and duct changes (dilatation, inflammation, and fibrosis) that could be exacerbated by a high fat diet that also inducing partial insulin resistance (Rouse 2014A). A second study evaluated the time course and dose-dependence of exenatide-induced pancreatic injury in mice. In male C57BL/6 mice, exenatide-related adverse effects on the exocrine pancreas were dose-dependent and treatment-duration-dependent and characterized by acinar cell injury and cell adaptations (hypertrophy, hyperplasia, and proliferation / regeneration), along with inflammation resulting in secondary injury in blood vessels, ducts, and adipose (Rouse 2014B). Exenatide-related histological changes in the pancreas in mice were exacerbated by a high fat diet, potentially due to oxidative stress from increased lipid metabolism. Because of uncertain human relevance of pancreatic injury by incretin-based drugs in C57BL/6 mice, the value of these studies for predicting human safety is unknown.

An evaluation of nonclinical assessments supporting marketing applications for incretin-based drugs by the FDA and the European Medicines Agency that included more than 250 toxicology studies conducted in approximately 18,000 healthy animals (15,480 rodents and 2,475 non-rodent mammals) showed no overt pancreatic toxicity or pancreatitis (Egan 2014). In lifetime rodent carcinogenicity studies, there were no incretin-based drug-related pancreatic tumors in mice or rats, even at high multiples of human exposure. FDA also required sponsors of marketed incretin-based drugs to evaluate pancreatic toxicity in 3-month studies in rodent models of

T2DM, and no drug-related adverse effects were reported, including the study of liraglutide in ZDF rats conducted by Novo Nordisk to satisfy a nonclinical postmarketing requirement. In the absence of overt pancreatic injury from incretin-based therapies in healthy animals or rodent models of T2DM, the FDA no longer routinely requires sponsors developing incretin-based therapies to perform dedicated pancreatic safety studies in rodents.

Risks of developing pancreatic ductal adenocarcinoma from treatment of diabetes were discussed by representatives of academia, industry, and government at a 2013 workshop on Pancreatitis-Diabetes-Pancreatic Cancer sponsored by the National Institute of Diabetes and Digestive and Kidney Disease and the National Cancer Institute. Despite concerns raised by reports in the medical literature and lay press about the risk of pancreatic cancer in patients treated with GLP-1 receptor agonists or DPP-4 inhibitors, there was no evidence of drug-related pancreatitis or pancreatic cancer in animal studies of incretin-acting drugs submitted to FDA and FDA had not seen a convincing signal between the use of incretin-acting drugs and pancreatic cancer in humans (Andersen 2013).

Conclusions

Human relevance of GLP-1 receptor agonist-induced rodent thyroid C-cell tumors remains unknown, and although there is no conclusive evidence that liraglutide or other GLP-1 receptor agonists cause MTC in humans, the latency of GLP-1 receptor agonist-induced C-cell tumors in rodents suggests the duration of exposure in humans to date may be insufficient to either elicit or detect it. The risk of pancreatitis in the 'Warnings and Precautions' section of the Victoza label is based on an increased incidence of pancreatitis in clinical studies of liraglutide and postmarketing reports, but liraglutide does not cause pancreatitis or pancreatic cancer in studies in normoglycemic mice, rats, and monkeys or diabetic rats. Human relevance of liraglutide-induced rodent thyroid C-cell tumors and the relation to liraglutide treatment for pancreatitis or pancreatic cancer in humans is being evaluated using human data, and additional mechanistic studies of approved GLP-1 receptor agonists in animals are likely to be of limited value for labeling or regulatory decisions.

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CLINICAL AND STATISTICAL EFFICACY SUMMARY

Dr. Condarco has reviewed clinical efficacy in detail. Overall, she has concluded that LEADER was a well-conducted trial with no trial integrity issues that would preclude approval.

LEADER- Design and Methods

Primary objective: To assess the effect of treatment with liraglutide compared to placebo for at least 3.5 years and up to 5 years on the incidence of CV events, as defined by the primary and secondary endpoints in adults with T2DM that are at high risk for CV events.

Secondary objectives: To assess the efficacy and safety with regard to clinically important events or other surrogate parameters of treatment with liraglutide compared to placebo in adults with T2DM that are at high risk for CV events.

Trial sites: A total of 417 sites in 32 countries screened subjects, of which 410 sites randomized subjects to treatment.

Study design: LEADER was a multi-center, multi-national, double-blinded trial. Subjects were randomized 1:1 to liraglutide or placebo in addition to standard of care therapy, as decided by the subject's physician. All subjects were started on 0.6 mg of liraglutide or the equivalence of placebo. The dose was escalated to 1.2 mg after one week followed by another dose escalation to 1.8 mg after one additional week.

The trial duration was driven by both MACE event numbers (at least 611 EAC confirmed MACEs) and observation time. At a *minimum*, all subjects were to have a treatment period of 42 months (in addition to a 30 day follow-up period). The trial included an 18 month recruitment period, therefore allowing for a maximum treatment period of 60 months.

Inclusion/Exclusion criteria:
The LEADER inclusion and exclusion criteria are shown in Table 1.

The purpose of the inclusion/exclusion criteria was threefold. First, the criteria were meant to enrich the subject population with subjects at risk for CV events. Specifically, the inclusion criteria specified that subjects aged ≥50 years with established CVD (also called criterion '3a' by the protocol) or subjects aged ≥60 years with well-established risk factors for CVD (i.e. criterion '3b') could be enrolled; second, the criteria were to limit the risk to subjects by excluding subjects with severe/unstable disease, and third, the criteria were to enroll a pre-specified number of subjects with moderate or severe renal insufficiency.

The enrollment criteria were broad with regard to allowed medications, by including both oral antidiabetic drugs (OADs) and basal insulin/pre-mix insulin.

Table 1. Key inclusion and exclusion criteria

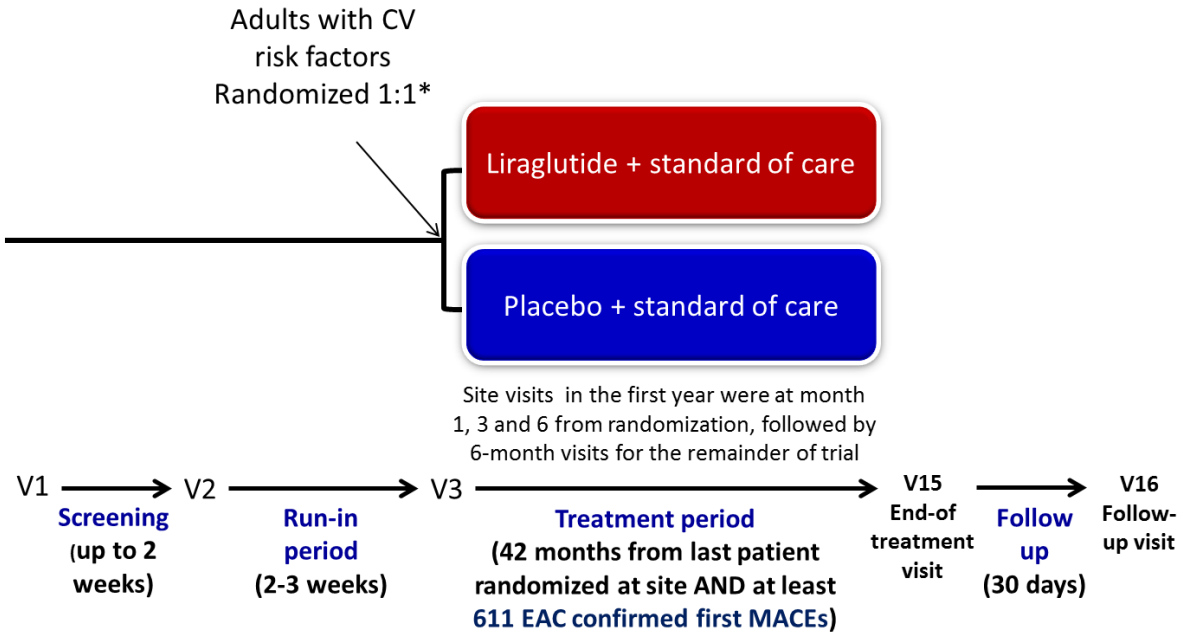
Key Inclusion criteria

Men or women with T2DM and:	
Age	
• *≥50 years at screening plus:	a) prior MI b) prior stroke or prior transient ischemic attack (TIA) c) prior coronary, carotid or peripheral arterial revascularization d) >50% stenosis on angiography or other imaging of coronary, carotid or lower extremity arteries e) history of symptomatic CVD documented by positive exercise stress test or any cardiac imaging, or unstable angina with ECG changes f) asymptomatic cardiac ischemia documented by positive nuclear imaging test or exercise test or dobutamine stress echo g) chronic heart failure NYHA class II-III h) chronic renal failure, having clinically reached a stage corresponding to a glomerular filtration rate < 60 mL/min/1.73 m^2 per Modification of Diet in Renal Disease (MDRD) or < 60 mL/min per Cockcroft-Gault formula
• ^*Or* ≥60 years at screening plus:	i) microalbuminuria or proteinuria j) hypertension and left ventricular hypertrophy by ECG or imaging k) left ventricular systolic or diastolic dysfunction by imaging l) ankle/brachial index <0.9
HbA1c	≥7% at screening
Antidiabetic therapies	Antidiabetic drug naïve or treated with one or more OADS or treated with human NPH insulin or long-acting insulin analogue or premixed insulin, alone or in combination with OAD(s)
Key Exclusion criteria	
Antidiabetic therapies	• Use of insulin other than human NPH, or long-acting insulin analogue or premixed insulin within 3 months prior to screening. Short-term use of other insulin during this period in connection with intercurrent illness was allowed, at Investigator's discretion • Use of a GLP-1 receptor agonist or pramlintide or any DPP-4 inhibitor within the 3 months prior to screening
CV risks	• An acute coronary or cerebrovascular event in the previous 14 days • Currently planned coronary, carotid or peripheral artery revascularization • Chronic heart failure NYHA class IV
Renal disease	• Current continuous renal replacement therapy • Estimated glomerular filtration rate (eGFR) (as per MDRD) < 30 mL/min/1.73 m^2 at screening *(applicable after a target number of 220 subjects with eGFR < 30 mL/min/1.73 m^2 were randomized)*
Liraglutide labeled contraindication	• Family or personal history of MEN 2 or familial medullary thyroid carcinoma (FMTC) • Personal history of non-familial medullary thyroid carcinoma

*Criterion 3a
^Criterion 3b

A schematic of the trial design is shown in Figure 2.

Figure 2. LEADER trial design



Abbreviations: EAC: event adjudication committee, MACE: Major adverse cardiovascular event, V1: screening visit, V2 start of run-in period, V3: randomization and start of treatment, CV: cardiovascular
*Dose of investigational drug was titrated 0.6 mg weekly to a maximum tolerated dose of 1.8 mg as add-on to standard of care treatment
Source: modified figure from CTR, Figure 9-1

An independent, blinded, external Event Adjudication Committee (EAC) was established to prospectively and centrally adjudicate pre-defined events of interest. The EAC was made up of four subcommittees: cardiovascular, microvascular, pancreatitis and neoplasm. Two adjudicators from the respective sub-committee evaluated each event of interest; see Table 2. The pre-specified definitions used for adjudication of CV events were established to conform to the 2010 [12] version of the FDA Standardized Definitions for Cardiovascular Outcomes Trials. The definitions of the non-CV events were based on internationally recognized recommendations approved by applicable EAC experts; refer to Dr. Condarco's review. Of note, 'silent MI' was included in the MI component of MACE, and thus contributed to the overall primary endpoint findings.

Table 2. EAC subgroups and number of adjudicators

EAC subgroup	Medical specialty	Events reviewed
Cardiovascular*	cardiologists neurologists	Cardiovascular events Neurological events
Microvascular	nephrologists ophthalmologists	Nephropathy events Retinopathy events
Pancreatitis	gastroenterologists	Pancreatitis events

[12] Standardized Definitions for Endpoint Events in Cardiovascular Trials. FDA Center for Drug Evaluation and Research (CDER). Draft Version October 20, 2010.

Neoplasm*	oncologists endocrinologists	Oncologists reviewed neoplasm events, excluding thyroid neoplasm**
**In case of thyroid disease resulting in a thyroidectomy, and or thyroid neoplasm, the Adjudicators were 1 endocrinologist and 1 oncologist. In cases where thyroidectomy was performed, the primary adjudicators reviewed both the local pathology report and the report of a central (external) pathologist who has reviewed the pathology specimen independently. If the specimen was unavailable, the primary adjudicators reviewed only the local pathology report. *adjudicated ALL deaths		

Two groups of subjects were specified: completers and non-completers. Completer subjects either had a MACE event, non-CV death or had direct contact with the investigator at visit 16 (i.e., end of study visit; refer to schematic on previous page). Completers also had known or unknown vital status (if previously experienced non-fatal MI or non-fatal stroke) at visit 16.

All first EAC confirmed MACE events, from randomization (visit 3) and before visit 16 that were reported before database lock (DBL) were considered for analyses. Of note, in the case of a stroke or MI that was linked to a CV death by the EAC, but the CV death occurred after V16, the stroke or MI *would* be counted as fatal and the CV death would be included in analyses.

Adverse events and vital status were collected from multiple sources beyond just site visits and phone contact for events sent for EAC adjudication and vital status, e.g. next of kin, health care providers, etc.

LEADER - Results

Subject Demographics

Overall, subjects randomized to liraglutide and placebo were well balanced with regard to demographic baseline characteristics. As shown in Table 3, the mean (SD) age of subjects was 64 (7.2) years [range: 49- 91]. 54% of subjects were 65 years of age or less and ~9% were greater than 75 years of age. 64% were men. The population was made up of ~78% White, 10% Asian and ~8% Black subjects. There were 12% subjects with Hispanic ethnicity. The distribution by region was highest for Europe, North America and "Rest of world", with ~7% of subjects coming from Asia. The North American region consisted of subjects from the U.S. and Canada. Of these, 2514 subjects were from the U.S. (a little over one quarter of subjects).

Table 3. Subject Demographics

	Liraglutide (n=4668)	**Placebo (n=4672)**
Age, mean ± SD – yr.	64.2 (7.2)	64.4 (7.2)
<65 n (%)	2512 (53.8)	2499 (53.5)
65-74 n (%)	1738 (37.2)	1755 (37.6)
75-84 n (%)	401 (8.6)	393 (8.4)

≥85 n (%)	17 (0.4)	25 (0.5)
Female sex, n (%)	1657 (35.5)	1680 (36)
Race, no (%)		
White	3616 (77.5)	3622 (77.5)
Black/African American	370 (7.9)	407 (8.7)
Asian	471 (10.1)	465 (10)
American Indian or Alaskan Native	5 (0.1)	6 (0.1)
Native Hawaiian or other Pacific Islander	4 (<0.1)	4 (<0.1)
Other	202 (4.3)	168 (3.6)
Ethnic group (Hispanic), no. (%)	580 (12.4)	554 (11.9)
Region, no %)		
Europe	1639 (35.1)	1657 (35.5)
North America	1401 (30)	1446 (31)
U.S. Subgroup of North America	*1247 (26)*	*1267 (27)*
Asia	360 (7.7)	351 (7.5)
Rest of world	1268 (27.2)	1218 (26.1)

N: Number of subjects, %: Percentage of subjects,
Region is defined as Europe, North America (US, Canada), Asia (China, Taiwan, Korea, India), and the Rest of the world (Brazil, Mexico, Australia, South Africa, Turkey, Russian Federation, United Arab Emirates.
Source: CTR, modified table 10-2, page 183

Overall, subjects randomized to liraglutide and placebo were well balanced with regard to demographic baseline disease characteristics. Table 4 shows the baseline concomitant illness and medical history of subjects enrolled. The information regarding CVD, T2DM complications, and pancreas and gallbladder history was systematically collected in specific medical history forms. In addition to these forms, investigators could report other concomitant illnesses (listed as "concomitant illnesses" in Table 4). Therefore, information captured under this category may vary from other information in the table (e.g. hypertension ~25% under this category, but >90% in the CVD form).

On average, subjects were obese (mean BMI 32.5 kg/m^2) and had an average duration of diabetes of ~13 years. CV history included hypertension for most subjects (>90%), followed by a history of ischemic heart disease (>50%) and a history of MI (in a third of subjects). About 18% had a history of heart failure and slightly more than 10% of subjects had a history of ischemic stroke. More than half of subjects were previous smokers or current smokers.

With regard to microvascular complications[13] present at screening, diabetic nephropathy and diabetic neuropathy were common by clinical history (~40% and ~35% respectively). About 20% of subjects had diabetic retinopathy. The presence or absence of neuropathy and retinopathy was based on reported history alone. The presence or absence of nephropathy was corroborated with screening eGFR measurements. eGFR at baseline was similar between treatment groups when calculated by the MDRD or CKD-EPI formulas, with an average of ~80 ml/min/1.73m^2, with >60% of subjects either having mild or moderate renal failure.

[13] The information regarding microvascular complications was based on a specific CRF form; therefore, patients could have a history of nephropathy without meeting the more strict definition used for the chronic kidney failure evaluation of the selection criteria used in the trial.

With regard to other comorbidities of interest, gallstone disease (~12%) was more common than cholecystitis (~7%) or pancreatitis (~3%). The average HbA1c for either group was 8.7%. The average lipid values were similar between treatment groups.

CV drug therapies included anti-hypertensives (>90% of subjects), antiplatelet agents (two-thirds of subjects), and lipid lowering agents (three-quarters of subjects).

Table 4. Baseline disease characteristics

Baseline characteristics	**Liraglutide (n= 4668)**	**Placebo (n=4672)**
BMI, kg/m^2 mean ± SD	32.5 (6.3)	32.5 (6.3)
Body weight, kg mean ± SD	91.9 (21.2)	91.6 (20.8)
Systolic blood pressure, mmHg, mean ± SD	135.9 (17.8)	135.9 (17.7)
Diastolic blood pressure, mmHg, mean ± SD	77.2 (10.3)	77.0 (10.1)
Heart rate (beats/minute), mean ± SD	72.7 (11.3)	72.5 (11.4)
Duration of diabetes, year(s), mean ± SD	12.8 (8.0)	12.9 (8.1)

Any Cardiovascular history n (%)	4588 (98.3)	4603 (98.5)
Hypertension	4261 (91.3)	4250 (91.0)
Ischemic heart disease	2542 (54.5)	2517 (53.9)
MI	1434 (30.7)	1373 (29.4)
PCI performed	1302 (27.9)	1266 (27.1)
Heart failure	835 (17.9)	832 (17.8)
CABG performed	782 (16.8)	749 (16.0)
Left ventricular diastolic dysfunction	782 (16.8)	799 (17.1)
Left ventricular systolic dysfunction	521 (11.2)	478 (10.2)
Ischemic stroke	512 (11.0)	526 (11.3)
Transient ischemic attack	257 (5.5)	310 (6.6)
Hemorrhagic stroke	53 (1.1)	50 (1.1)
Smoking, n (%)		
Previous smoker	2151 (46.1)	2189 (46.9)
Never smoked	1950 (41.8)	1920 (41.1)
Current smoker	567 (12.1)	563 (12.1)
Microvascular complications n (%)		
Diabetic nephropathy	1882 (40.3)	1917 (41.0)
Diabetic neuropathy	1614 (34.6)	1615 (34.6)
Diabetic retinopathy	978 (21.0)	899 (19.2)
Diabetic foot ulcer	208 (4.5)	196 (4.2)
eGFR, ml/min/1.73m^2 (MDRD), mean ± SD	80.2 (27.5)	80.6 (27.2)
Severe n (%)	117 (2.5)	107 (2.3)
Moderate n (%)	999 (21.4)	935 (20.0)
Mild n (%)	1932 (41.4)	1975 (42.3)
Normal n (%)	1620 (34.7)	1655 (35.4)
eGFR, ml/min/1.73m^2 (CKD-EPI), mean ± SD	78.9 (22.4)	79.3 (21.8)
Concomitant illnesses n (%)*		
Hyperlipidemia	1467 (31.4)	1475 (31.6)
Dyslipidemia	1309 (28.0)	1303 (27.9)
Hypertension	1182 (25.3)	1228 (26.3)
Obesity	837 (17.9)	804 (17.2)
Osteoarthritis	700 (15.0)	693 (14.8)
Pancreatitis n (%)	146 (3.1)	118 (2.5)
Gallstone disease n (%)	569 (12.2)	534 (11.4)
Cholecystitis n (%)	343 (7.3)	324 (6.9)
HbA1c %), mean ± SD	8.7 (1.6)	8.7 (1.5)
LDL (mg/dL), mean ± SD	88.4 (36.6)	88.8 (36.2)
HDL (mg/dL), mean ± SD	44.7 (12.1)	44.9 (12.1)
Total Cholesterol (mg/dL), mean ± SD	168.1 (44.7)	168.5 (46.1)
Triglycerides (mg/dL), mean ± SD	184.7 (124.5)	184.3 (158.2)
Baseline diabetes medications, n ( )		
OAD only	2436 (52.2)	2375 (50.8)
Insulin only	361 (7.7)	377 (8.1)
Insulin +OAD	1677 (35.9)	1754 (37.5)
Not on insulin/OAD	194 (4.2)	166 (3.6)
Blood glucose lowering drugs (excluding insulin)	4113 (88.1)	4129 (88.4)
Metformin	3540(75.8)	3604(77.1)
SU	2370(50.8)	2363(50.6)
Alpha glucosidase inhibitors	139(3.0)	123(2.6)
TZD	296(6.3)	279(6.0)
DPP4 inhibitors	4(<0.1)	2(<0.1)
GLP1 receptor agonist	0	2(<0.1)
SGLT2 inhibitors	0	0
Glinides	178(3.8)	172(0.1)
Other	0	1(<0.1)

Insulin treatment at baseline	2038 (43.7)	2131(45.6)
Baseline CVD medications, n (%)		
Antihypertensive therapy	4329 (92.7)	4303 (92.1)
Beta blockers	2652 (56.8)	2529 (54.1)
Calcium channel blockers	1538 (32.9)	1479 (31.7)
ACE inhibitors	2417 (51.8)	2350 (50.3)
Angiotensin receptor blockers	1488 (31.9)	1486 (31.8)
Renin inhibitors	42 (0.9)	40 (0.9)
Others	468 (10.0)	454 (9.7)
Diuretics	1953 (41.8)	1953 (41.8)
Loop diuretics	824 (17.7)	837 (17.9)
Thiazides	829 (17.8)	788 (16.9)
Thiazide-like diuretics	325 (7.0)	355 (7.6)
Aldosterone antagonists	254 (5.4)	251 (5.4)
Lipid lowering drugs	3564 (76.3)	3515 (75.2)
Statins	3405 (72.9)	3336 (71.4)
Ezetemibe	165 (3.5)	169 (3.6)
Fibrates	412 (8.8)	432 (9.2)
Niacin	95 (2.0)	95 (2.0)
Other lipid lowering drugs	8 (0.2)	14 (0.3)
Platelet aggregation inhibitors	3205 (68.7)	3121 (66.8)
Acetylsalicylic acid (ASA)	2977 (63.8)	2899 (62.1)
Clopidogrel, tioclopidine, pasugrel, tigagrelor	720 (15.4)	745 (15.9)
Anti-thrombotic medication	314 (6.7)	327 (7.0)
Vitamin K antagonists	295 (6.3)	301 (6.4)
Direct thrombin inhibitors	17 (0.4)	12 (0.3)
Direct factor Xa inhibitors	0 (0.0)	1 (<0.1)
Heparin group	5 (0.1)	14 (0.3)

*showing concomitant illnesses affecting at least 15% of subjects at screening. This information was obtained from the investigators reporting any other concomitant illness, and therefore this information was not systematically collected.

Source: CTR, modified table 10-3 page 184, table 10-9, page 189, Table 10-11, page 191; Table 10-16, page 196, table 10-14, page 194, table 10-17, page 197.

Overall, 81% of subjects had established CVD and had an age ≥50 years; while ~19% of subjects had risk factors for CVD and were ≥60 years of age. A quarter of the subjects had chronic kidney disease (CKD) (defined as eGFR<60mL/min/1.73m^2 per MDRD).

Overall, 80% of subjects were on blood glucose lowering drugs (excluding insulin) of which, metformin was the most common OAD used (>three-quarters of subjects). Notably, there were no subjects taking SGLT2is, and only 1 subject in the placebo group was taking a GLP-1 RA. About 44% of subjects were on some sort of insulin treatment at baseline. Only ~4 % of subjects did not receive any antidiabetic treatment at baseline.

Table 5 shows the antidiabetic and other CV medications started after baseline. When comparing by treatment group after baseline (Table 4), there were generally more OADs started for the placebo arm than liraglutide arm. Only 2% - 3% of subjects started a SGLT2i after baseline. Insulin use at baseline was slightly lower for liraglutide than placebo; however, insulin was initiated after baseline in a higher percentage of subjects for placebo than liraglutide (43% vs. 29%, respectively).

When evaluating the CV medications used post baseline, there were a slightly higher number of subjects on placebo who started a CV medication as compared to liraglutide with the exception of antithrombotics which were similar between treatment groups.

Table 5. Medications started exclusively after baseline

Medications n (%)	Liraglutide (n= 4668)	Placebo (n=4672)
Blood glucose lowering drugs (excluding insulin)	1012 (21.7)	1358 (29.1)
Metformin	249 (5.3)	299 (6.4)
SU	349 (7.5)	505 (10.8)
Alpha glucosidase inhibitors	83(1.8)	146 (3.1)
TZD	99 (2.1)	160(3.4)
DPP4 inhibitors	149 (3.2)	170 (3.6)
GLP1 receptor agonists	87 (1.9)	139 (3.0)
SGLT2 inhibitors	100(2.1)	130 (2.8)
Glinides	85 (1.8)	137 (2.9)
Other	0 (0)	1 (<0.1)
Insulin treatment after baseline	1346 (28.8)	2019 (43.2)
Premix	282 (6.0)	440 (9.4)
Short acting	586 (12.6)	915 (19.6)
Intermediate acting	273 (5.8)	386 (8.3)
Long acting	619 (13.3)	940 (20.1)
Other insulin	31 (0.7)	43 (0.9)
Insulin naïve	1830 (39.2)	1343 (28.7)
Antihypertensive therapy	1452 (31.1)	1584 (33.9)
Beta blockers	445 (9.5)	486 (10.4)
Calcium channel blockers	465 (10.0)	557 (11.9)
ACE inhibitors	331 (7.1)	375 (8.0)
Angiotensin receptor blockers	368 (7.9)	456 (9.8)
Renin inhibitors	5 (0.1)	9 (0.2)
Others	274 (5.9)	309 (6.6)
Diuretics	851 (18.2)	1025 (21.9)
Loop diuretics	484 (10.4)	572 (12.2)
Thiazides	216 (4.6)	293 (6.3)
Thiazide-like diuretics	125 (2.7)	156 (3.3)
Aldosterone antagonists	236 (5.1)	238 (5.1)
Lipid lowering drugs	667 (14.3)	738 (15.8)
Statins	439 (9.4)	520 (11.1)
Ezetemibe	68 (1.5)	73 (1.6)
Fibrates	172 (3.7)	164 (3.5)
Niacin	22 (0.5)	31 (0.7)
Other lipid lowering drugs	15 (0.3)	16 (0.3)
Platelet aggregation inhibitors	701 (15.0)	773 (16.5)
Acetylsalicylic acid (ASA)	378 (8.1)	423 (9.1)
Clopidogrel, tioclopidine, pasugrel, tigagrelor	387 (8.3)	416 (8.9)
Anti-thrombotic medication	601 (12.9)	615 (13.2)
Vitamin K antagonists	174 (3.7)	193 (4.1)
Direct thrombin inhibitors	49 (1.0)	45 (1.0)
Direct factor Xa inhibitors	78 (1.7)	95 (2.0)
Heparin group	402 (8.6)	393 (8.4)

The term "started after baseline" covers initiation of concomitant medication registered at any time after randomization (visit 3).

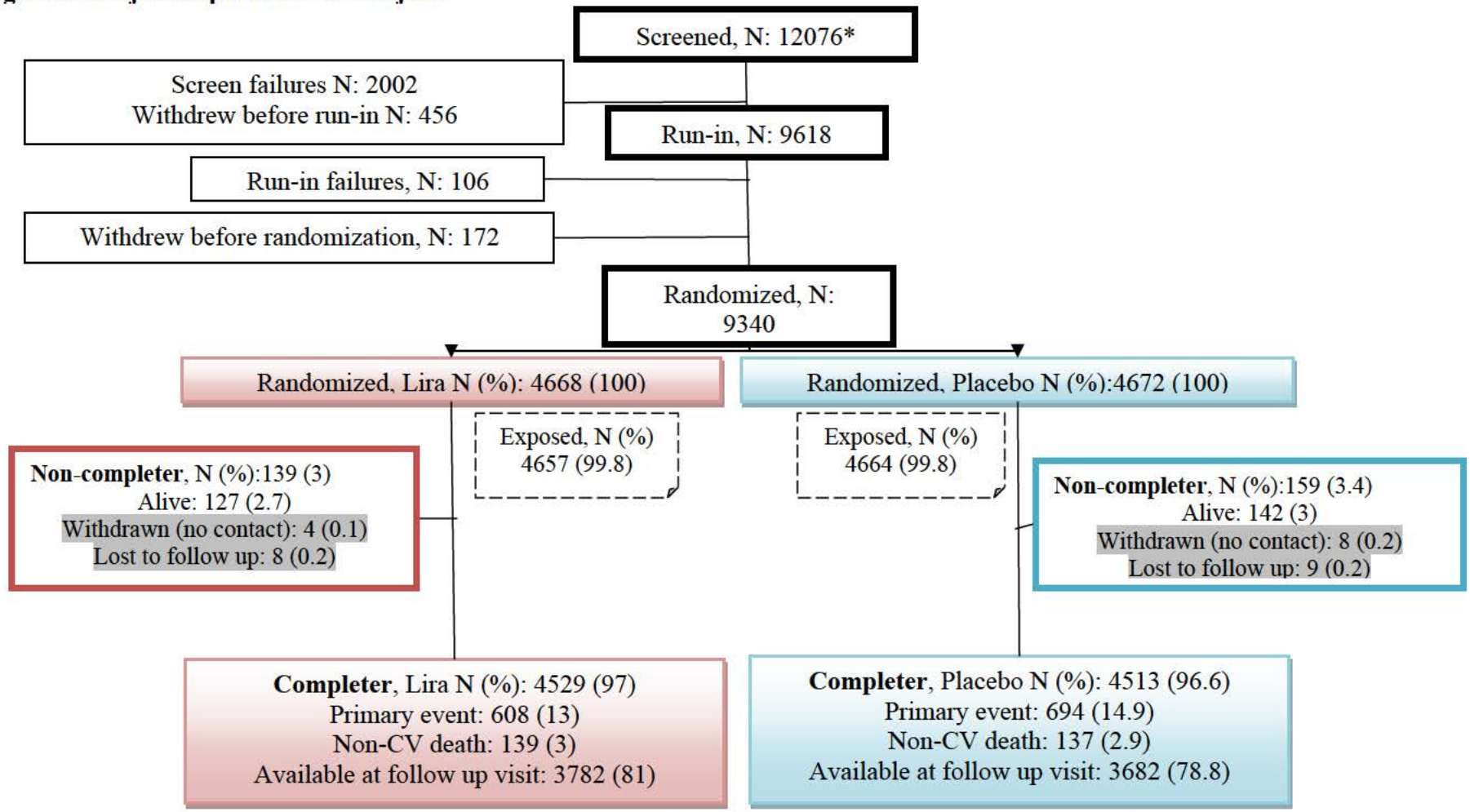
Source: Source, table 10-15, table 10-18 and table 10-17.

Subject Disposition

The figure below shows the subject disposition. In total 12,076 subjects were screened. Between the screening period and randomization, 2736 subjects were lost/ withdrawn. 9,340 subjects were randomized 1:1 to liraglutide (4,668) or placebo (4,672). Over 99% subjects were exposed to liraglutide or placebo during the trial.

A similar percentage of subjects in each arm completed the trial, ~97% of subjects randomized to liraglutide or placebo.

Figure 3. Subject disposition – all subjects



Unknown vital status. *Two subjects were screened twice, and one patient randomized twice for a total of 12078 screens. The number shown in the table reflects the actual number of patients screened. N: Number of subjects %: Proportion of subjects. Run-in: This is defined as the period between screening and randomization. Subjects who were in multiple categories before randomization were counted only once following this hierarchy: Screening failures > Withdrew before run-in > Run-in failures > Withdrew before randomization. Lost-to-follow-up was determined at the follow-up visit (visit16). Subjects, who withdrew but allowed contact, were included in the 'completed trial' category. The 'alive' category includes those subjects who were not available in person but for whom vital status was available. The 'available at follow-up visit' category includes subjects with whom personal contact could be established at the follow-up visit (visit 16). Subjects who were available at follow-up and with a primary event were counted as 'primary' event. Source: information in CTR Table 10-1, page 180.

Table 6 and Table 7 summarize observation time (time on-study) and exposure time (time on-treatment). Median exposure to treatment in this trial was 3.52 years (min 0.00, max 5.01 years), and mean (SD) exposure was 3.07 (1.27) years. More than 70% of subjects were exposed for 90% or more of the observation time, whereas 6.7% of liraglutide-treated subjects and 5.9% of placebo-treated subjects were exposed for less than 10% of the observation time. The trial's observation time was shortened due to meeting the pre-specified 611 events were earlier than expected. The Sponsor initiated a staggered close down of trial sites, 3-6 months prior to when the last randomized subject at the site had been in the trial for 42 months. Most randomized subjects were exposed; only 19 subjects were not exposed to investigational treatment (11 for liraglutide and 8 for placebo).

Exploratory analyses by sex and age (data not shown) were consistent with the overall exposure results.

Table 6. Summary of Mean and Median Trial Observation and Treatment Exposure

	Liraglutide	Placebo
Number of subjects	4668	4672
Total years in trial (patient-years of observation)	17822	17741
Median years of observation including follow-up period	3.84	3.84
Total years in trial excluding follow-up period	17341	17282
Median years of observation excluding follow-up period	3.75	3.75
Total years of exposure to trial drug	14502	14157
Median years of exposure to trial drug	3.52	3.51
Subjects with 1 or more drug holidays, N (%) (exposed and alive subjects at follow-up)	1687 (36.1)	1584 (33.9)

Source: LEADER CSR, Table 14.2.2

Table 7. Summary of Categorical Exposure

	Liraglutide	Placebo
Number of subjects	4668	4672
Exposed, N (%)		
N	4657 (100.0)	4664 (100.0)
0-1 years	571 (12.3)	608 (13.0)
1-2 years	318 (6.8)	410 (8.8)
2-3 years	357 (7.7)	412 (8.8)
3-4 years	2482 (53.3)	2363 (50.7)
4-5 years	927 (19.9)	869 (18.6)
5-6 years	2 (<0.1)	2 (<0.1)

Source: LEADER CSR, Table 14.2.5

Estimated raw incidence of outcomes based on this follow-up is shown in Table 8.

Table 8. Estimated Raw Incidence per 100 Subject Years

	Liraglutide N=4668	Placebo N=4672
MACE	3.41	3.91
CV Death	1.23	1.57
Non-fatal MI	1.58	1.79
Non-fatal Stroke	0.89	1.00
All-Cause Deaths	2.14	2.52
Non CV Death	0.91	0.95

Source: Statistical Reviewer's analysis

Primary MACE

Results are shown for the Full Analysis Set population (FAS) unless otherwise specified. The FAS included all randomized subjects. The statistical evaluation followed the intention-to-treat (ITT) principle, with subjects contributing to the evaluation 'as randomized'. The pre-specified primary analysis for the primary endpoint, time to first MACE event, is shown in Table 9. The upper bound of the 95% CI is less than 1.3 which rules out a 30% risk increase for this endpoint. The HR of 0.87 results in a 13% risk reduction of a MACE event occurring in the liraglutide group over placebo. Statistical superiority of liraglutide over placebo was also confirmed for the primary MACE endpoint because at 0.97, the upper bound of the 95% CI is less than 1.0. About 97% of the subjects completed this study. Therefore, no missing data imputations were conducted. However, the sponsor did tipping point analyses to assess the possible impact of missing values on treatment effect.

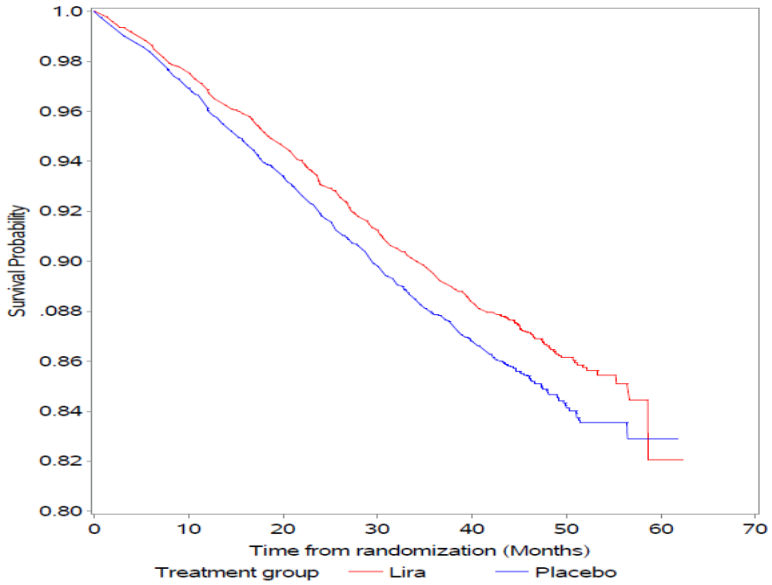
Table 9. Description of primary analysis – Time to first MACE event

	Liraglutide	Placebo	Hazard ratio [95% CI]	
	N (%)	N (%)		
FAS	4668	4672		
Primary endpoint: MACE*	608 (13.02)	694 (14.85)	0.87 [0.78; 0.97]	2-sided P value for HR≥1.0: 0.011
		Components		
Cardiovascular death	219 (4.7)	278 (6)	0.78 [0.66;0.93]	
Non-fatal stroke	159 (3.41)	177 (3.79)	0.89 [0.72;1.11]	
Non-fatal MI	281 (6.02)	317 (6.79)	0.88 [0.75;1.03]	

N: number (%) percent of patients with a first EAC confirmed MACE between randomization date and follow up date.
*Contains the **first** MACE event which includes: cardiovascular death, non-fatal MI, non-fatal stroke
HR < 1.0 indicates treatment benefit of liraglutide
Analyzed using a Cox regression model with treatment as a fixed factor.
Source: FDA Statistical Reviewer

Figure **4** shows the estimated Kaplan-Meier curve for time to first MACE by treatment groups.

Figure 4. Kaplan-Meier Plot Time to First EAC-Confirmed MACE



Source: Statistical Reviewer's analysis

Pre-specified sensitivity analyses for the primary endpoint were conducted by the sponsor and appeared to adequately support the primary analysis according to the FDA biostatistics review. These included a per protocol analysis, an on-treatment analysis, i.e. MACE event occurring while on randomized treatment, an on-treatment plus 30 days analysis, and an analysis adjusting for the covariates of sex, region, baseline age (continuous), diabetes duration (continuous), prior cardiovascular events at baseline (yes/no), antidiabetic medication at baseline (none/1 OAD/>1 OAD/Insulin +/- OAD), smoking history (never/prior/current), and eGFR (continuous) at screening.

Secondary Endpoints

The pre-defined secondary time-to-event CV and mortality endpoints were:

- time from randomization to first occurrence of an expanded composite MACE outcome, defined as either CV death, non-fatal MI, non-fatal stroke, coronary revascularization, hospitalization for unstable angina pectoris, or hospitalization for heart failure
- time from randomization to all-cause death
- time from randomization to non-CV death
- time from randomization to each individual component of the expanded composite MACE outcome

While none of the secondary endpoints was pre-specified in the testing hierarchy, there are some secondary endpoints of interest that will be discussed. These endpoints are used

as exploratory endpoints to support the primary endpoint. Therefore, all the following analyses are exploratory and need to be interpreted with caution.

Expanded MACE

Table 10 shows the results for the secondary endpoint, time to first occurrence of an expanded MACE[14] (defined above). Numerically time to experiencing an expanded MACE event was lower in the liraglutide group than the placebo group.

Table 10. Description of secondary analysis – Time to first expanded MACE event

	Liraglutide	Placebo	Hazard ratio (95% CI)
	N (%)	N (%)	
FAS	4668	4672	
Expanded MACE	948 (20.3)	1062 (23)	0.88 [0.81; 0.96]
Components			
Hospitalization for unstable angina pectoris	122 (2.6)	124 (2.7)	0.980 [0.763;1.258]
Coronary revascularization	405 (8.7)	441 (9.4)	0.912 [0.797;1.044]
Hospitalization for heart failure	218 (4.7)	248 (5.3)	0.872 [0.727;1.046]

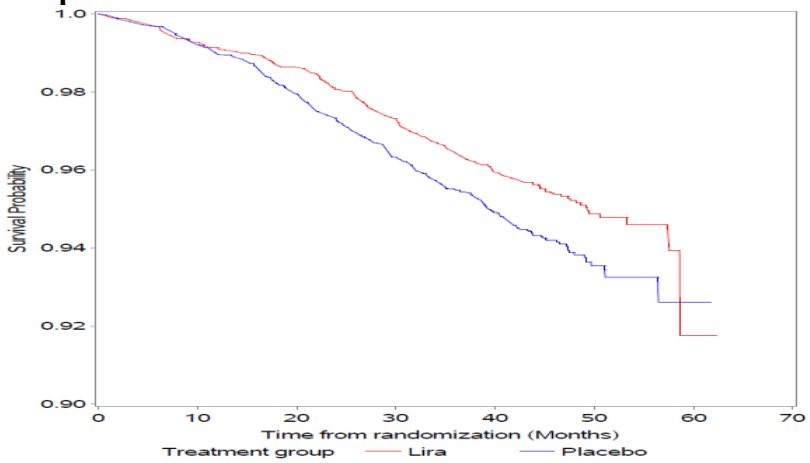
N: number (%) percent of patients with a first EAC confirmed expanded MACE between randomization date and follow up date.
*Contains the **first** expanded MACE event which includes: cardiovascular death, non-fatal MI, non-fatal stroke, coronary revascularization, hospitalization for unstable angina pectoris, or hospitalization for heart failure
HR < 1.0 indicates treatment benefit of liraglutide
Analyzed using a Cox regression model with treatment as a fixed factor.
Source: FDA Statistical Reviewer

CV Death

As previously shown in Table 9 there were fewer CV deaths in the liraglutide group compared to placebo, with a 22% decrease in CV death risk for liraglutide relative to those on placebo [HR 0.78 (0.66; 0.93)]. When adjusted for additional covariates (sex, region, baseline age (continuous), diabetes duration (continuous), prior cardiovascular events at baseline (yes/no), antidiabetic medication at baseline (none/1 OAD/>1 OAD/Insulin +/- OAD), smoking history (never/prior/current), and eGFR (continuous) at screening) the results were similar to those just having treatment in the model (results not shown).The Kaplan-Meier curves for time to first CV death are shown in Figure 5.

14 Subjects were allowed to contribute only once to this analysis with their first event. If a subject had more than one event on the same day of onset, the applicant defined the priority classification for first event as: cardiovascular death > non-fatal myocardial infarction > non-fatal stroke > hospitalization for UAP > hospitalization for heart failure > coronary revascularization. Recurrent events were not counted in the analyses.

Figure 5. Kaplan-Meier Plot- Time to First Confirmed Cardiovascular Death



Source: Statistical Reviewer's analysis

CV death - discussion

CV deaths were made up of deaths due to "unknown cause" and deaths determined by the EAC to be CV-related.

The EAC charter defined deaths for which there was no clearly documented non-vascular cause as a death due to "unknown cause". According to the LEADER protocol, deaths that were adjudicated as due to "unknown cause" by the CV adjudication committee were to be categorized as CV deaths. Close to 30% of CV deaths (~18% of all deaths) in both treatment arms were adjudicated as due to "unknown cause" (see Table 11).

The adjudication committee classified deaths as CV-related if the clinical information available met the EAC Charter definition (see Dr. Condarco's review for definitions) of; an MI-related death, a stroke-related death or belonged to one of the other categories of CV deaths that were not MI or stroke-related. According to the Sponsor's study report, CV deaths were regarded as due to stroke or MI only if the EAC chair determined that the death was directly MI or stroke related during multiple event review. Categorization of non-MI and non-stroke related deaths were performed after database lock by the Sponsor and are shown under the subheading 'Sponsor sub-classification' in Table 11. Deaths classified by the Sponsor as "other CV causes" included EAC identified vascular events such as: ruptured aortic aneurysm, thromboembolic disease, gangrene, pulmonary embolism, cardiac arrest and complications of vascular/cardiac surgery.

Table 11. CV deaths by cause

	Liraglutide	Placebo
	N (%)	N (%)
FAS	4668	4672
PYO	17822	17741
Total (all cause) deaths	*381 (8.2)*	*447 (9.6)*
*Death due to "unknown cause"**	*70 (1.5)*	*81 (1.7)*
CV death (includes death due to "unknown cause"):	**219 (4.7)**	**278 (6.0)**
EAC confirmed MI	17 (0.4)	26 (0.6)
EAC confirmed stroke	15 (0.3)	25 (0.5)
Death not linked to EAC confirmed MI or stroke	117 (2.5)	146 (3.1)
Sponsor sub-classification		
Sudden cardiac death	51 (1.1)	74 (1.6)
Acute MI	4 (<0.1)	15 (0.3)
HF or cardiogenic shock	25 (0.5)	31 (0.7)
Cerebrovascular event	4 (<0.1)	4 (<0.1)
Other CV cause	15 (0.3)	14 (0.3)
Unclassifiable	18 (0.4)	8 (0.2)

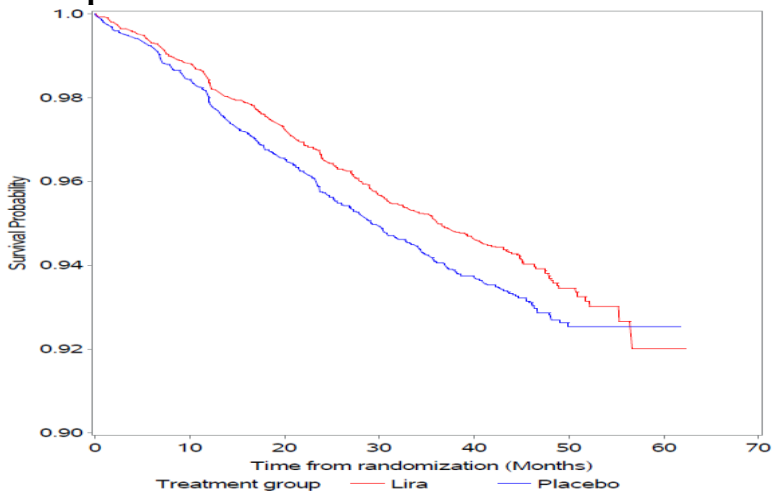
*per protocol deaths of unknown cause were categorized as CV death.
The total number of adjudicated deaths classified with 'unknown cause' includes 3 subjects (b) (6) where the EAC Chair during multiple events review had linked the deaths to an EAC-confirmed MI ((b) (6)) and stroke (b) (6) occurring within the same subject.
In this table, these 3 linked deaths are only counted in unknown cause. In other outputs only related to EAC-confirmed MI or stroke, these 3 EAC-confirmed MI or stroke events that were evaluated by the EAC Chair as precipitating the subjects death will be counted as 'fatal MI' or 'fatal stroke' as applicable. Source: Table 12-15

Nonfatal MI

As previously shown in Table 9, numerically the risk of experiencing a non-fatal MI was 12% lower for liraglutide subjects relative to those on placebo. The upper limit of the 95% CI was greater than 1, but the trend favors liraglutide.

Figure 6 shows the Kaplan-Meier plot for time to first non-fatal MI.

Figure 6. Kaplan-Meier Plot - Time to First Confirmed Non-Fatal MI



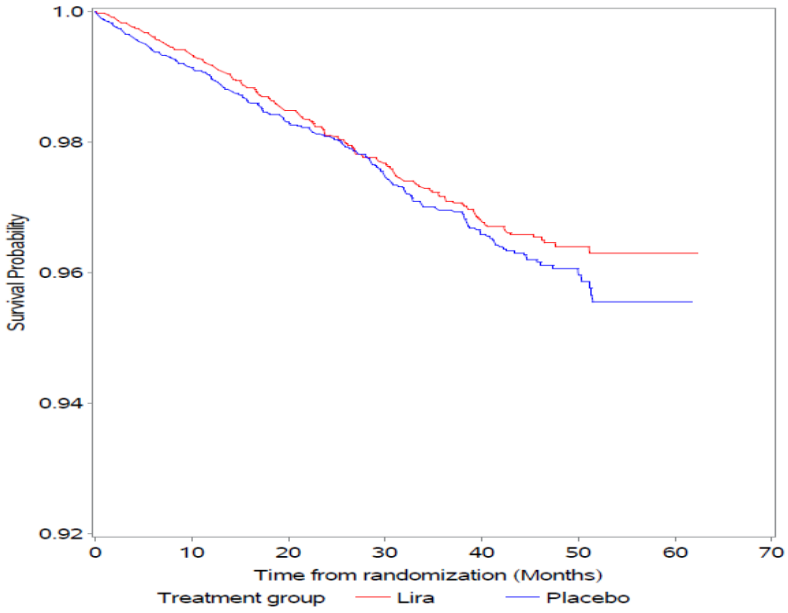
Source: Statistical Reviewer's analysis

Nonfatal stroke

As previously shown in Table 9, numerically the risk of experiencing a non-fatal stroke was 11% lower for liraglutide subjects relative to those on placebo. The upper limit of the 95% CI was greater than 1, but the trend favors liraglutide.

Figure 7 shows the Kaplan-Meier plot for non-fatal stroke.

Figure 7. Kaplan Meier Plot- Time to First Confirmed Non-Fatal Stroke



Source: Statistical Reviewer's analysis

All MI and all stroke

Another way to examine the data is to pool fatal and nonfatal MI and to pool fatal and nonfatal stroke. Numerically the risks of experiencing a total MI were lower for liraglutide subjects compared to those on placebo. The hazard ratio of 0.85 corresponds to a 15% relative risk reduction of a total MI occurring in the liraglutide group compared to placebo. Numerically the risks of experiencing total stroke were lower for liraglutide subjects compared to those on placebo. The hazard ratio of 0.87 reflects a 13 % relative risk reduction of total stroke occurring in the liraglutide group compared to placebo. However, for both analyses the upper limit of the 95% CI was greater than 1, but the trends are in the same direction as MACE. See Dr. Hamilton's review for data analyses.

All-cause death and non-CV death

The number and proportion of subjects experiencing all-cause deaths and non-CV deaths are summarized in Table 12. (MACE and CV death were also included in the table for the reader's convenience). A total of 162 (3.5%) deaths in subjects randomized to liraglutide and 169 (3.6%) in subjects randomized to placebo were reported and adjudicated as non-CV deaths [HR 0.952 (95% CI: 0.768, 1.181)]. The upper bound for the 95% CI for non-CV death was greater than 1, showing that there was no difference between liraglutide and placebo for this endpoint. All-cause death was subdivided into CV death and non-CV death. The favorable trend (for liraglutide) in all-cause death seems to be driven by CV death.

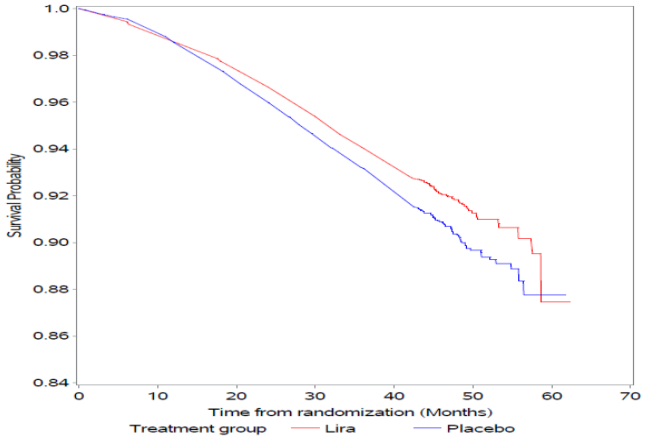
Table 12. Confirmed Deaths

	Liraglutide N=4668 n (%)	Placebo N=4672 n (%)	Hazard Ratio (95% CI)
MACE	608 (13.0)	694 (14.9)	0.87 (0.78, 0.97)
CV Death	219 (4.7%)	278 (6.0%)	0.78 (0.66, 0.93)
Non-CV Death	**162 (3.5%)**	**169 (3.6%)**	**0.95 (0.76, 1.18)**
All-Cause Death	**381 (8.2%)**	**447 (9.6%)**	**0.85 (0.74, 0.97)**

Source: Statistical Reviewer's analysis
HR < 1.0 indicates treatment benefit of liraglutide

Figure 8 shows the Kaplan Meier curve for all-cause death.

Figure 8. Kaplan-Meier Plot- Time to Confirmed All-Cause Death



Source: Statistical Reviewer's analysis

Non-CV deaths - discussion

As previously discussed, the CV EAC subcommittee adjudicated all deaths as CV or non-CV deaths and provided the likely cause of death. The causes provided by the adjudicators for the non-CV deaths were further subclassified by the sponsor post-database lock according to the non-CV death categories defined in the EAC charter.[15] Therefore, although the adjudicators provided a non-CV death cause, the sponsor was responsible for further sub-classifying non-CV deaths.[16] Sponsor death classifications based on EAC narrative descriptions were reviewed and generally appear to be appropriate. Nevertheless, accurate classification can be challenging given multiple comorbidities, contemporaneous medical events leading to death, missing information, and absence of strict rules to classify deaths according to the immediate or underlying cause. The sub-classifications and subsequent analysis as shown below should take those limitations into account.

An overview of the *post hoc* classification of EAC-confirmed non-CV deaths is shown in Table **13** for events from randomization to follow-up. The most frequently reported causes of non-CV deaths were malignancy and infection/sepsis; these were seen at similar frequencies in both treatment groups. Although the numbers are small, we note

[15] Non-CV death was defined as any death not covered by the cardiac death or vascular death categories and was further categorized into following groups: pulmonary causes, renal causes, gastrointestinal causes, infection (includes sepsis), non-infectious [e.g., systemic inflammatory response syndrome (SIRS)], malignancy (i.e., new malignancy, worsening of prior malignancy), hemorrhage- not intracranial, accidental/trauma, suicide, non-cardiovascular system organ failure (e.g., hepatic failure), non-cardiovascular surgery, other non-cardiovascular.

[16] Note that non-CV deaths were not adjudicated according to the non-CV secondary endpoints by the CV subcommittee, therefore, a death classified as non-CV death and characterized with an EAC-assigned plausible cause of death of, for example, "pancreatitis", would only count as an EAC-confirmed pancreatitis event if it had independently been confirmed as such event by the relevant (pancreatitis) EAC sub-committee.

the observed slight imbalance in adjudicated renal deaths not in favor of liraglutide. Renal safety, including deaths is discussed further in the Clinical Safety Summary. In 8 deaths in the liraglutide group and 12 deaths in the placebo group, the cause of the non-CV death could not be classified.[17]

Table 13. EAC-confirmed deaths reported with liraglutide and placebo

	Liraglutide	Placebo	Total
	N (%)	N (%)	N (%)
FAS	4668	4672	
PYO	17822	17741	
Total deaths	381 (8.2)	447 (9.6)	447
Unknown cause	70 (1.5)	81 (1.7)	151 (1.6)
Known cause of death	311 (6.7)	366 (7.8)	677 (7.2)
EAC confirmed MI	17 (0.4)	26 (0.6)	43 (0.5)
EAC confirmed stroke	15 (0.3)	25 (0.5)	40 (0.4)
Death not linked to EAC confirmed MI or stroke	117 (2.5)	146 (3.1)	263 (2.8)
Non-cardiovascular deaths (sponsor sub-classification)	162 (3.5)	169 (3.6)	169
Pulmonary	7 (0.1)	12 (0.3)	19 (0.2)
Renal causes	11 (0.2)	5 (0.1)	16 (0.2)
GI causes	4 (<0.1)	2 (<0.1)	6 (<0.1)
Infection	37 (0.8)	41 (0.9)	78 (0.8)
Non-infectious (e.g. SIRS)	1 (<0.1)	1 (<0.1)	2 (<0.1)
Malignancy	65 (1.4)	67 (1.4)	132 (1.4)
Hemorrhage (non-intracranial)	6 (0.1)	4 (<0.1)	10 (0.1)
Accidental/trauma	12 (0.3)	14 (0.3)	26 (0.3)
Suicide	1 (<0.1)	2 (<0.1)	3 (<0.1)
System organ failure (non-CV)	5 (0.1)	3 (<0.1)	8 (<0.1)
Non-CV surgery	2 (<0.1)	1 (<0.1)	3 (<0.1)
Other non-CV Death	3 (<0.1)	5 (0.1)	8 (<0.1)
Unclassifiable	8 (0.2)	12 (0.3)	20 (0.2)

The total number of adjudicated deaths classified with 'unknown cause' includes 3 subjects ((b) (6)), where the EAC Chair during multiple events review had linked the deaths to an EAC-confirmed MI (b) (6)) and stroke (b) (6)) occurring within the same subject. In this table, these 3 linked deaths are only counted in unknown cause. In other outputs only related to EAC-confirmed MI or stroke, these 3 EAC-confirmed MI or stroke events that were evaluated by the EAC Chair as precipitating the subjects death will be counted as 'fatal MI' or 'fatal stroke' as applicable.

Source: CSR, table 12-15, page 318

Subgroup Analyses

17 'Unclassifiable' was used when the 2 adjudicators did not enter a comparable cause of death for a specific event (e.g., pneumonia and hip fracture).

Subgroup analyses were performed on the primary endpoint, CV death and all-cause death by age, sex, country, race, and HbA1c. Table 14 summarizes the efficacy results in these subgroups. The hazard ratio for the subgroup of US was greater than 1 across all three endpoints in the table below, although the 95% confidence interval includes 1. The nominal p value for the test of interaction between region (US vs. Non-US) and treatment for the MACE endpoint was 0.048, which suggests there may be some quantitative difference in treatment effects for US and non-US subgroups. The Sponsor performed numerous *post hoc* analyses to evaluate differences to explain the findings. Demographic characteristics showed slight differences between the US population and the non-US population. In particular patients in the US had a larger BMI, lower systolic, diastolic blood pressure, and total cholesterol, longer diabetes duration and lower mean eGFR (MDRD). Patients in the US also used more insulin, diuretics, lipid lowering drugs and platelet aggregation inhibitors. Slight differences in changes in HbA1c, changes in body weight and changes in systolic blood pressure were also observed. However, none of the interaction p values comparing these parameters by US and Non-US population was statistically significant. Please refer to Dr. Condarco's review for details. The Office of Biostatistics review states that the US subgroup results could be due to chance. In other words, the test for interaction provides marginal evidence that there may be some quantitative but not qualitative difference in observed treatment effects for these subgroups. The statistical reviewers concluded that weighed with the results of the primary MACE and its components, and all-cause death for overall population, the LEADER study supports the claim that Victoza reduces cardiovascular risk for the overall population studied in LEADER. I agree with this conclusion. Of note, in the Advisory Committee background materials and presentations the sponsor attempted to explain the US subgroup findings as a result of a difference in exposure to trial product, i.e. lower in the US vs. non-US; however, the Office of Biostatistics stated that there is insufficient evidence to support this point. The final conclusions of OB in this regard are pending at the time of this review. However, these additional considerations would not impact the overall benefit risk assessment and regulatory recommendation.

Table 14. Subgroup Analyses of MACE, CV Death, All-Cause Death

Group	Category	N	MACE HR (95% CI)	CV DEATH HR (95% CI)	ALL-CAUSE DEATH HR (95% CI)
Age	Under Age 60	2321	0.78 (0.62, 0.98)	0.60 (0.42, 0.87)	0.71 (0.52, 0.97)
	60 and Older	7019	0.90 (0.79, 1.02)	0.85 (0.69, 1.04)	0.89 (0.76, 1.04)
Sex	Female	3337	0.88 (0.72, 1.08)	0.81 (0.60, 1.10)	0.83 (0.66, 1.06)
	Male	6003	0.86 (0.76, 0.98)	0.77 (0.62, 0.95)	0.85 (0.72, 1.01)
Country	Outside US	6826	0.81 (0.71, 0.92)	0.70 (0.57, 0.86)	0.77 (0.65, 0.90)
	US	**2514**	**1.03 (0.84, 1.25)***	**1.04 (0.75, 1.46)**	**1.09 (0.84, 1.40)**
Race	White	7238	0.90 (0.80, 1.02)	0.84 (0.68, 1.03)	0.91 (0.77, 1.06)
	Black or African American	777	0.87 (0.59, 1.27)	0.78 (0.44, 1.39)	0.78 (0.50, 1.23)
	Asian	936	0.70 (0.46, 1.05)	0.60 (0.31, 1.16)	0.69 (0.42, 1.13)
	Other	389	0.60 (0.37, 1.00)	0.47 (0.23. 0.93)	0.49 (0.27, 0.89)
HbA1c	<= 8.3	4768	0.89 (0.76, 1.05)	0.86 (0.66, 1.13)	0.87 (0.71, 1.07)
	> 8.3%	4572	0.84 (0.72, 0.98)	0.71 (0.57, 0.91)	0.82 (0.68, 0.98)

Source: Statistical Reviewer's analysis
HR < 1.0 indicates treatment benefit of liraglutide
*p=0.048

The sponsor also performed a subgroup analysis based on the enrollment criteria 3a and 3b. 3a is the enrollment criterion requiring established CV disease and 3b is the criterion requiring CV risk factors (Refer to Table 1 above). The 3b subgroup had a HR of 1.20 [0.86; 1.67] 95% CI); with a test for interaction of *p*-value of 0.04. Approximately 19% of randomized patients were in this subgroup; and this subgroup accounted for only approximately 10% of first MACE events. These results were also discussed at the EMDAC meeting with committee members expressing some level of concern that the benefit may be only observed in higher risk patients. From a statistical standpoint, the Office of Biostatistics review states that these subgroup results could be due to chance. In other words, the test for interaction provides marginal evidence that there may be some quantitative but not qualitative difference in observed treatment effects for these subgroups and again concluded that weighed with the results of the primary MACE and its components, and all-cause death for overall population, the LEADER study supports the claim that Victoza reduces cardiovascular risk for the overall population studied in LEADER. Nevertheless, from a clinical standpoint, the data to support a CV benefit claim in 'at risk' patients, i.e. instead of those with established CV disease is insufficiently robust to recommend indicating liraglutide for these patients for CV risk reduction.

Additional endpoints

This section will focus on the traditional risk factors that contribute to CVD. Since the end of treatment visit could take place any time between 42 and 60 months the Sponsor

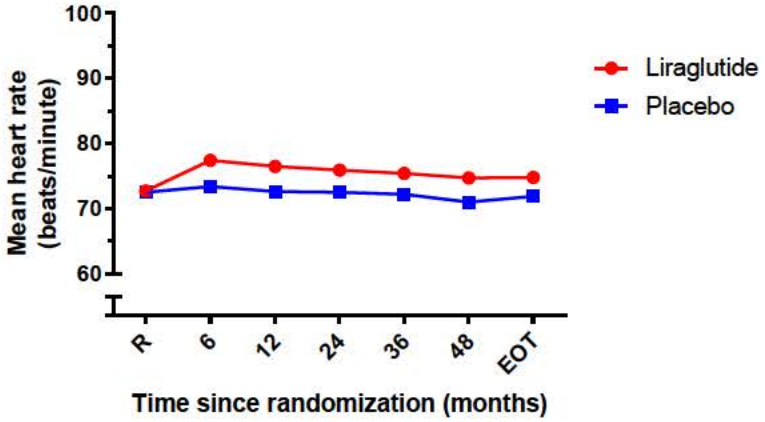
presented the results from change from baseline to 3 years (2 years for waist circumference) therefore presenting a fixed treatment period for all subjects.

Heart Rate

Liraglutide is labeled for having an increase from baseline in mean resting heart rate of 2-3 beats per minute compared to placebo. LEADER was looked upon to help elucidate the clinical implications, if any, on cardiovascular outcomes in patients with T2DM. The data shown below suggest that this increase in heart rate does not result in excess cardiovascular risk to patients. Whether or not the increase in heart rate is somewhat mitigating the cardioprotective effect of liraglutide is unknown.

Figure 9 shows the mean heart rate by visit in the trial. Both liraglutide and placebo had a similar baseline. After 6 months the mean heart rate increased for liraglutide and remained elevated as compared to placebo. In a pre-specified analysis of the change in heart rate from baseline to a 3 year assessment, the mean heart rate was statistically significantly higher in the liraglutide group compared to the placebo group (Lira-placebo treatment difference 2.98 beats/min [95% confidence interval 2.54;3.42] ; nominal $p<0.001$).

Figure 9. Mean heart rate by visit



Source: Dr. Condarco's review

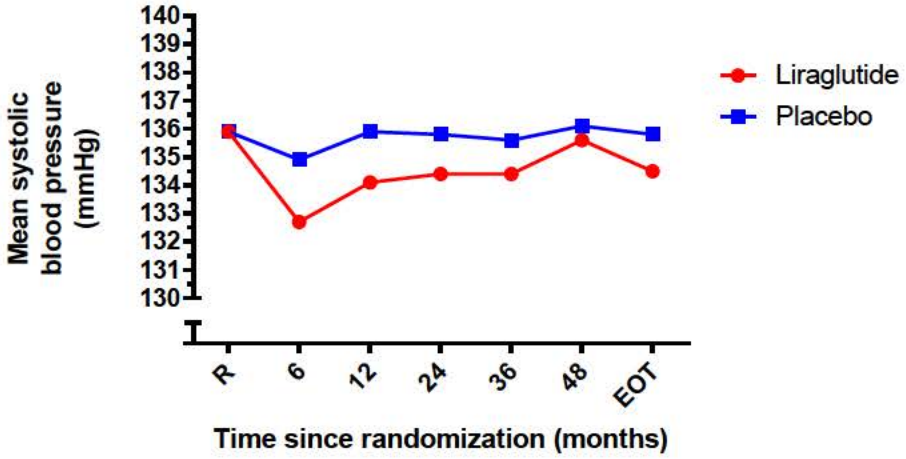
Blood Pressure

At baseline systolic and diastolic blood pressure was similar between treatment groups (mean systolic blood pressure 135.9 mmHg and diastolic blood pressure approximately 77 mmHg). Over 90% of subjects had a history of hypertension and over 90% of subjects were on antihypertensive therapy.

Figure 10 shows the mean systolic blood pressure over time. Liraglutide experienced a decrease in systolic blood pressure noted at month 6. Although the blood pressure

decrease varied throughout the trial, the systolic blood pressure remained lower for liraglutide than placebo for any point in the trial.

Figure 10. Mean systolic blood pressure by visit

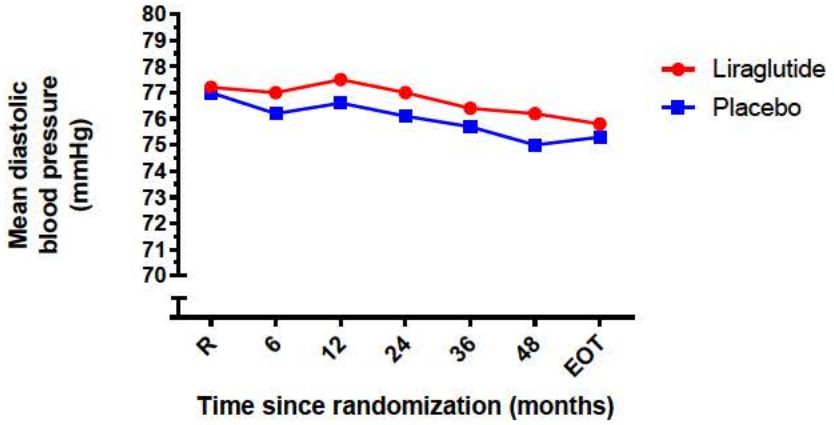


Source: Dr. Condarco's review

In an analysis of the change in systolic blood pressure from baseline to a 3 year assessment, the mean systolic blood pressure was lower in the liraglutide group (adjusted mean decrease -1.4 mmHg) compared to the placebo group (adjusted mean decrease -0.2 mmHg) with a liraglutide -placebo treatment difference of -1.199 mmHg [95% confidence interval -1.916;-0.483]; nominal p=0.001.

Estimated mean diastolic blood pressure over time is shown in Figure 11. Liraglutide and placebo had similar baseline values at randomization. Initially measures increased slightly for both groups until the first year, after which values decreased for both treatment arms. With the exception of the randomized visit, the measures for liraglutide diastolic blood pressure remained higher than placebo over time.

Figure 11. Mean diastolic blood pressure by visit



Source: Dr. Condarco's review

In an analysis of the change in diastolic blood pressure from baseline to a 3 year assessment, there was a smaller decrease in diastolic blood pressure with liraglutide (mean decrease of -0.8 mmHg) than placebo (mean decrease of -1.3 mmHg) with a Liraglutide -placebo treatment difference of +0.587 mmHg [95% confidence interval 0.187;0.987] ; nominal p=0.004.

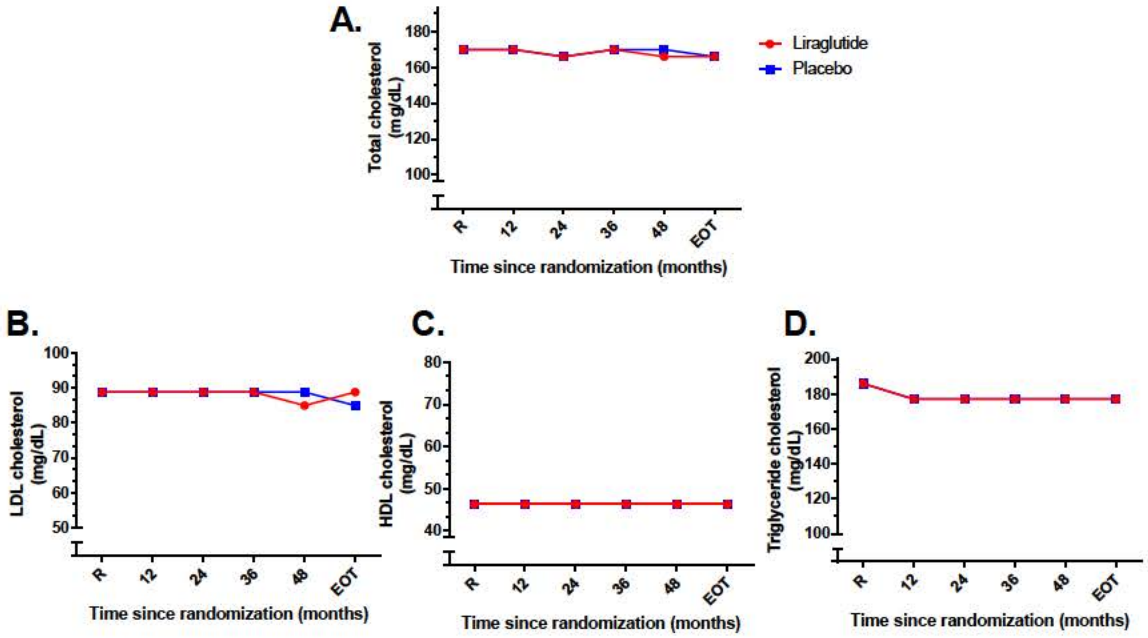
It is unknown to what extent the blood pressure effects of liraglutide contribute to its cardiovascular effect(s).

Lipids

Across lipid measures, including LDL, HDL, total cholesterol and triglycerides, values were similar between liraglutide and placebo (refer to Table 4). A similar proportion of subjects were using lipid lowering agents at baseline and a similar proportion of subjects started lipid lowering therapy after baseline (Table 5).

Figure 12 shows the mean lipid measures for liraglutide and placebo over time. Across different measures, there was no clear difference between treatment arms. Total, LDL and HDL cholesterol, tended to be stable from baseline; triglycerides decreased from baseline during the first year and remained stable for the remainder of the study.

Figure 12. Mean lipid measures over time, A: total cholesterol; B: LDL cholesterol, C: HDL cholesterol; D: triglycerides



Source: Dr. Condarco's review

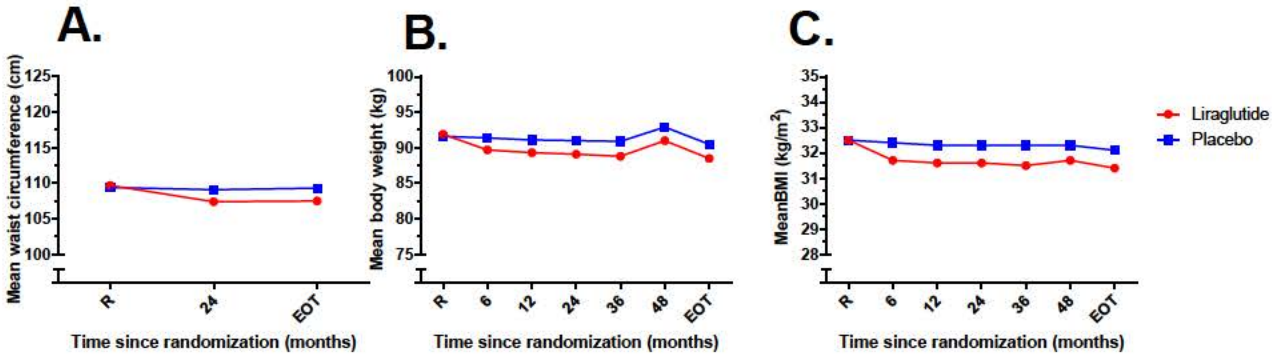
When compared to baseline, at 3 years, there was a mean adjusted decrease in total cholesterol for liraglutide (-1.3 mg/dL), and a small adjusted increase for placebo (+0.3 mg/dL); there was a mean adjusted increased in HDL for both liraglutide (+1.5 mg/dL) and placebo (+1.2 mg/dL); there was a mean adjusted decrease in LDL for liraglutide (-1.5 mg/dL) and a slight adjusted increase for placebo (0.1 mg/dL); there was a slight decrease in triglycerides for both liraglutide (-7.9 mg/dL) and placebo (-6.4 mg/dL).

These data suggest that the cardioprotective effects of liraglutide are not mediated through lipid improvements, which is not unexpected.

Body weight, BMI and waist circumference

Figure 13 shows the mean values over time for waist circumference, body weight and mean BMI. Overall, baseline values were similar between treatment groups. After randomization, liraglutide values tended to decrease and remain lower than placebo for body weight, BMI and waist circumference.

Figure 13. A: mean waist circumference over time; B: mean body weight over time; C: mean BMI over time.



Source: tables: see Dr. Condarco's review

Liraglutide subjects had an adjusted mean decrease in weight of -2.7 kg vs. -0.5 kg for placebo with a liraglutide-placebo difference of ~2.3 kg favoring liraglutide. Similarly, liraglutide had an adjusted mean decrease in BMI of -0.96 kg/m^2 vs. -0.16 kg/m^2 for placebo, with a liraglutide-placebo difference of~ 0.8 kg/m^2 favoring liraglutide.[18]

Changes in waist circumference also favored liraglutide. Liraglutide had an adjusted mean decrease in waist circumference of -2 cm compared to placebo which had a decrease of -0.02 cm. The liraglutide-placebo difference was ~2 cm favoring liraglutide compared to placebo.[19]

These liraglutide associated changes in body weight/body composition are not unexpected although the role of body weight change on the cardioprotective effect of liraglutide remains unknown; it should not necessarily be concluded that the CV outcomes data would apply to use of liraglutide for weight management.

HbA1c

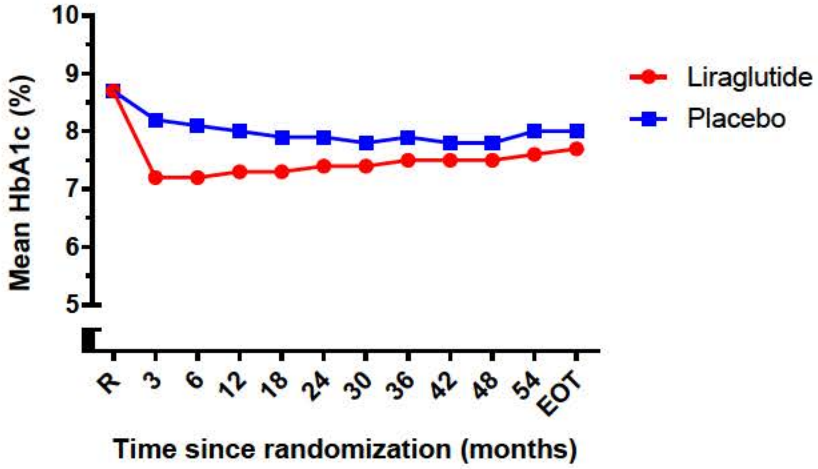
HbA1c was measured every 3 months for the first year and every 6 months subsequently. At baseline, HbA1c was the same between treatment groups, 8.7%. Figure 14 shows that after randomization, the HbA1c decreased for both treatment groups. At 3 months of treatment there was a larger HbA1c decrease for liraglutide than placebo. After 3 months of treatment, the HbA1c for placebo tended to remain somewhat stable; while HbA1c tended to increase over time for liraglutide. Despite the HbA1c increase seen after month 3, the HbA1c for liraglutide remained persistently lower than placebo throughout the trial.

[18] For body weight change, the liraglutide-placebo treatment difference was -2.264 kg [95% confidence interval -2.539; -1.99], nominal P<0.001, while the liraglutide-placebo treatment difference for BMI was -0.806 [95% confidence interval -0.903; -0.709], nominal P<0.001.

[19] For body waist circumference the liraglutide-placebo treatment difference was -1.984cm [95% confidence interval -2.298; -1.669], nominal P<0.001.

The change from baseline to month 36 for HbA1c was -1.2% for liraglutide and -0.8% for placebo-treated subjects. (liraglutide-placebo treatment difference -0.396 [95% confidence interval -0.453; -0.338]; nominal p<0.001).

Figure 14. Mean HbA1c by visit



Source: see Dr. Condarco's review

To what extent reduction in HbA1c contributed to the overall MACE findings is unknown.

Microvascular endpoints

The two prespecified microvascular endpoints included: time to randomization to first occurrence of a composite microvascular outcome and time from randomization to each individual component of the composite microvascular outcome for nephropathy and retinopathy outcomes separately; see Table 15.

Table 15. Microvascular disease was an adjudicated outcome with the following categories

Diabetic retinopathy • Need for retinal photocoagulation or treatment with intravitreal agents • Vitreous hemorrhage • Development of diabetes-related blindness
Nephropathy • New onset of persistent* macroalbuminuria • Persistent* doubling of serum creatinine level and eGFR per MDRD ≤ 45 mL/min/1.73m^2 • Need for continuous renal-replacement therapy (in the absence of an acute reversible cause) • Death due to renal disease
*Persistent was defined as requiring a confirmatory measurement within 12 weeks in the protocol; however the EAC charter did not specify any specific time point. Macroalbuminuria was defined as either a 24 hour urine collection above 300 mg, or as a ratio above 300 mg albumin/g creatinine in a spot sample

Capture of information regarding microvascular complications of diabetes at baseline was recorded in the CRF at Visit1. There was no pre-specified ophthalmological evaluation of subjects during the trial, i.e. the outcomes listed in Table 15 were based on spontaneous reporting. Nephropathy events were captured, in part, by regular measurement of creatinine and urine albumin as well as adverse event reporting.

Table 16 shows the results of the composite microvascular endpoint. In total 771 (8.3%) subjects experienced a first EAC confirmed microvascular event. Of these, 7.6% (355 subjects) were randomized to liraglutide and 8.9% (416 subjects) were randomized to placebo, and the overall composite endpoint numerically favored liraglutide over placebo. FDA notes that in the results of this trial, the frequency of renal events is much higher than the frequency of retinal events; the endpoint, therefore, is more a measure of an effect on the kidneys and not a complete picture of microvascular outcomes.
The retinopathy and nephropathy components of the microvascular endpoint were in opposition. With the exception of death due to renal disease, most of the first EAC confirmed nephropathy events favored liraglutide, while the first EAC confirmed retinopathy findings generally favored placebo.

Table 16. EAC confirmed microvascular events

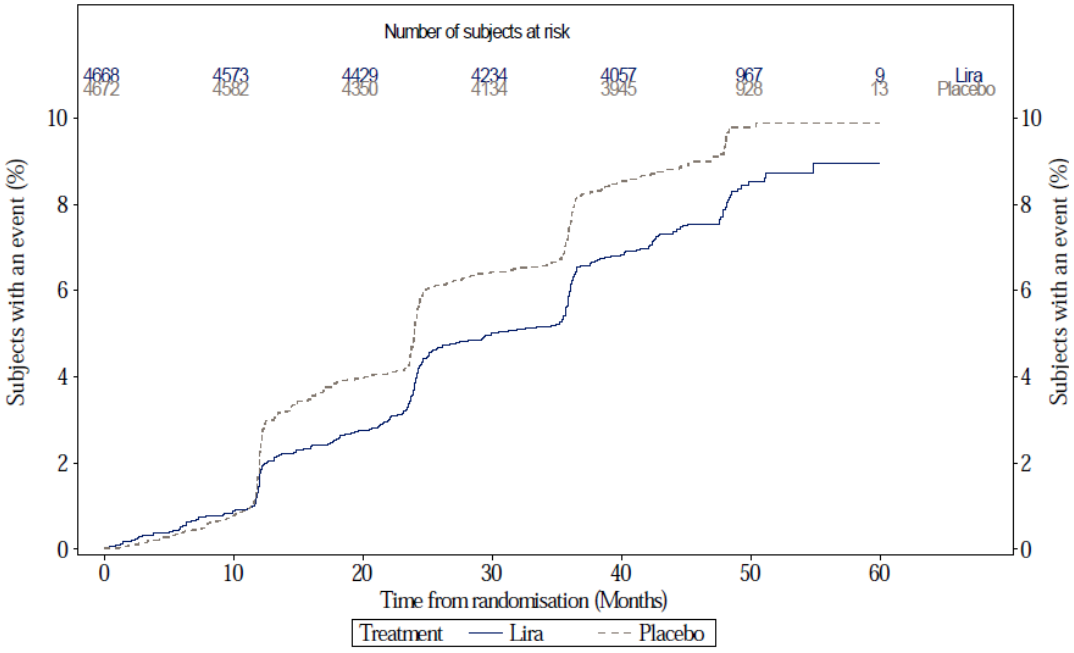
	Liraglutide			Placebo		
	N (%)	**E**	**R**	**N (%)**	**E**	**R**
FAS	4668			4672		
PYO	17822			17741		
EAC confirmed microvascular endpoint	355 (7.6)	355	1.99	416 (8.9)	416	2.34
EAC confirmed nephropathy	268 (5.7)	268	1.50	337 (7.2)	337	1.90
New onset of persistent macroalbuminuria	161 (3.4)	161	0.90	215 (4.6)	215	1.21
Persistent doubling of serum creatinine*	87 (1.9)	87	0.49	97 (2.1)	97	0.55
Need for continuous renal-replacement therapy	56 (1.2)	56	0.31	64 (1.4)	64	0.36
Death due to renal disease	8 (0.2)	8	0.04	5 (0.1)	5	0.03
EAC confirmed retinopathy	106 (2.3)	106	0.59	92 (2.0)	92	0.52
Treatment with photocoagulation or intravitreal agents	100 (2.1)	100	0.56	86 (1.8)	86	0.48
Development of diabetes-related blindness	0 (0.0)	0	0	1 (0.0)	1	0.01
Vitreous hemorrhage	32 (0.7)	32	0.18	22 (0.5)	22	0.12

*Persistent doubling of serum creatinine and eGFR<=45 ml/min/1.73 m^2 per MDRD
Source: modified CTR Table 11-11, page 246

The additional 61 microvascular cases in the placebo than the liraglutide group, resulted in a hazard ratio for time to first EAC-confirmed microvascular event of 0.84 [95% confidence interval; 0.73-0.969], nominal p=0.016.

In the Kaplan-Meier plot of EAC-confirmed first microvascular event over time (Figure 15), the risk of microvascular events appears lower for liraglutide than for placebo after approximately 10 months.

Figure 15. Kaplan-Meier plot- time to first EAC-confirmed microvascular event



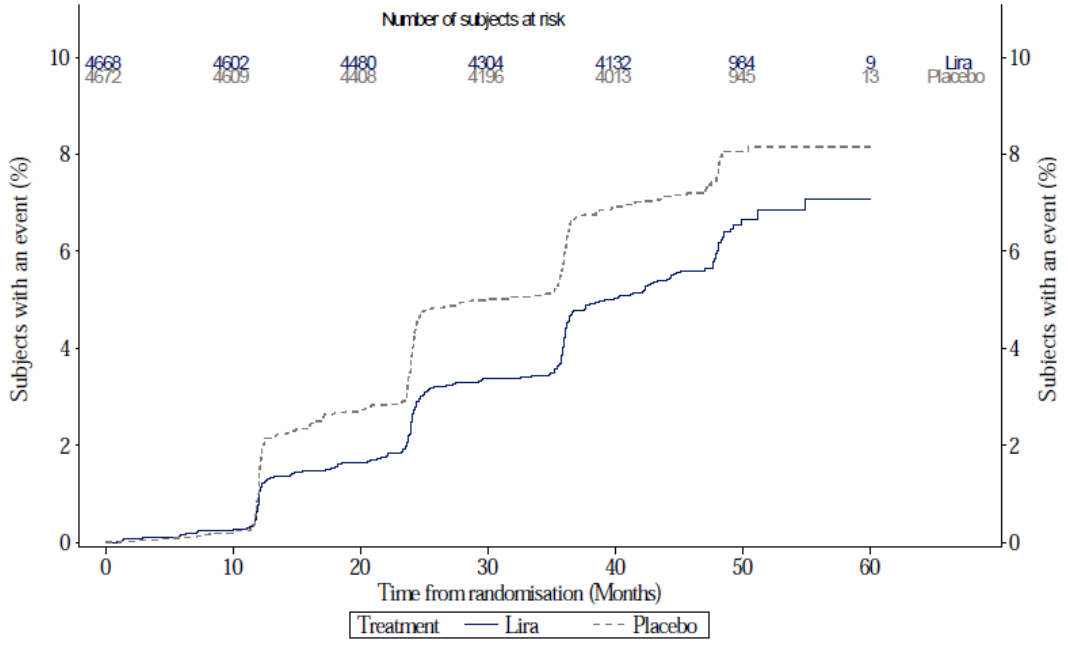
breviations: EAC: event adjudication committee; FAS: full analysis set; Lira: liraglutide.
Source: CSR Figure 11-12, page 248

Nephropathy endpoint

The nephropathy endpoint was composed of two laboratory based assessments (new onset of persistent urine albumin ≥300mg/g creatinine [macro-albuminuria], or persistent doubling of serum creatinine level and eGFR ≤ 45 mL/min/1.73 m^2 per MDRD) and two clinical assessments (need for continuous renal-replacement therapy in absence of acute reversible cause and death due to renal disease).

As shown previously in Table 16, the EAC confirmed nephropathy events tended to favor liraglutide over placebo, with the exception of death due to renal disease. The Kaplan-Meier plot in Figure 16 appears similar to the microvascular composite endpoint likely reflecting the relatively larger number of nephropathy (vs. retinopathy) events.

Figure 16. Kaplan-Meier plot of time to EAC-confirmed nephropathy



Abbreviations: EAC: event adjudication committee; FAS: full analysis set; Lira: liraglutide.
Source: CTR figure 11-13, page 249

The additional 69 EAC confirmed first nephropathy events in the placebo than the liraglutide group, resulted in a hazard ratio for time to first EAC-confirmed nephropathy event of 0.78 [95% confidence interval; 0.67-0.92], nominal p=0.003. This difference appears to be largely driven by EAC confirmed persistent macroalbuminuria events.

The clinical relevance of the findings for the nephropathy composite endpoint is uncertain. First, the composite was driven by laboratory test findings. Also, the effects of treatment on albuminuria may not reflect clinical outcomes in diabetic nephropathy, and therapies may have acute and reversible pharmacologic effects on albuminuria that may differ from the long-term effects on renal function and disease progression. LEADER specified a 'persistent change' in laboratory tests for the evaluation of the nephropathy endpoint as it is more likely to capture chronic, irreversible changes in renal function rather than acute, reversible changes. Whether this adequately captured diabetic nephropathy disease progression is unclear.

With regard to the clinical components of the nephropathy composite endpoint, one component of the endpoint in trials evaluating diabetic nephropathy that is commonly used is progression to end-stage disease, defined by initiation of chronic dialysis (i.e., dialysis that is ongoing after a specified period of time), renal transplant, or a sustained eGFR <15 mL/min/1.73m^2. In the LEADER trial, although the hemodialysis endpoint excludes acute reversible causes, there is no specified time period to define "chronic" dialysis.

Further, the EAC definitions for renal death did not provide adjudicators guidance on the identification of patients who died due to renal disease. The adjudication of "death due to renal disease" was based on the nephrologists' clinical judgment. Although there is no obvious definition of renal death, it is generally defined as a death occurring after a patient refuses or a physician withholds renal replacement therapy (i.e., initiation of chronic dialysis or renal transplantation) or in cases where dialysis is unavailable. The definition often excludes deaths due to another primary process and/or when another cause is adjudicated (e.g., sepsis, end-stage heart failure, malignancy). Given the complexity in this definition, FDA generally recommends that renal death be adjudicated with explicit rules for adjudication.

The trends in mean eGFR and creatinine appeared similar between treatment groups (Figure 24 in Summary of Clinical Safety).

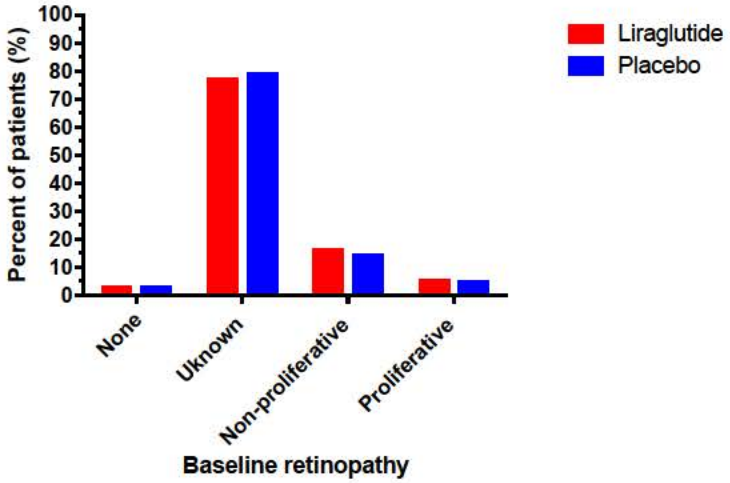
Retinopathy endpoint

'Retinopathy' (defined as a composite endpoint of: need for retinal photocoagulation or treatment with intravitreal agents, vitreous hemorrhage, and onset of diabetes related blindness -Snellen visual acuity of 20/200 [6/60] or less, or visual field of <20 degrees in the better eye with best correction) was a pre-specified, adjudicated, secondary endpoint; the results of analyses generally did not favor liraglutide. In the liraglutide group there was a higher number of patients who had photocoagulation or need for intravitreal agents and patients with vitreous hemorrhage. Of note, even though retinopathy events were adjudicated, there was no routine clinical funduscopic evaluation of subjects during the trial and events were captured only through spontaneous reporting. In addition, the Ophthalmology consultant had concerns about the reliability of the retinopathy-related outcomes in the protocol. Please refer to section titled: Summary of OPHTHALMOLOGY CONSULT: RETINOPATHY.

The retinopathy status of subjects at screening was based on information (medical history) entered in the eCRF by the investigators. As previously described, mean HbA1c at baseline was similar between treatments at 8.7%, reflecting that this was a relatively poorly controlled population with T2DM and with longstanding diabetes. Out of the 20.1% (21.0% in the liraglutide group and 19.2% in the placebo group) of all subjects who had diabetic retinopathy at screening 14.9% had non-proliferative retinopathy and 4.7% had proliferative retinopathy. No formal evaluation was made based on fundoscopy/fundosphotography to assess retinopathy at screening.

FDA notes that the lack of formal evaluations is problematic in trying to assess whether the groups were equal at baseline, although in a large randomized trial such as LEADER, this concern is less problematic. Over three-quarters of patients in either treatment arm had unknown baseline retinopathy status, while 2.5% of patients in either treatment arm had no retinopathy at screening; see Figure 17. Further, the absence of formal grading (readings of retinal fundus photography) of the level of retinopathy in this trial limits the ability to evaluate the effect of treatment intervention on ophthalmic endpoints.

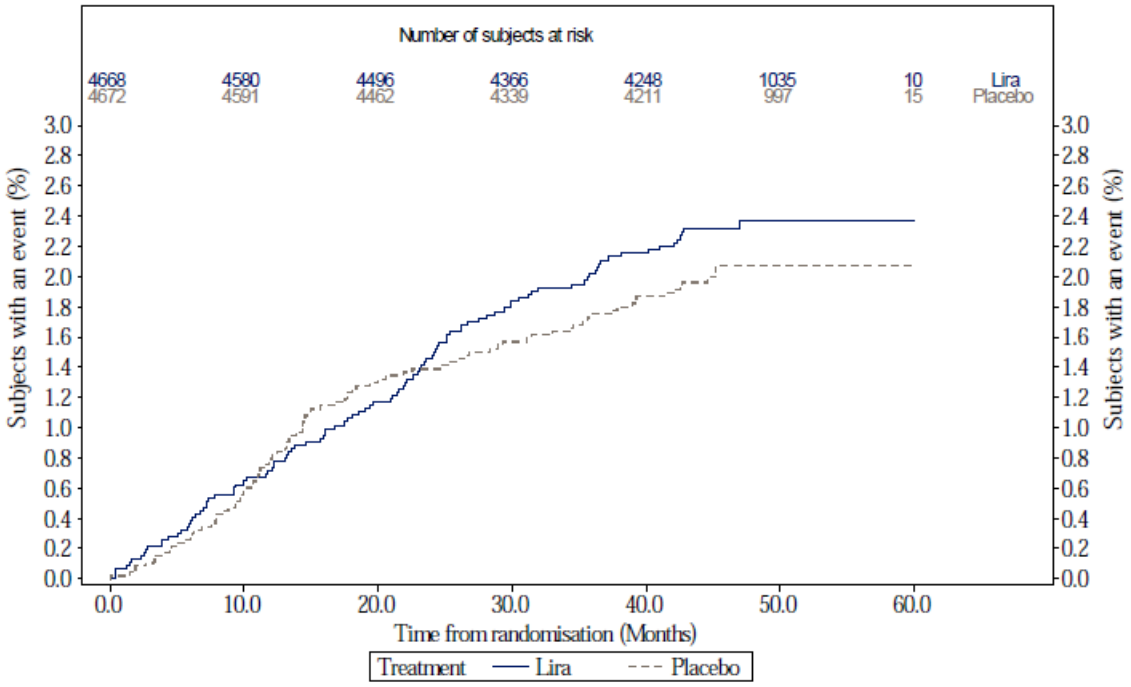
Figure 17. Baseline retinopathy status at screening



Source: CSR, Table 12-34, page 361

Figure 18 shows the time to first EAC confirmed retinopathy event. The percent of patients with a retinopathy event was higher for liraglutide until ~month 12 at which point the curves cross and the proportion of patients with a retinopathy event is lower for liraglutide than placebo until month 23-25, when the proportion of patients is again higher for liraglutide than placebo. The analysis of time to first EAC confirmed retinopathy event had a hazard ratio of 1.149 [95% confidence interval 0.869; 1.519], nominal P=0.33.

Figure 18. Kaplan-Meier plot of time to first EAC-confirmed retinopathy

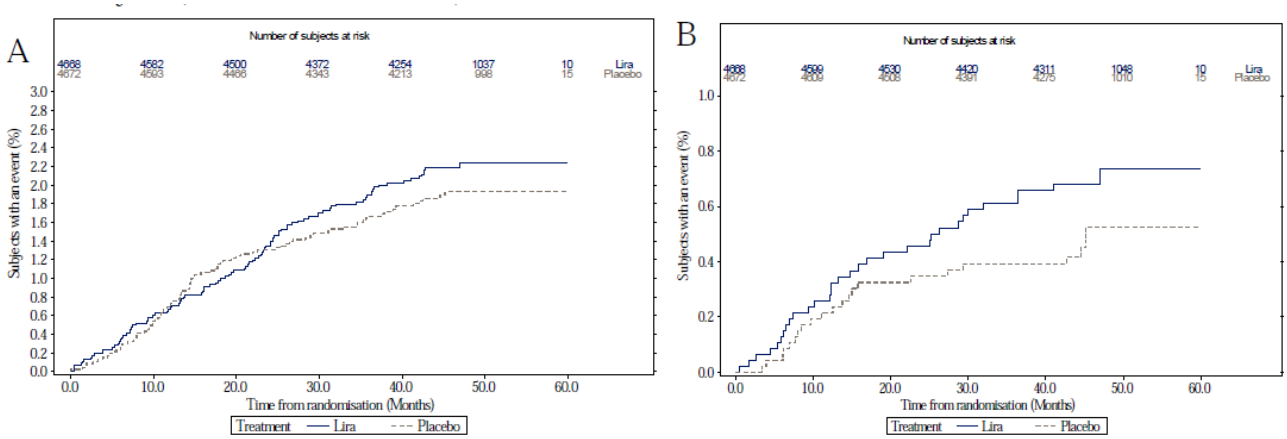


Abbreviation: EAC: event adjudication committee; FAS: full analysis set; Lira: liraglutide.
Source: CTR, figure 11-15, page 253

The analysis of individual retinopathy criteria is shown in Table 16. Overall there were numerical differences which were higher for liraglutide than placebo for the proportion of patient who had treatment with photocoagulation or intravitreal agents (2.1% vs. 1.8% respectively), and photocoagulation or intravitreal agents (0.7% vs. 0.5% respectively).

Figure 19 shows the time to first event of the individual retinopathy endpoint components (with the exception of diabetic related blindness, since there was only one event in the trial, in the placebo group).

Figure 19. Kaplan-Meier plots of retinopathy event types- A: time to first EAC confirmed treatment with photocoagulation or intravitreal agents. B: Time to first EAC-confirmed vitreous hemorrhage



Note: The y-axes are adjusted to the proportion of subjects with events for each of the individual endpoints.

Abbreviations: EAC: event adjudication committee; FAS: full analysis set; Lira: liraglutide.

Source: CTR, figure 11-16, page 254

FDA notes that "time to" events involving retinopathy, even when measured on an accepted retinopathy scale (i.e., ETDRS [Early Treatment Diabetic Retinopathy Study]) are problematic because rapid drops in Hemoglobin A1c (HbA1c) result in an increase in diabetic retinopathy during the first year in which the HbA1c decreased. See Ophthalmology Consult for further discussion.

CLINICAL SAFETY (NON-THYROID) SUMMARY

Dr. Julie Golden reviewed non-thyroid, non CV clinical safety of this sNDA. Please see her review for details. Recall that PMR 1589-3 stated that 'This trial must also assess adverse events of interest including the long-term effects of Victoza (liraglutide) injection on potential biomarkers of medullary thyroid carcinoma (e.g., serum calcitonin) as well as the long-term effects of Victoza (liraglutide) injection on pancreatitis, renal safety, serious hypoglycemia, immunologic reactions, and neoplasms.' This section summarizes the LEADER findings with regard to these safety issues.

Neoplasms

Neoplasms were included in the PMR because of a numeric imbalance in malignant neoplasms (no particular cell type) noted at the time of approval of Victoza. Although it was recognized that the LEADER study duration would not likely be adequate to definitively address long-latency safety issues such as malignancies, it was felt that important information could still be garnered from LEADER especially if collected in a rigorous manner. In LEADER all potential neoplasms were sent to the EAC for adjudication. The EAC classified neoplasms according to the organ affected/tissue of origin[20] and malignancy status.[21]

Neoplasms Overall

Table 17 shows EAC-confirmed overall neoplasm events. The estimated HR (liraglutide:placebo) for EAC-confirmed neoplasms in LEADER was 1.12 (95% CI 0.99, 1.28). For malignant neoplasms the HR was 1.06 (0.90, 1.25).

20 Prostate, breast, colon and rectum, urinary bladder, uterine, melanoma of the skin, skin (non-melanoma), thyroid, lymphoma, kidney and renal pelvis, oral cavity and pharynx, esophageal, leukemias, ovarian, pancreatic, gastric, hepatic/biliary, testicular, cervical/vaginal, bone-soft tissue, other-specify [EAC-confirmed neoplasm events categorized as tissue of origin 'other' were classified by the sponsor post database lock (i.e., unblinded) according to the organ system affected utilizing free text fields in the eCRF]
21 Benign, malignant, pre-malignant/carcinoma *in situ*/borderline, unclassified

Table 19. EAC-Confirmed Neoplasm Events, Including Thyroid Neoplasms

	Liraglutide			Placebo		
	N (%)	E	R	N (%)	E	R
Number of subjects	**4668**			**4672**		
PYO	**17822**			**17741**		
EAC-confirmed neoplasms (overall)	470 (10.1)	595	3.34	419 (9.0)	528	2.98
Malignant	296 (6.3)	356	2.00	279 (6.0)	326	1.84
Pre-malignant	37 (0.8)	40	0.22	26 (0.6)	30	0.17
Benign	168 (3.6)	196	1.10	145 (3.1)	171	0.96
Unclassified	3 (0.1)	3	0.02	1 (<0.1)	1	0.01

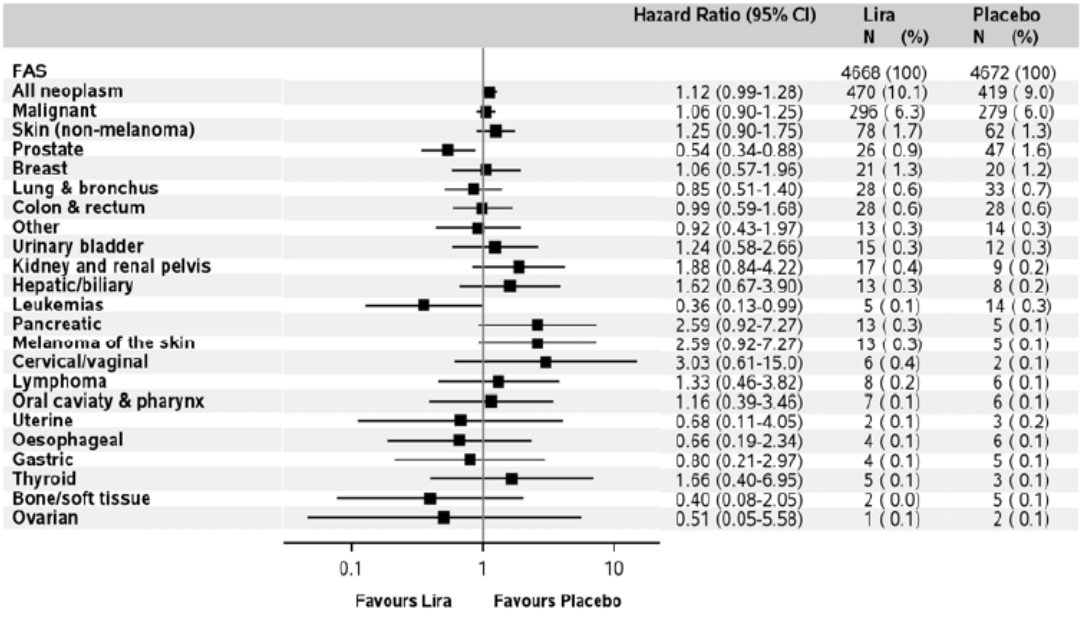
N: number of subjects; %: proportion of subjects; E: number of events; PYO: patient-years of observation; R: event rate per 100 observation years; EAC: event adjudication committee
Index events with EAC onset date from randomization date to follow-up are included
The index event is the event selected among multiple events if these were assessed and confirmed to be 1 and the same event

Source: Summary of Clinical Safety, Table 2-17

Malignant Neoplasms

The most frequently occurring EAC-confirmed malignant neoplasm in both treatment groups was malignant skin (non-melanoma) neoplasms. HRs for EAC-confirmed malignant neoplasms for which at least 1 event occurred in each treatment group are shown in Figure 20. Imbalances not in favor of liraglutide (5 events or more in the liraglutide group vs. placebo group) included malignant neoplasms of the hepatic/biliary system, kidney and renal pelvis, pancreas, and skin (melanoma and non-melanoma).

Figure 20. EAC-Confirmed Malignant Neoplasm Hazard Ratios by Tissue Type



FAS: full analysis set, CI: confidence interval.
%: proportion in percent of subjects with an event. N: number of subjects.
Hazard ratios are derived from the Cox model with treatment as only covariate.
Proportions are calculated based on number of female subjects for breast, cervical/vaginal, uterine and ovarian neoplasms, and based on number of male subjects for prostate neoplasms.

Source: LEADER CSR, Figure 14.3.1.131

Because of the emphasis placed on pathological diagnosis for confirmation by adjudication, the sponsor notes that the adjudication process for neoplasms may have high specificity but potentially may have reduced the sensitivity of the analysis. Therefore, additional supportive analyses of investigator-reported adverse events of malignant neoplasms were performed utilizing MedDRA searches. Based on these searches, a small number of malignant neoplasms were identified that were ultimately not confirmed by the EAC. See Dr. Golden's review for details.

Specific Tissue Types

Pancreas

Pancreatic safety is an ongoing area of interest with incretin based therapies (i.e., DPP-4 inhibitors and GLP-1 receptor agonists). A 2013 research publication reported on pancreatic cellular changes, including exocrine cell proliferation and dysplasia and α-cell hyperplasia, in a series of patients with diabetes who had been exposed to incretin based therapy (sitagliptin or exenatide) suggesting a potential link between these drugs and abnormal pancreatic exocrine or endocrine cell growth.[22] In response, FDA, in concert with the European Medicines Agency (EMA), performed a comprehensive review of all

22 Butler AE, et al. Marked expansion of exocrine and endocrine pancreas with incretin therapy in humans with increased exocrine pancreas dysplasia and the potential for glucagon-producing neuroendocrine tumors. Diabetes 2013; 62(7): 2595-604.

clinical, nonclinical and post-marketing data available for these therapies, and in a perspective published in 2014 concluded that the available data did not support a the presence of a causal relationship between these therapies and pancreatic toxicity or pancreatic cancer.[11] Nevertheless, pancreas safety with liraglutide remains an area of interest, and the LEADER trial, a large, long, randomized controlled trial, was to further inform this.

As was noted in Figure 20 and outlined further in Table 18, a numeric imbalance was observed in this trial for EAC-confirmed malignant pancreatic neoplasms [HR 2.59 (95% CI 0.92, 7.27)]. An additional neoplasm in the liraglutide group classified as pre-malignant was also EAC-confirmed. Dr. Golden's assessment of the pancreatic cancer data from LEADER follows. I agree with her conclusions.

Table 18. EAC-Confirmed Pancreatic Neoplasm Events

	Liraglutide			Placebo		
	N (%)	**E**	**R**	**N (%)**	**E**	**R**
Number of subjects	**4668**			**4672**		
PYO	**17822**			**17741**		
EAC-confirmed pancreatic neoplasms	15 (0.3)	16	0.09	7 (0.1)	7	0.04
Malignant	13 (0.3)	14	0.08	5 (0.1)	5	0.03
Pre-malignant	1 (<0.1)	1	0.01	0	0	0
Benign	1 (<0.1)	1	0.01	2 (<0.1)	2	0.01
Unclassified	0	0	0	0	0	0

N: number of subjects; %: proportion of subjects; E: number of events; PYO: patient-years of observation; R: event rate per 100 observation years; EAC: event adjudication committee
Index events with EAC onset date from randomization date to follow-up are included
The index event is the event selected among multiple events if these were assessed and confirmed to be 1 and the same event

Source: Summary of Clinical Safety, Table 2-19

In both treatment groups (Table 19), the majority of subjects with pancreatic neoplasm were male (liraglutide 71.4%; placebo: 80.0%). Subjects treated with liraglutide tended to be younger than those treated with placebo. More subjects treated with liraglutide vs. placebo with pancreatic cancer were previous or current smokers. One subject in the liraglutide group had a medical history of chronic pancreatitis (subject (b) (6). Information on family history of pancreatic cancer was limited: 7 subjects in the liraglutide group had no family history of pancreatic cancer; the rest of the information on family history (for both liraglutide- and placebo- treated subjects) was unavailable.

Table 19. Demographics and Baseline Characteristics, Subjects with EAC-Confirmed Malignant or Pre-Malignant Pancreatic Neoplasms

	Liraglutide N=14	**Placebo N=5**
Age group (yrs)		
< 65	6 (42.9)	1 (20.0)
65-74	8 (57.1)	2 (40.0)
75-84	0	2 (40.0)
≥ 85	0	0
Age (yrs)		
Mean (SD)	65.2 (4.1)	70.4 (6.2)
Median	65.5	70.0
Min, Max	59.0, 71.0	63.0, 78.0
Sex, female	4 (28.6)	1 (20.0)
Smoking status		
Current	3 (21.4)	1 (20.0)
Never	5 (35.7)	3 (60.0)
Previous	6 (42.9)	1 (20.0)
Race		
White	11 (78.6)	4 (80.0)
Black or African American	1 (7.1)	1 (20.0)
Asian	1 (7.1)	0
Other	1 (7.1)	0
Ethnicity, Hispanic or Latino	1 (7.1)	0
BMI, kg/m^2		
Mean (SD)	31.8 (4.5)	29.3 (2.5)
Median	30.8	29.3
Min, Max	23.6, 39.4	26.2, 32.8
Duration of Diabetes (yrs)		
Mean (SD)	12.8 (6.9)	9.8 (6.1)
Median	12.6	8.9
Min, Max	1.2, 23.7	4.7, 20.2

Source: ISS, Tables 7.3.13-7.3.15

In the liraglutide group, EAC-confirmed malignant pancreatic neoplasms were diagnosed in 5 subjects during year 1, in 4 subjects during year 2,[23] and in 5 subjects after year 2. In the placebo group, 2 subjects with events were diagnosed in year 1 and 3 in year 2; no additional EAC-confirmed malignant pancreatic neoplasms occurred after year 2.

Details of the EAC-confirmed pancreatic neoplasms are presented in

23 One subject, (b) (6) had two EAC-confirmed malignant pancreatic neoplasm events: one diagnosed in year 1 and one diagnosed in year 2 of the trial. This subject is discussed further later in this section.

Table 20; to summarize:

- The majority of events were ductal adenocarcinomas (liraglutide: 10 of 15 events; placebo: 5 of 5 events). In the liraglutide group, 3 events were categorized as 'Other' and in the remaining 2, information on histopathology was unknown.

- In the majority of cases, histological grade was unknown (liraglutide: 10 of 15 events; placebo: 4 of 5 events). The histological grade for the additional events in the liraglutide group were Grade 1 (1 event) or Grade 2 (3 events) and in the placebo group, the 1 event with known histological grade was Grade 3. One event in the liraglutide group was an intraductal papillary mucinous neoplasm (subject (b) (6) and was of moderate dysplasia. As this was not a pre-specified option in the assessment form, the external reviewer selected 'PanIN 1B' as histological grade for this event.

- The majority of events were stage IIA or higher (liraglutide: 12 of 15 events, placebo: 4 of 5 events). Seven events in the liraglutide group and 2 events in the placebo group were stage IV; of these, 4 events in the liraglutide group and 1 event in the placebo group were diagnosed less than 1.5 years into the trial. Staging was unknown for 2 events in the liraglutide group.

Table 20. Characteristics of EAC-Confirmed Pre-Malignant and Malignant Pancreatic Neoplasms

Pat ID/Age/Sex/Country EAC Malignancy Status	Study day	Histopathology	Grade	AJCC Staging			
				T	N	M	Stage
Liraglutide							
(b) (6) /64/M/GRC Malignant	765	Ductal adenocarcinoma	Unk	cT3	cN0	cM0	IIA
(b) (6) /63/F/GRC Malignant	374	Ductal adenocarcinoma	G2	pT3	pN1	cM0	IIB
(b) (6) /68/M/SRB Malignant	505	Unk	Unk	cT2	cN1	cM0	IIB
(b) (6) /70/M/NOR Malignant	278	Ductal adenocarcinoma	Unk	cT3	cN0	cM1	IV
(b) (6) 70/M/AUT Malignant	517	Ductal adenocarcinoma	Unk	cT3	cN1	cM1	IV
(b) (6) /71/M/KOR Malignant	1268	Ductal adenocarcinoma	G1	pT3	pN0	cM0	IIA
(b) (6) /59/F/BRA Malignant	162	Unk	Unk	cT3	cN0	cM1	IV

Pat ID/Age/Sex/Country EAC Malignancy Status	Study day	Histopathology	Grade	AJCC Staging			
				T	N	M	Stage
(b) (6) /60/F/RUS Malignant	936	Ductal adenocarcinoma	Unk	cT3	cN0	pM1	IV
(b) (6) /67/M/ISR Malignant	214	Ductal adenocarcinoma	G2	pT2	pN1	cM0	IIB
(b) (6) /60/M/TUR Malignant	1297	Ductal adenocarcinoma	Unk	cT2	cN0	cM1	IV
(b) (6) /66/F/USA Malignant	853	Ductal adenocarcinoma	Unk	cT4	cN1	cM1	IV
(b) (6) /69/M/USA Malignant	277	Ductal adenocarcinoma*	Unk	NA	NA	cM1	IV
	280	Ductal adenocarcinoma	Unk	NA	NA	cM1	IV
(b) (6) /61/M/USA Malignant	1	Other/1.8cm pancreatic mass however there is no cytology or pathology confirming an adenocarcinoma	Unk	NA	NA	NA	Unk
	589	Other/Cholangiocarcinoma There is a 3.4 cm liver mass with pathology confirming an adenocarcinoma	G2	NA	cN1	cM0	Unk/≥IIB
(b) (6) /65/M/USA Pre-Malignant/Carcinoma In Situ/Borderline	1415	Other/Intraductal papillary mucinous neoplasm (IPMN)	PanIN IB	pT0	pN0	cM0	0
Placebo							
(b) (6) /70/F/DEU	531	Ductal adenocarcinoma	Unk	cT1	cN0	cM1	IV
	531	Ductal adenocarcinoma*	Unk	cT1	cN0	cM1	IV
(b) (6) /75/M/DNK Malignant	525	Ductal adenocarcinoma	Unk	cT3	cN0	cM0	IIA
(b) (6) /66/M/SWE Malignant	43	Ductal adenocarcinoma	G3	pT3	pN0	cM0	IIA
(b) (6) /63/M/AUS Malignant	695	Ductal adenocarcinoma	Unk	cT3	cN0	cM1	IV
(b) (6) /78/M/USA Malignant	326	Ductal adenocarcinoma	Unk	cT1	cN0	cM0	IA
* Considered the index event in a multiple events review							

Source: ISS, Table 7.12.5

As described in the discussion of malignant neoplasms overall, a small imbalance of events ultimately not confirmed by the EAC within the HLGT 'Gastrointestinal neoplasms malignant and unspecified' was noted (i.e., 0 events in the liraglutide group and 5 in the placebo group; refer to **Error! Reference source not found.**). Therefore, a MedDRA search was also conducted to identify malignant pancreatic neoplasms (i.e.,

pancreatic neoplasms within the HLGT 'Gastrointestinal neoplasms malignant and unspecified') irrespective of their adjudication status by the EAC. This search, shown in Table 21, identified 11 events in the liraglutide group and 10 events in the placebo group.

Table 21. Investigator-Reported Malignant Pancreatic Neoplasms, MedDRA Search

	Liraglutide N=4668	Placebo N=4672
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	11 (0.2)	10 (0.2)
Gastrointestinal neoplasms malignant and unspecified	11 (0.2)	10 (0.2)
Adenocarcinoma pancreas	4 (0.1)	1 (<0.1)
Pancreatic carcinoma	4 (0.1)	7 (0.1)
Pancreatic carcinoma metastatic	2 (<0.1)	2 (<0.1)
Pancreatic carcinoma stage IV	1 (<0.1)	0

N: number of subjects; %: proportion of subjects
Sorted by system organ class, high level group term, and preferred term in alphabetical order

Source: LEADER CSR, Table 12-42

In the liraglutide group, all of the 11 events reported by the investigator captured by the MedDRA search (occurring in 11 subjects) were also confirmed by the EAC as being events of malignant pancreatic neoplasms (subjects (b) (6), (b) (6)). The MedDRA search did not capture 3 events in 2 subjects (subjects (b) (6)) in the liraglutide group that were also EAC-confirmed as pancreatic malignancy: the preferred terms were 'pancreatic neoplasm' (2 events) and 'lymphadenopathy' (1 event). Subject (b) (6) ('pancreatic neoplasm') is listed above in Table 20.

Subject (b) (6) is a more complex case and is described further: this subject had 2 EAC-confirmed malignant pancreatic neoplasms: one with onset on day 1 (before trial product was administered) and one with onset on day 586. In addition, the subject had one EAC-confirmed malignant hepatic or biliary neoplasm (intrahepatic cholangiocarcinoma) with onset on day 594. The table below describes the investigator-reported terms and study days and the EAC-assigned tissue and study days:

Table 22. EAC-Confirmed Malignant Neoplasm Events for Subject (b) (6)

AE#	Reported term/preferred term	EAC-assigned tissue of origin	Investigator onset date (study day)	EAC onset date (study day)
3	Stable 2cm hypodense lesion in the head of the pancreas/Pancreatic neoplasm	Pancreatic	09 Jun 2011 (study day 1)	09 Jun 2011 (study day 1)
4	Intrahepatic cholangiocarcinoma/ Cholangiocarcinoma	Hepatic/biliary	09 Jun 2011 (study day 1)	22 Jan 2013 (study day 594
5	Borderline, nonspecific enlarged peripancreatic lymph node/ Lymphadenopathy	Pancreatic	17 Jan 2013 (study day 589)	17 Jan 2013 (study day 589)

#: Number; AE: adverse event; EAC: event adjudication committee

Source: Response to FDA Request 08 Feb 2017, Table 1-1

A review of pathology reports provided in the EAC adjudication package noted that pancreatic biopsy did not show malignancy. Clinical notes from Oncology reported intrahepatic cholangiocarcinoma. Nevertheless, multiple EAC adjudicators confirmed 'malignant pancreatic neoplasm' in this subject.

In the placebo group, 5 events (occurring in 5 subjects) of the 10 events captured by the MedDRA search were *not confirmed* by the EAC as being events of malignant pancreatic neoplasms (subjects (b) (6) and (b) (6)). Of these, 1 event in subject (b) (6) was confirmed by the EAC as a malignant lymphoma. Table 23 below provides summaries of the 4 other subjects with investigator-reported events of malignant pancreatic neoplasms not confirmed by the EAC as malignant pancreatic neoplasms. The 4 subjects had investigator-reported adverse events of 'pancreatic carcinoma' (3 subjects) or 'pancreatic carcinoma metastatic' (1 subject). The outcome of all 4 cases was fatal; these cases were all EAC-confirmed (by the EAC cardiovascular subcommittee adjudicating deaths) as non-cardiovascular deaths with 'malignancy' or 'pancreatic cancer' assessed as plausible cause of death. In these cases, malignancies were diagnosed by imaging; tissue biopsy either was not done due to the terminal nature of the cancer or was not available. It is noted that 1 subject – (b) (6) – appeared to have symptoms of abdominal pain that started before trial screening. One subject was diagnosed in year 1 and 2 subjects after year 2.

Table 23. Summarized Details for Subjects with Investigator-Reported Adverse Events of Malignant Pancreatic Neoplasms Not Confirmed By the EAC Neoplasm Subcommittee[24]

Subject ID/ Age[a]/ Sex/ BMI/ Country/ Treatment	Preferred term	Study day/Duration (days)/Outcome/Death day	EAC confirmed (by EAC neoplasm committee)	Adjudication for death (by EAC cardiovascular committee)	
				EAC death day/EAC evaluation	Plausible cause of death (Adj 1/Adj 2)
(b) (6)/ 72/ F/ 28.8/ Romania/ Placebo	Pancreatic carcinoma	137/ 178/ Fatal/ 315	No	315/ Non-CV death	Malignancy/ Pancreatic Cancer
	Summary of details: *Subject:* Medical history includes T2DM, heart failure, symptomatic cardiac ischemia, hypertension, left ventricular hypertrophy, gallstone disease, hypercholesterolemia, and cholecystitis (chronic). *Event:* The subject presented with 4 month history of 20 kg weight loss, loss of appetite, nausea, asthenia, fatigue, abdominal pain, and hyperglycemia. Outcome fatal, details on disease progression not available. No autopsy was performed. Imaging: Abdominal echography and CT scan showed necrotizing lesion (47/48 mm) in uncinate process. Tumor markers CA 19-9 122.5 (ref range 0-39). Microscopic examination: No. Treatment of event: Subject denied surgery; recommendation for oncological follow-up (not further specified).				
(b) (6)/ 80/ M/ 25.8/ France/ Placebo	Pancreatic carcinoma metastatic	1248/ 32/ Fatal/ 1279	No	1279/ Non-CV death	Malignancy/ Pancreatic ca
	Summary of details: *Subject:* Medical history includes T2DM, vascular dementia, chronic renal failure, non-proliferative diabetic retinopathy, hypertension, peripheral arterial disease, dyslipidemia, prostate cancer, laryngotracheitis, and depression. Previous smoker. *Event:* The subject presented with abdominal pain that led to an abdominal ultrasound showing hepatic nodules and pancreas tissue damage. Outcome fatal, details on disease progression not available. No autopsy was performed. Imaging: CT scan showed a 44 mm tissue lesion at the level of the body of the pancreas and dilation of ductus (20 mm). Hypodense lesions of the hepatic parenchyma. Tumor markers: CA 19-9 21000 (ref. range not provided). CEA 18 (no units or ref. range). Microscopic examination: No. Treatment of event: Palliative; an opinion requested from onco-geriatricians recommends performing palliative treatment because of the alteration of the general condition and the demential syndrome that would not permit the subject to support chemotherapy.				
(b) (6)/ 67/ M/ 25.0/ Israel/ Placebo	Pancreatic carcinoma	20/ 448/ Fatal/ 467	No[b]	n/a[c]	n/a[c]
	Cardiac arrest	467/ 1/ Fatal/ 467	n/a	467/ Non-CV death	Malignancy/ pancreatic cA
	Summary of details: *Subject:* Medical history includes T2DM, hyperlipidemia, vitamin D deficiency, erectile dysfunction, abdominal pain, hypertension, and carotid artery stenosis. Previous smoker.				

24 All events occurred in the Placebo Group

	Event: The subject presented with worsening of abdominal pain that had existed prior to screening. Weight loss of about 17 kg over the past 5 months and intermittent constipation. Admitted to the hospital for symptoms worsening: lack of appetite, nausea and vomiting, abdominal pain, and rise in hepatic enzymes and bilirubin. Outcome fatal, details on disease progression are not available. There is no information about autopsy. Imaging: Abdominal US and CT scan showed lesion (exceeds 60 mm) in pancreas body with signs of local spread and pressure on the pancreas duct and distal dilation to the lesion. Metastases in the liver and lymphadenopathy. Tumor markers: Cancer signs, CEA, CA 19-9 (not further specified). Microscopic examination: No. Treatment of event: Apparently receiving chemotherapy for "neoplasm to the pancreas with metastases to the liver"; neoplasm not suitable for surgery.				
(b) (6) / 69/ F/ 41.8/ Turkey/ placebo	Pancreatic carcinoma	1079/ 34/ Fatal/ 1112	No	1112/ Non-CV death	Malignancy/pancreatic ca
	Summary of details: *Subject:* Medical history includes T2DM, hypertension, asthma, sleep apnea, hyperlipidemia, neuropathy, left ventricular hypertrophy, and gallstone disease. Never smoker. *Event:* The subject presented with indigestion and swelling, which led to further investigations. Outcome fatal, details on disease progression not available. Son reported that the cause of death was pancreas cancer. There is no information about autopsy. Imaging: PET scanning showed lesions (increased Ga-68 DOTATATE involvement) with heterogeneous borders in the head and body section of pancreas/extending into peripancreatic and paraaortocaval area (pancreatic NET?). Tumor markers: No. Microscopic examination: No. Treatment of event: No available information.				
Note: most information was taken from the sponsor's summary in the CSR; the reviewer filled in some details with source documentation in adjudication packages. Adj 1: adjudicator 1; adj 2: adjudicator 2; BMI: body mass index; CA 19-9: cancer antigen 19-9; CEA: carcinoembryonic antigen; EAC: event adjudication committee; F: female; M: male; n/a: not applicable; NET: neuroendocrine tumor; CV: cardiovascular; ref.: reference; T2DM: type 2 diabetes mellitus a Baseline value b Adj 2 originally adjudicated as pancreatic cancer, but changed determination due to lack of diagnostic pathology c Adjudication of fatal event based on other adverse event number					

Source: LEADER CSR, Table 12-43, and adjudication packages (some details)

Finally, a case of EAC-confirmed cholangiocarcinoma in a subject treated with liraglutide (patient (b) (6)) was discovered incidentally in a review of the narrative for the fatal acute gallstone disease events (see the Acute Gallstone Section of this review), with clinical information possibly suggestive for pancreatic cancer. This patient was noted to have a pancreatic mass and no pathology was available in the source documentation. This case is also described in the Oncology consult review (page 131).

In summary, although an imbalance was reported for subjects with EAC-confirmed malignant pancreatic neoplasm (liraglutide 13, placebo 5), there appears to be some uncertainty regarding the adjudicators' findings. One subject in the liraglutide group with EAC-confirmed 'malignant pancreatic neoplasm' also had cholangiocarcinoma and a confusing clinical history that was not clarified by source documentation, another liraglutide-treated subject with EAC-confirmed cholangiocarcinoma had clinical information potentially suggestive of pancreatic cancer, and 4 additional subjects in the placebo group potentially had fatal pancreatic cancer that could not be confirmed due to

lack of tissue for diagnosis. The reader is referred to the FDA Oncology consult review for further discussion and interpretation (page 131). The overall conclusion of both the Clinical reviewer and Oncology consultants is that the available data to date regarding liraglutide and pancreatic cancer do not seem to support a causal link. I agree with this conclusion.

Breast

Although breast cancer was not identified as a safety area of concern in the Victoza clinical development program, a numerical imbalance was observed in the phase 3 program that evaluated the 3 mg dose of liraglutide for chronic weight management (Saxenda). Upon the approval of Saxenda, postmarketing studies were required to assess the risk of breast cancer associated with liraglutide, including evaluation of data from the (at the time ongoing) LEADER trial.[25] Therefore, breast cancer was a safety area of interest for the review of sNDA 027. Please see Dr. Golden's review for details.

In summary, the numbers of breast cancer events in LEADER were small and balanced among treatment arms. Although these findings did not appear to suggest an increased risk of breast cancer associated with Victoza, limitations of this trial include a relatively short treatment duration for a breast cancer assessment.

Colon/Rectum

An imbalance in colorectal neoplasms was noted in the Saxenda development program; as reported in the Saxenda label. Therefore, colorectal cancer was a safety area of interest for the review of sNDA 027. Dr. Golden reviewed these in detail and found no concerning imbalance in events of colorectal cancer.

Skin

The incidences of EAC-confirmed malignant skin neoplasms – both non-melanoma and melanoma – were numerically higher in the liraglutide- vs. the placebo-treated groups. EAC-confirmed pre-malignant or malignant non-melanoma skin neoplasms were first reported shortly after randomization and occurred throughout the trial in both treatment groups. After month 4, there was a higher proportion of subjects with an event in the liraglutide group compared to the placebo group. EAC-confirmed pre-malignant or malignant melanoma events had onset shortly after randomization and occurred at comparable rates in the 2 treatment groups until around month 18 into the trial. After this time, events continued to accrue at a similar and constant rate in the liraglutide group, whereas, for the placebo group, only 2 additional events occurred. Overall rates were low [non-melanoma: liraglutide n=78 (1.7%), placebo n=62 (1.3%); melanoma: liraglutide

25 PMR 2802-7: To assess the risk of breast cancer associated with liraglutide in the LEADER (Liraglutide Effect and Action in Diabetes:Evalaution of Cardiovascular Outcome Results) cardiovascular outcomes trial. To assess this risk, collect information on baseline cancer risk and potential confounders for all identified cases of breast cancer in the trial, including (but not limited to) prior history of breast cancer, family history of breast cancer, BRCA1/BRCA2 status, age at menopause, history of radiation to the chest, age at menarche, and current/prior use of hormonal therapy.

n=13 (0.3%), placebo n=5 (0.1%)]. The overall clinical, temporal and numerical pattern of skin malignancies is not suggestive of a concerning safety signal.

Pancreatitis

As noted in the Warnings and Precautions section of the Victoza label, acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis, has been reported post-marketing in patients treated with Victoza,[26] and an imbalance in pancreatitis not in favor of liraglutide was noted in both Victoza and Saxenda (liraglutide for chronic weight management) clinical trials. Post-marketing reports of acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis, in GLP-1-based therapies have led to warnings regarding pancreatitis in drug labeling for the class. However, it should be noted that retrospective cohort studies have suggested an increased background risk of acute pancreatitis among individuals with type 2 diabetes (up to 1.5- to 3-fold).[27,28,29]

Adverse Events

According to the LEADER protocol, pancreatitis or acute severe and persistent abdominal pain leading to suspicion of pancreatitis was to be recorded as a MESI. Pancreatitis events were adjudicated by the EAC pancreatitis subcommittee, composed of 3 gastroenterologists.

The clinical evaluation of acute and chronic pancreatitis by the EAC was based on the criteria presented below. For a diagnosis of acute pancreatitis to be fulfilled, 2 of the 3 diagnostic criteria were to be present. Severity was based on the revised Atlanta criteria.[30,31] For a diagnosis of chronic pancreatitis to be fulfilled, the first of the 3 criteria (i.e., characteristic imaging findings) and at least 1 of the other 2 remaining criteria were to be present.

26 This is a class-labeling warning for all incretin-based therapies.
27 Girman, CJ, et al. Patients with type 2 diabetes mellitus have higher risk for acute pancreatitis compared with those without diabetes. Diabetes Obes Metabol. 2010;12:766-71.
28 Lai, SW, et al. Risk of acute pancreatitis in type 2 diabetes and risk reduction on anti-diabetic drugs: a population-based cohort study in Taiwan. Am J Gastroenterol. 2011;106:1697-704.
29 Noel, RA, et al. Increased risk of acute pancreatitis and biliary disease observed in patients with type 2 diabetes: a retrospective cohort study. Diabetes Care. 2009;32:834-8.
30 Banks PA, et al. Classification of acute pancreatitis – 2012: revision of the Atlanta classification and definitions by international consensus. Gut. 2013; 62(1): 102-11.
31 Mild acute pancreatitis: no organ failure and no local or systemic complications; moderately severe acute pancreatitis: organ failure that resolves within 48 h (transient organ failure) and/or local or systemic complications without persistent organ failure; severe acute pancreatitis: persistent organ failure (>48 h) (single/multiple organs)

Table 24. EAC Evaluation of Pancreatitis

Event type	Adjudication outcome
Pancreatitis	Acute pancreatitis Y/N • Severe acute upper abdominal pain • Elevated levels of pancreatic enzymes (lipase, amylase) 3xULN • Characteristic imaging finding (ultrasound, CT, MRI)
	Severity • Mild acute pancreatitis • Moderately severe acute pancreatitis • Severe acute pancreatitis • Unable to distinguish between moderately severe and severe acute pancreatitis • Unable to assess severity
	Chronic pancreatitis Y/N • Characteristic imaging finding (ultrasound, CT, MRI) • Abnormal pancreatic function tests • Characteristic histological findings
CT: computed tomography; EAC: event adjudication committee; MRI: magnetic resonance imaging; N: no; ULN: upper limit of normal; Y: yes	

Source: LEADER CSR, Table 9-7

In this trial, a total of 141 potential pancreatitis events were sent for adjudication, of which 52 non-duplicate events in 43 subjects were confirmed by the EAC. A similar proportion of subjects in both treatment groups experienced EAC-confirmed events of pancreatitis (Table 25).

Table 25. EAC-Confirmed Pancreatitis Events

	Liraglutide		Placebo	
	N=4668 n (%)	PYO=17822 Events (Rate/100 PY)	N=4672 n (%)	PYO=17735 Events (Rate/100 PY)
EAC-confirmed pancreatitis	18 (0.4)	19 (0.11)	25 (0.5)	33 (0.19)
Acute	18 (0.4)	19 (0.11)	23 (0.5)	31 (0.17)
Chronic	0	0	2 (<0.1)	2 (0.01)

Source: LEADER CSR, Table 12-48

An analysis of time to first EAC-confirmed acute pancreatitis event estimated the HR for liraglutide vs. placebo as 0.78 (95% CI 0.42, 1.44).

Dr. Golden's extensive review of the pancreatitis data follows. I agree with her assessment.

A similar proportion of pancreatitis events in both treatment groups were associated with presence of gallstones at the time of the event (Table 26). This information was obtained from a *post hoc* review of the individual case narratives by the sponsor where presence of gallstone disease at the time of the event was defined either by imaging or by ALT ≥3×ULN (in case imaging was not available). Gallbladder disorders are discussed further in the subsection below. An additional summary of baseline factors in subjects with and

without EAC-confirmed acute pancreatitis is shown in Table 27. A higher proportion of subjects with events of acute pancreatitis in the placebo group had a history of pancreatitis, biliary disease, or hypercalcemia at baseline compared to those subjects treated with liraglutide.

Table 26. Overview of EAC-Confirmed Pancreatitis Cases

	Liraglutide		Placebo	
	N (%)	E	N (%)	E
Total Subjects/Events	18 (100)	19	25 (100)	33
Presence of gallstones at time of event*				
Yes	7 (38.9)	7	11 (44.0)	14
Gallstones confirmed by imaging	6 (33.3)	6	8 (32.0)	9
Imaging suggestive of acute gallstone disease	0	0	2 (8.0)	3
ALT ≥ 3x ULN	1 (5.6)	1	1 (4.0)	2
No	12 (66.7)	12	15 (60.0)	19
Information not available	0	0	0	0
Medical history of gallstone disease/cholecystitis**				
Yes	2 (11.1)	2	6 (24.0)	7
Gallstone disease	1 (5.6)	1	5 (20.0)	6
Cholecystitis	1 (5.6)	1	5 (20.0)	6
No	16 (88.9)	17	19 (76.0)	26
Medical history of pancreatitis**				
Yes	2 (11.1)	2	6 (24.0)	7
No	16 (88.9)	17	19 (76.0)	26
Alcohol use*				
Current	1 (5.6)	1	1 (4.0)	1
Previous	0	0	1 (4.0)	1
No	4 (22.2)	4	3 (12.0)	4
Information not available	13 (72.2)	14	20 (80.0)	27
Treatment*				
None, observation	1 (5.6)	1	4 (16.0)	4
Standard	14 (77.8)	14	19 (76.0)	26
Intensive	1 (5.6)	1	0	0
Other	3 (16.7)	3	3 (12.0)	3

N: number of subjects, E: number of events, ULN: upper limit of normal
* Based on *post hoc* review of the individual case narratives by the sponsor
** Based on data from the clinical database
ALT ≥ 3x ULN includes events with elevated ALT ≥ 3x ULN, for which imaging was either not performed, was inconclusive, or did not show signs of acute gallstone disease

Source: Summary of Clinical Safety, Table 2-29

Table 27. Baseline Risk Factors for EAC-Confirmed Acute Pancreatitis

	Subjects with acute pancreatitis		All subjects	
	Liraglutide N (%)	**Placebo N (%)**	**Liraglutide N (%)**	**Placebo N (%)**
Number of subjects	18 (100.0)	23 (100.0)	4668 (100.0)	4672 (100.0)
History of pancreatitis acute/chronic	2 (11.1)	6 (26.1)	147 (3.1)	120 (2.6)
History of biliary disease	2 (11.1)	6 (26.1)	730 (15.6)	689 (14.7)
BMI at baseline ≥ 30-<35 kg/m^2	8 (44.4)	8 (34.8)	1523 (32.6)	1470 (31.5)
BMI at baseline ≥ 35 kg/m^2	6 (33.3)	7 (30.4)	1424 (30.5)	1398 (29.9)
Hypertriglyceridemia at baseline	9 (50.0)	10 (43.5)	2323 (49.8)	2288 (49.0)
Hypercalcemia at baseline	1 (5.6)	4 (17.4)	211 (4.5)	201 (4.3)
Smoker at baseline	3 (16.7)	3 (13.0)	567 (12.1)	563 (12.1)

N: number of subjects; %: percentage of subjects; EAC: event adjudication committee
Medical history of pancreatitis and biliary disease are reported in specific forms in the CRF
Hypertriglyceridemia at baseline is determined as a baseline triglyceride measurement above upper normal limit
Hypercalcemia at baseline is determined as a baseline calcium measurement above upper normal limit

Source: LEADER CSR, Table 12-50

The EAC confirmed acute pancreatitis with the diagnostic criterion of 'severe acute abdominal pain' in 95% of liraglutide events and 100% of placebo events, with 'elevated blood levels of pancreatic enzymes' in 68% of liraglutide events and 87% of placebo events, and with 'characteristic imaging finding' in 58% of liraglutide events and 55% of placebo events.

The majority of acute pancreatitis events were classified by the EAC as mild (17/19, 89.5% liraglutide events and 26/31, 83.9% placebo events). No liraglutide events and 4 (12.9%) placebo events were adjudicated as moderately severe. Three events were considered severe: 2 events in subjects treated with liraglutide (10.5%) and 1 event in a subject treated with placebo (3.2%). In addition, 1 event of EAC-confirmed pancreatitis – in a subject treated with placebo (subject (b) (6) – had a fatal outcome.

There were more subjects with investigator-reported events of acute and chronic pancreatitis events *not* confirmed by the EAC in the liraglutide group than placebo group. Table 28 outlines the MedDRA preferred terms reported by the investigator that were and were not ultimately confirmed by the EAC. In particular, there were more subjects with AEs of 'pancreatitis', 'pancreatitis acute', and 'pancreatitis chronic' not confirmed as pancreatitis by the EAC in the liraglutide group.

Table 28. Subjects with Adverse Events Submitted to the EAC Pancreatitis Subcommittee as Investigator-Reported by Preferred Term

	Liraglutide N=4668	Placebo N=4672
EAC-Confirmed	18 (0.4)	25 (0.5)
Pancreatitis acute	9 (0.2)	15 (0.3)
Pancreatitis	9 (0.2)	9 (0.2)
Pancreatitis chronic	1 (<0.1)	2 (<0.1)
Pancreatitis relapsing	1 (<0.1)	1 (<0.1)
Abdominal pain	0	1 (<0.1)
Lipase increased	0	1 (<0.1)
No AE recorded	1 (<0.1)	0
EAC Not Confirmed	53 (1.1)	21 (0.4)
Pancreatitis	14 (0.3)	5 (0.1)
Pancreatitis acute	9 (0.2)	4 (0.1)
Pancreatitis chronic	9 (0.2)	3 (0.1)
Lipase increased	6 (0.1)	1 (<0.1)
Abdominal pain	4 (0.1)	2 (<0.1)
Amylase increased	4 (0.1)	1 (<0.1)
Abdominal pain upper	3 (0.1)	0
Chronic gastritis	1 (<0.1)	2 (<0.1)
Cholecystitis	1 (<0.1)	0
Gastroenteritis viral	1 (<0.1)	0
Pancreatic atrophy	1 (<0.1)	0
Pancreatic enzymes increased	1 (<0.1)	0
Cholecystitis chronic	0	1 (<0.1)
Edematous pancreatitis	0	1 (<0.1)
Pancreatic cyst	0	1 (<0.1)
No AE recorded	5 (0.1)	4 (0.1)

Source: Response to FDA request Apr 21, 2017

The sponsor also provided an assessment of pancreatitis events not confirmed by the EAC by diagnostic criteria (acute, Table 29; chronic, Table 30):

Table 29. Summary of Acute Pancreatitis Events Not Confirmed by the EAC

	Liraglutide		Placebo	
	N (%)	E	N (%)	E
Non-confirmed acute pancreatitis*	43 (100)	50	19 (100)	21
Diagnostic criteria fulfilled*				
• Severe acute upper abdominal pain and elevated blood levels of pancreatic enzymes ≥3xULN	0	0	1 (5.3)	1
• Severe acute abdominal pain only	5 (11.6)	6	2 (10.5)	2
• Elevated blood levels of pancreatic enzymes ≥3xULN only	20 (46.5)	23	7 (36.8)	9
• Characteristic imaging only#	1 (2.3)	1	1 (5.3)	1
• No diagnostic criteria fulfilled	18 (41.9)	20	8 (42.1)	8
Number of diagnostic parameters with information available				
0	3 (7.0)	3	0 (0.0)	0
1	4 (9.3)	4	1 (5.3)	1
2	16 (37.2)	17	7 (36.8)	8
3	23 (53.5)	26	11 (57.9)	12
Reason for investigation*				
• Abdominal pain	18 (41.9)	20	14 (73.7)	14
• Elevated pancreatic enzymes	16 (37.2)	20	5 (26.3)	7
• Incidental imaging finding	1 (2.3)	1	0 (0.0)	0
• Abdominal pain and elevated pancreatic enzymes	3 (7.0)	3	0 (0.0)	0
• Other	3 (7.0)	3	0 (0.0)	0
• Information not available	3 (7.0)	3	0 (0.0)	0

* Based on sponsor review of documents in the source document package, available to the EAC
# Characteristic imaging: US, CT, or MRI
Diagnostic criteria for acute pancreatitis: any 2 of the following 3 criteria of severe acute upper abdominal pain, elevated blood levels of pancreatic enzymes (lipase/amylase) ≥ 3x ULN, characteristic imaging finding (US, CT, MRI)
EAC: event adjudication committee; ULN: upper limit of normal; US: ultrasound; CT: computed tomography; MRI: magnetic resonance imaging
Events included in the table were categorized by the sponsor as 'acute pancreatitis' based on available clinical information in the source document package available to the EAC (i.e., related to diagnostic criteria) indicating presence of an acute element in the course of the disease under investigation

Source: ISS, Table 7.4.10

Table 30. Summary of Chronic Pancreatitis Events Not Confirmed by the EAC

	Liraglutide		Placebo	
	N (%)	E	N (%)	E
Non-confirmed chronic pancreatitis*	11 (100.0)	11	4 (100.0)	5
Diagnostic criteria fulfilled*#				
• Characteristic imaging only	8 (72.7)	8	4 (100.0)	5
• Abnormal pancreatic function tests only	0 (0.0)	0	0 (0.0)	0
• Characteristic histological finding and abnormal pancreatic function tests only	0 (0.0)	0	0 (0.0)	0
• Characteristic histological finding only	0 (0.0)	0	0 (0.0)	0
• No diagnostic criteria fulfilled	3 (27.3)	3	0 (0.0)	0
Number of diagnostic parameters with information available				
0	0 (0.0)	0	0 (0.0)	0
1	11 (100.0)	11	4 (100.0)	5
2	0 (0.0)	0	0 (0.0)	0
3	0 (0.0)	0	0 (0.0)	0
Reason for investigation*				
• Abdominal pain	5 (45.5)	5	2 (50.0)	3
• Elevated pancreatic enzymes	3 (27.3)	3	1 (25.0)	1
• Incidental imaging finding	3 (27.3)	3	1 (25.0)	1
• Abdominal pain and elevated pancreatic enzymes	0 (0.0)	0	0 (0.0)	0
• Other	0 (0.0)	0	0 (0.0)	0

* Based on available clinical information in source document packages provided to the EAC for the individual events
# Diagnostic criteria for chronic pancreatitis: characteristic imaging finding (US, CT, MRI) with abndomral pancreatic function tests or characteristic histological findings
EAC: event adjudication committee; ULN: upper limit of normal; US: ultrasound; CT: computed tomography; MRI: magnetic resonance imaging
Events included in the table were categorized by the sponsor as 'chronic pancreatitis' based on available clinical information in the source document package available to the EAC (i.e., related to diagnostic criteria) indicating no presence of an acute element in the course of the disease under investigation

Source: ISS, Table 7.4.11

Dr. Golden notes that although events were not confirmed due to not meeting diagnostic criteria, a substantial number of events did not have a full panel of diagnostic parameters with information available in order to make a determination.

An exploratory analysis[32] of investigator-reported pancreatitis (irrespective of adjudication status) using a MedDRA search for terms that include 'pancreatitis'[33] resulted in 46 subjects (1.0%) treated with liraglutide and 34 (0.7%) treated with placebo with reported events.

Dr. Golden concluded that although pancreatitis was not EAC-confirmed more frequently with liraglutide in this trial, it was notable there were more subjects with investigator-

32 Conducted by Dr. Golden
33 Terms found in the search: 'edematous pancreatitis', 'pancreatitis', 'pancreatitis acute', 'pancreatitis chronic', and pancreatitis relapsing'

reported events of pancreatitis *not* confirmed by the EAC in the liraglutide group vs. the placebo group. Events not confirmed by the EAC did not meet strict pre-defined diagnostic criteria (for example, in some cases only an increase in pancreatic enzymes – which can be associated with liraglutide treatment – was observed). However, as approximately half the events not confirmed by the EAC did not have full diagnostic information available, it is possible that liraglutide-associated pancreatitis was not fully characterized in this trial by the adjudication procedure. I agree with her assessment.

Overall, the data from LEADER are not sufficiently definitive to exonerate liraglutide as a cause of pancreatitis, and currently labeling in section the Warnings and Precautions section should remain. With regard to the current Limitation of Use (LOU) for patients with a known history of pancreatitis, i.e. that liraglutide has not been studied in this condition LEADER enrolled some subjects with a history of pancreatitis thus supporting removal of this LOU. While LEADER results suggest that a history of pancreatitis does not appear to notably contribute to the risk of acute pancreatitis events, it is reasonable to retain the lack of clarity on this issue in labeling (move to section 5) given the concerns noted here about the adjudication process.

Acute Gallstone Disease

The association of liraglutide and gallstone-related disorders, including cholelithiasis and cholecystitis, was first described in the Saxenda phase 3 program, and acute gallbladder disease has been included in the Warnings and Precautions section of the Saxenda label. Although obesity and weight loss are associated with an increased risk for gallstone formation, gallstones were associated with Saxenda at least partially independent of weight loss, raising the possibility that liraglutide may have direct gallbladder effects.

In the LEADER trial, AEs of acute gallstone disease were collected and recorded as MESIs, although they were not adjudicated by the EAC. The specific event that was to be considered MESI by the investigator was 'acute gallstone disease (biliary colic or acute cholecystitis)'. Events of acute gallstone disease were identified via a MedDRA search using pre-specified standardized MedDRA queries (SMQs).

If a subject had an event of gallstones (perhaps diagnosed incidentally) but this event was not considered by the investigator to be serious or an acute gallstone MESI, it would not be recorded in the sponsor's analyses of acute gallstone disease. There were a number of AEs identified that were not captured in the sponsor's search because they were not considered SAEs or MESIs. Gallbladder-related AEs (according to the MedDRA search) regardless of SAE/MESI status were reviewed; this analysis did not change the overall assessment of gallstone events and summary data are not shown.

In the LEADER trial, SAEs and non-serious MESIs of "acute gallstone disease" were observed more frequently in the liraglutide group than in the placebo group (Table 31 and Figure 21). 4 subjects with acute gallstone disease events had a fatal outcome, 3 in the liraglutide group and 1 in the placebo group.

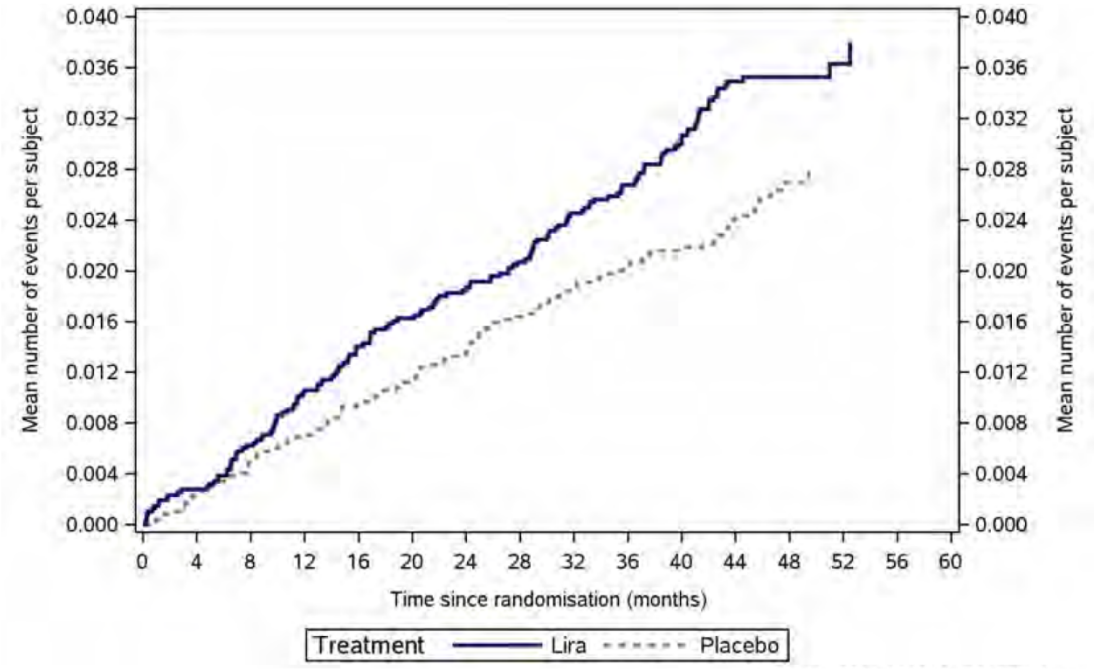
Table 31. Acute Gallstone Disease SAEs and Non-Serious MESIs

	Liraglutide			Placebo		
	N (%)	E	R	N (%)	E	R
Number of subjects	4668			4672		
PYO	17822			17741		
Events	145 (3.1)	160	0.90	90 (1.9)	115	0.65

N: number of subjects; %: proportion of subjects; E: number of events; PYO: patient-years of observation; R: event rate per 100 patient-years of observation; MESI: medical event of special interest as reported by the investigator; SAE: serious adverse event

Source: LEADER CSR, Table 12-51

Figure 21. Acute Gallstone Disease, Event Rate Over Time



Source: Summary of Clinical Safety, Figure 2-32

Overall, the proportion of subjects with baseline risk factors for gallbladder disease was similar between the 2 treatment groups; subjects on placebo who had an event were slightly more likely to have had a history of biliary disease at baseline than those on liraglutide with an event, and subjects without an event.

Although there were several subjects with large amounts of weight loss, particularly in the liraglutide group, there was not a clear relationship between degree or rapidity of weight loss and development of a gallstone-related AE. Across all weight loss cut-offs,

liraglutide was associated with a greater risk of AEs, potentially suggesting a weight-loss independent etiology.

These data suggest that use of liraglutide as Victoza (i.e. not just as Saxenda) carries a risk of acute gallbladder disease; this information should be added to product labeling in Section 6: Adverse Reactions.

Hypoglycemia

As with all glucose-lowering drugs, hypoglycemia is a safety concern of interest. However, for liraglutide assessment of 'serious' hypoglycemia was part of the PMR because of an imbalance in such events in the original development program. These events appeared to be primary related to concomitant use of drugs known to cause hypoglycemia, e.g. sulfonylureas and insulin.

In the LEADER trial, subjects were provided with glucometers and blood glucose was always to be measured when there was suspicion of a hypoglycemic episode. All plasma glucose values < 70 mg/dL and values > 70 mg/dL when hypoglycemic symptoms had occurred were recorded by the subjects in diaries. A dedicated 'Hypoglycemia Form' collected information on hypoglycemia in the trial, based on information transcribed from subject diaries.

Hypoglycemia episodes were defined according to the American Diabetes Association (ADA) classification[34]. An additional sponsor definition – plasma glucose of 56 mg/dL with or without symptoms of hypoglycemia – was used to identify subjects with 'minor' hypoglycemic episodes.

The term 'confirmed hypoglycemia' was used when a subject had an episode that met the definition of severe hypoglycemia (an episode requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions) and/or an episode of 'minor' hypoglycemia.

Hypoglycemia episodes are presented in Table 32. As shown below, the rate of hypoglycemia occurrences, and in particular, the rates of and proportions of subjects with 'confirmed', 'severe', and 'documented' symptomatic hypoglycemia episodes were slightly less in the liraglutide group as compared with those in the placebo group.

34 Workgroup on Hypoglycemia, American Diabetes Association. Defining and reporting hypoglycemia in diabetes: a report from the American Diabetes Association Workgroup on Hypoglycemia. Diabetes Care. 2005;28(5):1245-9.

Table 32. Hypoglycemia Episodes by Classification

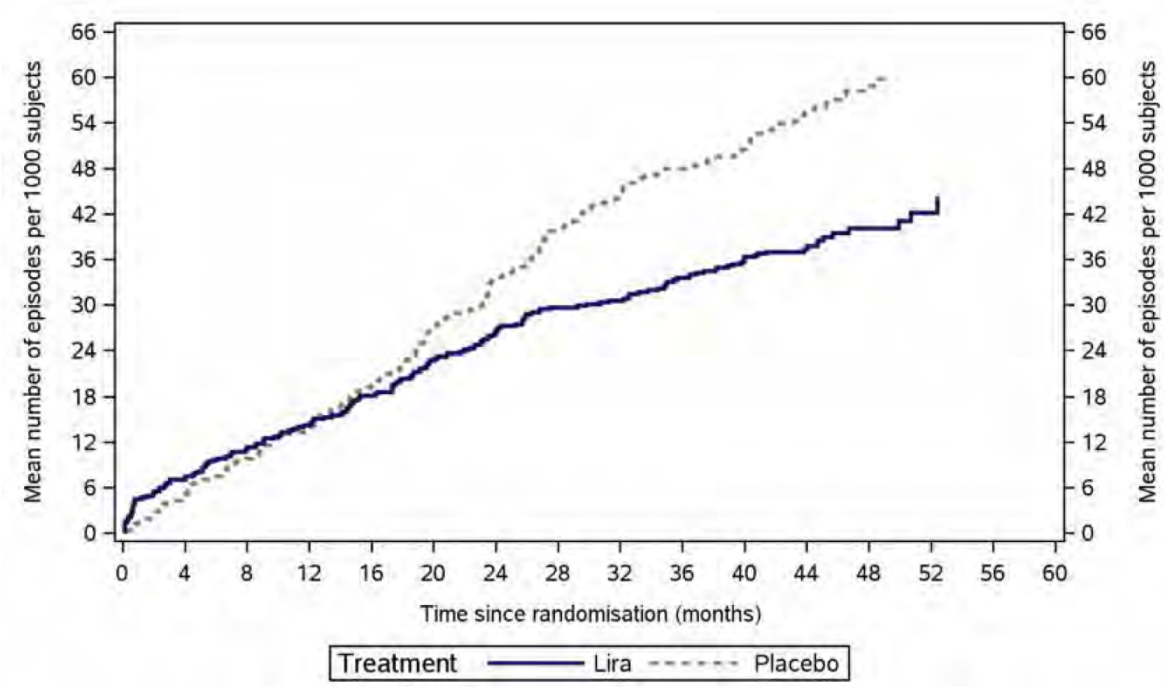
	Liraglutide			Placebo		
	N (%)	E	R	N (%)	E	R
Number of subjects	4668			4672		
PYO	17341			17282		
Hypoglycemic episodes						
Confirmed	2039 (43.68)	12177	70.2	2130 (45.59)	15756	91.2
ADA	3262 (69.88)	53438	308.2	3177 (68.00)	61937	358.4
Severe	114 (2.44)	178	1.0	153 (3.27)	255	1.5
Documented symptomatic	2409 (51.61)	26514	152.9	2431 (52.03)	34322	198.6
Asymptomatic	2479 (53.11)	25131	144.9	2360 (50.51)	25823	149.4
Probable symptomatic	148 (3.17)	300	1.7	148 (3.17)	259	1.5
Relative	433 (9.28)	1315	7.6	429 (9.18)	1278	7.4

N: number of subjects; %: proportion of subjects; E: number of events; PYO: patient-years of observation; R: event rate per 100 patient-years of observation; ADA: American Diabetes Association
Hypoglycemic episodes on and after randomization date and up to visit 15 are included (episodes with a missing date are included)

Source: SCS, Table 2-34

Figure 22 shows the mean number of severe hypoglycemic episodes per 1000 subjects during the trial. After approximately 16 months, the curves begin to separate in favor of liraglutide, although it is noted that there appears to be a small increase of severe hypoglycemia in the liraglutide arm vs. placebo in the first few months of the trial.

Figure 22. Severe Hypoglycemia, Mean Number of Episodes



Source: LEADER CSR, Figure 12-40

Severe and confirmed hypoglycemia episodes were primarily seen in subjects treated with insulin, sulfonylurea (SU)/glinides or a combination of these at baseline (i.e., 90% of subjects with severe hypoglycemia in either treatment group were on insulin and/or SU/glinides at baseline), see Table 33.

Table 33. Documented Symptomatic Hypoglycemia According to Use of Anti-Diabetes Medications at Baseline

	Liraglutide	**Placebo**
N	**4668**	**4672**
Insulin	**1272**	**1334**
SU/glinides	**1604**	**1566**
Insulin and SU/glinides	**766**	**797**
Not on insulin or SU/glinides	**1026**	**975**
Severe episodes	114 (2.4)	153 (3.3)
Insulin	54 (4.3)	68 (5.1)
SU/glinides	27 (1.7)	34 (2.2)
Insulin and SU glinides	22 (2.9)	36 (4.5)
Not on insulin or SU/glinides	11 (1.1)	15 (1.5)
Confirmed episodes	2039 (43.7)	2130 (45.6)
Insulin	658 (51.7)	770 (57.7)
SU/glinides	679 (42.3)	659 (42.1)
Insulin and SU glinides	450 (58.8)	443 (55.6)
Not on insulin or SU/glinides	252 (24.6)	258 (26.5)

N: number of subjects; %: proportion of subjects; SU: sulfonylurea

Source: SCS, Table 2-35

As outlined in the efficacy summary, anti-diabetes medications were generally well-balanced among randomized groups at baseline (Table 4), while more patients on placebo began using anti-diabetes medications, particularly insulin, during the trial (Table 5). The greater initiation of insulin and SU/glinides in the placebo group during the trial (and/or potentially lower doses used in the liraglutide arm) likely explains the lower rate of hypoglycemia in the liraglutide treatment arm. Overall, the results of LEADER are reassuring that liraglutide is not causing an excess of hypoglycemia compared to standard of care and allays the concern which prompted the PMR requirement.

Renal Safety

Liraglutide is not known to be nephrotoxic. However, it is likely that dehydration (due to GLP-1 associated nausea, vomiting and diarrhea) may lead to acute kidney injury in some cases. The Victoza label describes renal failure associated with liraglutide use as follows:

There have been postmarketing reports of acute renal failure and worsening of chronic renal failure, which may sometimes require hemodialysis in VICTOZA-treated patients. Some of these events were reported in patients without known underlying renal disease. A

majority of the reported events occurred in patients who had experienced nausea, vomiting, diarrhea, or dehydration.

In LEADER, the sponsor undertook an efficacy evaluation of a composite microvascular endpoint that included nephropathy (and retinopathy) components, utilizing a microvascular EAC subcommittee to adjudicate events.

The following summary of acute renal failure events utilized the SAE and MESI preferred terms within the MedDRA 'Acute renal failure' SMQ (Table 34). Overall (not shown in the table), the most frequently reported events were acute kidney injury (2.4% vs. 2.1%), proteinuria (1.4% vs. 2.0%), renal failure (0.5% vs. 0.8%), and renal impairment (0.4% vs. 0.3%) in the liraglutide and placebo groups, respectively.

Table 34. Investigator-Reported Acute Renal Failure by MedDRA Search

	Liraglutide N=4668	**Placebo N=4672**
'Acute renal failure' SMQ SAE or non-SAE MESI	234 (5.0)	262 (5.6)
Fatal	18 (0.4)	14 (0.3)
Acute kidney injury	10 (0.2)	8 (0.2)
Renal failure	4 (0.1)	6 (0.1)
Azotemia	1 (<0.1)	0
Blood creatinine increased	1 (<0.1)	0
Nephritis	1 (<0.1)	0
Renal impairment	1 (<0.1)	0
Tubulointerstitial nephritis	0	1 (<0.1)
SAE (fatal and non-fatal)	151 (3.2)	146 (3.1)
Acute kidney injury	108 (2.3)	94 (2.0)
Renal failure	20 (0.4)	31 (0.7)
Renal impairment	14 (0.3)	10 (0.2)
Blood creatinine increased	6 (0.1)	3 (0.1)
Azotemia	3 (0.1)	2 (<0.1)
Proteinuria	2 (<0.1)	3 (0.1)
Renal tubular necrosis	1 (<0.1)	5 (0.1)
Tubulointerstitial nephritis	1 (<0.1)	3 (0.1)
Nephropathy toxic	1 (<0.1)	2 (<0.1)
Acute prerenal failure	1 (<0.1)	1 (<0.1)
Blood urea increased	1 (<0.1)	1 (<0.1)
Glomerular filtration rate decreased	1 (<0.1)	0
Nephritis	1 (<0.1)	0
Product withdrawn permanently	22 (0.5)	28 (0.6)

Source: ISS, Appendix 7.6, Tables 7.6.53 and 7.6.74, and reviewer created from LEADER datasets

Renal events with a fatal outcome are identified differently than the adjudicated non-cardiovascular deaths categorized *post hoc* as renal, because any number of investigator-reported AEs may be considered as contributing to a subject's death. In the analysis

above utilizing the MedDRA SMQ, similar proportions of subjects in the liraglutide and placebo groups had fatal events of acute kidney injury or renal failure. Likewise, SAEs of acute kidney injury and renal failure were similarly distributed, with greater SAEs of acute kidney injury in the liraglutide group and greater SAEs of renal failure in the placebo group. The liraglutide group was associated with an increased incidence of renal impairment, blood creatinine increased, and azotemia.

Fatal renal events (identified by the above search of investigator-reported events) in subjects who were treated with liraglutide were reviewed. Most deaths reported as acute renal failure leading to death were renal complications of other conditions. In the 4 subjects categorized by the EAC *post hoc* as 'renal' deaths ((b) (6), and (b) (6), subjects developed a worsening of renal function while in the trial prior to the fatal event. In addition to these 4 subjects with EAC-confirmed renal death, 7 liraglutide-treated subjects were identified as EAC-confirmed non-CV renal deaths (as noted in Table **13**, a total of 11 subjects in the liraglutide group and 5 subjects in the placebo group died due to EAC-confirmed renal causes according to the *post hoc* classification). Most EAC-confirmed 'renal' deaths were related to worsening of chronic renal failure. There were no clear cases of liraglutide causing GI volume losses (i.e., vomiting, diarrhea) that contributed to fatal renal failure in the trial.

An analysis was conducted of acute renal failure SAEs and non-serious MESIs according to baseline renal impairment. The following table, which includes a tabulation of events overall and for the 4 most frequent preferred terms, demonstrates that although 'acute renal failure' events were seen slightly less frequently in liraglutide subjects in all categories of baseline renal impairment, in subjects with normal, mild, and moderate impairment, this favorable trend appears to be driven by events of proteinuria. In subjects with severe renal impairment, the slight trend is driven by fewer 'renal failure' events in the liraglutide group, although the numbers are small.

Table 35. Acute Renal Failure SMQ SAEs/MESIs by Baseline Renal Impairment Category

	Normal Renal Function		Mild Renal Impairment		Moderate Renal Impairment		Severe Renal Impairment	
	Lira N=1620	Placebo N=1655	Lira N=1932	Placebo N=1975	Lira N=999	Placebo N=935	Lira N=405	Placebo N=366
Total	34 (2.1)	45 (2.7)	78 (4.0)	86 (4.4)	100 (10.0)	108 (11.6)	22 (18.8)	23 (21.5)
Acute kidney injury	16 (1.0)	10 (0.6)	36 (1.9)	31 (1.6)	49 (4.9)	49 (5.2)	10 (8.5)	9 (8.4)
Proteinuria	12 (0.7)	31 (1.9)	24 (1.2)	35 (1.8)	25 (2.5)	27 (2.9)	3 (2.6)	2 (1.9)
Renal impairment	2 (0.1)	1 (0.1)	7 (0.4)	2 (0.1)	6 (0.6)	8 (0.9)	5 (4.3)	4 (3.7)
Renal failure	2 (0.1)	1 (0.1)	6 (0.3)	7 (0.4)	14 (1.4)	22 (2.4)	3 (2.6)	8 (7.5)
Lira: liraglutide								

Source: ISS, Appendix 7.6, Tables 7.6.58, 7.6.62, 7.6.66, and 7.6.70

Renal Laboratory Parameters

Serum creatinine and estimated glomerular filtration rate (eGFR) were reviewed for renal safety. The shift table indicates that a similar proportion of subjects in each treatment group shifted from low or normal baseline creatinine to high creatinine by the end of treatment (Table 36).

Table 36. Serum Creatinine Shift Table, Baseline to End of Treatment

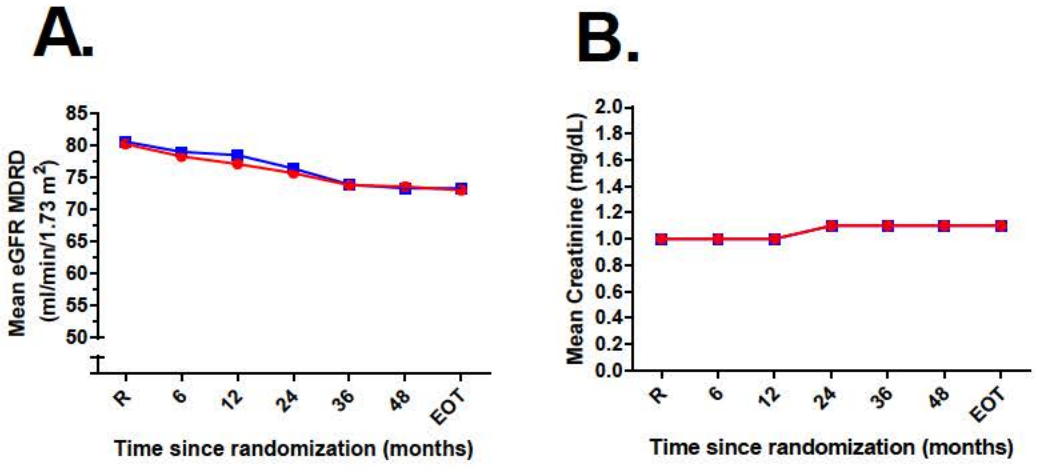
	Liraglutide Baseline			Placebo Baseline		
Visit 15 (Month 60)	**Low**	**Normal**	**High**	**Low**	**Normal**	**High**
Low	53 (1.1)	44 (0.9)	3 (0.1)	60 (1.3)	50 (1.1)	1 (<0.1)
Normal	135 (2.9)	2102 (45.0)	107 (2.3)	110 (2.4)	2056 (44.0)	97 (2.1)
High	2 (<0.1)	479 (10.3)	786 (16.8)	3 (0.1)	508 (10.9)	679 (14.5)
Missing	52 (1.1)	582 (12.5)	323 (4.9)	56 (1.2)	677 (14.5)	375 (8.0)

Source: LEADER CSR, Table 14.3.5.41

Estimated GFR (eGFR) values (Figure 23) were similar at baseline and the values decreased throughout the trial in both treatment groups. An analysis of mean changes in eGFR by baseline renal function did not show a trend for eGFR worsening among the groups with baseline renal impairment. Serum creatinine over time was also similar between treatment groups. An analysis of mean changes in serum creatinine by baseline renal function did not show a trend for creatinine worsening among the groups with baseline renal impairment.

Figure 24. A: mean eGFR MDRD over time, B: mean serum creatinine over time

(red=liraglutide; blue=placebo)



Source: Dr. Condarco's figure

In summary, a review of renal laboratory data does not suggest a worsening of renal function with liraglutide overall or by baseline renal insufficiency. Investigator-reported acute renal failure SAEs/MESIs were similar between groups. Although the liraglutide group was associated with fewer AEs of proteinuria, the clinical significance of this is unclear (see discussion in the Efficacy Summary, Nephropathy endpoint, page 53). An imbalance in renal deaths (as categorized by the EAC) not in favor of liraglutide was noted; these events generally reflected a worsening of chronic renal insufficiency. Overall, the results of LEADER do not change the known benefit risk assessment with regard to renal function, i.e. LEADER does not clearly demonstrate a benefit with regard to diabetic nephropathy nor does it suggest any worsening renal safety signal.

Immunogenicity

As liraglutide is a peptide product, there is potential risk for immunogenicity, including antibody formation and hypersensitivity reactions.

In the LEADER trial, immunogenicity events suspected by the investigator to be related to trial product were to be recorded as MESIs. Immunogenicity events were not adjudicated by the EAC and the evaluation is based on predefined MedDRA searches of SAEs and non-serious MESIs for events of allergic reaction, injection site reaction, and immune complex disease.

Table 37. Terms Included in the MedDRA Search for Immunogenicity Events

Included SMQs and HLTs
Allergic reactions
SMQ Anaphylactic reaction (narrow terms only)
SMQ Anaphylactic/anaphylactoid shock conditions (narrow terms only)
SMQ Angioedema (narrow terms only)
SMQ Severe cutaneous adverse reactions (narrow terms only)
SMQ Hypersensitivity (narrow terms only)
Immune complex disease
Immune complex disease (broad search):
SMQ Systemic lupus erythematosus (broad and narrow terms)
SMQ Vasculitis (broad and narrow terms)
SMQ Guillain-Barre syndrome (narrow terms only)
Immune complex disease (narrow search):
SMQ Systemic lupus erythematosus (narrow terms only)
SMQ Vasculitis (narrow terms only)
SMQ Guillain-Barre syndrome (narrow terms only)
HLT: high level term; SMQ: standardized MedDRA query; NEC: not elsewhere classified

Injection site reactions were part of the predefined search but not discussed in this review
Source: LEADER CSR, Table 9-12

Blood samples for determination of anti-liraglutide antibodies were drawn at randomization, at 12, 24, 36, and 48 months, and at follow-up in all trial subjects in the

U.S. (i.e., a subset of the total population). All antibody positive samples were characterized for cross-reactivity to native GLP-1 (present vs. not present). Positive samples from the follow-up visit (or last available visit, if a follow-up visit sample was not available) were characterized for *in vitro* neutralizing effect (present vs. not present) against liraglutide and against native GLP-1.

Allergic Reactions, Anaphylaxis, and Angioedema

The proportion of subjects with events of 'allergic reaction' (as described in Table 37)[35] reported as SAEs or non-serious MESIs and the rate of such events were higher in the liraglutide group (1.3%, 0.42 events per 100 PYO) than in the placebo group (0.9%, 0.27 events per 100 PYO).

Five events identified by the search were fatal, occurring in 4 subjects in the liraglutide group and 1 subject in the placebo group; however upon review, none of the cases appeared to be due to hypersensitivity reactions.

The proportions of 'allergic reaction' events that were serious were 0.6% for liraglutide and 0.5% for placebo (Table 38), severe 0.3% liraglutide and 0.2% placebo, and led to permanent treatment discontinuation 0.2% liraglutide and <0.1% placebo.

Table 38. Fatal and Nonfatal Serious Allergic Reaction Adverse Events

	Liraglutide N=4668	**Placebo N=4672**
Total SAEs	**26 (0.6)**	**25 (0.5)**
Angioedema	6 (0.1)	7 (0.1)
Circulatory collapse	4 (0.1)	6 (0.1)
Drug hypersensitivity	4 (0.1)	1 (<0.1)
Contrast media allergy	3 (0.1)	0
Anaphylactic reaction	2 (<0.1)	1 (<0.1)
Bronchospasm	2 (<0.1)	1 (<0.1)
Hypersensitivity	1 (<0.1)	2 (<0.1)
Laryngeal edema	1 (<0.1)	1 (<0.1)
Immune thrombocytopenic purpura	1 (<0.1)	0
Shock	1 (<0.1)	0
Skin necrosis	1 (<0.1)	0
Swollen tongue	1 (<0.1)	0
Dermatitis	0	1 (<0.1)
Dermatitis contact	0	1 (<0.1)
Eczema	0	1 (<0.1)
Rhinitis allergic	0	1 (<0.1)
Toxic epidermal necrolysis	0	1 (<0.1)
Urticaria papular	0	1 (<0.1)

Source: LEADER CSR, Table 14.3.1.2.131

Details regarding specific SAEs are as follows:

35 Note that AEs from the various relevant SMQs included in the search might not reflect true allergy.

- Angioedema: A total of 15 SAEs of angioedema were reported in 6 subjects in the liraglutide group (8 events) and 7 subjects in the placebo group (7 events). All liraglutide-treated subjects had reasonable alternative etiologies reported.

- Anaphylaxis: Three SAEs of anaphylactic reaction were reported in 2 subjects in the liraglutide group and 1 subject in the placebo group. All had reasonable alternative etiologies reported, and in all cases treatment with the trial product continued.

- Drug hypersensitivity: Four SAEs were reported in the liraglutide group and 1 in the placebo group. All events in patients on liraglutide were attributable to other agents.

- Immune thrombocytopenic purpura: The SAE of 'immune thrombocytopenic purpura' occurred in a 68 year old male (subject (b) (6) in conjunction with pneumonia after being treated with liraglutide for 2 months. He continued to have low platelets for at least 4 months (as reported in the narrative), as low as 3 x 10^3 /μL. The subject was treated with prednisone and remained on the study drug. The event was reported as recovered 1 year later.

Immune Complex Disease

Immune complex disease, or type III hypersensitivity reaction, was evaluated using a broad and narrow MedDRA search with terms shown in Table 37, above.

The events captured from the narrow MedDRA search (SAEs or non-serious MESIs only) are shown in Table 39. All 3 events in the liraglutide group were reported as SAEs.

Table 39. Immune Complex Disease, Narrow SMQ

	Liraglutide N=4668	Placebo N=4672
Total events	3 (<0.1)	10 (0.2)
Musculoskeletal and connective tissue disorders	1 (<0.1)	6 (0.1)
Polymyalgia rheumatica	1 (<0.1)	6 (0.1)
Nervous system disorders	0 (0.0)	2 (<0.1)
Chronic inflammatory demyelinating polyradiculopathy	0 (0.0)	1 (<0.1)
Guillain-Barre syndrome	0 (0.0)	1 (<0.1)
Skin and subcutaneous tissue disorders	1 (<0.1)	0 (0.0)
Chronic pigmented purpura	1 (<0.1)	0 (0.0)
Vascular disorders	1 (<0.1)	2 (<0.1)
Granulomatosis with polyangiitis	1 (<0.1)	0 (0.0)
Thromboangiitis obliterans	0 (0.0)	1 (<0.1)
Vasculitis necrotizing	0 (0.0)	1 (<0.1)

N: number of subjects, %: proportion of subjects
Adverse events identified by using MedDRA search criteria

Source: LEADER CSR, Table 12-63

In addition to the SAE and non-SAE MESI events presented above, 3 additional non-SAE, non-MESI 'immune complex disease' events were reported by the investigator in 1 subject on liraglutide and 2 subjects on placebo; all 3 events were reported as 'polymyalgia rheumatica'.

The broad 'immune complex disease' MedDRA search, by definition, included terms that were not specific to immune complex disease. The 2 most frequent terms in the search were 'proteinuria' (liraglutide 1.4% vs. placebo 2.0%) and 'arthritis' (0.3% vs. 0.1%). Other terms were similar between treatment groups.

Anti-Liraglutide Antibodies

A subset of subjects in the LEADER trial (US sites) was evaluated for anti-liraglutide antibodies. The numbers and proportions of subjects who developed positive anti-liraglutide antibodies at some point in the trial in each group were: liraglutide 11/1247 (0.9%) and placebo 2/1267 (0.2%). The titers were reportedly low for all positive samples.

In 5 of the 11 subjects in the liraglutide group who developed anti-liraglutide antibodies during the trial, antibodies showed cross-reactivity to native GLP-1. No subject developed neutralizing antibodies. Of the 11 liraglutide-treated subjects who at some point during the trial had an anti-liraglutide positive sample, 4 tested positive at one visit and negative at the subsequent visits, 5 tested positive at the follow-up visit only, and 2 tested positive at 2 or more subsequent visits including the final visit. None of the subjects with anti-liraglutide antibodies in either treatment group reported SAEs/MESIs of allergic reaction, injection site reaction, or immune complex disease. HbA1c changes

by antibody (positive, cross-reactive, or negative) were similar among those with and without antibodies, with no obvious pattern to suggest an association with loss of efficacy. The Office of Biotechnology Products provided consultative review regarding the adequacy of the assays used in LEADER. It was noted that these are adequate and improved upon those used in the original liraglutide development program, and that the data are acceptable for labeling.

Diabetic Foot Ulcers

In light of recent regulatory action for canagliflozin[36], Dr. Golden conducted a focused safety review of adverse events that could be related to lower extremity amputation. The MedDRA search to capture events of diabetic foot ulcer was developed by the sponsor prior to the database lock, and consisted of a combination of high level terms with a few added and a few deselected preferred terms:

Table 40. HLTs and PTs Included in the MedDRA Search for Diabetic Foot Ulcers

Included HLTs	
	HLT Diabetic complications dermal (Primary and secondary terms)
	HLT Limb therapeutic procedures (Primary and secondary terms)
	HLT Musculoskeletal necrosis and vascular insufficiency (Primary and secondary terms)
	HLT Non-site specific necrosis and vascular insufficiency NEC (Primary and secondary terms)
	HLT Skin and subcutaneous tissue ulcerations (Primary terms only)
Included extra PTs:	
	Wound
	Skin necrosis
Excluded PTs:	
	Arteriosclerosis
	Arteriosclerotic gangrene
	Compartment syndrome
	Steal syndrome
	Vascular graft occlusion
HLT: high level term; NEC: not elsewhere classified; PT: preferred term	

Source: Response to FDA Request 03 April 2017, Table 1-3

A total of 181 subjects (3.9%) treated with liraglutide vs. 198 subjects (4.2%) treated with placebo had SAE/MESI events of diabetic foot ulcer according to the sponsor's MedDRA search. The proportions of subjects with the preferred term 'diabetic foot' were 2.8% vs. 3.3% liraglutide- and placebo-treated subjects, respectively.

36 In July 2017 canagliflozin-containing products were updated to include a boxed warning for lower limb amputation.

The sponsor conducted a *post hoc* review of the individual case narratives to further describe the complications of foot ulcers, such as amputations[37] (Table 41).

A total of 44/4668 liraglutide-treated subjects (0.9%) and 67/4672 placebo-treated subjects (1.4%) reported diabetic foot ulcer events with subsequent amputation according to this *post hoc* review.

Table 41. Foot Ulcers and Associated Complications

	Liraglutide			Placebo		
	N	**E**	**(%)**	**N**	**E**	**(%)**
Number of subjects with events*	181	268		198	304	
Number of subjects with events, narrative review*#	176	260	(100)	191	291	(100)
Amputation**						
Yes	44	60	(23.1)	67	78	(26.8)
Yes, one or several toes	33	42	(16.2)	42	45	(15.5)
Yes, foot, crus, or leg	13	16	(6.2)	30	33	(11.3)
Yes, not specified	1	2	(0.8)	0	0	(0.0)
No	144	197	(75.8)	133	206	(70.8)
Unknown	3	3	(1.2)	6	7	(2.4)
Peripheral revascularization**						
Yes	20	24	(9.2)	23	26	(8.9)
No	157	231	(88.8)	173	256	(88.0)
Unknown	5	5	(1.9)	8	9	(3.1)
Infection**						
Yes	107	146	(56.2)	131	162	(55.7)
No	81	109	(41.9)	81	117	(40.2)
Unknown	5	5	(1.9)	10	12	(4.1)
Involvement of underlying structures**						
Yes	64	86	(33.1)	80	98	(33.7)
No	128	170	(65.4)	118	177	(60.8)
Unknown	4	4	(1.5)	16	16	(5.5)

%: proportion of events out of total foot ulcer events with narrative; 'infection': presence of clinical signs of infection, incl redness, warmth, pain, purulence discharge; 'involvement of underlying structures': tendon, joint capsule of bone
* Events are identified by MedDRA search
# 21 events in 2 subjects (8 in the liraglutide and 13 in the placebo group), not related to foot ulcers, or reported as complications to a reported foot ulcer were excluded from narrative review
** Based on *post hoc* review of the individual case narratives performed by the sponsor

Source: Summary of Clinical Safety, Table 2-16

A similar proportion of subjects with medical history of peripheral vascular disease had events of diabetic foot ulcer [liraglutide: 51 of 567 subjects (8.9%), placebo: 63 of 600

37 Procedures and surgeries (other than revascularization procedures) were not to be reported as separate adverse events, but were to be reported as part of the adverse event(s) leading to the procedure. The amputations in this analysis were only assessed when occurring in relation to foot ulcer events.

subjects (10.5%)] and diabetic foot ulcer resulting in amputation [liraglutide: 6 subjects (1.0%), placebo: 5 subjects (0.8%)] reported during the trial.

The analysis did not capture events identified by the investigator as MESI 'diabetic foot ulcer' if the term was not included in the MedDRA search as per Table 40; 56 such events in 50 subjects were identified in a separate search.[38] Four events in 4 subjects treated with liraglutide and 8 events in 7 subjects treated with placebo did not have any event captured by the MedDRA search for diabetic foot ulcer, as they were associated with nonspecific preferred terms such as peripheral ischemia and soft tissue infection. Of 22 events not co-reported with events captured by the MedDRA search for diabetic foot ulcer, 15 events (liraglutide: 6 events in 4 subjects, placebo: 9 events in 9 subjects) resulted in an amputation according to the description in the narrative.

CLINICAL SAFETY SUMMARY: MEDULLARY THYROID CANCER

This section presents the results of analyses from LEADER related to the potential risk of MTC.

Calcitonin
Elevated serum calcitonin is a potential biomarker of C-cell neoplasia, especially levels ≥50 ng/L (1). In LEADER, serum calcitonin was measured using a chemiluminescent immunometric assay performed by a central laboratory (ICONPLC, Dublin, Ireland). The lower limit of quantification (LLQ) of the assay was 2.0 ng/L, and the ULN was 8.4 ng/L in men and 5.0 ng/L in women. Calcitonin concentrations ≥20 ng/L were considered elevated. Serum calcitonin was measured fasting at baseline and at study visits 1, 7, 9, 11, 13, and 15 in all subjects[39]. As a precautionary measure, subjects who had calcitonin below the upper limit of normal (ULN) at screening AND calcitonin values ≥2x ULN at visit 15 were scheduled to have another blood calcitonin test after an off-drug follow-up period at visit 16. An independent calcitonin monitoring committee (CMC) consisting of thyroidologists assessed all events of confirmed elevated calcitonin ≥20 ng/L and provided clinical advice to investigators regarding further investigation and treatment of subjects.

Consistent with the enrollment criteria for LEADER, baseline calcitonin was ≤50 ng/L in all subjects. A similar proportion of subjects had calcitonin ≥ULN at baseline in each

38 Twenty-two events in 21 patients were evaluated as *not* being related to diabetic foot ulcers and 34 events in 29 patients were evaluated as being related to diabetic foot ulcers. Of those 34 events: 12 events occurred in 11 patients who had co-reported events captured by the MedDRA search for diabetic foot ulcer representing the same clinical case; 10 events occurred in 8 patients who had another separate event reported during the trial captured by the MedDRA search for diabetic foot ulcer; and 12 events occurred in 11 patients who had no event(s) captured by the MedDRA search for diabetic foot ulcer.
39 visit 1 occurred 4-5 weeks prior to the start of study drug, and visits 7, 9, 11, and 13 occurred 12, 24, 36, and 48 months after the start of study drug, respectively; visit 15 was an end of treatment visit that occurred 42 months + 90 days after the last subject was randomized, thus timing of visit 15 was variable for each study subject.

treatment group in male subjects (liraglutide: 21.5%; placebo: 22.0%) and female subjects (liraglutide: 3.2%; placebo: 2.7%). In both sexes, lower eGFR, higher BMI, and smoking were associated with higher baseline calcitonin, as expected (2,3).

The proportion of subjects with post-baseline calcitonin ≥20 ng/L at any study visit was similar between the liraglutide and placebo groups (3.1% vs 3.0%, respectively). In both treatment groups, median calcitonin concentrations were stable throughout the trial, with a slight overall decrease in men from 3.9 ng/L at screening to 2.5 ng/L at treatment end and no change in women from screening (1.0 ng/L) to treatment end. Among male subjects who met criteria for a visit 16 calcitonin measurement (130 men in the liraglutide group and 149 men in the placebo group), the median calcitonin at visit 16 was 5.9 ng/L in the liraglutide group and 7.8 ng/L in the placebo group. Among female subjects meeting criteria for a visit 16 calcitonin measurement (62 women in liraglutide group and 65 women in the placebo group), median calcitonin at visit 16 was 1.0 ng/L in both groups.

Calcitonin elevations above 50 ng/L are considered a more specific marker of potential C-cell hyperplasia compared to calcitonin ≥20 but less than 50 ng/L (1). There was no difference in the number of patients with any post-baseline calcitonin ≥50 ng/L between the liraglutide and placebo groups (liraglutide: n=16, 0.34% *vs* placebo: n=17, 0.36%).

Only 1 subject (ID (b) (6), liraglutide group) had consistent increases in calcitonin over time; all other subjects with calcitonin elevations during the study period exhibited fluctuating levels without consistent increases. Subject (b) (6) is a 67 year-old Indian male non-smoker with no history of histamine H2-receptor antagonist or proton pump inhibitor use, i.e. medications known to increase serum calcitonin levels (4). His baseline calcitonin was 19.2 ng/L in September 2011 and increased to 70.4 ng/L by September 2012. Study drug was discontinued in November 2012, and neck ultrasound and sestamibi scan were performed. Both imaging studies were normal, with no evidence of thyroid nodules or parathyroid gland hyperplasia. One month after discontinuing study drug, his calcitonin continued to increase, reaching 258 ng/L in November 2012. Three years after stopping study drug, the patient's calcitonin had further increased to 280 ng/L without structural evidence of thyroid disease.

Based on AE reporting, 'blood calcitonin increased' was reported at a slightly lower frequency and rate in the liraglutide group (0.9%, 0.24 events per 100 patient years of observation (PYO)) compared with the placebo group (1.1%, 0.31 events per 100 PYO).

Thyroid neoplasms

One endocrinologist and one oncologist on the EAC performed ongoing adjudication and assessment of all thyroid neoplasms. After EAC confirmation, all malignant and pre-malignant thyroid neoplasms were also confirmed by a blinded external endocrinologist to allow for further characterization (but not re-adjudication) of EAC-confirmed thyroid neoplasms.

Thyroid neoplasm classifications were based on EAC-confirmed cytology or pathology reports. New thyroid neoplasms were classified as benign, pre-malignant, or malignant, and further sub-typed as i.) C-cell hyperplasia, ii.) medullary microcarcinoma (carcinoma *in situ*), iii.) medullary carcinoma, or iv.) non-C cell.

Seven subjects (0.15%) in the liraglutide group had events of thyroid neoplasm, compared to three subjects (0.06%) in the placebo group (Table 42). There were no notable differences in demographic or baseline characteristics between liraglutide- and placebo-randomized subjects with events of thyroid neoplasms (data not shown). Malignant or pre-malignant thyroid neoplasms were observed in 5 liraglutide-randomized subjects, compared to 4 placebo-randomized subjects.

The majority of malignant thyroid neoplasms in the liraglutide group occurred within the first 12 months of the trial (4 of 5 events), and 1 event occurred after month 40. All malignant thyroid neoplasms in the placebo group including the event of MTC (discussed below) occurred after month 16.

Table 42. Thyroid Neoplasms in LEADER

Neoplasm	**Liraglutide (N=4,668 subjects) [n, (%)]**	**Placebo (N=4,672 subjects) [n, (%)]**
Total	7 (0.15%)	3 (0.06%)
Benign	2 (0.04%)	0 (0.0%)
Pre-malignant	0 (0.0%)	1 (0.02%)
Malignant	5 (0.11%)	3 (0.06%)
Sub-type		
C-cell hyperplasia	0 (0.0%)	0 (0.0%)
Medullary micro-carinoma (in situ)	0 (0.0%)	1 (0.02%)*
Medullary carcinoma	0 (0.0%)	1 (0.02%)*
Papillary thyroid cancer	5 (0.11%)	3 (0.06%)*
Thyroidectomy performed (i.e., pathology report available)	6	3
Total	7 (0.15%)	3 (0.06%)

[1]Source: Table 12-45, NDA 22341
*1event of medullary carcinoma, 2 events of medullary microcarcinoma, and 1 event of PTC occurred in a single patient in the placebo group.

There were no cases of MTC in liraglutide-randomized subjects, compared to 1 subject in the placebo group with MTC (Subject (b) (6)). Subject (b) (6) is a 72-year old male who underwent right hemi-thyroidectomy for removal of two thyroid nodules that were suspicious for follicular thyroid cancer on fine needle aspiration (FNA). Pathology from the right hemi-thyroidectomy revealed a 2 mm focus of medullary carcinoma without

local metastases (pT1pN0pMx). Completion left thyroidectomy with central lymph node dissection was performed and pathology revealed a 1 cm focus of follicular variant PTC and 2 foci (~1 mm) of medullary microcarcinoma in a background of C-cell hyperplasia (pT1aN0Mx). Genetic testing for multiple endocrine neoplasia type 2 and familial medullary thyroid cancer was negative. Of note, this subject had a mildly elevated serum calcitonin (up to 25.4 ng/L) prior to thyroidectomy, which declined to the normal range after the right hemi-thyroidectomy.

There were no on-treatment events of isolated C-cell hyperplasia. The placebo-randomized subject described above (Subject (b) (6) was found to have MTC on a background of C-cell hyperplasia according to the surgical pathology report. One liraglutide-randomized subject (Subject (b) (6)) with a confirmed malignant thyroid neoplasm (classified as 'other' and of papillary origin) during the trial had one focus of C-cell hyperplasia *prior to randomization* to study treatment.

Conclusions
Data from the LEADER trial do not demonstrate an increased risk of thyroid neoplasm overall, C-cell hyperplasia, or MTC in subjects randomized to liraglutide compared to placebo. Mild elevations in serum calcitonin levels (>20 ng/L) were seen equally as frequently in the liraglutide and placebo groups (~3%), and no cases of C-cell hyperplasia or cases of MTC were seen in any subject in the liraglutide group during the trial period.

Limitations to these data include small overall rates of any thyroid neoplasms in the study population (0.1% of subjects in the both the liraglutide and placebo groups) and relatively short duration of follow up (median 3.8 years) to observe an increased incidence in thyroid cancer event rates, given the generally slow-growing nature of thyroid malignancies. As noted by FDA reviewers at the time of approval of Victoza, because the background rate for medullary thyroid carcinoma is very low, a clinical trial, even a large trial such as LEADER was not expected to have meaningful power to rule out an increased risk for medullary thyroid carcinoma with liraglutide unless this risk is substantial, and by extension, a clinical trial is not expected to have meaningful power to detect patients with an increase in calcitonin that is caused by medullary thyroid carcinoma or by a pre-neoplastic lesion that is destined to become medullary thyroid carcinoma. Evaluation of thyroid tumors in patients using liraglutide or any approved long-acting GLP-1 agonist is ongoing through postmarketing requirements including epidemiologic studies and CVOTs for other long-acting GLP-1 agonists.

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Summary of ONCOLOGY CONSULT: PANCREATIC CANCER

BACKGROUND

Based on concerns about a potential causal relationship between exposure to GLP-1 RAs and pancreatic adenocarcinoma identified in post-marketing reports, in 2013-2014, FDA and EMA independently reviewed research investigating a possible relationship between treatment with GLP-1-based therapies and pancreatic cancer and pancreatitis (see also Butler et al, Diabetes 2013; 62: 2595-2604 and EMA Assessment report for GLP-1 based therapies at http://www.ema.europa.eu/docs/en_GB/document_library/Report/2013/08/WC500147026.pdf).

In 2014, FDA published its assessment of this pancreatic cancer signal (http://www.nejm.org/doi/pdf/10.1056/NEJMp1314078), based on assessment of nonclinical studies and clinical data. FDA reviewed 250 toxicology studies, required sponsors to conduct a 3-month pancreatic toxicity study in a rodent-model of diabetes, and performed its own pancreatic toxicology studies with exenatide. Other than nonspecific microscopic findings in one study in a high-fat-diet mouse model conducted by FDA, the toxicology studies did not identify overt pancreatic toxic effects from exposure to GLP-1 RAs. Additionally, FDA examined relevant clinical safety databases and concluded that these data were inconclusive and not sufficiently compelling to support incorporation of changes regarding the potential pancreatic cancer signal in product labeling. FDA acknowledged that systematic identification and documentation of new cases of pancreatic cancer in future cardiovascular outcomes trials and other clinical trials could provide additional information in the future.

DOP2 REVIEW

An external adjudication committee (EAC) identified cases of malignant pancreatic neoplasms in 13 patients in the liraglutide arm and 5 in the placebo arm. One patient adjudicated as having cholangiocarcinoma was identified by the DMEP reviewer as a possible case of pancreatic cancer. In addition, there were 4 deaths in the placebo group considered related to pancreatic cancer by the investigator that were not positively adjudicated due to a lack of tissue. Based on DOP2's assessment, 13 patients in the liraglutide arm are reasonably likely to have had pancreatic cancer versus 8 patients in the placebo arm (Table 43).

Table 43. DOP2 Assessment of Adjudicated Pancreatic Cancer Cases in LEADER

Patient ID	Arm	Synopsis of Narrative	Time from Randomization to Event	DOP2 Assessment	Concurrence with EAC diagnosis
(b) (6)	Treatment	66 year old man presented with weight loss and abdominal pain, had CT scan findings of a lesion in the body of the pancreas. A biopsy showed adenocarcinoma.	25 months	Definite	yes
	Treatment	63 year old woman admitted with abdominal pain, anorexia, and weight loss. Patient underwent panceaticoduodenectomy showing ductal carcinoma T3N1Mx.	9 months	Definite	yes
	Treatment	69 year old man presented with jaundice and MRI showed a lesion in the head of the pancreas. A CA19-9 was elevated, although in the setting of hyperbilirubinemia. A resection was done, and the diagnosis based on the "macroscopic appearance" of the tumor.	17 months	Probable	yes
	Treatment	71 year old man with multiple medical problems admitted for severe dyspnea. During the hospitalization, the patient was diagnosed with metastatic pancreatic cancer to lungs and liver (no details provided). Anatomic-pathology cause of death was metastatic pancreatic carcinoma.	16 months	Definite	yes
	Treatment	75 year old man with a recent diagnosis of colon cancer underwent CT imaging showing a new head of pancreas lesion. He underwent pancreaticoduodenectomy. Adenocarcinoma was confirmed histologically.	42 months	Definite	yes
	Treatment	59 year old woman presented with lumbar back pain, nausea, and jaundice. MRI showed pancreatic neoplasm with hepatic metastasis. Pathology report was not diagnostic. No autopsy was performed.	4 months	Probable	yes
	Treatment	63 year old woman presented with pruritus and jaundice, was found to have a head of the pancreas lesion on ultrasound. Multiple hepatic metastases were found intraoperatively at the time of attempted resection. Patient was clinically staged as T3N1M1. Histology confirmed adenocarcinoma.	31 months	Definite	yes
	Treatment	68 year old man was admitted for abdominal pain and jaundice, had CT showing a lesion in the uncinate process. A total pancreatectomy was performed and pathology showed adenocarcinoma T3N1M0.	7 months	Definite	yes
	Treatment	63 year old man was admitted with icterus and fatigue. A 4 cm mass was seen in the pancreas as well as hepatic lesions. A biopsy showed adenocarcinoma of the pancreas.	42 months	Definite	yes

(b) (6)

Treatment	68 year old woman with cardiac disease was admitted with shortness of breath. On CT angiogram, a pulmonary embolus and a mass in the head/neck of pancreas were visualized. Further imaging showed gastrohepatic ligament and celiac lymphadenopathy. FNA was nondiagnostic.	28 months	Possible	yes
Treatment	69 year old man presented with progressive syncope and weight loss. Abdominal imaging revealed thickening near the tail of pancreas that was biopsied as well as multiple hepatic and pulmonary lesions. Biopsy confirmed ductal carcinoma.	9 months	Definite	yes
Treatment	72 year old man with ~ 1 year of abdominal pain and probable duodenal compression from a tumor in the head of pancreas eventually developed cholestasis requiring biliary stenting. Peritoneal carcinomatosis was seen at laparotomy and histology revealed adenocarcinoma.	9 months	Definite	yes
Treatment	61 year old man underwent abdominal scan and was found to have a mass in the head of pancreas as well as a lesion in the liver. On frozen section at the time of exploratory laparotomy, the pancreatic lesion was negative for malignancy, but a section from the liver showed adenocarcinoma. DOP2 assessment is that this patient most likely has intrahepatic cholangiocarcinoma.	<1 month; patient did not receive study drug prior to event	No	no
Treatment	82 year old woman presented with right-sided abdominal pain and on ERCP was found to have a pancreatic mass, confirmed on CT. A follow up CT showed a dilated gall bladder. Ultrasound showed gallstones and mild ductal dilatation. The case was adjudicated as cholangiocarcinoma, but based on the narrative and patient record found in the adjudication package, a diagnosis of pancreatic cancer is reasonable.	8 months	Possible	no
Placebo	72 year old woman with weight loss and abdominal pain was found to have a head of pancreas lesion and two hepatic lesions on CT scan. Histologic exam showed adenocarcinoma.	17 months	Definite	yes
Placebo	77 year old man presented with weight loss, jaundice, and abdominal pain. CT showed pancreatic mass. FNA showed adenocarcinoma.	18 months	Definite	yes
Placebo	65 year old asymptomatic man with an incidentally discovered large cystic tumor underwent resection. Pathology showed “malignant tumor”.	1 month	Probable	yes
Placebo	65 year old man underwent CT scan showing pancreatic and liver lesions. Cytology from ascites drainage revealed adenocarcinoma	22 months	Definite	yes

(b) (6)

Placebo	79 year old man presented with right upper quadrant pain and underwent and esophagogastroduodenoscopy with biopsy for a pancreatic lesion. No results are available in the narrative but the patient was diagnosed with pancreatic carcinoma.	11 months	Probable	yes
Placebo	73 year old woman with 6 months of nausea and weight loss presented with vomiting. A CT confirmed a pancreatic uncinate tumor CA19-9 was 122 IU (upper limit 39 IU)	4 months	Possible	NA
Placebo	84 year old man presented with abdominal pain. Abdominal ultrasound showed 4.4 cm "tissue damage" in the pancreas and hepatic nodules. A CA19-9 was 21,000.	41 months	Probable	NA
Placebo	67 year old man with 5 months of weight loss was admitted with abdominal pain. He underwent ultrasound showing a mass in the pancreas extending to the abdominal wall and superior mesenteric artery. A CT scan showed liver lesions and adenopathy.	< 1 month	Probable	NA
Placebo	72 year old woman presented with indigestion and swelling. A ^{68}Gallium Dotatate scan was performed showing uptake in the pancreas, liver and left adrenal. It is unclear if pathologic staging was performed. This patient most likely has a neuroendocrine tumor.	10 months	Unlikely	NA

ASSESSMENT AND RECOMMENDATION

Pancreatic adenocarcinoma is an aggressive malignancy with a high mortality rate. It is most commonly diagnosed at an advanced stage; only 30% of patients are eligible to undergo resection with curative intent. Despite the advanced presentation at diagnosis and aggressive clinical course typically observed in patients with pancreatic cancer, quantitative analysis of the timing of genetic evolution suggests that at least a decade takes place between the initial mutation and development of the first malignant (non-metastatic) pancreatic cancer cell and that approximately 5 additional years are required for the primary tumor to develop metastatic potential (https://www.ncbi.nlm.nih.gov/pubmed/20981102). This suggests that a direct causal role for liraglutide in the initial development of pancreatic cancer in patients participating in the LEADER trial is unlikely given the short latency period between exposure and diagnosis of pancreatic cancer. There is insufficient information available to elucidate whether treatment plays a role in accelerating the evolution of primary or metastatic disease following occurrence of the initial mutation that will ultimately lead to clinically evident pancreatic cancer, given the relative short follow-up period (median follow-up of 3.5 years).

There is a slight imbalance in the number of cases of pancreatic cancer that occurred in patients who received liraglutide in the LEADER trial (13/4668, or 0.28% in the treatment arm vs. n=8/4672, or 0.17% in the placebo arm); however, the number of cases is too small to permit conclusions regarding whether this imbalance is due to chance

alone, an acceleration in the development of pancreatic cancer due to treatment with liraglutide, or other patient risk factors.

In summary, taking into consideration the totality of information available, the additional information provided in LEADER does not appear to substantively alter the original FDA and EMA conclusions regarding the lack of sufficient information to conclusively determine whether long term exposure to GLP-RAs increase the risk of pancreatic cancer. Longer follow-up (e.g., 10 years) is recommended to further characterize the relationship between GLP-1 RAs and the development of pancreatic cancer.

I agree with DOP2's recommendations and conclusions; I do not recommend updating liraglutide labeling with information about pancreatic cancer.

Summary of OPHTHALMOLOGY CONSULT: RETINOPATHY

Summary: 'Retinopathy' (defined as a composite endpoint of: need for retinal photocoagulation or treatment with intravitreal agents, vitreous hemorrhage, and onset of diabetes related blindness -Snellen visual acuity of 20/200 [6/60] or less, or visual field of <20 degrees in the better eye with best correction) was a pre-specified, adjudicated, secondary endpoint; the results of analyses generally did not favor liraglutide. In the liraglutide group there was a higher number of patients who had photocoagulation or need for intravitreal agents and patients with vitreous hemorrhage. Of note, even though retinopathy events were adjudicated, there was no routine clinical funduscopic evaluation of subjects during the trial, and the retinopathy status of subjects at screening was based on information (medical history) entered in the eCRF by the investigators.

Endpoints: Within multiple secondary objectives was the following time-to event:

- time from randomization to first occurrence of a composite microvascular outcome, defined as any one of the following:
    - need for retinal photocoagulation or treatment with intravitreal agents
    - vitreous hemorrhage
    - onset of diabetes-related blindness (defined as Snellen visual acuity of 20/200 [6/60] or less, or visual field of <20 degrees in the better eye with best correction possible)
    - new or worsening nephropathy (defined as new onset of persistent urine albumin ≥300 mg/g creatinine (macro-albuminuria), or persistent doubling of serum creatinine level and eGFR ≤ 45 mL/min/1.73 m2 per MDRD
    - need for continuous renal replacement therapy in the absence of an acute reversible cause
    - death due to renal disease
- time from randomization to each individual component of the composite microvascular outcome and to the retinopathy and nephropathy composite outcomes separately.

Reviewer's Comment:

1. *The composite microvascular outcome as defined in this protocol is not recommended to be used as an outcome measure. It combines equally, events of unequal clinical severity, unequal clinical significance and unequal expected frequency. As noted in the results of this trial, the frequency of renal events is much higher than the frequency of retinal events. The endpoint therefore is more a measure of an effect on the kidneys and not a complete picture of microvascular outcomes.*

2. *The "need for retinal photocoagulation or treatment with intravitreal agents" is not a good endpoint. In spite of clinical trials demonstrating the clinical benefits and clinical consequences of retinal photocoagulation, there is not uniform agreement on*

the clinical characteristics that should dictate the timing of photocoagulation treatment. Up until the advent of Vascular Endothelial Growth Factor (VEGF) inhibitor use, clinical trials would have suggested that the use be based on having proliferative retinopathy. Presently, VEFG inhibitors can be used to treat proliferative retinopathy. In addition, cost, reimbursement, medical alternatives and a variety of individual interests can influence the "need" or "actual" retinal photocoagulation treatment. There are examples in clinical trials over the past 15 years of specific retinopathy treatment criteria for photocoagulation being defined at the start of a clinical trial, yet multiple investigators choose to either perform photocoagulation before the criteria was met or choose to not perform photocoagulation even though the predefined criteria was met.

There are clinical trials demonstrating the clinical benefits and potential clinical consequences of intravitreal injections, but like retinal photocoagulation, there is not uniform agreement on the timing for administering intravitreal agents. In addition, cost, reimbursement, and a variety of individual interests can influence the "need" or "actual" administration of intravitreal agents.

3. *While the protocol described this measure as the "need for treatment," it appears that the Event Adjudication Committee Charter required actual treatment in order to valid this endpoint. This could have resulted in some events being counted when they were not actually needed and some events not being counted because the treatment was not performed.*

4. *The onset of diabetes-related blindness (defined as Snellen visual acuity of 20/200 [6/60] or less, or visual field of <20 degrees in the better eye with best correction possible) is not a good endpoint because it is difficult to judge whether the blindness was diabetes related. There are increased frequencies of many ocular conditions (e.g., cataracts, macular edema, retinal vein occlusions) leading to a loss of visual acuity in patients with diabetes. This does not necessarily mean that any loss of vision due to one of these conditions is necessarily due to the diabetes. Some of the conditions leading to a visual acuity of 20/200 or worse are potentially reversible (i.e., cataracts, macular edema, vitreous hemorrhage) and some are not. The clinical significance of this endpoint depends on whether the blindness is reversible or not.*

5. *Vitreous hemorrhage could have been a reasonable endpoint, particularly if it was qualified by the duration that it was present. However, the frequency of the event is often low even in an untreated group and therefore the endpoint is of limited utility unless the number of enrolled subjects is very large (i.e., larger than this trial). Vitreous hemorrhages which do not resolve within 3 months (often leading to a need for a vitrectomy) are much more significant than those which resolve more quickly without any significant intervention.*

6. *"Time to" events involving retinopathy, even when measured on an accepted retinopathy scale (i.e., ETDRS [Early Treatment Diabetic Retinopathy Study]) are*

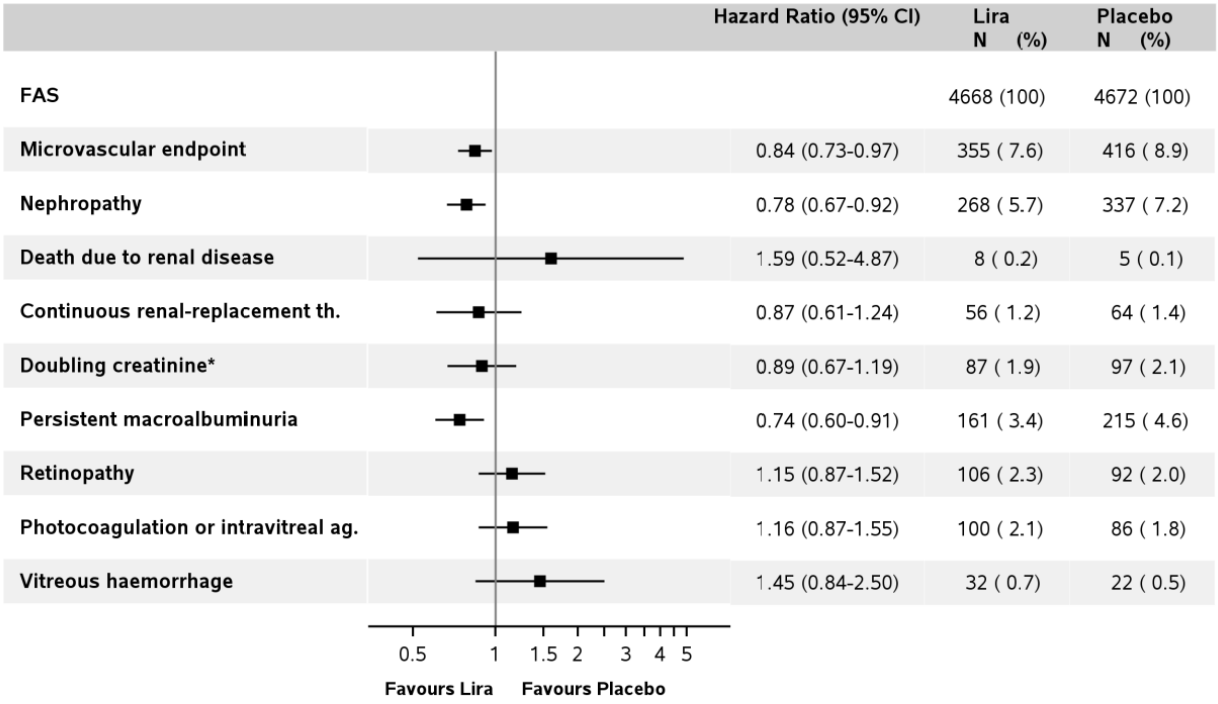
problematic because rapid drops in Hemoglobin A1c (HbA1c) result in an increase in diabetic retinopathy during the first year in which the HbA1c decreased. The most well-known of the studies to demonstrate this was the Diabetic Control and Complications Trial (DCCT). The DCCT study demonstrated that rapid decreases in HbA1c resulted in increased retinopathy. The control group did not catch up until Year 3. While the DCCT demonstrated this finding in Type 1 diabetics, it is true for both Type 1 and Type 2 diabetics [Literature examples include by are not limited to Arch Ophthalmol. 2006;124:38-45. and Diabetes Research and Clinical Practice. 2014;103(3):e37-39.]

History of diabetes and microvascular complications

Mean HbA_{1c} at baseline was similar between treatments at 8.7%, reflecting that this was a relatively poorly controlled population with T2DM and with longstanding diabetes close to 13 years. Out of the 20.1% (21.0% in the liraglutide group and 19.2% in the placebo group) of all subjects who had diabetic retinopathy at screening 14.9% had non-proliferative retinopathy and 4.7% had proliferative retinopathy. No formal evaluation was made based on fundoscopy/fundosphotography to assess retinopathy at screening."

Reviewer's Comment: *The lack of formal evaluations is problematic in trying to assess whether the groups were equal at baseline. It is hoped that the randomization provided equal baselines between groups. The absence of formal grading (readings of retinal fundus photography) of the level of retinopathy in this trial severely limits the ability to evaluate the effect of treatment intervention on ophthalmic endpoints in this population.*

Forest plot of treatment contrasts for components of the EAC-confirmed microvascular endpoint – FAS

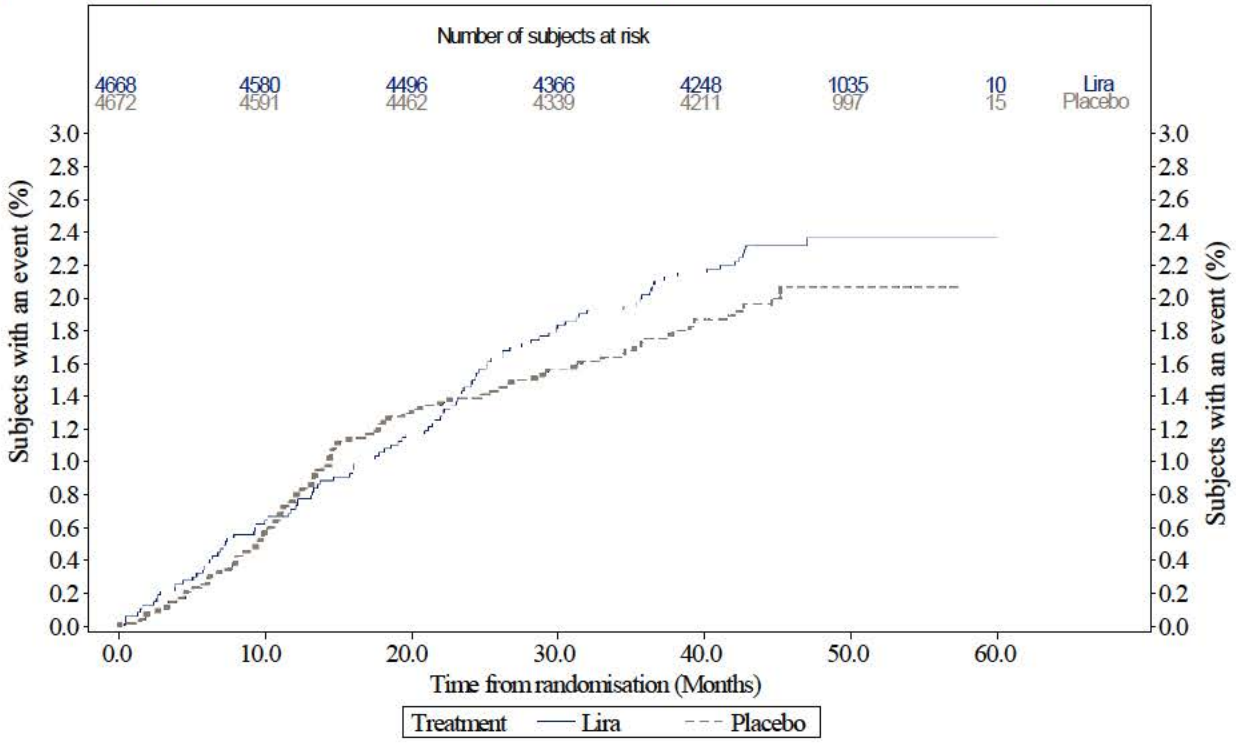


Abbreviations: %: proportion in percent of subjects with an event; CI: confidence interval; eGFR-MDRD: estimated glomerular filtration rate per modification of diet in renal disease; Doubling creatinine: persistent doubling of serum creatinine and eGFR-MDRD ≤45 mL/min/1.73 m^2; FAS: full analysis set; Lira: liraglutide; N: number of subjects. Source: CTR Figure 11-11

	Lira				Placebo			
	N	(%)	E	R	N	(%)	E	R
Number of Subjects	4668				4672			
PYO	17822				17741			
EAC confirmed microvascular endpoint	355	(7.6)	355	1.99	416	(8.9)	416	2.34
EAC confirmed nephropathy	268	(5.7)	268	1.50	337	(7.2)	337	1.90
New onset of persistent macro albuminuria	161	(3.4)	161	0.90	215	(4.6)	215	1.21
Persistent doubling of serum creatinine*	87	(1.9)	87	0.49	97	(2.1)	97	0.55
Need for continuous renal-replacement therapy	56	(1.2)	56	0.31	64	(1.4)	64	0.36
Death due to renal disease	8	(0.2)	8	0.04	5	(0.1)	5	0.03
EAC confirmed retinopathy	106	(2.3)	106	0.59	92	(2.0)	92	0.52
Treatment with photocoagulation or intravitreal agents	100	(2.1)	100	0.56	86	(1.8)	86	0.48
Development of diabetes-related blindness	0	(0.0)	0	0.00	1	(0.0)	1	0.01
Vitreous hemorrhage	32	(0.7)	32	0.18	22	(0.5)	22	0.12

N: Number of subjects, %: Proportion of subjects, E: Number of events, PYO: Patient years of observation R: Event rate per 100 patient years of observation, EAC confirmed microvascular endpoint is a composite of EAC confirmed nephropathy and retinopathy. Only first (index) events after randomization and until follow-up are included. For sub groups the first event within each sub group is selected, *Persistent doubling of serum creatinine and eGFR <=45 ml/min/1.73 m2 per MDRD. Source: CTR Table 11-11

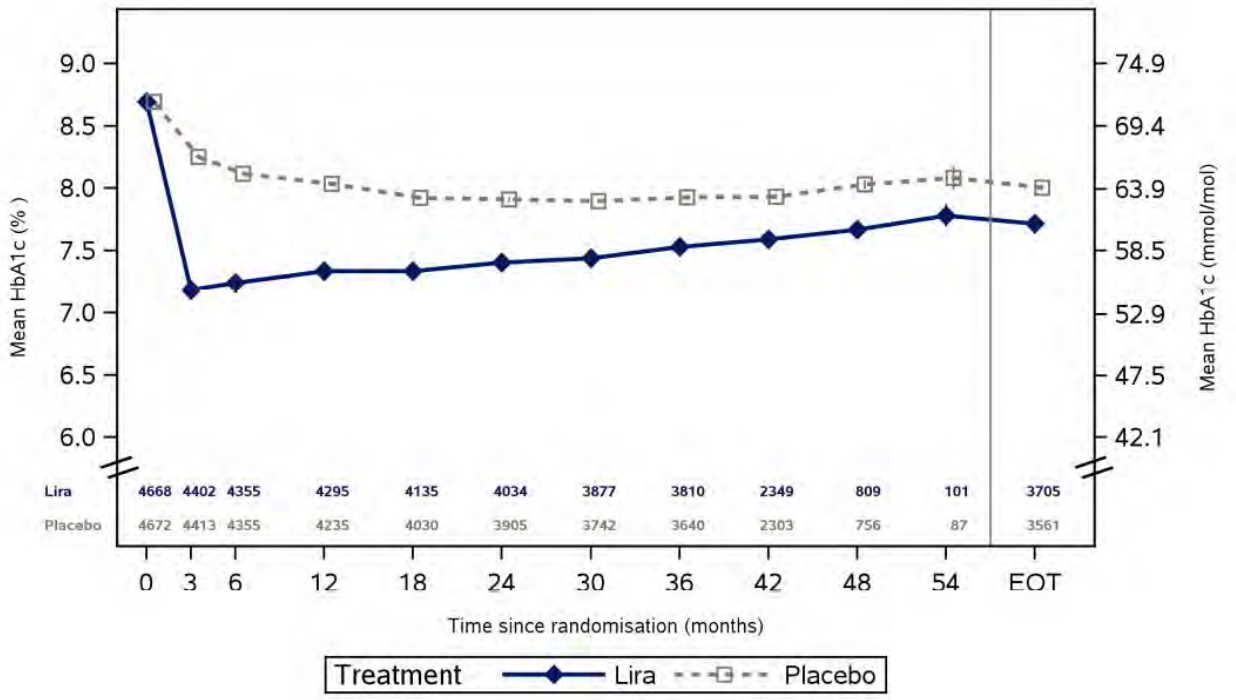
Application Figure 11–15
Kaplan-Meier plot of time to first EAC-confirmed retinopathy – FAS Individual retinopathy criteria



Abbreviation: EAC: event adjudication committee; FAS: full analysis set; Lira: liraglutide.
Source: CTR Figure 11-15

Reviewer's Comment: *There were no statistically significant differences between groups in any of the ophthalmic measurements. As noted above, with the exception of the vitreous hemorrhage endpoint, the ophthalmic endpoints measured in this study are not accurate representations of diabetic complications in the eye, nor are they measures of improvement in ophthalmic parameters of diabetic disease.*

Estimated mean HbA_{1c} over time



Note: Estimated data. The numbers are the number of subjects with an observed value who contributed to the analysis. Error bars: +-standard error (mean). Vertical grey line separates last scheduled and EOT visit.
Abbreviations: EOT: end of treatment; FAS: full analysis set; HbA_{1c}: glycosylated hemoglobin; Lira: liraglutide.
Source: CTR Figure 11-18

Reviewer's Comment: *As noted in the graph above, there was a decrease in HbA1c in the Lira group within the first 3 months of treatment. Progression of diabetic retinopathy is known to be positively correlated with elevated HbA1c and with rapid (i.e., within 3 month period) decreases in HbA1c. The mean HbA1c does not provide enough information to be able to predict whether an increase in retinopathy would be expected to be seen in a significant number of patients. Based on literature studies, the patients at greatest risk for increasing their retinopathy levels are subjects with at least early retinopathy changes and HbA1c decreases of at least 2 to 3 percentage points in 3 months. In this study, only about 15% of patients demonstrated a 2.5 to 3 point or more decrease in HbA1c in the first three months.*

Conclusions:

1. Neither the composite microvascular outcome, nor the ophthalmic components of the composite microvascular outcome as defined in this protocol are recommended to be used as an outcome measure. The composite combines equally, events of unequal clinical severity, unequal clinical significance and unequal expected frequency.

2. The effect of liraglutide on retinopathy cannot be adequately evaluated in this supplemental application because individual subjects retinopathy levels were not graded and therefore potential changes in retinopathy severity cannot be determined.

3. The numerical imbalances observed in the "retinopathy" endpoints were not statistically significant and do not raise a concern because the individual endpoints are not reliable measures of ocular disease. The potential differences in the clinical criteria, coupled with cost, reimbursement, medical alternatives and a variety of individual interests can influence the "need" or "actual" retinal photocoagulation or intravitreal injection treatment making the proposed endpoint unreliable.

   The onset of diabetes-related blindness (defined as Snellen visual acuity of 20/200 [6/60] or less, or visual field of <20 degrees in the better eye with best correction possible) is also not particularly useful as an endpoint because of the low frequency and the difficulty judging whether the blindness was diabetes related. There are increased frequencies of many ocular conditions (e.g., cataracts, macular edema, retinal vein occlusions) leading to a loss of visual acuity in patients with diabetes. This does not necessarily mean that any (or most) loss of vision due to one of these conditions is necessarily due to the diabetes. Some of the conditions leading to a visual acuity of 20/200 or worse are potentially reversible (i.e., cataracts, macular edema, vitreous hemorrhage) and some are not. The clinical significance of this endpoint depends on whether the blindness is reversible or not.

   Vitreous hemorrhage that does not resolve within three months may be a reasonable endpoint, however, in this trial, the duration of persistence was not recorded. The frequency of the event is low even in an untreated group and therefore the endpoint is of limited utility unless the number of enrolled subjects is very large (i.e., larger than this trial). Vitreous hemorrhages which do not resolve within 3 months (often leading to a need for a vitrectomy) are much more significant than those which resolve more quickly without any significant intervention.

4. "Time to" events involving retinopathy, even when measured on an accepted retinopathy scale (i.e., ETDRS [Early Treatment Diabetic Retinopathy Study]) are problematic because rapid drops in HbA1c can result in an increase in diabetic retinopathy during the first year in which the HbA1c decreased. While the Diabetic Control and Complications Trial is the most well-known trial to demonstrate these events, it is true for both Type 1 and Type 2 diabetics [Literature examples of Type 2 studies include by are not limited to Arch Ophthalmol. 2006;124:38-45. and Diabetes Research and Clinical Practice. 2014;103(3):e37-39.]

Advisory Committee Meeting

The Endocrinologic and Metabolic Drugs Advisory Committee met on June 20, 2017 at the FDA White Oak Campus in Silver Spring, Maryland to discuss the current application. Please refer to the Official Transcript for detailed information and to Dr. Condarco's and Golden's reviews for summary information. At the meeting the following points were discussed and voting questions asked.

1. DISCUSSION POINT: LEADER assessed several non-CV safety outcomes including medullary thyroid carcinoma, pancreatic neoplasm, and pancreatitis. Please discuss whether the data presented today inform the potential for a causal relationship between liraglutide use and these non-CV safety outcomes. Please also discuss whether additional studies should be conducted to further evaluate these.

Meeting discussion: Most members were found the non-CV safety data, in general, to be reassuring. Comments included consideration to whether the boxed warning for MTC was still needed. Dr. Burman, a thyroid expert, stated that the boxed warning should be continued because of the long-latency of MTC, although he was largely assuaged that there doesn't appear to be a link between liraglutide and c-cell changes. Members recommended that FDA continue the thyroid cancer registry. Members found the pancreatitis data unremarkable. With regard to pancreatic cancer panel members noted that there is no preclinical support for a causal association. Dr. Konstam noted that it is not possible to quantify risk increase, if any, because event rate are so small.

2. DISCUSSION POINT: Please comment on the design, conduct, and results of LEADER and whether LEADER…

    a. Adequately addresses the post-approval CV risk assessment as recommended in the 2008 FDA Guidance
    b. Provides substantial evidence establishing that liraglutide reduces the risk of major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke) in adults with type 2 diabetes mellitus and high cardiovascular risk.

    In your discussion, consider the patient population enrolled (e.g., baseline cardiovascular disease history), reliability of the results (e.g., impact of missing data), the clinical meaningfulness of the results, and the consistency of the results across the components of the MACE endpoint and subgroups.

3. VOTING QUESTING: Do the results of LEADER establish that use of liraglutide in patients with Type 2 Diabetes Mellitus (T2DM) is not associated with unacceptably high cardiovascular risk?
    Results: Yes-19, No-0, abstain-0

The panel members unanimously agreed that LEADER adequately addressed the post-approval CV risk assessment as recommended in the 2008 FDA Guidance and demonstrated no increased risk for MACE.

4. VOTING QUESTION: Does the LEADER trial provide the substantial evidence needed to establish that liraglutide 1.8 mg daily reduces cardiovascular risk in patients with T2DM?

5. **Results: Yes-17, No-2, abstain-0**

    a. If yes, discuss the population for whom you believe this benefit applies. If no, comment on what additional data would be needed.

The large majority of panel members voted that LEADER provided substantial evidence to establish that liraglutide 1.8 mg daily reduces cardiovascular risk in patients with T2DM. A large part of the discussion centered around the subgroup findings (U.S. vs. non-U.S. and eligibility populations 3a and 3b). Dr. Oakes summarized the views of many members regarding the U.S. subgroup findings when he stated that all the components of MACE were trending in the right direction, and that while the p value [for the subgroup analysis of U.S. vs. non-U.S.] should be taken seriously the totality of the results shouldn't be ignored. The subgroup results provide evidence that liraglutide may be acting slightly differently but no strong evidence that there is no effect in the U.S. subgroup and that the whole population should be the focus of conclusions. The two members who voted no cited concerns about the subgroup analyses and stated that they would want a second trial that showed benefit in a U.S. population. Members were also concerned about the 3a vs. 3b subgroup findings, and there was large support for limiting the indication for patients with established cardiovascular disease.

Recommended Regulatory Action

I recommend Approval of this Supplement.

Benefit Risk Assessment (BRA) and Labeling Recommendations

LEADER is a multi-center, multi-national, randomized, double-blinded, placebo-controlled cardiovascular outcomes trial (CVOT) in which 9340 subjects with increased cardiovascular (CV) risk and type 2 diabetes mellitus (T2DM) were randomized in a 1:1 ratio to liraglutide or placebo as add-on to standard of care treatment. The duration of LEADER was driven by both the number of events and treatment period. The trial ended when all subjects had had a minimum treatment period of 42 months (plus a follow-up period of 30 days) and at least 611 event adjudication committee (EAC) confirmed Major Cardiovascular Events (MACE) events were recorded. The large sample size with multinational participating sites minimizes bias as does the blinded trial design. The trial was adequately conducted with no trial integrity issues that affected confidence in results.

The amount of missing data for the primary MACE analysis was low (3%), and vital status was available for over 99% of subjects.

LEADER was designed according to FDA Guidance[40] to demonstrate that treatment with liraglutide does not result in an unacceptably increased CV risk, in response to the postmarketing requirement (PMR) established at the time of initial FDA approval of Victoza. The trial was designed to demonstrate non-inferiority (against the upper-bound 95% confidence interval of 1.3) of the treatment of liraglutide versus placebo on the composite of three-point MACE: CV death, non-fatal stroke, or non-fatal MI. I conclude that the trial has successfully demonstrated no excess CV risk as per the Guidance. Results of LEADER demonstrated non-inferiority of liraglutide compared to placebo for the primary endpoint, time to first MACE, as the upper bound for the hazard ratio (HR) was less than 1.3 using a Cox proportional regression model [HR, 95% confidence interval (CI) = 0.87 (0.78, 0.97)].

Statistical superiority on time to first MACE was also demonstrated as the upper bound for the HR was less than 1. For the three components that make up the MACE endpoint, the HR and 95% CI were: 0.78 (0.66, 0.93) for time to first CV death, 0.88 (0.75, 1.03) for time to first non-fatal MI, and 0.89 (0.72, 1.11) for time to first non-fatal stroke. Statistical results were robust with a 2-sided p value of 0.011 for primary MACE and consistent trends among all three MACE components providing substantial evidence of effectiveness for a CV risk reduction indication. Further the results are clinically meaningful with a 22% relative risk reduction in CV death, 12% relative risk reduction in non-fatal MI, and 11% risk reduction in nonfatal stroke as compared to standard of care.

LEADER is a single trial conducted in accordance to the Agency's guidance for industry on new diabetic therapies. Although the evidentiary standard to support a new efficacy claim has typically relied on two or more adequate and well controlled clinical studies,[41] the FDA has previously relied on a single, adequate and well controlled trial in circumstances where a single trial has provided "highly reliable and statistically strong evidence of an important clinical benefit, such as an effect on survival, and a confirmatory study would have been difficult to conduct on ethical grounds,"[42]. For example, on December 2, 2016, FDA approved a new indication for empagliflozin, the reduction of the risk of CV death in patients with CV disease, based on the results of a single trial (i.e., the EMPA-REG outcomes trial). I believe that the results of LEADER are consistent with the cited guidance and are adequate to support a new efficacy claim

[40] Guidance for Industry. Diabetes mellitus — evaluating cardiovascular risk in new antidiabetic therapies to treat type 2 diabetes. Silver Spring, MD: Food and Drug Administration, December, 2008 http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071627.pdf

[41] Section 505 (d) of the Federal Food, Drug, and Cosmetic Act

[42] Guidance for Industry. Providing clinical evidence of effectiveness for human drug and biological products. Silver Spring, MD: Food and Drug Administration, May,1998 https://www.fda.gov/downloads/Drugs/GuidanceCompliance%20RegulatoryInformation/Guidances/UCM078749.pdf+Providing+clinical+evidence+of+effectiveness+for+human+and+bio&client=FDAgov&site=FDAgov&lr=&proxystylesheet=FDAgov&output=xml_no_dtd&ie=UTF-8&access=p&oe=UTF-8

regarding cardiovascular risk reduction. However, I recommend a modification of the Applicant's proposed indication to the following: *as an adjunct to standard treatment of cardiovascular risk factors to reduce the risk of major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke) in adults with type 2 diabetes mellitus and established cardiovascular disease.* The rationale for this recommendation is based on the fact that 1) most (approximately 90%) of the MACE events in LEADER occurred in the '3a' subgroup, i.e. those with established cardiovascular disease 2) the population studied in LEADER was for the most part patients with established cardiovascular disease, 3) the evidence for CV benefit was less robust in patients without established CV disease, and 4) a strong opinion was voiced from the EMDAC due to these aspects of LEADER including a high level of concern about the unforeseen negative impact, i.e. risk, to medical practice of approving the cardiovascular indication for such a large number of patients in the absence of more robust evidence of the benefit.

LEADER also evaluated microvascular efficacy endpoints, specifically, a composite of nephropathy and retinopathy events: need for retinal photocoagulation or treatment with intravitreal agents; vitreous hemorrhage; onset of diabetes related blindness; new or worsening nephropathy; need for continuous renal-replacement therapy in absence of acute reversible cause and death due to renal disease. The trends observed for adjudicated nephropathy and retinopathy events went in opposite directions. With the exception of death due to renal disease, most of the first confirmed nephropathy events favored liraglutide over placebo, while the first adjudicated confirmed retinopathy findings generally favored placebo over liraglutide. However, there are significant concerns about definitions used to define microvascular endpoints, their method of capture, and analysis methods. The Applicant's proposal to include these microvascular outcome endpoints in labeling, therefore, is not acceptable.

In addition to evaluating CV safety of liraglutide, LEADER assessed other safety parameters of interest including neoplasms (e.g. thyroid and pancreatic cancer), pancreatitis, renal safety, 'serious' hypoglycemia, and immunological reactions. I conclude that these additional safety issues were adequately addressed in LEADER and support the conclusion that the PMR can be considered fulfilled. A high level summary of each of these is presented below along with labeling recommendations pertaining to these issues.

Neoplasms: Overall malignant neoplasms were reported in 6.3% of liraglutide-treated subjects vs. 6.0% of placebo-treated subjects [HR 1.06 (95% CI 0.90, 1.25)] suggesting no excess risk. The longer duration of follow up time in LEADER, as compared to the original glycemic controls trials, provides more reliable data to assess malignancy risk. Based on these data and to align with other GLP-1 receptor agonist products I recommend that the 'Malignancy' subsection be removed from section 6 of the PI. Of note, there were very few reported thyroid cancer events of the non-C cell type, i.e. non-MTC thyroid cancers which is insufficient to further elucidate the relationship between

liraglutide and thyroid cancer; it seems reasonable to that the thyroid cancer subsection (i.e. papillary thyroid cancer) remains in the PI.

MTC: No cases of MTC were observed in liraglutide-randomized subjects and one case occurred in a placebo-randomized subject. Calcitonin assessments were unremarkable. While the results of the trial do not suggest an increased risk of MTC due to liraglutide treatment, caution should be exercised in drawing definitive conclusions due to limitations of the trial including the limited number of cases of thyroid neoplasms observed in LEADER and the relatively short trial duration for a malignancy endpoint. It is acknowledged that development of MTC may require longer exposure and be clinically manifest after a long-latency period. Therefore, I believe there is insufficient data to warrant removal of the boxed warning for MTC.

Pancreatic cancer: An imbalance was reported for subjects with event adjudication committee (EAC)-confirmed malignant pancreatic neoplasm: 13 subjects (0.3%) treated with liraglutide vs. 5 subjects (0.1%) on placebo. However, there is some uncertainty regarding the adjudication determinations, which could impact the case count. The overall conclusion of the Oncology consultants is that data generated from LEADER do not appear to substantively alter the original conclusions regarding the lack of sufficient information to conclusively determine whether long term exposure to GLP-RAs increase the risk of pancreatic cancer. Therefore, at this time I believe there is no basis to add this information to product labeling.

Pancreatitis: Overall, a total of 141 potential pancreatitis events were sent for adjudication and 52 events in 43 subjects were confirmed by the EAC; 18 subjects (0.4%) in the liraglutide group (all 18 acute) and 25 (0.5%) in the placebo group (23 acute and 2 chronic). The majority of events were considered mild; 2 events in subjects treated with liraglutide (2/18) and 1 event in a subject treated with placebo (1/25) were adjudicated as severe acute pancreatitis. Approximately one-third of the events in both treatment groups were associated with gallstones. Although the findings appear reassuring, the primary reviewer found that there were more subjects with investigator-reported events of pancreatitis *not* confirmed by the EAC in the liraglutide group vs. the placebo group, including preferred terms of 'pancreatitis' [14 (0.3%) vs. 5 (0.1%), respectively] and 'acute pancreatitis' [9 (0.2%) vs. 4 (0.1%)]. Events that were not confirmed by the EAC did not meet strict pre-defined diagnostic criteria (for example, only were associated with an increase in pancreatic enzymes), and approximately half the events not confirmed by the EAC did not have sufficient diagnostic information available to confirm an event. It remains possible that the adjudication criteria were too strict to allow a meaningful assessment of pancreatitis risk. Further, given the regulatory history of labeling of pancreatitis for liraglutide and for GLP-1 receptor agonist products in general based on controlled trials and postmarketing safety data updating the liraglutide PI to include the adjudicated pancreatitis data from LEADER is not justified, and in fact, may mitigate the risk message. I do recommend removal of the Limitation of Use for pancreatitis and addition to the following in Section 5.2: *VICTOZA has been studied in a limited number of patients with a history of pancreatitis. It is unknown if patients with a history of*

pancreatitis are at higher risk for development of pancreatitis on VICTOZA. The rationale is that in LEADER patients with a history of pancreatitis were included which lessens the concern. However, LEADER was not able to elucidate whether patients with a history of pancreatitis are at a higher risk of development of pancreatitis and it is reasonable to retain this language.

Renal safety: 234 liraglutide-treated subjects (5.0%) vs. 262 placebo-treated subjects (5.6%) had at least 1 acute renal failure-related event based on AE reporting, with most of the small imbalance in favor of liraglutide being driven by fewer events of 'proteinuria'. A small number of subjects died of renal causes as categorized *post hoc* by the CV EAC, with a slight imbalance not in favor of liraglutide [liraglutide 11 (0.2%) vs. placebo 5 (0.1%)]. Most EAC-confirmed 'renal' deaths were related to worsening of chronic renal failure. In contrast, most investigator-reported 'acute renal failure' deaths were related to renal complications of a non-renal condition. These data do not change the overall benefit risk assessment of liraglutide and do not warrant a labeling modification.

Severe hypoglycemia: Severe hypoglycemia was reported in 2.4% of liraglutide-treated subjects and 3.3% of placebo-treated subjects. A slight imbalance was seen in the first few months of the trial in which liraglutide subjects reported more events than placebo; after the first year, events in subjects treated with placebo increased over time to a greater extent than those treated with liraglutide. Severe hypoglycemia episodes were primarily seen in subjects concomitantly treated with insulin, sulfonylureas/glinides, or a combination of these drugs at baseline. In addition, more subjects on placebo than liraglutide started new anti-diabetes medications, including insulin, during the trial. It is likely that the numeric imbalance favoring liraglutide stems from the increased use of hypoglycemia-causing drugs, e.g. sulfonylureas, insulin, in the placebo group, but the data demonstrate that the inherent risk of severe hypoglycemia due to use of liraglutide remains. Therefore, these data do not alter the current benefit risk assessment with regard to hypoglycemia and do not warrant any labeling changes.

Immunogenicity: Investigator-reported adverse events within a search of terms related to 'allergic reaction' were greater in the liraglutide group (1.3%) vs. the placebo group (0.9%); however, certain specific serious adverse events (SAEs) in the liraglutide group such as angioedema, drug hypersensitivity, and anaphylactic reaction often were associated with alternative etiologies. Events of 'immune complex disease' (by MedDRA search) were infrequently reported. Anti-drug antibodies (ADAs) were reported in 11/1247 (0.9%) liraglutide-treated subjects and 2/1267 (0.2%) placebo-treated subjects. In 5 of the 11 subjects in the liraglutide group with ADAs, antibodies showed cross-reactivity to native GLP-1. No subjects developed neutralizing antibodies. Antibodies did not appear to be associated with events of allergic disease, injection site reaction, or immune complex disease, or with loss of efficacy (HbA1c), but as there were very few subjects with antibodies, the ability to characterize the risk is limited. The immunogenicity information from LEADER does not alter the previously established benefit risk assessment. However, the addition of antibody data to section 6.3 of the PI is

appropriate according to current best labeling practices. The Office of Biotechnology Products has confirmed that the assays used in LEADER are acceptable.

Additional Labeling Issues

Changes are being made to align with hypersensitivity reaction updates made to Tanzeum and Trulicity labels on 8/1/17.

Removal of the Limitation of Use (LOU) for first line therapy: The demonstration of CV benefit changes the overall benefit risk assessment for patients with established cardiovascular disease and justifies use of liraglutide as first line therapy. The rationale for removing the LOU for all patients is related to the rationale for its placement at the time of approval. The LOU was included at the time of product approval to prominently provide prescribers with information about use of an unfamiliar new product. The Division intended to inform prescribers to consider alternative therapies in light of the potential MTC risk. The REMS for Victoza has been successful in informing prescribers of this information such that the LOU is no longer needed. It is important to note that the safety consideration, i.e. potential MTC risk that led to the LOU is still maintained in a boxed warning.

Gall bladder disease: Addition to 6.2: In the LEADER trial *[see Clinical Studies (14.2)]*, the incidence of cholelithiasis was 1.5% (3.9 cases per 1000 patient years of observation) in VICTOZA-treated and 1.1% (2.8 cases per 1000 patient years of observation) in placebo-treated patients, both on a background of standard of care. The incidence of acute cholecystitis was 1.1% (2.9 cases per 1000 patient years of observation) in VICTOZA-treated and 0.7% (1.9 cases per 1000 patient years of observation) in placebo-treated patients.

Sponsor's proposed claims for microvascular disease reduction: With regard to nephropathy endpoints, the microvascular definitions, method of capture, and analysis methods do not support a labeling claim of a reduction in microvascular disease.

Claims for (b) (4) I agree with Dr. Parola's conclusion that the data provided are not sufficient (b) (4) (b) (4) and should not be included in labeling.

PLLR: The proposed label submitted with S027 also includes revised labeling intended to comply with the Pregnancy and Lactation Labeling Rule (PLLR). Two products from

Novo Nordisk containing liraglutide include PLLR compliant labeling: Saxenda, a product for weight management, and Xultophy, a combination of liraglutide and insulin degludec approved for the treatment of T2DM. Information about the use of liraglutide in pregnancy and lactation in the revised Victoza label will be based on the PLLR compliant Xultophy label.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

None are recommended.

- Recommendation for other Postmarketing Requirements and Commitments

This supplemental application contained the final report for postmarketing requirement PMR 1589-3 and fulfills this requirement. None are recommended as new PMRs or PMCs.

- Recommended Comments to Applicant

None are recommended.

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/s/

LISA B YANOFF
08/25/2017

JEAN-MARC P GUETTIER
08/25/2017

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022341Orig1s027

MEDICAL REVIEW(S)

Clinical Safety Review
LEADER Trial

Application Type	NDA SE1
Application Number	22341
Priority or Standard	Standard
Submit Date	October 25, 2016
Received Date	October 25, 2016
PDUFA Goal Date	August 25, 2017
Division / Office	DMEP / ODE2
Reviewer Name	Julie Golden
Review Completion Date	July 17, 2017
Established Name	Liraglutide
Trade Name	Victoza
Therapeutic Class	GLP-1 receptor agonist
Applicant	Novo Nordisk, Inc.

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1 Executive Summary

1.1 LEADER Trial

The safety of liraglutide (tradename: Victoza) for the sponsor's proposed indication in patients with type 2 diabetes mellitus (T2DM) is based on review of the clinical study report (CSR) and supporting documentation for the LEADER trial. This safety review focuses on the non-cardiovascular safety findings in LEADER. Dr. Tania Condarco is the primary reviewer for the cardiovascular and microvascular endpoints, including cardiovascular safety. Thyroid cancer in the LEADER trial has been reviewed separately by Dr. Shannon Sullivan.

LEADER is a cardiovascular outcomes trial conducted in 9340 subjects with T2DM. Subjects were treated in a randomized fashion with Victoza 1.8 mg daily or placebo up to a maximum of 5 years, with a median exposure to treatment of 3.5 years.

In general, subjects were well-matched with respect to demographics and baseline characteristics. Average age was 64 years, with 9% of subjects over the age of 75. A total of 36% of subjects were female, 30% were from North America, 77% were white, 8% black, 10% Asian, and 12% Hispanic. Mean BMI was 32.5 kg/m^2, mean duration of diabetes was 12.8 years, and mean HbA1c was 8.7%. More than half of subjects were previous or current smokers.

The safety areas of interest in the LEADER trial were either events associated with glucagon-like peptide-1 receptor agonists (GLP-1 RAs) or similar drugs, events related to type 2 diabetes mellitus (T2DM) or its treatment, or events that have specifically been associated with liraglutide in treatment of T2DM (Victoza) or for chronic weight management (tradename: Saxenda, dose: 3 mg daily). In the LEADER trial, serious adverse events (SAEs) and pre-specified serious and non-serious medical events of special interest (MESIs) were to be reported by the investigator and were systematically collected. Non-cardiovascular, non-microvascular, non-thyroid cancer MESIs in LEADER included deaths, neoplasms, thyroid disease, pancreatitis, acute gallstone disease, hypoglycemia, diabetic foot ulcer, and immunogenicity events. Additional areas of interest included renal and hepatic safety.

In addition, an external independent event adjudication committee (EAC) consisting of 4 subcommittees performed ongoing blinded adjudication and assessment of deaths and certain pre-defined MESIs. Relevant to this safety review are the adjudication findings from the cardiovascular subcommittee (fatal events), pancreatitis subcommittee (acute and chronic pancreatitis), and the neoplasm subcommittee (neoplasms by tissue/organ and malignancy status).

Safety assessment in this trial was comprehensive and well-considered. The sponsor's use of multiple independent adjudication committees for safety allowed for process that was objective and perhaps less vulnerable to bias. A limitation is that because the EAC only confirmed events that met certain strict criteria, some events may have been underestimated. This issue is addressed in the review where possible.

There were 828 randomized subjects who died in the treatment period of the LEADER trial, of which 391 (8.4%) were randomized to Victoza and 461 (9.6%) to placebo. Most deaths (828) occurred during the treatment period (between the randomization and follow-up visits) and 24 deaths occurred between the follow-up visit and database lock. The numbers and proportions of all-cause mortality during the treatment period were 381 (8.2%) and 447 (9.6%) for Victoza and placebo, respectively [hazard ratio (HR) 0.85 (95% CI 0.74, 0.97)]. The majority of deaths were adjudicated as cardiovascular (CV) deaths. A total of 162 (3.5%) deaths in subjects randomized to Victoza and 169 (3.6%) in subjects randomized to placebo were adjudicated as non-CV deaths [HR 0.95 (95% CI: 0.77, 1.18)]. No difference in the rate of non-CV death overall was observed between groups. The most frequently reported causes of non-CV death were malignancy and infection/sepsis; these were seen at similar frequencies in both treatment groups. A small number of deaths were classified as 'renal' by the EAC, with an imbalance not in favor of Victoza [11 (0.2%) vs. 5 (0.1%)]. Most EAC-confirmed 'renal' deaths were related to worsening of chronic renal failure.

Approximately half of the subjects in LEADER reported an SAE, with no difference observed between groups overall. The most frequently reported SAEs were in the 'Cardiac disorders', 'Infections and infestations', and 'Surgical and medical procedures' system organ classes (SOCs), with the incidences in subjects in the Victoza group similar to those in the placebo group. SAEs by SOC occurring at a somewhat greater incidence in the Victoza group include 'Musculoskeletal and connective tissue disorders' (primarily due to arthritis-related terms), 'Vascular disorders' (imbalance noted across a number of terms, including blood pressure disorders and deep vein thrombosis), and 'Hepatobiliary disorders' (particularly gallbladder-related disorders).

The proportion of subjects on Victoza and placebo with SAEs/MESIs leading to permanent treatment discontinuation were 9.6% and 7.3%, respectively. The majority of the imbalance occurred during the first 4 months of the trial and was primarily due to the known gastrointestinal effects of liraglutide (e.g., nausea, vomiting, and diarrhea).

As noted above, a number of adverse events (AEs) were considered of particular interest. These AEs are summarized below:

- Neoplasms: While neoplasms were a pre-specified adverse event of interest in LEADER, the trial was not powered to detect any pre-defined increased risk of any particular neoplasm. In the LEADER trial, all potential neoplasms were sent to the EAC for adjudication. A pathological diagnosis was considered of foremost

importance in confirming an event. The EAC classified neoplasms according to the organ affected/tissue of origin and malignancy status. For EAC-confirmed neoplasms overall, 10.1% of Victoza-treated subjects vs. 9.0% of placebo-treated subjects reported an event. Malignant neoplasms were reported in 6.3% of Victoza-treated subjects vs. 6.0% of placebo-treated subjects [HR 1.06 (95% CI 0.90, 1.25)]. Note that the HRs presented in this section should be considered exploratory. Specific neoplasms of interest (with the exception of thyroid) are discussed further:

- Pancreatic: Given ongoing uncertainty regarding the role of incretin mimetics in pancreatic cancer, in 2014 FDA conducted a review of available nonclinical, clinical trial, and post-marketing data, and concluded at the time that the available data did not support a causal association. Nevertheless, new clinical trial data (for example, from LEADER) to further assess this safety issue remain of interest. An imbalance was reported for subjects with event adjudication committee (EAC)-confirmed malignant pancreatic neoplasm: 13 subjects (0.3%) treated with Victoza vs. 5 subjects (0.1%) on placebo. However, FDA considers there to be some uncertainty regarding the adjudication determinations, which could impact the case count. An FDA Oncology consult team independently reviewed the pancreatic cancer information in LEADER and provided a consultative review. Their overall conclusion is that data generated from LEADER do not appear to substantively alter the original FDA conclusions regarding the lack of sufficient information to conclusively determine whether long term exposure to GLP-RAs increase the risk of pancreatic cancer.

- Breast: Because a numerical imbalance was observed in the phase 3 program that evaluated Saxenda for weight management, post-marketing studies were required to assess the risk of breast cancer associated with liraglutide, including the collection and assessment of data from the LEADER trial. In LEADER, 21 (1.3%) women on Victoza vs. 20 (1.2%) women on placebo developed an EAC-confirmed malignant breast neoplasm [HR 1.06 (95% CI 0.57, 1.96)]. Baseline characteristics, risk factors, and breast cancer staging were similar in the Victoza and placebo treatment groups. Findings in this trial did not appear to suggest an increased risk of breast cancer associated with Victoza.

- Colorectal: An imbalance in colorectal neoplasms was noted in the Saxenda development program, both benign and malignant. In LEADER, the majority of EAC-confirmed colorectal neoplasms were benign, with a numerically higher proportion in Victoza- vs. placebo-treated subjects [Victoza 140, 3.0% vs. placebo 123, 2.6%; HR 1.13 (0.89, 1.45)]. A similar number and proportion of subjects in each treatment group had EAC-confirmed malignant and pre-malignant colorectal neoplasms. The majority of benign colorectal neoplasms were sessile serrated polyps or adenomas with no or

low grade dysplasia. Findings in this trial did not appear to suggest an increased risk of colorectal cancer associated with Victoza.

- Skin: The incidences of EAC-confirmed malignant skin neoplasms – both non-melanoma and melanoma – were numerically higher in the Victoza- vs. the placebo-treated groups [non-melanoma: Victoza n=78 (1.7%), placebo n=62 (1.3%); melanoma: Victoza n=13 (0.3%), placebo n=5 (0.1%)]. The majority of non-melanoma skin neoplasm events were reported as basal cell carcinoma, and the majority of events occurred on the head, neck, or extremities (i.e., sun-exposed areas of the body). Baseline risk factors were similar among the treatment groups. For the melanoma events, the majority of events occurred on the head, neck, or extremities. Although more subjects with melanoma on Victoza had a reported risk factor at baseline (i.e., UV light exposure or history of skin cancer), skin cancer risk factors were generally balanced between treatment groups overall at baseline. Whether the observed imbalance represents a true risk of Victoza is unclear.

- Pancreatitis: As noted above, pancreas safety has historically been an area of interest with incretin mimetics. Acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis, has been reported post-marketing in patients treated with Victoza, and an imbalance in pancreatitis not in favor of liraglutide was noted in both Victoza and Saxenda clinical trials. In the LEADER trial, pancreatitis or acute severe and persistent abdominal pain leading to suspicion of pancreatitis was to be recorded as a MESI. Pancreatitis events and their severity were adjudicated by the EAC pancreatitis subcommittee, based on pre-defined criteria. A total of 141 potential pancreatitis events were sent for adjudication and 52 events in 43 subjects were confirmed by the EAC; 18 subjects (0.4%) in the Victoza group (all acute) and 25 (0.5%) in the placebo group (23 acute and 2 chronic). The majority of events were considered mild; 2 events in subjects treated with Victoza (2/18) and 1 event in a subject treated with placebo (1/23) were adjudicated as severe acute pancreatitis. Approximately one-third of the events in both treatment groups were associated with gallstones. Although the findings appear reassuring, it was noted that there were more subjects with investigator-reported events of pancreatitis *not* confirmed by the EAC in the Victoza group vs. the placebo group, including preferred terms of 'pancreatitis' [14 (0.3%) vs. 5 (0.1%), respectively] and 'acute pancreatitis' [9 (0.2%) vs. 4 (0.1%)]. Events that were not confirmed by the EAC did not meet strict pre-defined diagnostic criteria (for example, only were associated with an increase in pancreatic enzymes). Approximately half the events not confirmed by the EAC did not have full diagnostic information available to confirm an event.

- Acute gallstone disease: Gallstone-related disorders, including cholelithiasis and cholecystitis were reported in association with Saxenda in the development program for weight management. Although obesity and weight loss are associated with an

increased risk for gallstone formation, gallstones were associated with Saxenda at least partially independent of weight loss, raising the possibility that liraglutide may have direct gallbladder effects. In the LEADER trial, AEs of acute gallstone disease (biliary colic or acute cholecystitis) were collected and recorded as MESIs, although they were not adjudicated by the EAC. In a pre-specified search of SAEs/MESIs, 145 subjects (3.1%) treated with Victoza and 90 subjects (1.9%) treated with placebo had at least 1 reported event, such as cholelithiasis or cholecystitis. The majority of events required hospitalization or cholecystectomy. There was not a clear relationship between degree or rapidity of weight loss and development of a gallstone-related event in subjects treated with Victoza.

- Hypoglycemia: In the LEADER trial, blood glucose was measured when there was suspicion of a hypoglycemic episode, and events were captured on a dedicated form. Hypoglycemia episodes were defined according to the American Diabetes Association (ADA) classification; severe hypoglycemia is an episode requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions. Severe hypoglycemia was reported in 2.4% of Victoza-treated subjects and 3.3% of placebo-treated subjects. A slight imbalance was seen in the first few months of the trial in which Victoza subjects reported more events than placebo; after the first year, events in subjects treated with placebo increased over time to a greater extent than those treated with Victoza. Severe hypoglycemia episodes were primarily seen in subjects concomitantly treated with insulin, sulfonylureas/glinides, or a combination of these drugs at baseline. In addition, more subjects on placebo than Victoza started new anti-diabetes medications, including insulin, during the trial.

- Renal safety: Events of diabetic nephropathy were adjudicated in LEADER and are discussed separately in the efficacy review. Acute renal failure was evaluated using a search of pre-defined investigator-reported adverse event terms (such as 'acute kidney injury', 'proteinuria', 'renal failure', and 'renal impairment'). In this assessment, 234 Victoza-treated subjects (5.0%) vs. 262 placebo-treated subjects (5.6%) had at least 1 acute renal failure-related event, with most of the small imbalance in favor of Victoza being driven by fewer events of 'proteinuria'. The majority of events were considered serious (Victoza 3.2%, placebo 3.1%). As noted above, a small number of subjects were adjudicated (*post hoc*) to have died due to renal causes, with a slight imbalance not in favor of Victoza. Similarly, the investigator-reported adverse event search identified 18 subjects (0.4%) treated with Victoza and 14 subjects (0.3%) treated with placebo with an acute renal failure event that led to a fatal outcome. Most investigator-reported 'acute renal failure' deaths were related to renal complications of other conditions.

- Hepatic safety: A slight imbalance in the proportion of subjects with ALT elevations was seen in LEADER, not in favor of Victoza. The sponsor undertook a process of adjudicating certain ALT elevations by blinded independent hepatologists; the

majority of events were considered unlikely due to Victoza. Similarly, a small number of acute hepatic SAEs were seen in Victoza-treated subjects but seem unlikely related to the drug due to confounding factors or negative rechallenges. Nevertheless, increases in ALT and AST associated with liraglutide were also seen in the Saxenda development program, so the LEADER findings are consistent with the previous trial experience. In addition, elevations of liver enzymes, hyperbilirubinemia, cholestasis, and hepatitis have been reported post-marketing.

- Immunogenicity: In the LEADER trial, immunogenicity events suspected by the investigator to be related to trial product were to be recorded as MESIs. Immunogenicity events were not adjudicated by the EAC and the evaluation is based on predefined searches of SAEs and non-serious MESIs for events of allergic reaction, injection site reaction (ISR), and immune complex disease. Although AEs within the 'allergic reaction' search were greater in the Victoza group (1.3%) vs. the placebo group (0.9%), specific SAEs in the Victoza group such as angioedema, drug hypersensitivity, and anaphylactic reaction appeared in most cases to be associated with alternative etiologies. ISRs and events of 'immune complex disease' (by MedDRA search) were infrequently reported. The proportion of subjects with ISRs was higher in the Victoza group (0.7%) vs. the placebo group (0.3%). None of the ISRs were reported as serious or severe.

  Blood samples for determination of anti-drug antibodies (ADAs) were drawn yearly at US sites. Positive ADAs were reported in 11/1247 (0.9%) Victoza-treated subjects and 2/1267 (0.2%) placebo-treated subjects. In 5 of the 11 subjects in the Victoza group with ADAs, antibodies showed cross-reactivity to native GLP-1. No subjects developed neutralizing antibodies. Antibodies did not appear to be associated with SAEs/MESIs of allergic disease, injection site reaction, or immune complex disease, or with loss of efficacy (HbA1c), but as there were very few subjects with antibodies, the ability to characterize the risk is limited.

1.2 Advisory Committee Meeting

On June 20, 2017, the Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) convened to discuss this application. The following question relevant to the safety review was asked of the committee:

The Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial was a cardiovascular (CV) outcomes trial conducted as a postmarketing requirement to evaluate CV safety as per the 2008 FDA Guidance titled Diabetes Mellitus – Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes. Additional non-CV safety concerns related to liraglutide and other incretin mimetics were also evaluated in LEADER, including potential risk of medullary thyroid carcinoma, pancreatic neoplasm, and pancreatitis. For each of these non-CV safety concerns, please comment on whether the data presented today inform of a

causal relationship with liraglutide use. In your discussion, please comment on whether additional studies should be conducted to further evaluate the non-CV safety concern(s).

The committee generally agreed that event rates of the highlighted non-safety concerns were extremely low in comparison to the CV event rates, and that the all-cause mortality benefit outweighed the non-CV safety concerns. Regarding pancreatic cancer, it was generally felt that the numbers were too small and duration of the trial too short to conclude a causal relationship with the drug. Committee members were generally reassured by the pancreatitis findings in this trial, but did note the imbalance in gallbladder disease. Committee members also did not feel that animal data were informative for the pancreatic signal.

1.3 Benefit-Risk Summary

In summary, small imbalances were seen for a number of adverse events noted above, but these risks have been well-characterized and, in my opinion, are outweighed by the CV benefit for Victoza identified in LEADER. Specifically for pancreatic cancer, I agree with the committee that the numbers are too small and duration is too short to definitively rule the risk in or out. It should be noted that the hazard ratios for malignancies of various tissue types were observed both in favor and not in favor of Victoza. At this time, LEADER does not appear to change the 2014 FDA assessment for GLP-1 RAs and pancreatic cancer. With respect to pancreatitis, I am less reassured by the lack of a signal in the adjudicated event analysis given the limitations of the trial, which required diagnosis based on strict EAC definitions but did not require full pancreatitis data collection per protocol. Based on review of the investigator-reported terms, I believe the previously identified post-marketing signal for pancreatitis with Victoza is not dismissed by the findings in this trial. I would therefore recommend that pancreatitis remain a Warnings and Precautions (W&P) in Victoza labeling. In addition, a new signal was observed in this trial for gallbladder disease, including cholelithiasis and cholecystitis. This may be a class effect, and was observed previously with Saxenda. I would recommend acute gallstone disease be labeled in W&P for Victoza as it is in the Saxenda label.

2 Methods

2.1 Identification, Categorization, and Evaluation of Adverse Events

The safety areas of interest in this review of the LEADER trial were either events associated with GLP-1 RAs or similar drugs, events related to T2DM or its treatment, or events that have specifically been associated with liraglutide in treatment of T2DM (Victoza) or for chronic weight management (Saxenda).

In the LEADER trial, SAEs and pre-specified serious and non-serious MESIs were to be reported by the investigator and were therefore systematically collected. According to the protocol, a MESI is a predefined event of scientific and medical concern that the

sponsor continues to monitor. A MESI could be serious or non-serious and did not necessarily have a causal relationship with the trial product.

Table 1 below describes the MESIs and other areas of interest for this trial, and whether or not these events were independently adjudicated by the event adjudication committee (EAC). The specific process for collection, adjudication, and analysis of safety issues of interest are discussed for the respective safety issues in Section 9 of this review (Targeted Safety Issues).

Table 1. Safety Areas of Interest

Events of interest in safety evaluation	Sent for adjudication	MedDRA search criteria	Based on eCRF/laboratory measurement
Pre-defined MESIs[a]			
Deaths (cardiovascular and non-cardiovascular deaths)	X		
Acute coronary syndrome (myocardial infarction, hospitalization for unstable angina pectoris)	X		
Cerebrovascular events (stroke, transient ischemic attack)	X		
Hospitalization for heart failure	X		
Nephropathy	X		
Diabetic retinopathy	X		
Diabetic foot ulcer		X	
Neoplasms (excluding thyroid neoplasm)	X		
Thyroid neoplasms and thyroid disease	X[b]	X	
Calcitonin values ≥ 20 ng/L as marker for medullary thyroid cancer			X (laboratory measurement)
Pancreatitis	X		
Acute gallstone disease		X	
Severe hypoglycemic events			X (hypoglycemia form, eCRF)
Immunogenicity events (allergic reactions, injection site reactions, immune complex disease, and anti-liraglutide antibody formation)		X	X (antibody measurement)
Additional areas of interest			
Renal safety (including events of acute renal failure)		X	X (laboratory measurement)
Hepatic safety (including drug-related hepatic disorders)		X	X (laboratory measurement)
Suicidality/self-injury		X	
Rare events		X	
Suspected transmission of an infectious agent via trial product[c]		X	
Overdose		X	

AE: adverse event; eCRF: electronic case report form; MedDRA: medical dictionary for regulatory activities; MESI: medical event of special interest
a Medication errors and AEs leading to permanent treatment discontinuation were also defined as MESIs in LEADER
b Thyroid neoplasms and events sent for thyroidectomy (partial or total) for any reason during the trial
c No events potentially related to suspected transmission of infectious agent via trial product were captured using the sponsor's MedDRA search; this MESI is therefore not discussed further in this review.

Source: Summary of Clinical Safety, Table 1-2

Non-serious adverse events and non-MESIs were not required to be reported, but could be reported if evaluated as related to trial product by the investigator or if other local

requirements applied.[1] Non-serious AEs and non-MESIs (including events listed in 'additional areas of interest' in the table above) were therefore not systematically collected. These data in some cases are reviewed for completeness, but are limited by the nature of the data collection.

In addition, an external independent event adjudication committee (EAC) consisting of 4 subcommittees performed ongoing blinded adjudication and assessment of deaths and pre-defined MESIs. Confirmed events were categorized based on the definitions and classifications below (and described in the EAC Charter):

[1] The sponsor did a blinded review of all non-serious non-MESIs during the trial to identify potential MESIs or SAEs that had not been reported as such. Queries were sent to sites for those AEs for consideration for assignment. Any upgrades to SAE and MESI were done at the investigator's discretion.

Table 2. Classification of Events Adjudicated by the EAC

Adjudicated event type	EAC committee responsible for adjudication
Fatal events • Cardiovascular death • Non-cardiovascular death • Undetermined cause of death	Cardiovascular subcommittee
Acute coronary syndrome • Myocardial infarction • Hospitalization for unstable angina pectoris	Cardiovascular subcommittee
Cerebrovascular event • Stroke • Transient ischemic attack	Cardiovascular subcommittee
Hospitalization for heart failure	Cardiovascular subcommittee
Coronary revascularization procedure	Cardiovascular subcommittee
Diabetic retinopathy • Need for retinal photocoagulation or treatment with intravitreal agents • Vitreous hemorrhage • Development of diabetes-related blindness	Microvascular subcommittee
Nephropathy • New onset of persistent macroalbuminuria • Peristent doubling of serum creatinine level and eGFR per MDRD ≤ 45 mL/min/1.73m^2 • Need for continuous renal-replacement therapy (in the absence of an acute reversible cause) • Death due to renal disease	Microvascular subcommittee
Pancreatitis • Acute pancreatitis • Chronic pancreatitis	Pancreatitis subcommittee
Neoplasm (excluding thyroid neoplasm) • Malignant neoplasm • Pre-malignant/carcinoma *in situ*/borderline neoplasm • Benign neoplasm • Neoplasms of uncertain or unknown behavior (unclassified)	Neoplasm subcommittee
Thyroid neoplasm • C-cell hyperplasia • Medullary microcarcinoma (carcinoma *in situ*) • Medullary carcinoma • Other	Neoplasm subcommittee
EAC: event adjudication committee; eGFR (per MDRD); estimated glomerular filtration rate per modification of diet in renal disease	

Source: Summary of Clinical Safety, Table 1-3

The use of multiple independent EACs for safety allowed for process that was objective and perhaps less vulnerable to bias. A limitation is that because the EAC only confirmed events that met certain strict criteria, some events may have been underestimated. This issue is addressed in the review where possible.

The Medical Dictionary for Regulatory Activities (MedDRA) version 18.0 was used to code AEs in LEADER. I assessed the categorization of events by comparing the verbatim terms used by investigators to the preferred terms (PTs), focusing on events that led to discontinuation of treatment. Based on this evaluation, I believe that AEs were generally categorized appropriately.

2.2 Routine Clinical Testing

Laboratory, ECG, and vital sign testing were conducted according to the schedule in Table 3. In my opinion, these assessments were adequate for a trial of this size and scope.

Table 3. Routine Clinical Testing

	Screening (V1)	Rand. (V3)	6 mo (V6)	12 mo (V7)	24 mo (V9)	36 mo (V11)	48 mo (V13)	60 mo/EOT (V15)	Follow-up/EOT + 30d (V16)
Biochemistry[a]	X[b]	X[c]	X	X	X[c]	X	X	X[c]	
Hematology[d]		X			X			X	
Calcitonin[e]	X			X	X	X	X	X	X[f]
Anti-drug antibodies[g]		X		X	X	X	X		X
Urine albumin: creatinine ratio		X		X	X	X	X	X	
Urine hCG[h,i]	X							X	
12-lead ECG		X		X	X	X	X	X	
Vital signs[j]	X	X	X	X	X	X	X	X	
Self-monitored plasma glucose[k,l]		←	—	—	—	—	—	→	

a lipase, amylase, creatinine, total bilirubin, ALT
b creatinine only
c plus calcium, potassium, and sodium
d hemoglobin, hematocrit, platelets, RBC, WBC
e for subjects with calcitonin ≥ 50 ng/L, procalcitonin, calcitonin gene-related peptide, and carcinoembryonic antigen also measured
f only subjects with calcitonin > 2x ULN at V15 and < ULN at screening
g only in a subset of subjects
h women of child-bearing potential
i will be conducted anytime menstrual period is missed
j systolic blood pressure, diastolic blood pressure, heart rate
k throughout according to investigator's instructions
l subjects will record hypoglycemic events from visit 3

Source: Reviewer created from LEADER protocol

3 Exposure and Demographics

The dose used in the trial was 1.8 mg once daily. Subjects were started with a dose of 0.6 mg/day and dose-escalated over a period of 3 to 4 weeks to a maintenance dose of 1.8 mg/day. If the maximum dose was not tolerated or otherwise associated with unacceptable adverse events, a gradual reduction in dose (to 1.2 mg/day or 0.6 mg/day) was allowed at the investigator's discretion. A total of 84.8% of the total exposure to Victoza during the trial was to the 1.8 mg dose (Table 4).

Table 4. Liraglutide Exposure by Dose

Dose	Proportion of Exposure According to Dose
0.6 mg	5.5%
1.2 mg	9.6%
1.8 mg	84.8%
Exposure divided into the per-protocol doses of Victoza including the in-total 2-weeks dose escalation period from 0.6% to 1.2 mg and 1.2 mg to 1.8 mg, respectively, after randomization	

Source: LEADER CSR, Table 14.2.25

Table 5 and Table 6 below summarize observation time (time on-study) and exposure time (time on-treatment). Median exposure to treatment in this trial was 3.52 years (min 0.00, max 5.01 years), and mean (SD) exposure was 3.07 (1.27) years. More than 70% of subjects were exposed for 90% of more of the observation time, whereas 6.7% of Victoza-treated subjects and 5.9% of placebo-treated subjects were exposed for less than 10% of the observation time.

Table 5. Summary of Mean and Median Trial Observation and Treatment Exposure

	Victoza	Placebo	Total
Number of subjects	4668	4672	9340
Total years in trial (patient-years of observation)	17822	17741	35563
Median proportion of years of observation including follow-up period	3.84	3.84	3.84
Total years in trial excluding follow-up period	17341	17282	34623
Median proportion of years of observation excluding follow-up period	3.75	3.75	3.75
Total years of exposure to trial drug	14502	14157	28659
Median proportion of years of exposure to trial drug	3.52	3.51	3.52
Subjects with 1 or more drug holidays, N (%) (exposed and alive subjects at follow-up)	1687 (36.1)	1584 (33.9)	3271 (35.0)
Mean proportion of time on trial drug	0.84	0.82	0.83
Median proportion of time on trial drug	1.00	1.00	1.00

Source: LEADER CSR, Table 14.2.2

Table 6. Summary of Categorical Exposure

	Victoza	Placebo	Total
Number of subjects	4668	4672	9340
Exposed, N (%)			
N	4657 (100.0)	4664 (100.0)	9321 (100.0)
0-1 years	571 (12.3)	608 (13.0)	1179 (12.6)
1-2 years	318 (6.8)	410 (8.8)	728 (7.8)
2-3 years	357 (7.7)	412 (8.8)	769 (8.3)
3-4 years	2482 (53.3)	2363 (50.7)	4845 (52.0)
4-5 years	927 (19.9)	869 (18.6)	1796 (19.3)
5-6 years	2 (<0.1)	2 (<0.1)	4 (<0.1)

Source: LEADER CSR, Table 14.2.5

Study duration was adequate for the majority of safety concerns. Certain safety issues – such as cancer – that may take years or even decades to develop may not be fully characterized, even in a 3- to 5-year trial.

In general, subjects were well-matched with respect to demographics and baseline characteristics. Average age was 64 years, with 9% of subjects over the age of 75. A total of 36% of subjects were female, 30% were from North America, 77% were white, 8% black, 10% Asian, and 12% Hispanic. Mean BMI was 32.5 kg/m^2, mean duration of diabetes was 12.8 years, and mean HbA1c was 8.7%. More than half of subjects were previous or current smokers.

Regarding other medical history, 2.4% of subjects had severe renal impairment at baseline, 2.8% had a history of pancreatitis, 11.8% had a history of gallbladder disease, and 20.1% had diabetic retinopathy, 34.6% had diabetic neuropathy, and 40.7% had diabetic nephropathy at screening. A total of 5.6% reported a history of neoplasm (any type). Medical history was generally well-balanced among the groups.

Similar proportions of subjects in the 2 treatment groups at baseline were on antihypertensive therapy (92.4%), diuretics (41.8%), statins (72.2%), anti-platelet therapy (67.7%), and anticoagulants (6.7%).

4 Deaths

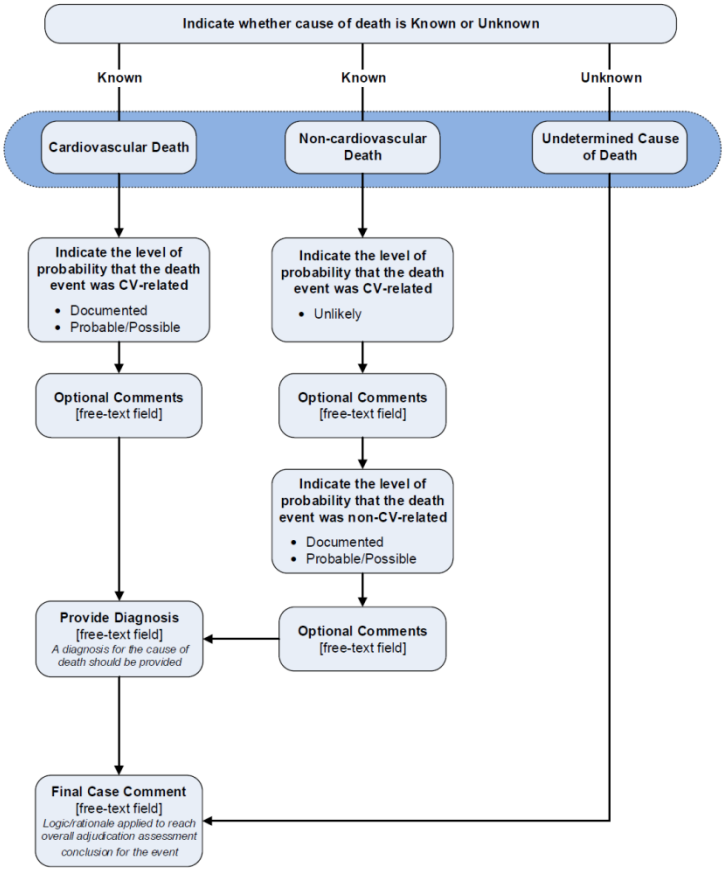
A total of 852 randomized subjects died in the LEADER trial, of which 391 (8.4%) were randomized to Victoza and 461 (9.9%) to placebo. Most deaths (828) occurred during the treatment period (between the randomization and follow-up visits) and 24 deaths occurred between the follow-up visit and database lock.[2]

[2] One additional death was reported after closure of the trial: subject (b) (6), a 73-year-old male, died more than 2.5 years after the last dose of Victoza. No further information of the fatal outcome was available. During the trial, the subject had EAC-confirmed events of non-fatal stroke, hospitalization for

The numbers and proportions of all-cause mortality during the treatment period were 381 (8.2%) and 447 (9.6%) for Victoza and placebo, respectively [hazard ratio (HR) 0.847 (95% CI 0.739, 0.971)]. A *post hoc* sensitivity analysis evaluating all-cause mortality, only including events on randomized treatment, showed proportions of 2.6% and 3.5% for Victoza and placebo, respectively [HR 0.719 (95% CI 0.568, 0.911)].

All deaths in randomized subjects were sent for adjudication by the cardiovascular EAC to identify potential cardiovascular (CV) deaths (Figure 1).

Figure 1. Death Adjudication Process



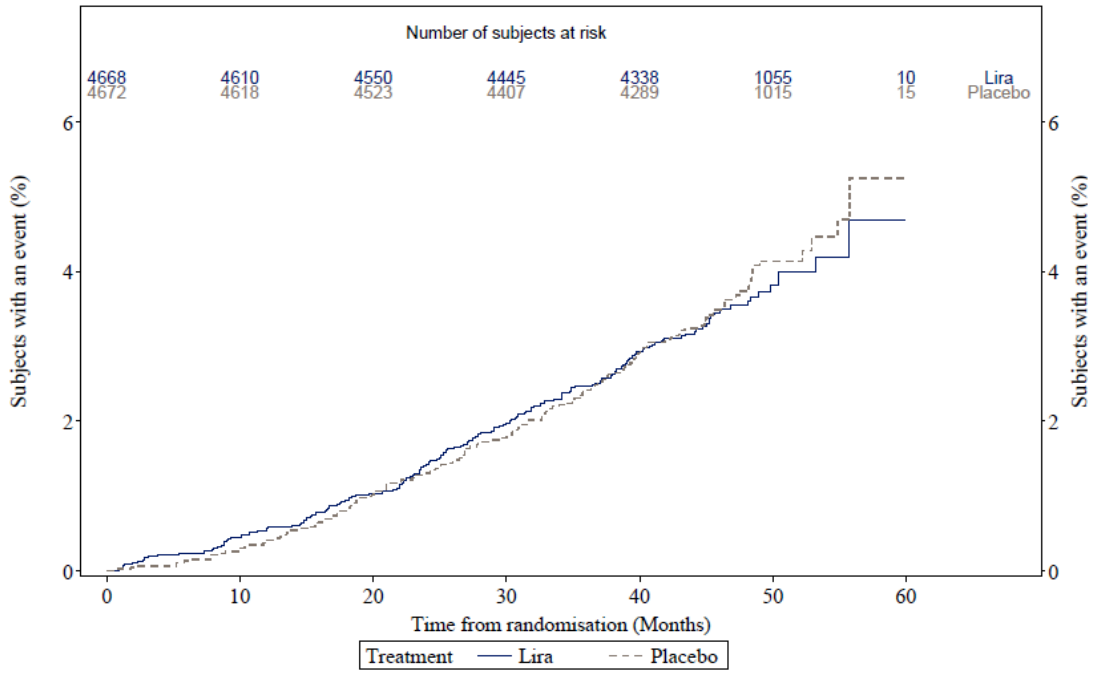
Source: Event Adjudication Committee Charter, Death Event Adjudication Assessment Logic Flow

A total of 508 deaths (59.6%) were confirmed by the EAC as CV deaths and 344 (40.4%) were confirmed as non-CV deaths. Deaths for which a cause could not be determined (Victoza n=70, 1.5%; placebo n=81, 1.7%) were adjudicated as CV deaths. This section of the review will focus on EAC-confirmed non-CV deaths.

heart failure, nephropathy, and malignant and benign colorectal neoplasms. The death was not adjudicated and is not described or analyzed further.

A total of 162 (3.5%) deaths in subjects randomized to Victoza and 169 (3.6%) in subjects randomized to placebo were reported and adjudicated as non-CV deaths [HR 0.952 (95% CI: 0.768, 1.181)]. No difference in the rate of non-CV death overall was observed between groups, as shown in the Kaplan-Meier plot below.

Figure 2. Kaplan-Meier Plot of Time to Non-Cardiovascular Death



Source: LEADER CSR, Figure 14.2.76

The diagnoses provided by the adjudicators for the non-CV fatal events were classified by the sponsor post-database lock according to the non-CV death categories defined in the EAC charter.[3] Therefore, although the adjudicators provided a non-CV death diagnosis, the sponsor was responsible for further sub-classifying non-CV deaths.[4]

An overview of the *post hoc* classification of EAC-confirmed non-CV deaths is shown in Table 7 for events from randomization to follow-up. The most frequently reported causes of non-CV deaths were malignancy and infection (including sepsis); these were

[3] Non-cardiovascular death was defined as any death not covered by the cardiac death or vascular death categories and was further categorized into following groups: pulmonary causes, renal causes, gastrointestinal causes, infection (includes sepsis), non-infectious [e.g., systemic inflammatory response syndrome (SIRS)], malignancy (i.e., new malignancy, worsening of prior malignancy), hemorrhage- not intracranial, accidental/trauma, suicide, non-cardiovascular system organ failure (e.g., hepatic failure), non-cardiovascular surgery, other non-cardiovascular.

[4] Note that non-CV deaths were not adjudicated according to the non-CV secondary endpoints by the CV subcommittee, therefore, a death classified as non-CV death and characterized with an EAC-assigned plausible cause of death of, for example, "pancreatitis", would only count as an EAC-confirmed pancreatitis event if it had independently been confirmed as such event by the relevant (pancreatitis) EAC sub-committee.

seen at similar frequencies in both treatment groups. Although the numbers are small, the observed slight imbalance in adjudicated renal deaths not in favor of Victoza is noted. Renal safety, including deaths is discussed further in Section 9.5. In 8 deaths in the Victoza group and 12 deaths in the placebo group, the cause of the non-CV death could not be classified.[5]

Table 7. EAC-Confirmed Deaths, Randomization to Follow-Up

	Victoza N=4668 n (%)	**Placebo N=4672 n (%)**	**Total N=9340 n (%)**
Deaths, all-causes	381 (8.2)	447 (9.6)	828 (8.9)
Unknown cause	70 (1.5)	81 (1.7)	151 (1.6)
Cardiovascular death	149 (3.2)	197 (4.2)	346 (3.7)
Non-cardiovascular death (sponsor sub-classification)	162 (3.5)	169 (3.6)	331 (3.5)
Malignancy	65 (1.4)	67 (1.4)	132 (1.4)
Infection	37 (0.8)	41 (0.9)	78 (0.8)
Accidental/trauma	12 (0.3)	14 (0.3)	26 (0.3)
Pulmonary	7 (0.1)	12 (0.3)	19 (0.2)
Renal	11 (0.2)	5 (0.1)	16 (0.2)
Hemorrhage (non-intracranial)	6 (0.1)	4 (<0.1)	10 (0.1)
System organ failure (non-CV)	5 (0.1)	3 (<0.1)	8 (<0.1)
Other non-CV death	3 (<0.1)	5 (0.1)	8 (<0.1)
Gastrointestinal	4 (<0.1)	2 (<0.1)	6 (<0.1)
Non-CV surgery	2 (<0.1)	1 (<0.1)	3 (<0.1)
Suicide	1 (<0.1)	2 (<0.1)	3 (<0.1)
Non-infectious (e.g., SIRS)	1 (<0.1)	1 (<0.1)	2 (<0.1)
Unclassifiable[5]	8 (0.2)	12 (0.3)	20 (0.2)
The total number of adjudicated deaths with 'unknown cause' includes 3 subjects (b) (6) where the EAC Chair during multiple events review had linked the deaths to an EAC-confirmed MI (b) (6) and stroke (6 (b) (6)) occurring within the same subject. In this table, these 3 linked deaths are only counted in 'unknown cause'.			

Source: LEADER CSR, Table 12-15

Sponsor death classifications based on EAC descriptions were reviewed (see Section 13.1 in the appendix) and generally appear to be appropriate. Nevertheless, as shown in the examples in Section 13.1.1, clear classification can be challenging given multiple comorbidities and events leading to death. The above sub-classifications and subsequent analysis should therefore be considered exploratory.

An evaluation of investigator-reported AEs in cases of death adjudicated as "unknown cause" was also conducted. The majority were reported as preferred term 'death' (Victoza 40, 0.9%; placebo 39, 0.8%) within the 'General disorders and administration conditions' system organ class (SOC). The following is a listing by SOC.

[5] 'Unclassifiable' was used when the 2 adjudicators did not enter a comparable cause of death for a specific event (e.g., pneumonia and hip fracture).

Table 8. AEs Leading to Death as Reported by Investigators, Adjudicated as "Unknown Cause"

SOC	Victoza N=4668 n (%)	Placebo N=4672 n (%)
General disorders and administration site conditions	48 (1.0)	47 (1.0)
Cardiac disorders	10 (0.2)	19 (0.4)
Nervous system disorders	3 (0.1)	3 (0.1)
Respiratory, thoracic and mediastinal disorders	3 (0.1)	2 (<0.1)
Vascular disorders	3 (0.1)	2 (<0.1)
Infections and infestations	2 (<0.1)	5 (0.1)
Renal and urinary disorders	2 (<0.1)	2 (<0.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (<0.1)	2 (<0.1)
Blood and lymphatic system disorders	1 (<0.1)	0
Injury, poisoning and procedural complications	1 (<0.1)	0
Metabolism and nutrition disorders	0	2 (<0.1)
Gastrointestinal disorders	0	1 (<0.1)
Psychiatric disorders	0	1 (<0.1)

Source: Response to FDA Information Request 20 March 2017, Appendix 1, Table 25

5 Serious Adverse Events

This section is a compilation of fatal and non-fatal SAEs as reported by the investigator.[6] A total of 13,641 SAEs were reported in 50.0% of subjects, with no difference observed between groups overall (Table 9).

[6] In addition to the SAEs described in this section, 37 events in 33 subjects (18 subjects in the Victoza group and 15 subjects in the placebo group) were upgraded from non-serious MESIs to SAEs based on assessment by the sponsor. The upgraded events were mainly related to hypoglycemia and neoplasms.

Table 9. Serious Adverse Events, Summary

	Victoza N=4668 n (%)	**Placebo N=4672 n (%)**
SAEs, total	2320 (49.7)	2354 (50.4)
MESI SAEs	1536 (32.9)	1613 (34.5)
Severity		
Severe	1429 (30.6)	1483 (31.7)
Moderate	1331 (28.5)	1368 (29.3)
Mild	513 (11.0)	530 (11.3)
Missing	2 (<0.1)	2 (<0.1)
Related		
Probable	48 (1.0)	41 (0.9)
Possible	242 (5.2)	244 (5.2)
Unlikely	2230 (47.8)	2270 (48.6)
Missing	1 (<0.1)	6 (0.1)
Outcome		
Fatal	382 (8.2)	447 (9.6)
Not recovered	507 (10.9)	522 (11.2)
Recovered with sequelae	206 (4.4)	218 (4.7)
Recovering	74 (1.6)	51 (1.1)
Recovered	1954 (41.9)	1992 (42.6)
Unknown	6 (0.1)	6 (0.1)
Action taken		
Product withdrawn temporarily	643 (13.8)	658 (14.1)
Product withdrawn permanently	194 (4.2)	246 (5.3)
Dose reduced	16 (0.3)	3 (<0.1)
Dose increased	1 (<0.1)	0
Dose not changed	1545 (33.1)	1605 (34.4)
Unknown	13 (0.3)	15 (0.3)
Missing	725 (15.5)	739 (15.8)

Source: LEADER CSR, Table 12-16

The most frequently reported SAEs were in the 'Cardiac disorders', 'Infections and infestations', and 'Surgical and medical procedures' SOCs, with the incidences in subjects in the Victoza group similar to those in the placebo group. SAEs by SOC occurring at a greater incidence in the Victoza group include 'Musculoskeletal and connective tissue disorders', 'Vascular disorders', and 'Hepatobiliary disorders' (Table 10).

Table 10. SAEs by System Organ Class

	Victoza N=4668		Placebo N=4672	
	n	%	n	%
Cardiac disorders	870	18.6	957	20.5
Infections and infestations	527	11.3	569	12.2
Surgical and medical procedures	493	10.6	509	10.9
Nervous system disorders	372	8.0	383	8.2
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	300	6.4	306	6.5
Gastrointestinal disorders	271	5.8	286	6.1
Renal and urinary disorders	270	5.8	274	5.9
General disorders and administration site conditions	227	4.9	255	5.5
Injury, poisoning and procedural complications	224	4.8	240	5.1
Musculoskeletal and connective tissue disorders	216	4.6	198	4.2
Respiratory, thoracic and mediastinal disorders	213	4.6	255	5.5
Vascular disorders	210	4.5	179	3.8
Metabolism and nutrition disorders	185	4.0	245	5.2
Hepatobiliary disorders	122	2.6	78	1.7
Skin and subcutaneous tissue disorders	100	2.1	116	2.5
Eye disorders	69	1.5	74	1.6
Reproductive system and breast disorders	56	1.2	40	0.9
Investigations	54	1.2	68	1.5
Blood and lymphatic system disorders	54	1.2	46	1.0
Psychiatric disorders	31	0.7	38	0.8
Endocrine disorders	23	0.5	9	0.2
Ear and labyrinth disorders	15	0.3	13	0.3
Immune system disorders	12	0.3	5	0.1
Congenital, familial and genetic disorders	8	0.2	6	0.1
Social circumstances	0	0.0	2	0.0

Source: Reviewer created from LEADER datasets

Preferred terms that drive the small imbalance of SAEs in the 'Musculoskeletal and connective tissue disorders' SOC include osteoarthritis (Victoza 1.6%, placebo 1.4%) and arthritis (Victoza 0.3%, placebo 0.1%).

An evaluation of MedDRA high level group terms (HLGT) within the SOC 'Vascular disorders' demonstrated that the imbalances not in favor of Victoza were due to small imbalances across a number of terms (Table 11). Within the 'Embolism and thrombosis' HLGT, the majority of the imbalance in SAEs was seen in the PT 'deep vein thrombosis' (Victoza n=20, 0.4%; placebo n=10, 0.2%). Importantly, there was no increased incidence of 'pulmonary embolism' AEs/SAEs[7] in the Victoza (n=21, 0.4%) vs. placebo group (n=24, 0.5%).

[7] All pulmonary embolism AEs were SAEs

Table 11. Vascular Disorders SAEs, by HLGT

	Victoza N=4668	Placebo N=4672
Vascular disorders SOC	210 (4.5)	179 (3.8)
Arteriosclerosis, stenosis, vascular insufficiency and necrosis	78 (1.7)	75 (1.6)
Vascular hypertensive disorders	50 (1.1)	43 (0.9)
Decreased and nonspecific blood pressure disorders and shock	42 (0.9)	32 (0.7)
Embolism and thrombosis	30 (0.6)	16 (0.3)
Aneurysms and artery dissections	13 (0.3)	8 (0.2)
Vascular disorders NEC	11 (0.2)	8 (0.2)
Vascular hemorrhagic disorders	3 (0.1)	5 (0.1)
Lymphatic vessel disorders	2 (<0.1)	2 (<0.1)
Vascular inflammations	2 (<0.1)	2 (<0.1)
Venous varices	1 (<0.1)	2 (<0.1)

Source: Reviewer created from LEADER datasets

A higher proportion of events from the MedDRA high level term (HLT) category 'Cholecystitis and cholelithiasis' were reported in the Victoza group (2.0% vs. 1.3%); these events drive the imbalance observed in the 'Hepatobiliary disorders' SOC. Gallbladder-related events are discussed further in Section 9.3. Two reported SAEs of 'hepatic failure' in Victoza-treated subjects are discussed in Section 9.6.1.

While reviewing other SAE terms, the following imbalances were noted:

- A slightly higher proportion of subjects in the Victoza group reported SAEs of the PT acute kidney injury (2.3% vs. 2.0%). Renal events are discussed further in Section 9.5.1.

- Although a small imbalance in the PT 'sepsis' was noted in the Victoza vs. placebo group (1.0% vs. 0.7%), there was no difference in groups in the 'Sepsis, bacteremia, viremia and fungemia NEC' HLT (1.5% vs. 1.6%), which includes PTs such as 'urosepsis' and 'septic shock'.

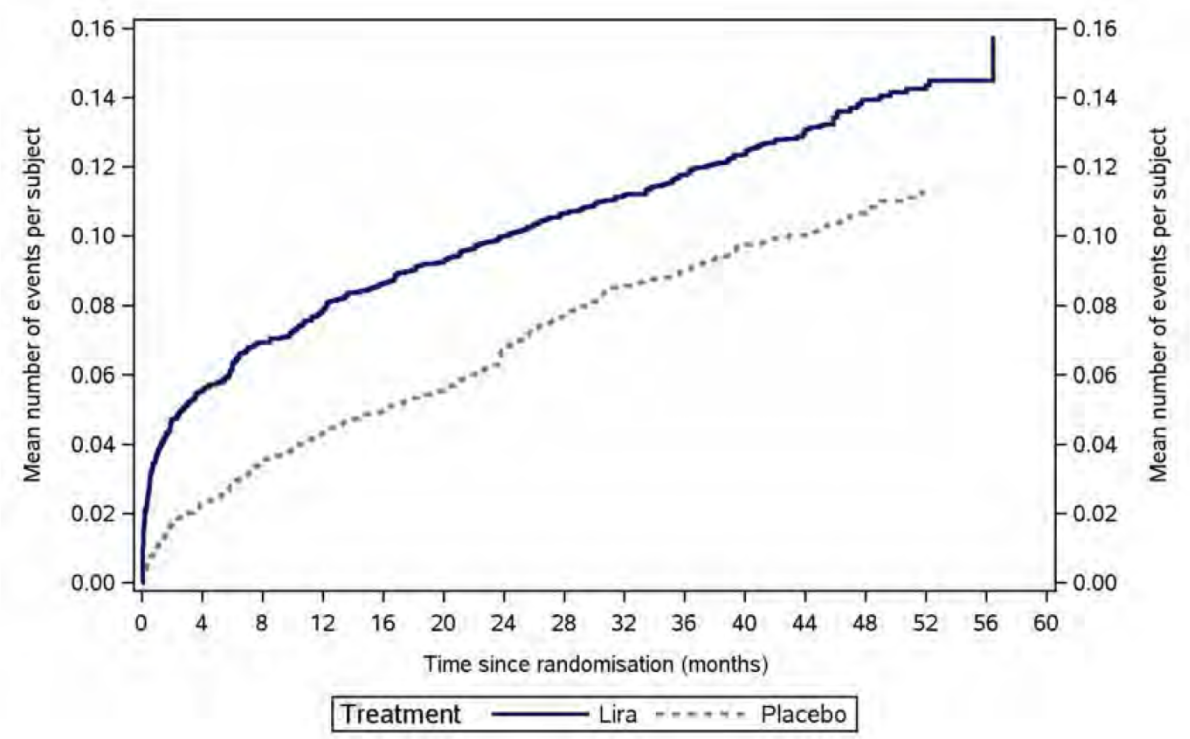
- An imbalance in SAEs not in favor of Victoza that contained 'carotid' in the preferred term was observed in an exploratory search (see Section 13.2.1 in the appendix); the clinical significance is unclear as Victoza was associated with a numerically lower incidence of EAC-confirmed cerebrovascular index events, including ischemic stroke (see the review of efficacy).

6 Adverse Events Leading to Treatment Discontinuation

According to the protocol, any AEs leading to treatment discontinuation were to be recorded as a MESI; however, some AEs leading to discontinuation were not reported as MESIs by the investigator. The sponsor only presented AEs leading to permanent discontinuation that were specifically categorized as SAEs or non-serious MESIs.

The proportion of subjects on Victoza and placebo with SAEs or non-serious MESIs leading to permanent treatment discontinuation were 9.6% and 7.3%, respectively. The majority of the imbalance occurred during the first 4 months (Figure 3) and was primarily due to the known gastrointestinal effects of liraglutide (nausea 1.6% vs. 0.4%, vomiting 0.7% vs. <0.1%, and diarrhea 0.6% vs. 0.1%).

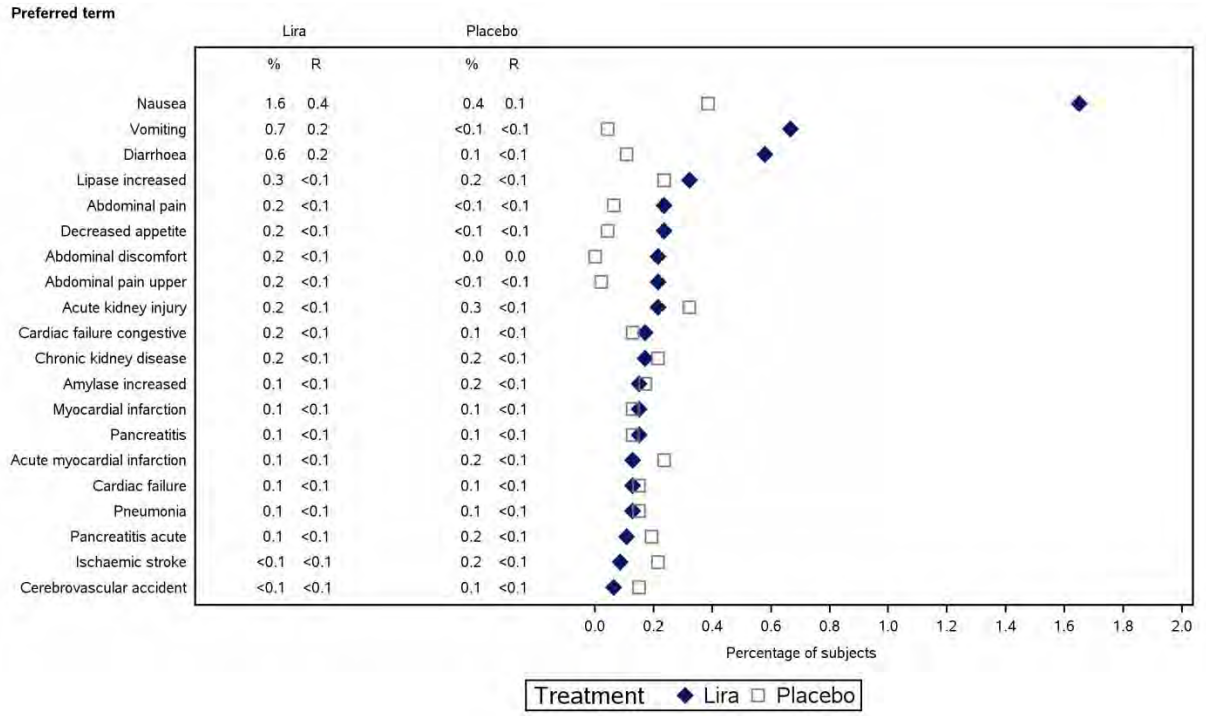
Figure 3. Adverse Events (SAEs/MESIs) Leading to Permanent Treatment Discontinuation of Trial Product



Source: LEADER CSR, Figure 12-51

The 20 most frequent events leading to permanent discontinuation are presented in the figure below:

Figure 4. SAEs and MESIs Leading to Permanent Treatment Discontinuation



Note: Percentages are sorted by descending frequency in the liraglutide group. The selection criterion of the 20 most frequent cut-offs is based on the percentages of the total population. MedDRA version 18.0
Abbreviations: %: percentage of subjects experiencing at least one event; FAS: full analysis set; Lira: liraglutide; MESI: medical event of special interest; R: event rate per 100 patient years of observation.

Source: LEADER CSR, Figure 12-52

As noted above, the sponsor only presented AEs leading to permanent discontinuation that were either categorized as SAEs or non-serious MESIs; nevertheless, there were 47 events that led to permanent treatment discontinuation that were *not* classified as SAE or MESI events (despite the fact that discontinuations due to AEs were to be reported as MESIs). Most of these non-SAE, non-MESI discontinuation events were reported as single preferred terms. Two events of non-SAE, non-MESI 'depression' that led to treatment discontinuation were reported in Victoza-treated subjects. Suicidality is discussed further in Section 9.10.

7 Severe and Other Significant Adverse Events

This section presents SAEs or non-serious MESIs considered 'severe' by the investigator. The following table categorizes the severe AEs by MedDRA SOC. Overall, a similar proportion of AEs were considered severe in each group.

Table 12. Severe SAEs or Non-Serious MESIs by System Organ Class

	Victoza N=4668		Placebo N=4672	
	n	%	n	%
'Severe' SAEs or non-SAE MESIs	1502	32.2	1533	32.8
Cardiac disorders	526	11.3	572	12.2
Infections and infestations	277	5.9	279	6.0
Surgical and medical procedures	268	5.7	292	6.3
Nervous system disorders	214	4.6	221	4.7
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	176	3.8	179	3.8
Renal and urinary disorders	165	3.5	159	3.4
Gastrointestinal disorders	146	3.1	122	2.6
General disorders and administration site conditions	136	2.9	150	3.2
Metabolism and nutrition disorders	122	2.6	144	3.1
Respiratory, thoracic and mediastinal disorders	120	2.6	143	3.1
Injury, poisoning and procedural complications	103	2.2	116	2.5
Vascular disorders	100	2.1	102	2.2
Musculoskeletal and connective tissue disorders	83	1.8	74	1.6
Hepatobiliary disorders	47	1.0	37	0.8
Skin and subcutaneous tissue disorders	43	0.9	56	1.2
Eye disorders	30	0.6	27	0.6
Blood and lymphatic system disorders	17	0.4	18	0.4
Reproductive system and breast disorders	17	0.4	9	0.2
Psychiatric disorders	15	0.3	17	0.4
Investigations	9	0.2	19	0.4
Ear and labyrinth disorders	9	0.2	3	0.1
Endocrine disorders	7	0.1	4	0.1
Immune system disorders	5	0.1	2	0.0
Congenital, familial and genetic disorders	4	0.1	0	0.0
Social circumstances	0	0	1	0

Source: LEADER CSR, Table 14.3.1.1.46

Regarding specific SOCs with potential imbalances of interest:

- The majority of the imbalance in severe AEs not in favor of Victoza was seen in the 'Gastrointestinal disorders' SOC; specifically in the preferred terms nausea, vomiting, and diarrhea. Severe events of pancreatitis reported by the investigator (preferred terms 'pancreatitis' and 'pancreatitis acute') were evenly matched between treatment groups. (See Section 9.2.1, below, for a discussion of adjudicated pancreatitis severity by revised Atlanta criteria.[8])

- The majority of the severe AE imbalance in the 'Musculoskeletal and connective tissue disorders' SOC was due to a small imbalance in osteoarthritis: Victoza 0.7% vs. placebo 0.5%.

[8] Banks PA, et al. Classification of acute pancreatitis – 2012: revision of the Atlanta classification and definitions by international consensus. Gut. 2013; 62(1): 102-11.

- The majority of the imbalance in the 'Hepatobiliary disorders' SOC is due to cholecystitis- and cholelithiasis-related terms. See further discussion of acute gallstone disease in Section 9.3.

In addition to the 'severe' events above, the sponsor identified 4 events in 3 Victoza-treated subjects that were identified in the pre-defined MedDRA search of 'rare' SAEs/MESIs and considered 'plausible' due to a temporal association and lack of alternative etiologies. These cases are summarized here as they are not discussed elsewhere in this review:

- Subject (b) (6) (Victoza) was hospitalized due to an incidental finding of pancytopenia 515 days after randomization. The outcome was fatal. (According to the EAC documentation, the subject was hospitalized due to knee pain and found to have pancytopenia on routine blood work. She was 'found dead' in the hospital bed for unknown reasons.) Relevant information to support the diagnosis (e.g., laboratory investigations) was not available. The subject was treated with several concomitant drugs, but no new drug had been introduced within 12 months preceding the event.[9]

- Subject (b) (6) (Victoza) reported 2 events of 'neutropenic sepsis'. Both events were considered secondary to recently diagnosed myeloid leukemia (60 days before first event of 'neutropenic sepsis') and recent infection with methicillin resistant *Staphylococcus aureus*. The subject continued on unchanged trial product and recovered.

- Subject (b) (6) (Victoza) reported 1 event of 'fibrillary glomerulonephritis' on trial day 590. The subject had a medical history of chronic renal disease; the specific diagnosis was established during the trial by biopsy. The event outcome was reported as 'not recovered' (considered a chronic condition) and the subject discontinued trial product permanently.

8 Common Adverse Events

This summary is based on investigator-reported events identified in the MedDRA search of SAEs and non-serious MESIs. In total, 62.3% of Victoza-treated subjects and 60.8% of placebo-treated subjects reported an event during the trial (randomization to follow-up). Table 13 enumerates the AEs by SOC as well as the 20 most frequent AEs by PT. Most of these events are addressed in other sections of this review.

[9] Reviewer comment: This is the only SAE/MESI reported as 'pancytopenia' in LEADER. A small excess of Victoza-treated subjects were found to have leukocytes below the normal range, but leukocytes <2 x10^9/L as measured in the trial was rare. Similar proportions of subjects were observed to have low platelet and hemoglobin counts among the groups. See Section 10.

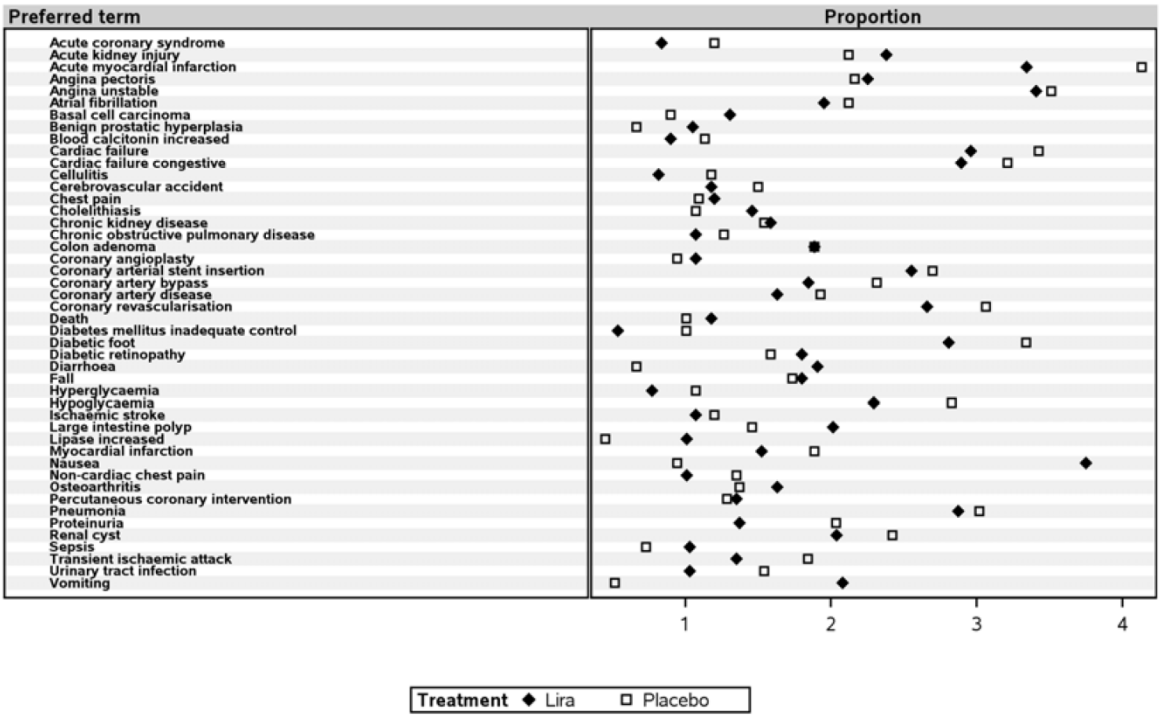
Table 13. SAEs or MESIs by SOC and 20 Most Frequent PTs

	Victoza N=4668 n (%)	Placebo N=4672 n (%)
Cardiac disorders	935 (20.0)	1026 (22.0)
Angina unstable	159 (3.4)	164 (3.5)
Acute myocardial infarction	156 (3.3)	193 (4.1)
Cardiac failure	138 (3.0)	160 (3.4)
Cardiac failure congestive	135 (2.9)	150 (3.2)
Angina pectoris	105 (2.2)	101 (2.2)
Atrial fibrillation	91 (1.9)	99 (2.1)
Gastrointestinal disorders	689 (14.8)	447 (9.6)
Nausea	175 (3.7)	44 (0.9)
Vomiting	97 (2.1)	24 (0.5)
Large intestine polyp	94 (2.0)	68 (1.5)
Diarrhea	89 (1.9)	31 (0.7)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	554 (11.9)	533 (11.4)
Colon adenoma	88 (1.9)	88 (1.9)
Infections and infestations	551 (11.8)	577 (12.4)
Pneumonia	134 (2.9)	141 (3.0)
Surgical and medical procedures	529 (11.3)	558 (11.9)
Coronary revascularization	124 (2.7)	143 (3.1)
Coronary arterial stent insertion	119 (2.5)	126 (2.7)
Coronary artery bypass	86 (1.8)	108 (2.3)
Renal and urinary disorders	453 (9.7)	524 (11.2)
Acute kidney injury	111 (2.4)	99 (2.1)
Renal cyst	95 (2.0)	113 (2.4)
Nervous system disorders	415 (8.9)	440 (9.4)
General disorders and administration site conditions	301 (6.4)	282 (6.0)
Metabolism and nutrition disorders	273 (5.8)	310 (6.6)
Hypoglycemia	107 (2.3)	132 (2.8)
Skin and subcutaneous tissue disorders	264 (5.7)	265 (5.7)
Diabetic foot	131 (2.8)	156 (3.3)
Injury, poisoning and procedural complications	262 (5.6)	278 (6.0)
Fall	84 (1.8)	81 (1.7)
Respiratory, thoracic and mediastinal disorders	242 (5.2)	294 (6.3)
Musculoskeletal and connective tissue disorders	239 (5.1)	212 (4.5)
Vascular disorders	214 (4.6)	181 (3.9)
Eye disorders	175 (3.7)	162 (3.5)
Hepatobiliary disorders	173 (3.7)	122 (2.6)
Investigations	166 (3.6)	167 (3.6)
Endocrine disorders	125 (2.7)	106 (2.3)
Reproductive system and breast disorders	93 (2.0)	69 (1.5)
Blood and lymphatic system disorders	61 (1.3)	60 (1.3)
Psychiatric disorders	43 (0.9)	44 (0.9)
Ear and labyrinth disorders	22 (0.5)	14 (0.3)
Immune system disorders	17 (0.4)	9 (0.2)
Congenital, familial and genetic disorders	13 (0.3)	11 (0.2)
Social circumstances	0	2 (<0.1)

Source: LEADER CSR, Table 14.3.1.1.6

Common AEs by preferred term are also presented in the following figure. The majority of the imbalances not in favor of Victoza were seen in the well-characterized gastrointestinal side effects of nausea, vomiting, and diarrhea. Other PTs with unfavorable imbalances are also noted in Sections 5 (SAEs; osteoarthritis, sepsis), 9.1.3.3 (colorectal neoplasms), 9.3 (acute gallstone disease), 9.5.1 (renal disorders), and 9.8 (eye disorders). Although the preferred term 'death' is reported slightly more frequently in the Victoza group than the placebo group, non-cardiovascular deaths were similar between treatment groups and all-cause mortality favored Victoza, driven by a lower incidence of cardiovascular deaths (see Section 4 for further details).

Figure 5. SAEs and MESIs by Preferred Term, Incidence ≥ 1%



Source: LEADER CSR, Figure 14.3.1.1.15

Less common, although potentially relevant AEs for which there is an imbalance not in favor of Victoza include dizziness (0.5% vs. 0.3%) and syncope (0.9% vs. 0.6%).

9 Targeted Safety Issues

9.1 Neoplasms

In the LEADER trial, all potential neoplasms were sent to the EAC for adjudication. Documentation utilized by the EAC considered acceptable for a neoplasm diagnosis was as follows:

Adjudication of neoplasms

a. A pathologic diagnosis, either by histology or cytology, is of foremost importance.
b. If pathologic diagnosis is not available, citation wherein there is extensive disease present on imaging and markedly abnormal tumor markers, (e.g. skeletal lesions with markedly elevated prostate specific antigen) will be considered.
c. If the principal investigator submits a Clinical Narrative or if there is other dated source documentation that describes a diagnosis of neoplasm but the original report is unavailable, then, it will be accepted as diagnostic of a neoplasm.
d. Entries solely in the NN clinical eCRF are not considered source documentation and are not acceptable documentation of a neoplasm.
e. A radiologic appearance of tumors alone is generally not acceptable as diagnostic of a neoplasm, even if it was treated as such (with exception to c). Visualization of a lesion on endoscopy or scans does not represent a neoplastic growth unless proven histologically (with exception to c).

Source: Adjudication Committee Charter, Appendix C

The EAC classified neoplasms according to the organ affected/tissue of origin[10] and malignancy status.[11] In addition, for positively adjudicated malignant and pre-malignant breast, pancreatic, or thyroid neoplasm events, or malignant colorectal neoplasm events, 1 neoplasm reviewer provided TNM classification (tumor, node, metastasis), grade, size, and histopathology, and where applicable, information on receptor status and gene mutation status based on information in the event adjudication source document package and eCRF. One neoplasm reviewer also provided histopathology, grade, and size for positively adjudicated benign and pre-malignant colorectal neoplasm events.

The EAC conducted a multiple events review if a subject had more than 1 EAC-confirmed event of the same event type (for neoplasms, multiple events review was performed across the neoplasm and thyroid disease requiring thyroidectomy and/or thyroid neoplasm adjudication queue). The EAC Chair evaluated whether these constituted separate events or if they were related to the same event. If 2 or more EAC-confirmed events were determined to be 1 and the same event during multiple events review, the EAC Chair grouped the relevant events and selected 1 as the “index” event based on clinical importance, i.e., the event that led to the chain of events. This event (only) was included in the statistical analyses and summaries of EAC-confirmed events, whereas the other “duplicate” events were disregarded. Therefore, when "index events” are described in this review, this refers to events that were selected as "index" within a

[10] Prostate, breast, colon and rectum, urinary bladder, uterine, melanoma of the skin, skin (non-melanoma), thyroid, lymphoma, kidney and renal pelvis, oral cavity and pharynx, esophageal, leukemias, ovarian, pancreatic, gastric, hepatic/biliary, testicular, cervical/vaginal, bone-soft tissue, other-specify [EAC-confirmed neoplasm events categorized as tissue of origin ‘other’ were classified by the sponsor post database lock (i.e., unblinded) according to the organ system affected utilizing free text fields in the eCRF]

[11] Benign, malignant, pre-malignant/carcinoma *in situ*/borderline, unclassified

group of combined events as well as EAC-confirmed events that were not part of a group (i.e., either marked as "separate event" following multiple events review or events that did not qualify for multiple events review).

9.1.1 Neoplasms Overall

The estimated hazard ratio (Victoza:placebo) for EAC-confirmed neoplasms overall in LEADER was 1.12 (95% CI 0.99, 1.28). For malignant neoplasms the HR was 1.06 (0.90, 1.25).

Table 14. EAC-Confirmed Neoplasm Events, Including Thyroid Neoplasms

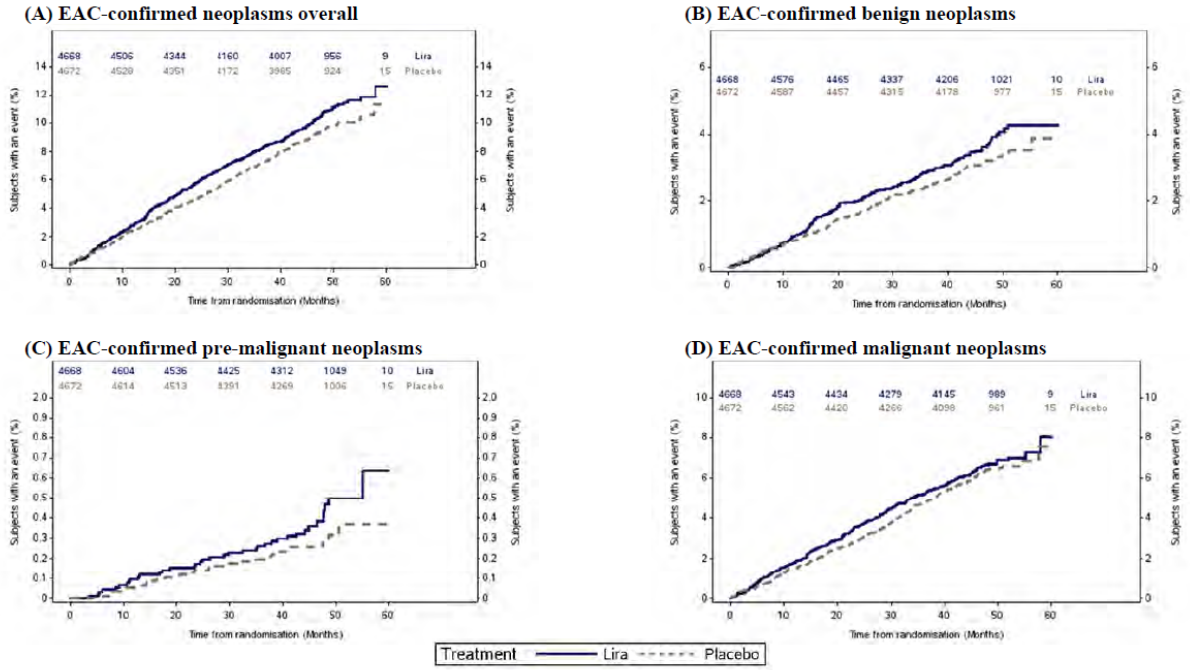
	Victoza			Placebo		
	N (%)	**E**	**R**	**N (%)**	**E**	**R**
Number of subjects	**4668**			**4672**		
PYO	**17822**			**17741**		
EAC-confirmed neoplasms (overall)	470 (10.1)	595	3.34	419 (9.0)	528	2.98
Malignant	296 (6.3)	356	2.00	279 (6.0)	326	1.84
Pre-malignant	37 (0.8)	40	0.22	26 (0.6)	30	0.17
Benign	168 (3.6)	196	1.10	145 (3.1)	171	0.96
Unclassified	3 (0.1)	3	0.02	1 (<0.1)	1	0.01

N: number of subjects; %: proportion of subjects; E: number of events; PYO: patient-years of observation; R: event rate per 100 observation years; EAC: event adjudication committee
Index events with EAC onset date from randomization date to follow-up are included
The index event is the event selected among multiple events if these were assessed and confirmed to be 1 and the same event

Source: Summary of Clinical Safety, Table 2-17

The Kaplan-Meier plots of first EAC-confirmed neoplasms overall and by malignancy status are shown in the figures below:

Figure 6. Kaplan-Meier Plots of Time to First EAC-Confirmed Neoplasm Index Event, Overall and by Malignancy Status

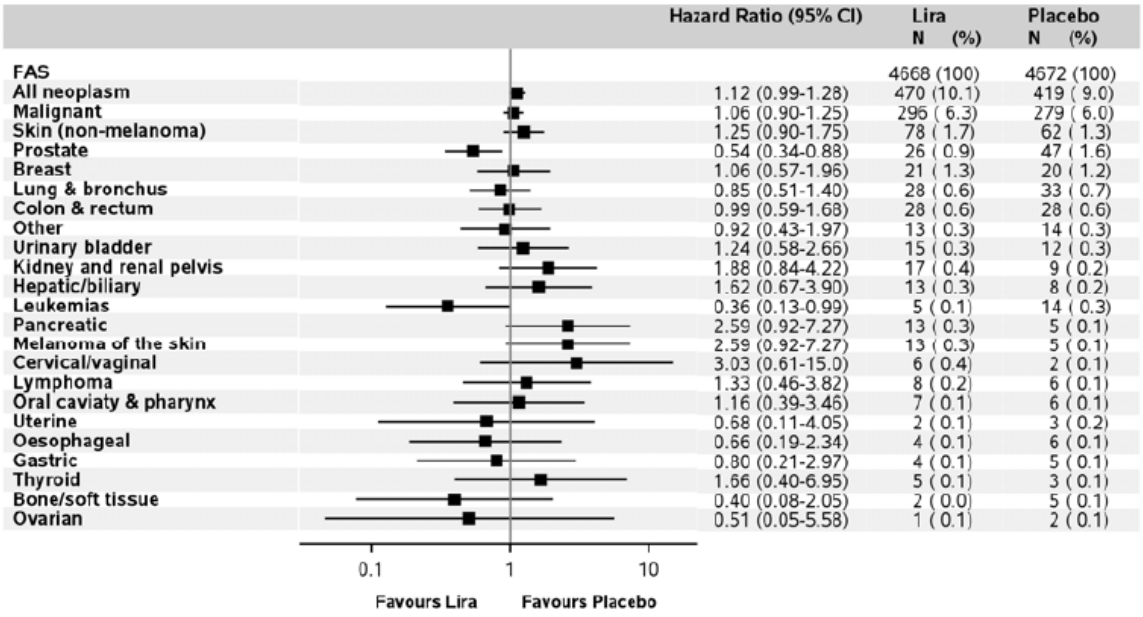


Note: The scales of the vertical axis vary between the four plots displayed in the figure.
Abbreviations: EAC: event adjudication committee; FAS: full analysis set; Lira: liraglutide.
Source: Summary of Clinical Safety, Figure 2-22

9.1.2 Malignant Neoplasms

The most frequently occurring EAC-confirmed malignant neoplasm in both treatment groups was malignant skin (non-melanoma) neoplasms. Other EAC-confirmed malignant neoplasms for which at least 1 event occurred in each treatment group is shown below in Figure 7. Imbalances not in favor of Victoza (5 events or more in the Victoza group vs. placebo) included malignant neoplasms of the hepatic/biliary system, kidney and renal pelvis, pancreas, and skin (melanoma and non-melanoma).

Figure 7. EAC-Confirmed Malignant Neoplasm Hazard Ratios by Tissue Type



FAS: full analysis set, CI: confidence interval.
%: proportion in percent of subjects with an event. N: number of subjects.
Hazard ratios are derived from the Cox model with treatment as only covariate.
Proportions are calculated based on number of female subjects for breast, cervical/vaginal, uterine and ovarian neoplasms. and based on number of male subjects for prostate neoplasms.

Source: LEADER CSR, Figure 14.3.1.131

Specific neoplasms, including those of special interest (breast, colorectal, and pancreatic) and skin (unfavorable imbalances in both melanoma and non-melanoma malignant neoplasms) are discussed further in the subsections below. Thyroid cancer is reviewed separately by a thyroid cancer expert in the Division (Dr. Sullivan).

Because of the emphasis placed on pathological diagnosis for confirmation by adjudication, the sponsor notes that the adjudication process for neoplasms may have high specificity but potentially may have reduced the sensitivity of the analysis. Therefore, additional supportive analyses of investigator-reported adverse events of malignant neoplasms were performed utilizing the following MedDRA searches:

Table 15. SMQs and HLTs Included in the Searches for Malignant Neoplasms

Included SMQs and HLTs
Malignant neoplasms (all types)
SMQ Malignant tumors
Malignant breast neoplasms
SMQ Breast malignant tumors (narrow and broad terms)
Malignant colorectal neoplasms
HLT Lower gastrointestinal neoplasms benign (only PTs which are also within the SMQ Malignant tumors)
HLT Colorectal and anal neoplasms malignancy unspecified (only PTs which are also within the SMQ Malignant tumors)
HLT Colorectal neoplasms malignant (only PTs which are also within the SMQ Malignant tumors)
HLT Anal and colorectal neoplasms NEC (only PTs which are also within the SMQ Malignant tumors)
HLT Anal canal neoplasms malignant (only PTs which are also within the SMQ Malignant tumors)
All colorectal neoplasms
HLT Lower gastrointestinal neoplasms benign
HLT Colorectal and anal neoplasms malignancy unspecified
HLT Colorectal neoplasms malignant
HLT Anal and colorectal neoplasms NEC
HLT Anal canal neoplasms malignant
Malignant pancreatic neoplasms
HLT Pancreatic neoplasms (only PTs which are also within the SMQ Malignant tumors)
Malignant prostate neoplasms
HLT Prostate malignant tumors (narrow and broad terms)
Malignant melanoma of the skin
HLT Skin melanomas (excl ocular) (only PTs which are also within the SMQ Malignant tumors)
Malignant skin (non-melanoma) neoplasms
HLT Skin neoplasms malignant and unspecified (excl melanoma) (only PTs which are also within the SMQ Malignant tumors)
Malignant thyroid neoplasms
HLT Thyroid neoplasms malignant
HLT: high level term; PT: preferred term; SMQ: standardized MedDRA query

Source: LEADER CSR, Table 9-9

Based on this search, a small number of malignant neoplasms were identified that were ultimately not confirmed by the EAC. The results by HLGT are shown in Table 16 below. Small imbalances were noted in gastrointestinal malignancies (discussed further in the pancreatic cancer discussion below) and skin malignancies (investigator-reported preferred terms for malignant skin neoplasms are outlined in Table 34). The 1 investigator-reported 'breast neoplasm malignant or unspecified' that was not

confirmed by the EAC occurred in subject (b) (6) a male subject with gynecomastia on spironolactone and no clear neoplasm.

Table 16. Investigator-Reported Adverse Events of Malignant Neoplasm Not Confirmed by the EAC

	Victoza N=4668 n (%)	Placebo N=4672 n (%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	26 (0.6)	33 (0.7)
Breast neoplasms malignant and unspecified (incl nipple)	1 (<0.1)	0
Endocrine neoplasms malignant and unspecified	1 (<0.1)	1 (<0.1)
Gastrointestinal neoplasms malignant and unspecified	0	5 (0.1)
Hepatobiliary neoplasms malignant and unspecified	0	2 (<0.1)
Lymphomas non-Hodgkin's B-cell	0	2 (<0.1)
Lymphomas non-Hodgkin's unspecified histology	1 (<0.1)	1 (<0.1)
Metastases	4 (0.1)	4 (0.1)
Miscellaneous and site unspecified neoplasms malignant and unspecified	1 (<0.1)	0
Plasma cell neoplasms	1 (<0.1)	0
Renal and urinary tract neoplasms malignant and unspecified	2 (<0.1)	3 (<0.1)
Reproductive neoplasms female malignant and unspecified	2 (<0.1)	1 (<0.1)
Reproductive neoplasms male malignant and unspecified	0	2 (<0.1)
Respiratory and mediastinal neoplasms malignant and unspecified	5 (<0.1)	5 (<0.1)
Skin neoplasms malignant and unspecified	8 (0.2)	5 (0.1)
Soft tissue neoplasms malignant and unspecified	0	2 (<0.1)

Source: LEADER CSR, Table 12-46

9.1.3 Specific Tissue Types

9.1.3.1 Pancreas

Pancreatic safety is an ongoing area of interest with incretin mimetics (i.e., DPP-4 inhibitors and GLP-1 receptor agonists). A 2013 research publication reported on pancreatic cellular changes, including exocrine cell proliferation and dysplasia and α-cell hyperplasia, in a series of patients with diabetes who had been exposed to incretin based therapy (sitagliptin or exenatide) suggesting a potential link between these drugs and abnormal pancreatic exocrine or endocrine cell growth.[12] In response, FDA, in concert with the European Medicines Agency (EMA), performed a comprehensive review of all clinical, nonclinical and post-marketing data available for these therapies, and in a perspective published in 2014 concluded that the available data did not support a the presence of a causal relationship between these therapies and pancreatic toxicity or pancreatic cancer.[13] Nevertheless, pancreas safety with liraglutide remains an area of

[12] Butler AE, et al. Marked expansion of exocrine and endocrine pancreas with incretin therapy in humans with increased exocrine pancreas dysplasia and the potential for glucagon-producing neuroendocrine tumors. Diabetes 2013; 62(7): 2595-604.
[13] Egan AG, et al. Pancreatic safety of incretin-based drugs – FDA and EMA assessment. N Engl J Med 2014; 370:794-7.

interest, and the LEADER trial, a large, long, randomized controlled trial, was to further inform this.

As was noted in Figure 7 above and outlined further in Table 17, a numeric imbalance was observed in this trial for EAC-confirmed malignant pancreatic neoplasms [HR 2.59 (95% CI 0.92, 7.27)]. An additional neoplasm in the Victoza group classified as pre-malignant was also EAC-confirmed. In this section, some analyses include subjects with malignant events only and some include subjects with both malignant and pre-malignant events.

Table 17. EAC-Confirmed Pancreatic Malignancy Events

	Victoza			Placebo		
	N (%)	**E**	**R**	**N (%)**	**E**	**R**
Number of subjects	**4668**			**4672**		
PYO	**17822**			**17741**		
EAC-confirmed pancreatic neoplasms	15 (0.3)	16	0.09	7 (0.1)	7	0.04
Malignant	13 (0.3)	14	0.08	5 (0.1)	5	0.03
Pre-malignant	1 (<0.1)	1	0.01	0	0	0
Benign	1 (<0.1)	1	0.01	2 (<0.1)	2	0.01
Unclassified	0	0	0	0	0	0

N: number of subjects; %: proportion of subjects; E: number of events; PYO: patient-years of observation; R: event rate per 100 observation years; EAC: event adjudication committee
Index events with EAC onset date from randomization date to follow-up are included
The index event is the event selected among multiple events if these were assessed and confirmed to be 1 and the same event

Source: Summary of Clinical Safety, Table 2-19

A summary of demographics and baseline characteristics for subjects with EAC-confirmed pre-malignant or malignant pancreatic neoplasms are shown in Table 18, below. In both treatment groups, the majority of subjects were male (Victoza 71.4%; placebo: 80.0%). Subjects treated with Victoza tended to be younger than those treated with placebo. More subjects treated with Victoza vs. placebo with pancreatic cancer were previous or current smokers. One subject in the Victoza group had a medical history of chronic pancreatitis (subject (b) (6). Information on family history of pancreatic cancer was limited: 7 subjects in the Victoza group had no family history of pancreatic cancer, the rest of the information on family history (for both Victoza- and placebo- treated subjects) was unavailable.

Table 18. Demographics and Baseline Characteristics, Subjects with EAC-Confirmed Malignant or Pre-Malignant Pancreatic Neoplasms

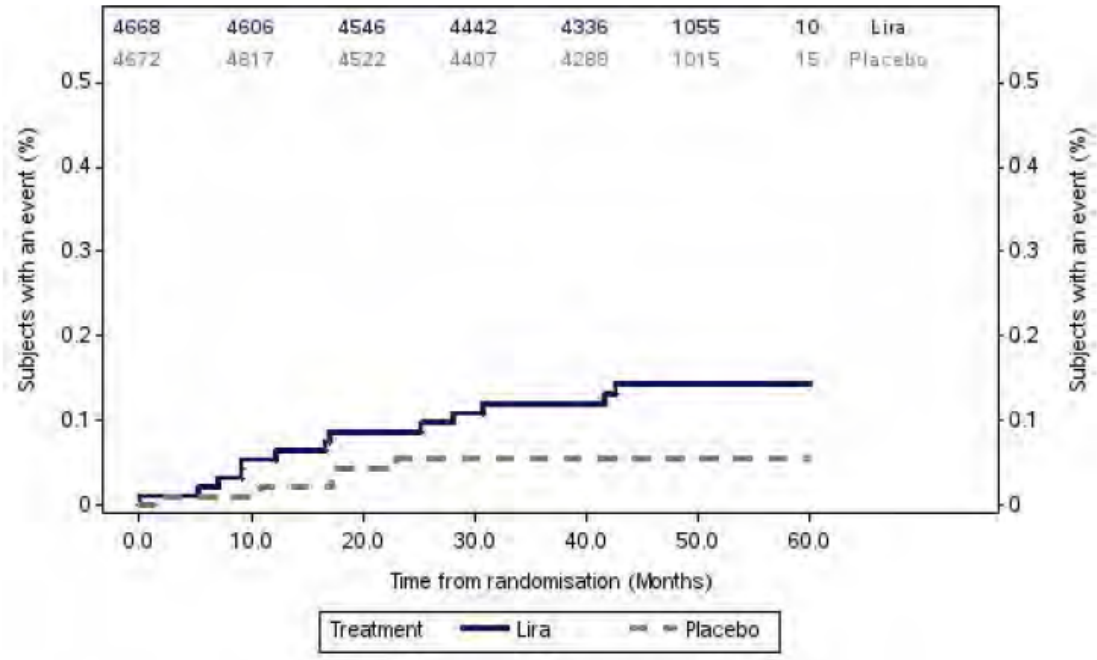
	Victoza N=14	Placebo N=5
Age group (yrs)		
< 65	6 (42.9)	1 (20.0)
65-74	8 (57.1)	2 (40.0)
75-84	0	2 (40.0)
≥ 85	0	0
Age (yrs)		
Mean (SD)	65.2 (4.1)	70.4 (6.2)
Median	65.5	70.0
Min, Max	59.0, 71.0	63.0, 78.0
Sex, female	4 (28.6)	1 (20.0)
Smoking status		
Current	3 (21.4)	1 (20.0)
Never	5 (35.7)	3 (60.0)
Previous	6 (42.9)	1 (20.0)
Race		
White	11 (78.6)	4 (80.0)
Black or African American	1 (7.1)	1 (20.0)
Asian	1 (7.1)	0
Other	1 (7.1)	0
Ethnicity, Hispanic or Latino	1 (7.1)	0
BMI, kg/m^2		
Mean (SD)	31.8 (4.5)	29.3 (2.5)
Median	30.8	29.3
Min, Max	23.6, 39.4	26.2, 32.8
Duration of Diabetes (yrs)		
Mean (SD)	12.8 (6.9)	9.8 (6.1)
Median	12.6	8.9
Min, Max	1.2, 23.7	4.7, 20.2

Source: ISS, Tables 7.3.13-7.3.15

In the Victoza group, EAC-confirmed malignant pancreatic neoplasms were diagnosed in 5 subjects during year 1, in 4 subjects during year 2,[14] and in 5 subjects after year 2. In the placebo group, 2 subjects with events were diagnosed in year 1 and 3 in year 2; no additional EAC-confirmed malignant pancreatic neoplasms occurred after year 2. See Figure 8 for the Kaplan-Meier plot.

[14] One subject, (b) (6) had 2 EAC-confirmed malignant pancreatic neoplasm events: 1 diagnosed in year 1 and 1 diagnosed in year 2 of the trial. This subject is discussed further later in this section.

Figure 8. EAC-Confirmed Malignant Pancreatic Neoplasm Events



Abbreviations: EAC: event adjudication committee; FAS: full analysis set; Lira: liraglutide.
Source: LEADER CSR, Figure 12-33

Summary details of the EAC-confirmed pre-malignant or malignant pancreatic neoplasms are as follows; listings are presented in Section 13.2.2 of the appendix:

- The majority of events were ductal adenocarcinomas (Victoza: 10 of 15 events; placebo: 5 of 5 events). In the Victoza group, 3 events were categorized as 'Other' and in the remaining 2, information on histopathology was unknown.

- In the majority of cases, histological grade was unknown (Victoza: 10 of 15 events; placebo: 4 of 5 events). The histological grade for the additional events in the Victoza group were Grade 1 (1 event) or Grade 2 (3 events) and in the placebo group, the 1 event with known histological grade was Grade 3. One event in the Victoza group was an intraductal papillary mucinous neoplasm (subject (b) (6)) and was of moderate dysplasia. As this was not a pre-specified option in the assessment form, the external reviewer selected 'PanIN 1B' as histological grade for this event.

- The majority of events were stage IIA or higher (Victoza: 12 of 15 events, placebo: 4 of 5 events). Seven events in the Victoza group and 2 events in the placebo group were stage IV; of these, 4 events in the Victoza group and 1 event in the placebo group were diagnosed less than 1.5 years into the trial. Staging was unknown for 2 events in the Victoza group.

As described in the above discussion of malignant neoplasms overall, a small imbalance of events ultimately not confirmed by the EAC within the HLGT 'Gastrointestinal neoplasms malignant and unspecified' was noted (i.e., 0 events in the Victoza group and 5 in the placebo group; refer to Table 16). Therefore, a MedDRA search was also conducted to identify malignant pancreatic neoplasms (i.e., pancreatic neoplasms within the HLGT 'Gastrointestinal neoplasms malignant and unspecified') irrespective of their adjudication status by the EAC. This search, shown in Table 19, presents a similar proportion of events by treatment group.

Table 19. Investigator-Reported Malignant Pancreatic Neoplasms, MedDRA Search

	Victoza N=4668	Placebo N=4672
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	11 (0.2)	10 (0.2)
Gastrointestinal neoplasms malignant and unspecified	11 (0.2)	10 (0.2)
Adenocarcinoma pancreas	4 (0.1)	1 (<0.1)
Pancreatic carcinoma	4 (0.1)	7 (0.1)
Pancreatic carcinoma metastatic	2 (<0.1)	2 (<0.1)
Pancreatic carcinoma stage IV	1 (<0.1)	0
N: number of subjects; %: proportion of subjects Sorted by system organ class, high level group term, and preferred term in alphabetical order		

Source: LEADER CSR, Table 12-42

In the Victoza group, all of the 11 events reported by the investigator captured by the MedDRA search (occurring in 11 subjects) were also confirmed by the EAC as being events of malignant pancreatic neoplasms (subjects (b) (6) and (b) (6). The MedDRA search did not capture 3 events in 2 subjects (subjects (b) (6) and (b) (6) in the Victoza group that were also EAC-confirmed as pancreatic malignancy: the preferred terms were 'pancreatic neoplasm' (2 events) and 'lymphadenopathy' (1 event).

- Subject (b) (6) ('pancreatic neoplasm') is listed in Table 87 in the appendix.

- Subject (b) (6) is a more complex case and is described further: this subject had 2 EAC-confirmed malignant pancreatic neoplasms: 1 with onset on day 1 (before trial product was administered) and 1 with onset on day 586. In addition, the subject had 1 EAC-confirmed malignant hepatic or biliary neoplasm (intrahepatic cholangiocarcinoma) with onset on day 594. The table below describes the investigator-reported terms and study days and the EAC-assigned tissue and study days:

Table 20. EAC-Confirmed Malignant Neoplasm Events for Subject (b) (6)

AE#	Reported term/preferred term	EAC-assigned tissue of origin	Investigator onset date (study day)	EAC onset date (study day)
3	Stable 2cm hypodense lesion in the head of the pancreas/Pancreatic neoplasm	Pancreatic	09 Jun 2011 (study day 1)	09 Jun 2011 (study day 1)
4	Intrahepatic cholangiocarcinoma/ Cholangiocarcinoma	Hepatic/biliary	09 Jun 2011 (study day 1)	22 Jan 2013 (study day 594
5	Borderline, nonspecific enlarged peripancreatic lymph node/ Lymphadenopathy	Pancreatic	17 Jan 2013 (study day 589)	17 Jan 2013 (study day 589)

#: Number; AE: adverse event; EAC: event adjudication committee

Source: Response to FDA Request 08 Feb 2017, Table 1-1

A review of pathology reports provided in the EAC adjudication package noted that pancreatic biopsy did not show malignancy. Clinical notes from the Division of Oncology 2 (DOP2) consult reported intrahepatic cholangiocarcinoma. Nevertheless, multiple EAC adjudicators confirmed 'malignant pancreatic neoplasm' in this subject.

In the placebo group, 5 events (occurring in 5 subjects) of the 10 events captured by the MedDRA search were *not confirmed* by the EAC as being events of malignant pancreatic neoplasms (subjects (b) (6) and (b) (6) Of these, 1 event in subject (b) (6) was confirmed by the EAC as a malignant lymphoma. Table 21 below provides summaries of the 4 other subjects with investigator-reported events of malignant pancreatic neoplasms not confirmed by the EAC as malignant pancreatic neoplasms. The 4 subjects had investigator-reported adverse events of 'pancreatic carcinoma' (3 subjects) or 'pancreatic carcinoma metastatic' (1 subject). The outcome of all 4 cases was fatal; these cases were all EAC-confirmed (by the EAC cardiovascular subcommittee adjudicating deaths) as non-cardiovascular deaths with 'malignancy' or 'pancreatic cancer' assessed as plausible cause of death. In these cases, malignancies were diagnosed by imaging; tissue biopsy either was not done due to the terminal nature of the cancer or was not available. It is noted that 1 subject – (b) (6) – appeared to have symptoms of abdominal pain that started before trial screening. One subject was diagnosed in year 1 and 2 subjects after year 2.

Table 21. Summarized Details for Subjects with Investigator-Reported Adverse Events of Malignant Pancreatic Neoplasms Not Confirmed By the EAC Neoplasm Subcommittee

Subject ID/ Age[a]/ Sex/ BMI/ Country/ Treatment	Preferred term	Study day/Duration (days)/Outcome/Death day	EAC confirmed (by EAC neoplasm committee)	Adjudication for death (by EAC cardiovascular committee)	
				EAC death day/EAC evaluation	Plausible cause of death (Adj 1/Adj 2)
(b) (6) 72/ F/ 28.8/ Romania/ Placebo	Pancreatic carcinoma	137/ 178/ Fatal/ 315	No	315/ Non-CV death	Malignancy/ Pancreatic Cancer
	Summary of details: *Subject:* Medical history includes T2DM, heart failure, symptomatic cardiac ischemia, hypertension, left ventricular hypertrophy, gallstone disease, hypercholesterolemia, and cholecystitis (chronic). *Event:* The subject presented with 4 month history of 20 kg weight loss, loss of appetite, nausea, asthenia, fatigue, abdominal pain, and hyperglycemia. Outcome fatal, details on disease progression not available. No autopsy was performed. Imaging: Abdominal echography and CT scan showed necrotizing lesion (47/48 mm) in uncinate process. Tumor markers CA 19-9 122.5 (ref.range 0-39). Microscopic examination: No. Treatment of event: Subject denied surgery; recommendation for oncological follow-up (not further specified).				
(b) (6) / 80/ M/ 25.8/ France/ Placebo	Pancreatic carcinoma metastatic	1248/ 32/ Fatal/ 1279	No	1279/ Non-CV death	Malignancy/ Pancreatic ca
	Summary of details: *Subject:* Medical history includes T2DM, vascular dementia, chronic renal failure, non-proliferative diabetic retinopathy, hypertension, peripheral arterial disease, dyslipidemia, prostate cancer, laryngotracheitis, and depression. Previous smoker. *Event:* The subject presented with abdominal pain that led to an abdominal ultrasound showing hepatic nodules and pancreas tissue damage. Outcome fatal, details on disease progression not available. No autopsy was performed. Imaging: CT scan showed a 44 mm tissue lesion at the level of the body of the pancreas and dilation of ductus (20 mm). Hypodense lesions of the hepatic parenchyma. Tumor markers: CA 19-9 21000 (ref. range not provided). CEA 18 (no units or ref. range). Microscopic examination: No. Treatment of event: Palliative; an opinion requested from onco-geriatricians recommends performing palliative treatment because of the alteration of the general condition and the demential syndrome that would not permit the subject to support chemotherapy.				
(b) (6) / 67/ M/ 25.0/ Israel/ Placebo	Pancreatic carcinoma	20/ 448/ Fatal/ 467	No[b]	n/a[c]	n/a[c]
	Cardiac arrest	467/ 1/ Fatal/ 467	n/a	467/ Non-CV death	Malignancy/ pancreatic cA
	Summary of details: *Subject:* Medical history includes T2DM, hyperlipidemia, vitamin D deficiency, erectile dysfunction, abdominal pain, hypertension, and carotid artery stenosis. Previous smoker. *Event:* The subject presented with worsening of abdominal pain that had existed prior to				

	screening. Weight loss of about 17 kg over the past 5 months and intermittent constipation. Admitted to the hospital for symptoms worsening: lack of appetite, nausea and vomiting, abdominal pain, and rise in hepatic enzymes and bilirubin. Outcome fatal, details on disease progression are not available. There is no information about autopsy. Imaging: Abdominal US and CT scan showed lesion (exceeds 60 mm) in pancreas body with signs of local spread and pressure on the pancreas duct and distal dilation to the lesion. Metastases in the liver and lymphadenopathy. Tumor markers: Cancer signs, CEA, CA 19-9 (not further specified). Microscopic examination: No. Treatment of event: Apparently receiving chemotherapy for "neoplasm to the pancreas with metastases to the liver"; neoplasm not suitable for surgery.				
(b) (6)/ 69/ F/ 41.8/ Turkey/ placebo	Pancreatic carcinoma	1079/ 34/ Fatal/ 1112	No	1112/ Non-CV death	Malignancy/pancreatic ca
	Summary of details: *Subject:* Medical history includes T2DM, hypertension, asthma, sleep apnea, hyperlipidemia, neuropathy, left ventricular hypertrophy, and gallstone disease. Never smoker. *Event:* The subject presented with indigestion and swelling, which led to further investigations. Outcome fatal, details on disease progression not available. Son reported that the cause of death was pancreas cancer. There is no information about autopsy. Imaging: PET scanning showed lesions (increased Ga-68 DOTATATE involvement) with heterogeneous borders in the head and body section of pancreas/extending into peripancreatic and paraaortocaval area (pancreatic NET?). Tumor markers: No. Microscopic examination: No. Treatment of event: No available information.				
Note: most information was taken from the sponsor's summary in the CSR; the reviewer filled in some details with source documentation in adjudication packages. Adj 1: adjudicator 1; adj 2: adjudicator 2; BMI: body mass index; CA 19-9: cancer antigen 19-9; CEA: carcinoembryonic antigen; EAC: event adjudication committee; F: female; M: male; n/a: not applicable; NET: neuroendocrine tumor; CV: cardiovascular; ref.: reference; T2DM: type 2 diabetes mellitus a Baseline value b Adj 2 originally adjudicated as pancreatic cancer, but changed determination due to lack of diagnostic pathology c Adjudication of fatal event based on other adverse event number					

Source: LEADER CSR, Table 12-43, and adjudication packages (some details)

Finally, a case of EAC-confirmed cholangiocarcinoma in a subject treated with Victoza (subject (b) (6)) was discovered incidentally in a review of the narrative for the fatal acute gallstone disease events (see Acute Gallstone Disease, section 9.3 of this review), with clinical information possibly suggestive for pancreatic cancer. This subject was noted to have a pancreatic mass and no pathology was available in the source documentation. This case is also described in the Oncology consult review.

In summary, although an imbalance was observed for subjects with EAC-confirmed malignant pancreatic neoplasm (Victoza 13, placebo 5), there appears to be some uncertainty regarding the numbers of cases contributing to the imbalance. One subject in the Victoza group with EAC-confirmed 'malignant pancreatic neoplasm' also had cholangiocarcinoma and a confusing clinical history that was not clarified by source

documentation, and 4 additional subjects in the placebo group potentially had fatal pancreatic cancer that could not be confirmed due to lack of tissue for diagnosis.

9.1.3.2 Breast

Although breast cancer was not identified as a safety area of concern after the Victoza review of phase 3 trials supporting its approval, a numerical imbalance was observed in the phase 3 program that evaluated the 3 mg dose of liraglutide for chronic weight management (Saxenda). In the Adverse Reactions section of the Saxenda label (recently updated with additional information from a 3-year trial), the following is stated:

In Saxenda clinical trials, breast cancer confirmed by adjudication was reported in 17 (0.7%) of 2379 Saxenda-treated women compared with 3 (0.2%) of 1300 placebo-treated women, including invasive cancer (13 Saxenda-and 2 placebo-treated women) and ductal carcinoma in situ *(4 Saxenda-and 1 placebo-treated woman). The majority of cancers were estrogen-and progesterone-receptor positive. There were too few cases to determine whether these cases were related to Saxenda. In addition, there are insufficient data to determine whether Saxenda has an effect on pre-existing breast neoplasia.*

Upon the approval of Saxenda, post-marketing studies were required [post-marketing requirement (PMR)] to assess the risk of breast cancer associated with liraglutide, including evaluation of data from the (at the time ongoing) LEADER trial.[15] Therefore, this breast neoplasm subsection will include information collected as part of the breast cancer PMR using data from LEADER. Note that the PMR assessed EAC-confirmed *malignant* breast neoplasms, whereas information provided in the LEADER study report included *pre-malignant* breast neoplasms in addition to malignant neoplasms. Malignancy status will be stated for each finding in this section.

The proportion of female subjects with EAC-confirmed breast neoplasms are summarized overall and by malignancy status in Table 22. A total of 41 index events of EAC-confirmed breast cancer with onset date after randomization were reported in 41 female subjects in LEADER: 21 subjects with 21 events in the Victoza group (1.3%, 0.33 events/100 PYO) and 20 subjects with 20 events in the placebo group (1.2%, 0.31 events/100 PYO) [exact odds ratio (95% CI) 1.07 (0.55, 2.08)]. An additional 2 female subjects in the Victoza group (subjects (b) (6) and (b) (6)) were diagnosed with breast cancer during the trial, but the EAC determined the onset dates of these events to be prior to randomization.

[15] PMR 2802-7 states: To assess the risk of breast cancer associated with liraglutide, collect information on baseline cancer risk and potential confounders for all identified cases of breast cancer in the trial, including (but not limited to) prior history of breast cancer, family history of breast cancer, BRCA1/BRCA2 status, age at menopause, history of radiation to the chest, age at menarche, and current/prior use of hormonal therapy.

Of the EAC-confirmed malignant and pre-malignant breast neoplasms, approximately half of the Victoza events and the majority of placebo events were ductal/intraductal carcinomas (Victoza: 13 of the 24 events; placebo: 17 of the 21 events).

In the Victoza group, 1 male subject (subject (b) (6) had an EAC-confirmed benign breast neoplasm (preferred term: intraductal papilloma of breast[16]), and in the placebo group, 1 female subject (subject (b) (6)) had an EAC-confirmed pre-malignant breast neoplasm with onset after follow-up. Neither case is included in the table below or discussed further in this section (and note that denominators in the analyses below only include women).

Table 22. EAC-Confirmed Breast Neoplasm Index Events by Malignancy Status in Female Subjects

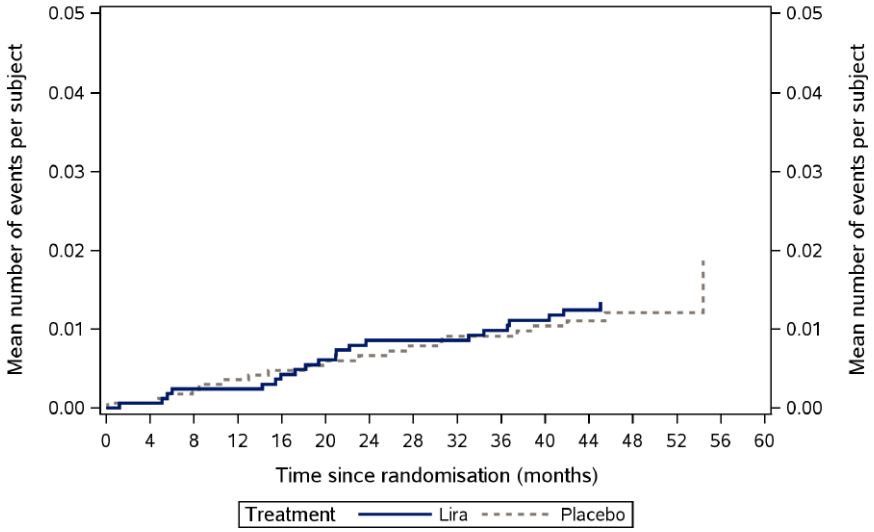
	Victoza			Placebo		
	N (%)	**E**	**R**	**N (%)**	**E**	**R**
Number of subjects	**1657**			**1680**		
PYO	**6320**			**6370**		
EAC-confirmed breast neoplasms	24 (1.4)	24	0.38	22 (1.3)	22	0.35
Benign	0	0	0	1 (0.1)	1	0.02
Malignant	21 (1.3)	21	0.33	20 (1.2)	20	0.31
Pre-malignant	3 (0.2)	3	0.05	1 (0.1)	1	0.02
Unclassified	0	0	0	0	0	0

N: number of subjects; %: proportion of subjects; E: number of events; PYO: patient-years of observation; R: event rate per 100 observation years; EAC: event adjudication committee
Index events with EAC onset date from randomization date to follow-up are included
The index event is the event selected among multiple events if these were assessed and confirmed to be 1 and the same event

Source: LEADER CSR, Table 12-39

[16] Verbatim term: Intraductal papilloma associated with ductal hyperplasia without atypia located at the left nipple

Figure 9. Mean Cumulative Events of EAC-Confirmed Malignant Breast Neoplasms



EAC: Event adjudication committee; Lira: Liraglutide.
Observation time is defined as the time between randomisation and last contact.

Source: NDA 206321 PMR, Breast Cancer Report, Figure 5-1

In order to fulfill the (Saxenda) PMR requirement for further assessment of breast cancer risk, baseline risk factors were collected retrospectively by way of a dedicated questionnaire (adapted from reference [17]), and grading, staging,[18] and receptor status was provided by an external breast cancer expert[19] based on information in source documentation. In order to provide context to the questionnaire information, individual and population-based absolute risks were estimated based on available information using the International Breast Intervention Study (IBIS) breast cancer risk evaluation tool.[20]

Of the 41 subjects with breast cancer, interviews were obtained from 39 (95.1%). One subject in the Victoza group was unwilling to be interviewed (subject (b) (6)) and one subject in the placebo group was not contacted due to a decision from the relevant Institutional Review Board (subject (b) (6)). For 2 subjects, information for the interview was provided by relatives, because the subject was too ill (subject (b) (6) placebo, information provided by her husband) or had died (subject (b) (6) placebo, information provided by her daughter). Details of the individual EAC-confirmed malignant breast neoplasms can be found in Table 88 in the appendix (Section 13.2.3). This section summarizes the available information.

[17] Goodwin PJ, et al. Breast cancer prognosis in BRCA1 and BRCA2 mutation carriers: an International Prospective Breast Cancer Family Registry population-based cohort study. J Clin Oncol (2012); 30(1):19-26.
[18] Singletary SE, et al. Revision of the American Joint Committee on Cancer staging system for breast cancer. J Clin Oncol (2002); 20(17): 3628-36.
[19] Pamela Goodwin, University of Toronto, Canada
[20] Tyrer J, et al. A breast cancer prediction model incorporating familial and personal risk factors. Stat Med (2004); 23(7): 1111-30.

The table below summarizes observation and exposure time in the subjects with malignant breast neoplasms and in women in the trial overall by treatment group. The median number of days on treatment was similar in subjects with EAC-confirmed breast cancer and in the overall female patient population in both treatment groups.

Table 23. Time in Trials and Time to Diagnosis in All Female Subjects and in Those with EAC-Confirmed Breast Cancer

	Victoza		Placebo	
	All female subjects	**Subjects with EAC-confirmed malignant breast neoplasms**	**All female subjects**	**Subjects with EAC-confirmed malignant breast neoplasms**
N	1657	21	1680	20
Observation days				
Mean (SD)	1392.8 (234.5)	1421.0 (137.3)	1384.8 (236.9)	1440.6 (169.5)
Median	1401.0	1398.0	1401.0	1410.0
Min; max	10.0; 1875.0	1206.0; 1688.0	56.0; 1877.0	1050.0; 1765.0
Days on treatment				
Mean (SD)	1130.5 (466.1)	1073.1 (474.2)	1112.9 (452.5)	1018.6 (533.4)
Median	1285.0	1277.0	1283.0	1275.5
Min; max	0.0; 1828.0	75.0; 1641.0	1.0; 1829.0	91.0; 1650.0
Time to diagnosis from baseline				
Mean (SD)		686.9 (397.1)		698.4 (464.2)
Median		637.0		657.0
Min; max		35.0; 1373.0		4.0; 1658.0
EAC: event adjudication committee; SD: standard deviation				

Source: NDA 206321 PMR, Breast Cancer Report, Table 7-1

Table 24 below summarizes the demographics and baseline characteristics of female subjects with malignant breast neoplasms and overall by treatment. In general, the baseline characteristics were similar among groups.

Table 24. Characteristics of All Female Subjects and Those with EAC-Confirmed Malignant Breast Neoplasms

	Victoza		Placebo	
	All female subjects	**Subjects with EAC-confirmed malignant breast neoplasms**	**All female subjects**	**Subjects with EAC-confirmed malignant breast neoplasms**
Number of subjects	**1657**	**21**	**1680**	**20**
Age at baseline (years)				
Mean (SD)	64.2 (7.3)	68.1 (7.6)	64.6 (7.0)	64.0 (6.1)
Median	64.0	68.0	64.0	64.0
Min; max	50.0; 91.0	53.0; 82.0	50.0; 88.0	54.0; 77.0
Age at diagnosis (years)				
Mean (SD)		70.6 (7.7)		66.5 (6.3)
Median		69.6		66.7
Min; max		56.8; 83.9		55.4; 80.1
Race				
White	1238 (74.7)	17 (81.0)	1230 (73.2)	13 (65.0)
Black	188 (11.3)	0	221 (13.2)	4 (20.0)
Asian	1253 (9.2)	3 (14.3)	154 (9.2)	2 (10.0)
Other	78 (4.7)	1 (4.8)	75 (4.5)	1 (5.0)
Ethnicity				
Hispanic	249 (15.0)	3 (14.3)	257 (15.3)	2 (10.0)
Not Hispanic	1408 (85.0)	18 (85.7)	1423 (84.7)	18 (90.0)
Height at baseline (m)				
N (%)	1653 (99.8)	21 (100)	1679 (99.9)	10 (100)
Mean (SD)	1.58 (0.07)	1.57 (0.08)	1.59 (0.07)	1.61 (0.07)
Median	1.58	1.57	1.58	1.63
Min; max	1.33; 1.81	1.42; 1.71	1.37; 1.83	1.44; 1.71
Fasting body weight at baseline (kg)				
N (%)	1656 (99.9)	21 (100)	1679 (99.9)	20 (100)
Mean (SD)	84.4 (19.5)	80.9 (15.9)	85.0 (19.5)	89.1 (18.8)
Median	82.1	80.4	82.9	92.1
Min; max	39.4; 179.4	53.4; 112.8	38.0; 170.3	53.0; 132.0
Body mass index at baseline (kg/m^2)				
N (%)	1653 (99.8)	21 (100)	1678 (99.9)	20 (100)
Mean (SD)	33.5 (6.8)	32.9 (5.7)	33.7 (6.9)	34.2 (6.8)
Median	32.8	32.1	32.8	34.8
Min; max	17.3; 66.5	23.3; 45.2	17.1; 81.0	21.0; 48.4
Duration of diabetes at screening (years)				
N (%)	1651 (99.6)	21 (100)	1680 (100)	20 (100)
Mean (SD)	13.2 (8.2)	12.9 (8.3)	13.6 (8.4)	15.9 (7.4)
Median	11.7	11.8	12.1	16.0
Min; max	0.1; 54.9	0.1; 36.1	0.1; 61.0	2.8; 29.8

EAC: event adjudication committee; SD: standard deviation

Source: NDA 206321 PMR, Breast Cancer Report, Table 7-2

The neoplasms were distributed across histological grades in both treatment groups with no notable differences between treatment groups; see Table 88. In the Victoza

group, 12 out of 18 (66.7%)[21], and in the placebo group, 11 out of 15 (73.3%) malignant breast neoplasms with sufficient information to perform AJCC staging were at stage IIA or above (Table 25).

Table 25. Summary of Breast Cancer Staging, Malignant Neoplasms[22]

	Victoza	Placebo
Total number of subjects with events	21	20
Stage		
0	0	0
IA	6 (28.6)	4 (20.0)
IB	0	0
IIA	1 (4.8)	6 (30.0)
IIB	1 (4.8)	3 (15.0)
IIIA	0	1 (5.0)
IIIB	1 (4.8)	0
IIIC	0	0
IV	4 (19.0)	1 (5.0)
Unknown	8 (38.1)	5 (25.0)

Source: NDA 206321 PMR, Breast Cancer Report, Table 83

The majority of malignant breast neoplasms in both treatment groups were estrogen receptor (ER) and progesterone receptor (PgR) positive. Two malignant breast neoplasms in the Victoza group and 3 in the placebo group were ER, PgR, and HER2 negative; see Table 88.

Gene mutation status (BRCA1, BRCA2, p53, PALB2, or 'Other') was unknown for all subjects.

The change in weight (% and kg) in all female subjects and subjects who developed breast cancer is shown in Table 26. At the end of trial, subjects who developed breast cancer lost more weight on average than those who did not develop breast cancer on Victoza; the converse was found in placebo-treated subjects.

[21] Note that some of the Victoza subjects categorized as 'unknown' in Table 25 were considered unknown/>IIA (i.e., at least stage IIA) by Dr. Goodwin

[22] Pre-malignant staging: in the Victoza group, 1 neoplasm was stage 0, 1 stage IA, and 1 unknown; in the placebo group, 1 neoplasm was stage 0

Table 26. Weight Changes, Female Subjects with Malignant Breast Neoplasms and Female Subjects Overall

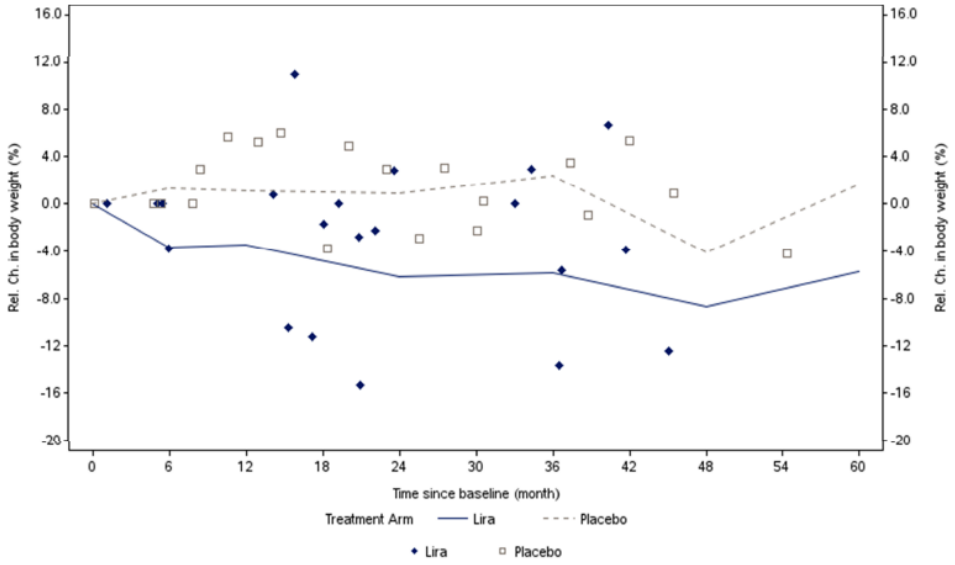
	Victoza		Placebo	
	All female subjects	**Subjects with EAC-confirmed malignant breast neoplasms**	**All female subjects**	**Subjects with EAC-confirmed malignant breast neoplasms**
Number of subjects	1631	21	1655	20
At end of trial (kg)				
Mean (SD)	-3.0 (7.6)	-3.9 (5.3)	-1.0 (6.6)	1.7 (6.2)
Median	-2.3	-2.7	-0.6	1.4
Min; max	-87.5; 77.8	-15.3; 6.6	-46.5; 26.0	-10.6; 14.0
At end of trial (%)				
Mean (SD)	-3.3 (8.2)	-4.8 (6.2)	-1.0 (7.5)	1.8 (6.8)
Median	-2.8	-2.9	-0.7	1.5
Min; max	-50.3; 107.8	-16.9; 7.9	-45.1; 44.8	-10.7; 14.7
At time of diagnosis (kg)				
Mean (SD)		-2.1 (5.5)		1.5 (3.0)
Median		-0.9		0.5
Min; max		-13.5; 11.0		-2.9; 7.0
At time of diagnosis (%)				
Mean (SD)		-2.8 (6.7)		1.3 (3.2)
Median		-1.7		0.6
Min; max		-15.3; 11.0		-4.2; 6.0

EAC: event adjudication committee; SD: standard deviation

Source: NDA 206321 PMR, Breast Cancer Report, Table 7-3

Figure 10 suggests that weight loss at the time of breast cancer diagnosis is not appreciably different than the mean weight loss at comparable study dates in female trial participants overall for either treatment group. These weight data are limited by the infrequent site visits (only annually after the first year).

Figure 10. Percent Change in Body Weight at Time of Breast Cancer Diagnosis



EAC: Event Adjudication Committee, Lira: Liraglutide, Rel. Ch.: Relative change
Lines corresponds to the observed mean change from baseline for lira and placebo groups.
Symbols indicate the "subjects with an event" at the time of event.

Source: NDA 206321 PMR, Breast Cancer Report, Figure 7-1

A summary of results of responses to the questionnaires are as follows:

- Alcohol use was low: less than a fifth of the subjects with malignant breast neoplasms in both treatment groups reported having ever consumed alcohol at least once per week for a period of 6 months or longer; and even fewer (1 with Victoza and 1 with placebo) reported current alcohol use.

- Mean age at menarche in subjects with malignant breast neoplasms was similar for the Victoza and the placebo group (13.2 years and 13.1 years, respectively).

- The majority of subjects in both treatment groups had had children (19 subjects in the Victoza group and 17 subjects in the placebo group), with no subjects in the Victoza group and 3 subjects in the placebo group reported having their first child after the age of 30. The subjects in the Victoza group had a higher mean number of pregnancies than the subjects in the placebo group (5.1 versus 2.9 pregnancies).

- More subjects on Victoza (84.2%) vs. placebo (52.9%) ever breastfed; the mean duration among those who breastfed was 25.1 months for Victoza subjects and 18.8 months for placebo subjects.

- All subjects were postmenopausal and the age of menopause was similar in the 2 treatment groups.

- Four Victoza-treated subjects and 8 placebo-treated subjects ever used menopausal hormone therapy.

- The average total number of mammograms was similar in the 2 treatment groups. In the Victoza group, 11 out of 20 subjects had ≤ 5 mammograms, 3 subjects had > 35 mammograms, and 6 subjects answered 'don't know'. In the placebo group, 7 of 19 subjects had ≤ 5 mammograms, 8 subjects had >5 and ≤ 35 mammograms, 1 subject had > 35 mammograms, and 3 subjects answered 'don´t know'. Mean age of first mammogram in the Victoza group was 55.9 years and 46.7 years for the placebo group, and the average number of mammograms within the last 5 years was 2.6 in the Victoza group and 3.6 in the placebo group. More than half of the subjects in both treatment groups indicated that the reason for the last mammogram prior to the diagnosis of the malignant breast neoplasms was screening.

- Three subjects in the Victoza group and none in the placebo group had a previous diagnosis of breast cancer. Two subjects in the placebo group had history of other cancers (colorectal and uterine).

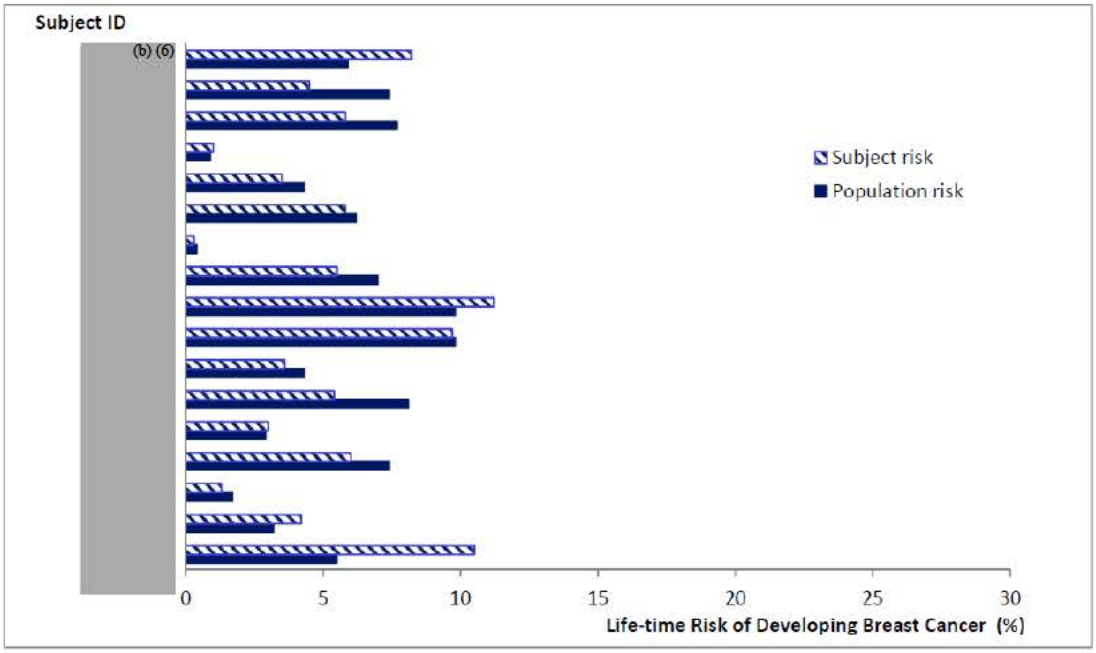
- Three subjects in the Victoza group and 6 subjects in the placebo group had a first degree relative with breast cancer.

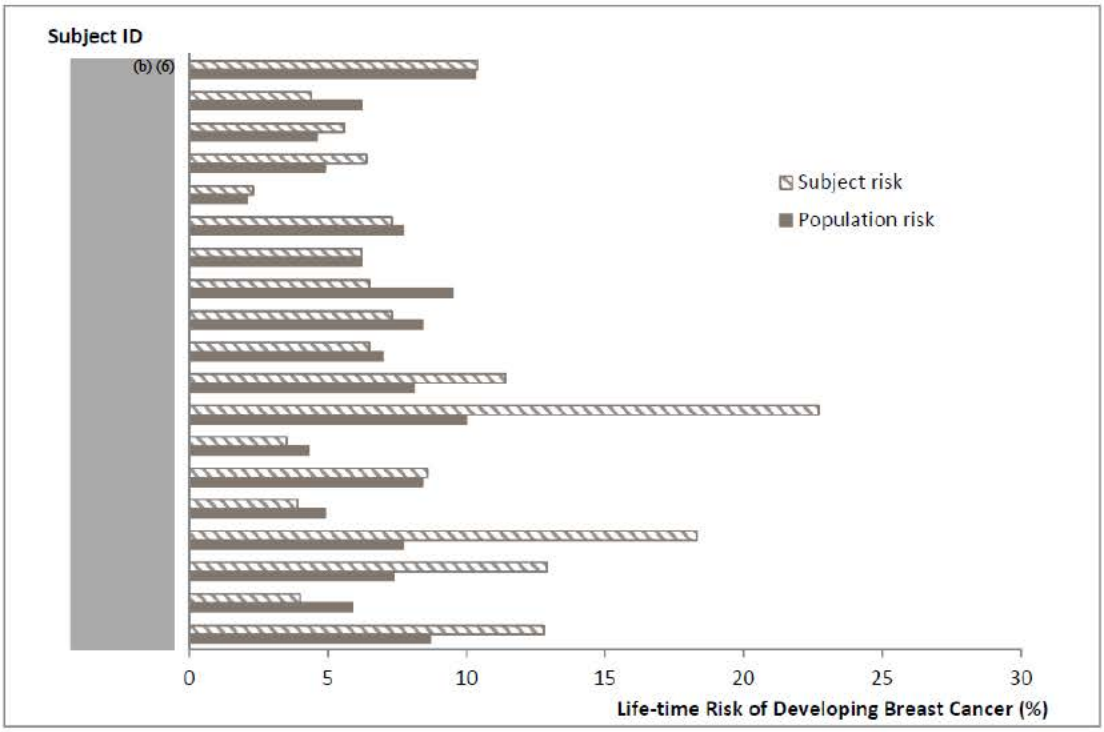
The IBIS tool utilized the information obtained from the questionnaires to estimate individual and population-based absolute risks; the estimates presented here use information on risk factors at the time of diagnosis.

The 3 subjects in the Victoza group with a previous history of breast cancer and 2 subjects (1 Victoza, 1 placebo) who were not interviewed are excluded.

The findings are shown below:

Figure 11. Lifetime Risk of Developing Breast Cancer in Subjects with EAC-Confirmed Breast Cancer Versus Corresponding Population Risk (Top/Blue: Victoza, Bottom/Gray: Placebo)





*A combination of oestrogen and progesterone was used as MHT when calculating life time risk for this female subject, since there was no indication of removal of uterus.

Source: Source: NDA 206321 PMR, Breast Cancer Report, Appendix 9, Figures 1 and 2

In addition to the above data collection for the Saxenda PMR, the sponsor also summarized baseline signs and symptoms and reason for investigation for the subjects with malignant and pre-malignant breast neoplasms from subject narratives:

Table 27. EAC-Confirmed Malignant and Pre-Malignant Breast Neoplasm Index Events

	Victoza N (%)	Placebo N (%)
Number of subjects with events	24	21
Signs/symptoms present at baseline*		
Yes	0	1 (4.8)
No	23 (95.8)	20 (95.2)
Information not available	1 (4.2)	0
Reason for investigation*		
Screening	5 (20.8)	8 (38.1)
Symptoms	14 (58.3)	9 (42.9)
Follow-up due to previous breast lesion	1 (4.2)	1 (4.8)
Other	1 (4.2)	2 (9.5)
Information not available	3 (12.5)	1 (4.8)

N: number of subjects; %: proportion of subjects out of N; EAC: event adjudication committee
* Based on sponsor narrative review
'No': specifically reported that no symptom was present at baseline

Source: ISS, Appendix 7.3, Table 7.3.27

In summary, the proportion of women in LEADER with breast cancer was similar in the Victoza and placebo treatment groups, as were baseline characteristics, risk factors, and breast cancer staging. Although these findings did not appear to suggest an increased risk of breast cancer associated with Victoza, limitations of this trial include a relatively short treatment duration for a breast cancer assessment.

9.1.3.3 Colon/Rectum

An imbalance in colorectal neoplasms was noted in the Saxenda development program; as reported in the Saxenda label:

In Saxenda clinical trials, benign colorectal neoplasms (mostly colon adenomas) confirmed by adjudication were reported in 20 (0.6%) of 3291 Saxenda-treated (b) (4) *compared with 7 (0.4%) of 1843 placebo-treated* (b) (4)*. Six positively adjudicated cases of malignant colorectal neoplasms were reported in 5 Saxenda-treated* (b) (4) *(0.2%, mostly adenocarcinomas) and 1 in a placebo-treated* (b) (4) *(0.1%, neuroendocrine tumor of the rectum).*

Table 28 below summarizes EAC-confirmed colorectal neoplasms by malignancy status. The majority of EAC-confirmed colorectal neoplasms were benign, with a numerically higher proportion in Victoza- vs. placebo-treated subjects [162 events in 140 Victoza subjects, 3.0% and 146 events in 123 placebo subjects, 2.6%; HR 1.13 (0.89, 1.45)]. A similar number and proportion of subjects in each treatment group had EAC-confirmed

malignant and pre-malignant colorectal neoplasms (Table 28; malignant colorectal neoplasm HR 0.99 (0.59, 1.68)).

Table 28. EAC-Confirmed Colorectal Neoplasm Index Events by Malignancy Status

	Victoza			Placebo		
	N (%)	**E**	**R**	**N (%)**	**E**	**R**
Number of subjects	**4668**			**4672**		
PYO	**17822**			**17741**		
EAC-confirmed colorectal neoplasms	167 (3.6)	198	1.11	145 (3.1)	176	0.99
Malignant	28 (0.6)	31	0.17	28 (0.6)	29	0.16
Pre-malignant	3 (0.1)	3	0.02	1 (<0.1)	1	0.01
Benign	140 (3.0)	162	0.91	123 (2.6)	146	0.82
Unclassified	2 (<0.1)	2	0.01	0	0	0

N: number of subjects; %: proportion of subjects; E: number of events; PYO: patient-years of observation; R: event rate per 100 observation years; EAC: event adjudication committee
Index events with EAC onset date from randomization date to follow-up are included
The index event is the event selected among multiple events if these were assessed and confirmed to be 1 and the same event

Source: Summary of Clinical Safety, Table 2-20

Benign and pre-malignant colorectal neoplasms in both treatment groups were assessed (Table 29) in a blinded review by an independent gastroenterologist for the sponsor. The majority were classified as *"Tubular adenoma with no or low grade dysplasia <10 mm in size or sessile serrated polyp <10 mm in size and no dysplasia"*.

Table 29. EAC-Confirmed Benign and Pre-Malignant Neoplasms, Risk of Malignant Transformation

	Victoza		Placebo	
	N (%)	E	N (%)	E
Total subjects/events	141	165	124*	148
Classification				
High grade dysplasia any size adenoma	12 (8.5)	15	10* (8.1)	11
Sessile serrated polyp with cytological dysplasia (any size) or traditional serrated adenoma	2 (1.4)	2	3 (2.4)	3
Adenoma ≥ 10 mm in size or sessile serrated polyp ≥ 10 mm in size and no dysplasia	21 (14.9)	23	34 (27.4)	36
Villous adenoma < 10 mm in size	2 (1.4)	2	9 (7.3)	9
Tubular adenoma with no or low grade dysplasia < 10 mm in size or sessile serrated polyp < 10 mm in size and no dysplasia	91 (64.5)	95	67 (54.0)	70
Hyperplastic polyps	1 (0.7)	1	1 (0.8)	1
Unclassifiable	24 (17.0)	27	17 (13.7)	18

* Subject (b) (6) (placebo group) was included in this output in error as this was a case of a malignant EAC-confirmed colorectal neoplasm event. The event is counted in the category 'High grade dysplasia any size adenoma'. The subject is correctly accounted for in the total number of subjects with a malignant colorectal neoplasm (Table 28).
Risk of malignant transformation was assessed by the independent gastroenterologist using: Lieberman et al. 2012[23]
For combined events only the event with worst risk of progression to colon cancer is included.

Source: Summary of Clinical Safety, Table 2-21

Table 30 below summarizes the indication for the first colonoscopy and relevant medical history in subjects with EAC-confirmed benign and pre-malignant colorectal neoplasms. In a slightly higher proportion of subjects in the Victoza group compared to the placebo group, the colorectal neoplasms were identified via colonoscopy performed due to a personal history of colorectal neoplasms. However, baseline information on relevant medical history in relation to colon adenomas were not systematically collected, nor were colonoscopies performed at baseline or during the trial in a systematic fashion.

[23] Lieberman DA, et al; United States Multi-Society Task Force on Colorectal Cancer. Guidelines for colonoscopy surveillance after screening and polypectomy: a consensus update by the US Multi-Society Task Force on Colorectal Cancer. Gastroenterology. 2012 Sep;143(3):844-57.

Table 30. EAC-Confirmed Benign and Pre-Malignant Colorectal Neoplasm Index Events, Summary Based on Individual Case Narrative Information

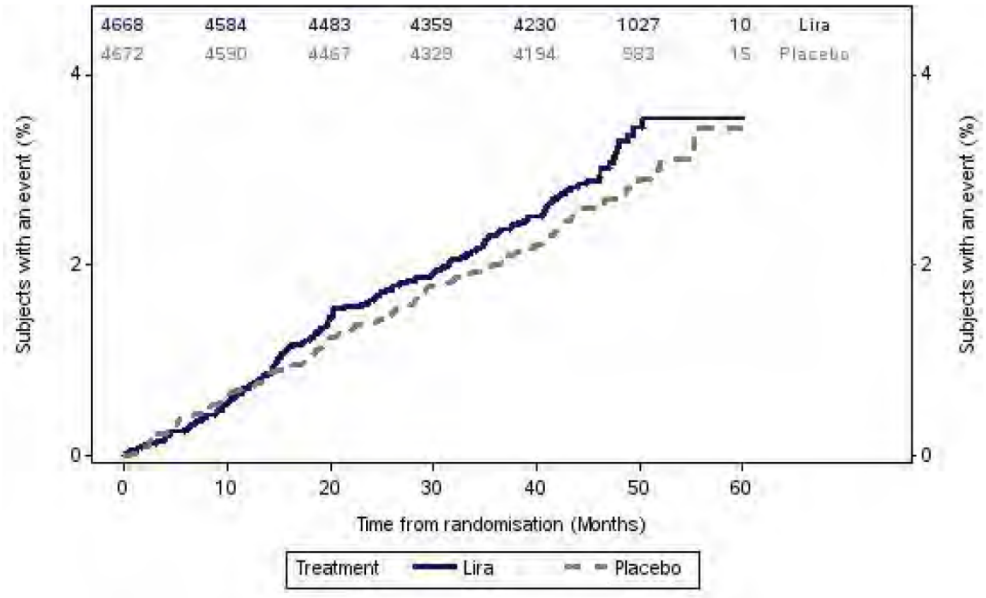
	Victoza		Placebo	
	N (%)	E	N (%)	E
Number of subjects/events	141 (100)	165	123 (100)	147
Available narrative for review	138 (97.9)	158	119 (96.7)	138
Indication for first colonoscopy*#				
Symptoms	56 (39.7)	58	57 (46.3)	58
Screening colonoscopy	34 (24.1)	36	29 (23.6)	29
Family history of colorectal neoplasms	1 (0.7)	1	7 (5.7)	7
Personal history of colorectal neoplasms	48 (34.0)	54	33 (26.8)	40
Personal history of inflammatory bowel disease	4 (2.8)	5	0	0
Incidental finding on imaging for other purpose	0	0	2 (1.6)	2
Other	3 (2.1)	3	1 (0.8)	1
Information not available	7 (5.0)	8	9 (7.3)	10
Relevant medical history*				
No relevant history	75 (53.2)	78	82 (66.7)	89
Relevant history	65 (46.1)	80	40 (32.5)	48
Inflammatory bowel disease	2 (1.4)	2	0	0
Colon adenoma(s)	46 (32.6)	61	31 (25.2)	38
Colorectal cancer	3 (2.1)	3	4 (3.3)	5
Other cancer	10 (7.1)	10	3 (2.4)	3
Other neoplasm	0	0	2 (1.6)	2
Other	4 (2.8)	4	0	0
Information not available	6 (4.3)	7	9 (7.3)	10

N: number of subjects; %: proportion of subjects out of N; E: number of events
* Based on narrative review. For events identified by the EAC/ICON, no narrative exists unless there exists a duplicate event with a narrative.
# Colonoscopy leading to diagnosis of EAC-confirmed index event with earliest EAC onset date in a subject.
'No relevant history': it was specifically reported that no symptom was present at baseline
'Information not available': the information was not reported in the narrative or the case narrative was not available

Source: Summary of Clinical Safety, Table 2-22

The Kaplan-Meier curve shown below illustrates the time-course for first EAC-confirmed benign colorectal neoplasm event. Separation of the curves appears to occur around month 14.

Figure 12. EAC-Confirmed Benign Colorectal Neoplasms, First Index Events



Source: LEADER CSR, Figure 12-32

In summary, although more events of benign colorectal neoplasms were EAC-confirmed in the Victoza group vs. the placebo group, a similar proportion of subjects had malignant colorectal neoplasms during the trial in each treatment group. An evaluation of indication for colonoscopy suggests that Victoza-treated subjects with benign lesions were more likely to have had a personal history of colorectal neoplasms than those treated with placebo, and ascertainment bias is possible. However, the lack of systematic collection of risk factors and colonoscopies does not allow for a full causality assessment.

9.1.3.4 Skin

As noted in Figure 7, the incidences of EAC-confirmed malignant skin neoplasms – both non-melanoma and melanoma – were numerically higher in the Victoza- vs. the placebo-treated groups [non-melanoma: Victoza n=78 (1.7%), placebo n=62 (1.3%); melanoma: Victoza n=13 (0.3%), placebo n=5 (0.1%)]. This section will address both types of skin cancer observed in LEADER, and including pre-malignant as well as malignant neoplasms.

Details of non-melanoma malignant and pre-malignant skin neoplasms were summarized by the sponsor as seen in Table 31. The majority of events were reported as basal cell carcinoma, and the majority of events occurred on the head, neck, or extremities (i.e., sun-exposed areas of the body). All subjects with non-melanoma malignant and pre-malignant skin neoplasms were white, with the exception of 1 Asian subject in the placebo group. Baseline risk factors for skin neoplasms in subjects with EAC-confirmed non-melanoma pre-malignant and malignant neoplasms were generally similar among treatment groups.

Table 31. Characteristics of EAC-Confirmed Non-Melanoma Pre-Malignant and Malignant Skin Neoplasms

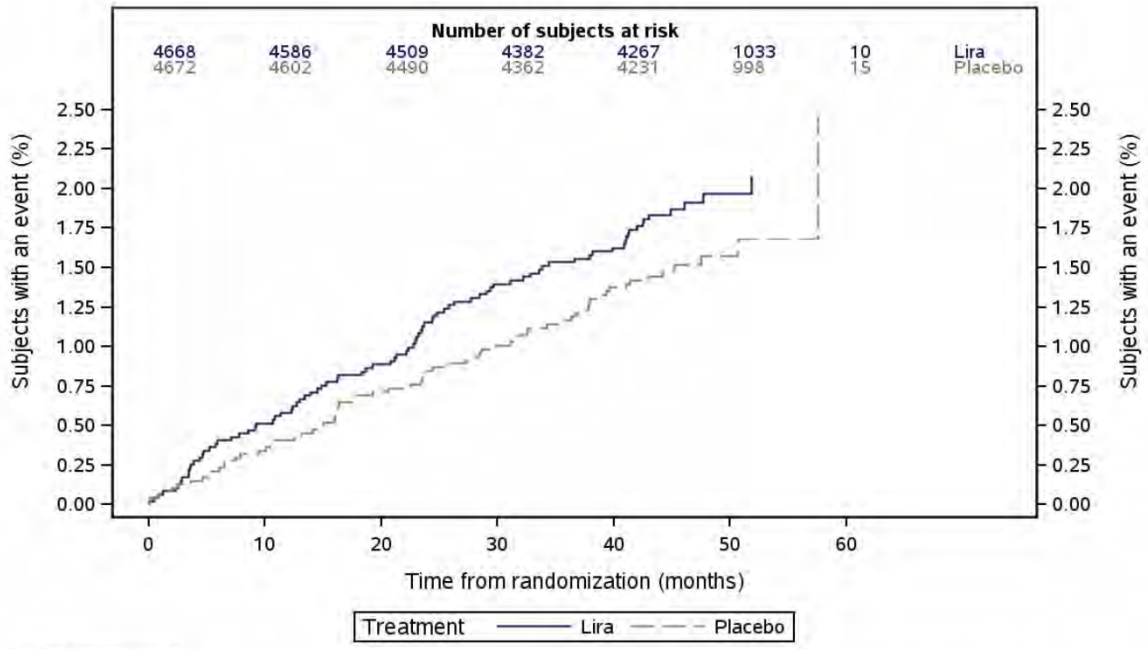
	Victoza		Placebo	
	N (%)	E	N (%)	E
Number of subjects/events	87 (100)	133	70 (100)	103
Available narrative for review	82 (94.3)	120	69 (98.6)	99
Type*				
Basal cell carcinoma	56 (64.4)	74	39 (55.7)	46
Squamous cell carcinoma	38 (43.7)	42	34 (48.6)	45
Other	4 (4.6)	4	7 (10.0)	7
Not specified	0	0	1 (1.4)	1
Information not available	10 (11.5)	13	4 (5.7)	4
Site of lesion*				
Head or neck	54 (62.1)	66	40 (57.1)	53
Extremities	26 (29.9)	29	17 (24.3)	23
Other	16 (18.4)	25	17 (24.3)	19
Information not available	10 (11.5)	13	6 (8.6)	8
Risk factors*	38 (43.7)	64	32 (45.7)	52
UV light exposure	15 (17.2)	26	12 (17.1)	25
Actinic keratosis	14 (16.1)	27	9 (12.9)	12
H. papilloma virus	0	0	0	0
Immunosuppression	0	0	0	0
Skin cancer	23 (26.4)	39	21 (30.0)	37
Family history of skin cancer	4 (4.6)	9	3 (4.3)	15
No reported risk factors	45 (51.7)	56	37 (52.9)	47
Information not available	10 (11.5)	13	4 (5.7)	4

N: number of subjects; %: proportion of subjects out of N; E: number of events; UV: ultraviolet
* Based on narrative review. For events identified by the EAC/ICON, no narrative exists unless there exists a duplicate event with a narrative.
'Information not available': the information was not reported in the narrative or the case narrative was not available

Source: Summary of Clinical Safety, Table 2-24

EAC-confirmed pre-malignant or malignant non-melanoma skin neoplasms were first reported shortly after randomization and occurred throughout the trial in both treatment groups. Curves appear to separate after month 4, with a higher proportion of subjects with an event in the Victoza group compared to the placebo group (Figure 13).

Figure 13. Kaplan-Meier Plot of Time to First EAC-Confirmed Pre-Malignant or Malignant Non-Melanoma Skin Neoplasm



Source: Summary of Clinical Safety, Figure 2-27

Regarding malignant and pre-malignant melanoma, an imbalance was also observed not in favor of Victoza (Table 32).

Table 32. EAC-Confirmed Skin Melanoma by Malignancy Status

	Victoza			Placebo		
	N (%)	E	R	N (%)	E	R
Number of subjects	**4668**			**4672**		
PYO	**17822**			**17741**		
EAC-confirmed melanoma of the skin						
Malignant	13 (0.3)	13	0.07	5 (0.1)	5	0.03
Pre-malignant	7 (0.1)	7	0.04	4 (0.1)	4	0.02

N: number of subjects; %: proportion of subjects; E: number of events; PYO: patient-years of observation; R: event rate per 100 observation years; EAC: event adjudication committee
Index events with EAC onset date from randomization date to follow-up are included
The index event is the event selected among multiple events if these were assessed and confirmed to be 1 and the same event

Source: Summary of Clinical Safety, Table 2-25

In the subjects with EAC-confirmed malignant or pre-malignant melanoma, demographics were similar among treatment groups; all subjects were white.

Table 33 presents the site of lesion and risk factor history in subjects with EAC-confirmed melanoma. Although more subjects with melanoma on Victoza had a reported risk factor at baseline (i.e., UV light exposure or history of skin cancer), risk

factors were generally balanced between treatment groups overall at baseline. Furthermore, the numbers of subjects were small, making attribution difficult.

Table 33. Characteristics of EAC-Confirmed Pre-Malignant and Malignant Melanomas

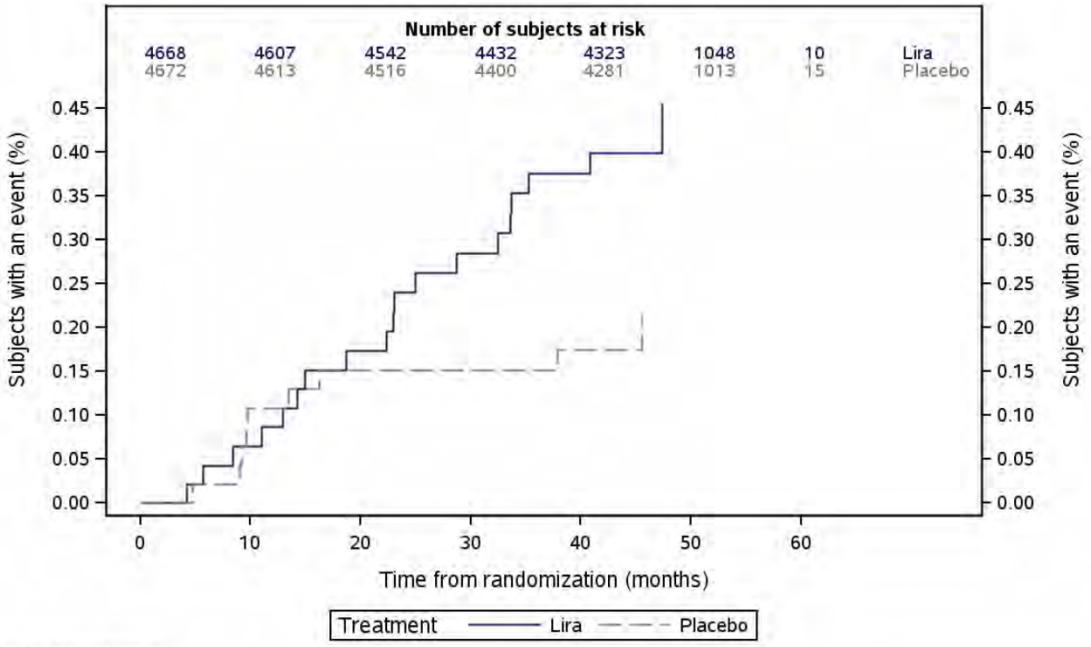
	Victoza		Placebo	
	N (%)	E	N (%)	E
Number of subjects/events	19 (100)	20	9 (100)	9
Available narrative for review	19 (100)	20	9 (100)	9
Site of lesion*				
Head or neck	7 (36.8)	7	3 (33.3)	3
Extremities	6 (31.6)	6	2 (22.2)	2
Other	5 (26.3)	6	4 (44.4)	4
Information not available	1 (5.3)	1	0	0
Risk factors*	11 (57.9)	12	2 (22.2)	2
UV light exposure	5 (26.3)	6	0	0
Multiple benign or atypical nevi	0	0	0	0
Multiple moles	0	0	0	0
Immunosuppression	0	0	0	0
Skin cancer	6 (31.6)	6	0	0
Family history of skin cancer	2 (10.5)	2	2 (22.2)	2
No reported risk factors	8 (42.1)	8	7 (77.8)	7
Information not available	0	0	0	0

N: number of subjects; %: proportion of subjects out of N; E: number of events
* Based on narrative review. For events identified by the EAC/ICON, no narrative exists unless there exists a duplicate event with a narrative.
'Information not available': the information was not reported in the narrative or the case narrative was not available

Summary of Clinical Safety, Table 2-26

As seen in the figure below, EAC-confirmed pre-malignant or malignant melanoma events had onset shortly after randomization and occurred at comparable rates in the 2 treatment groups until around month 18 into the trial. After this time, events continued to accrue at a similar and constant rate in the Victoza group, whereas, for the placebo group, only 2 additional events occurred.

Figure 14. Kaplan-Meier Plot of Time to First EAC-Confirmed Pre-Malignant or Malignant Melanoma



Source: Summary of Clinical Safety, Figure 2-28

An exploratory analysis of investigator-reported skin cancer was conducted utilizing the HLGT ''Skin neoplasms malignant and unspecified'; the results support the EAC-confirmed imbalance in investigator-reported basal cell carcinoma and malignant melanoma/melanoma *in situ*.

Table 34. Investigator-Reported Skin Cancer

	Victoza N=4668 n (%)	**Placebo N=4672 n (%)**
HLGT 'Skin neoplasms malignant and unspecified' AEs	96 (2.1)	68 (1.5)
Basal cell carcinoma	61 (1.3)	42 (0.9)
Squamous cell carcinoma of skin	22 (0.5)	20 (0.4)
Malignant melanoma	12 (0.3)	7 (0.1)
Bowen's disease	5 (0.1)	3 (0.1)
Malignant melanoma in situ	4 (0.1)	0
Metastatic malignant melanoma	2 (<0.1)	2 (<0.1)
Skin cancer	2 (<0.1)	2 (<0.1)
Keratoacanthoma	2 (<0.1)	1 (<0.1)
Neoplasm skin	2 (<0.1)	1 (<0.1)
Lentigo maligna	1 (<0.1)	1 (<0.1)
Carcinoma in situ of skin	1 (<0.1)	0
Neuroendocrine carcinoma of the skin	0	1 (<0.1)

Source: Reviewer created from LEADER datasets

In summary, the incidences of EAC-confirmed malignant skin neoplasms – both non-melanoma and melanoma – were numerically higher in the Victoza - vs. the placebo-treated groups. A similar imbalance was also seen in the investigator-reported adverse event search. Whether this represents a true risk of skin cancer with liraglutide is unclear.

9.2 Pancreatitis

As noted in the Warnings and Precautions section of the Victoza label, acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis, has been reported post-marketing in patients treated with Victoza,[24] and an imbalance in pancreatitis not in favor of liraglutide was noted in both Victoza and Saxenda (liraglutide for chronic weight management) clinical trials. Post-marketing reports of acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis, in GLP-1-based therapies have led to warnings regarding pancreatitis in drug labeling for the class. However, it should be noted that retrospective cohort studies have suggested an increased background risk of acute pancreatitis among individuals with type 2 diabetes (up to 1.5- to 3-fold).[25,26,27]

9.2.1 Adverse Events

According to the LEADER protocol, pancreatitis or acute severe and persistent abdominal pain leading to suspicion of pancreatitis was to be recorded as a MESI. Pancreatitis events were adjudicated by the EAC pancreatitis subcommittee, composed of 3 gastroenterologists.

The clinical evaluation of acute and chronic pancreatitis by the EAC was based on the criteria presented below. For a diagnosis of acute pancreatitis to be fulfilled, 2 of the 3 diagnostic criteria were to be present. Severity was based on the revised Atlanta criteria.[8,28] For a diagnosis of chronic pancreatitis to be fulfilled, the first of the 3 criteria (i.e., characteristic imaging findings) and at least 1 of the other 2 remaining criteria were to be present.

[24] This is a class-labeling warning for all incretin-based therapies.
[25] Girman, CJ, et al. Patients with type 2 diabetes mellitus have higher risk for acute pancreatitis compared with those without diabetes. Diabetes Obes Metabol. 2010;12:766-71.
[26] Lai, SW, et al. Risk of acute pancreatitis in type 2 diabetes and risk reduction on anti-diabetic drugs: a population-based cohort study in Taiwan. Am J Gastroenterol. 2011;106:1697-704.
[27] Noel, RA, et al. Increased risk of acute pancreatitis and biliary disease observed in patients with type 2 diabetes: a retrospective cohort study. Diabetes Care. 2009;32:834-8.
[28] Mild acute pancreatitis: no organ failure and no local or systemic complications; moderately severe acute pancreatitis: organ failure that resolves within 48 h (transient organ failure) and/or local or systemic complications without persistent organ failure; severe acute pancreatitis: persistent organ failure (>48 h) (single/multiple organs)

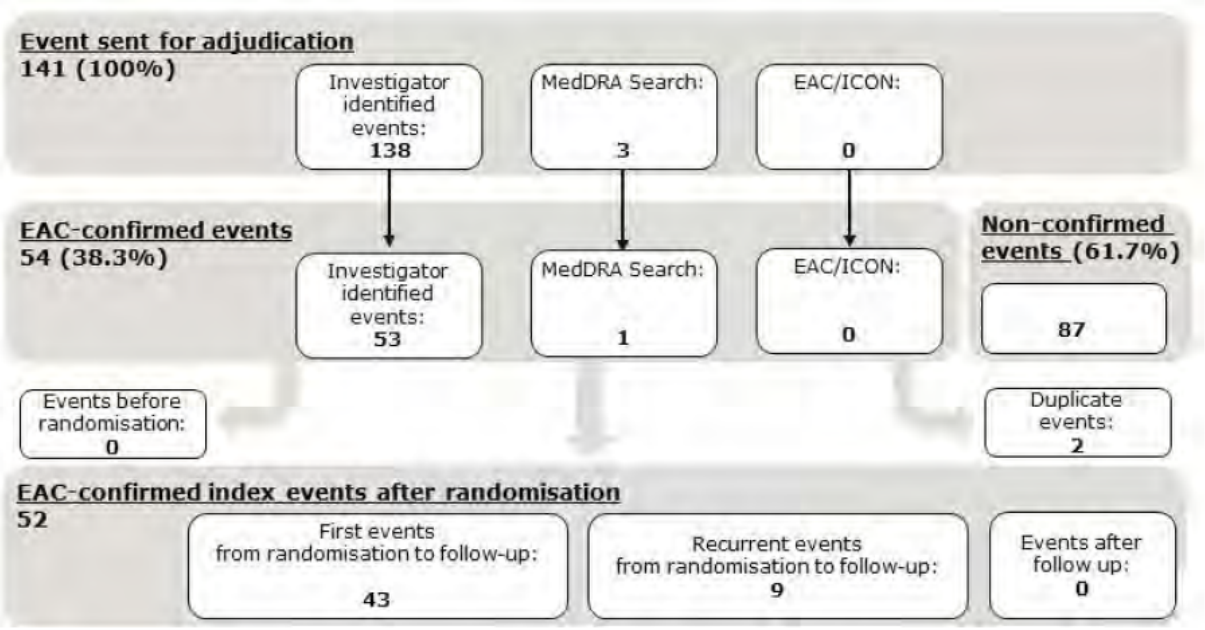
Table 35. EAC Evaluation of Pancreatitis

Event type	Adjudication outcome
Pancreatitis	Acute pancreatitis Y/N • Severe acute upper abdominal pain • Elevated levels of pancreatic enzymes (lipase, amylase) 3xULN • Characteristic imaging finding (ultrasound, CT, MRI)
	Severity • Mild acute pancreatitis • Moderately severe acute pancreatitis • Severe acute pancreatitis • Unable to distinguish between moderately severe and severe acute pancreatitis • Unable to assess severity
	Chronic pancreatitis Y/N • Characteristic imaging finding (ultrasound, CT, MRI) • Abnormal pancreatic function tests • Characteristic histological findings
CT: computed tomography; EAC: event adjudication committee; MRI: magnetic resonance imaging; N: no; ULN: upper limit of normal; Y: yes	

Source: LEADER CSR, Table 9-7

In this trial, a total of 141 potential pancreatitis events were sent for adjudication and 52 events in 43 subjects were confirmed by the EAC (Figure 15).

Figure 15. Adjudication Flow for Pancreatitis



Note: Full analysis set.
Abbreviations: EAC: event adjudication committee; ECG: electrocardiogram; ICON: adjudication vendor (contract research organisation); MedDRA: Medical Dictionary for Regulatory Activities.

Source: LEADER CSR, Figure 12-36

A similar proportion of subjects in both treatment groups experienced EAC-confirmed events of pancreatitis (Table 36).

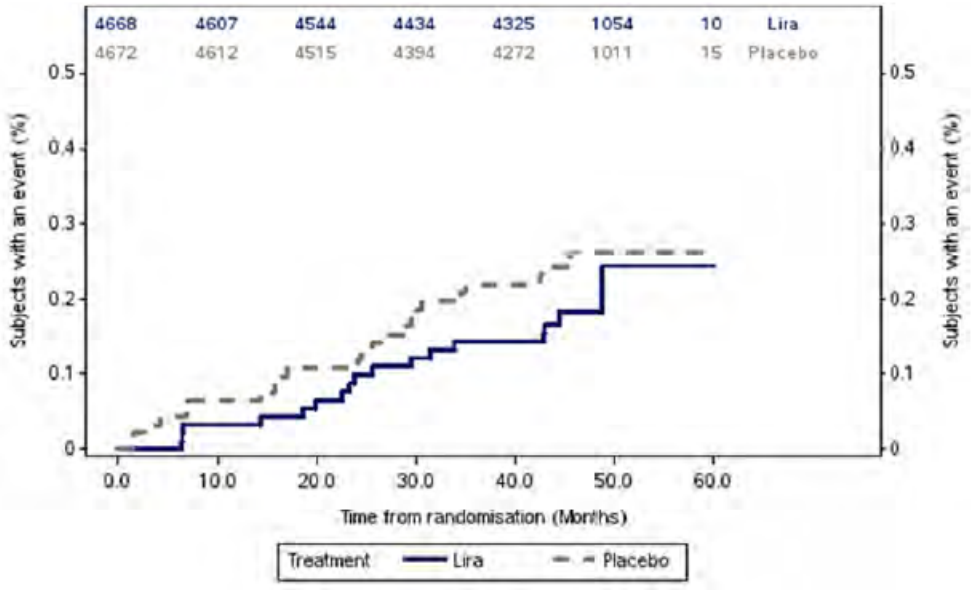
Table 36. EAC-Confirmed Pancreatitis Events

	Victoza		Placebo	
	N=4668 n (%)	PYO=17822 Events (Rate/100 PY)	N=4672 n (%)	PYO=17735 Events (Rate/100 PY)
EAC-confirmed pancreatitis	18 (0.4)	19 (0.11)	25 (0.5)	33 (0.19)
Acute	18 (0.4)	19 (0.11)	23 (0.5)	31 (0.17)
Chronic	0	0	2 (<0.1)	2 (0.01)

Source: LEADER CSR, Table 12-48

A *post hoc* Cox analysis of time to first EAC-confirmed acute pancreatitis event demonstrated an estimated hazard ratio for Victoza vs. placebo of 0.78 (95% CI 0.42, 1.44). The Kaplan-Meier plot of first event is shown in the following figure.

Figure 16. Time to First EAC-Confirmed Pancreatitis Event



Source: LEADER CSR, Figure 12-37

A similar proportion of pancreatitis events in both treatment groups were associated with presence of gallstones at the time of the event (Table 37). This information was obtained from a *post hoc* review of the individual case narratives by the sponsor where presence of gallstone disease at the time of the event was defined either by imaging or by ALT ≥3×ULN (in case imaging was not available). Gallbladder disorders are discussed further in the subsection below. An additional summary of baseline factors in subjects with and without EAC-confirmed acute pancreatitis is shown in Table 38. A higher proportion of subjects with events of acute pancreatitis in the placebo group had a history of pancreatitis, biliary disease, or hypercalcemia at baseline compared to those subjects treated with Victoza.

Table 37. Overview of EAC-Confirmed Pancreatitis Cases

	Victoza		Placebo	
	N (%)	E	N (%)	E
Total Subjects/Events	18 (100)	19	25 (100)	33
Presence of gallstones at time of event*				
Yes	7 (38.9)	7	11 (44.0)	14
Gallstones confirmed by imaging	6 (33.3)	6	8 (32.0)	9
Imaging suggestive of acute gallstone disease	0	0	2 (8.0)	3
ALT ≥ 3x ULN	1 (5.6)	1	1 (4.0)	2
No	12 (66.7)	12	15 (60.0)	19
Information not available	0	0	0	0
Medical history of gallstone disease/cholecystitis**				
Yes	2 (11.1)	2	6 (24.0)	7
Gallstone disease	1 (5.6)	1	5 (20.0)	6
Cholecystitis	1 (5.6)	1	5 (20.0)	6
No	16 (88.9)	17	19 (76.0)	26
Medical history of pancreatitis**				
Yes	2 (11.1)	2	6 (24.0)	7
No	16 (88.9)	17	19 (76.0)	26
Alcohol use*				
Current	1 (5.6)	1	1 (4.0)	1
Previous	0	0	1 (4.0)	1
No	4 (22.2)	4	3 (12.0)	4
Information not available	13 (72.2)	14	20 (80.0)	27
Treatment*				
None, observation	1 (5.6)	1	4 (16.0)	4
Standard	14 (77.8)	14	19 (76.0)	26
Intensive	1 (5.6)	1	0	0
Other	3 (16.7)	3	3 (12.0)	3

N: number of subjects, E: number of events, ULN: upper limit of normal
* Based on *post hoc* review of the individual case narratives by the sponsor
** Based on data from the clinical database
ALT ≥ 3x ULN includes events with elevated ALT ≥ 3x ULN, for which imaging was either not performed, was inconclusive, or did not show signs of acute gallstone disease

Source: Summary of Clinical Safety, Table 2-29

Table 38. Baseline Risk Factors for EAC-Confirmed Acute Pancreatitis

	Subjects with acute pancreatitis		All subjects	
	Victoza N (%)	Placebo N (%)	Victoza N (%)	Placebo N (%)
Number of subjects	18 (100.0)	23 (100.0)	4668 (100.0)	4672 (100.0)
History of pancreatitis acute/chronic	2 (11.1)	6 (26.1)	147 (3.1)	120 (2.6)
History of biliary disease	2 (11.1)	6 (26.1)	730 (15.6)	689 (14.7)
BMI at baseline ≥ 30-<35 kg/m^2	8 (44.4)	8 (34.8)	1523 (32.6)	1470 (31.5)
BMI at baseline ≥ 35 kg/m^2	6 (33.3)	7 (30.4)	1424 (30.5)	1398 (29.9)
Hypertriglyceridemia at baseline	9 (50.0)	10 (43.5)	2323 (49.8)	2288 (49.0)
Hypercalcemia at baseline	1 (5.6)	4 (17.4)	211 (4.5)	201 (4.3)
Smoker at baseline	3 (16.7)	3 (13.0)	567 (12.1)	563 (12.1)

N: number of subjects; %: percentage of subjects; EAC: event adjudication committee
Medical history of pancreatitis and biliary disease are reported in specific forms in the CRF
Hypertriglyceridemia at baseline is determined as a baseline triglyceride measurement above upper normal limit
Hypercalcemia at baseline is determined as a baseline calcium measurement above upper normal limit

Source: LEADER CSR, Table 12-50

The EAC confirmed acute pancreatitis with the diagnostic criterion of 'severe acute abdominal pain' in 95% of Victoza events and 100% of placebo events, with 'elevated blood levels of pancreatic enzymes' in 68% of Victoza events and 87% of placebo events, and with 'characteristic imaging finding' in 58% of Victoza events and 55% of placebo events.

The majority of acute pancreatitis events were classified by the EAC as mild (17/19, 89.5% Victoza events and 26/31, 83.9% placebo events). No Victoza events and 4 (12.9%) placebo events were adjudicated as moderately severe. Three events were considered severe: 2 events in subjects treated with Victoza (2/18) and 1 event in a subject treated with placebo (1/23). Severe events are discussed below:

- Subject (b) (6) (Victoza): This was a 57 year old female who was treated with drug for 896 days prior to the onset of pancreatitis, which occurred in the setting of a work-up for lung carcinoma and adrenal gland abnormality (symptoms developed after a needle puncture of the adrenal gland; pancreatitis was considered to be post-interventional). The subject recovered from the pancreatitis with no dose change.

- Subject (b) (6) (Victoza): This was a 66 year old male subject with a history of excessive alcohol consumption and obesity who had onset of pancreatitis on study day 956, after presenting with abdominal pain, vomiting, and diarrhea. A CT scan showed diffuse moderate inflammatory change around the pancreas from the head to the tail consistent with pancreatitis. There was a question of a tiny calcification near the expected position of the ampulla which was thought to possibly represent gallstone pancreatitis. Lipase was 53868 U/L. The subject was admitted to the ICU; the course was complicated by the development of ascites and anasarca, acute

kidney injury, and hypoxemic respiratory failure requiring intubation. He was ultimately discharged to a rehabilitation facility.

- Subject (b) (6) (placebo): This was a 62 year old female with pancreatitis onset on day 501, who also presented with myocardial infarction, developed septic shock and hypoxic encephalopathy, and ultimately died due to respiratory failure from pneumonia.

In addition, 1 event of EAC-confirmed pancreatitis – in a subject treated with placebo (subject (b) (6)) – had a fatal outcome.

Additional details of Victoza-treated subjects with EAC-confirmed acute pancreatitis are as follows:

- 7 subjects discontinued Victoza due to the event
  - In 2 subjects, Victoza was later reintroduced without recurrence of pancreatitis
  - In 1 subject, EAC-confirmed pancreatitis recurred 146 days after discontinuation; the subject was also diagnosed with gallstones at that time
  - In 2 subjects, additional events of pancreatitis were reported by the investigator after drug discontinuation; however, these events were not confirmed by the EAC

- 5 subjects (including the 1 subject with the EAC-confirmed pancreatitis recurrence above) discontinued Victoza 30 to 637 days prior to the pancreatitis event

- 7 subjects who had pancreatitis while on Victoza continued the drug with no change; all subjects recovered without relapse of pancreatitis. According to FDA dataset and narrative review, 3 of these subjects reportedly had gallstones associated with the pancreatitis diagnosis, one of whom (subject (b) (6)) was treated with cholecystectomy.

There were more subjects with investigator-reported events of acute and chronic pancreatitis events *not* confirmed by the EAC in the Victoza group than placebo group. Table 39 outlines the MedDRA preferred terms reported by the investigator that were and were not ultimately confirmed by the EAC. In particular, there were more subjects with AEs of 'pancreatitis', 'pancreatitis acute', and 'pancreatitis chronic' not confirmed as pancreatitis by the EAC in the Victoza group. A summary table of AEs of 'pancreatitis acute' in the Victoza group not confirmed and confirmed by the EAC is in the appendix (Section 13.2.4), to provide perspective for EAC decision-making.

Table 39. Subjects with Adverse Events Submitted to the EAC Pancreatitis Subcommittee as Investigator-Reported by Preferred Term

	Victoza N=4668	Placebo N=4672
EAC-Confirmed	18 (0.4)	25 (0.5)
Pancreatitis acute	9 (0.2)	15 (0.3)
Pancreatitis	9 (0.2)	9 (0.2)
Pancreatitis chronic	1 (<0.1)	2 (<0.1)
Pancreatitis relapsing	1 (<0.1)	1 (<0.1)
Abdominal pain	0	1 (<0.1)
Lipase increased	0	1 (<0.1)
No AE recorded	1 (<0.1)	0
EAC Not Confirmed	53 (1.1)	21 (0.4)
Pancreatitis	14 (0.3)	5 (0.1)
Pancreatitis acute	9 (0.2)	4 (0.1)
Pancreatitis chronic	9 (0.2)	3 (0.1)
Lipase increased	6 (0.1)	1 (<0.1)
Abdominal pain	4 (0.1)	2 (<0.1)
Amylase increased	4 (0.1)	1 (<0.1)
Abdominal pain upper	3 (0.1)	0
Chronic gastritis	1 (<0.1)	2 (<0.1)
Cholecystitis	1 (<0.1)	0
Gastroenteritis viral	1 (<0.1)	0
Pancreatic atrophy	1 (<0.1)	0
Pancreatic enzymes increased	1 (<0.1)	0
Cholecystitis chronic	0	1 (<0.1)
Edematous pancreatitis	0	1 (<0.1)
Pancreatic cyst	0	1 (<0.1)
No AE recorded	5 (0.1)	4 (0.1)

Source: Response to FDA request Apr 21, 2017, Appendix 1, Table 5

The sponsor also provided an assessment of pancreatitis events not confirmed by the EAC by diagnostic criteria (acute, Table 40; chronic, Table 41):

Table 40. Summary of Acute Pancreatitis Events Not Confirmed by the EAC

	Victoza		Placebo	
	N (%)	E	N (%)	E
Non-confirmed acute pancreatitis*	43 (100)	50	19 (100)	21
Diagnostic criteria fulfilled*				
• Severe acute upper abdominal pain and elevated blood levels of pancreatic enzymes ≥3xULN	0	0	1 (5.3)	1
• Severe acute abdominal pain only	5 (11.6)	6	2 (10.5)	2
• Elevated blood levels of pancreatic enzymes ≥3xULN only	20 (46.5)	23	7 (36.8)	9
• Characteristic imaging only#	1 (2.3)	1	1 (5.3)	1
• No diagnostic criteria fulfilled	18 (41.9)	20	8 (42.1)	8
Number of diagnostic parameters with information available				
0	3 (7.0)	3	0 (0.0)	0
1	4 (9.3)	4	1 (5.3)	1
2	16 (37.2)	17	7 (36.8)	8
3	23 (53.5)	26	11 (57.9)	12
Reason for investigation*				
• Abdominal pain	18 (41.9)	20	14 (73.7)	14
• Elevated pancreatic enzymes	16 (37.2)	20	5 (26.3)	7
• Incidental imaging finding	1 (2.3)	1	0 (0.0)	0
• Abdominal pain and elevated pancreatic enzymes	3 (7.0)	3	0 (0.0)	0
• Other	3 (7.0)	3	0 (0.0)	0
• Information not available	3 (7.0)	3	0 (0.0)	0

* Based on sponsor review of documents in the source document package, available to the EAC
# Characteristic imaging: US, CT, or MRI
Diagnostic criteria for acute pancreatitis: any 2 of the following 3 criteria of severe acute upper abdominal pain, elevated blood levels of pancreatic enzymes (lipase/amylase) ≥ 3x ULN, characteristic imaging finding (US, CT, MRI)
EAC: event adjudication committee; ULN: upper limit of normal; US: ultrasound; CT: computed tomography; MRI: magnetic resonance imaging
Events included in the table were categorized by the sponsor as 'acute pancreatitis' based on available clinical information in the source document package available to the EAC (i.e., related to diagnostic criteria) indicating presence of an acute element in the course of the disease under investigation

Source: ISS, Table 7.4.10

Table 41. Summary of Chronic Pancreatitis Events Not Confirmed by the EAC

	Victoza		Placebo	
	N (%)	E	N (%)	E
Non-confirmed chronic pancreatitis*	11 (100.0)	11	4 (100.0)	5
Diagnostic criteria fulfilled*#				
• Characteristic imaging only	8 (72.7)	8	4 (100.0)	5
• Abnormal pancreatic function tests only	0 (0.0)	0	0 (0.0)	0
• Characteristic histological finding and abnormal pancreatic function tests only	0 (0.0)	0	0 (0.0)	0
• Characteristic histological finding only	0 (0.0)	0	0 (0.0)	0
• No diagnostic criteria fulfilled	3 (27.3)	3	0 (0.0)	0
Number of diagnostic parameters with information available				
0	0 (0.0)	0	0 (0.0)	0
1	11 (100.0)	11	4 (100.0)	5
2	0 (0.0)	0	0 (0.0)	0
3	0 (0.0)	0	0 (0.0)	0
Reason for investigation*				
• Abdominal pain	5 (45.5)	5	2 (50.0)	3
• Elevated pancreatic enzymes	3 (27.3)	3	1 (25.0)	1
• Incidental imaging finding	3 (27.3)	3	1 (25.0)	1
• Abdominal pain and elevated pancreatic enzymes	0 (0.0)	0	0 (0.0)	0
• Other	0 (0.0)	0	0 (0.0)	0

* Based on available clinical information in source document packages provided to the EAC for the individual events
# Diagnostic criteria for chronic pancreatitis: characteristic imaging finding (US, CT, MRI) with abndomral pancreatic function tests or characteristic histological findings
EAC: event adjudication committee; ULN: upper limit of normal; US: ultrasound; CT: computed tomography; MRI: magnetic resonance imaging
Events included in the table were categorized by the sponsor as 'chronic pancreatitis' based on available clinical information in the source document package available to the EAC (i.e., related to diagnostic criteria) indicating no presence of an acute element in the course of the disease under investigation

Source: ISS, Table 7.4.11

It is notable that although events were not confirmed due to not meeting diagnostic criteria, a substantial number of events did not have a full panel of diagnostic parameters with information available in order to make a determination.

An exploratory analysis[29] of investigator-reported pancreatitis (irrespective of adjudication status) using a MedDRA search for terms that include 'pancreatitis'[30] resulted in 46 subjects (1.0%) treated with Victoza and 34 (0.7%) treated with placebo with reported events.

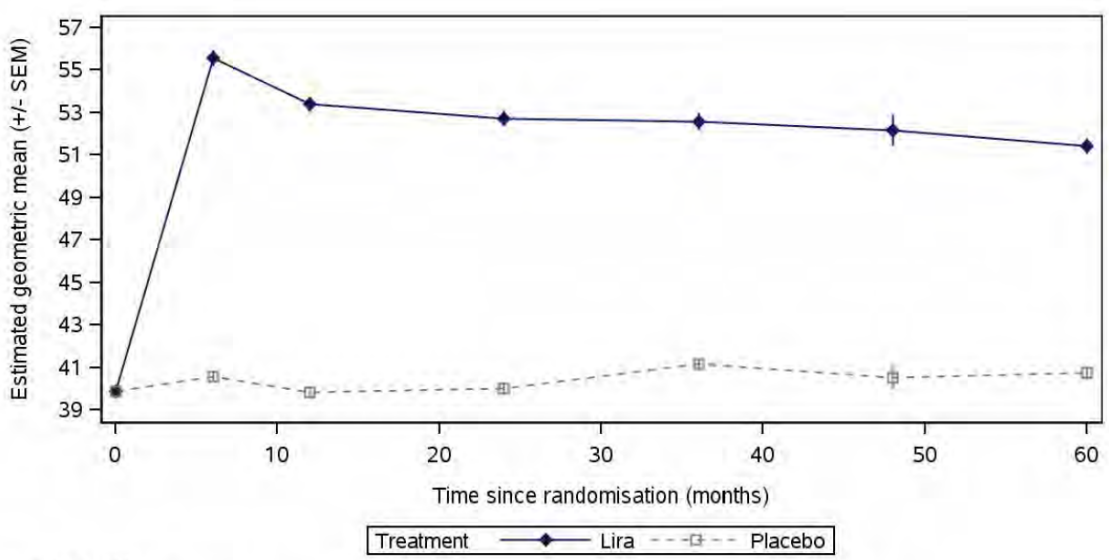
[29] Conducted by the reviewer
[30] Terms found in the search: 'edematous pancreatitis', 'pancreatitis', 'pancreatitis acute', 'pancreatitis chronic', and pancreatitis relapsing'

9.2.2 Lipase and Amylase

Liraglutide has been associated with elevations in lipase and amylase of unclear clinical significance in the absence of other symptoms and signs of pancreatitis. Lipase and amylase was measured routinely in LEADER at baseline and at 6, 12, 24, 36, and 48 months, and at end of treatment. The reference range for lipase was 16-63 U/L and for amylase 28-100 U/L.

As shown in Figure 17 and Figure 18, Victoza was associated with a mean increase in lipase and amylase, which persisted during the trial as compared with placebo.

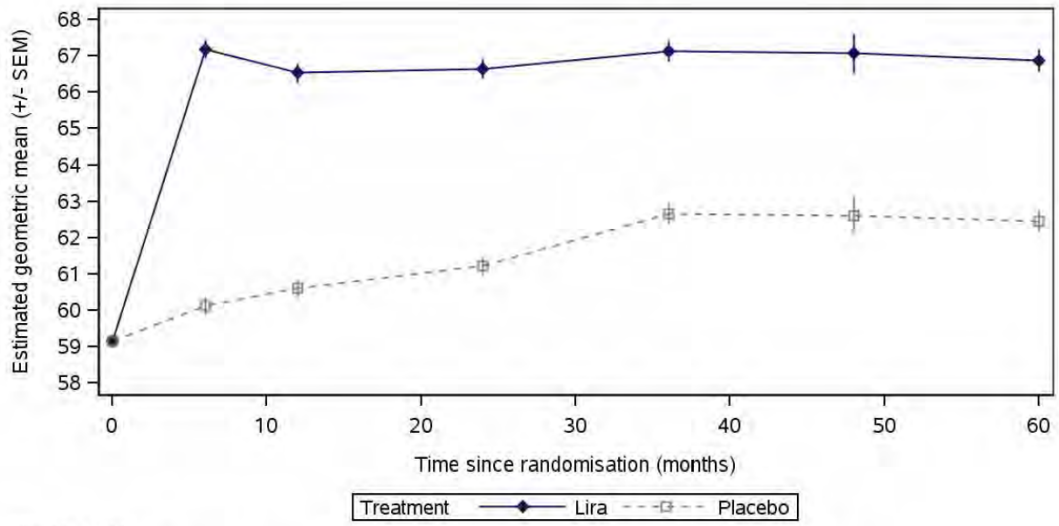
Figure 17. Lipase Values, Estimated Means



Lira: Liraglutide
Estimated means (+/- SEM) are estmated using MMRM on the log-transformed responses with treatment, sex, region and antidiabetic therapy at baseline as fixed effects and baseline lipase and age as covariates. all nested within visit. The means and error bars are calculated on the log scale before being back transformed to the original scale.
SEM: Standard error of the mean, MMRM: Mixed model for repeated measurements.

Source: LEADER CSR, Figure 14.3.5.81

Figure 18. Amylase Values, Estimated Means



Lira: Liraglutide
Estimated means (+/- SEM) are estmated using MMRM on the log-transformed responses with treatment, sex, region and antidiabetic therapy at baseline as fixed effects and baseline amylase and age as covariates. all nested within visit. The means and error bars are calculated on the log scale before being back transformed to the original scale.
SEM: Standard error of the mean, MMRM: Mixed model for repeated measurements.

Source: LEADER CSR, Figure 14.3.5.94

More subjects in the Victoza group had elevations of lipase and amylase with various cut-offs as compared with placebo; however, few in either treatment group with scheduled post-baseline elevations in lipase and amylase were diagnosed with acute pancreatitis (Table 42, Table 43, and Table 44).

Table 42. Abnormal Lipase and Amylase Values

	Victoza N=4668	**Placebo N=4672**
Lipase		
>ULN to 1.5x ULN	2393 (51.3)	1484 (31.8)
>1.5x to 2x ULN	1098 (23.5)	620 (13.3)
>2x to 5x ULN	829 (17.8)	490 (10.5)
>5x ULN	140 (3.0)	91 (1.9)
Amylase		
>ULN to 1.5x ULN	1354 (29.0)	1070 (22.9)
>1.5x to 2x ULN	399 (8.5)	306 (6.5)
>2x to 5x ULN	177 (3.8)	148 (3.2)
>5x ULN	9 (0.2)	7 (0.1)

Source: LEADER CSR, Table 14.3.5.102

Table 43. EAC-Confirmed Acute Pancreatitis Events in Subjects with at Least 1 Scheduled Post-Baseline Lipase Measurement ≥ ULN

	Victoza				Placebo			
	N	**(%)**	**E**	**R**	**N**	**(%)**	**E**	**R**
Number of subjects with at least 1 post-baseline lipase measurement ≥ 3xULN	351				200			
PYO	1370				789			
Acute pancreatitis	0	(0.0)	0	0.00	3	(1.5)	3	0.38
Number of subjects with at least 1 post-baseline lipase measurement ≥ 2xULN	816				446			
PYO	3186				1753			
Acute pancreatitis	2	(0.2)	2	0.06	5	(1.1)	6	0.34
Number of subjects with at least 1 post-baseline lipase measurement ≥ 1xULN	2626				1640			
PYO	10175				6378			
Acute pancreatitis	10	(0.4)	11	0.11	14	(0.9)	21	0.33

%: proportion of subjects; E: number of events; EAC: event adjudication committee; N: number of subjects; PYO: patient-years of observation; R: event rate per 100 observation years; ULN: upper limit of normal for lipase is 63 U/L
Index events with EAC onset date from randomization date and onwards are included.
Measurements from planned visits are included in the table. Subjects with lipase above ULN at baseline have not been excluded.

Source: Summary of Clinical Safety, Table 2-30

Table 44. EAC-Confirmed Acute Pancreatitis Events in Subjects with at Least 1 Post Baseline Amylase Measurement ≥ ULN

	Victoza				Placebo			
	N	**(%)**	**E**	**R**	**N**	**(%)**	**E**	**R**
Number of subjects with at least 1 post-baseline amylase measurement ≥ 3xULN	0				0			
PYO	0				0			
Acute pancreatitis	0	(0.0)	0	0.00	0	(0.0)	0	0.00
Number of subjects with at least 1 post-baseline amylase measurement ≥ 2xULN	165				129			
PYO	635				490			
Acute pancreatitis	0	(0.0)	0	0.00	1	(0.8)	3	0.61
Number of subjects with at least 1 post-baseline amylase measurement ≥ 1xULN	1400				1084			
PYO	5416				4155			
Acute pancreatitis	5	(0.4)	5	0.09	9	(0.8)	14	0.34

%: proportion of subjects; E: number of events; EAC: event adjudication committee; N: number of subjects; PYO: patient-years of observation; R: event rate per 100 observation years; ULN: upper limit of normal for amylase is 100 U/L
Index events with EAC onset date from randomization date and onwards are included.
Measurements from planned visits are included in the table. Subjects with amylase above ULN at baseline have not been excluded.

Source: Summary of Clinical Safety, Table 2-31

In summary, although pancreatitis was not EAC-confirmed more frequently with Victoza in this trial, it was notable there were more subjects with investigator-reported events of pancreatitis *not* confirmed by the EAC in the Victoza group vs. the placebo group. Events not confirmed by the EAC did not meet strict pre-defined diagnostic criteria (for example, in some cases only an increase in pancreatic enzymes – which can be associated with liraglutide treatment – was observed). However, as approximately half the events not confirmed by the EAC did not have full diagnostic information available, it is possible that Victoza-associated pancreatitis was not fully characterized in this trial by the adjudication procedure.

9.3 Acute Gallstone Disease

Gallstones are very common in adults in Western societies. Estimates range from 10 to 20% of the adult population that have or will have gallstones; of these, 20% are estimated to develop symptoms (biliary pain) or complications (e.g., acute cholecystitis, cholangitis, or pancreatitis).[31] Gallstones are diagnosed with ultrasonography, and when symptomatic, are generally treated with cholecystectomy.

Conditions that support formation of gallstones include cholesterol supersaturation of bile, pronucleating factors exceeding antinucleating factors (such as bile salt concentrations), and decreases in gallbladder motility.[32] Risk factors for cholesterol stone formation include female sex, increasing age, genetics/ethnicity, obesity, and rapid weight loss. Metabolic disorders associated with abdominal obesity such as insulin resistance, hypertriglyceridemia, and low HDL-cholesterol have been described in association with cholelithiasis, but the independent effects of each of these factors in the pathogenesis is unclear.[33]

Gallstone-related disorders, including cholelithiasis and cholecystitis, was a novel safety finding in the Saxenda phase 3 program as it had not been previously described with Victoza. Acute gallbladder disease has been included in Section 5 (Warnings and Precautions) of the Saxenda label. Although obesity and weight loss are associated with an increased risk for gallstone formation, gallstones were associated with Saxenda at least partially independent of weight loss, raising the possibility that liraglutide may have direct gallbladder effects. Although another GLP-1 receptor agonist was shown to reduce cholecystokinin-induced gallbladder emptying compared with placebo in fasting healthy individuals,[34] a recently published study in individuals with type 2 diabetes

[31] Stinton LM and Shaffer EA. Epidemiology of gallbladder disease: cholelithiasis and cancer. Gut Liver. 2012; 6(2): 172-87.
[32] Gurusamy KS and Davidson BR. Gallstones. BMJ, 2014; 348: g2669.
[33] Shaffer EA. Epidemiology of gallbladder stone disease. Best Pract Res Clin Gastroenterol. 2006; 20(6): 981-96.
[34] Keller J, et al. Effect of exenatide on cholecystokinin-induced gallbladder emptying in fasting healthy subjects. Regul Pept 2012; 179(1-3):77-83.

suggested that liraglutide did not have an effect on gallbladder emptying, but was associated with changes in bile acids.[35]

In the LEADER trial, AEs of acute gallstone disease were collected and recorded as MESIs, although they were not adjudicated by the EAC. The specific event that was to be considered MESI by the investigator was 'acute gallstone disease (biliary colic or acute cholecystitis)'. Events of acute gallstone disease were identified via a MedDRA search using pre-specified standardized MedDRA queries (SMQs).

If a subject had an event of gallstones (perhaps diagnosed incidentally), but this event was not considered by the investigator to be serious or an acute gallstone MESI, it would not be recorded in the analyses of acute gallstone disease. There were a number of AEs identified in the MedDRA search not captured below because they were not considered SAEs or MESIs. All gallbladder-related AEs (according to the MedDRA search) regardless of SAE/MESI status are included in Table 90 in the appendix; this analysis does not change the overall assessment of gallstone events.

In the LEADER trial, SAEs and non-serious MESIs of 'acute gallstone disease' were observed more frequently in the Victoza group than in the placebo group (Table 45 and Figure 19).

[35] Smits MM, et al. Biliary effects of liraglutide and sitagliptin, a 12-week randomized placebo-controlled trial in type 2 diabetes patients. Diabetes Obes Metab 2015; 18: 1217-25.

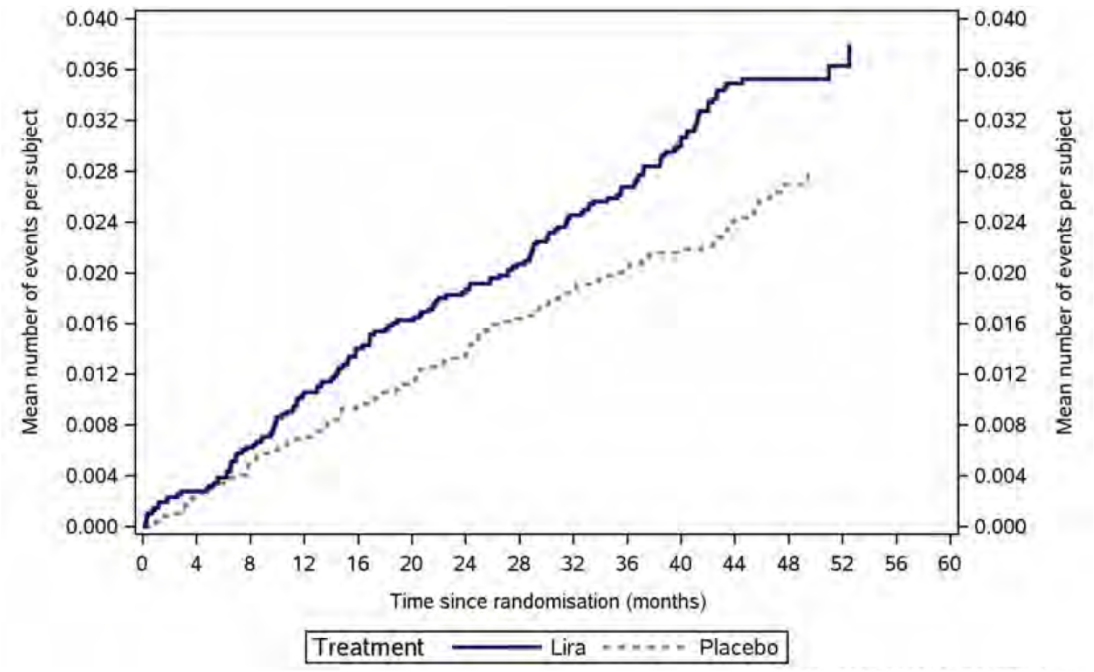
Table 45. Acute Gallstone Disease SAEs and Non-Serious MESIs

	Victoza			Placebo		
	N (%)	E	R	N (%)	E	R
Number of subjects	4668			4672		
PYO	17822			17741		
Events	145 (3.1)	160	0.90	90 (1.9)	115	0.65
Serious						
Yes	111 (2.4)	124	0.70	69 (1.5)	91	0.51
No	35 (0.7)	36	0.20	24 (0.5)	24	0.14
Severity						
Severe	40 (0.9)	45	0.25	31 (0.7)	44	0.25
Moderate	75 (1.6)	78	0.44	48 (1.0)	53	0.30
Mild	35 (0.7)	37	0.21	18 (0.4)	18	0.10
Related						
Probable	5 (0.1)	5	0.03	3 (<0.1)	4	0.02
Possible	29 (0.6)	29	0.16	14 (0.3)	16	0.09
Unlikely	113 (2.4)	125	0.70	74 (1.6)	95	0.54
Missing	1 (<0.1)	1	<0.01	0 (0.0)	0	0.00
Outcome						
Fatal	3 (<0.1)	3	0.02	1 (<0.1)	1	<0.01
Not recovered	32 (0.7)	33	0.19	16 (0.3)	16	0.09
Recovered with sequelae	0 (0.0)	0	0.00	4 (<0.1)	4	0.02
Recovering	3 (<0.1)	4	0.02	1 (<0.1)	1	<0.01
Recovered	109 (2.3)	120	0.67	71 (1.5)	93	0.52
Action taken						
Product withdrawn temporarily	35 (0.7)	38	0.21	16 (0.3)	22	0.12
Product withdrawn permanently	3 (<0.1)	3	0.02	6 (0.1)	8	0.05
Dose reduced	3 (0.1)	3	0.02	0 (0.0)	0	0.00
Dose increased	0 (0.0)	0	0.00	0 (0.0)	0	0.00
Dose not changed	68 (1.5)	74	0.42	50 (1.1)	59	0.33
Unknown	1 (<0.1)	1	<0.01	0 (0.0)	0	0.00
Missing	37 (0.8)	41	0.23	24 (0.5)	26	0.15

N: number of subjects; %: proportion of subjects; E: number of events; PYO: patient-years of observation; R: event rate per 100 patient-years of observation; MESI: medical event of special interest as reported by the investigator; SAE: serious adverse event

Source: LEADER CSR, Table 12-51

Figure 19. Acute Gallstone Disease, Event Rate Over Time



Source: Summary of Clinical Safety, Figure 2-32

As seen in Table 45 above, 4 subjects with acute gallstone disease events had a fatal outcome, 3 in the Victoza group and 1 in the placebo group:

- Subject (b) (6) (Victoza): This was an 87 year old female with a history of hypercholesterolemia, chronic renal failure, heart failure, and myocardial infarction/coronary artery disease, who was hospitalized after over 2 years of treatment with abdominal pain and respiratory distress. She was diagnosed with acalculous cholecystitis and treated with antibiotics and percutaneous drainage of the gallbladder. The subject developed atrial fibrillation and multiple organ failure including heart failure, respiratory failure, and acute renal failure. Hemodialysis was started and the subject was stabilized, but she died approximately 1 week later. Cause of death was stated as septic shock due to cholecystitis, acute renal failure, and heart failure.

- Subject (b) (6) (Victoza): This was a 70 year old male with a history of hypertriglyceridemia, hypercholesterolemia, heart failure, and ischemic heart disease who was hospitalized after approximately 2 years of treatment for an investigation of jaundice associated with fever, nausea, vomiting, myalgia, and abdominal pain. He was diagnosed with a bacterial liver abscess/biliary fistula and subsequently developed acute renal failure and hemodynamic shock. The subject

died due to hemodynamic shock, sepsis, and bacterial liver abscess. Autopsy was not performed.[36,37]

- Subject (b) (6) (Victoza): This was an 81 year old female with a history of coronary artery disease, hypercholesterolemia, hypertriglyceridemia, and colonic polyps. She was treated with drug for 9 months. Approximately 6 weeks after discontinuation, she reported symptoms of abdominal pain, nausea, and vomiting, and was admitted 1 month later for a planned cholecystectomy. During an ERCP, a pancreatic mass was found and the cholecystectomy was postponed. She was readmitted about 1 week later with nausea, vomiting, and diarrhea. Colonoscopy revealed sigmoid colon compression with rectal mass. CT scan revealed dilated gallbladder with mass. After a complicated hospital course and stay at an acute nursing care facility, she died under hospice care 4 months later due to stage IV cholangiocarcinoma. No autopsy was performed.

- Subject (b) (6) (placebo): This was a 71 year old male with a history of dyslipidemia (on a "cholesterol lowering drug") and renal lithiasis who was treated for 4 years. Three days prior to the event, he presented with gastric ulcer. On the day of the event, the subject exhibited sudden epigastric and right hypochondriac pain followed by nausea and vomiting. He was treated with analgesics and antibiotics, and an ultrasound showed a distended gallbladder with multiple gallstones. He was diagnosed with acute calculous cholecystitis. He died following surgical (post-cholecystectomy) complications.

The sponsor conducted a *post hoc* narrative review of acute gallstone disease AEs for hospitalization or relevant procedures; increases in events of hospitalization or cholecystectomy are consistent with the increased incidence overall of acute gallstone disease in this trial:

Table 46. Acute Gallstone Disease, Related Procedures

	Victoza N=4668	**Placebo N=4672**
	n (%)	n (%)
Hospitalization*	91 (1.9)	56 (1.2)
Cholecystectomy	81 (1.7)	52 (1.1)
ERCP**	3 (0.1)	4 (0.1)
* At time of the event ** With papillotomy, endoscopic crush, or prosthesis insertion		

Source: ISS, Table 7.5.1

[36] Reviewer comment: Although unknown in this case if the subject had gallstones, biliary fistulas can be a rare complication of cholelithiasis [see ref. 37].
[37] Duzgun AP, et al. Internal biliary fistula due to cholelithiasis: a single-centre experience. World J Gastroenterol 2007; 13(34): 4606-9.

The majority of the imbalance in acute gallstone disease was due to events of 'cholelithiasis' and 'cholecystitis acute'; Table 47 shows the events by preferred term:

Table 47. Acute Gallstone Disease by Preferred Term (SAEs and Non-Serious MESIs)

	Victoza		Placebo	
Preferred Term	**n**	**%**	**n**	**%**
Cholelithiasis	68	1.5	50	1.1
Cholecystitis acute	36	0.8	21	0.4
Cholecystitis	14	0.3	12	0.3
Cholecystitis chronic	10	0.2	5	0.1
Biliary colic	8	0.2	3	0.1
Cholangitis acute	4	0.1	0	0
Bile duct stone	3	0.1	1	<0.1
Cholecystitis infective	3	0.1	1	<0.1
Cholangitis	2	<0.1	4	0.1
Gallbladder disorder	2	<0.1	1	<0.1
Jaundice cholestatic	1	<0.1	2	<0.1
Cholecystectomy	1	<0.1	1	<0.1
Biliary fistula	1	<0.1	0	0
Cholestasis	1	<0.1	0	0
Gallbladder perforation	1	<0.1	0	0
Hyperplastic cholecystopathy	1	<0.1	0	0
Jaundice	1	<0.1	0	0
Bile duct stenosis	0	0	1	<0.1
Biliary cirrhosis	0	0	1	<0.1
Biliary sepsis	0	0	1	<0.1
Biliary tract infection	0	0	1	<0.1
Gallbladder abscess	0	0	1	<0.1
Gallbladder empyema	0	0	1	<0.1

Source: LEADER CSR, Table 14.3.1.2.30

Overall, the proportion of subjects with risk factors for gallbladder disease was similar in the 2 treatment groups; subjects on placebo who had an event were slightly more likely to have had a history of biliary disease at baseline than those on Victoza with an event, and subjects without an event.

Table 48. Risk Factors for Acute Gallstone Disease at Baseline

	Subjects with acute gallstone disease		All subjects	
	Victoza N (%)	Placebo N (%)	Victoza N (%)	Placebo N (%)
Number of subjects	145 (100)	90 (100)	4668 (100)	4672 (100)
History of biliary disease	22 (15.2)	21 (23.3)	730 (15.6)	689 (14.7)
BMI at baseline ≥ 30-<35 kg/m^2	59 (40.7)	28 (31.1)	1523 (32.6)	1470 (31.5)
BMI at baseline ≥ 35 kg/m^2	40 (27.6)	25 (27.8)	1424 (30.5)	1398 (29.9)
Hypertriglyceridemia at baseline	77 (53.1)	49 (54.4)	2323 (49.8)	2288 (49.0)
Hypercholestero emia at baseline	32 (22.1)	17 (18.9)	1022 (21.9)	1005 (21.5)
Hypercalcemia at baseline	13 (9.0)	3 (3.3)	211 (4.5)	201 (4.3)
Female	56 (38.6)	35 (38.9)	1657 (35.5)	1680 (36.0)

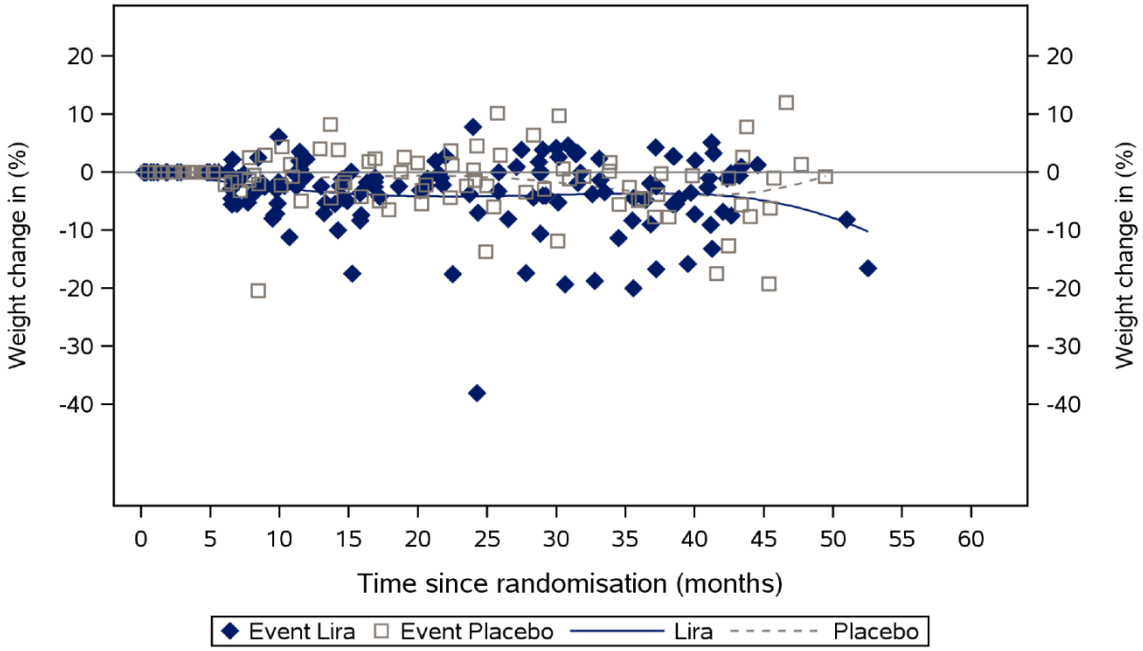
N: number of subjects; %: percentage of subjects; EAC: event adjudication committee
Medical history of biliary disease is reported in the gallbladder history form in the CRF
Hypertriglyceridemia at baseline is determined as a baseline triglyceride measurement above upper normal limit
Hypercholesterolemia at baseline is determined as a baseline cholesterol measurement above upper normal limit
Hypercalcemia at baseline is determined as a baseline calcium measurement above upper normal limit

LEADER CSR, Table 12-52

As mentioned previously, weight loss (particularly rapid or large) is also considered a risk factor for development of cholelithiasis. Acute gallbladder disease was first noted in association with liraglutide in the Saxenda development program (liraglutide for chronic weight management), raising the question of a weight loss-mediated etiology. The Saxenda label notes that, "*Substantial or rapid weight loss can increase the risk of cholelithiasis; however, the incidence of acute gallbladder disease was greater in Saxenda-treated subjects than in placebo-treated subjects even after accounting for the degree of weight loss.*"

As seen in Figure 20 and Table 49, below, although there were several subjects with large amounts of weight loss, particularly in the Victoza group, there was not a clear relationship between degree or rapidity of weight loss and development of a gallstone-related AE. Across all weight loss cut-offs, Victoza was associated with a greater risk of AEs, potentially suggesting a weight-loss independent etiology.

Figure 20. Percent Body Weight Change From Baseline at First Onset of Acute Gallstone Disease Event



Smoothed Lines are generated using the Penalized B-splines for the liraglutide and placebo groups,
Symbols represent change from baseline for individual subjects at event onset.

Source: ISS, Figure 7.5.4

Table 49. Relationship of Acute Gallstone Disease Event to Body Weight Loss

	Victoza				Placebo			
	N	**(%)**	**E**	**R**	**N**	**(%)**	**E**	**R**
Number of subjects	4668				4672			
PYO	17822				17741			
Events	145	(4.1)	160	0.90	90	(1.9)	115	0.65
Weight gain	29	(0.6)	33	0.19	26	(0.6)	30	0.17
Weight loss								
0-5%	76	(1.6)	83	0.47	49	(1.0)	57	0.32
>5-10%	25	(0.5)	26	0.15	9	(0.2)	10	0.06
>10%	16	(0.3)	17	0.10	7	(0.1)	18	0.10
Weight parameter missing	1	(<0.1)	1	<0.01	0	(0.0)	0	0.00
Weight loss is calculated from baseline to the nearest visit before the acute gallstone adverse event (with an observed weight assessment)								

Source: ISS, Table 7.5.2

Table 50, which presents acute gallstone disease events according to weight loss at 3 years of the trial, suggests that the proportion of subjects with events of acute gallstone disease increased with increasing weight loss in the placebo group only.

Table 50. Acute Gallstone Disease According to Weight Loss at 3 Years

	Victoza				Placebo			
	N	(%)	E	R	N	(%)	E	R
FAS	4668				4672			
Weight gain	1203				1731			
Weight loss								
0-5%	1448				1262			
>5-10%	752				481			
>10%	432				206			
Missing weight	833				992			
PYO	17822				17741			
Weight gain	4735				6824			
Weight loss								
0-5%	5722				4987			
>5-10%	2971				1900			
>10%	1712				812			
Missing weight	2682				3218			
Acute gallstone disease event	145				90			
Weight gain	26	(2.2)	29	0.6	28	(1.6)	30	0.4
Weight loss								
0-5%	48	(3.3)	53	0.9	18	(1.4)	24	0.5
>5-10%	23	(3.1)	26	0.9	17	(3.5)	20	1.1
>10%	15	(3.5)	16	0.9	11	(5.3)	15	1.8
Weight parameter missing	33	(4.0)	36	1.3	16	(1.6)	26	0.8

%: proportion of subjects; E: number of events; FAS: full analysis set; N: number of subjects; R: event rate per 100 observation years; PYO: patient-years of observation
Event rate in each category is calculated according to the corresponding PYO in each category.
Proportion of subjects is calculated according to the number of subjects in each category.

Source: Summary of Clinical Safety, Table 2-33

9.4 Hypoglycemia

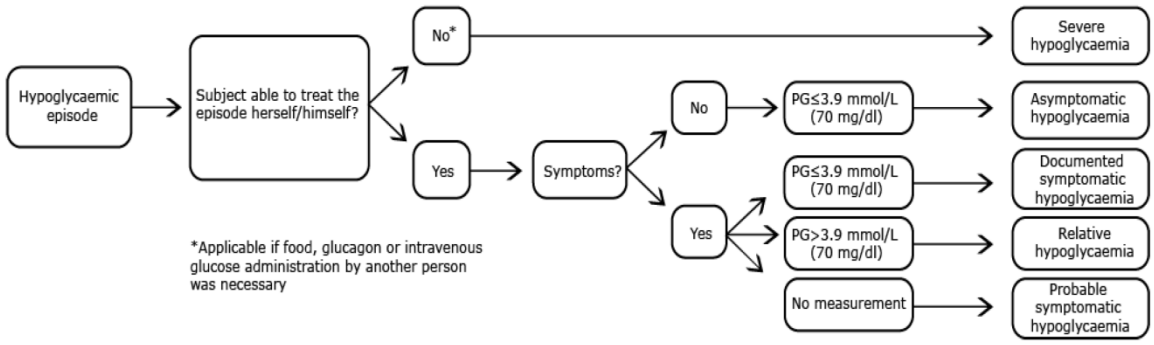
As with all glucose-lowering drugs, hypoglycemia is a safety concern of interest. In the LEADER trial, blood glucose was always to be measured when there was suspicion of a hypoglycemic episode. All plasma glucose values < 70 mg/dL and values > 70 mg/dL when hypoglycemic symptoms had occurred were recorded by the subjects in diaries. A dedicated 'Hypoglycemia Form' collected information on hypoglycemia in the trial, based on information transcribed from subject diaries:

- date of hypoglycemic episode
- time of hypoglycemic episode
- time of last main meal prior to episode
- whether the episode was symptomatic
- whether the episode was in relation to exercise
- whether seizure or coma developed
- whether the subject was able to treat him/herself (if not answered, the investigator was to provide an explanation in the eCRF)

- the plasma glucose level before treating the episode (if available)

Hypoglycemia episodes were defined according to the American Diabetes Association (ADA) classification,[38] as outlined in Figure 21.

Figure 21. ADA Classification of Hypoglycemia



Source: LEADER CSR, Figure 9-4

An additional sponsor definition – a plasma glucose of 56 mg/dL with or without symptoms of hypoglycemia – was used to identify subjects with 'minor' hypoglycemic episodes.

The term 'confirmed hypoglycemia' was used when a subject had an episode that met the definition of severe hypoglycemia (an episode requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions) and/or an episode of 'minor' hypoglycemia.

Finally, the term 'nocturnal hypoglycemia' was used if the time of onset was between 00:01 and 05:59.

A hypoglycemic episode form had to be completed for all hypoglycemic episodes. If the hypoglycemic episode fulfilled the criteria for an SAE and/or a MESI, a hypoglycemic episode form, an AE form, and a safety information form had to be completed. Severe hypoglycemic episodes were considered to be MESIs.

Hypoglycemia and nocturnal hypoglycemia episodes are presented in Table 51 according to the ADA classification and according to the sponsor's definition of 'minor' hypoglycemia (i.e., included in the 'confirmed' hypoglycemia definition). As shown below, the rate of hypoglycemia occurrences, and in particular, the rates of and proportions of subjects with 'confirmed', 'severe', and 'documented' symptomatic

[38] Workgroup on Hypoglycemia, American Diabetes Association. Defining and reporting hypoglycemia in diabetes: a report from the American Diabetes Association Workgroup on Hypoglycemia. Diabetes Care. 2005;28(5):1245-9.

hypoglycemia episodes were slightly less in the Victoza group as compared with those in the placebo group.

Table 51. Hypoglycemia Episodes by Classification

	Victoza			Placebo		
	N (%)	**E**	**R**	**N (%)**	**E**	**R**
Number of subjects	4668			4672		
PYO	17341			17282		
Hypoglycemic episodes						
Confirmed	2039 (43.68)	12177	70.2	2130 (45.59)	15756	91.2
ADA	3262 (69.88)	53438	308.2	3177 (68.00)	61937	358.4
Severe	114 (2.44)	178	1.0	153 (3.27)	255	1.5
Documented symptomatic	2409 (51.61)	26514	152.9	2431 (52.03)	34322	198.6
Asymptomatic	2479 (53.11)	25131	144.9	2360 (50.51)	25823	149.4
Probable symptomatic	148 (3.17)	300	1.7	148 (3.17)	259	1.5
Relative	433 (9.28)	1315	7.6	429 (9.18)	1278	7.4
Nocturnal hypoglycemic episodes						
Confirmed	682 (14.61)	2048	11.8	807 (17.27)	3102	17.9
ADA	1279 (27.40)	6755	39.0	1342 (28.72)	8823	51.1
Severe	25 (0.54)	35	0.2	34 (0.73)	55	0.3
Documented symptomatic	917 (19.64)	4309	24.8	1016 (21.75)	6037	34.9
Asymptomatic	614 (13.15)	2197	12.7	646 (13.83)	2440	14.1
Probable symptomatic	30 (0.64)	49	0.3	33 (0.71)	73	0.4
Relative	100 (2.14)	165	1.0	109 (2.33)	218	1.3

N: number of subjects; %: proportion of subjects; E: number of events; PYO: patient-years of observation; R: event rate per 100 patient-years of observation; ADA: American Diabetes Association
Hypoglycemic episodes on and after randomization date and up to visit 15 are included (episodes with a missing date are included)

Source: SCS, Table 2-34

Severe episodes of hypoglycemia were further characterized, as shown in Table 52. The majority of events were considered “symptomatic episodes”.

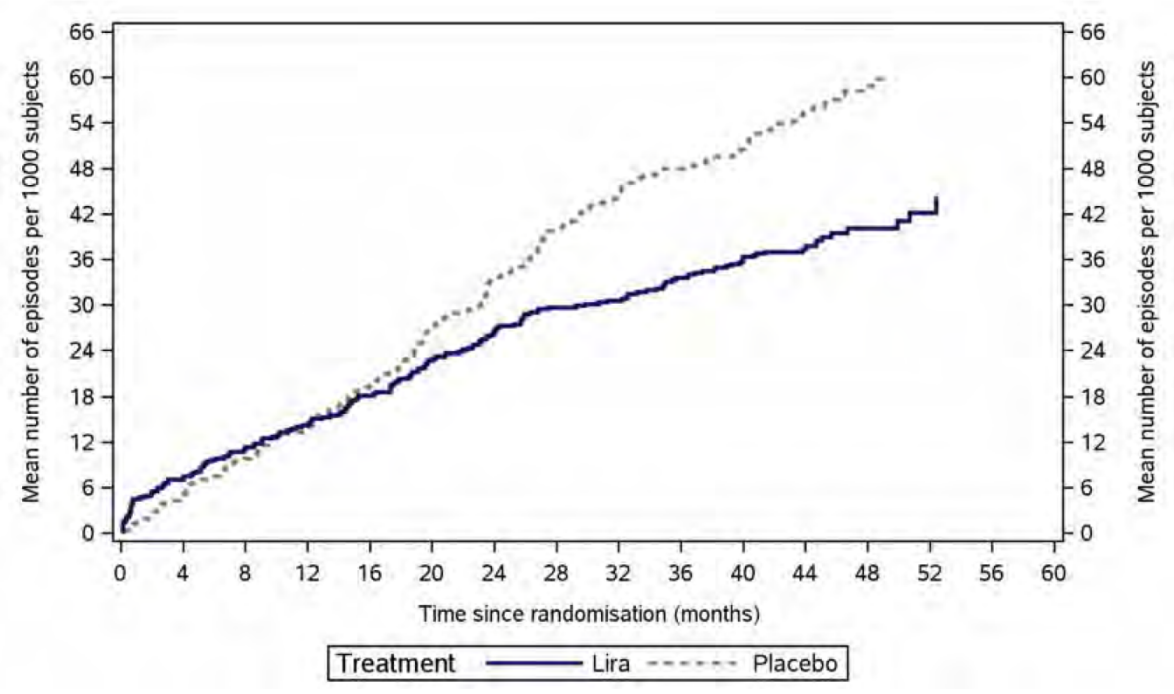
Table 52. Characteristics of Severe Hypoglycemic Episodes

	Victoza			Placebo		
	N (%)	E	R	N (%)	E	R
Number of subjects	4668			4672		
PYO	17341			17282		
Severe hypoglycemia episodes	114 (2.44)	178	1.03	153 (3.27)	255	1.48
Episodes with seizure or coma	21 (0.4)	26	0.15	18 (0.4)	18	0.10
Symptomatic episodes	111 (2.4)	170	0.98	145 (3.1)	240	1.39
Episodes related to exercise	9 (0.2)	9	0.05	11 (0.2)	13	0.08
Registered as an SAE	55 (1.2)	70	0.40	88 (1.9)	111	0.64

Source: LEADER CSR, Table 14.3.1.2.210

Figure 22 shows the mean number of severe hypoglycemic episodes per 1000 subjects during the trial. After approximately 16 months, the curves begin to separate in favor of Victoza, although it is noted that there appears to be a small increase of severe hypoglycemia in the Victoza arm vs. placebo in the first few months of the trial. Severe hypoglycemia by time is further presented in Table 53; these data show that slightly more subjects had hypoglycemia episodes in the first 4 months of the trial and the events decrease over time, particularly in the Victoza group.

Figure 22. Severe Hypoglycemia, Mean Number of Episodes



Source: LEADER CSR, Figure 12-40

Table 53. Severe Hypoglycemic Episodes by Time

	Victoza		Placebo	
	N (%)	E	N (%)	E
Total severe	114 (2.44)	178	153 (3.27)	255
1-4 months	26 (0.56)	35	18 (0.39)	24
5-8 months	15 (0.32)	17	17 (0.36)	22
9-12 months	13 (0.28)	14	11 (0.24)	19
13-16 months	15 (0.32)	18	20 (0.43)	26
17-20 months	10 (0.21)	21	24 (0.51)	34
21-24 months	10 (0.21)	17	17 (0.36)	29
25-28 months	11 (0.24)	14	22 (0.47)	28
29-32 months	4 (0.09)	4	16 (0.34)	19
33-36 months	12 (0.26)	13	9 (0.19)	16
37-40 months	10 (0.21)	12	11 (0.24)	11
41-44 months	5 (0.11)	5	14 (0.30)	18
45-48 months	4 (0.09)	5	7 (0.15)	7
49-52 months	2 (0.04)	2	2 (0.04)	2
53-56 months	1 (0.02)	1	0	0

Source: LEADER CSR, Table 14.3.1.2.216

An exploratory analysis was conducted to assess if discontinuations due to hypoglycemia early on in the program contributed to the pattern seen in the figure above.[39] More subjects on Victoza discontinued drug permanently due to hypoglycemia (3 subjects on Victoza discontinued permanently in the first few weeks), but overall, the numbers were small and therefore unlikely to contribute to the separating of curves in favor of Victoza later in the trial.

[39] Note that the data source used to generate the requested output differs from the data source used in the reporting of severe hypoglycemic episodes in the submission documents. Information on treatment discontinuation due to an adverse event was not captured on the hypoglycemia form. Therefore, the adverse events form (on which potential treatment discontinuation was captured by the field *'Action taken to trial product'*) was used as the data source for the purpose of generating Table 54.

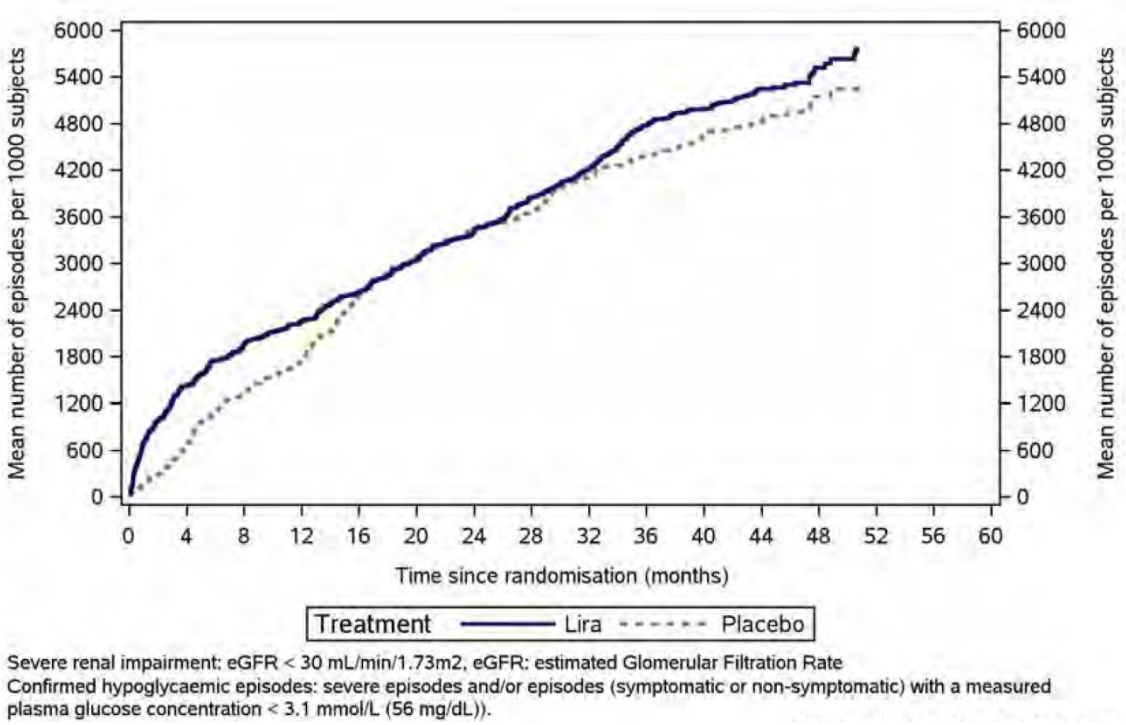
Table 54. Severe Hypoglycemia MESIs Leading to Permanent Discontinuation

	Victoza N=4668	**Placebo N=4672**
Total	9 (0.2)	3 (0.1)
Hypoglycemia	6 (0.1)	1 (<0.1)
Hypoglycemic unconsciousness	3 (0.1)	1 (<0.1)
Hypoglycemic coma	0	1 (<0.1)
Events by time		
0-<4 months	3 (0.1)	0
4-<8 months	1 (<0.1)	1 (<0.1)
8-<12 months	1 (<0.1)	0
12-<16 months	0	0
16-<20 months	0	0
20-<24 months	0	0
24-<28 months	0	2 (<0.1)
28-<32 months	0	0
32-<36 months	2 (<0.1)	0
36-<40 months	1 (<0.1)	0
40-<44 months	0	0
44-<48 months	0	0
48-<52 months	1 (<0.1)	0
Note: this summary is based on AEs reported by the investigator to have led to permanent discontinuation of trial product and categorized by the investigator as a MESI severe hypoglycemic event.		

Source: Response to FDA request, Apr 21, 2017, Table 1-3

Other analyses were conducted in patient populations potentially at greater risk for hypoglycemia, including subjects with renal impairment and those on certain anti-diabetes medications such as sulfonylureas and/or insulin. Subjects with severe renal impairment on Victoza experienced a higher rate of confirmed hypoglycemia episodes throughout the trial (Figure 23).

Figure 23. Confirmed Hypoglycemic Episodes, Subjects with Severe Renal Impairment



Severe renal impairment: eGFR < 30 mL/min/1.73m2, eGFR: estimated Glomerular Filtration Rate
Confirmed hypoglycaemic episodes: severe episodes and/or episodes (symptomatic or non-symptomatic) with a measured plasma glucose concentration < 3.1 mmol/L (56 mg/dL)).

Source: LEADER CSR, Figure 14.3.1.2.227

Severe and confirmed hypoglycemia episodes were primarily seen in subjects treated with insulin, sulfonylurea (SU)/glinides or a combination of these at baseline (i.e., 90% of subjects with severe hypoglycemia in either treatment group were on insulin and/or SU/glinides at baseline), see Table 55.

Table 55. Documented Symptomatic Hypoglycemia According to Use of Anti-Diabetes Medications at Baseline

	Victoza	**Placebo**
N	**4668**	**4672**
Insulin	**1272**	**1334**
SU/glinides	**1604**	**1566**
Insulin and SU/glinides	**766**	**797**
Not on insulin or SU/glinides	**1026**	**975**
Severe episodes	114 (2.4)	153 (3.3)
Insulin	54 (4.3)	68 (5.1)
SU/glinides	27 (1.7)	34 (2.2)
Insulin and SU/glinides	22 (2.9)	36 (4.5)
Not on insulin or SU/glinides	11 (1.1)	15 (1.5)
Confirmed episodes	2039 (43.7)	2130 (45.6)
Insulin	658 (51.7)	770 (57.7)
SU/glinides	679 (42.3)	659 (42.1)
Insulin and SU/glinides	450 (58.8)	443 (55.6)
Not on insulin or SU/glinides	252 (24.6)	258 (26.5)

N: number of subjects; %: proportion of subjects; SU: sulfonylurea

Source: SCS, Table 2-35

To put the above into perspective, Table 56 below outlines the use of anti-diabetes medications at baseline (generally well-balanced among randomized groups) and during the trial (greater use of all types, but particularly insulin, in the placebo group). The greater initiation of insulin and SU/glinides in the placebo group during the trial (and/or potentially lower doses used in the Victoza arm) could explain at least some of the separation of hypoglycemia curves in the trial over time.

Table 56. Anti-Diabetes Medications at Baseline and Started Exclusively After Baseline

	Victoza N=4668	Placebo N=4672
Anti-Diabetes Medications at Baseline		
Blood glucose lowering drugs (excluding insulin)	4113 (88.1)	4129 (88.4)
Metformin	3540 (75.8)	3604 (77.1)
SU	2370 (50.8)	2363 (50.6)
Alpha glucosidase inhibitors	139 (3.0)	123 (2.6)
TZD	296 (6.3)	279 (6.0)
DPP4 inhibitors	4 (<0.1)	2 (<0.1)
GLP1 receptor agonist	0	2 (<0.1)
SGLT2 inhibitors	0	0
Glinides	178 (3.8)	172 (3.7)
Other	0	1 (<0.1)
Insulin	2038 (43.7)	2131 (45.6)
Premix	445 (9.5)	463 (9.9)
Short-acting	42 (0.9)	26 (0.6)
Intermediate-acting	547 (11.7)	600 (12.8)
Long-acting	1041 (22.3)	1077 (23.1)
Other insulins	23 (0.5)	14 (0.3)
Insulin-naïve	2630 (56.3)	2541 (54.4)
Anti-Diabetes Medications Started Exclusively After Baseline		
Blood glucose lowering drugs (excluding insulin)	1012 (21.7)	1358 (29.1)
Metformin	249 (5.3)	299 (6.4)
SU	349 (7.5)	505 (10.8)
Alpha glucosidase inhibitors	83 (1.8)	146 (3.1)
TZD	99 (2.1)	160 (3.4)
DPP4 inhibitors	149 (3.2)	170 (3.6)
GLP1 receptor agonist	87 (1.9)	139 (3.0)
SGLT2 inhibitors	100 (2.1)	130 (2.8)
Glinides	85 (1.8)	137 (2.9)
Other	0	1 (<0.1)
Insulin	1346 (28.6)	2019 (43.2)
Premix	282 (6.0)	440 (9.4)
Short-acting	586 (12.6)	915 (19.6)
Intermediate-acting	273 (5.8)	386 (8.3)
Long-acting	619 (13.3)	940 (20.1)
Other insulins	31 (0.7)	37 (0.9)
Insulin-naïve*	1830 (39.2)	1343 (28.7)

N: number of subjects; %: proportion of subjects; SU: sulfonylurea; TZD: thiazolidinedione; DPP4: dipeptidyl peptidase-4; GLP1: glucagon-like peptide-1; SGLT-2: sodium-dependent glucose transporter 2; a subjects will be excluded from the anti-diabetes medications started exclusively after baseline tallies if the subjects at baseline was treated with medication from the pertinent sub-groups
* subjects who remain insulin-naïve during the trial

Source: LEADER CSR, Tables 10-17 and 10-18

9.5 Renal Safety

The Victoza label describes renal failure associated with liraglutide use as follows:

There have been postmarketing reports of acute renal failure and worsening of chronic renal failure, which may sometimes require hemodialysis in VICTOZA-treated patients. Some of these events were reported in patients without known underlying renal disease. A majority of the reported events occurred in patients who had experienced nausea, vomiting, diarrhea, or dehydration.

9.5.1 Adverse Events

The sponsor undertook an efficacy evaluation of a composite microvascular endpoint (secondary endpoint) that included nephropathy (and retinopathy) components, utilizing a microvascular EAC subcommittee to adjudicate events. See the clinical efficacy review for details. The following section will be a review of investigator-reported renal events, with a specific focus on renal deaths, since there was a slight imbalance of deaths adjudicated as non-cardiovascular and categorized as 'renal', not in favor of Victoza (Victoza 11, 0.2%; placebo 5, 0.1%; see Section 4).

The following summary of acute renal failure events utilized the SAE and MESI preferred terms within the MedDRA 'Acute renal failure' SMQ (Table 57). Overall (not shown in the table), the most frequently reported events were acute kidney injury (2.4% vs. 2.1%), proteinuria (1.4% vs. 2.0%), renal failure (0.5% vs. 0.8%), and renal impairment (0.4% vs. 0.3%) in the Victoza and placebo groups, respectively.

Table 57. Investigator-Reported Acute Renal Failure by MedDRA Search

	Victoza N=4668	**Placebo N=4672**
'Acute renal failure' SMQ SAE or non-SAE MESI	234 (5.0)	262 (5.6)
Fatal	18 (0.4)	14 (0.3)
Acute kidney injury	10 (0.2)	8 (0.2)
Renal failure	4 (0.1)	6 (0.1)
Azotemia	1 (<0.1)	0
Blood creatinine increased	1 (<0.1)	0
Nephritis	1 (<0.1)	0
Renal impairment	1 (<0.1)	0
Tubulointerstitial nephritis	0	1 (<0.1)
SAE (fatal and non-fatal)	151 (3.2)	146 (3.1)
Acute kidney injury	108 (2.3)	94 (2.0)
Renal failure	20 (0.4)	31 (0.7)
Renal impairment	14 (0.3)	10 (0.2)
Blood creatinine increased	6 (0.1)	3 (0.1)
Azotemia	3 (0.1)	2 (<0.1)
Proteinuria	2 (<0.1)	3 (0.1)
Renal tubular necrosis	1 (<0.1)	5 (0.1)
Tubulointerstitial nephritis	1 (<0.1)	3 (0.1)
Nephropathy toxic	1 (<0.1)	2 (<0.1)
Acute prerenal failure	1 (<0.1)	1 (<0.1)
Blood urea increased	1 (<0.1)	1 (<0.1)
Glomerular filtration rate decreased	1 (<0.1)	0
Nephritis	1 (<0.1)	0
Severity		
Severe	90 (1.9)	82 (1.8)
Moderate	116 (2.5)	120 (2.6)
Mild	41 (0.9)	76 (1.6)
Product withdrawn permanently	22 (0.5)	28 (0.6)

Source: ISS, Appendix 7.6, Tables 7.6.53 and 7.6.74, and reviewer created from LEADER datasets

Renal events with a fatal outcome are identified differently than the adjudicated non-cardiovascular deaths categorized *post hoc* as renal, because any number of investigator-reported AEs may be considered as contributing to a subject's death. In the analysis above utilizing the MedDRA SMQ, similar proportions of subjects in the Victoza and placebo groups had fatal events of acute kidney injury or renal failure. Likewise, SAEs of acute kidney injury and renal failure were similarly distributed, with greater SAEs of acute kidney injury in the Victoza group and greater SAEs of renal failure in the placebo group. The Victoza group was associated with an increased incidence of renal impairment, blood creatinine increased, and azotemia.

Fatal renal events (identified by the above search of investigator-reported events) in subjects who were treated with Victoza were reviewed; brief narratives can be found in the appendix (section 13.3.1.1). Most deaths reported as acute renal failure leading to death were renal complications of other conditions. In the 4 subjects categorized by the EAC *post hoc* as 'renal' deaths ((b) (6), and (b) (6) subjects developed a worsening of renal function while in the trial prior to the fatal event. In addition to these 4 subjects with EAC-confirmed renal death, 7 Victoza-treated subjects were identified as EAC-confirmed non-CV renal deaths (a total of 11 subjects in the Victoza group and 5 subjects in the placebo group died due to EAC-confirmed renal causes according to the *post hoc* classification). Brief narratives of these events can also be found in the appendix (section 13.3.1.2). Most EAC-confirmed 'renal' deaths were related to worsening of chronic renal failure. There were no clear cases of Victoza causing GI volume losses (i.e., vomiting, diarrhea) that contributed to fatal renal failure in the trial.

An analysis was conducted of acute renal failure SAEs and non-serious MESIs according to baseline renal impairment. The following table, which includes a tabulation of events overall and for the 4 most frequent preferred terms, demonstrates that although 'acute renal failure' events were seen slightly less frequently in Victoza subjects in all categories of baseline renal impairment, in subjects with normal, mild, and moderate impairment, this favorable trend appears to be driven by events of proteinuria. In subjects with severe renal impairment, the slight trend is driven by fewer 'renal failure' events in the Victoza group, although the numbers are small.

Table 58. Acute Renal Failure SMQ SAEs/MESIs by Baseline Renal Impairment Category

	Normal Renal Function		Mild Renal Impairment		Moderate Renal Impairment		Severe Renal Impairment	
	Victoza N=1620	Placebo N=1655	Victoza N=1932	Placebo N=1975	Victoza N=999	Placebo N=935	Victoza N=405	Placebo N=366
Total	34 (2.1)	45 (2.7)	78 (4.0)	86 (4.4)	100 (10.0)	108 (11.6)	22 (18.8)	23 (21.5)
Acute kidney injury	16 (1.0)	10 (0.6)	36 (1.9)	31 (1.6)	49 (4.9)	49 (5.2)	10 (8.5)	9 (8.4)
Proteinuria	12 (0.7)	31 (1.9)	24 (1.2)	35 (1.8)	25 (2.5)	27 (2.9)	3 (2.6)	2 (1.9)
Renal impairment	2 (0.1)	1 (0.1)	7 (0.4)	2 (0.1)	6 (0.6)	8 (0.9)	5 (4.3)	4 (3.7)
Renal failure	2 (0.1)	1 (0.1)	6 (0.3)	7 (0.4)	14 (1.4)	22 (2.4)	3 (2.6)	8 (7.5)

Source: ISS, Appendix 7.6, Tables 7.6.58, 7.6.62, 7.6.66, and 7.6.70

9.5.2 Renal Laboratory Parameters

The following parameters were monitored for renal function: creatinine, estimated glomerular filtration rate (eGFR), and urinary albumin-to-creatinine ratio (UACR); see Section 2.2 for timing of routine renal testing in the LEADER trial.

Geometric mean creatinine values at baseline were similar in the 2 treatment groups: Victoza 0.93 mg/dL and placebo 0.92 mg/dL. Values increased in the trial in both

treatment groups. It is noted that although there appears to be a small favorable (for Victoza) change in creatinine over the first 3 years of the trial, slightly more subjects on Victoza had creatinine values considered "high" (i.e., above the reference range) over the course of treatment, including at baseline (Table 59). The shift table indicates that the majority of subjects with high values at the end of treatment were also high at baseline (Table 60).

Table 59. Serum Creatinine by Visit, Number and Proportion of Subjects with Values Above the Normal Range

	Victoza N=4668 n (%)	**Placebo N=4672 n (%)**
Visit 1		
N	4665	4668
High	1154 (24.7)	1097 (23.5)
Visit 3 (Day 0)		
N	4597	4586
High	1201 (26.1)	1131 (24.7)
Visit 6 (Month 6)		
N	4349	4356
High	1190 (27.4)	1129 (25.9)
Visit 7 (Month 12)		
N	4288	4237
High	1216 (28.4)	1126 (26.6)
Visit 9 (Month 24)		
N	4031	3911
High	1253 (31.1)	1130 (28.9)
Visit 11 (Month 36)		
N	3806	3634
High	1255 (33.0)	1148 (31.6)
Visit 13 (Month 48)		
N	812	755
High	269 (33.1)	242 (32.1)
Visit 15 (EOT)		
N	3711	3564
High	1267 (34.1)	1190 (33.4)
N: number of subjects; %: proportion of subjects; high: above normal range; EOT: end-of-treatment visit Values that have been re-tested are not included		

Source: LEADER CSR, Table 14.3.5.37

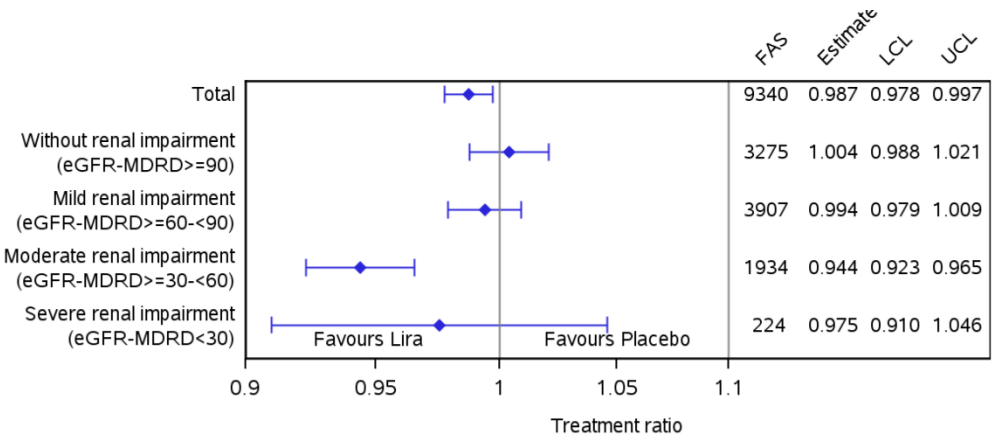
Table 60. Serum Creatinine Shift Table, Baseline to End of Treatment

	Victoza Baseline			Placebo Baseline		
Visit 15 (Month 60)	**Low**	**Normal**	**High**	**Low**	**Normal**	**High**
Low	53 (1.1)	44 (0.9)	3 (0.1)	60 (1.3)	50 (1.1)	1 (<0.1)
Normal	135 (2.9)	2102 (45.0)	107 (2.3)	110 (2.4)	2056 (44.0)	97 (2.1)
High	2 (<0.1)	479 (10.3)	786 (16.8)	3 (0.1)	508 (10.9)	679 (14.5)
Missing	52 (1.1)	582 (12.5)	323 (4.9)	56 (1.2)	677 (14.5)	375 (8.0)

Source: LEADER CSR, Table 14.3.5.41

The following analysis presents serum creatinine by baseline renal function. From a safety perspective, there does not appear to be a trend for creatinine worsening among the renal impairment groups.

Figure 24. Forest Plot of Creatinine Ratio to Baseline at 3-Year Visit by Baseline Renal Function



Note: The analysis was performed *post-hoc*. Treatment, sex, region and antidiabetic therapy at baseline are included as covariates, all nested within visit. For the analyses per subgroup, the model also includes the interaction between and subgroup nested within visit. Treatment ratios are estimated with an unstructured covariance matrix on the log transformed responses.

Abbreviations: Lira: Liraglutide; FAS: Full analysis set; eGFR-MDRD (ml/min/1.73 m2): Estimated glomerular filtration rate using the modification of diet in renal disease formula. MMRM: Mixed model for repeated measurements; LCL/UCL: Lower/upper 95% confidence interval.

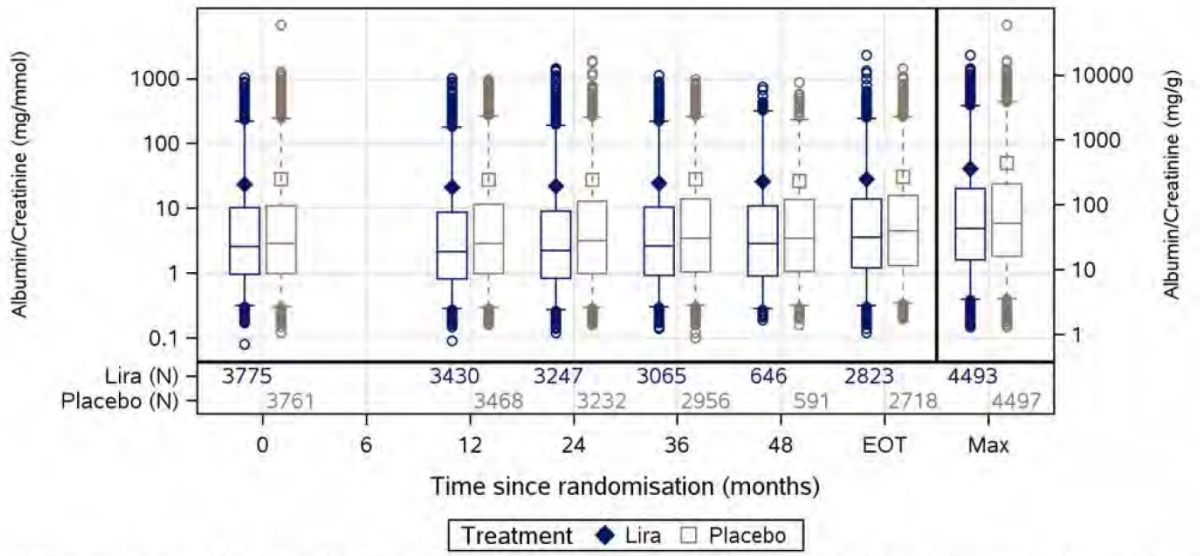
Source: Summary of Clinical Safety, Figure 5-3

Estimated GFR (eGFR) values were similar at baseline and the values decreased throughout the trial in both treatment groups. The pattern of eGFR change over time across renal impairment groups was similar to the renal impairment subgroup analysis shown for serum creatinine An analysis of mean changes in eGFR by baseline renal function did not show a trend for eGFR worsening among the groups with baseline renal impairment.

The urinary albumin-to-creatinine ratio (UACR) approximates daily albumin excretion, and was measured yearly in LEADER. At baseline, mean UACR values were similar in both treatment groups. During the trial, estimated geometric mean UACR decreased to

below the baseline value at month 12, then increased slightly to month 24, returning to baseline levels by month 36 and increased further to month 48, and to end of treatment. In the placebo group, the geometric mean UACR slowly increased throughout the trial. Figure 25 illustrates observed values over time by treatment group in a box plot:

Figure 25. Urinary Albumin-to-Creatinine Ratio



Reference ranges for Albumin/Creatinine ratio (mg/mmol) for the samples analysed between 28JUN2010 and 08FEB2011 [0;2.26] and the samples analysed on/after 09FEB2011 the ranges are [0;3.39].
Observed data. Whiskers are from 2.5%-97.5%.
Number of subjects (N) appear in the lower panel. EOT: End of Trial visit. Max: Maximum measurement across trial.
Albumin/Creatinine is measured at the 0, 12, 24, 36, 48 and 60 month visits.

Source: LEADER CSR, Figure 14.3.5.204

Results (UACR ratio from baseline to 3-year visit) were similar among baseline renal impairment groups.

In summary, a review of renal laboratory data does not suggest a worsening of renal function with Victoza overall or by baseline renal insufficiency. Investigator-reported acute renal failure SAEs/MESIs were similar between groups. Although the Victoza group was associated with fewer AEs of proteinuria, the clinical significance of this is unclear. An imbalance in renal deaths (as categorized by the EAC) not in favor of Victoza was noted; these events generally reflected a worsening of chronic renal insufficiency. The contribution of Victoza in these cases is uncertain.

9.6 Hepatic Safety

Hepatic safety has been assessed in LEADER with adverse events via a MedDRA search, as well as with relevant study laboratory data. Although liraglutide is not known definitively as a cause of drug-induced liver injury (DILI), alterations in liver enzymes

(Saxenda) and bilirubin (Victoza) have been seen in clinical trials and are included in the respective labels. One case of autoimmune hepatitis associated with liraglutide use has been reported in the literature.[40] Post-marketing sections of the Saxenda and Victoza labels mention that there have been elevations of liver enzymes, hyperbilirubinemia, cholestasis, and hepatitis reported.

9.6.1 Adverse Events

The sponsor conducted a search of the MedDRA SMQ 'Drug induced hepatic disorders', utilizing those AEs that were reported as SAEs or non-serious MESIs. This analysis is limited in that hepatic-related events were not pre-specified as MESIs for reporting purposes. An exploratory review of events that included those not reported as SAEs or non-serious MESIs did not reveal any additional events or imbalances of interest, so this section will focus on the sponsor's analysis.

[40] Kern E, et al. Liraglutide-induced autoimmune hepatitis. JAMA Internal Med. 2014; 174(6):984-7.

Table 61. Hepatic SAEs or MESIs

	Victoza N=4668		Placebo N=4672	
Hepatic MESIs and SAEs	53	1.1	57	1.2
Hepatic cyst	8	0.2	15	0.3
Hepatocellular carcinoma	5	0.1	4	0.1
Hepatic cirrhosis	4	0.1	6	0.1
International normalized ratio increased	3	0.1	6	0.1
Hemangioma of liver	3	0.1	5	0.1
Hepatic lesion	3	0.1	4	0.1
Hepatic cancer	3	0.1	1	<0.1
Hepatic encephalopathy	3	0.1	0	0
Hepatic steatosis	3	0.1	0	0
Ascites	2	<0.1	1	<0.1
Alanine aminotransferase increased	2	<0.1	0	0
Gamma-glutamyltransferase increased	2	<0.1	0	0
Hepatic failure	2	<0.1	0	0
Hepatic neoplasm	2	<0.1	0	0
Hepatitis acute	2	<0.1	0	0
Esophageal varices hemorrhage	2	<0.1	0	0
Jaundice cholestatic	1	<0.1	2	<0.1
Liver disorder	1	<0.1	2	<0.1
Focal nodular hyperplasia	1	<0.1	1	<0.1
Hepatic cancer metastatic	1	<0.1	1	<0.1
Hepatomegaly	1	<0.1	1	<0.1
Portal hypertension	1	<0.1	1	<0.1
Cholestasis	1	<0.1	0	0
Cryptogenic cirrhosis	1	<0.1	0	0
Hepatic calcification	1	<0.1	0	0
Hepatopulmonary syndrome	1	<0.1	0	0
Hepatorenal syndrome	1	<0.1	0	0
Jaundice	1	<0.1	0	0
Liver function test abnormal	1	<0.1	0	0
Chronic hepatic failure	0	0	2	<0.1
Hepatic enzyme increased	0	0	2	<0.1
Ammonia increased	0	0	1	<0.1
Autoimmune hepatitis	0	0	1	<0.1
Biliary cirrhosis	0	0	1	<0.1
Chronic hepatitis	0	0	1	<0.1
Drug-induced liver injury	0	0	1	<0.1
Granulomatous liver disease	0	0	1	<0.1
Hepatic mass	0	0	1	<0.1
Ischemic hepatitis	0	0	1	<0.1

Source: ISS, Appendix 7.10, Table 7.10.2

The 2 SAEs of 'hepatic failure' in subjects on Victoza (vs. none on placebo) – 1 of which was a fatal event – appeared unlikely related to the drug. Two additional fatal events in Victoza subjects (seen in the above table) were 'cryptogenic cirrhosis' and 'hepatorenal syndrome'; both events occurred in the same subject. The 2 subjects treated with

Victoza with AEs of 'acute hepatitis' (1 MESI: subject (b) (6) 1 SAE: subject (b) (6)) both had negative rechallenges with the drug. Three SAEs of hepatic encephalopathy in Victoza-treated subjects appeared unlikely related to the drug. Narratives for these events can be found in the appendix, section 13.3.2.1. In addition, an SAE of 'jaundice' was reported in subject (b) (6) 2 years after discontinuing Victoza, and an SAE of 'jaundice cholestatic' in subject (b) (6) was confounded by other events, including heart failure.

9.6.2 Hepatic Laboratory Parameters

Routine liver-related laboratory testing in the LEADER trial included ALT and total bilirubin (see Section 7.2.4); therefore those parameters were used to support a hepatic safety assessment.

Table 62 summarizes the proportions of subjects in each treatment group with abnormalities by various cut-offs in ALT and total bilirubin, as well as the proportions of subjects with concomitant ALT >3x ULN and bilirubin >2x ULN (i.e., at the same assessment).

Table 62. Abnormal ALT and Bilirubin Values

	Victoza N=4668	Placebo N=4672
ALT (screening to follow-up)		
>1x to 3x ULN	851 (18.2)	767 (16.4)
>3x to 5x ULN	27 (0.6)	19 (0.4)
>5x to 20x ULN	12 (0.3)	9 (0.2)
>20x ULN	0	0
Total bilirubin (screening to follow-up)		
>1x to 1.5x ULN	251 (5.4)	216 (4.6)
>1.5x to 3x ULN	64 (1.4)	56 (1.2)
>3x to 10x ULN	5 (0.1)	5 (0.1)
>10x ULN	0	0
ALT ≥ 3x ULN (post-baseline)	34 (0.7)	26 (0.5)
ALT ≥ 3x ULN (subjects with baseline ALT < ULN)	22/4241 (0.5)	13/4295 (0.3)
ALT > 3x ULN and total bilirubin > 2x ULN (screening to follow-up)	4 (0.1)	2 (<0.1)

Source: Response to FDA Request dated 13 Apr 2017, Table 4

Two independent external DILI experts provided blinded assessment of cases of ALT ≥5x ULN and/or ALT ≥3x ULN/total bilirubin ≥2x ULN in the trial, prior to database lock.[41] The Victoza cases are summarized briefly in the appendix (section 13.3.2.2); all cases were considered not likely Victoza-related, except one considered "possible" (subject

[41] Note that the numbers of subjects in this list are slightly different than those in the tables since the tables utilize 'greater than' laboratory cut-offs, while the blinded clinical expert review utilized 'greater than or equal to' cut-offs

(b) (6)). The majority of cases were not considered drug-related due to the long latency period, negative rechallenge, confounding factors, and/or the value was increased at baseline.

9.7 Immunogenicity

As Victoza is a peptide product, there is potential risk for immunogenicity, including antibody formation and hypersensitivity reactions.

In the LEADER trial, immunogenicity events suspected by the investigator to be related to trial product were to be recorded as MESIs. Immunogenicity events were not adjudicated by the EAC and the evaluation is based on predefined MedDRA searches of SAEs and non-serious MESIs for events of allergic reaction, injection site reaction, and immune complex disease.

Table 63. Terms Included in the MedDRA Search for Immunogenicity Events

Included SMQs and HLTs
Allergic reactions
SMQ Anaphylactic reaction (narrow terms only)
SMQ Anaphylactic/anaphylactoid shock conditions (narrow terms only)
SMQ Angioedema (narrow terms only)
SMQ Severe cutaneous adverse reactions (narrow terms only)
SMQ Hypersensitivity (narrow terms only)
Injection site reactions
HLT Administrations site reactions NEC
HLT Application and instillation site reactions
HLT Infusion site reactions
HLT Injection site reactions
Immune complex disease
Immune complex disease (broad search):
SMQ Systemic lupus erythematosus (broad and narrow terms)
SMQ Vasculitis (broad and narrow terms)
SMQ Guillain-Barre syndrome (narrow terms only)
Immune complex disease (narrow search):
SMQ Systemic lupus erythematosus (narrow terms only)
SMQ Vasculitis (narrow terms only)
SMQ Guillain-Barre syndrome (narrow terms only)
HLT: high level term; SMQ: standardized MedDRA query; NEC: not elsewhere classified

Source: LEADER CSR, Table 9-12

Blood samples for determination of anti-liraglutide antibodies were drawn at randomization, at 12, 24, 36, and 48 months, and at follow-up in all trial subjects in the US (i.e., a subset of the total population). All antibody positive samples were characterized for cross-reactivity to native GLP-1 (present vs. not present). Positive

samples from the follow-up visit (or last available visit, if a follow-up visit sample was not available) were characterized for *in vitro* neutralizing effect (present vs. not present) against liraglutide and against native GLP-1.

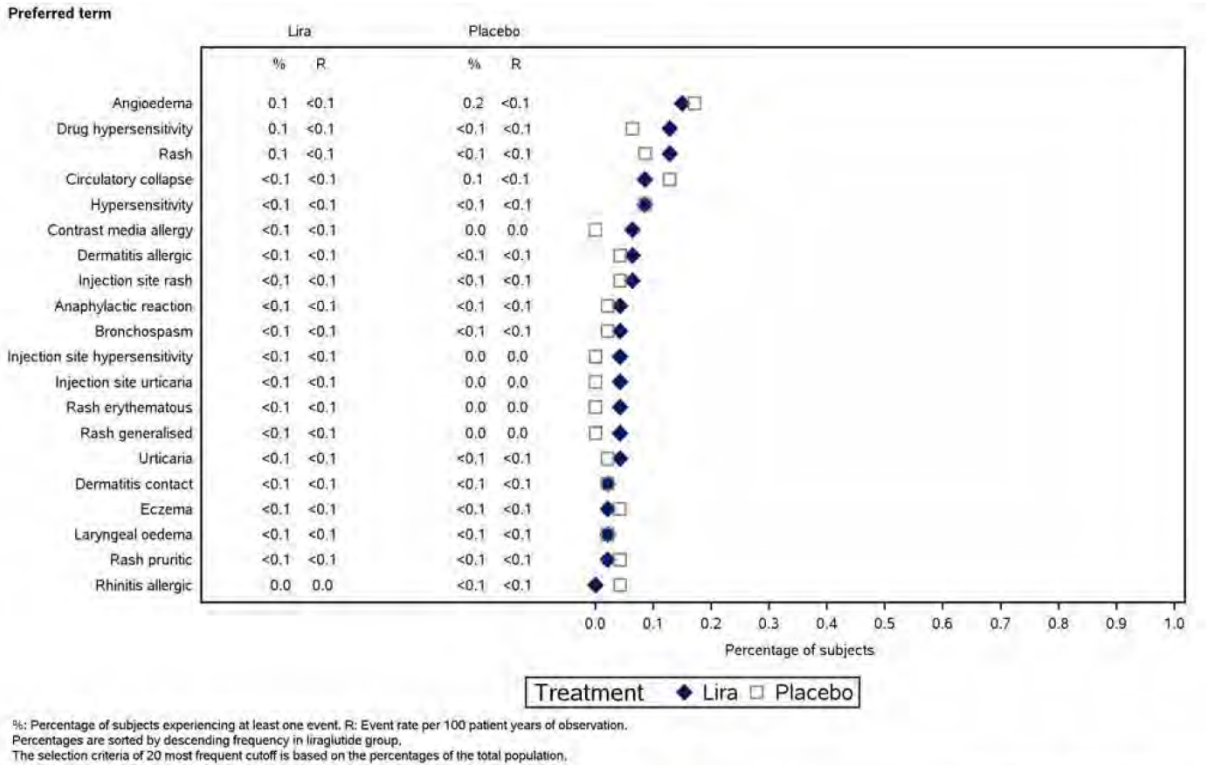
9.7.1 Adverse Events

9.7.1.1 Allergic Reactions, Anaphylaxis, and Angioedema

The proportion of subjects with events of 'allergic reaction' (as described in Table 63)[42] reported as SAEs or non-serious MESIs and the rate of such events were higher in the Victoza group (1.3%, 0.42 events per 100 PYO) than in the placebo group (0.9%, 0.27 events per 100 PYO).

The most frequently reported events with an incidence of Victoza greater than placebo were 'drug hypersensitivity', 'rash', and 'contrast media allergy'. The following figure outlines the most common allergy AEs overall:

Figure 26. Allergic Reaction SAEs and Non-Serious MESIs



Source: LEADER CSR, Figure 14.3.1.2.118

Five events identified by the search were fatal, occurring in 4 subjects in the Victoza group and 1 subject in the placebo group; however upon review, none of the cases appeared to be due to hypersensitivity reactions:

[42] Note that AEs from the various relevant SMQs included in the search might not reflect true allergy.

- Subject (b) (6) (Victoza) – 84 year old male subject who died due to "sudden circulatory arrest" in his home after approximately 3.5 years in the trial; this case was adjudicated as a cardiovascular death.

- Subject (b) (6) (Victoza) – 62 year old female subject with a history of asthma, chronic cardiac failure, and history of myocardial infarction experienced "shortness of breath (bronchospasm)" and died after approximately 1.5 years in the trial; this case was adjudicated as a cardiovascular death.

- Subject (b) (6) (Victoza) – 65 year old female subject with a history of myocardial infarction died suddenly after over 2.5 years in the trial. ("Suddenly she went pale and then red and her head hung back. An attempt was made to revive her but unsuccessful. Paramedics pronounced her dead at the scene.") The event was reported as "circulatory collapse"; this case was adjudicated as a cardiovascular death.

- Subject (b) (6) (Victoza) – 70 year old male subject who died of "bacterial liver abscess", "hemodynamic shock", "acute renal failure", and "biliary fistula" (case is described in Section 9.3) after approximately 2 years in the trial.

- Subject (b) (6) (placebo) – 67 year old subject with a history of myocardial infarction who died suddenly at home; this case was adjudicated as a cardiovascular death.

The proportions of 'allergic reaction' events that were serious were 0.6% for Victoza and 0.5% for placebo, severe 0.3% Victoza and 0.2% placebo, and led to permanent discontinuation 0.2% Victoza and <0.1% placebo.

Serious AEs are summarized below:

Table 64. Serious Allergic Reaction Adverse Events

	Victoza N=4668	**Placebo N=4672**
Total SAEs	26 (0.6)	25 (0.5)
Angioedema	6 (0.1)	7 (0.1)
Circulatory collapse	4 (0.1)	6 (0.1)
Drug hypersensitivity	4 (0.1)	1 (<0.1)
Contrast media allergy	3 (0.1)	0
Anaphylactic reaction	2 (<0.1)	1 (<0.1)
Bronchospasm	2 (<0.1)	1 (<0.1)
Hypersensitivity	1 (<0.1)	2 (<0.1)
Laryngeal edema	1 (<0.1)	1 (<0.1)
Immune thrombocytopenic purpura	1 (<0.1)	0
Shock	1 (<0.1)	0

Skin necrosis	1 (<0.1)	0
Swollen tongue	1 (<0.1)	0
Dermatitis	0	1 (<0.1)
Dermatitis contact	0	1 (<0.1)
Eczema	0	1 (<0.1)
Rhinitis allergic	0	1 (<0.1)
Toxic epidermal necrolysis	0	1 (<0.1)
Urticaria papular	0	1 (<0.1)

Source: LEADER CSR, Table 14.3.1.2.131

Details regarding specific SAEs noted above are as follows:

- Angioedema: A total of 15 SAEs of angioedema were reported in 6 subjects in the Victoza group (8 events) and 7 subjects in the placebo group (7 events). All Victoza-treated subjects had alternative etiologies reported:

  - Subject (b) (6): ACE-inhibitor; subject recovered and continued on Victoza
  - Subject (b) (6) ACE-inhibitor; subject was on Victoza for approximately 1 month (discontinued for dysgeusia), angioedema event occurred 4 years later
  - Subject (b) (6): ACE-inhibitor; subject recovered and continued on Victoza
  - Subject (b) (6) ACE-inhibitor; subject was on Victoza for approximately 1 year (discontinued for nausea and vomiting), angioedema event occurred 3 years later
  - Subject (b) (6): ACE-inhibitor[43]
  - Subject (b) (6): glimepiride; subject had been on Victoza for approximately 3 years prior to event and then restarted Victoza 5 months after the event (for an additional 4 months) without recurrence

- Anaphylaxis: Three SAEs of anaphylactic reaction were reported in 2 subjects in the Victoza group and 1 subject in the placebo group. All had alternative etiologies reported, and in all cases treatment with the trial product continued. The alternative etiologies for the 2 Victoza subjects were as follows:

  - Subject (b) (6): multiple wasp stings
  - Subject (b) (6) food (cinnamon)

- Drug hypersensitivity: Four SAEs were reported in the Victoza group and 1 in the placebo group. The Victoza subjects are described below; all were attributed to other agents:

[43] Reviewer comment: This subject appears to have had several episodes of angioedema, swollen tongue, asthma, etc. that were attributed to other causes. However, she was on and off Victoza intermittently for several years and based on the time course and narratives, I cannot exclude a contribution of Victoza to these events.

- Subject (b) (6): loperamide and nitrofurantoin
- Subject (b) (6): Dilaudid (hydromorphone)
- Subject (b) (6): ACE-inhibitor (case described under angioedema, above)
- Subject (b) (6): statin[44]

- Immune thrombocytopenic purpura: The SAE of 'immune thrombocytopenic purpura' occurred in a 68 year old male (subject (b) (6)) in conjunction with pneumonia after being treated with Victoza for 2 months. He continued to have low platelets for at least 4 months (as reported in the narrative), as low as 3 x 10^3 /µL. The subject was treated with prednisone and remained on the study drug. The event was reported as recovered 1 year later.

9.7.1.2 Injection Site Reactions

The proportion of subjects with injection site reactions (ISRs) was higher in the Victoza group (0.7%) vs. the placebo group (0.3%). None of the ISRs were reported as serious or severe. Action taken in response to the ISR is as follows:

Table 65. Injection Site Reactions, Action Taken

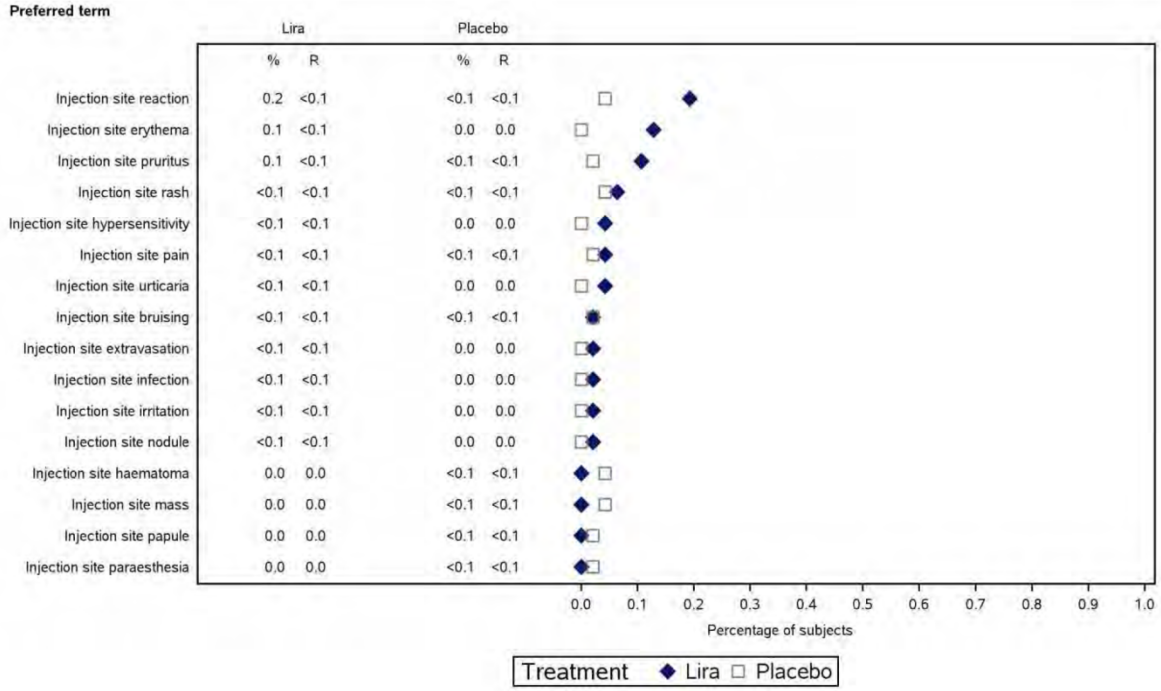
	Victoza N=4668	Placebo N=4672
Product withdrawn temporarily	7 (0.1)	4 (0.1)
Product withdrawn permanently	7 (0.1)	3 (0.1)
Dose reduced	4 (0.1)	1 (<0.1)
Dose not changed	15 (0.3)	3 (0.1)
Missing	0	2 (<0.1)

Source: LEADER CSR, Table 12-61

The figure below outlines the 20 most frequent preferred terms related to ISRs:

[44] Reviewer comment: Upon case review, this appears to be a case of statin myopathy, not allergy

Figure 27. Injection Site Reactions, Most Frequently Reported



Note: The selection criterion of 20 most frequent cut-offs is based on the percentage of the total population. Percentages are sorted by decreasing frequency in the liraglutide group.

Source: LEADER CSR, Figure 12-46

9.7.1.3 Immune Complex Disease

Immune complex disease, or type III hypersensitivity reaction, was evaluated using a broad and narrow MedDRA search with terms shown in Table 63, above.

The events captured from the narrow MedDRA search (SAEs or non-serious MESIs only) are shown in Table 66. All 3 events in the Victoza group were reported as SAEs, and the narratives can be found in the appendix, section 13.3.3.

Table 66. Immune Complex Disease, Narrow SMQ

	Victoza N=4668	Placebo N=4672
Total events	3 (<0.1)	10 (0.2)
Musculoskeletal and connective tissue disorders	1 (<0.1)	6 (0.1)
Polymyalgia rheumatica	1 (<0.1)	6 (0.1)
Nervous system disorders	0 (0.0)	2 (<0.1)
Chronic inflammatory demyelinating polyradiculopathy	0 (0.0)	1 (<0.1)
Guillain-Barre syndrome	0 (0.0)	1 (<0.1)
Skin and subcutaneous tissue disorders	1 (<0.1)	0 (0.0)
Chronic pigmented purpura	1 (<0.1)	0 (0.0)
Vascular disorders	1 (<0.1)	2 (<0.1)
Granulomatosis with polyangiitis	1 (<0.1)	0 (0.0)
Thromboangiitis obliterans	0 (0.0)	1 (<0.1)
Vasculitis necrotizing	0 (0.0)	1 (<0.1)

N: number of subjects, %: proportion of subjects
Adverse events identified by using MedDRA search criteria

Source: LEADER CSR, Table 12-63

In addition to the SAE and non-SAE MESI events presented above, 3 additional non-SAE, non-MESI 'immune complex disease' events were reported by the investigator in 1 subject on Victoza and 2 subjects on placebo; all 3 events were reported as 'polymyalgia rheumatica'.

The broad 'immune complex disease' MedDRA search, by definition, included terms that were not specific to immune complex disease. The 2 most frequent terms in the search were 'proteinuria' (Victoza 1.4% vs. placebo 2.0%) and 'arthritis' (0.3% vs. 0.1%). Other terms were similar between treatment groups.

9.7.2 Anti-Liraglutide Antibodies

A subset of subjects in the LEADER trial (US sites) was evaluated for anti-liraglutide antibodies. The numbers and proportions of subjects who developed positive anti-liraglutide antibodies at some point in the trial in each group were: Victoza 11/1247 (0.9%) and placebo 2/1267 (0.2%). The titers were reportedly low for all positive samples.

In 5 of the 11 subjects in the Victoza group who developed anti-liraglutide antibodies during the trial, antibodies showed cross-reactivity to native GLP-1. No subject developed neutralizing antibodies. Of the 11 Victoza-treated subjects who at some point during the trial had an anti-liraglutide positive sample, 4 tested positive at one visit and negative at the subsequent visits, 5 tested positive at the follow-up visit only, and 2 tested positive at 2 or more subsequent visits including the final visit. None of the

subjects with anti-liraglutide antibodies in either treatment group reported SAEs/MESIs of allergic reaction, injection site reaction, or immune complex disease.

HbA1c changes by antibody (positive, cross-reactive, or negative) are shown below in Table 67. In general, HbA1c changes were similar among those with and without antibodies, with no obvious pattern to suggest an association with loss of glycemic efficacy.

Table 67. Change from Baseline in HbA1c by Antibody Status, Subjects on Victoza

	Positive antibody measurement	**Cross-reacting antibody measurement**	**Negative antibody measurement**
Number of subjects	11	5	1234
Baseline HbA1c (%)			
Visit 3			
N	11	5	1234
Mean (SD)	9.2 (1.2)	8.8 (1.6)	8.8 (1.6)
Median	9.1	8.3	8.4
Min; Max	7.3; 11.1	7.3; 11.1	4.7; 15.4
Change from baseline HbA1c (%)			
Visit 5 (Month 3)			
N	11	5	1131
Mean (SD)	-1.6 (1.1)	-1.4 (1.3)	-1.6 (1.3)
Median	-1.4	-1.4	-1.4
Min; Max	-3.5; 0.4	-3.3; 0.4	-7.4; 3.9
Visit 6 (Month 6)			
N	11	5	1127
Mean (SD)	-1.6 (1.3)	-1.6 (1.7)	-1.6 (1.5)
Median	-1.3	-1.3	-1.4
Min; Max	-4.2; 0.5	-4.2; 0.5	-7.3; 8.7
Visit 7 (Month 12)			
N	11	5	1081
Mean (SD)	-1.3 (1.5)	-1.2 (2.0)	-1.4 (1.5)
Median	-1.3	-1.4	-1.3
Min; Max	-4.2; 0.6	-4.2; 0.6	-6.6; 4.6
Visit 8 (Month 18)			
N	10	5	1022
Mean (SD)	-1.5 (1.5)	-1.7 (2.1)	-1.4 (1.6)
Median	-1.2	-1.6	-1.2
Min; Max	-5.0; 0.6	-5.0; 0.6	-8.4; 7.0

	Positive antibody measurement	Cross-reacting antibody measurement	Negative antibody measurement
Visit 9 (Month 24)			
N	10	5	969
Mean (SD)	-0.8 (2.4)	-0.5 (3.3)	-1.3 (1.7)
Median	-1.1	-1.1	-1.2
Min; Max	-4.9; 4.1	-4.9; 4.1	-7.7; 5.2
Visit 10 (Month 30)			
N	10	5	896
Mean (SD)	-1.2 (1.7)	-1.2 (2.2)	-1.3 (1.6)
Median	-0.8	-0.6	-1.2
Min; Max	-4.9; 0.6	-4.9; 0.6	-7.7; 4.5
Visit 11 (Month 36)			
N	10	5	869
Mean (SD)	-0.9 (1.4)	-0.9 (1.9)	-1.1 (1.7)
Median	-1.0	-0.8	-1.1
Min; Max	-3.7; 1.3	-3.7; 1.3	-7.4; 8.0
Visit 12 (Month 42)			
N	4	2	514
Mean (SD)	-0.7 (0.7)	-0.5 (1.1)	-1.2 (1.6)
Median	0.9	-0.5	-1.2
Min; Max	-1.2; 0.3	-1.2; 0.3	-6.7; 7.1
Visit 13 (Month 48)			
N	2	1	231
Mean (SD)	0.2 (0.6)	0.6	-1.0 (1.8)
Median	0.2	0.6	-1.1
Min; Max	-0.2; 0.6	0.6; 0.6	-6.4; 6.9
Visit 14 (Month 54)			
N	1	1	33
Mean (SD)	-0.2	-0.2	-0.5 (1.8)
Median	-0.2	-0.2	-0.5
Min; Max	-0.2; -0.2	-0.2; -0.2	-3.2; 6.1
Visit 15 (EOT)			
N	7	4	812
Mean (SD)	-1.1 (1.7)	-1.8 (1.8)	-1.0 (1.9)
Median	-1.1	-1.4	-1.0
Min; Max	-4.3; 1.5	-4.3; -0.1	-7.8; -7.3

	Positive antibody measurement	Cross-reacting antibody measurement	Negative antibody measurement
Visit 15 (EOT) LOCF			
N	11	5	1234
Mean (SD)	-1.1 (1.7)	-1.2 (2.1)	-1.0 (1.9)
Median	-1.1	-1.2	-0.9
Min; Max	-4.3; 1.5	-4.3; 1.3	-7.8; 7.3

N: number of subjects; SD: standard deviation; EOT: end-of-trial visit; LOCF: last observation carried forward
Positive antibody measurement: all subjects with a positive antibody measurement at any point during the trial
Cross-reactive antibody measurement: all subjects with a positive antibody measurement at any point during the trial
Negative antibody measurement: all subjects with only negative antibody measurements at any point during the trial
There were no subjects with neutralizing antibodies

Source: ISS, Appendix 7.8, Table 7.8.13

9.8 Eye Disorders

As noted above in the renal safety subsection, microvascular events (nephropathy and retinopathy) were assessed and adjudicated as a composite secondary efficacy endpoint. Adjudicated retinopathy events are discussed in the clinical efficacy review; this subsection describes investigator-reported eye disorder SAEs and non-serious MESIs, utilizing the eye disorder SOC (Table 68). The incidence of AEs of diabetic retinopathy (1.8% vs. 1.6%) and vitreous hemorrhage (0.5% vs. 0.2%) do not favor Victoza.

Table 68. Investigator-Reported Eye Disorder SAEs and MESIs, at Least 2 Events in the Victoza Group

	Victoza N=4668 n (%)	Placebo N=4672 n (%)
Eye disorders SOC, SAEs and MESIs	175 (3.7)	162 (3.5)
Diabetic retinopathy	84 (1.8)	74 (1.6)
Cataract	24 (0.5)	33 (0.7)
Vitreous hemorrhage	22 (0.5)	10 (0.2)
Diabetic retinal edema	6 (0.1)	8 (0.2)
Macular edema	5 (0.1)	9 (0.2)
Retinopathy	4 (0.1)	9 (0.2)
Retinopathy proliferative	4 (0.1)	3 (0.1)
Retinopathy hemorrhagic	4 (0.1)	1 (<0.1)
Macular fibrosis	3 (0.1)	4 (0.1)
Retinal vein occlusion	3 (0.1)	2 (<0.1)
Retinal artery occlusion	3 (0.1)	1 (<0.1)
Optic ischemic neuropathy	2 (<0.1)	3 (0.1)
Retinal hemorrhage	2 (<0.1)	2 (<0.1)
Maculopathy	2 (<0.1)	1 (<0.1)
Amaurosis	2 (<0.1)	0
Blindness unilateral	2 (<0.1)	0
Diplopia	2 (<0.1)	0
Retinal detachment	2 (<0.1)	0
Retinal infarction	2 (<0.1)	0
Vitreous adhesions	2 (<0.1)	0

Source: LEADER CSR, Table 14.3.1.1.7

Four SAE/MESIs of 'blindness' were reported: 2 events of 'blindness unilateral', both in the Victoza group, and 2 events of 'diabetic blindness', 1 event in the Victoza group and 1 event in the placebo group. Neither of the events of 'blindness unilateral' was sent to the EAC for adjudication, and neither event of 'diabetic blindness' was EAC-confirmed as 'diabetic blindness'.[45] [Only 1 event in the placebo group was EAC-confirmed as 'diabetic blindness' (preferred term: retinopathy).] Brief narratives of the 3 'blindness' SAE/MESIs in the Victoza group can be found in the appendix, section 13.3.4.

9.9 Diabetic Foot Ulcers

The MedDRA search to capture events of diabetic foot ulcer was developed by the sponsor prior to the database lock, and consisted of a combination of high level terms with a few added and a few deselected preferred terms:

Table 69. HLTs and PTs Included in the MedDRA Search for Diabetic Foot Ulcers

Included HLTs	
	HLT Diabetic complications dermal (Primary and secondary terms)
	HLT Limb therapeutic procedures (Primary and secondary terms)
	HLT Musculoskeletal necrosis and vascular insufficiency (Primary and secondary terms)
	HLT Non-site specific necrosis and vascular insufficiency NEC (Primary and secondary terms)
	HLT Skin and subcutaneous tissue ulcerations (Primary terms only)
Included extra PTs:	
	Wound
	Skin necrosis
Excluded PTs:	
	Arteriosclerosis
	Arteriosclerotic gangrene
	Compartment syndrome
	Steal syndrome
	Vascular graft occlusion

HLT: high level term; NEC: not elsewhere classified; PT: preferred term

Source: Response to FDA Request 03 April 2017, Table 1-3

Other potentially relevant AEs such as "extremity necrosis" were not included in the search.

A total of 181 subjects (3.9%) treated with Victoza vs. 198 subjects (4.2%) treated with placebo had SAE/MESI events of diabetic foot ulcer according to the sponsor's MedDRA

[45] Defined as: Snellen visual acuity of 20/200 [6/60] or less or visual field of less than 20 degrees, in the better eye with best correction possible

search. The proportions of subjects with the preferred term 'diabetic foot' were 2.8% vs. 3.3% Victoza- and placebo-treated subjects, respectively.

The sponsor conducted a *post hoc* review of the individual case narratives to further describe the complications (Table 70). A total of 44/4668 Victoza-treated subjects (0.9%) and 67/4672 placebo-treated subjects (1.4%) reported diabetic foot ulcer events with subsequent amputation according to this *post hoc* review.

Table 70. Foot Ulcers and Associated Complications

	Victoza			Placebo		
	N	**E**	**(%)**	**N**	**E**	**(%)**
Number of subjects with events*	181	268		198	304	
Number of subjects with events, narrative review*#	176	260	(100)	191	291	(100)
Amputation**						
Yes	44	60	(23.1)	67	78	(26.8)
Yes, one or several toes	33	42	(16.2)	42	45	(15.5)
Yes, foot, crus, or leg	13	16	(6.2)	30	33	(11.3)
Yes, not specified	1	2	(0.8)	0	0	(0.0)
No	144	197	(75.8)	133	206	(70.8)
Unknown	3	3	(1.2)	6	7	(2.4)
Peripheral revascularization**						
Yes	20	24	(9.2)	23	26	(8.9)
No	157	231	(88.8)	173	256	(88.0)
Unknown	5	5	(1.9)	8	9	(3.1)
Infection**						
Yes	107	146	(56.2)	131	162	(55.7)
No	81	109	(41.9)	81	117	(40.2)
Unknown	5	5	(1.9)	10	12	(4.1)
Involvement of underlying structures**						
Yes	64	86	(33.1)	80	98	(33.7)
No	128	170	(65.4)	118	177	(60.8)
Unknown	4	4	(1.5)	16	16	(5.5)

%: proportion of events out of total foot ulcer events with narrative; 'infection': presence of clinical signs of infection, incl. redness, warmth, pain, purulence discharge; 'involvement of underlying structures': tendon, joint capsule of bone
* Events are identified by MedDRA search
# 21 events in 2 subjects (8 in the Victoza and 13 in the placebo group), not related to foot ulcers, or reported as complications to a reported foot ulcer were excluded from narrative review
** Based on *post hoc* review of the individual case narratives performed by the sponsor

Source: Summary of Clinical Safety, Table 2-16

A similar proportion of subjects with medical history of peripheral vascular disease had events of diabetic foot ulcer [Victoza: 51 of 567 subjects (8.9%), placebo: 63 of 600

subjects (10.5%)] and diabetic foot ulcer resulting in amputation [Victoza: 6 subjects (1.0%), placebo: 5 subjects (0.8%)] reported during the trial.

The analysis did not capture events identified by the investigator as MESI 'diabetic foot ulcer' if the term was not included in the MedDRA search as per Table 69; 56 such events in 50 subjects were identified in a separate search.[46] Four events in 4 subjects treated with Victoza and 8 events in 7 subjects treated with placebo did not have any event captured by the MedDRA search for diabetic foot ulcer, as they were associated with nonspecific preferred terms such as peripheral ischemia and soft tissue infection. Of 22 events not co-reported with events captured by the MedDRA search for diabetic foot ulcer, 15 events (Victoza: 6 events in 4 subjects, placebo: 9 events in 9 subjects) resulted in an amputation according to the description in the narrative.

9.10 Suicidality

The assessment of suicidality is a standard part of the safety review for any obesity drug with a centrally acting mechanism,[47,48,49,50] and was assessed prospectively in the original review of liraglutide for chronic weight management (Saxenda). A small imbalance in events of suicidal ideation was noted in the Saxenda review, and a warning for suicidal ideation and behavior was included in Section 5.8 of the Saxenda label. Although no imbalance has been observed in Victoza trials, similar prospective assessments have not been conducted.

To identify events potentially related to suicidality and self-injury, a MedDRA search was performed based on the SMQ 'suicidality/self-injury' among SAEs and non-serious MESIs. As suicidality was not considered a MESI in this trial, events were generally captured because they were SAEs or led to treatment discontinuation. As shown in Table 71, the incidence of suicidality events was similar between treatment groups:

Table 71. Suicide/Self-Injury SMQ, SAEs or Non-Serious MESIs

	Victoza N=4668	**Placebo N=4672**
Total events	8 (0.2)	7 (0.1)
Psychiatric disorders	6 (0.1)	7 (0.1)

[46] Twenty-two events in 21 subjects were evaluated as *not* being related to diabetic foot ulcers and 34 events in 29 subjects were evaluated as being related to diabetic foot ulcers. Of those 34 events: 12 events occurred in 11 subjects who had co-reported events captured by the MedDRA search for diabetic foot ulcer representing the same clinical case; 10 events occurred in 8 subjects who had another separate event reported during the trial captured by the MedDRA search for diabetic foot ulcer; and 12 events occurred in 11 subjects who had no event(s) captured by the MedDRA search for diabetic foot ulcer.
[47] Egan A. FDA Clinical Review of NDA 21888 (rimonabant), EMDAC 13 Jun 2007.
[48] Golden J. FDA Clinical Review of NDA 22529 (lorcaserin), EMDAC 16 Sep 2010 and 10 May 2012.
[49] Roberts M. FDA Clinical Review of NDA 22580 (phentermine/topiramate), EMDAC 15 July 2010 and 22 Dec 2012.
[50] Craig E. FDA Clinical review of NDA 200063 (naltrexone/bupropion), EMDAC 7 Dec 2010.

Suicidal and self-injurious behaviors NEC	6 (0.1)	7 (0.1)
Completed suicide	1 (<0.1)	4 (0.1)
Suicidal ideation	1 (<0.1)	1 (<0.1)
Suicide attempt	4 (0.1)	2 (<0.1)
Injury, poisoning and procedural complications	2 (<0.1)	0 (0.0)
Product use issues	2 (<0.1)	0 (0.0)
Intentional overdose	2 (<0.1)	0 (0.0)

Source: Summary of Clinical Safety, Table 2-39

As shown above, 1 subject on Victoza and 4 subjects on placebo had fatal events of completed suicide [note that the EAC only confirmed 2 of the placebo deaths as 'suicide'; 1 was adjudicated as 'unknown' and 1 as carbon monoxide poisoning (i.e., accidental)]. The following is a summary of the EAC-confirmed fatal suicide event in the subject on Victoza:

- Subject (b) (6) was a 57 year old male without a history of psychiatric disorders at baseline, who was treated with drug for 427 days and committed suicide by hanging on study day 1164 (i.e., the subject had stopped trial drug nearly 2 years prior to committing suicide). According to the subject's wife, the subject had started to neglect his health a few months prior to the event, thought possibly due to undiagnosed depression. No other psychiatric AEs were reported during the trial and no further information was provided.

The 2 events of intentional overdose in Victoza-treated subjects appeared unlikely to be suicidal in nature:

- Subject (b) (6) reported an overdose of morphine and metformin for "pain relief". Of note, several years earlier, an SAE of accidental overdose of morphine for sciatic pain was reported.

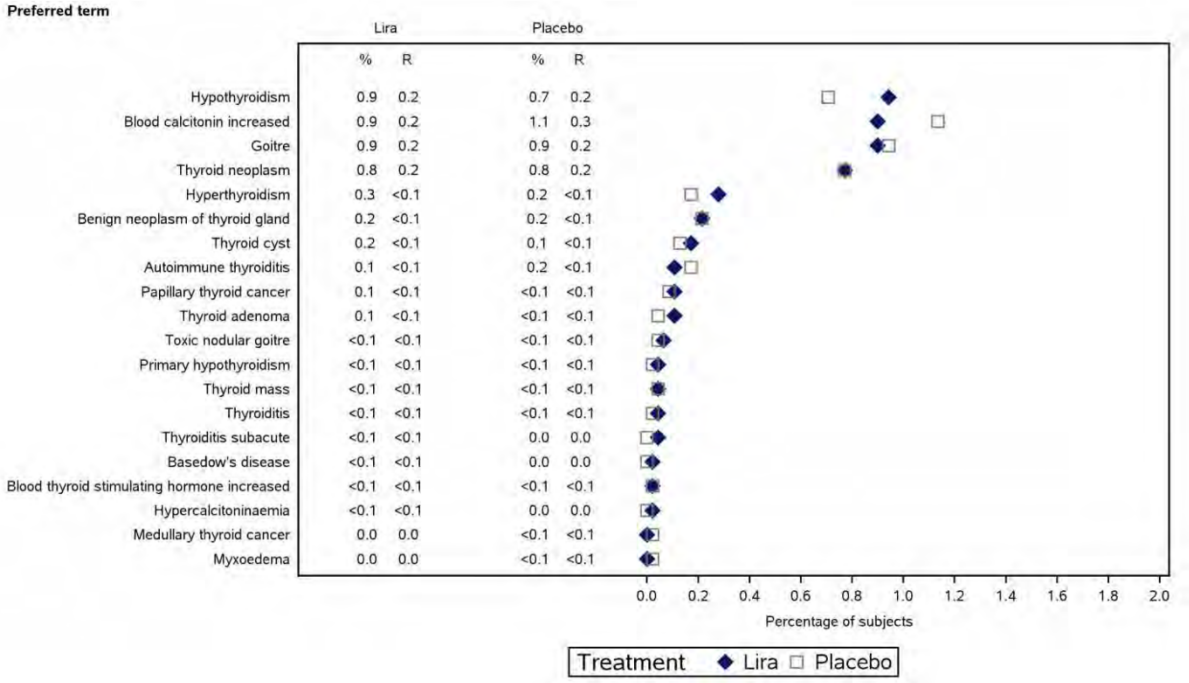
- Subject (b) (6) was reportedly taking trial product twice daily (i.e., double dose) due to financial reasons of not having insulin.

9.11 Thyroid Disorders

Thyroid disease is an adverse event of interest given the nonclinical findings of hyperplasia/neoplasia of rodent thyroid C-cells. Please refer to Dr. Sullivan's review of thyroid cancer and calcitonin for more details. This section will describe non-neoplasm disorders of the thyroid gland. The EAC adjudicated thyroid disease requiring thyroidectomy and thyroid neoplasms. Events of thyroid disease were otherwise evaluated utilizing a pre-specified MedDRA search. Overall, 4.2% of subjects in the Victoza group and 4.1% in the placebo group reported a serious adverse event or non-serious MESI of thyroid disease during the trial. The most frequent events identified in the search were 'hypothyroidism', 'blood calcitonin increased', and 'goiter'. The events

with an imbalance not in favor of Victoza were 'hypothyroidism' (0.9% vs. 0.7%, Victoza vs. placebo, respectively) and 'hyperthyroidism' (0.3% vs. 0.2%).

Figure 28. Thyroid Disease SAEs and MESIs, 20 Most Frequent Events



Source: LEADER CSR, Figure 12-35

9.12 Overdose

The potential for drug abuse was not assessed in this trial. Liraglutide is not a scheduled drug.

To identify events potentially related to overdose, a MedDRA search was performed based on all events within the 'overdose' HLGT as well as selected PTs among all systematically recorded AEs (SAEs and non-serious MESIs). PTs included 'accidental overdose', 'completed suicide', intentional overdose', 'overdose', 'prescribed overdose' and 'suicide attempt'. Suicide and intentional overdose events are discussed further in Section 9.10.

Overall, 30 subjects (0.6%) in the Victoza group and 28 subjects (0.6%) in the placebo group reported events of 'overdose' by MedDRA search.

Table 72. Overdose, SAEs or MESIs

	Victoza N=4668 n (%)	**Placebo N=4672 n (%)**
'Overdose' events by MedDRA search	30 (0.6)	28 (0.6)
Injury, poisoning and procedural complications	25 (0.5)	22 (0.5)
Accidental overdose	13 (0.3)	8 (0.2)
Overdose	12 (0.3)	15 (0.3)
Intentional overdose	2 (<0.1)	0
Psychiatric disorders	5 (0.1)	6 (0.1)
Suicide attempt	4 (0.1)	2 (<0.1)
Completed suicide	1 (<0.1)	4 (0.1)

N: number of subjects; %: proportion of subjects; MESI: medical event of special interest as reported by the investigator; SAE: serious adverse event
Adverse events identified using MedDRA search criteria.

Source: Summary of Clinical Safety, Table 5-19

Three events in Victoza-treated subjects co-reported adverse events in association with the overdose:

- Subject (b) (6) had an accidental overdose (took product twice daily for 3 days) and reported AEs of abdominal pain and diarrhea.

- Subject (b) (6) intentionally increased trial drug dosage to 3.6 mg for 2 weeks because his insulin was running out due to financial issues; the co-reported AE was hyperglycemia (blood glucose 400 mg/dL). The subject was hospitalized with renal failure about a month later.

- Subject (b) (6) did not take an overdose of trial medication, but took an accidental overdose of oxycodone and paracetamol for pain relief on one occasion. The subject also administered insulin glargine (dose not reported) and did not measure blood glucose on that day. Hypoglycemic unconsciousness was also reported on the same day.

9.13 Human Reproduction and Pregnancy Data

No patients became pregnant during the trial. There was one pregnancy in a partner to a male patient. The baby was reportedly healthy and no SAEs were reported.

10 Laboratory Findings

Laboratory tests monitored in this trial included: lipase, amylase, creatinine, total bilirubin, ALT, calcium, potassium, and sodium; hemoglobin, hematocrit, platelets, RBC, and WBC; anti-drug antibodies; and calcitonin. See Section 9.2.2 for results of lipase and amylase, Section 9.5.2 for renal laboratory paramaters, Section 9.6.2 for hepatic laboratory parameters, and Section 9.7.2 for anti-drug antibodies. Refer to Dr. Sullivan's review for calcitonin results. The table below briefly describes outliers in calcium, potassium, sodium, and hematology parameters. In general, incidence of laboratory outliers was similar between groups.

Table 73. Laboratory Parameters, Categorical Summary of Abnormal Values

	Victoza N=4668 n (%)	**Placebo N=4672 n (%)**
Calcium		
>ULN to 11.5 mg/dL	696 (14.9)	635 (13.6)
>11.5 to 12.5 mg/dL	13 (0.3)	9 (0.2)
>12.5 to 13.5 mg/dL	0	1 (<0.1)
>13.5 mg/dL	1 (<0.1)	0
<LLN to 8.0 mg/dL	65 (1.4)	49 (1.0)
<8.0 to 7.0 mg/dL	19 (0.4)	19 (0.4)
<7.0 to 6.0 mg/dL	5 (0.1)	10 (0.2)
<6.0 mg/dL	0	1 (<0.1)
Potassium		
>ULN to 5.5 mmol/L	452 (9.7)	469 (10.0)
>5.5 to 6.0 mmol/L	215 (4.6)	221 (4.7)
>6.0 to 7.0 mmol/L	54 (1.2)	56 (1.2)
>7.0 mmol/L	10 (0.2)	3 (0.1)
<LLN to 3.0 mmol/L	174 (3.7)	149 (3.2)
<3.0 to 2.5 mmol/L	8 (0.2)	6 (0.1)
<2.5 mmol/L	0	0
Sodium		
>ULN to 150 mmol/L	97 (2.1)	103 (2.2)

	Victoza N=4668 n (%)	**Placebo N=4672 n (%)**
>150 to 155 mmol/L	8 (0.2)	3 (0.1)
>155 to 160 mmol/L	0	0
>160 mmol/L	3 (0.1)	0
<LLN to 130 mmol/L	113 (2.4)	112 (2.4)
<130 to 120 mmol/L	22 (0.5)	22 (0.5)
<120 mmol/L	0	1 (<0.1)
Platelets		
<LLN to 75 $x10^9$/L	344 (7.4)	364 (7.8)
< 75 to 50 $x10^9$/L	13 (0.3)	10 (0.2)
< 50 to 25 $x10^9$/L	1 (<0.1)	3 (0.1)
< 25 $x10^9$/L	0	2 (<0.1)
Leukocytes		
<LLN to 3 $x10^9$/L	67 (1.4)	57 (1.2)
<3 to 2 $x10^9$/L	39 (0.8)	34 (0.7)
<2 to 1 $x10^9$/L	5 (0.1)	3 (0.1)
<1 $x10^9$/L	0	0
Hemoglobin		
>1x ULN to 2 g/dL above ULN	132 (2.8)	120 (2.6)
>2 g/dL above ULN to 4 g/dL above ULN	7 (0.1)	4 (0.1)
>4g/dL above ULN	0	0
<LLN to 10 g/dL	1670 (35.8)	1705 (36.5)
<10 to 8 g/dL	168 (3.6)	159 (3.4)
<8 g/dL	11 (0.2)	18 (0.4)

Source: LEADER CSR, Tables 14.3.5.102 and 14.3.5.160

11 Other Safety Explorations

11.1 Drug-Demographic Interactions

See Dr. Condarco's efficacy review for demographic subgroup analyses of MACE. This section will summarize adverse events by age, sex, and race groups.

11.1.1 Age

No trend for death or SAEs by age group was observed in LEADER (Table 74 and Table 75).

Table 74. Deaths by Baseline Age Group

	Victoza	Placebo
<65 years	**N=2512**	**N=2499**
Deaths	149 (5.9)	187 (7.5)
Cardiovascular deaths	92 (3.7)	129 (5.2)
Non-cardiovascular deaths	57 (2.3)	58 (2.3)
65-74 years	**N=1738**	**N=1755**
Deaths	172 (9.9)	177 (10.1)
Cardiovascular deaths	93 (5.4)	107 (6.1)
Non-cardiovascular deaths	79 (4.5)	70 (4.0)
75-84 years	**N=401**	**N=393**
Deaths	54 (13.5)	70 (17.8)
Cardiovascular deaths	32 (8.0)	345 (8.7)
Non-cardiovascular deaths	22 (5.5)	36 (9.2)
≥85 years	**N=17**	**N=25**
Deaths	6 (35.3)	13 (52.0)
Cardiovascular deaths	2 (11.8)	8 (32.0)
Non-cardiovascular deaths	4 (23.5)	5 (20.0)

Source: Summary of Clinical Safety, Table 5-2

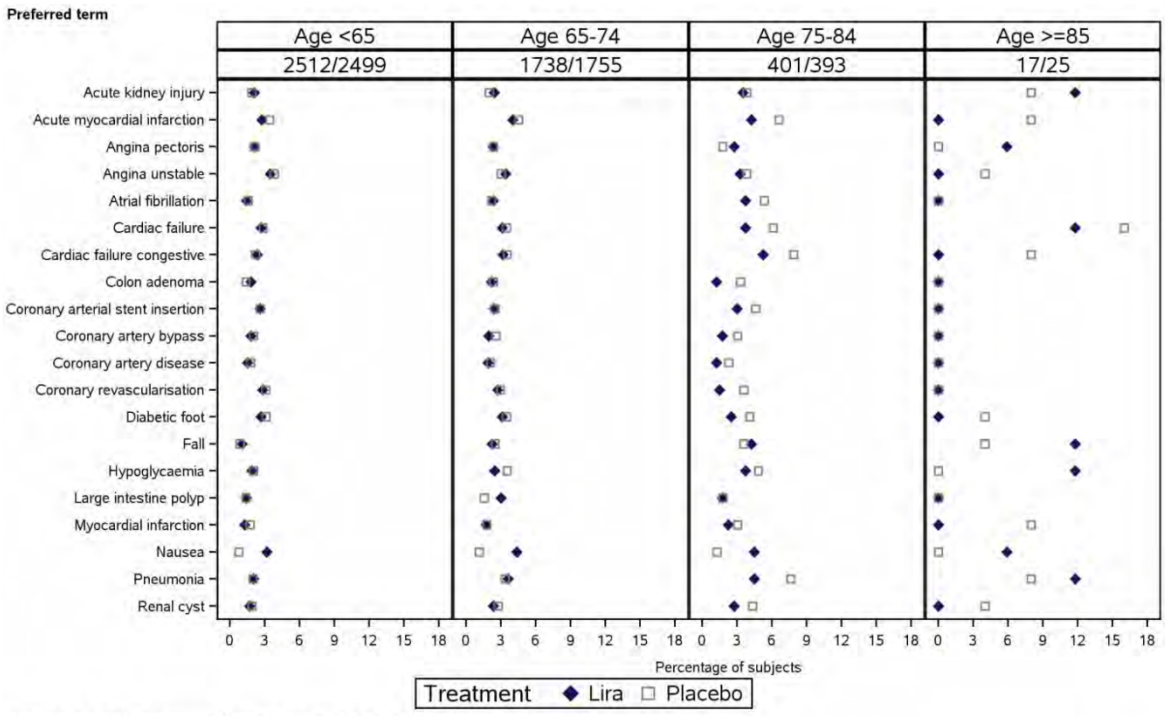
Table 75. SAEs or MESIs by Baseline Age Group

	Victoza			Placebo		
	N (%)	E	R	N (%)	E	R
Number of subjects	**4668**			**4672**		
Age < 65 years	2512			2499		
Age 65 to 74 years	1738			1755		
Age 75 to 84 years	401			393		
Age ≥ 85 years	17			25		
Years of observation						
Age < 65 years	9706.3			9540.7		
Age 65 to 74 years	6559.0			6683.6		
Age 75 to 84 years	1499.8			1445.6		
Age ≥ 85 years	57.3			71.2		
Events (SAEs and non-serious MESIs)						
Age < 65 years	1442 (57.4)	4454	45.9	1412 (56.5)	4331	45.4
Age 65 to 74 years	1154 (66.4)	3857	58.8	1114 (63.5)	3627	54.3
Age 75 to 84 years	298 (74.3)	1063	70.9	292 (74.3)	1243	86.0
Age ≥ 85 years	15 (88.2)	47	82.1	21 (84.0)	59	82.9
Serious adverse events						
Age < 65 years	1118 (44.5)	3164	32.6	1141 (45.7)	3185	33.4
Age 65 to 74 years	937 (53.9)	2705	41.2	947 (54.0)	2791	41.8
Age 75 to 84 years	252 (62.8)	741	49.4	248 (63.1)	975	67.4
Age ≥ 85 years	13 (76.5)	33	57.6	18 (72.0)	47	66.0
Severe adverse events						
Age < 65 years	690 (27.5)	1536	15.8	702 (28.1)	1598	16.7
Age 65 to 74 years	627 (36.1)	1369	20.9	627 (35.7)	1380	20.6
Age 75 to 84 years	176 (43.9)	361	24.1	190 (48.3)	545	37.7
Age ≥ 85 years	9 (52.9)	20	34.9	14 (56.0)	34	47.8
Product withdrawn permanently						
Age < 65 years	184 (7.3)	252	2.6	155 (6.2)	219	2.3
Age 65 to 74 years	195 (11.2)	272	4.1	135 (7.7)	188	2.8
Age 75 to 84 years	67 (16.7)	98	6.5	47 (12.0)	69	4.8
Age ≥ 85 years	1 (5.9)	1	1.7	3 (12.0)	3	4.2

Source: Summary of Clinical Safety, Table 5-3

The following figure shows the 20 most frequent SAEs/MESIs by age group. Limited conclusions can be drawn from the group of subjects ≥ 85 years given the small sample size and very small numbers of events, including 'fall' and 'hypoglycemia'. This is shown further in Table 76, where confirmed and severe hypoglycemia events differ by only 1 subject respectively among the treatment groups.

Figure 29. SAEs or MESIs by Baseline Age Group, 20 Most Frequently Reported Preferred Terms



Note: xx/xx in second row corresponds to number of subjects in the liraglutide and placebo groups respectively. The selection criterion of the 20 most frequent cut-offs is based on the percentages of the total population. The preferred terms are sorted in alphabetically order.

Source: Summary of Clinical Safety, Figure 5-1

Table 76. Hypoglycemia Episodes by Baseline Age Group

	Victoza			Placebo		
	N (%)	**E**	**R**	**N (%)**	**E**	**R**
<65 years	**2512**			**2499**		
Confirmed	1057 (42.1)	6294	66.7	1085 (43.4)	7974	85.9
Severe	49 (2.0)	90	1.0	65 (2.6)	140	1.5
65-74 years	**1738**			**1755**		
Confirmed	788 (45.3)	4557	71.3	856 (48.8)	6655	102.1
Severe	47 (2.7)	56	0.9	65 (3.7)	90	1.4
75-84 years	**401**			**393**		
Confirmed	184 (45.9)	1271	86.9	180 (45.8)	1088	77.0
Severe	16 (4.0)	27	1.8	22 (5.6)	24	1.7
≥85 years	**N=17**			**N=25**		
Confirmed	10 (58.8)	55	103.5	9 (36.0)	39	55.6
Severe	2 (11.8)	5	9.4	1 (4.0)	1	1.4

Source: Summary of Clinical Safety, Table 5-4

11.1.2 Sex

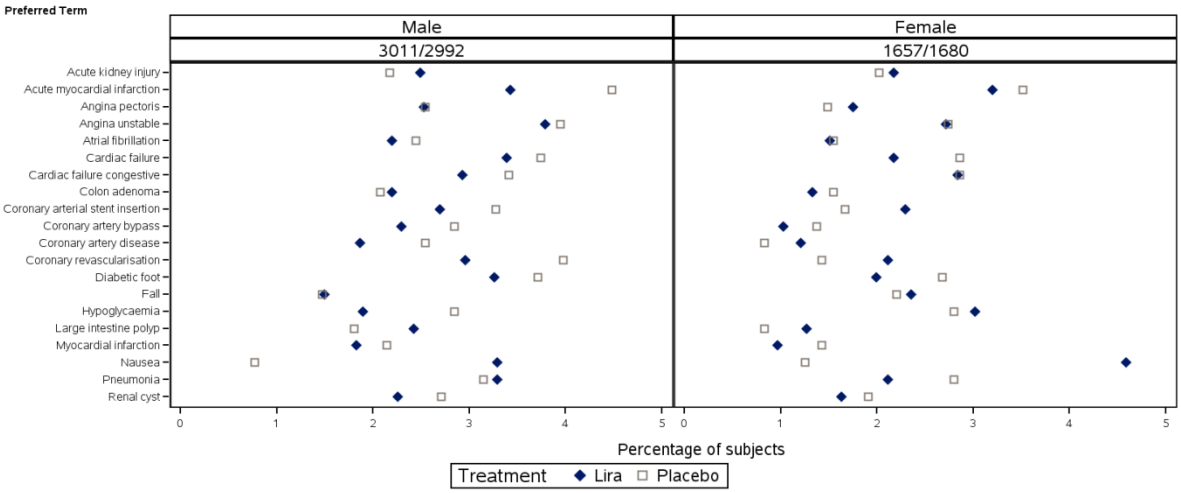
As seen in Table 77 and Figure 30, the distribution and pattern of events did not suggest any notable differences between males and females.

Table 77. SAEs or MESIs by Sex

	Victoza			Placebo		
	N (%)	E	R	N (%)	E	R
Number of subjects	**4668**			**4672**		
Male	3011			2992		
Female	1657			1680		
Years of observation						
Male	11502.7			11371.3		
Female	6319.6			6369.8		
Events (SAEs and non-serious MESIs)						
Male	1924 (63.9)	6374	55.4	1897 (63.4)	6271	55.1
Female	985 (59.4)	3047	48.2	942 (56.1)	2989	46.9
Serious adverse events						
Male	1549 (51.4)	4466	38.8	1580 (52.8)	4738	41.7
Female	771 (46.5)	2177	34.4	774 (46.1)	2260	35.5
Severe adverse events						
Male	1014 (33.7)	2181	19.0	1037 (34.7)	2362	20.8
Female	488 (29.5)	1105	17.5	496 (29.5)	1195	18.8
Product withdrawn permanently						
Male	277 (9.2)	386	3.4	226 (7.6)	329	2.9
Female	170 (10.3)	237	3.8	114 (6.8)	150	2.4

Source: Response to FDA request, Apr 21, 2017, Appendix 1, Table 1

Figure 30. SAEs or MESIs by Sex, 20 Most Frequently Reported Preferred Terms



Lira: Liraglutide
Note: xx/xx in second row corresponds to number of subjects in the liraglutide and placebo groups respectively.
The selection criterion of the 20 most frequently reported adverse events is based on the percentages of the total population.
The preferred terms are sorted in alphabetically order.

Source: Response to FDA request, Apr 21, 2017, Appendix 1, Figure 2

11.1.3 Race

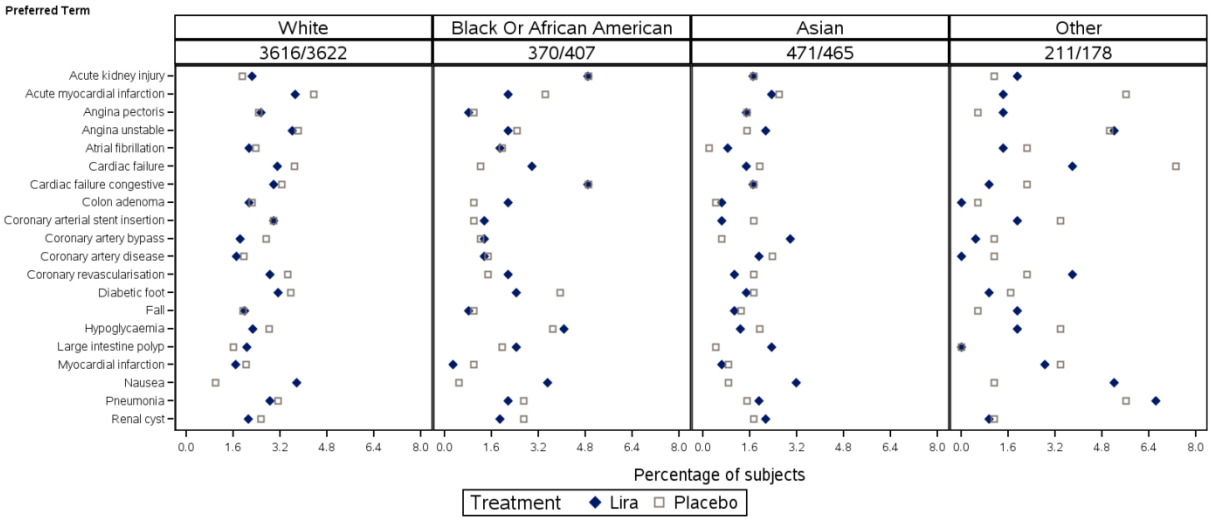
The majority of the patient population in LEADER was white and of non-Hispanic or Latino origin. Asian and black or African American subjects each constituted approximately 10% and 8% of the total trial population, respectively. Asian subjects overall reported fewer SAEs and MESIs, but the incidences were generally similar among treatment groups for all race groups.

Table 78. SAEs or MESIs by Race

	Victoza			Placebo		
	N (%)	E	R	N (%)	E	R
Number of subjects	**4668**			**4672**		
White	3616			3622		
Black or African American	370			407		
Asian	471			465		
Other	211			178		
Years of observation						
White	13864.7			13841.5		
Black or African American	1389.7			1522.2		
Asian	1770.8			1734.4		
Other	797.1			643.0		
Events (SAEs and non-serious MESIs)						
White	2319 (64.1)	7594	54.8	2262 (62.5)	7620	55.1
Black or African American	228 (61.6)	752	54.1	248 (60.9)	792	52.0
Asian	235 (49.9)	730	41.2	220 (47.3)	566	32.6
Other	127 (60.2)	345	43.3	109 (61.2)	282	43.9
Serious adverse events						
White	1857 (51.4)	5289	38.1	1896 (52.3)	5742	41.5
Black or African American	185 (50.0)	574	41.3	205 (50.4)	604	39.7
Asian	178 (37.8)	521	29.4	161 (34.6)	421	24.3
Other	100 (47.4)	259	32.5	92 (51.7)	231	35.9
Severe adverse events						
White	1179 (32.6)	2533	18.3	1216 (33.6)	2899	20.9
Black or African American	134 (36.2)	310	22.3	135 (33.2)	288	18.9
Asian	111 (23.6)	270	15.2	111 (23.9)	219	12.6
12.6Other	78 (37.0)	173	21.7	71 (39.9)	151	23.5
Product withdrawn permanently						
White	370 (10.2)	524	3.8	265 (7.3)	378	2.7
Black or African American	30 (8.1)	34	2.4	35 (8.6)	47	3.1
Asian	29 (6.2)	42	2.4	30 (6.5)	41	2.4
Other	18 (8.5)	23	2.9	10 (5.6)	13	2.0

Source: Response to FDA request, Apr 21, 2017, Appendix 1, Table 3

Figure 31. SAEs or MESIs by Race, 20 Most Frequently Reported Preferred Terms



Lira: Liraglutide
Note: xx/xx in second row corresponds to number of subjects in the liraglutide and placebo groups respectively.
The selection criterion of the 20 most frequently reported adverse events is based on the percentages of the total population.
The preferred terms are sorted in alphabetically order.

Source: Response to FDA request, Apr 21, 2017, Appendix 1, Figure 4

11.2 Drug-Disease Interactions

The sponsor conducted analyses of MACE by baseline renal function and heart failure; see the efficacy review for details. Sections 9.4 and 9.5 respectively discuss hypoglycemia and acute renal failure AEs as well as renal laboratory data by baseline renal impairment. See the efficacy review for any subgroup analyses of EAC-confirmed microvascular events. This section will provide an overview of AEs by baseline renal function and heart failure.

11.2.1 Renal Impairment

Deaths and AEs were evaluated by baseline renal function. There was no consistent pattern or trend in the incidence of non-CV deaths or SAEs across degrees of renal impairment (Table 79 and Table 80).

Table 79. Deaths by Baseline Renal Function

	Victoza	Placebo
Normal renal function	**N=1620**	**N=1655**
Deaths	75 (4.6)	104 (6.3)
Cardiovascular deaths	45 (2.8)	65 (3.9)
Non-cardiovascular deaths	30 (1.9)	39 (2.4)
Mild renal impairment	**N=1932**	**N=1975**
Deaths	162 (8.4)	165 (8.4)
Cardiovascular deaths	94 (4.9)	104 (5.3)
Non-cardiovascular deaths	68 (3.5)	61 (3.1)
Moderate renal impairment	**N=999**	**N=935**
Deaths	119 (11.9)	150 (16.0)
Cardiovascular deaths	69 (6.9)	92 (9.8)
Non-cardiovascular deaths	50 (5.0)	58 (6.2)
Severe renal impairment	**N=117**	**N=107**
Deaths	25 (21.4)	28 (26.2)
Cardiovascular deaths	11 (9.4)	17 (15.9)
Non-cardiovascular deaths	14 (12.0)	11 (10.3)

Source: Summary of Clinical Safety, Table 5-6

Table 80. SAEs and MESIs by Baseline Renal Function

	Victoza			Placebo		
	N (%)	E	R	N (%)	E	R
Number of subjects	**4668**			**4672**		
Normal renal function	1620			1655		
Mild renal impairment	1932			1975		
Moderate renal impairment	999			935		
Severe renal impairment	117			107		
Years of observation						
Normal renal function	6269.0			6345.9		
Mild renal impairment	7407.9			7582.5		
Moderate renal impairment	3740.1			3446.4		
Severe renal impairment	405.4			366.3		
Events (SAEs and non-serious MESIs)						
Normal renal function	895 (55.2)	2717	43.3	886 (53.5)	2473	39.0
Mild renal impairment	1206 (62.4)	3796	51.2	1190 (60.3)	3728	49.2
Moderate renal impairment	704 (70.5)	2458	65.7	680 (72.7)	2647	76.8
Severe renal impairment	104 (88.9)	450	111.0	83 (77.6)	412	112.5
Serious adverse events						
Normal renal function	719 (44.4)	1942	31.0	728 (44.0)	1880	29.6
Mild renal impairment	948 (49.1)	2652	35.8	978 (49.5)	2789	36.8
Moderate renal impairment	562 (56.3)	1720	46.0	573 (61.3)	2012	58.4
Severe renal impairment	91 (77.8)	329	81.2	75 (70.1)	317	86.5
Severe adverse events						
Normal renal function	421 (26.0)	870	13.9	441 (26.6)	913	14.4
Mild renal impairment	615 (31.8)	1302	17.6	609 (30.8)	1311	17.3
Moderate renal impairment	393 (39.3)	920	24.6	414 (44.3)	1127	32.7
Severe renal impairment	73 (62.4)	194	47.9	69 (64.5)	206	56.2
Product withdrawn permanently						
Normal renal function	102 (6.3)	126	2.0	100 (6.0)	141	2.2
Mild renal impairment	193 (10.0)	270	3.6	109 (5.5)	147	1.9
Moderate renal impairment	129 (12.9)	189	5.1	108 (11.6)	158	4.6
Severe renal impairment	23 (19.7)	38	9.4	23 (21.5)	33	9.0

Source: Summary of Clinical Safety, Table 5-7

11.2.2 Heart Failure Status

New York Heart Association (NYHA) class IV was an exclusion criterion in LEADER. Deaths and AEs were evaluated by baseline heart failure status (no heart failure and NYHA class I, II, and III). There was no consistent pattern or trend in the incidence of non-CV deaths or SAEs across NYHA class at baseline (Table 81 and Table 82).

Table 81. Deaths by NYHA Class at Baseline

	Victoza	Placebo
No heart failure	**N=3836**	**N=3851**
Deaths	262 (6.8)	319 (8.3)
Cardiovascular deaths	143 (3.7)	194 (5.0)
Non-cardiovascular deaths	119 (3.1)	125 (3.2)
NYHA class I	**N=179**	**N=169**
Deaths	21 (11.7)	22 (13.0)
Cardiovascular deaths	13 (7.3)	16 (9.5)
Non-cardiovascular deaths	8 (4.5)	6 (3.6)
NYHA class II	**N=545**	**N=546**
Deaths	80 (14.7)	88 (16.1)
Cardiovascular deaths	50 (9.2)	54 (9.9)
Non-cardiovascular deaths	30 (5.5)	34 (6.2)
NYHA class III	**N=108**	**N=106**
Deaths	18 (16.7)	18 (17.0)
Cardiovascular deaths	13 (12.0)	14 (13.2)
Non-cardiovascular deaths	5 (4.6)	4 (3.8)

N: number of subjects; NYHA: New York Heart Association

Source: Summary of Clinical Safety, Table 5-13

Table 82. SAEs or MESIs by NYHA Class at Baseline

	Victoza			Placebo		
	N (%)	E	R	N (%)	E	R
Number of subjects	**4668**			**4672**		
No heart failure	3836			3851		
NYHA class I	179			169		
NYHA class II	545			546		
NYHA class III	108			106		
Years of observation						
No heart failure	14775.4			14744.5		
NYHA class I	671.7			626.2		
NYHA class II	1982.4			1983.6		
NYHA class III	392.8			386.6		
Events (SAEs and non-serious MESIs)						
No heart failure	2377 (62.0)	7430	50.3	2296 (59.6)	7195	48.8
NYHA class I	116 (64.8)	424	63.1	112 (66.3)	411	65.6
NYHA class II	338 (62.0)	1273	64.2	364 (66.7)	1391	70.1
NYHA class III	78 (72.2)	294	74.8	67 (63.2)	263	68.0
Serious adverse events						
No heart failure	1864 (48.6)	5094	34.5	1873 (48.6)	5313	36.0
NYHA class I	97 (54.2)	314	46.7	103 (60.9)	328	52.4
NYHA class II	288 (52.8)	994	50.1	320 (58.6)	1147	57.8
NYHA class III	71 (65.7)	241	61.3	58 (54.7)	210	54.3
Severe adverse events						
No heart failure	1192 (31.1)	2547	17.2	1188 (30.8)	2602	17.6
NYHA class I	65 (36.3)	159	23.7	70 (41.4)	184	29.4
NYHA class II	192 (35.2)	463	23.4	230 (42.1)	633	31.9
NYHA class III	53 (49.1)	117	29.8	45 (42.5)	138	35.7
Product withdrawn permanently						
No heart failure	363 (9.5)	491	3.3	275 (7.1)	373	2.5
NYHA class I	19 (10.6)	27	4.0	13 (7.7)	21	3.4
NYHA class II	57 (10.5)	92	4.6	48 (8.8)	77	3.9
NYHA class III	8 (7.4)	13	3.3	4 (3.8)	8	2.1

N: number of subjects; %: proportion of subjects; E: number of events; PYO: patient-years of observation; R: event rate per 100 observation years; NYHA: New York Heart Association; SAE: serious adverse event

Source: Summary of Clinical Safety, Table 5-14

Hypoglycemia was assessed by heart failure status. There was no consistent pattern or trend in the incidence of confirmed or severe hypoglycemia by increasing heart failure severity.

11.3 Drug-Drug Interactions

Safety (AEs overall and hypoglycemia) was evaluated in patients using pre-mix insulin at baseline and at least the following 26 weeks (i.e., the duration of a typical phase 3

diabetes trial). Table 83 enumerates the 20 most frequently reported SAEs and MESIs in the whole population and in patients on pre-mix insulin.

Table 83. SAEs and MESIs in Patients on Pre-Mix Insulin at Baseline and the Following 26 Weeks and Total Population, 20 Most Frequently Reported

	Patients on Pre-Mix Insulin		Total Randomized Population	
	Victoza N=436	Placebo N=437	Victoza N=4668	Placebo N=4672
Hypoglycemia	5.0%	4.8%	2.3%	2.8%
Diabetic foot	4.8%	5.0%	2.8%	3.3%
Cardiac failure	4.6%	4.8%	3.0%	3.4%
Cardiac failure congestive	4.6%	4.8%	2.9%	3.2%
Acute kidney injury	4.4%	3.2%	2.4%	2.1%
Diabetic retinopathy	3.9%	3.2%	1.8%	1.6%
Coronary arterial stent insertion	3.4%	1.6%	2.5%	2.7%
Nausea	3.0%	1.6%	3.7%	0.9%
Acute myocardial infarction	2.8%	4.8%	3.3%	4.1%
Angina pectoris	2.8%	2.3%	2.2%	2.2%
Angina unstable	2.8%	2.7%	3.4%	3.5%
Fall	2.8%	1.8%	1.8%	1.7%
Myocardial infarction	2.8%	1.6%	1.5%	1.9%
Renal cyst	2.8%	3.2%	2.0%	2.4%
Basal cell carcinoma	2.5%	1.6%	1.3%	0.9%
Coronary revascularization	2.1%	2.5%	2.7%	3.1%
Pneumonia	2.1%	3.9%	2.9%	3.0%
Chronic kidney disease	1.8%	2.1%	1.6%	1.5%
Coronary artery bypass	1.4%	3.0%	1.8%	2.3%
Cellulitis	0.9%	3.2%	0.8%	1.2%

Source: ISS, Appendix 7.11, Figure 7.11.52 and LEADER CSR, Table 14.3.1.1.7

Events of hypoglycemia were explored further in this population. Although there does not appear to be worsening of severe or confirmed hypoglycemia in patients on Victoza and pre-mix insulin compared to those on placebo and pre-mix insulin based on proportions of patients with events, individual patients with severe hypoglycemia events on Victoza and pre-mix insulin reported a greater number of events as compared to patients with events on placebo and pre-mix insulin.

Table 84. Hypoglycemic Events by Classification According to Treatment with Pre-Mix Insulin at Baseline and the Following 26 Weeks

	Victoza			Placebo		
	N (%)	**E**	**R**	**N (%)**	**E**	**R**
Premix insulin						
FAS	436			437		
PYO	1502			1514		
Confirmed	250 (57.3)	1738	115.7	257 (58.8)	2302	152.0
Severe	23 (5.3)	52	3.5	26 (6.0)	34	2.2
No premix insulin						
FAS	4232			4235		
PYO	15839			15768		
Confirmed	1789 (42.3)	10439	65.9	1873 (44.2)	13454	85.3
Severe	91 (2.2)	126	0.8	127 (3.0)	221	1.4

N: number of patients; E: number of episodes; %: proportion of patients; FAS: full analysis set; R: episode rate per 100 observation years; PYO: patient years of observation

Source: Summary of Clinical Safety, Table 5-17

12 Advisory Committee Meeting

On June 20, 2017, the Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) convened to discuss this application. The following question relevant to this safety review was asked of the committee:

The Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial was a cardiovascular (CV) outcomes trial conducted as a postmarketing requirement to evaluate CV safety as per the 2008 FDA Guidance titled Diabetes Mellitus – Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes. Additional non-CV safety concerns related to liraglutide and other incretin mimetics were also evaluated in LEADER, including potential risk of medullary thyroid carcinoma, pancreatic neoplasm, and pancreatitis. For each of these non-CV safety concerns, please comment on whether the data presented today inform of a causal relationship with liraglutide use. In your discussion, please comment on whether additional studies should be conducted to further evaluate the non-CV safety concern(s).

Committee members commented that the CV effect in the LEADER trial 'dwarfed' the non-CV safety effect. In addition, the all-cause mortality benefit was noted as an important factor consider in the overall benefit-risk assessment of liraglutide. However, because the event rates of the highlighted non-safety concerns (pancreatic and thyroid) were extremely low in comparison to the CV event rates, the effect of the drug on these outcomes, if any, was unknown.

This section will address comments on the pancreatic safety portion of this question; refer to Dr. Sullivan's review for EMDAC comments on medullary thyroid carcinoma risk.

Specifically regarding pancreatic cancer, committee members commented that the numbers of events in this trial were too few and duration too short to attribute pancreatic cancer events to liraglutide; however, others felt that these limitations could not completely dismiss the concern at this time. Some members commented they thought that pancreatic cancer should be followed longer term. Committee members were generally reassured by the (adjudicated) pancreatitis findings in this trial, but did note the imbalance in gallbladder disease. Committee members also did not feel that animal data were informative or relevant for the pancreatic signal.

13 Appendices

13.1 Non-Cardiovascular Death

The following table describes the non-cardiovascular deaths as categorized by the adjudicators (in cases where adjudicator 2 is blank, there was agreement between the adjudicators) and the *post hoc* categorization as assigned by the sponsor.

Table 85. Categorization of Non-Cardiovascular Death

Pt ID	Treatment	Adjudicator 1	Adjudicator 2	*Post hoc* Category
(b) (6)	Victoza	aspiration		ACCIDENTAL/TRAUMA
	Victoza	aspiration	Aspiration pneumonia	ACCIDENTAL/TRAUMA
	Victoza	car accident trauma	mva	ACCIDENTAL/TRAUMA
	Victoza	carbon monoxide poisoning	Carbonmonoxide poisoning	ACCIDENTAL/TRAUMA
	Victoza	mva		ACCIDENTAL/TRAUMA
	Victoza	MVA	trauma	ACCIDENTAL/TRAUMA
	Victoza	trauma		ACCIDENTAL/TRAUMA
	Victoza	trauma	tbi sah	ACCIDENTAL/TRAUMA
	Victoza	trauma	trauma	ACCIDENTAL/TRAUMA
	Victoza	trauma	trauma ich	ACCIDENTAL/TRAUMA
	Victoza	Trauma		ACCIDENTAL/TRAUMA
	Victoza	Trauma		ACCIDENTAL/TRAUMA
	Victoza	bowel obstruction	bowel obstruction	GASTROINTESTINAL
	Victoza	bowel strangulation	sepsis	GASTROINTESTINAL
	Victoza	GI catastrophe	bowel perf	GASTROINTESTINAL
	Victoza	Sepsis	Perforated bowel	GASTROINTESTINAL
	Victoza	GI bleed		HAEMORRHAGE
	Victoza	GIB	GI bleed	HAEMORRHAGE
	Victoza	GIB	ugib	HAEMORRHAGE
	Victoza	lower gi bleed		HAEMORRHAGE
	Victoza	UGIB		HAEMORRHAGE
	Victoza	UGIB	Fatal Bleding (vericeal)	HAEMORRHAGE
	Victoza	endocarditis	endocarditis	INFECTION (INCLUDES SEPSIS)
	Victoza	infectious complications		INFECTION (INCLUDES SEPSIS)
	Victoza	pna		INFECTION (INCLUDES SEPSIS)
	Victoza	pna	death from complications of MSA and resp failure	INFECTION (INCLUDES SEPSIS)
	Victoza	pna	pna	INFECTION (INCLUDES SEPSIS)
	Victoza	pna	pna	INFECTION (INCLUDES SEPSIS)
	Victoza	pna	Pneumonia	INFECTION (INCLUDES SEPSIS)
	Victoza	pna	Pneumonia Sepsis	INFECTION (INCLUDES SEPSIS)
	Victoza	pna	sepsis	INFECTION (INCLUDES SEPSIS)

Pt ID	Treatment	Adjudicator 1	Adjudicator 2	*Post hoc* Category
(b) (6)	Victoza	PNA	Pneumonia	INFECTION (INCLUDES SEPSIS)
	Victoza	PNA led to respiratory arrest	Pneumonia	INFECTION (INCLUDES SEPSIS)
	Victoza	PNA sepsis	sepsis	INFECTION (INCLUDES SEPSIS)
	Victoza	pneumonia		INFECTION (INCLUDES SEPSIS)
	Victoza	Pneumonia		INFECTION (INCLUDES SEPSIS)
	Victoza	Pneumonia		INFECTION (INCLUDES SEPSIS)
	Victoza	possible pna related death		INFECTION (INCLUDES SEPSIS)
	Victoza	probable sepsis		INFECTION (INCLUDES SEPSIS)
	Victoza	probable sepsis		INFECTION (INCLUDES SEPSIS)
	Victoza	respiratory failure due to PNA	PNA	INFECTION (INCLUDES SEPSIS)
	Victoza	sepsis		INFECTION (INCLUDES SEPSIS)
	Victoza	sepsis		INFECTION (INCLUDES SEPSIS)
	Victoza	sepsis	sepsis	INFECTION (INCLUDES SEPSIS)
	Victoza	sepsis	sepsis	INFECTION (INCLUDES SEPSIS)
	Victoza	sepsis	sepsis	INFECTION (INCLUDES SEPSIS)
	Victoza	sepsis	sepsis	INFECTION (INCLUDES SEPSIS)
	Victoza	sepsis	Sepsis	INFECTION (INCLUDES SEPSIS)
	Victoza	sepsis	Sepsis	INFECTION (INCLUDES SEPSIS)
	Victoza	sepsis	septic shock	INFECTION (INCLUDES SEPSIS)
	Victoza	Sepsis	sepsis	INFECTION (INCLUDES SEPSIS)
	Victoza	sepsis ards esld	hap	INFECTION (INCLUDES SEPSIS)
	Victoza	sepsis esrd	kidney failure pna	INFECTION (INCLUDES SEPSIS)
	Victoza	Sepsis with respiratory failure		INFECTION (INCLUDES SEPSIS)
	Victoza	sepsis/copd	sepsis	INFECTION (INCLUDES SEPSIS)
	Victoza	septic shock	sepsis	INFECTION (INCLUDES SEPSIS)
	Victoza	Septic Shock	sepsis	INFECTION (INCLUDES SEPSIS)
	Victoza	septis due to cholangitis		INFECTION (INCLUDES SEPSIS)
	Victoza	urosepsis	urosepsis	INFECTION (INCLUDES SEPSIS)
	Victoza	AML	respiratory arrest	MALIGNANCY
	Victoza	bladder ca		MALIGNANCY
	Victoza	brain tumor	Brain tunor	MALIGNANCY
	Victoza	brain tumor	malignancy	MALIGNANCY
	Victoza	Brain tumor	malignancy	MALIGNANCY
	Victoza	Cancer	pancreatic cancer	MALIGNANCY
	Victoza	Carcinoid	malignancy	MALIGNANCY
	Victoza	Cholangiocarcinoma	Cholangiocarcinoma	MALIGNANCY
	Victoza	cholangiocarninoma	cholangiocarninoma	MALIGNANCY
	Victoza	esophageal CA	Esophageal Cancer	MALIGNANCY
	Victoza	Esophageal CA	Esophageal Cancer	MALIGNANCY
	Victoza	hcc	malignancy	MALIGNANCY
	Victoza	HCC	hcc	MALIGNANCY
	Victoza	head and neck cancer	head and neck ca	MALIGNANCY
	Victoza	lung ca		MALIGNANCY
	Victoza	lung ca		MALIGNANCY
	Victoza	lung ca		MALIGNANCY
	Victoza	lung ca	lung ca	MALIGNANCY
	Victoza	lung ca	lung ca	MALIGNANCY
	Victoza	lung ca	lung ca	MALIGNANCY
	Victoza	lung ca	lung ca	MALIGNANCY
	Victoza	lung ca	lung CA	MALIGNANCY
	Victoza	lung ca	Lung cancer	MALIGNANCY

Pt ID	Treatment	Adjudicator 1	Adjudicator 2	*Post hoc* Category
(b) (6)	Victoza	lung ca	Lung Cancer	MALIGNANCY
	Victoza	lung ca	malignancy	MALIGNANCY
	Victoza	lung ca	metastatic cancer	MALIGNANCY
	Victoza	lung ca	PNA malignancy	MALIGNANCY
	Victoza	malignancy		MALIGNANCY
	Victoza	malignancy		MALIGNANCY
	Victoza	malignancy		MALIGNANCY
	Victoza	malignancy	cholangiocarcinoma	MALIGNANCY
	Victoza	malignancy	color ca	MALIGNANCY
	Victoza	malignancy	gastric ca	MALIGNANCY
	Victoza	malignancy	GI bleed in setting of cancer	MALIGNANCY
	Victoza	malignancy	liver mass	MALIGNANCY
	Victoza	malignancy	lung ca	MALIGNANCY
	Victoza	malignancy	lung ca	MALIGNANCY
	Victoza	malignancy	lung CA	MALIGNANCY
	Victoza	malignancy	lymphoma	MALIGNANCY
	Victoza	malignancy	malignant melanoma	MALIGNANCY
	Victoza	malignancy	metastatic ca	MALIGNANCY
	Victoza	malignancy	metastatic cancer	MALIGNANCY
	Victoza	malignancy	metastatic cancer	MALIGNANCY
	Victoza	malignancy	panc ca	MALIGNANCY
	Victoza	malignancy	pancreatic ca	MALIGNANCY
	Victoza	malignancy	Pancreatic cancer	MALIGNANCY
	Victoza	malignancy	Renal Cancer	MALIGNANCY
	Victoza	Malignancy	Pancreatic cancer	MALIGNANCY
	Victoza	MAlignancy	squamous cell carcinoma	MALIGNANCY
	Victoza	malignancy sepsis	malignancy	MALIGNANCY
	Victoza	malignsancy	Liver Cancer	MALIGNANCY
	Victoza	mesothelioma	Mesothelioma. infection	MALIGNANCY
	Victoza	Met lung CA		MALIGNANCY
	Victoza	metastatic cancer	hcc	MALIGNANCY
	Victoza	MSOF. Malignancy.	Liver cancer	MALIGNANCY
	Victoza	multiple myeloma	Myeloma	MALIGNANCY
	Victoza	pancreatic ca	pancreatic ca	MALIGNANCY
	Victoza	pancreatic ca	pancreatic ca	MALIGNANCY
	Victoza	Pancreatic Cancer	malignancy	MALIGNANCY
	Victoza	pancreatitis or pancreatic ca		MALIGNANCY
	Victoza	periteoneal carcinosis	malignancy	MALIGNANCY
	Victoza	pna and worsening pancreatic ca	pancreatc ca	MALIGNANCY
	Victoza	probable lung ca	lung ca	MALIGNANCY
	Victoza	probable melanoma related		MALIGNANCY
	Victoza	Prostate CA	Prostate Cancer	MALIGNANCY
	Victoza	cirrhosis		NON-CARDIOVASCULAR SYSTEM ORGAN FAILURE (E.G., HEPATIC FAILURE)
	Victoza	cirrhosis	cirrhosis	NON-CARDIOVASCULAR SYSTEM ORGAN FAILURE (E.G., HEPATIC FAILURE)
	Victoza	cirrhosis	liver failure	NON-CARDIOVASCULAR SYSTEM ORGAN FAILURE (E.G., HEPATIC FAILURE)

Pt ID	Treatment	Adjudicator 1	Adjudicator 2	*Post hoc* Category
(b) (6)	Victoza	ESLD	cirrhosis	NON-CARDIOVASCULAR SYSTEM ORGAN FAILURE (E.G., HEPATIC FAILURE)
	Victoza	liver failure	Liver disease	NON-CARDIOVASCULAR SYSTEM ORGAN FAILURE (E.G., HEPATIC FAILURE)
	Victoza	death from non-CV surgery		NON-CV PROCEDURE OR SURGERY
	Victoza	UTI and complications of catheter insertion		NON-CV PROCEDURE OR SURGERY
	Victoza	anaphylaxis		NON-INFECTIOUS (E.G., SYSTEMIC INFLAMMATORY RESPONSE SYNDROME
	Victoza	parkinsons	parkinsons	OTHER NON-CV DEATH
	Victoza	Seizure	Hyponatremia and seizures	OTHER NON-CV DEATH
	Victoza	skin lesions?		OTHER NON-CV DEATH
	Victoza	copd		PULMONARY
	Victoza	copd	copd	PULMONARY
	Victoza	copd	copd	PULMONARY
	Victoza	probable copd		PULMONARY
	Victoza	probablye respiratory failure secondary to copd		PULMONARY
	Victoza	pulm fibrosis and resp failure	pulmonary disease	PULMONARY
	Victoza	severe copd		PULMONARY
	Victoza	AKI	ARF	RENAL
	Victoza	ARF		RENAL
	Victoza	CKD		RENAL
	Victoza	end stage renal disease	renal failure	RENAL
	Victoza	gastroenteritis and subsequent renal failure		RENAL
	Victoza	renal failure		RENAL
	Victoza	renal failure		RENAL
	Victoza	renal failure	probable renal failure	RENAL
	Victoza	renal failure	renal failure	RENAL
	Victoza	Renal Failure		RENAL
	Victoza	renal faliure		RENAL
	Victoza	suicide	Suicide	SUICIDE
	Victoza	abscess sepsis	complications of rectal surgery	UNCLASSIFIABLE
	Victoza	died of peritonitis postoperatively	Rectal Carcinoma	UNCLASSIFIABLE
	Victoza	encephalopathy	sepsis encephalopathy	UNCLASSIFIABLE
	Victoza	malignancy	Sepsis	UNCLASSIFIABLE
	Victoza	post op complications	aspiration related to recetal ca	UNCLASSIFIABLE
	Victoza	sepsis	death 2/2 to complications from amputation likely	UNCLASSIFIABLE
	Victoza	stroke renal failure		UNCLASSIFIABLE
	Victoza	Trauma	Pneumonia	UNCLASSIFIABLE
	Placebo	choked	Choking on food	ACCIDENTAL/TRAUMA
	Placebo	choking on food	likely choking death	ACCIDENTAL/TRAUMA
	Placebo	co poisoning		ACCIDENTAL/TRAUMA

Pt ID	Treatment	Adjudicator 1	Adjudicator 2	*Post hoc* Category
(b) (6)	Placebo	fall. ich.	ich due to fall	ACCIDENTAL/TRAUMA
	Placebo	fall. massive ICH.	Brain hemorrhage s/p fall	ACCIDENTAL/TRAUMA
	Placebo	fall. sdh.	trauma/fall	ACCIDENTAL/TRAUMA
	Placebo	homocide	trauma - gunshot	ACCIDENTAL/TRAUMA
	Placebo	ied during fire	Smoke inhalation	ACCIDENTAL/TRAUMA
	Placebo	MVA	Trauma	ACCIDENTAL/TRAUMA
	Placebo	probable mva	probable mva	ACCIDENTAL/TRAUMA
	Placebo	trauma		ACCIDENTAL/TRAUMA
	Placebo	trauma		ACCIDENTAL/TRAUMA
	Placebo	trauma	mva	ACCIDENTAL/TRAUMA
	Placebo	Trauma	Trauma	ACCIDENTAL/TRAUMA
	Placebo	c. difficile	complications of colitis	GASTROINTESTINAL
	Placebo	gallbladder disease	complications of acute abdomen	GASTROINTESTINAL
	Placebo	GI bleed	gi bleed	HAEMORRHAGE
	Placebo	gib		HAEMORRHAGE
	Placebo	ugib	ugib	HAEMORRHAGE
	Placebo	UGIB	GI Bleeding	HAEMORRHAGE
	Placebo	? sepsis	sepsis	INFECTION (INCLUDES SEPSIS)
	Placebo	complications of diabetic ulcer	sepsis	INFECTION (INCLUDES SEPSIS)
	Placebo	complications of pna	pna/sepsis	INFECTION (INCLUDES SEPSIS)
	Placebo	complications of sjogrens	PNA	INFECTION (INCLUDES SEPSIS)
	Placebo	encephalitis?	pna encephalitis	INFECTION (INCLUDES SEPSIS)
	Placebo	hospitalized for PNA	Pneumonia	INFECTION (INCLUDES SEPSIS)
	Placebo	Infection - Sepsis	sepsis	INFECTION (INCLUDES SEPSIS)
	Placebo	Infection Abdominal sepsis		INFECTION (INCLUDES SEPSIS)
	Placebo	infectious	urosepsis complications	INFECTION (INCLUDES SEPSIS)
	Placebo	likely TB		INFECTION (INCLUDES SEPSIS)
	Placebo	meningitis	Meningits	INFECTION (INCLUDES SEPSIS)
	Placebo	necrotizing cholecystitis		INFECTION (INCLUDES SEPSIS)
	Placebo	pea arrest likely 2/2 infection sepsis	complications of osteomyelitis	INFECTION (INCLUDES SEPSIS)
	Placebo	pna		INFECTION (INCLUDES SEPSIS)
	Placebo	pna		INFECTION (INCLUDES SEPSIS)
	Placebo	pna	pna	INFECTION (INCLUDES SEPSIS)
	Placebo	pna	pna and sepsis	INFECTION (INCLUDES SEPSIS)
	Placebo	pna	probable pna	INFECTION (INCLUDES SEPSIS)
	Placebo	pna	Respiratory failure	INFECTION (INCLUDES SEPSIS)
	Placebo	PNA		INFECTION (INCLUDES SEPSIS)
	Placebo	PNA	PNA	INFECTION (INCLUDES SEPSIS)
	Placebo	pna sepsis	pneumonia	INFECTION (INCLUDES SEPSIS)
	Placebo	Pneumonia leading to respiratory arrest		INFECTION (INCLUDES SEPSIS)
	Placebo	Respiratory infection	septic shock	INFECTION (INCLUDES SEPSIS)
	Placebo	sepsis		INFECTION (INCLUDES SEPSIS)
	Placebo	sepsis		INFECTION (INCLUDES SEPSIS)
	Placebo	sepsis	pna	INFECTION (INCLUDES SEPSIS)
	Placebo	sepsis	sepsis	INFECTION (INCLUDES SEPSIS)
	Placebo	sepsis	sepsis	INFECTION (INCLUDES SEPSIS)
	Placebo	sepsis	sepsis	INFECTION (INCLUDES SEPSIS)
	Placebo	sepsis	Sepsis related to skin infection	INFECTION (INCLUDES SEPSIS)

Pt ID	Treatment	Adjudicator 1	Adjudicator 2	*Post hoc* Category
(b) (6)	Placebo	sepsis	Sepsis with multiorgan failure	INFECTION (INCLUDES SEPSIS)
	Placebo	Sepsis		INFECTION (INCLUDES SEPSIS)
	Placebo	Sepsis	sepsis	INFECTION (INCLUDES SEPSIS)
	Placebo	Sepsis 2/2 ischemic bowel	Infectious	INFECTION (INCLUDES SEPSIS)
	Placebo	sepsis due to dialysis catheter infection	sepsis	INFECTION (INCLUDES SEPSIS)
	Placebo	sepsis respiratory failure	Pneumonia and multisystem failure	INFECTION (INCLUDES SEPSIS)
	Placebo	Sepsis Respiratory Failure		INFECTION (INCLUDES SEPSIS)
	Placebo	Sepsis. Multisystem dysfunction	Sepsis. Multisystem dysfunction	INFECTION (INCLUDES SEPSIS)
	Placebo	septic shock	sepsis	INFECTION (INCLUDES SEPSIS)
	Placebo	septic shock	Sepsis	INFECTION (INCLUDES SEPSIS)
	Placebo	bladder cancer complications		MALIGNANCY
	Placebo	Cancer		MALIGNANCY
	Placebo	cholangiocarcinoma	cholangiocarcinoma	MALIGNANCY
	Placebo	GI bleed	gi malignancy	MALIGNANCY
	Placebo	Leukemia		MALIGNANCY
	Placebo	likely malignancy	metastatic ca	MALIGNANCY
	Placebo	Lung Adenocarcinoma	malignancy	MALIGNANCY
	Placebo	lung ca		MALIGNANCY
	Placebo	lung ca	lung ca	MALIGNANCY
	Placebo	lung ca	lung ca	MALIGNANCY
	Placebo	lung ca	Lung Cancer	MALIGNANCY
	Placebo	lung ca	Lung Cancer	MALIGNANCY
	Placebo	lung ca	Lung Cancer	MALIGNANCY
	Placebo	lung CA		MALIGNANCY
	Placebo	lung CA	lung ca	MALIGNANCY
	Placebo	lung CA	lung CA	MALIGNANCY
	Placebo	lung CA	lung cancer	MALIGNANCY
	Placebo	lung CA	malignancy	MALIGNANCY
	Placebo	lung ca sepsis	lung CA	MALIGNANCY
	Placebo	Lung Cancer	Lung CA	MALIGNANCY
	Placebo	Lung Cancer	malignancy	MALIGNANCY
	Placebo	Lung cancer PNA	Lung Cancer	MALIGNANCY
	Placebo	malignancy		MALIGNANCY
	Placebo	malignancy		MALIGNANCY
	Placebo	malignancy		MALIGNANCY
	Placebo	malignancy	bladder ca	MALIGNANCY
	Placebo	malignancy	breast cancer	MALIGNANCY
	Placebo	malignancy	cholangiocarcinoma	MALIGNANCY
	Placebo	malignancy	colon ca	MALIGNANCY
	Placebo	malignancy	complications of myeloma/prostate ca	MALIGNANCY
	Placebo	malignancy	gastric ca	MALIGNANCY
	Placebo	malignancy	gastric CA	MALIGNANCY
	Placebo	malignancy	leukemia	MALIGNANCY
	Placebo	malignancy	liver ca	MALIGNANCY
	Placebo	malignancy	Lung Cancer	MALIGNANCY
	Placebo	malignancy	lymphoma	MALIGNANCY
	Placebo	malignancy	metastatic ca	MALIGNANCY

Pt ID	Treatment	Adjudicator 1	Adjudicator 2	*Post hoc* Category
(b) (6)	Placebo	malignancy	metastatic cancer	MALIGNANCY
	Placebo	malignancy	ovarian ca	MALIGNANCY
	Placebo	malignancy	pancreatic ca	MALIGNANCY
	Placebo	malignancy	pancreatic cA	MALIGNANCY
	Placebo	malignancy	Pancreatic Cancer	MALIGNANCY
	Placebo	malignancy	peritoneal carcinosis	MALIGNANCY
	Placebo	malignancy	Pneumonia complicating cancer	MALIGNANCY
	Placebo	malignancy	rectal ca	MALIGNANCY
	Placebo	malignancy	renal cell ca	MALIGNANCY
	Placebo	malignancy	squamous cell CA	MALIGNANCY
	Placebo	malignancy	stage 4 breast ca	MALIGNANCY
	Placebo	malignancy	stage iv merkel call ca	MALIGNANCY
	Placebo	Malignancy	metastatic lung CA	MALIGNANCY
	Placebo	metastatic ca	hcc	MALIGNANCY
	Placebo	metastatic cancer	malignancy	MALIGNANCY
	Placebo	Metastatic Lung CA		MALIGNANCY
	Placebo	multiple myeloma	Multiple Myeloma	MALIGNANCY
	Placebo	ovarian cancer	disseminated ovarian cancer	MALIGNANCY
	Placebo	pancreatic ca	malignancy	MALIGNANCY
	Placebo	pancreatic ca	pancreatic ca	MALIGNANCY
	Placebo	pancreatic CA	Pancreatic Cancer	MALIGNANCY
	Placebo	pancreatic cancer	pancreatic ca	MALIGNANCY
	Placebo	pancreatic mass		MALIGNANCY
	Placebo	peritoneal carcinomatosis	Peritoneal Carcinomatosis	MALIGNANCY
	Placebo	Pneumonitis	Malignancy	MALIGNANCY
	Placebo	probable malignancy		MALIGNANCY
	Placebo	prostate ca		MALIGNANCY
	Placebo	sepsis	Pancreatic Cancer	MALIGNANCY
	Placebo	squamous cell ca complications		MALIGNANCY
	Placebo	TLS plus sepsis	MDS	MALIGNANCY
	Placebo	cirrhosis	End-stage liver disease	NON-CARDIOVASCULAR SYSTEM ORGAN FAILURE (E.G., HEPATIC FAILURE)
	Placebo	cirrhosis	ESLD	NON-CARDIOVASCULAR SYSTEM ORGAN FAILURE (E.G., HEPATIC FAILURE)
	Placebo	multisystem failure/esrd		NON-CARDIOVASCULAR SYSTEM ORGAN FAILURE (E.G., HEPATIC FAILURE)
	Placebo	post op death	respiratory failure secondary to surgery	NON-CV PROCEDURE OR SURGERY
	Placebo	dka		NON-INFECTIOUS (E.G., SYSTEMIC INFLAMMATORY RESPONSE SYNDROME
	Placebo	dehydration		OTHER NON-CV DEATH
	Placebo	encephalopathy related to remote cva	encephalopathy related to remote cva	OTHER NON-CV DEATH
	Placebo	end-stage Parkinsons	PARKINSONS	OTHER NON-CV DEATH
	Placebo	Gangrene - diabetic foot		OTHER NON-CV DEATH
	Placebo	possible spinal disease		OTHER NON-CV DEATH
	Placebo	chronic lung disease	pseudomonal pna	PULMONARY

Pt ID	Treatment	Adjudicator 1	Adjudicator 2	*Post hoc* Category
(b) (6)	Placebo	copd	copd	PULMONARY
	Placebo	copd	copd	PULMONARY
	Placebo	copd	COPD	PULMONARY
	Placebo	copd	end stage copd	PULMONARY
	Placebo	copd	Endstage COPD	PULMONARY
	Placebo	Hypoxic respiratory failure	likely PNA	PULMONARY
	Placebo	PNA	repiratory failure/copd	PULMONARY
	Placebo	pulmonary fibrosis		PULMONARY
	Placebo	resp failure		PULMONARY
	Placebo	respiratory	copd	PULMONARY
	Placebo	Respiratory disease		PULMONARY
	Placebo	esrd	esrd	RENAL
	Placebo	renal failure		RENAL
	Placebo	renal failure		RENAL
	Placebo	renal failure		RENAL
	Placebo	renal failure		RENAL
	Placebo	suicide	suicide	SUICIDE
	Placebo	suicide	SUICIDE	SUICIDE
	Placebo	brain lesion	sepsis	UNCLASSIFIABLE
	Placebo	COPD ESRD		UNCLASSIFIABLE
	Placebo	death due to diabetes complications		UNCLASSIFIABLE
	Placebo	death due to endocarditis	subdural hematoma	UNCLASSIFIABLE
	Placebo	end stage liver disease	sepsis	UNCLASSIFIABLE
	Placebo	malignancy	sepsis	UNCLASSIFIABLE
	Placebo	no cv event. likely copd or overdose	septic shock	UNCLASSIFIABLE
	Placebo	noncv death		UNCLASSIFIABLE
	Placebo	Pneumonia	hip fracture	UNCLASSIFIABLE
	Placebo	recent bka uti numerous comorbidities	sepsis	UNCLASSIFIABLE
	Placebo	sepsis	respiratory failure	UNCLASSIFIABLE
	Placebo	Sepsis	renal failure	UNCLASSIFIABLE

Reviewer created from LEADER datasets

13.1.1 Examples of Non-Cardiovascular Death Adjudicator Classification

The examples below demonstrate that classification can be challenging given multiple comorbidities and events leading to death. The above sub-classifications and subsequent analysis should therefore be considered exploratory.

- Two subjects (subject (b) (6) and (b) (6) treated with Victoza were categorized as having died due to a gastrointestinal cause, although the adjudicators differed in each case with both a GI cause (bowel strangulation, perforated bowel, respectively) and a sepsis cause being given.

- Subject (b) (6) was a 69 year old male treated with Victoza with liver cirrhosis, who died (according to the narrative) from hospital acquired pneumonia, acute respiratory distress syndrome, coronary artery disease, and chronic liver disease with portal hypertension and metabolic encephalopathy. Adjudicator causes of

death (verbatim) were “sepsis ards [acute respiratory distress syndrome] esld [end stage liver disease]” and “hap [hospital acquired pneumonia]”. This death was categorized as “infection (includes sepsis)”.

- Subject (b) (6) was a 59 year old male on Victoza with chronic renal failure on hemodialysis (not received for 4 days) who presented with fluid overload and uremic encephalopathy. After treatment, including hemodialysis, he was improving, but subsequently was intubated for “poor respiratory efforts” and airway protection. He died 10 days later due to “ventilation associated pneumonia”. Adjudicator causes of death (verbatim) were “sepsis esrd [end stage renal disease]” and “kidney failure pna [pneumonia]”. This death was categorized as “infection (includes sepsis)”.

- Subject (b) (6) was a 60 year old female on Victoza with a history of coronary heart disease and left ventricular dysfunction who presented with respiratory symptoms consistent with congestive heart failure and leukopenia. During the hospitalization, she was diagnosed with acute myeloid leukemia. Several days later (after treatment for the congestive heart failure and subsequent renal insufficiency), “respiratory distress” was reported; she was “found on the floor, pulseless”. Resuscitation was unsuccessful. Adjudicator causes of death (verbatim) were “AML [acute myeloid leukemia]” and “respiratory arrest”. This death was categorized as “malignancy”.

- Subject (b) (6) was a 60 year old female on Victoza who was hospitalized for months with “necrotizing uretrovaginitis” and was found incidentally (angiogram) to have an almost completely occluded abdominal aorta caused by atherosclerosis. Cause of death was “massive ulcer”; ulcers could not heal because of the occluded abdominal aorta. This event was adjudicated as “other non-CV death”.

- Subject (b) (6) was a 79 year old male on placebo who was diagnosed with pancreatic cancer during the trial and had multiple hospitalizations for treatment and placement of a biliary stent complicated by biliary duct obstruction. Within 8 months, he was admitted to the hospital with urosepsis and dehydration. He went into cardiac arrest and given the subject’s extremely poor prognosis, the decision was made not to initiate resuscitation. It was reported the subject died from septic shock (adjudicator 1 description), and the pancreatic cancer was also considered fatal (adjudicator 2 description). The *post hoc* classification was “malignancy”.

13.2 Other Adverse Event Tables

13.2.1 Carotid-Related SAEs

The following table is an exploration of adverse events that include the term ‘carotid’. This reviewer analysis was conducted after imbalances were noted incidentally in a review of SAE preferred terms. This is not a validated search and was conducted for exploratory purposes only.

Table 86. Carotid-Related SAEs

	Victoza N=4668	Placebo N=4672
'Carotid'-related SAEs	53 (1.1)	30 (0.6)
Carotid artery stenosis	28 (0.6)	16 (0.3)
Carotid endarterectomy	19 (0.4)	14 (0.3)
Carotid artery stent insertion	6 (0.1)	2 (<0.1)
Carotid revascularization	6 (0.1)	2 (<0.1)
Carotid angioplasty	5 (0.1)	0
Carotid artery occlusion	3 (<0.1)	2 (<0.1)
Carotid artery aneurysm	2 (<0.1)	0
Carotid arteriosclerosis	1 (<0.1)	1 (<0.1)
Carotid artery bypass	1 (<0.1)	0
Internal carotid artery kinking	1 (<0.1)	0
Carotid artery restenosis	0	2 (<0.1)
Carotid artery disease	0	1 (<0.1)

Source: Reviewer created from LEADER datasets

13.2.2 EAC-Confirmed Malignant or Pre-Malignant Pancreatic Neoplasms

Details of the subjects with EAC-confirmed pancreatic neoplasms are presented in the table below:

Table 87. Characteristics of EAC-Confirmed Pre-Malignant and Malignant Pancreatic Neoplasms

Pat ID/Age/Sex/Country EAC Malignancy Status	Study day	Histopathology	Grade	Size (mm)	AJCC Staging			
					T	N	M	Stage
Victoza								
(b) (6) /64/M/GRC Malignant	765	Ductal adenocarcinoma	Unk		cT3	cN0	cM0	IIA
(b) (6) /63/F/GRC Malignant	374	Ductal adenocarcinoma	G2	35	pT3	pN1	cM0	IIB
(b) (6) /68/M/SRB Malignant	505	Unk	Unk	33	cT2	cN1	cM0	IIB
(b) (6) /70/M/NOR Malignant	278	Ductal adenocarcinoma	Unk	27	cT3	cN0	cM1	IV
(b) (6) /70/M/AUT Malignant	517	Ductal adenocarcinoma	Unk		cT3	cN1	cM1	IV
(b) (6) /71/M/KOR Malignant	1268	Ductal adenocarcinoma	G1	35	pT3	pN0	cM0	IIA
(b) (6) /59/F/BRA Malignant	162	Unk	Unk		cT3	cN0	cM1	IV

Pat ID/Age/Sex/Country EAC Malignancy Status	Study day	Histopathology	Grade	Size (mm)	AJCC Staging			
					T	N	M	Stage
(b) (6) /60/F/RUS Malignant	936	Ductal adenocarcinoma	Unk	40	cT3	cN0	pM1	IV
(b) (6) /67/M/ISR Malignant	214	Ductal adenocarcinoma	G2	35	pT2	pN1	cM0	IIB
(b) (6) /60/M/TUR Malignant	1297	Ductal adenocarcinoma	Unk	40	cT2	cN0	cM1	IV
(b) (6) 66/F/USA Malignant	853	Ductal adenocarcinoma	Unk	35	cT4	cN1	cM1	IV
(b) (6) /69/M/USA Malignant	277	Ductal adenocarcinoma*	Unk		NA	NA	cM1	IV
	280	Ductal adenocarcinoma	Unk		NA	NA	cM1	IV
(b) (6) /61/M/USA Malignant	1	Other/1.8cm pancreatic mass however there is no cytology or pathology confirming an adenocarcinoma	Unk	18	NA	NA	NA	Unk
	589	Other/Cholangiocarcinoma There is a 3.4 cm liver mass with pathology confirming an adenocarcinoma	G2	34	NA	cN1	cM0	Unk/≥IIB
(b) (6) /65/M/USA Pre-Malignant/Carcinoma In Situ/Borderline	1415	Other/Intraductal papillary mucinous neoplasm (IPMN)	PanIN IB	48	pT0	pN0	cM0	0
Placebo								
(b) (6) /70/F/DEU	531	Ductal adenocarcinoma	Unk	37	cT1	cN0	cM1	IV
	531	Ductal adenocarcinoma*	Unk	37	cT1	cN0	cM1	IV
Malignant								
(b) (6) /75/M/DNK Malignant	525	Ductal adenocarcinoma	Unk	25	cT3	cN0	cM0	IIA
(b) (6) /66/M/SWE Malignant	43	Ductal adenocarcinoma	G3	25	pT3	pN0	cM0	IIA
(b) (6) /63/M/AUS Malignant	695	Ductal adenocarcinoma	Unk	43	cT3	cN0	cM1	IV
(b) (6) 1/78/M/USA Malignant	326	Ductal adenocarcinoma	Unk	13	cT1	cN0	cM0	IA
* Considered the index event in a multiple events review								

Source: ISS, Table 7.12.5

13.2.3 EAC-Confirmed Malignant Breast Neoplasms

Details of the subjects with EAC-confirmed breast cancer are presented in the table below:

Table 88. Characteristics of Subjects with EAC-Confirmed Breast Cancer

Pat ID/Age/Race/BMI/Country	Study day	Histopath	Grade	Size (mm)	AJCC Staging				E/P/HER2
					T	N	M	Stage	
Victoza									
(b) (6) 69/W/37.6/DEU	155	Ductal	G2	8	pT1b	pN0(i+)	cM0	IA	Neg/Neg/Pos
66/W/31.4/ITA	1008	Invasive, NOS	Unk	11	cT1c	NA	NA	Unk	Unk/Unk/Unk
75/W/26.2/BEL	525	Ductal	G3	12	pT1c	pN0	cM0	IA	Pos/Pos/Neg
78/W/32.7/DNK	639	Mucinous (colloid)	Unk	65	cT4	cN0	cM1	IV	Pos/Unk/Neg
61/W/31.4/SWE	1115	Ductal	G1	30	cT2	pN0(i-)	cM0	IIA	Pos/Pos/Neg
65/W/27.4/GBR	676	Lobular	G2		cT4	cUnk	cM1	IV	Pos/Pos/Neg
	676	Lobular	G2		cT4	cUnk	cM1	IV	Pos/Pos/Neg
(b) (6) 74/W/37.2/GBR	1272	Ductal	G3	37	pT4d	pN3a	cM1	IV	Neg/Neg/Neg
61/A/25.8/IND	583	Ductal	Unk	60	pT4b	pN1	cM0	IIIB	Unk/Unk/Unk
	554	Ductal	Unk	60	pT4b	pN1	cM0	IIIB	Unk/Unk/Unk
70/A/33.2/TWN	1231	Invasive, NOS	G3	16	pT1c	pN1	NA	Unk/≥IIA	Unk/Unk/Unk
55/O*/38.5/BRA	485	Ductal	G2	22	cT2	NA	NA	Unk/≥IIA	Pos/Pos/Pos
53/W/31.6/RUS	1049	Other	G1	5	pT1a	pN0	cM0	IA	Unk/Unk/Unk
65/W/39.1/RUS	184	Other	G3		pT2	pN0	cM1	IV	Neg/Neg/Pos
	184	Other	G3		pT2	pN0	cM1	IV	Neg/Neg/Pos
82/W/33.1/TUR	470	Ductal	Unk	28	cT2	NA	cM0	Unk/≥IIA	Neg/Neg/Neg
66/W/45.2/CAN	722	Ductal	G2	18	pT1c	pN0	cM0	IA	Pos/Pos/Neg
70/W/31.7/USA	1374	Invasive, NOS	G1		NA	NA	NA	Unk	Pos/Pos/Neg
	1374	Invasive, NOS	G1		NA	NA	NA	Unk	Pos/Pos/Neg
74/W/29.5/USA	1120	Lobular	G1		pTX	pN0	NA	Unk	Pos/Pos/Neg
81/W/32.1/USA	434	Papillary	G1	5.5	pT1b	pN0	cM0	IA	Pos/Pos/Neg
71/W*/44.0/USA	638	Ductal	G2	34	pT2	pN1	cM0	IIB	Pos/Pos/Neg
62/A/23.3/USA	590	Lobular	G2		NA	pN1	NA	Unk/≥IIA	Pos/Pos/Neg
65/W*/28.0/USA	36	Ductal	G2	32	cT2	NA	NA	Unk/≥IIA	Pos/Neg/Neg
68/W/32.1/USA	169	Ductal	G3	20	pT1c	pN0	cM0	IA	Pos/Pos/Neg
Placebo									
(b) (6) 59/W/42.9/DEU	451	Ductal	G3	20	pT1c	pN0	cM0	IA	Pos/Pos/Neg
64/W/26.8/DEU	1386	Lobular	Unk	30	cT2	NA	pM1	IV	Pos/Pos/Pos
63/W/38.1/ITA	614	Ductal	G2	10	pT1b	pN1a	cM0	IIA	Pos/Pos/Neg
61/W/32.1/POL	842	Ductal	G2	25	pT2	pN1mi	NA	Unk	Pos/Pos/Neg
69/W/30.4/POL	918	Ductal	G2	20	pT1c	pN0	cM0	IA	Pos/Pos/Neg
61/W/37.6/SRB	164	Ductal	G2	8	pT1b	pN1	cM0	IIA	Pos/Pos/Neg
72/W/34.9/FRA	396	Ductal	G3	10	pT1b	pN0	cMo	IA	Pos/Pos/Neg
55/W/35.0/GBR	240	Mucinous (colloid)	G1	26	pT2	pN0	cM0	IIA	Pos/Pos/Neg
(b) (6) /66/A/29.1/IND	782	Ductal	G2	25	pT2	pN0	cM0	IIA	Pos/Pos/Neg
/64/O/21.0/ZAF	257	Ductal	Unk	Unk	NA	NA	NA	Unk	Unk/Unk/Unk
	316	Ductal	Unk	Unk	NA	NA	NA	Unk	Unk/Unk/Unk
/59/A/23.2/TWN	561	Ductal	G3	60	cT3	cN0	cM0	IIB	Neg/Neg/Neg
/56/W*/35.0/BRA	702	Invasive, NOS	G2	22	pT2	pN0(i+)	cM0	IIA	Neg/Neg/Neg
/67/W/33.6/RUS	146	Lobular	Unk	34	pT2	pN2a	cM0	IIIA	Unk/Unk/Unk
/60/W/39.6/CAN	1184	Ductal	G3	30	pT2	pN0	cM0	IIA	Pos/Neg/Neg
/77/34.7/USA	953	Ductal	G3	49	pT2	pN1	cM0	IIB	Pos/Pos/Neg
	933	Ductal	G3	49	pT2	pN1	cM0	IIB	Pos/Pos/Neg
/67/B/28.4/USA	1659	Ductal	Unk	4	cT1a	NA	NA	Unk	Pos/Neg/Pos
/73/B/44.5/USA	5	Ductal	G3	20	cT1c	pN0	cM0	IA	Neg/Neg/Neg
/68/B/37.5/USA	1141	Ductal	G2	9	pT1b	pN0	NA	Unk	Unk/Unk/Unk
/64/B/48.4/USA	1282	Ductal	G2	20	cT1c	NA	NA	Unk	Pos/Pos/Neg
/54/W*/31.4/USA	325	Ductal	G3	33	cT2	pN1	cM0	IIB	Pos/Neg/Pos
	325	Ductal	G3	33	cT2	pN1	cM0	IIB	Pos/Neg/Pos

* Hispanic/Latino ethnicity

Source: Source: NDA 206321 PMR, Breast Cancer Report, Appendix 6, Tables 1 and 2

13.2.4 Acute Pancreatitis

The following table summarizes AEs of acute pancreatitis as reported by the investigator (PT: 'pancreatitis acute') in the Victoza group that were not confirmed (N) and confirmed (Y) by the EAC.

Table 89. Summary of AEs (Investigator-Reported) of Acute Pancreatitis and Adjudication Status, Victoza-Treated Subjects

Subject ID	EAC-confirmed	Symptoms	Pancreatic enzymes	Imaging
(b) (6)	N	abdominal pain, vomiting, and diarrhea	lipase 301 U/L (ref. range 8 - 57 UI/L)	MRI normal CT several nonspec pulm micronodules and liver dysmorphia w/ homogenous steatosis, prob pancreas lipoma Endoscopic U/S - mod incr pancreas size and hepatic steatosis discretely inhomogeneous
	N	epigastric pain, pain worse after eating, nausea, vomiting and rapid pulse	Amylase 54 U/L (ref. range 25-115) Lipase 73 U/L (ref. range 114-286)	Abdominal u/s – normal CT abdomen -pancreatitis
	N	none	lipase 2420 U/L (normal range 0.00-190.00) amylase 1050 U/L	None (occurred post-ERCP)
	N	Unknown	Not reported	Not available
	N	rt upper abd pain; hematochezia w/ abd pain, distension & periumbilical ecchymosis	lipase 1599 U/L (ref. range 23-300) amylase 178 U/L (ref. range 30-110)	CT - No suggestive changes of pancreatitis.
	N	Abd pain	alpha amylase 221 U/L	U/S – "compaction of the pancreas"
	N	Abd pain, nausea	Lipase 690.2 U/L (ref. range 16.6-63.0) Amylase 255 U/L (ref. range 28.0-100-0)	CT - negative for acute pancreatitis
	N	sharp stabbing epigastric abdominal pain, radiating to the back, assoc w/ nausea	Lipase peak 761 U/L (73-286)	CT – no obvious abnormalities in pancreas
	N	diarrhea	lipase 7919 U/L, 12525 U/L, 5690 U/L, 3458 U/L, 1268 U/L, 1166 U/L, 1079 U/L, 1190 U/L, 965 U/L (73-393 U/L)	CT - enlargement of the head of the pancreas MRI – no obv pancreatic mass
	Y	epigastric pain	lipase 1328.2 U/L (13 - 60) amylase 1466 ug (58-283)	CT - mild inflammatory changes around the head of the pancreas, mild stranding
	Y	Nausea, vomiting, abd pain	amylase 141.0 U/L Lipase 80.0 U/L (Note: adjudication package described amylase=442 U/L (28-110) and lipase=924 U/L	u/s – no results avail

Subject ID	EAC-confirmed	Symptoms	Pancreatic enzymes	Imaging
			(< 67)	
(b) (6)	Y	Chest pain	lipase 740 U/L (Ref. range 0 - 60)	u/s – pancreas largely obscured, small amounts of perinephric fluid and trace ascites
	Y	Abd pain, nausea	amylase 130 U/L (ref. range 25-115), lipase 872 U/L (ref. range 50-245)	u/s- pancreas tail not well seen, rest of gland normal CT - minimal stranding along the inf margin of pancreas head, "potentially very early or mild pancreatitis could be considered, but it was not particularly prominent"
	Y	Abd pain	lipase 146 U/L (ref. range 23-200)	CT - Acute inflammatory stranding of mesentery surrounding pancreatic body and head
	Y	Abd pain	Lipase 8396 U/L (ref. range 73-393 U/L)	CT – no acute process (verbatim: acute on chronic pancreatitis)
	Y	Periumbilical pain, nausea	Not reported	CT- focal pancreatitis
	Y	Nausea, abd pain	lipase 2552 U/L (ref. range: 15-51)	CT - mild diffuse prominence of the pancreas with pancreatic edema
	Y	Severe abd pain, nausea, vomiting	amylase 3951 U/L (ref. range 25-115) lipase > 30000 (normal range 65-230)	u/s – pancreas not described

Source: Review created from LEADER case narratives and adjudication packages

13.2.5 MedDRA Search of Gallbladder Disease

If a subject had an event of gallstones (perhaps diagnosed incidentally) but this event was not considered by the investigator to be serious or an acute gallstone MESI, it would not be recorded in the sponsor's analyses of acute gallstone disease. There were a number of AEs identified that were not captured in the sponsor's search because they were not considered SAEs or MESIs. All gallbladder-related AEs (according to the MedDRA search), regardless of SAE/MESI status, are included below:

Table 90. Gallstone-Related AEs, Regardless of SAE/MESI Status

	Victoza		Placebo	
PT	n	%	n	%
All events	170	3.6	121	2.6
Cholelithiasis	84	1.8	76	1.6
Cholecystitis acute	36	0.8	21	0.4
Cholecystitis	15	0.3	12	0.3
Cholecystitis chronic	13	0.3	7	0.1
Biliary colic	8	0.2	3	0.1
Cholangitis acute	4	0.1	0	0
Bile duct stone	3	0.1	1	<0.1
Cholecystitis infective	3	0.1	1	<0.1
Gallbladder cholesterolosis	3	0.1	1	<0.1
Cholangitis	2	<0.1	4	0.1
Cholecystectomy	2	<0.1	3	0.1
Gallbladder disorder	2	<0.1	2	<0.1
Blood bilirubin increased	2	<0.1	1	<0.1
Abnormal faeces	2	<0.1	0	0
Jaundice	2	<0.1	0	0
Jaundice cholestatic	1	<0.1	2	<0.1
Biliary fistula	1	<0.1	0	0
Cholestasis	1	<0.1	0	0
Gallbladder non-functioning	1	<0.1	0	0
Gallbladder perforation	1	<0.1	0	0
Hyperbilirubinaemia	1	<0.1	0	0
Hyperplastic cholecystopathy	1	<0.1	0	0
Post cholecystectomy syndrome	1	<0.1	0	0
Biliary dyskinesia	0	0	2	<0.1
Bile duct stenosis	0	0	1	<0.1
Biliary cirrhosis	0	0	1	<0.1
Biliary sepsis	0	0	1	<0.1
Biliary tract infection	0	0	1	<0.1
Faeces pale	0	0	1	<0.1
Gallbladder abscess	0	0	1	<0.1
Gallbladder empyema	0	0	1	<0.1

Source: Reviewer created from LEADER datasets

13.3 Other Narratives

13.3.1 Renal Deaths (Victoza-Treated Subjects)

13.3.1.1 Investigator-reported acute renal failure events with fatal outcome

- Subject (b) (6) developed renal failure in the setting of lower extremity gangrene and sepsis. He died from cardiopulmonary arrest approximately 5 weeks after leg amputation. (EAC determination: non-CV death; *post hoc* classification: non-CV procedure or surgery)

- Subject (b) (6) had been diagnosed with new-onset macroalbuminuria (diabetic nephropathy) approximately 9 months prior to death. One day prior to death he was hospitalized for weakness and was found to have a worsening of congestive heart failure and renal failure. He died due to circulatory-respiratory failure. (EAC determination: CV death)

- Subject (b) (6) was hospitalized for acute renal failure 2 days after fever and a recent urinary tract infection. He died 17 hours after admission from cardiorespiratory arrest. Autopsy revealed necrotic bowel suggesting acute mesenteric ischemia, small multiple hemorrhages in the renal cortex, and polycystic kidneys. (EAC determination: CV death)

- Subject (b) (6) was hospitalized for acalculous cholecystitis and heart failure and underwent percutaneous drainage of the gallbladder; subsequently, the subject developed multisystem organ failure. Hemodialysis was started and the subject was stabilized, but she died 1 week later. Cause of death was stated as septic shock due to cholecystitis, acute renal failure, and heart failure. (EAC determination: non-CV death; *post hoc* classification: infection (includes sepsis))

- Subject (b) (6) was admitted to the hospital for rectal resection due to carcinoma of the rectum and had extensive blood loss and hypotension during the surgery resulting in acute renal failure. The subject remained on dialysis until his death approximately 1 month later. Cause of death was considered to be intra-abdominal bleeding and multi-organ failure after the rectal cancer operation. (EAC determination: non-CV death; *post hoc* classification: unclassifiable)

- Subject (b) (6) developed necrotizing infection of vagina and ureters attributed to aortic atherosclerotic occlusion. This was associated with complete loss of function of the left kidney. Ureteral ligation with bilateral percutaneous nephrostomy was performed. The subject died after several months in the hospital due to massive ulcer. (EAC determination: non-CV death; *post hoc* classification: other non-CV death)

- Subject (b) (6) developed cardiogenic shock after a myocardial infarction and was discharged after medical treatment, but died approximately 5 days later due to myocardial infarction and acute renal failure (no further information was available). (EAC determination: CV death)

- Subject (b) (6) was admitted to the hospital for acute kidney injury on chronic renal failure and worsening of existing heart failure (had several exacerbations in the prior years), and died 1 week later. (EAC determination: CV death)

- Subject (b) (6) developed ACS, cardiogenic shock, and acute kidney injury after having an upper GI bleed (after having been on study drug for almost 4 years). After 5 days with a grave prognosis, the family decided to withdraw support and the subject died. (EAC determination: non-CV death; *post hoc* classification: hemorrhage)

- Subject (b) (6) had a history of chronic renal insufficiency (creatinine 1.95 mg/dL 2 months prior to the start of the drug and 2.41 mg/dL on first day of treatment). Three weeks into the trial, the subject complained of swelling of face, body, and limbs, reduced urine output, and breathlessness and cough. She reportedly refused dialysis. One week later, serum creatinine was 5.7 mg/dL, and she died within 1 week. The cause of death was assumed to be acute renal failure. (EAC determination: non-CV death; *post hoc* classification: renal)

- Subject (b) (6) died of "acute renal failure" 7 months into the trial. No further information was available. (EAC determination: non-CV death; *post hoc* classification: renal)

- Subject (b) (6) developed acute renal failure and hemodynamic shock in the setting of sepsis, bacterial liver abscess, and biliary fistula. The subject died after approximately 10 days in the hospital due to all of the above. (EAC determination: non-CV death; *post hoc* classification: infection (includes sepsis))

- Subject (b) (6) had a worsening of renal failure during the trial period and started hemodialysis approximately 2 years into the trial. Approximately 16 months later she died due to "worsening of renal failure". No further information was available. (EAC determination: non-CV death; *post hoc* classification: renal)

- Subject (b) (6) presented with acute renal failure, gangrenous foot, and cardiopulmonary arrest 1 year after the trial drug was stopped. The subject died at home due to the above. No other information was available. (EAC determination: unknown)

- Subject (b) (6) was hospitalized due to pedal edema and dyspnea approximately 2 years into the trial. The cause of death was reported as uremic syndrome due to chronic renal failure. No other information was available. (EAC determination: non-CV death; *post hoc* classification: renal)

- Subject (b) (6) had increased creatinine, hypotension, and recurrent ventricular tachycardia post-operatively from coronary artery bypass graft surgery and died approximately 1 week after surgery. (EAC determination: CV death)

- Subject (b) (6) had a history of chronic renal failure. He was admitted to the hospital approximately 2.5 years into treatment with altered mental status attributed to acute renal failure, as well as diabetic foot ulcer, osteomyelitis, sepsis, rhabdomyolysis, and non-ST elevation myocardial infarction. Hemodialysis was refused and the subject died after approximately 1 week due to multi-organ failure and renal failure. (EAC determination: non-CV death; *post hoc* classification: unclassifiable)

- Subject (b) (6) developed C. difficile colitis and acute GI bleed after 3 years on study drug, and ultimately hemodynamic shock and cardiac arrest. Resuscitation was ultimately stopped because of poor prognosis and the subject died. Acute renal failure was described as part of the overall presentation. (EAC determination: non-CV death; *post hoc* classification: hemorrhage)

13.3.1.2 EAC-confirmed renal deaths (*post hoc* categorization)

In addition to 4 of the subjects above with acute renal failure leading to death according to the investigator and *post hoc* categorization of 'renal' death (based on EAC determination), the following Victoza-treated subjects were also considered to have died due to renal causes according to the EAC [investigator-reported preferred term (PT) noted in each narrative]:

- Subject (b) (6) (PT: Chronic kidney disease) had a history of chronic renal failure. Approximately 6 months into the trial he was observed to have a creatinine of 7.68 mg/dL and potassium of 6 mmol/L on routine clinical testing, reflecting worsening of chronic renal failure. He refused dialysis. Over the course of the next 8 months, creatinine increased. He had an episode of gastroenteritis 10 months after starting the drug with vomiting and loose stool with creatinine of 19.9 mg/dL. Although the subject started receiving dialysis, he died 1 month later, reportedly in association with a fever. No autopsy was performed.

- Subject (b) (6) (PT: Death) had several AEs of renal dysfunction as well as an event of worsening dilated cardiomyopathy during the trial prior to the fatal event. Two and ½ years after starting the trial and 4 months after discontinuing drug the subject was hospitalized for kidney problems, swelling, and shortness of breath. She died 2 weeks later.

- Subject (b) (6) (PT: Chronic kidney disease) was hospitalized for renal failure 3.5 years into the trial. He refused renal replacement therapy and died 1 week later.

- Subject (b) (6) (PT: Chronic kidney disease) was hospitalized after approximately 6 months of treatment with epigastric pain and vomiting and found to have an aortic aneurysm, which was treated conservatively, and creatinine of 5.6 mg/dL (baseline: 4.1 mg/dL). Dialysis was refused and 2 months later the subject died.

- Subject (b) (6) (PT: Chronic kidney disease) had progressive worsening of chronic renal failure over the course of several years but refused dialysis and died at home.

- Subject (b) (6) (PT: Chronic kidney disease) had been treated for 2 years prior to the event and had a history of chronic renal failure. He presented with a 1 month history of diarrhea and vomiting and creatinine of 5.07 mg/dL. The subject refused renal replacement therapy. Several weeks later he was hospitalized with community acquired pneumonia, vomiting, diarrhea, and uremia and died (cardiopulmonary resuscitation was not performed).

- Subject (b) (6) (PT: Chronic kidney disease) had a history of chronic renal failure on peritoneal dialysis. Two and ½ months after starting the trial, she died at home. No autopsy was performed.

13.3.2 Hepatic Events (Victoza-Treated Subjects)

13.3.2.1 Subjects with Selected Hepatic SAEs/MESIs

- Subject (b) (6) was a 66 year old male. After the subject had been treated for approximately 20 months, a severe event of "nonviral A,B,C acute hepatitis" associated with "acute hepatic insufficiency" and "right paracardiac pneumonia" was reported. Medical history included hepatic steatosis, obesity, myocardial infarction, and transient ischemic attack. The subject reported no history of pancreas or gallstone disease.

  The subject presented with symptoms of diffuse abdominal pain, emesis, chills, and jaundice along with hyperemia of the pharynx and enlarged liver, and was hospitalized. AST was 1696 U/L (ref: 2-46), ALT 4114 U/L (ref: 2-49), total bilirubin 5.71 mg/dL (ref: 0-1.0), and direct bilirubin 4.55 mg/dL (ref: 0-0.3). Three days later, AST was 616 U/L, ALT 2713 U/L, total bilirubin 5.05 mg/dL, and direct bilirubin 3.59 mg/dL. Hepatitis A, B, and C viral serologies were negative. Lung radiography showed 4/6 cm "right paracardiac pneumonic condensation". Epstein Barr virus and cytomegalovirus testing were not performed. Eight days later, AST was 91 U/L, ALT was 447 U/L, and total bilirubin was 1.52. An abdominal echography showed enlarged liver with inhomogeneous structure and no dilatation of the intrahepatic biliary ducts.

  The subject recovered and was discharged from the hospital. According to the investigator the acute hepatitis was caused by an unidentified infectious agent other than hepatic A, B, or C viruses.

  Action taken to the trial drug was product withdrawn temporarily and was re-introduced 2 weeks later at the same dosage; the adverse events did not re-appear.

- Subject (b) (6) was a 58 year old female treated for approximately 2 years and 9 months. Seven months after discontinuing the drug, the subject died of hepatic failure. Medical history included hepatitis C, gout, cocaine abuse, methamphetamine abuse, heart failure New York Heart Association (NYHA) class II, current smoker, alcohol abuse, liver cirrhosis, splenomegaly, chronic obstructive pulmonary disease, and rheumatoid arthritis. The subject had a history of heavy alcohol use, but after a rehabilitation program had not used drugs or alcohol. The subject had previously been admitted to the hospital in 2 months before drug discontinuation for anasarca. Since then on 2 occasions, the subject was admitted for diuretic medication non-adherence and severe protein calorie malnutrition secondary to anasarca. Several weeks before the fatal event, the subject went to the emergency room and was diagnosed with acute dehydration, acute renal failure, and acute hypotension; she recovered and was discharged to a long term care facility for assistance with daily living and medication compliance. However, approximately 2 weeks later the subject was admitted to the hospital from the skilled nursing facility in a hepatic coma. During admission, the subject was in and out of hepatic failure. The subject wanted comfort measures only, no life support and she died after 1 week. No autopsy was performed.

- Subject (b) (6) was a 67 year old female who had been treated with Victoza for over 2 years at the time of the event. Medical history included type 2 diabetes (15.8 year history), BMI 41.3 kg/m^2, hypertension, hypercholesterolemia, coronary artery disease, rheumatoid arthritis, ankylosing spondylitis, osteoporosis, nephropathy/moderate renal insufficiency, gout, ischemic stroke, and gallstone disease. ALT and total bilirubin values were within normal limits throughout the trial. She presented with hyperkalemia and weakness, as well as volume overload and shortness of breath. Diuresis did not improve her symptoms. She was also found to have a urine culture positive for VRE and was thought to have sepsis. Over the course of the week-long admission, renal and liver function continued to decline and the subject subsequently died. Primary diagnoses were hepatorenal syndrome secondary to cryptogenic cirrhosis, severe hepatic encephalopathy, respiratory failure, and urinary tract infection secondary to VRE with sepsis.

- Subject (b) (6) had a non-serious MESI of acute hepatitis on trial day 544. This was a 64 year old female with a history of T2DM, obesity, hypothyroidism, hypercholesterolemia, coronary artery disease, and cholecystectomy. Local laboratory data were obtained when the subject complained that she “felt bad”: ALT was 1213 U/L, AST was 876 U/L, and GGT was 54 U/L (5-36). An abdominal ultrasound was normal. The drug was withdrawn temporarily and follow-up labs were ALT 24 U/L, AST 21 U/L, and GGT 44 U/L. She was seen by a specialist who diagnosed “probable drug induced acute hepatitis”. She was restarted on Victoza at a dose of 0.3 mg, which was eventually increased to 1.2 mg. Nine months later she had another drug holiday for an event of acute gastroenteritis, but ultimately was

increased to 1.8 mg for the last 1.5 years of the trial. ALT obtained at the clinical site was within normal limits throughout the trial.

- Subject (b) (6) had a history of non-alcoholic steatohepatosis and recent hospitalization for hypercortisolism due to ACTH-producing pituitary tumor; several weeks later he "collapsed due to drowsiness", was found to have an ammonia level of 94 µmol/L (ref. < 40) and was diagnosed with "hepatic encephalopathy". The subject was treated with lactulose and recovered from event.

- Subject (b) (6) had been diagnosed with hepatic cirrhosis after about 2 years of treatment in the trial and presented with decompensated chronic liver disease including hepatic encephalopathy. Although he recovered from the acute event, he died 6 months later due to decompensated liver disease (in addition to the hepatic encephalopathy AE, an AE of hepatopulmonary syndrome was also reported).

- Subject (b) (6) had a history of chronic hepatitis C and current alcohol abuse prior to the trial. After approximately 10 months in the trial, he was diagnosed with metastatic hepatocellular carcinoma; 2 months later he was hospitalized with hepatic encephalopathy and died days later.

13.3.2.2 Subjects with Elevations in Liver Parameters

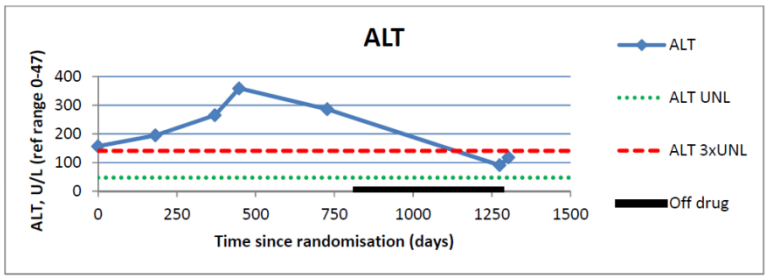
- Subject (b) (6): 56 yo male; on trial day 734, ALT increased to 831 U/L (>10x ULN). For the remainder of the visits, ALT was within normal reference range. The subject remained on the drug.

- Subject (b) (6): 66 yo female with remote history of cholecystectomy for gallstone disease. On trial day 39, a serious adverse event of "Hospitalization for worsening increased hepatic parameters – GGT 3,58 Ukat/l (ref range: 0,14-0,68)" was reported. Hepatitis markers and serology was negative (no further details) and an ultrasound showed moderate hepatic steatosis. On trial day 1277, ALT was increased to 246 U/L (>5x UNL). TBL, amylase, and lipase values were within normal reference ranges throughout the trial. The subject stopped trial treatment according to protocol on the day before the ALT increase. According to the investigator, no signs and/or symptoms were reported in relation to the observed increase in ALT. The subject was referred to general practitioner and additional local laboratory testing 7 mos later showed ALT, AST, and ALP within normal limits and GGT mildly elevated. No imaging or liver biopsy was performed. According to the investigator, at the time of the observed increase in ALT the subject had no other known potential etiologies or risk factors that could explain the observed increase in ALT.

- Subject (b) (6): 54 yo male with a history of hepatic steatosis and ALT 79 U/L at randomization. On trial days 347 and 711 ALT values were 193 U/L (>3x ULN) and

384 (>5x ULN), respectively. An ultrasound performed on day 722 confirmed fatty liver, and the subject was referred to a hepatologist. Additional local laboratory testing showed ALT 74 U/L (reference range <41), GGT 51 U/L (reference range 5-61), and negative anti-HCV. For the remainder of the trial visits ALT values were within the normal reference range.

- Subject (b) (6): 63 yo male with a history of cholecystitis and cholelithiasis with cholecystectomy and ALT at randomization 157 U/L. For the remainder of the visits, ALT was increased with a peak value of 359 (>5x ULN) on trial day 448. Total bilirubin and amylase were within normal reference ranges throughout the trial and lipase was normal at randomization, with mildly increased values thereafter. As shown in the figure, although ALT was decreasing on drug, values did not decrease to baseline until after study drug discontinuation:



Source: ISS, Appendix 7.14, Figures for subject (b) (6)

- Subject (b) (6) 73 yo female; on trial day 1597 (approximately 2.5 years after permanently discontinuing drug), the subject experienced ALT 583 U/L (>10x ULN) and total bilirubin 3.9 mg/dL (>2x ULN), symptoms of abdominal pain and jaundice, in association with "cholangitis" (according to adjudication package; an investigator co-reported pancreatitis AE was not confirmed by pancreatitis EAC subcommittee).

- Subject (b) (6): 57 yo female with a history of cholecystitis; ALT was 249 (>5x ULN) at randomization. Additional local laboratory testing at approximately 1 mo, 3 mo, and 3.5 mo showing ALT values of 256, 75 and 46 U/L (reference range 0-50) and ALP values of 142, 122, and 118 U/L (reference range 30-120), respectively. Ultrasound of abdomen suggested fatty liver and ANA titer was positive. ALT was within normal limits the rest of the trial.

- Subject (b) (6): 57 yo male; at randomization ALT was 98 U/L (>2x ULN) and increased to 886 (>10x ULN) on day 182. The subject was referred to a specialist at a gastroenterology clinic. Additional local laboratory testing showed ALT of 56 U/L (reference range 5-55), ALP within normal reference range, and GGT value 98 U/L (reference range reference range 3-73). Ultrasound showed fatty liver. For the rest of the trial both trial and additional local laboratory testing showed ALT values

mildly increased. TBL was within normal reference range throughout the trial. Amylase and lipase values were increased throughout the trial.

- Subject (b) (6): 67 yo male with a history of gallstones and hepatic steatosis; on trial day 366, ALT was 881 U/L (>10x ULN) and total bilirubin was 2.8 mg/dL (>2x ULN). For the remainder of the trial visits, ALT and total bilirubin were within normal reference ranges. No signs and/or symptoms were reported in relation to the observed increase in liver parameters. No additional laboratory testing, imaging, or liver biopsy was performed in relation to the increase. The subject did not receive any treatment for the increase and continued on trial product without any changes in dosing.

- Subject (b) (6) 55 yo female; approximately 2 years into the trial the subject was diagnosed with acute cholecystitis due to cholelithiasis. Trial product was withdrawn temporarily. After approximately 3 years in the trial, ALT was increased to 262 U/L (>5x UNL) and amylase was 165 U/L. Additional local laboratory testing 2 wks later showed ALT 47 U/L (ref. <33), AST 27 U/L (ref. <32), and TBL 0.83 mg/dL (ref. <1.2mg/dL). ALT was within normal reference range when next checked approximately 6 months later. Amylase values were mildly increased throughout the trial (<3x ULN).

- Subject (b) (6): 69 yo female; on trial day 185, ALT was increased to 235 U/L (=5x UNL) associated with nausea and abdominal pain. Of note, she had an SAE of acute pulmonary edema 4 months prior to the event of 'elevated ALT' (on trial day 54). Study drug was discontinued due to the nausea (days 185 to 729) and at the subsequent trial visits off-drug, ALT was within normal reference range. She restarted treatment approximately 1.5 yrs after the event for a 9.5 mo period (days 730-1016) but had no further laboratory assessments done during that period although she had several SAEs of acute pulmonary edema, congestive heart failure, and renal failure during that time. The subject died (sudden death) on day 1017. The 2 experts in liver disease agreed that this event of increased ALT was "possibly" related to drug, given the positive dechallenge and no further liver evaluations once she was rechallenged with drug.

- Subject (b) (6) 60 yo male with normal ALT and slightly elevated total bilirubin (1.2 mg/dL) at randomization. The subject was treated for 3.5 years and then stopped treatment according to the protocol, at which time ALT was within normal range and total bilirubin was 1.8 mg/dL. The subject was seen at that time by his general practitioner due to fatigue and sleep disturbance; a CT scan and biopsy showed pancreatic adenocarcinoma with metastasis to the liver. One week later, ALT was 217 U/L (>3x ULN) and total bilirubin was 6.1 mg/dL (>2x ULN).

- Subject (b) (6) 76 yo male with history of gallstone disease and cholecystitis; at randomization ALT was 312 U/L (>5x ULN) and total bilirubin was mildly increased

(1.5 mg/dL). Local laboratory testing 10 days later showed decreasing ALT to 73 U/L. ALT and total bilirubin was within normal reference range throughout the trial (on treatment).

- Subject (b) (6): 68 yo male; on trial day 345 the subject had an abscess on the right knee removed and was treated with vancomycin, ertapenem, and minocycline. On trial day 365, ALT was increased to 237 U/L (>5x UNL). For the remainder of the trial visits, ALT was within normal reference range (on treatment). Lipase was mildly elevated throughout the trial.

- Subject (b) (6): 60 yo male; on trial day 361 ALT was increased to 406 U/L (>5x ULN). The investigator reported nausea, occasional abdominal pain, and shortness of breath in in relation to the observed ALT increase and the subject was referred to additional local laboratory testing and evaluation. Three days later, "Cardiac failure congestive" was reported. Additional local laboratory testing on showed decreasing ALT 127 U/L (reference range 5-52) and normal values of AST, ALP, and TBL. The subject tested positive for hepatitis C antibody. Trial treatment was withdrawn.

- Subject (b) (6) 54 yo female with a history of drug and alcohol abuse, hepatitis C, and cirrhosis had an ALT of 211 U/L (>3x ULN) and total bilirubin 1.2 (>2x ULN) at randomization. ALT fluctuated between 80 and 185 U/L and total bilirubin increased to 3.6 mg/dL then decreased to 2.1 mg/dL at subsequent study visits. She was followed periodically by a gastroenterologist. Ultrasounds showed gallbladder distention and mild chronic pancreatitis.

13.3.3 Subjects on Victoza with 'Immune Complex Disease' SAEs

- Polymyalgia rheumatica: Subject (b) (6) was a 77 year old male with a history of diabetes, hyperlipidemia, non-proliferative retinopathy, hypertension, hemorrhagic stroke, and previous smoker. The subject was hospitalized after about 6 months in the trial with 3 weeks of pain in muscles and joints. C-reactive protein was 87 mg/dL (ref. < 8) and erythrocyte sedimentation rate was 64 mm (ref. < 20). He was diagnosed with polymyalgia rheumatica and treated with prednisolone. Biopsy of the temporal artery was negative.

- Chronic pigmented purpura: Subject (b) (6) was a 62 year old male with a history of diabetes, sleep apnea, morbid obesity, hyperlipidemia, dysphagia, gastroparesis, chronic cough, gout, chronic anemia, microalbuminuria, cardiomyopathy, chronic renal failure, fatty liver, non-proliferative retinopathy, peripheral neuropathy, and myocardial infarction. The subject developed a rash on his legs after approximately 3 years of treatment (approximately 1 week after permanent discontinuation of drug). He received an in-hospital evaluation during a hospitalization for congestive heart failure, and at that time it was attributed to a supratherapeutic INR (thought to be soft tissue hemorrhages). After hospitalization, he was again evaluated

because the rash progressively worsened. Skin biopsy showed pigmented purpuric dermatitis (Schamberg's disease).

- Granulomatosis with polyangiitis: Subject (b) (6) was a 73 year old male with a past medical history of diabetes, primary biliary cirrhosis, dyslipidemia, hepatic angioma, pulmonary hypertension, esophageal varices, portal hypertension, gastric ulcer, esophagitis, eczema, non-proliferative retinopathy, peripheral neuropathy, microalbuminuria, diabetic foot ulcer, coronary artery disease, hypertension, peripheral arterial disease, and a previous smoker. He was treated for 1 month with Victoza, after which it was permanently discontinued coincident with a pulmonary infection. Approximately 3 months later, the subject presented with a new pulmonary infection and was hospitalized 26 days later for exploration of the infection. A biopsy from the thorax suggested possible Wegener's disease. X-ray and CT scan showed infiltrates. Pulmonary biopsy showed focal angiitis. Antineutrophil cytoplasmic antibody was positive. After 1 year, the subject was considered recovered (had no further problems).

13.3.4 'Blindness' SAEs/MESIs in Victoza-Treated Subjects

- Subject (b) (6) ('blindness unilateral'): This 91 year old female subject was on study drug for almost 2 years when "blindness of the right eye" was reported. Medical history includes a 40-year history of T2DM, bilateral cataracts, bilateral glaucoma, and non-proliferative diabetic retinopathy. The subject developed right eye blindness due to glaucoma and ectopia lentis of the left eye.

- Subject (b) (6) ('diabetic blindness'): This 63 year old female was treated for approximately 1 year prior to the reported event of "diabetic related blindness, right eye". Medical history included a 19-year history of T2DM, proliferative retinopathy, and macroalbuminuria. She had 1 event of severe hypoglycemia approximately 8 months into the trial. On the day of the event, the subject complained of blurred vision and was suddenly unable to see. No further information was available. The subject did not receive treatment for the event, and the event was reported as not recovered.

- Subject (b) (6) ('blindness unilateral'): This 57 year old male subject was treated for approximately 7 months prior to the event, which was reported as "monocular vision loss, right eye". Medical history includes a 3-year history of T2DM, stroke, and high cholesterol. On the day of the event, the subject reported dizziness, vomiting, and onset of right blurred vision. Transient ischemic attack was ruled out and the diagnosis was changed to monocular vision loss. By report, the eye exam revealed a cataract. The subject was scheduled for cataract removal.

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/s/

JULIE K GOLDEN
07/17/2017

LISA B YANOFF
07/17/2017

CLINICAL REVIEW

Application Type	Supplemental NDA
Application Number(s)	22341
Priority or Standard	Standard
Submit Date(s)	October 25, 2016
Received Date(s)	October 25, 2016
PDUFA Goal Date	August 25, 2017
Division / Office	DMEP/ODE II
Reviewer Name(s)	Tania A. Condarco, M.D.
Review Completion Date	July 14, 2017
Established Name	Liraglutide injection
Trade Name	Victoza
Therapeutic Class	Glucagon-like peptide-1
Applicant	Novo Nordisk
Formulation(s)	Solution in a pre-filled, multi-dose pen
Dosing Regimen	Inject once daily at any time of day, independent of meals
Indication(s)	To improve glycemic control
Intended Population(s)	In adults with type 2 diabetes mellitus

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

This document contains the clinical efficacy and safety review of the cardiovascular, renal, and ophthalmological endpoints of the "Liraglutide effect and action in diabetes: evaluation of cardiovascular outcome results" trial, referred to as LEADER henceforth. Please refer to the reviews by Dr. Julie Golden (for non-thyroid safety review) and Dr. Shannon Sullivan (for thyroid safety review) for the review of additional safety parameters.

1.1 Recommendation on Regulatory Action

I recommend **approval** of this supplement for patients with established cardiovascular disease; this recommendation for approval is contingent on an acceptable safety evaluation and agreement on labeling. I defer to the review of Dr. Yanoff to determine the overall fulfillment of PMR #1583-9.

The recommendation for regulatory action in this review is based on the efficacy and safety evaluation of the cardiovascular, renal and ophthalmological safety and efficacy of LEADER. For a comprehensive risk/benefit analysis that incorporates all known efficacy and safety information, please refer to the cross discipline team leader memo written by Dr. Lisa Yanoff.

1.2 Risk Benefit Assessment

On October 25, 2016 Novo Nordisk submitted the prior approval efficacy supplement (PAS 027), containing the results of the LEADER study, to NDA 22341 (for liraglutide) to both fulfill the post-marketing requirement (PMR #1583-9) and to support a proposed new indication of reduction of the risk of major adverse cardiovascular events (MACE-defined in this study as a composite of cardiovascular death, non-fatal myocardial infarction or non-fatal stroke).

In the opinion of this reviewer, the LEADER trial provides adequate substantial evidence to demonstrate that liraglutide decreases the occurrence of MACE, including a reduction of cardiovascular death, in patients with type 2 diabetes mellitus and established cardiovascular disease, with somewhat limited information in two subgroups: United States and patients with risk factors for CV disease (as discussed below). Although the evidentiary standards to support an efficacy claim has typically relied on two or more clinical trials,[1] the FDA has previously relied on a single, well conducted and controlled study in circumstances where a single trial has provided "highly reliable and statistically strong evidence of an important clinical benefit, such as an effect on survival, and a

[1] Section 505 (d) of the Federal Food, Drug, and Cosmetic Act

confirmatory study would have been difficult to conduct on ethical grounds." [2] LEADER's adequate design is supported by the following features which minimized potential bias: 417 world-wide sites, double blinded design, randomization, use of a blinded Event Adjudication Committee to adjudicate events of interest and a pre-specified primary endpoint (of note secondary endpoints were not adjusted for multiplicity).

In addition, the overall trial conduct was adequate. Potential bias from sites with substantial (over a million dollars) financial interests was mitigated by the fact that only 1% of all randomized patients were randomized in these sites. Other trial components which mitigated potential bias included the lack of unblinding of trial results until trial completion (since LEADER did not have an interim efficacy analysis), and no identified changes to the protocol, adjudication charter, and statistical analysis plan while the trial was ongoing which would favor one treatment over another or affect the interpretation of data.

LEADER was a prospective, randomized, double-blinded, placebo-controlled, cardiovascular outcomes trial in 9,340 patients with type 2 diabetes and largely established cardiovascular disease. Following a mean duration of treatment of 3 years, compared to placebo, liraglutide ruled out a 30% relative increase in cardiovascular risk P<0.001), in accordance with the 2008 Guidance for Industry.[3] LEADER also showed superiority compared to placebo with a 13.2% relative risk reduction of MACE. MACE was experienced by 608 patients (13%) randomized to liraglutide and 694 patients (14.9%) randomized to placebo. There were 3.41 and 3.66 MACE events per 100 years observed in the liraglutide and placebo groups respectively resulting in a hazard ratio of 0.87 (95% confidence interval 0.78; 0.87; p=0.005 for superiority). Therefore, liraglutide prevented 0.25 major adverse cardiovascular events per every 100 patients treated for a year (or 2500 major adverse cardiovascular events per 1 million treated people for a year).

The robustness of the primary endpoint findings were supported by the overall low extent of missing data in the ascertainment of MACE. In total, ~3 % of patients (298 patients) did not complete the trial (meaning these patients did not have MACE, non-CV death or did not have direct contact with the investigator at the follow up visit). Of these patients, vital status was unavailable for 12 and 17 patients for liraglutide and placebo,

[2] Guidance for Industry. Providing clinical evidence of effectiveness for human drug and biological products. Silver Spring, MD: Food and Drug Administration, May,1998 https://www.fda.gov/downloads/Drugs/GuidanceCompliance%20RegulatoryInformation/Guidances/UCM078749.pdf+Providing+clinical+evidence+of+effectiveness+for+human+and+bio&client=FDAgov&site=FDAgov&lr=&proxystylesheet=FDAgov&output=xml_no_dtd&ie=UTF-8&access=p&oe=UTF-8

3 Guidance for Industry. Diabetes mellitus — evaluating cardiovascular risk in new antidiabetic therapies to treat type 2 diabetes. Silver Spring, MD: Food and Drug Administration, December, 2008 https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071627.pdf

respectively. Please see Dr. Hamilton's statistical review for the FDA's assessment of sensitivity analyses.

The reduction in MACE events was internally consistent (i.e., lower for liraglutide than placebo) when evaluating the time to the first event of the individual components of the composite MACE endpoint. In particular, liraglutide as compared to placebo resulted in a 21.7% relative risk reduction in cardiovascular death. There were 1.23 and 1.57 cardiovascular death events per 100 years observed on liraglutide and placebo respectively, resulting in a hazard ratio of 0.78 (95% confidence interval 0.66; 0.93; p=0.007). In this population, liraglutide prevented 0.34 cardiovascular deaths per every 100 patients treated for a year (or 3400 cardiovascular deaths per 1 million treated people for a year). Notably, the MACE findings persisted even after exploratory analyses which excluded the 30% of the cardiovascular deaths which resulted from an unknown cause and were presumed to be cardiovascular deaths.

The cardiovascular death findings drove the all-cause mortality findings, which showed benefit for liraglutide with a 15.3% relative risk reduction in liraglutide as compared to placebo. There were 2.14 and 2.52 death events per 100 years observed on liraglutide and placebo respectively, resulting in a hazard ratio of 0.85 (95% confidence interval 0.74; 0.97; p=0.017). In this population, liraglutide prevented 0.38 deaths per every 100 patients treated for a year (or 3800 deaths per 1 million treated people for a year).

The mechanism thru which liraglutide as compared to placebo, resulted in lower major cardiovascular events is unknown. However potential mediators to explain these findings include the larger: weight loss, decrease in HbA1c, and decrease in systolic blood pressure for liraglutide compared to placebo.

Despite the evidence of a cardiovascular protection shown in the overall findings of LEADER, it must be noted that there was a lack of a MACE benefit in two subgroups (the United States subgroup-which was not a pre-specified subgroup for analysis and patients with cardiovascular risk factors and age ≥ 60 years). These subgroups had a point estimate of the hazard ratios above 1, thereby suggesting possible inconsistencies in the effect for MACE across these subpopulations. Interpretation of the subgroup findings however must be done in light of multiple caveats including: that the US subgroup was not a pre-specified analysis, the population in these subgroups was a fragment of the overall population (i.e. the US subgroup was ~27% of randomized patients, while the cardiovascular risk factors group was ~19% of randomized patients), and the possibility that these findings may be explained by chance alone. The MACE findings in these subgroups was extensively discussed in the June 20, 2017 EMDAC meeting. Overall, I agree with the panel in that the overall primary MACE findings provides substantial evidence that liraglutide 1.8 mg reduces CV risk in type 2 diabetes.

In addition to the cardiovascular benefits discussed above, there is no conclusive evidence that liraglutide has a long-term beneficial effect on microvascular outcomes

including diabetic nephropathy. Further, treatment with liraglutide, as compared to placebo revealed potential evidence for worsening diabetic retinopathy (defined as a composite endpoint of diabetic blindness, vitreous hemorrhage and treatment with photocoagulation or intravitreal injections). However, these findings are in the context of a change in HbA1c of -1.2% for liraglutide and -0.8% for placebo after 36 months of treatment. Although the difference between treatment arms was mediated by numerical differences, (14 additional cases in liraglutide) - there was no clear evidence of increased rates of blindness associated with liraglutide use. Please see Dr. Chambers Ophthalmology consult review for further information.

The Division grappled with the contrasting findings of MACE as a whole compared to the MACE findings in the US and the MACE findings in the population without established cardiovascular disease, as discussed above. Overall, despite the subgroup findings and the lack of a clear mechanism to explain the reduction in MACE in the liraglutide group, the overall MACE findings remain; these suggest that use of liraglutide may result in a substantial cardiovascular benefit in patients with established cardiovascular disease.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None.

1.4 Recommendations for Postmarket Requirements and Commitments

None.

2 Introduction and Regulatory Background

2.1 Product Information

Liraglutide is a long acting glucagon-like peptide-1 (GLP-1) receptor agonist. The liraglutide mechanism of action for the lowering of glycemia is multifactorial. Liraglutide decreases glucagon secretion in a glucose dependent manner and activates the GLP-1 receptor resulting in a glucose dependent release of insulin. In addition, liraglutide also results in a delay in gastric emptying.

2.2 Tables of Currently Available Treatments for Proposed Indications

The recommended treatment of Type 2 diabetes mellitus includes life-style modifications in the early stages of the disease. Single or combination medical therapy

is often necessitated if hyperglycemia is uncontrolled with life-style modifications. A list of the available therapeutic options for type 2 diabetes is included in **Table 1**.

Table 1 – Therapeutic options for the treatment of type 2 diabetes mellitus

Pharmacologic Class	Approved Drug Products
Alpha-Glucosidase Inhibitors	acarbose; meglitol
Amylin Mimetics	Pramlintide
Biguanides	Metformin
Bile Acid Sequestrants	Colesevelam
Dopamine-2 Agonists	Bromocriptine
DPP-4 Inhibitors	Alogliptin; Linagliptin; Saxagliptin; Sitagliptin
GLP-1 Receptor Agonists	Albiglutide; Dulaglutide; Exenatide; Exenatide LAR, Liraglutide
Insulins and Insulin Analogues	Insulin Degludec; Insulin Detemir; Insulin Glargine; Insulin Isophane;
Meglitinides	Nateglinide; Repaglinide
SGLT2 Inhibitors	Canagliflozin; Dapagliflozin; Empagliflozin
Sulfonylureas	Chlorpropamide; Glimepiride; Glipizide; Glyburide (Glibenclamide); Tolazamide; Tolbutamide
Thiazolidinediones	Pioglitazone; Rosiglitazone

Despite the multiple pharmacological classes available for the treatment of diabetes, the disease progresses and may result in beta cell dysfunction and treatment failure over time.

Until December 2016, with the approval of the new indication for the reduction of the risk of cardiovascular death in patients with established cardiovascular disease for empagliflozin (trade name, Jardiance), there was no previously labeled antidiabetic medication shown to improve diabetic macrovascular complications. LEADER is the second study reviewed by the FDA which has suggested an improvement in cardiovascular outcomes.

2.3 Availability of Proposed Active Ingredient in the United States

Liraglutide is currently available as a single agent, for the treatment of type 2 diabetes and chronic weight management at different dosages and different trade names: Victoza is approved for the treatment of type 2 diabetes at doses of 1.2 mg or 1.8 mg daily. Saxenda is approved for the treatment of chronic weight management at a dose of 3 mg daily.

Liraglutide is also available as a fixed ratio combination with insulin degludec for the treatment of type 2 diabetes mellitus under the trade name Xultolphy 100/3.6.

2.4 Important Safety Issues With Consideration to Related Drugs

The important safety issues with long acting GLP-1 RA include: a boxed warning for thyroid C cell tumors, Warnings and Precautions for hypoglycemia, pancreatitis hypersensitivity reactions and renal impairment due to dehydration.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

In the 2008 Guidance for evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes,[4] the Division requested that Sponsors show that new antidiabetic therapies did not result in an unacceptable increase in cardiovascular risk.

Even though the liraglutide program was completed before the issuance of this guidance, the Division requested that all pending new drug applications also fulfill this guidance (including liraglutide). The Division standardized the approach of assessing cardiovascular safety in 3 applications that were affected by the new guidance (alogliptin, saxagliptin and liraglutide). These applications were asked to perform post hoc analyses of cardiovascular events using Standard MedDRA Queries to define 2 endpoints:

- First endpoint “Broad SMQ MACE” - included cardiovascular death and all preferred terms in the Standardized MedDRA Queries (SMQs) for “Myocardial Infarction” and “Central Nervous System Hemorrhages and Cerebrovascular Accidents.”
- Second endpoint “Custom MACE”- was a subset of “Broad SMQ MACE.” And included preferred terms that the three clinical reviewers for saxagliptin, alogliptin, and liraglutide independently felt represent events of myocardial infarction or stroke as reported by investigators.

The results of the pre-marketing MACE analyses are shown in **Table 2.**

In the April 2, 2009 advisory committee, the committee was asked to vote on the whether the Sponsor provided appropriate evidence of cardiovascular safety. In total 8 members voted “yes” and 5 members voted “no.” Despite the few events identified in the trials, the Division agreed with the Advisory Committees’ majority vote, that liraglutide fulfilled the spirit of the guidance and thus ruled out unacceptable excess cardiovascular risk relative to comparators, with a risk ratio of less than 1.8.

[4] https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071627.pdf

Table 2- MACE events in the pre-marketing liraglutide phase 2/3 programs

Table 12. Major adverse cardiovascular events (MACE) in the liraglutide phase 2/3 program (bolded values exceed the 1.8 goalpost described in the FDA diabetes cardiovascular guidance)

	Liraglutide events n (%)	Comparator events n (%)	Novo Nordisk Incidence ratio[1] (95% CI)	FDA exact Incidence ratio[2] (95% CI)	FDA fixed-effects Incidence ratio[3] (95% CI)
Total comparator	N=4257	N=2381			
Broad MACE					
Short-term population	51 (1.20)	35 (1.47)	0.87 (0.57, 1.34)	0.86 (0.55, 1.41)	0.83 (0.55, 1.27)
Long-term population	69 (1.62)	45 (1.89)	0.88 (0.61, 1.28)	0.90 (0.60, 1.36)	0.86 (0.59, 1.24)
Custom MACE					
Short-term population	13 (0.31)	13 (0.55)	0.72 (0.32, 1.61)	0.72 (0.30, 1.74)	0.63 (0.32, 1.24)
Long-term population	21 (0.49)	17 (0.71)	0.79 (0.41, 1.54)	0.80 (0.39, 1.64)	0.71 (0.39, 1.30)
Placebo comparator	N=4257	N=907			
Broad MACE					
Short-term population	51 (1.20)	9 (0.99)	1.04 (0.50, **2.16**)	1.04 (0.48, **2.17**)	0.86 (0.45, 1.65)
Long-term population	69 (1.62)	13 (1.43)	1.02 (0.54, **1.92**)	1.10 (0.56, **2.31**)	0.89 (0.50, 1.60)
Custom MACE					
Short-term population	13 (0.31)	3 (0.33)	0.80 (0.23, **2.83**)	0.78 (0.19, **4.76**)	0.52 (0.21, 1.25)
Long-term population	21 (0.49)	4 (0.44)	0.92 (0.30, **2.83**)	0.92 (0.28, **3.97**)	0.60 (0.26, 1.39)
Active comparator	N=4257	N=1474			
Broad MACE					
Short-term population	51 (1.20)	26 (1.76)	0.82 (0.51, 1.32)	0.82 (0.48, 1.33)	0.79 (0.49, 1.28)
Long-term population	69 (1.62)	32 (2.17)	0.85 (0.55, 1.29)	0.84 (0.53, 1.35)	0.83 (0.54, 1.27)
Custom MACE					
Short-term population	13 (0.31)	10 (0.68)	0.68 (0.28, 1.66)	0.68 (0.26, **1.83**)	0.60 (0.27, 1.31)
Long-term population	21 (0.49)	13 (0.88)	0.76 (0.36, 1.61)	0.76 (0.35, 1.72)	0.68 (0.34, 1.37)

Short-term population = randomized, controlled portions of all phase 2/3 trials up to the primary efficacy timepoint
Long-term population = short-term population plus controlled, open-label, voluntary extensions
[1]stratified, asymptotic Mantel-Haenszel
[2]stratified, exact
[3]stratified, fixed-effects Mantel-Haenszel meta-analysis with continuity correction of 0.5 for arms with zero MACE

Source: CDTL memo by Hylton V. Joffe, dated October 14, 2009.

During the original NDA review, FDA identified additional non-CV safety concerns prior to approval including: a potential risk of medullary thyroid carcinoma (MTC), identified in rodent carcinogenicity studies, and a risk of pancreatitis, identified in clinical studies of liraglutide and pharmacovigilance data for exenatide, a shorter-acting GLP-1 receptor agonist approved in 2005, and sitagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor approved for the treatment of T2DM in 2006.[5]

Victoza was approved on January 25, 2010 as an adjunct therapy to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus.

As part of the approval, the Sponsor had the following postmarketing requirement (1583-9), as described in the NDA approval letter:

> **1583-9**: A randomized, double-blind, controlled trial evaluating the effect of Victoza (liraglutide [rDNA origin]) injection on the incidence of major adverse cardiovascular events in patients with type 2 diabetes mellitus. This trial must also assess adverse events of interest including the long-term effects of Victoza

[5] Parks M, Rosebraugh C. Weighing Risks and Benefits of Liraglutide — The FDA's Review of a New Antidiabetic Therapy. New England Journal of Medicine 2010;362:774-7.

(liraglutide [rDNA origin]) injection on potential biomarkers of medullary thyroid carcinoma (e.g., serum calcitonin) as well as the long-term effects of Victoza (liraglutide [rDNA origin]) injection on pancreatitis, renal safety, serious hypoglycemia, immunological reactions, and neoplasms.

On April 8, 2015, Novo Nordisk filed a request for an extension for submission of the final report from April 2016 to November 2016. The request for extension was granted on October, 2015.

The current submission addresses the post-marketing requirement (PMR #1583-9) and was submitted as an efficacy supplement to support a new indication. The Sponsor also cross-references the Saxenda NDA 20632 in the submission.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The submission's integrity was evaluated by review of the changes in trial conduct, site inspections and evaluation of protocol deviations.

There were no apparent issues with data integrity or study conduct identified in the review of this application. The reviewer has included details regarding the changes to the study protocol, statistical analysis plan and EAC charter in the relevant sections of the review. Although there were multiple changes in each of these documents, it is important to note that LEADER did not have an interim assessment, and therefore remained blinded throughout its duration.

A summary of the important protocol deviations did not reveal changes that would favor one treatment over another or affect the interpretation of data.

In addition to the review of the documents related to trial conduct (described above), the following inspections of trial sites were performed by the Office of Scientific Investigations (OSI). Please refer to the OSI review for a discussion of specific inspection findings. The following sites were selected for inspection:

US SITES

- **Site 802/ Ahmed** (ranked #1 in site selection tool)**:** This site was had a high enrollment of patients (75). Investigator was inspected in 2014 and received a Warning Letter. In November 2015 he received an OAI which was downgraded to VAI. The sponsor did not audit this site.
- **Site 912 and 847/ Ismail-Beigi** (ranked #2 in site selection tool)**:** The sites enrolled 61 patients and have above average AEs and SAEs. The site has a previous complaint from 2009. The site has never been inspected, although the sponsor did audit the site,

- **Site 832/ Desouza** (ranked #5 in site selection tool): The site enrolled 82 patients, which is the highest US enroller. The site has been inspected, and the sponsor did not audit the site.
  - In the site inspection, it was noted that there were 3 patients who were listed as having a primary endpoint of non-fatal MI, with either conflicting investigator assessment or without much supporting data. These patients were:
    - Subject (b) (6) - (Placebo) Diagnosed with myocardial infarction on December 15, 2011 based on ECG. Investigator wrote that patient was asymptomatic and there was no other documentation to verify the primary endpoint. Review of the adjudication packet for this event revealed that both adjudicators felt that the ECG findings were consistent with a silent MI. One adjudicator felt these findings were due to inferior Q waves as compared to the ECG submitted dated 21 Dec 2010. Review of the ECGs does show differences in the inferior leads with a more prominent q wave on December 15, 2011, compared to the 2010 ECG.
    - Subject (b) (6) (placebo) – Patient was reported as having a non-fatal MI on March 18, 2014. During site investigation it was noted that the patient was reported as having elevated cardiac enzymes, but the inspector was unable to find any diagnosis of an MI. Review of the adjudication packet revealed that the patient was admitted to the hospital due to severe back pain secondary to a pathologic facture of L4 (from metastatic SCC) and findings of atrial fibrillation with RVR (on coumadin) with t wave inversions in the lateral leads, in the setting of elevated troponin max of 0.23 (reference<0.04 ng/mL) and CKMB of 7.1 (reference 0.5-6.3 ng/mL). The cardiology consult note states that it was unclear what his elevated troponin is secondary to. Both adjudicators agreed that the case was consistent with a silent NSTEMI.
    - Subject (b) (6) (liraglutide) – patient with slight troponin elevation and atrial flutter (refer to narrative located in section **MI discussion**).

Reviewer's comments: These three cases exemplify cases where the investigator interpretation of an event varies from the adjudicator's interpretation. It may be argued that the interpretation of the event was more "loosely" by the EAC than by the investigator. The Sponsor was asked to perform an exploratory evaluation of the primary endpoint which excluded silent MI's, in order potentially exclude events which could be interpreted more loosely (refer to section titled, "MI discussion" for further details). However, two additional events in the placebo group and one in the liraglutide group would not change the overall study conclusions.

BRAZIL SITES

- **Site 624/ Gross** (ranked #25 in site selection tool): The site enrolled 70 patients, which were 91% of screened patients. The site had few adverse events and higher than average deaths.

- **Site 631/ Rollin**. (ranked #87 in site selection tool): The site enrolled 40 patients which were 91% of the screened patients. There were many protocol violations from these sites.

The Sponsor notes that two sites were closed due to misconduct and one site was closed after IRB withdrawal of approval. The Sponsor performed source data verification for all transferred patients.[6]

In addition, on March 7, 2017, the Sponsor submitted additional serious adverse event narratives of 3 patients treated with liraglutide at one site (site 509) in China which were not submitted until after the finalization of the LEADER clinical report. The serious adverse events took place while the trial was being conducted and were detected during a quality check of hospital medical records by the Good Clinical Practice officer. These events were not reported to the investigator by the patient during the trial and the investigator did not have access to the hospital's medical records to be aware of these events:

- **Subject ID** (b) (6) **-** patient was hospitalized with chest pain on (b) (6) Coronary angiography showed right dominant type distribution of coronary artery. Stenosis was observed in anterior descending branch (>60%) and in right coronary artery (>30-40%). Left main coronary artery did not show stenosis. The troponin T high sensitive (TNT-HS) level was within normal range. No treatment for the SAE was provided, but the subject received antiplatelet therapy and treatment for hypertension.
- **Patient ID** (b) (6) developed symptoms of polydipsia, weight loss and glucose fluctuations for which he was hospitalized. Patient was treated with glucose-lowering drugs, anti-platelets and anti-hypertensive drugs.
- **Patient ID** (b) (6) - Patient had a cerebral infarction while not treated with liraglutide, but still participating in the trial. Patient was hospitalized for cerebral infarction and double lower limb weakness. CT scan showed multiple lacunar infarcts in the bilateral basal ganglion and centrum oval region. The patient was treated with antiplatelet therapy. The second SAE was a lung infection for which the patient was hospitalized.

Reviewer's comment: two narratives (patient ID (b) (6) **and** (b) (6) **) could have been potentially adjudicated as meeting the 3-point MACE definition. Although these events did not undergo formal adjudication by the EAC, since they were not captured during the trial, it is unlikely that these events would have changed the overall efficacy findings in the trial.**

[6] Site 469 (South Africa) was closed due to for cause audit for another trial. All patients were transferred to site 475. Site 165 (Italy) was closed due to findings during a sponsor audit in 2013. Patients were transferred to site 172. Site 804 (USA) was closed due to warning letter issued by the FDA on a previous inspection for another sponsor. The IRB then withdrew approval at the site and patients were transferred to site 841.

3.2 Compliance with Good Clinical Practices

The Sponsor states that LEADER was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization (ICH) and Good Clinical Practice (GCP) standards.

3.3 Financial Disclosures

Refer to section titled **Financial disclosures** in the appendix for specific details regarding the disclosure of investigators.

Approximately 3% of the investigators in the trial had disclosable financial interest in LEADER (58 out of 2019 total investigators). From these investigators, there were three sites (all outside the U.S) identified with significant financial contributions (each site received over $1 million). Although the financial contribution received by these three sites (sites: (b) (6), and (b) (6)) was significant enough to have possibly influenced the results in the involved sites, the number of patients randomized from these sites made up 1% of the total patients randomized in the trial (total of 94 patients). Because LEADER was a double blinded trial, which remained blinded until completion (i.e. did not have interim unblinding) and because the overall number of patients enrolled in the three sites with a large financial interest was small, it is unlikely that the overall results of the trial were affected by these three sites.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

There was no new CMC information included in this supplement.

4.2 Clinical Microbiology

There was no new microbiology information included in this supplement.

4.3 Preclinical Pharmacology/Toxicology

Please refer to the review by Anthony Parola for the FDA review of the studies submitted by the Sponsor.

The Sponsor submitted two non-clinical studies conducted to explore the mode of action of liraglutide's (b) (4). Specifically, both studies were meant to evaluate liraglutide's effect on atherosclerosis. One study evaluated liraglutide in ApoE

knock out mice (duration 6-12 weeks); the second study evaluated liraglutide in LDL receptor knock out mice (duration 17 weeks).

The Sponsor (b) (4)

4.4 Clinical Pharmacology

There was no clinical pharmacology information included in this supplement.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

The primary efficacy and safety data for this review were derived from a single trial, listed below:

Trial ID: EX2211-3748 – LEADER: Liraglutide effect and action in diabetes: Evaluation of cardiovascular outcome results - A long-term, multi-center, international, randomized double-blind, placebo-controlled trial to determine liraglutide effects on cardiovascular events

5.2 Review Strategy

The review of the LEADER study was conducted among three clinical reviewers. I was the primary clinical reviewer for the safety and efficacy of cardiovascular, renal and ophthalmologic endpoints. Julie Golden, MD was the primary reviewer for safety with the exception of thyroid cancer, which was reviewed by Shannon Sullivan, MD.

A separate efficacy statistical analysis was conducted by Kiya Hamilton, Ph.D.

The current review focuses on the efficacy findings that the Sponsor proposes to label. In addition, to reviewing the clinical trial report, I reviewed all versions of the study protocol, the SAP, the DMC charter, the Steering committee charter, and the EAC

charter. I also reviewed the DMC minutes (open and closed) and steering committee minutes.

5.3 Discussion of Individual Studies/Clinical Trials

The overall trial design is discussed in this section.

The Sponsor submitted the Liraglutide Effect an Action in Diabetes: Evaluation of cardiovascular outcome Results (LEADER) trial (also referred to as Trial 3748), to meet the postmarketing requirement 1583-9. This postmarketing requirement required that the Sponsor show that use of liraglutide, in patients with type 2 diabetes, would not result in an unacceptable increase in the risk of atherosclerotic cardiovascular disease, as outlined in the FDA guidance.[7]

The trial was designed to demonstrate non-inferiority (with a margin of 1.3) of the treatment of liraglutide (pooled doses 0.6,1.2, and 1.8 mg) versus placebo on the composite of three point of Major Cardiovascular Events (MACE): cardiovascular death, non-fatal stroke, or non-fatal myocardial infarction in patients with type 2 diabetes mellitus with increased cardiovascular risk.

Protocol amendments
The LEADER protocol had 5 substantial protocol changes ("substantial" refers to changes of the content of the protocol, rather than administrative changes, such as change of address, which also required a protocol change)**;** see **Table 39**, in the appendix.

In general, changes to the protocol were performed to increase recruitment (i.e. inclusion criteria allowing premixed insulin); increase retention (i.e. not exclude patients who were randomized in error due to age criteria or due to disallowed medications); and to implement a staggered closedown of sites after the target number of events were reached.

Reviewer's comment: The changes in the last amendment (amendment 39) of the protocol effectively shortened the total observation time in the trial but did not violate the original protocol. In review of the DMC minutes, it was noted that the DMC did not agree with Novo on the staggered approach for closing the trial because it would result in loss of data, i.e., the potential loss of safety-related data from a shortened follow up of patients.

Study Title: LEADER: liraglutide effect and action in diabetes: Evaluation of cardiovascular outcome results - A long-term, multi-center, international, randomized

[7] Guidance for Industry Diabetes Mellitus — Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes
http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm071627.pdf

double-blind, placebo-controlled trial to determine liraglutide effects on cardiovascular events

Primary objective: To assess the effect of treatment with liraglutide compared to placebo for at least 3.5 year and up to 5 years on the incidence of cardiovascular events, as defined by the primary and secondary endpoints in adults with T2DM that are at high risk for cardiovascular events.

Secondary objectives: To assess the efficacy and safety with regard to clinically important events or other surrogate parameters of treatment with liraglutide compared to placebo in adults with T2DM that are at high risk for cardiovascular events.

Trial sites: A total of 417 sites in 32 countries screened subjects, of which 410 sites randomized patients to treatment[8].

A total of 20 sites[9] screened or randomized subjects but were later closed during the trial; most sites closed due to resource issues; two closed due to misconduct and an additional trial closed after the IRB withdrew its approval.[10]

Study design: LEADER was a multi-center, multi-national, randomized, double-blinded, placebo controlled trial of T2DM patients at high risk for cardiovascular events, randomized to liraglutide or placebo in addition to standard of care therapy, as decided by the patient's physician.

The trial duration was driven by both MACE event numbers and duration. At a *minimum*, all subjects had to have a treatment period of 42 months (in addition to a 30 day follow-up period) *and* have achieved at least 611 EAC confirmed MACEs. The trial included an 18 month recruitment period, therefore allowing for a maximum treatment period of 60 months.

Reviewer's comment: The overall trial design is consistent with other cardiovascular outcomes trials which have been reviewed by the Division.

Inclusion/Exclusion criteria:

[8] An additional 28 trial sites were approved but did not screen or randomize any patients. OF these sites 3 sites (site 172 [Italy] and sites 938 and 939 [US] received patients from other sites.
[9] 1 Italy, 1 South Africa, 1 in the United Kingdom, 1 in the United Arab Emirates and 16 in the US
[10] Site 469 (South Africa) was closed prematurely due to a critical finding in a 'for-cause audit' performed by the sponsor in 2012 for another Novo Nordisk trial. The trial discontinued all trial activities and 33 active patients were transferred; site 165 (Italy) was closed due to clinical finding during a sponsor audit in June 2013 resulting in 25 patient transferred to another site. Site 804 (US) was closed due to a warning letter issued in July 2014 by the FDA after an inspection on a trial sponsored by another sponsor. The site did not adhere to applicable statutory requirements and regulations and thus the IRB withdrew the approval. 34 patients were transferred to another site.

The inclusion and exclusion criteria are shown in **Table 3.** In addition to the inclusion/exclusion criteria, there were randomization criteria which are discussed after this section.

The purpose of the inclusion/exclusion criteria was threefold. First, the criteria were meant to enrich the patient population with patients at risk for cardiovascular events; second, the criteria were to limit the risk to patients by excluding patients with severe/unstable disease, and third, the criteria were to enroll a pre-specified number of patients with moderate or severe renal insufficiency.

As with other cardiovascular outcome trials (CVOTs), a strategy to enrich the population with patients at high risk for cardiovascular events was implemented. Specifically, the inclusion criteria specified that patients aged ≥50 years with established cardiovascular disease or patients aged ≥60 years with well-established risk factors for cardiovascular disease could be enrolled.

The FDA requested that the Sponsor investigate the effectiveness and safety of liraglutide in subjects with moderate and severe renal impairment. To address this request, the Sponsor planned to include a total of 440 subjects with moderate and 220 subjects with severe renal impairment at screening. Once the 220 patients were randomized, no more patients with severe renal insufficiency were to be randomized.

The enrollment criteria were broad in regards to allowed medications, by including both oral antidiabetic drugs (OADs) and basal insulin/pre-mix insulin. The protocol was amended[11] to allow any patients who violated any of the exclusions for disallowed therapies could be reintroduced on randomization according to their original treatment allocation after a wash out period.

Table 3 – Inclusion and exclusion criteria

Inclusion criteria	
Informed consent in men or women with type 2 diabetes and	
Age	
• ≥50 years at screening plus:	a) prior myocardial infarction b) prior stroke or prior transient ischemic attack (TIA) c) prior coronary, carotid or peripheral arterial revascularization d) >50% stenosis on angiography or other imaging of coronary, carotid or lower extremity arteries e) history of symptomatic coronary heart disease documented by positive exercise stress test or any cardiac imaging, or unstable angina with ECG changes f) asymptomatic cardiac ischemia documented by positive nuclear imaging test or

[11] Protocol amendment 30: subjects could be reintroduced to treatment with randomized trial product if discontinuing the disallowed medication. In order to avoid a potential carry-over effect of the disallowed medication and to ensure continual antidiabetic treatment, reintroduction to randomized treatment was to be executed after the following wash-out periods: 1 day for subjects on fast acting insulin or pramlintide;5 days for subjects on once daily GLP-1 analogues or DPP-4 inhibitors,4 weeks for subjects on once weekly GLP-1 analogues.

	exercise test or dobutamine stress echo g) chronic heart failure NYHA class II-III h) chronic renal failure, having clinically reached a stage corresponding to a glomerular filtration rate < 60 mL/min/1.73 m^2 per Modification of Diet in Renal Disease (MDRD) or < 60 mL/min per Cockcroft-Gault formula
• *Or* ≥60 years at screening plus:	i) microalbuminuria or proteinuria j) hypertension and left ventricular hypertrophy by ECG or imaging k) left ventricular systolic or diastolic dysfunction by imaging l) ankle/brachial index <0.9
HbA1c	≥7% at screening
Antidiabetic therapies	Antidiabetic drug naïve or treated with one or more oral antidiabetic drugs or treated with human NPH insulin or long-acting insulin analogue or premixed insulin, alone or in combination with OAD(s)
Exclusion criteria	
Antidiabetic therapies	• Use of insulin other than human NPH, or long-acting insulin analogue or premixed insulin within 3 months prior to screening. Short-term use of other insulin during this period in connection with intercurrent illness was allowed, at Investigator's discretion • Use of a GLP-1 receptor agonist or pramlintide or any DPP-4 inhibitor within the 3 months prior to screening
Glycemic control	• Acute decompensation of glycemic control requiring immediate intensification of treatment to prevent acute complications of diabetes (e.g., diabetes ketoacidosis) in the previous 3 months
Cardiovascular risks	• An acute coronary or cerebrovascular event in the previous 14 days • Currently planned coronary, carotid or peripheral artery revascularization • Chronic heart failure NYHA class IV
Renal disease	• Current continuous renal replacement therapy • Estimated glomerular filtration rate (eGFR) (as per MDRD) < 30 mL/min/1.73 m^2 at screening. *(applicable after a target number of 220 subjects with eGFR < 30 mL/min/1.73 m^2 were randomized)*
Other Medical comorbidities	• End stage liver disease, defined as the presence of acute or chronic liver disease and recent history of one or more of the following: ascites, encephalopathy, variceal bleeding, bilirubin ≥ 2.0 mg/dL, albumin level ≤ 3.5 g/dL, prothrombin time ≥ 4 seconds prolonged, international normalized ratio (INR) ≥1.7 or prior liver transplant • A prior solid organ transplant or awaiting solid organ transplant • Malignant neoplasm requiring chemotherapy, surgery, radiation or palliative therapy in the previous 5 years. Patients with intraepithelial squamous cell carcinoma of the skin (Bowen's disease) treated with topical 5FU and subjects with basal cell skin cancer were allowed to enter the trial
Liraglutide labeled contraindication	• Family or personal history of multiple endocrine neoplasia type 2 (MEN 2) or familial medullary thyroid carcinoma (FMTC) • Personal history of non-familial medullary thyroid carcinoma
other	• Known or suspected hypersensitivity to trial product(s) or related products • Known use of non-prescribed narcotics or illicit drugs • Simultaneous participation in any other clinical trial of an investigational drug. Participation in a clinical trial with investigational stent(s) was allowed • Previous participation in this trial. Participation is defined as randomized • Females of childbearing potential who were pregnant, breast-feeding or intended to become pregnant or were not using adequate contraceptive methods^ • Receipt of any investigational medicinal product (IMP) within 30 days prior to this trial.$^{\Omega}$

^ UK: Adequate contraceptive measures are defined as established use of oral, injected or implanted hormonal methods of contraception, sterilization, intrauterine device or intrauterine system, or consistent use of barrier methods. Germany: Adequate contraceptive measures are implants, injectables, combined oral contraceptives, hormonal IUD (intrauterine device), sexual abstinence or vasectomized partner. Mexico: Adequate contraceptive measures are defined as birth control pills, Depo-Provera, Norplant, a hormonal IUD, and a diaphragm with spermicide or abstinence. Condom with spermicide must be used during sexual inter-course. Romania: Adequate contraceptive measures are defined as established use of oral, injected or implanted hormonal methods of contraception, sterilization, intrauterine device or intrauterine system, or consistent use of barrier methods
Ω Brazil: receipt of any investigational drug within one year prior to screening visit (visit 1), unless there is a direct benefit to the research subject at the Investigator's discretion

The following criteria were to be met for a patient to be randomized in LEADER:

1. Basal (non-stimulated) blood calcitonin concentration at screening<50 ng/L[12]
2. Demonstrate adherence to injection of ≥50% during the run-in period.

If patients were randomized and did not meet the second criteria, they were allowed to continue in the trial.

Withdrawal Criteria:
Of note there is a difference between the removal of patients from the trial (withdrawal criteria) and the discontinuation of investigational product. This section will focus on the former; the latter will be addressed subsequently.

A patient could withdraw from LEADER at any time. Withdrawal from the trial was to be done if:

1. Patient withdrew informed consent
2. Patient being pregnant or with the intention of becoming pregnant

Reviewer's comment: the limited withdrawal criteria likely contributed to the robust retention in this trial.

Even though patients may have withdrawn from the trial, information regarding the patient's vital status could still be obtained by evaluation of registries, depending on the local laws/regulations, thereby decreasing the amount of missing data for vital status.

Discontinuation of investigational product:
Temporary or permanent discontinuation of treatment with investigational product did not lead to withdrawal from the trial. Unless the trial treatment was discontinued due to a safety issue, patients were encouraged to re-start the treatment when appropriate.

[12] Of note, the cut off, for criteria 1 was revised from <100 to <50 after discussion with the FDA in Protocol amendment 8.

Discontinuation of investigational therapy was to be done for patients who were non-compliant with the eligibility criteria (calcitonin≥50 ng/L and not meeting inclusion/exclusion criteria) but were randomized.

Study procedures

A schematic of the trial design is shown in **Figure 1.** Of note, direct contact with the patient by phone was considered of equal value as site visit, thus patients were not asked to come for site visits unless laboratory measurements were required.

Patients attended visit 1 (screening visit) to assess their eligibility, based on the inclusion/exclusion criteria (discussed above)[13] and informed consent was signed. If eligible, the patient returned to Visit 2 and underwent a 2-3 week run-in period, in which the patient had to show that he/she could adhere to the injection regimen of the trial by using placebo. At visit 3, patients who had shown at least 50% adherence to the injection regimen and who were willing to continue in the trial were randomized 1:1 to once daily liraglutide or placebo as add-on to standard of care treatment.[14] Patients attended the site at 1, 3, and 6 months after randomization and every 6 months for a total period of up to 60 months and no less than 42 months after randomization. At each site, patients were scheduled for visit 15 within a period of 3 or 6 months prior to the last subject at the site reaching 42 months since randomization.[15] After the end of treatment visit, patients underwent a 30 day follow-up visit after discontinuing therapy. The follow-up visit was focused on assessment of safety[16] and ensuring vital status was accounted.[17]

[13] If a subject was re-screened, all procedures pertaining to visit 1 were to be repeated; a new informed consent was to be obtained and a new subject number allocated.

[14] Subjects received instructions related to handling of their background antidiabetic therapy, use of the pen-injector and injection techniques and were informed that the selected time of injection of investigational product was recommended to be consistent throughout the trial. Subjects were also supplied with a glucose-meter and instructions for use for self-measurements of fasting glucose. For subjects in the US, blood sampling for determination of anti-liraglutide antibodies was performed. Subjects were informed about precautions to avoid dehydration in case of gastrointestinal side effects. Investigator was to contact the subjects by phone between visits 3 and 4 to monitor and advise with respect to the dose escalation.

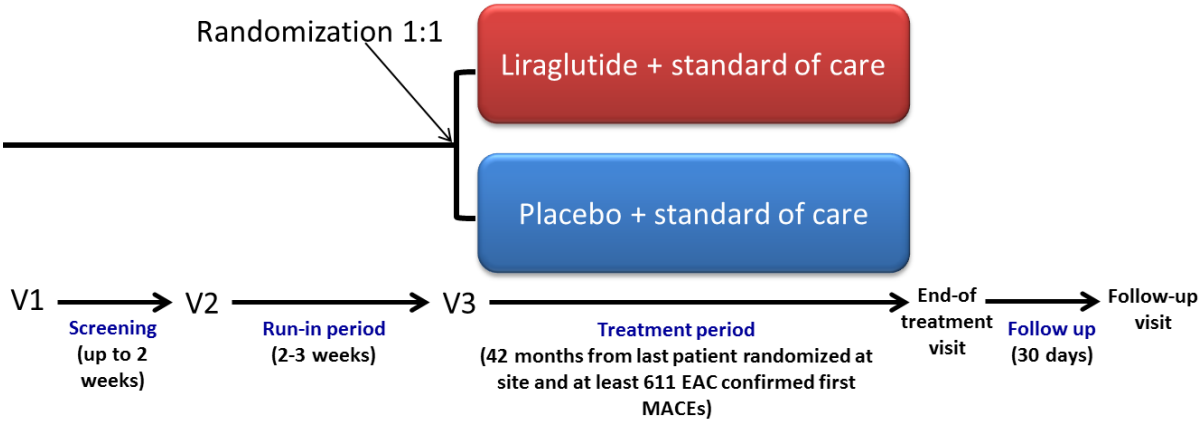
[15] This staggered site closure was included in amendment 39. During this closure phase at the site, subjects who had progressed to at least visit 12 (month 42) but had not reached visit 14 in the visit schedule had their next per-protocol visit converted to end of treatment visit (visit 15), omitting any in-between visits. To the extent possible, all examinations scheduled for the end of treatment visit (visit 15) were to be performed for all subjects regardless of their compliance with the protocol and adherence to treatment. Patients were switched to available treatments at the discretion of the investigator at visit 15. However, patients in the US, who had antibody sampling, were not allowed to initiate treatment with GLP-1 receptor agonists until after visit 16 (follow-up visit). For the remaining subjects, no restrictions were applied.

[16] Antibody sampling was done for patients in the US. A calcitonin sample was drawn for subjects who demonstrated a calcitonin level >2x upper limit of normal (ULN) at visit 15 and who had levels below ULN at screening. For subjects whose calcitonin value did not decrease by at least 50% between visits 15 and 16, the Investigator was to consider the need for further monitoring or referral to an endocrinologist.

[17] Investigators were to make every effort to contact all randomized subjects who were at risk of being lost to follow-up and to collect any available information related to trial outcomes. A subject was only

Refer to **Table 40** (in the appendix) for details regarding the trial flow chart.

Figure 1 – LEADER trial design



Abbreviations: EAC: event adjudication committee, MACE: Major adverse cardiovascular event, V1: screening visit, V2 start of run-in period, V3: randomization and start of treatment

Source: modified figure from CTR, Figure 9-1

Treatments:
Investigators were provided with open-labeled placebo to use in the run-in period

In the randomized portion of the trial, patients were randomized 1:1 in a double-blinded manner to receive daily doses of either liraglutide or placebo, which was added onto the patient's pre-trial OAD and or/insulin regimen.[18] Subjects were to continue on their current antidiabetic therapy with a suggested reduction in insulin at randomization (see Table 4 below).

considered lost to follow-up in case vital status could not be obtained at the end of the trial. Attempts to contact the subjects or their primary health care provider were to be documented in the subject's medical record and consisted of: to subjects: two phone calls and one written contact; to health care provider: calls until contact was established; to relatives/next of kin: two phone calls and one written contact; contact to relevant public registries, if available. For patients who withdrew prematurely, the investigator was to search relevant public registries for information on vital status, according to local regulations.

[18] As noted in the inclusion/exclusion criteria, the concomitant glucose-lowering treatments *excluded* the following: other GLP-1 receptor agonists, dipeptyl peptidase-4 (DPP-4) inhibitors and pramlintide. If these disallowed medications were introduced during the treatment period, the trial product was to be discontinued but could be reintroduced upon discontinuation of disallowed medication, at the discretion of the investigator (protocol amendment 30)

The following list describes the general approaches to dosing the investigational product in the trial:

- **Investigational drug presentation:** identical 3mL disposable pen injectors dialed a dose of 0.6, 1.2 and 1.8 mg
- **Time of administration of investigational drug:** at any time of day irrespective of meals, encouraged to keep injection time consistent from day to day
- **Location of administration of investigational drug:** subcutaneously in the abdomen, thigh or upper arm
- **Titration of investigational drug:** Starting dose was 0.6mg of liraglutide or placebo. Dose was to be increased by 0.6 mg increments each week to a maximum dose of 1.8 mg. The dose increase period could be extended based on the patients' tolerance to the trial product. And the dose could be reduced (to 1.2 mg or 0.6 mg) at any time at the discretion of the investigator.

Adjustments to concomitant medications

Investigators were free to add/adjust the dose(s) of any glucose-lowering drugs (including insulins) if glycemic targets were not achieved (with the exclusion of certain OADs as noted in footnote **18**). Recommendations regarding insulin dose reductions at randomization are shown in **Table 4.** The reduced dose was to be maintained after two weeks post-randomization. After this time period, the dose of insulin could be increased if needed to achieve optimal glycemic control[19]. Discontinuation of sulfonylureas was recommended, at randomization. There were also recommendations for initiation of basal insulin for insulin naïve patients.

Table 4 – Recommended adjustments of antidiabetic therapies at randomization

Patient population	Adjustments to anti-diabetic therapy
Patients on antidiabetic pre-trial therapy needing adjustment	
Premix insulin ±OAD(s) and HbA1c≤8%	Reduce total daily dose of premix insulin by a minimum of 20% at start of trial product
Premix insulin and HbA1c>8%	Consider insulin dose reduction
Basal insulin	20% reduction of basal insulin
Sulfonylurea	Discontinuation of sulfonylurea
Insulin naïve patients	
Initiate basal insulin at 10 units a day at evening or bedtime.	

If hypoglycemia required dose reduction of antidiabetic therapy, investigators were recommended to reduce or modify the dosing of non-investigational drugs[20] *before*

[19]For all trial subjects receiving insulin (i.e., ongoing treatment with insulin at the screening visit or insulin introduced after randomization), the generic or trade name and the total daily dose of insulin administered on the day preceding each trial visit (if available) was recorded in the concomitant medication form.
[20] Of note, doses and adjustments in relation to concomitant medications were not recorded systematically during the trial.

reducing the dose of the trial product. However, the measurement and recording of plasma glucose values was done according to individual recommendations from the investigator, and not recommended systematically.

In addition to the above recommendations, the Sponsor also emphasized the country-specific standard of care guidelines for type 2 diabetes including blood pressure and lipid lowering therapies.

Treatment compliance:

At each visit, the investigator reminded the patient to follow the protocol. During visits 3 to 5 the patient was to return all used, partially used and unused trial products. The trial staff was to determine the amount of trial product returned compared to what was dispensed and to encourage patients to take trial product as prescribed. The patients' diaries were collected at each site visit and kept as source data by the investigator. Relevant data (i.e., date of first dose of trial product, hypoglycemic episodes, trial product dose adjustment and concomitant medication) from the diaries were transcribed into the eCRF. The investigator was to ensure that all information was consistent with the source documentation.

Statistical Considerations:

The Statistical analysis was conducted by the Sponsor and an independent university-affiliated group: (b) (4).

There was no interim analysis planned or conducted for LEADER. However, as requested by the European Medicines Agency (EMA), there was a blinded-2 year follow-up report from the DMC.[21]

The following are changes to the Statistical Analysis Plan (SAP) **before** breaking the blind:

There were three versions of the SAP. The second version (V2) of the SAP had no content changes; therefore it will not be discussed further. The following changes were made in the third version of the SAP:

- Minor changes to the MedDRA search criteria for diabetic foot ulcer, immune complex disease, thyroid disease
- Added time from randomization to the first occurrence of a composite nephropathy outcome
- Added/updated sensitivity analyses, after discussions with regulatory authorities
- Subgroup analyses of the primary endpoint, HbA1c, secondary efficacy endpoints, were based on the eGFR randomization values (not the screening

[21] Report was submitted to IND061040 25 on June 2014 to the FDA - reflecting data from 18 April2014. There were 9340 patients randomized, and 708 patients with at least one primary outcome event.

value). The sensitivity analyses used the screening eGFR value, since this was the point in time where stratification was decided.

- Changes the wording of secondary endpoints from “unstable angina” to “hospitalization for unstable angina pectoris”; and from “hospitalization for “chronic” heart failure to “hospitalization for heart failure”; and from “revascularization” to “coronary revascularization.” Also the covariate in the sensitivity analyses of the primary endpoint and secondary analyses used the eGFR at randomization.

The following analyses are not present in the SAP and were specified post database lock:

- *Post-hoc* analysis of time to first EAC confirmed hospitalization for heart failure or all-cause death[22]
- *Post-hoc* analysis of competing risk analysis of time to first MACE with non-cardiovascular death as competing risk. [23]
- Medically qualified personnel at Novo further classified the following:
  - cardiovascular deaths with known cause
  - non-cardiovascular deaths.
  - neoplasms as tissue of origin ‘other’ to the organ system affected
- *Post-hoc* analysis with retinopathy at baseline included as a covariate in the cox regression analysis of retinopathy events, due to minor imbalance in medical history of retinopathy
- Exploratory analyses of change from baseline to the 3 year assessments performed for serum creatinine and urinary albumin-to creatinine ratio using MMRM
- Analyses of change from baseline to 3 year assessment and to end of treatment performed for BMI using the same statistical analyses used for body weight
- An exploratory logistic regression analysis for severe and confirmed hypoglycemia for patients with a high number of hypoglycemic episodes
- Cox regression analyses for EAC confirmed neoplasms

Reviewer’s comment: the additional statistical analyses specified post database lock (and hence post unblinding of data) is considered exploratory in this review.

Stratification:
A total of 220 patients with severe renal insufficiency were to be randomized in the trial and stratified according to eGFR estimated by MDRD (eGFR < 30 mL/min/1.73 m^2 versus eGFR ≥30 mL/min/1.73 m^2)

[22] The analysis was included because an increase in hospitalization for heart failure was reported for saxagliptin in SAVOR. The combination of hospitalization for heart failure with all-cause death was to ensure that potential deaths precipitated by heart failure were taken into account. The analysis was made in the FAS using the Cox regression model including treatment group as factor. The Cox regression model was used to estimate the hazard ratio (liraglutide/placebo) and the 2-sided 95% CI.
[23] Modelling of hazard ratios adjusted for competing risk was performed using the method based on the proportional subdistribution hazards model including treatment group as a fixed factor.

Sample size calculation:
The sample size was estimated based on time to first MACE using a log rank test for the full analysis set (FAS) which includes all randomized subjects and the following assumptions:

- An estimated primary outcome event rate of 1.8% per year for liraglutide and placebo.
- A uniform enrolment over 1.5 year with a maximum follow-up of 5 years (including the accrual period).
- A non-inferiority margin versus placebo of 1.3 for the upper limit of the 2-sided 95% confidence interval.
- A total drop-out rate (subjects lost to follow-up or withdrawn from the trial) of 10%.
- 90% power to reject the null hypothesis that the hazard ratio is > 1.3.

Based on the above assumptions, 8754 subjects were planned to be randomized. The expected number of events to obtain the 90% power was 611.

Of note, missing values were not replaced by imputed values unless otherwise specified.

Reviewer's comment: based on the higher risk population enrolled in the trial (than what was expected), as discussed in section 6.1.4 Analysis of Primary Endpoint(s)**, the trial was overpowered to rule out the 1.3 risk margin (non-inferiority margin) for MACE.**

Analysis sets:
There was no safety analysis set defined. The following analysis sets were defined in the statistical analysis plan:

- **Full analysis set** (FAS): which included all the randomized patients. The evaluation of the FAS followed the intention-to-treat (ITT) principle, and patients contribute to the evaluation as randomized. The FAS was used to analyze the primary and secondary endpoints.
- **Per Protocol** (PP) analysis set: included all patients who took at least one dose of the investigational drug and had less than 120 days of no exposure.

The following describes the time periods defined in this study:

- **Time to event date or time to censoring date**- calculated from the randomization date to the event/censoring date
- **Observation time (in FAS)** - duration from the date of randomization to date of last patient contact (therefore independent of endpoint of interest).
- **Observation time (in PP) -** duration from the date of randomization to date of last patient contact (therefore independent of endpoint of interest); or date where the accumulated period of no exposure to investigational drug exceeds 120 days, whichever comes first.

Evaluability of patients and censoring

The Clinical Trial Report (CTR) indicated that there were two groups of patients in the trial: completers and non-completers as defined in **Table 5.** The definitions of completers and non-completers were made prior to database lock and agreed upon by the Steering Committee in order to evaluate patient disposition and retention.[24] Completer patients either had a MACE event, non-CV death or had direct contact with the investigator at visit 16. Completers had known or unknown vital status (if experienced non-fatal MI or non-fatal stroke) at visit 16.

Non-completers, on the other hand had none of the three criteria of completers and were either known to be alive (without direct contact, and therefore it was unknown if they had a MACE event) or had unknown vital status. For the latter, patients were further subdivided to patients who withdrew consent and patients who were lost to follow up.

Table 5 –Categories to differentiate completers from non-completers

	MACE	Non-CV death	Contact at Visit 16	Vital Status at visit 16
Completer*	✓ OR	✓ OR	✓ Direct contact	Known or unknown^
Non-completer	X	X	X	• **Known to be alive** but no direct contact~ • **unknown vital status** o withdrew consent o lost to follow up

*completer patients include patients who withdrew from treatment, but continued in the trial
~ Direct contact was defined as either the patient attended visit 16 or the site was in contact by telephone with the patient.
^ patients experiencing non-fatal MI or non-fatal stroke would be classified as completers, even if vital status was not known at visit 16

The amended (Version 3) SAP detailed the process of evaluating patients for primary and secondary outcomes (this section was absent in the original SAP).

Censoring for primary endpoint

[24] In an information request dated 2/16/17 the Sponsor clarified the definitions of "completers" and "non-completers" (question 1) \\CDSESUB1\evsprod\NDA022341\0357\m1\us\re-fda-ir-20170209.pdf

All first EAC confirmed MACE events, from randomization (visit 3) and before visit 16 that were reported before data base lock (DBL) were considered for analyses[25]. As prespecified in the SAP, for patients who were potentially lost to follow up and for whom vital status was retrieved and confirmed as cardiovascular death by the EAC, only events with onset date prior to the planned visit 16 were included in the primary analysis.

Of note, in the case of a stroke or MI that was linked to a CV death by the EAC, but the CV death occurred after V16, the observation period was prolonged so that the stroke or MI would be counted as fatal. Hence the CV death would be included in summaries of MACE and time-to –event analysis of the primary event (if it was a first event).[26]

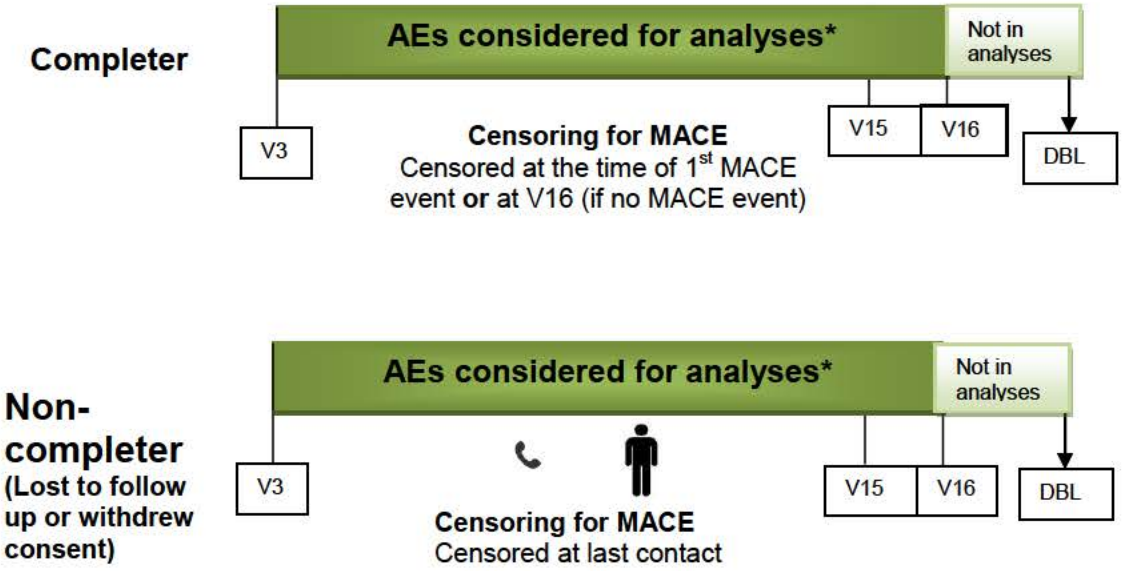
The collection of adverse events/vital status was prioritized by the Sponsor, as shown in **Figure 2.** Relevant events were collected from multiple sources beyond just site visits and phone contact for events sent for EAC adjudication and vital status.

The determination of whether a patient was considered lost to follow-up occurred at database lock (DBL). A Patient was considered lost to follow-up if the patient's vital status at the end of visit 16 remained unknown at data base lock.

The censoring of patients for the evaluation of the primary endpoint (i.e. MACE) is also shown in **Figure 2.** For patients lost to follow-up, censoring occurred at the last contact with the investigator; for all other patients, censoring occurred at the time of the MACE event or at visit 16. The censoring date was calculated from the randomization date.

[25] Events occurring after visit 16 were not considered for analysis but were listed in a separate listing.
[26] This comment was included in the Statistical Memo (on February 1, 2016), it was not included as part of the SAP.

Figure 2- Censoring of patients for MACE events



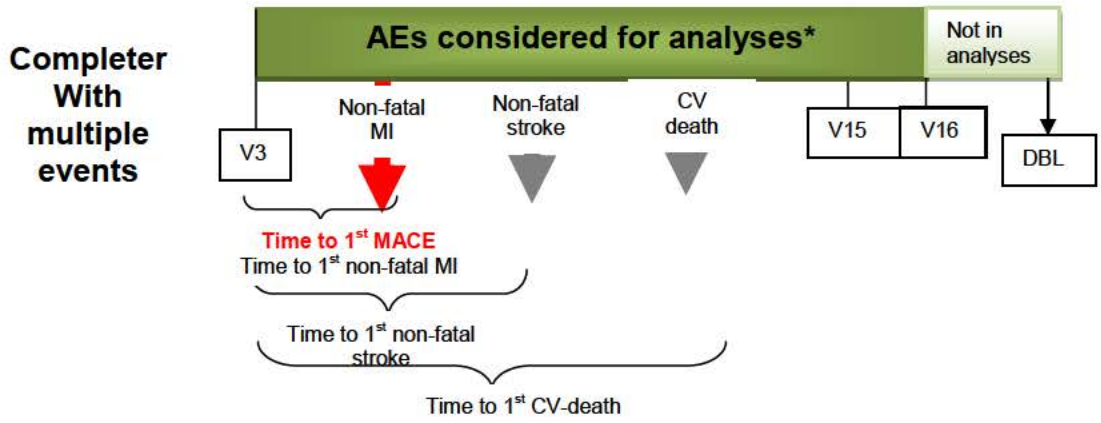
*source of AEs are described below:

Priority	Source	'Event-free' time	Events for EAC	Vital status
1	Site visit	X	X	
2	Phone	X	X	
3	NOK		X	X
4	HCP		X	X
5	Registry			X
6	Other			X

NOK: next of kin; HCP: health care provide

The trial specified that for patients experiencing more than one EAC confirmed cardiovascular event, the analysis of time to the first MACE event only applied to the first event identified. In the analyses of the individual MACE components (see **Figure 3**) the subject contributed with events to the individual analyses of time to first event of non-fatal MI, nonfatal stroke and to the analysis of time to cardiovascular death. In case events had the same date of onset the priority for selecting the first event was: cardiovascular death > non-fatal myocardial infarction > non-fatal stroke.

Figure 3 – Example of patients with multiple MACE events



Source: CTR figure 11-1, page 225

Index events
The adjudication of events is described in detail in the section titled **EAC Charter Summary**, in the appendix. In order to avoid double counting of events, the EAC Chair determined if multiple adjudicated events of the same category (i.e. multiple stent placements in one visit) would be classified as multiple events or as part of an index event (i.e. even though multiple stents may have been placed in one visit, each stent was not counted individually as an event; instead the procedure would be summarized under *one* index event of "stent placement"). As a general rule, the same events occurring in one visit counted as one event.

Definitions for adjudicated events
The pre-specified definitions used for adjudication of CV events were established to conform to the 2010[27] version of the FDA Standardized Definitions for Cardiovascular Outcomes Trials. The definitions of the non-CV events were based on internationally recognized recommendations approved by applicable EAC experts; refer to **Table 44**, in the Appendix. Of note, 'silent MI' was part of the MI component of MACE, and thus contributed to the overall primary endpoint findings.

Primary endpoint:

The primary endpoint was the time from randomization to first occurrence of a composite cardiovascular outcome: cardiovascular death, nonfatal myocardial infarction or nonfatal stroke (also referred to as MACE).

[27] Standardized Definitions for Endpoint Events in Cardiovascular Trials. FDA Center for Drug Evaluation and Research (CDER). Draft Version October 20, 2010.

The primary analysis for non-inferiority was made using the Cox regression model, including treatment group as factor. The Cox regression model was used to estimate the hazard ratio (liraglutide/placebo) and the 2-sided 95% confidence interval.

The non-inferiority of liraglutide versus placebo was considered confirmed if the upper limit of the two-sided 95% CI for the hazard ratio was below 1.3 or equivalent if the p-value for the one sided test of : H0: HR≥1.3 against Ha: HR<1.3 was less than 2.5% (or equivalent to 5% two-sided test).

If non-inferiority was established, then a superiority test was performed and considered confirmed if the upper limit of the two-sided 95% CI for the hazard ratio was below 1 or equivalent, if the p-value for the one-sided test of: H0: HR≥1 against Ha: HR<1 was less than 2.5%(or equivalent to 5% two-sided test).

The Sponsor did not adjust for multiplicity when testing for superiority, since the approach was a closed testing procedure.

Sensitivity analyses
Table 6 shows the primary and sensitivity analyses for the primary endpoint. Other than the pre-specified primary endpoint analysis and the PP population sensitivity analysis, the other sensitivity analyses, were added in version 3 of the SAP.

Table 6 – Pre-specified primary endpoint analysis and sensitivity analyses

	Analysis used	Population	Time period evaluated	Censoring criteria
Primary analysis	Cox regression model	FAS	Visit 3 to date of last patient contact	- Censor at the time of MACE event or at V16 (if no MACE event) or - (LFU) censor at last contact
PP population	Cox regression model	PP	V3 to date of last patient contact or to when the accumulated period of no exposure to IMP >120 days, whichever comes first.	Same as primary analysis or at the date where the accumulated period of no exposure to IMP >120 days (whichever comes first)
On treatment	Cox regression model	FAS	1. Events occurring on randomized treatment only and 2. Events no later than 30 days into an off treatment period (i.e. +30 days)	Patients without a first MACE on treatment or 30 days after (+30 days): censor at time of permanent discontinuation of IMP*
Excluding 30 days	Cox regression model	FAS	Visit 3 to V15 (excludes 30 days after randomization period)	Same as primary analysis
Additional covariates	Same as primary analysis**	FAS	Same as primary analysis	Same as primary analysis
Cluster effect	Random effect Cox	FAS	Same as primary analysis	Same as primary analysis

	regression using sites^ as random effects with treatment group as fixed factor and additional covariates**			
Stratified xrandomizatio n	Stratified cox regression with two strata: (eGFR< 30 mL/min/1.73 m^2 versus eGFR >30 mL/min/1.73 m^2)	FAS	Same as primary analysis	Same as primary analysis
*patients randomized but never exposed are censored at the date of randomization ^ countries were used instead of sites if there were convergence problems ** additional covariates included: sex, region, baseline age (continuous), diabetes duration (continuous), prior cardiovascular events at baseline (yes/no), anti-diabetic medication at baseline (None/1 OAD/>1OAD/Insulin +/-OAD), smoking history (never/prior/current), and eGFR (continuous) at screening LFU: lost to follow up, MACE: major cardiovascular event, IMP: investigational medicinal product				

Subgroup analyses for the primary endpoint

Exploratory analyses of the primary endpoint were evaluated for the following pre-specified subgroups (main effect and interaction with treatment):

- Age: <60 or ≥60 years
- BMI: ≤30 kg/m^2 or >30 kg/m^2
- HbA1c: ≤8.3% or >8.3%
- Diabetes duration: ≤11 years or >11 years
- Region: Europe, North America, Asia, and rest of world[29]
- Cardiovascular risk groups as per inclusion criteria[28]
- Chronic heart failure NYHA class II-III
- eGFR at screening: < 30 mL/min/1.73 m^2 per modification of diet in renal disease (MDRD)
- eGFR at screening: < 60 mL/min/1.73 m^2 per MDRD
- eGFR at screening: < 30 mL/min/1.73 m^2 per Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI)

[28] Age ≥ 50 years at screening and at least one of the below criteria (from **a** to **h** below): a) prior myocardial infarction, b) prior stroke or prior transient ischemic attack (TIA), c) prior coronary, carotid or peripheral arterial revascularization, d) >50% stenosis on angiography or other imaging of coronary, carotid or lower extremity, arteries, e) history of symptomatic coronary heart disease documented by positive exercise stress test or any cardiac imaging, or unstable angina with ECG changes, f) asymptomatic cardiac ischemia documented by positive nuclear imaging test or exercise test or dobutamine stress echo, g) chronic heart failure NYHA class II-III, h) chronic renal failure, having clinically reached a stage corresponding to a glomerular, filtration rate < 60 mL/min/1.73 m2 per Modification of Diet in Renal Disease (MDRD) or < 60 mL/min per Cockroft-Gault formula OR Age ≥ 60 years at screening and meeting at least one of the below criteria (from **i** to **l**):i) microalbuminuria or proteinuria j) hypertension and left ventricular hypertrophy by ECG or imaging, k) left ventricular systolic or diastolic dysfunction by imaging, l) ankle/brachial index <0.9

[29] North America (US, Canada), Asia (China, Taiwan, Korea, India) rest of the world (Brazil, Mexico, Australia, South Africa, Turkey, Russian Federation and UAE)

- Race: White, Black or African American, Asian or Other
- Ethnicity : Hispanic or Latino
- eGFR at screening: < 60 mL/min/1.73 m^2 per CKD-EPI
- Anti-diabetic medications at baseline:
  - No concomitant medications
  - 1 concomitant oral medication
  - >2 concomitant oral medications
  - Insulin with or without oral medications

Secondary time-to-event endpoints:
All secondary time-to-event endpoints were analyzed by Cox regression models using the FAS with treatment as a fixed factor. Additional covariates were included as described for the primary analysis. Of note, no adjustments were made for multiplicity testing.

The pre-specified secondary time to event endpoints are shown in **Table 7.**

Table 7 – Secondary time-to event endpoints

• Time to randomization to first occurrence of **expanded MACE**, either: ○ CV death ○ Non-fatal MI ○ Non-fatal stroke ○ Coronary revascularization ○ Hospitalization for unstable angina pectoris ○ Hospitalization for heart failure	• Time from randomization to first occurrence of a **composite microvascular outcome** defined as any one of the following: • Need for retinal photocoagulation or treatment with intravitreal agents • Vitreous hemorrhage • Onset of diabetes related blindness* • New or worsening nephropathy** • Need for continuous renal-replacement therapy in absence of acute reversible cause • Death due to renal disease
• Time from randomization to **non-CV death**	• Time to randomization to **all-cause death**
• Time from randomization to each individual component of expanded composite cardiovascular outcome	• Time from randomization to each individual component of the composite microvascular outcome and to the retinal and renal components separately
*Snellen visual acuity of 20/200 [6/60] or less , or visual field of <20 degrees in the better eye with best correction **defined as new onset of persistent urine albumin ≥300mg/g creatinine (macro-albuminuria) , or persistent doubling of serum creatinine level and eGFR ≤ 45 mL/min/1.73 m^2 per MDRD	

Exploratory analysis of the development and progression from baseline of albuminuria, nephropathy and renal impairment were also performed.

Other Secondary endpoints:
For the evaluation of data requiring a baseline value, baseline was defined as the value obtained at the randomization visit. If the value at randomization visit was missing and the assessment was also made at screening, the screening value was used as baseline. The exception to this baseline guidance was in the determination of baseline

eGFR. The baseline eGFR was *always* determined at screening (not randomization), since this value was used for stratification.[30]

Both change from baseline to the last assessment during the treatment period and change from baseline to the 3-year assessment during the treatment period was reported for:

- Body weight and waist circumference[31]
- HbA1c[32]
- Fasting[33] lipids (total cholesterol, low density lipoprotein [LDL][34] cholesterol, high density lipoprotein (HDL) cholesterol and triglycerides
- Blood pressure (systolic and diastolic)[35]
- Heart rate[36]
- eGFR as per MDRD at screening
- eGFR as per CKD-EPI at screening

These endpoints were analyzed using a repeated normal mixed model for change from baseline with treatment and anti-diabetic therapy at baseline, region, and sex as factors and corresponding baseline value and age at baseline as covariates with all effects nested within visit; using an unstructured covariance matrix. Supportive analyses for these endpoints were also performed.[37]

[30] In a statistical memo dated February 1, 2016 (before DBL), there is clarification regarding analyses that will be carried out using the **randomization** value of eGFR, which include: subgroup analyses of the primary endpoint; analyses of secondary efficacy endpoints as HbA1c stratified on eGFR; and the stratification of summaries for adverse events into four groups of renal function (eGFR). However the sensitivity analysis with a Cox regression stratified by renal function (eGFR) will be performed based on assessment at time of screening as this is the point in time where stratification was decided. Furthermore, the covariate in the sensitivity analysis of the primary endpoint and secondary analyses will also be by eGFR (MDRD) calculated at randomization.

[31] Body weight (without overcoat and shoes) was recorded at visits 1, 3, 6, 7, 9, 11, 13 and 15. Waist circumference was measured at visits 3, 9 and 15. The subject was measured in the standing position, with an empty bladder, and wearing light clothing. The waist circumference was to be measured to the nearest 0.5 cm (0.2 inches) using a non-stretchable measuring tape.

[32] HbA1c was drawn at visits 1, 3, and 5 to 15. HbA1c was measured in a central laboratory using high performance liquid chromatography

[33] Blood samples of fasting (at least 8 hours without food and or drink) lipids were done at visits 3, 7, 9, 11, 13 and 15.

[34] Was delivered in to groups, calculated and direct and merged without any correction.

[35] Was recorded at visits: 1, 3, 6, 7, 9, 11, 13, and 15. Caffeine, smoking and exercise were to be avoided at least 30 minutes before the measurement. Two measurements at intervals of >2 minutes were to be performed with no talking during the measurement. Before the first measurement was taken, the subject should sit for at least five minutes, with the legs uncrossed and the back and arm supported.

[36] Heart rate was recorded at visits 1,3,6,7,8,11, and 15. Heart rate was recorded over a period of 30 seconds or longer after resting for 5 minutes in a sitting position.

[37] The analysis will use an analysis covariance (ANCOVA) with treatment, anti-diabetic therapy at baseline, region, and sex as factors, and corresponding baseline value and age at baseline as covariates. Last observation carried forward (LOCF) will be used for imputing missing values.

HbA1c was analyzed by: age groups, severe renal impairment, NYHA class II or II at baseline.

Other secondary endpoint analyses included

- Patient reported outcomes (PROs) in a subset of patients[38]
- Incidence of hypoglycemia using the ADA severe and a plasma glucose value of <56 mg/dL with or without symptoms[39]
    - Of note, the analyses of hypoglycemia evaluated events reported until V15 (last treatment visit), since the period between V15 and V16 was off randomized treatment.
- Laboratory parameters (including hematology, biochemistry and antibody measurements)
- Concomitant anti-diabetic medications and time to first insulin use (for insulin naïve patients)
- SAEs and MESIs

Adverse events

This section will detail the definition, collection and adjudication process of the systematically collected adverse events: Medical Events of Special Interest (MESIs) and Serious Adverse Events (SAEs).

Figure 4 shows the relationship between adverse events reported. Overall, adverse events were either serious adverse events (SAEs) or non-serious adverse events.

An SAE was defined as: death; a life-threatening experience (event in which the patient was at risk of death); in-subject hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. An important medical event could be considered an SAE when, based on medical judgment, the event could jeopardize the patient and require medical or surgical intervention to prevent any of the listed events for an SAE.

- A patient was considered to be hospitalized when any of the following were met:
    - Patient is admitted to the hospital/inpatient and stays for treatment/observation for >24 hours
    - Patient is not admitted but stays in the hospital for treatment/observation for >24 hours
    - Administrative, trial-related, social purposes and planned surgical procedures hospitalizations do not constitute AEs or SAEs.

[38] PROs were assessed in subjects from Canada, Denmark, Germany, Ireland, Italy, Netherlands, Spain, Sweden, UK and US at visits 3, 7, 9, 11, 13 and 15 using the European Quality of Life 5 dimensional questionnaire (EQ-5D).

[39] A negative binomial regression model with log-link function and the logarithm of the observation time as offset were used for analysis. The model included treatment, sex, region and anti-diabetic therapy at baseline as factors and age at baseline as covariate.

Reviewer's comment: Although hospitalization for SAEs was defined for a period of >24 hours, there were differences in definitions of what constituted a "hospitalization" for the following categories (as specified in the EAC charter):

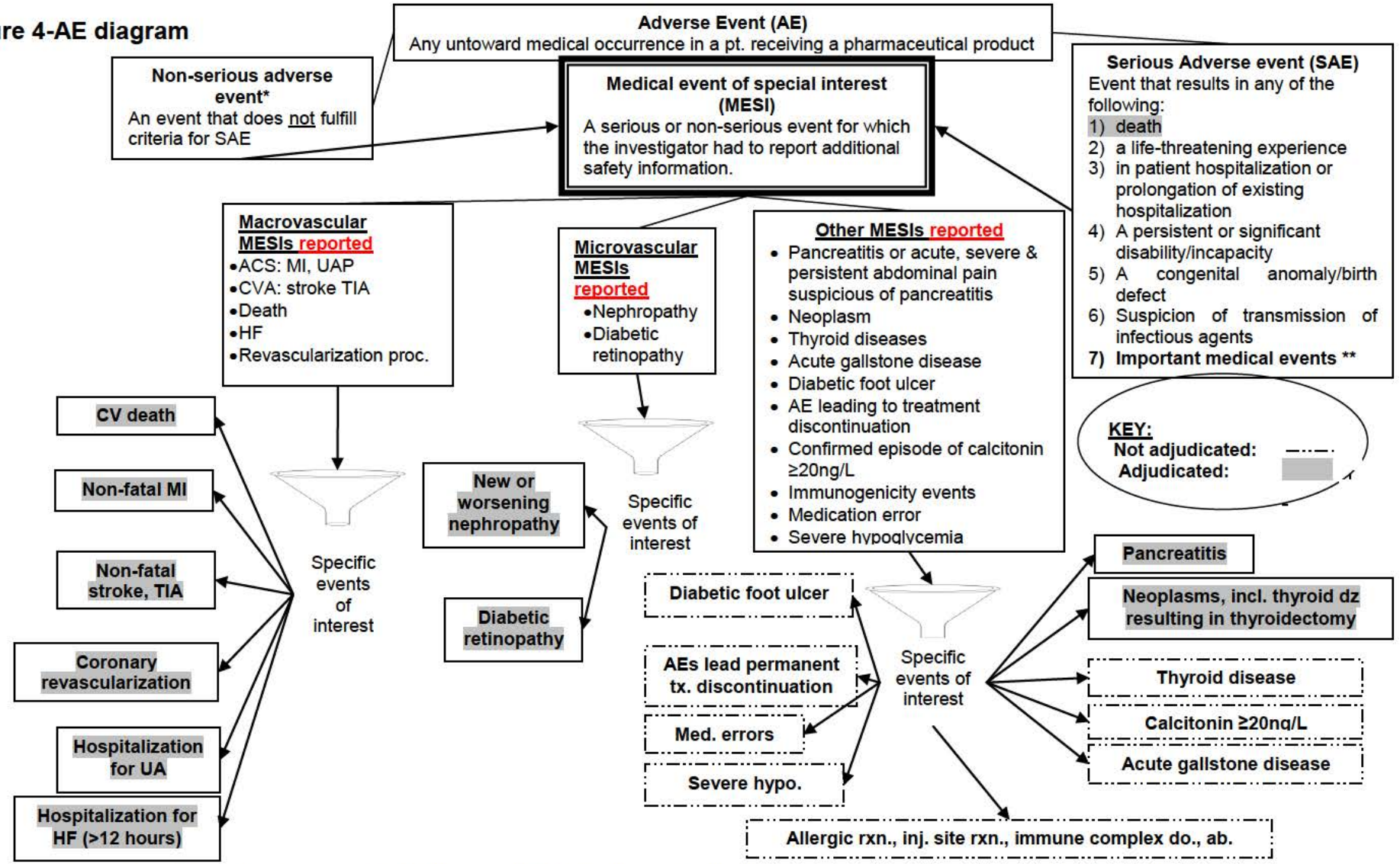
- **Hospitalization for heart failure: specified a hospitalization duration >12 hours**
- **Hospitalization of unstable angina: was defined as "an unscheduled visit to a healthcare facility and overnight admission (does not include chest pain observation units) within 48 hours of the most recent symptoms.**

Medical events of special interest (MESIs) were SAEs or non-SAEs predefined events that the Sponsor continued to monitor and which the investigator had to report additional safety information.

Medical events of special interest (MESI) and SAEs were to be followed until the event(s) "recovered", "recovered with sequela" or was "fatal". Cases of chronic conditions or cancer of SAEs/MESIs ongoing at the time of death (i.e., the patient died from another AE) could be closed with the outcome "recovered" or "not recovered". Cases could be closed with an outcome of "recovering when the patient had completed the trial and was expected to recover.

In order to capture relevant events of special interest, MESIs were defined more broadly than the specific events of interest (i.e., unstable angina pectoris (UAP) was the MESI, with an event of interest of hospitalization for UAP). **Figure 4** shows the relationship between the MESIs collected and the specific event of interest.

Figure 4-AE diagram



*non-serious AEs could be collected if evaluated as related to the trial product by investigator or if other local requirements applied—these were **not** systematically collected
** Event which may jeopardize the patient/require intervention to prevent an SAE. It can be AEs which suggest a significant hazard or puts the patient at risk, such as drug-interaction, contra-indications or precautions, occurrence of malignancies or development of drug dependency or drug abuse.
Proc. = procedures, ACS = acute coronary syndrome, MI= myocardial infarction, UAP= unstable angina, TIA=transient ischemic attack, CV=cardiovascular, HF=heart failure, incl.=including, med=medication, tx= treatment, rxn= reaction, do=disorder, ab=antibody, pt=patient, hypo=hypoglycemia

Adjudication of death and MESIs
For EAC confirmed events, onset date was the EAC adjudicated onset date and not necessarily the onset date reported by the electronic records.

As shown in **Figure 5,** adjudication process was managed by ICON, an external, independent company. Adjudication of deaths and relevant MESIs was done by the event adjudication committee (EAC) in a blinded manner. There were 5 paths for identification of events for adjudication: by investigators, by central ECG readers[40], out of range laboratory values suggestive of nephropathy, pre-defined MedDRA searches (i.e. PTQ searches),[41] and non-investigator reported events identified by the EAC or ICON during review of source data of another event.

The EAC had four sub-committees (cardiovascular, microvascular, pancreatitis and neoplasms). The events marked in **Figure 4** as "adjudicated" were evaluated by the EAC and confirmed or non-confirmed (with the exception of events in the screening failure). Each event sent for adjudication was evaluated independently by two primary adjudicators (refer to section **EAC Charter Summary** for details regarding the adjudication process).

Of note, adjudication of thyroid neoplasms was done by the neoplasm EAC sub-committee.[42] All patients who underwent a thyroidectomy (partial or total) had review of the pathology slides centrally in addition to evaluation at the site level. Both the site pathology report and central pathology report were to be reviewed by the EAC.

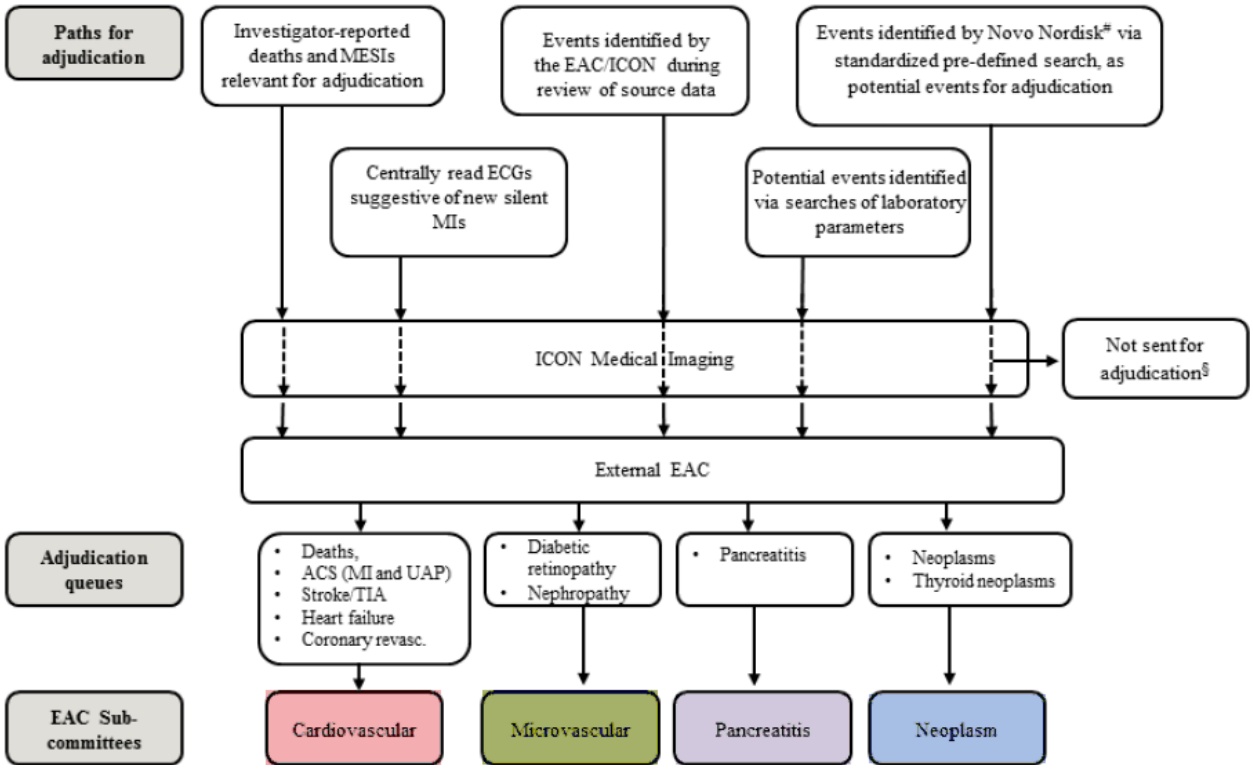
The adjudication of multiple related events was performed by the EAC Chair in a pre-specified manner in order to decrease double-counting of events (refer to section titled **EAC Charter Summary**).

The adjudication of deaths was done by the cardiovascular EAC-subcommittee as "cardiovascular" or "non-cardiovascular death." If the event preceding the death was relevant for adjudication, the preceding event was adjudicated by a second sub-committee; see **Figure 43** in the appendix.

[40] These readers evaluated all ECG readings from scheduled visits and unscheduled visit for new abnormalities. If the central ECG reader identified a significant new abnormality consistent with MI (presence of a new q-wave meeting ECG criteria for MI), the event was sent for adjudication and the investigator was asked to provide relevant source documents.
[41] On all reported AEs to identify potential events for adjudication; If an event was found, the event was sent to ICON for evaluated the event and provided a rationale for why an event should/should not proceed for adjudication.
[42] For patients scheduled for thyroidectomy, patients were asked to consent to have the thyroid tissue sample collected in a tissue bank for future testing of C-cells, such as RETY1062 phosphorylation. Subjects were also asked to consent to be tested (blood sample) to identify germline RET gene mutations associated with MEN 2 syndrome. This RET gene mutation detection was to be conducted in subjects with pathology reports confirming C-cell abnormality (medullary carcinoma or C-cell hyperplasia).

The adjudication of cardiovascular events, microvascular events, pancreatitis, and neoplasms is discussed in detail in section **EAC Charter Summary**, in the appendix**.**

Figure 5 – Pathways for adjudication of MESIs and deaths



#The Novo Nordisk Event Adjudication Group (NN-EAG); events identified by MedDRA searches using pre-defined search terms.

§Events not relevant for adjudication as judged by ICON based on their independent pre-evaluation.

Abbreviations: EAC: event adjudication committee; MedDRA: Medical dictionary for regulatory activities; MESI: medical event of special interest; MI: myocardial infarction; TIA: transient ischaemic attack; UAP: unstable angina pectoris.

Source: CTR Figure 9-3, modified by reviewer (addition of colors)

As shown in **Figure 4,** there were MESIs that were identified by the investigator, MedDRA searches, and by laboratory assessments, but were *not* adjudicated. These events included: acute gallstone disease[43], diabetic foot ulcers[44], immunogenicity

[43]SMQ Functional, inflammatory and gallstone related biliary disorders and SMQ Infectious biliary disorders

[44]Primary and secondary terms: HLT Diabetic complications dermal, HLT Limb therapeutic procedures, HLT Musculoskeletal necrosis and vascular insufficiency, HLT Non-site specific necrosis and vascular insufficiency NEC. Primary terms only: HLT Skin and subcutaneous tissue ulcerations, PT: Wound, PT: Skin necrosis
PTs excluded: Arteriosclerosis, arteriosclerotic gangrene, compartment syndrome, steal syndrome, vascular graft occlusion.

(allergic reactions,[45] injection site reactions[46], and immune complex disease[47]), medication errors[48], and thyroid disease[49]. Other MESIs that were not adjudicated and did not undergo MedDRA searches included: episodes of severe hypoglycemia (identified by the investigator ticking "no" in the eCRF for the question "subject able to treat himself/herself) and adverse events leading to permanent discontinuation of investigational product, if trial products were discontinued more than a few days (at the investigator's discretion).

Hypoglycemia

The hypoglycemia definitions are shown in **Table 8.** The definition included the American Diabetes Association definitions for hypoglycemia and the Novo Nordisk hypoglycemia, (a hybrid between documented symptomatic and asymptomatic hypoglycemia). In addition, the Sponsor defined a nocturnal period, if the hypoglycemia time of onset was between 00:01 and 05:59 (both inclusively). For all severe hypoglycemia episodes, a hypoglycemic episode form in addition to the AE form had to be filled out by the investigator.

Table 8 – Classification of hypoglycemia

	Symptoms? (Yes/No)	Glucose value	Patient able to self-treat (Yes/ No*)
ADA classification: Severe hypoglycemia	Yes	not necessary	No
ADA classification: Asymptomatic hypoglycemia	No	≤70 mg/dL	Yes
ADA classification: Documented symptomatic hypoglycemia	Yes	≤70 mg/dL	Yes
ADA classification: Relative hypoglycemia	Yes	>70 mg/dL	Yes
Novo Nordisk hypoglycemia	Yes or No	<56 mg/dL	yes
*No if food, glucagon, IV glucose was administered by another person due to severe central nervous system dysfunction associated with hypoglycemia			

Clinical laboratory tests

[45]SMQ Anaphylactic reaction (narrow terms only), SMQ Anaphylactic/anaphylactoid shock conditions (narrow terms only), SMQ Angioedema (narrow terms only), SMQ Severe cutaneous adverse reactions (narrow terms only), SMQ Hypersensitivity (narrow terms only)
[46]HLT Administration site reactions NEC, HLT Application and instillation site reactions, HLT Infusion site reactions, HLT Injection site reactions
[47]Immune complex disease (broad search): SMQ Systemic lupus erythematous, (broad and narrow terms) SMQ Vasculitis, (broad and narrow terms), SMQ Guillain-Barre syndrome (narrow terms only). Immune complex disease (narrow search): SMQ for Systemic lupus erythematous, (narrow terms only), SMQ Vasculitis, (narrow terms only), and SMQ Guillain-Barre syndrome (narrow terms only).
[48]HLGT Medication errors, HLGT Product use issues, HLGT Product quality issues, HLGT Device issues
[49]SMQ Hyperthyroidism, SMQ Hypothyroidism, HLGT Thyroid gland disorders (including both primary and secondary linked PTs), PT Biopsy thyroid gland, PT Blood calcitonin abnormal, PT Blood calcitonin increased, PT Ectopic calcitonin production, PT Hypercalcitoninemia

Table 9 shows the routine clinical laboratory tests that were to be performed throughout the duration of the study. The laboratory tests were performed at a central laboratory unless specified. The laboratory results (except for anti-liraglutide antibodies) were to be sent to the investigator on an ongoing basis. If a result was outside the normal range, the investigator was to judge and document if the abnormality was considered clinically significant or not.

Of note, a blinded, independent calcitonin monitoring committee provided recommendations with respect to follow-up of individual patients with elevated calcitonin levels (see appendix, **Table 49**).

Table 9- Clinical laboratory tests in LEADER

HbA1c (visit 1,3, and 5 to 15)	**Fasting **lipids (**visit 3, 7, 9,11,13 and 15) Total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides
Hematology (visit 3, 9 and 15) Hemoglobin, hematocrit, thrombocytes, erythrocytes, leucocytes	**Pregnancy test in females of child bearing potential** (visit 1and15)* Serum human chorionic gonadotropin Urine sticks pregnancy test at any time during the trial if a menstrual period was missed or as required by law
Biochemistry (visit 3,6,7,9,11, 13 and 15) Lipase$^{\Omega}$, amylase$^{\Omega}$, creatinine (also at visit 1 to calculate eGFR), total bilirubin, alanine aminotransferase$^{\Omega}$ **At visit 3,9 and 15** Total calcium, potassium, sodium	**Hormones** (visit 1,7, 9,11,13 and 15) Calcitonin **At visit 16:** Calcitonin for patients with calcitonin >2 times ULN at visit 15 and <ULN at screening ~
Antibodies (visit 3, 7, 9,11,13, and 16) Anti-liraglutide antibodies (in all patients allocated in the US)	**Urinalyses** (visit 3, 7, 9,11, 13 and 15) Urinary albumin-to creatinine ratio (if first morning urine)
Other laboratory tests (to be done as indicated) Tryptase (total and or mature tryptase)$^{£}$, anti-liraglutide and IgE isotype of anti-liraglutide antibodies,$^{£}$ levels of C3 and C4$^{¥}$	
*patients were instructed to notify investigator immediately if they or their partner became pregnant during the trial ******Fasting was defined at least 8 hours without food and or drink except for water ~For these patients, investigator was to consider further monitoring of the patient's calcitonin levels and/or referral to an endocrinologist $^{\Omega}$ additional measurements were to be done locally if persistent, severe abdominal pain suggestive of pancreatitis was reported $^{£}$to be done if acute hypersensitivity to trial product was suspected $^{¥}$ to be done if suspicion of immune complex disease HDL: high density lipoprotein; LDL: low density lipoprotein; ULN: upper limit of normal. Source, Table 9-15 in clinical trial report	

Other safety assessments

The Sponsor also assessed vital signs, including heart rate[50], an electrocardiogram[51] (ECG) and physical exams.[52] Of note, visit specific ECGs underwent central assessment by a blinded central cardiologist (see section **Electrocardiogram Review charter**)

Pancreatitis
In case of suspected/documented acute pancreatitis, the trial product was to be stopped and blood amylase, lipase and ALT were to be measured. If pancreatitis was confirmed based on symptoms, or laboratory measures, an abdominal ultrasound followed by CT scan or MRI was recommended. If acute pancreatitis was confirmed by the EAC adjudication the trial product was not to be re-started.

6 Review of Efficacy

Efficacy Summary

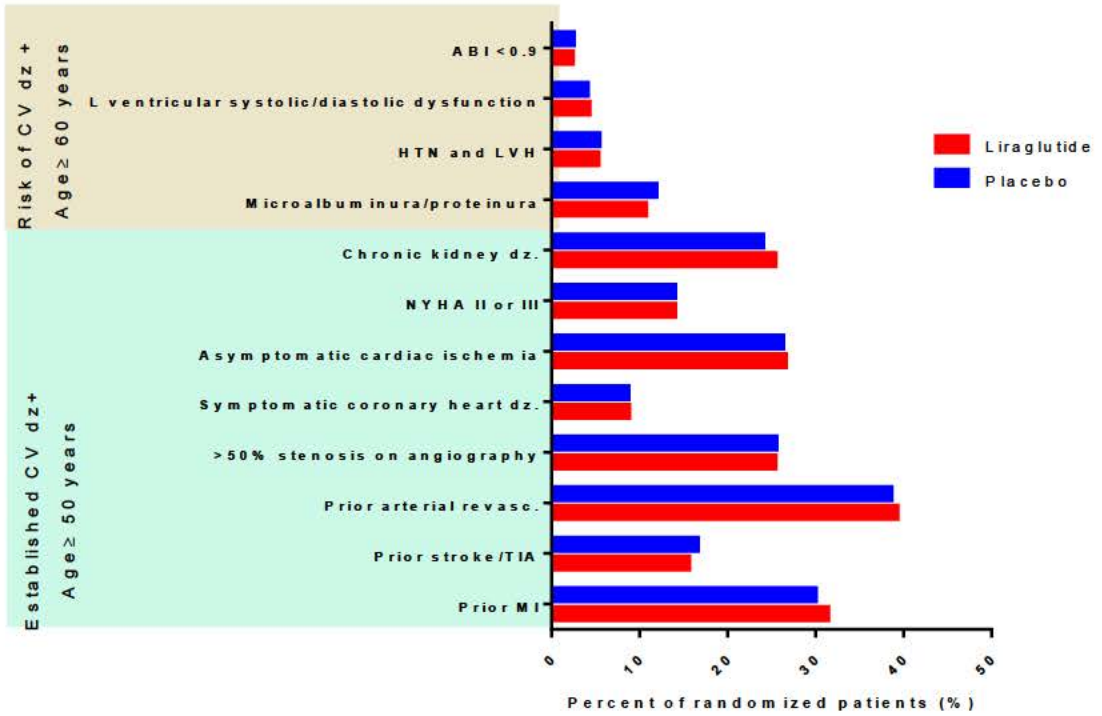
LEADER was a randomized, double-blinded, cardiovascular outcomes trial in which 9340 patients with increased cardiovascular risk and type 2 diabetes mellitus were randomized to liraglutide (n=4668) and placebo (n=4672), at a maximally tolerated dose, as add-on to standard of care treatment.

The patient population was enriched for cardiovascular events by enrolling patients with high cardiovascular risk, in fact, approximately eighty percent of the randomized population had established cardiovascular disease, as per inclusion criteria; see **Figure 6**. Liraglutide and placebo had similar medical histories and baseline anti-diabetic and cardiovascular drug therapies. Over the course of the trial, despite having similar baseline use of anti-diabetic, antihypertensive and lipid lowering medications, post-baseline initiation of these medications was seen in a higher percentage of patients randomized to placebo than liraglutide.

Close to 3% and 3.4% of patients randomized to liraglutide and placebo did not complete the trial of which, vital status was unavailable in less than 0.5% of patients in either group.

[50]Vital signs were assessed on visits 1,3,6,7,9,11,13,15. Heart rate was recorded over a period of 30 seconds or longer, after resting for 5 minutes in the sitting position
[51]ECG was done on visits 3,7,9,11,13,15. ECGs were interpreted as normal, abnormal, not clinically significant, abnormal, clinically significant by the investigator. For any abnormal ECG the investigator had to determine if the ECG fulfilled the criteria for an SAE or MESI.
[52]Physical exams occurred at visit 1 and 15 according to local procedure. The exam included general appearance, skin and lymph nodes, thyroid gland, cardiovascular system, respiratory system and abdomen.

Figure 6 –Baseline cardiovascular disease-related clinical characteristics in the randomized population



Source: reviewer graphed CTR, table 10-8, page 188. It should be noted that many subjects met more than one sub-criterion and that subjects with both established cardiovascular disease and risk factors are only counted in the established cardiovascular disease group. ABI: ankle brachial index; L: Left; HTN: hypertension; LVH: left ventricular hypertrophy; dz: disease; NYHA: New York Heart Association; revasc: revascularization; TIA: transient ischemic attack; MI: myocardial infarction

The primary endpoint was time to the first positively adjudicated occurrence of any component of the MACE composite endpoint (i.e. time from randomization to the first occurrence of cardiovascular death, non-fatal myocardial infarction or non-fatal stroke in the time frame from randomization to visit 16). A total of 608 (13%) patients randomized to liraglutide and 694 (14.9 %) patients randomized to placebo had a first MACE event. Based on a Cox proportional hazard model analysis, liraglutide ruled out a 30% relative increase in MACE, in accordance with the 2008 Guidance for Industry[53] ($p<0.001$). Statistical superiority for MACE was also shown with a 13% relative decrease for liraglutide compared to placebo ($p=0.005$), across multiple sensitivity analyses; see **Table 10**.

[53] *Diabetes Mellitus —Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes*

Subgroup analyses of the primary MACE endpoint showed unfavorable point estimates for two subgroups: North America (specifically the U.S. subgroup), and for patients over the age of 60 years old with cardiovascular risk factors. The p values for interaction for both of these subgroups provided marginal evidence that the size of treatment effect was different between these subgroups; however there was no strong evidence that the direction of treatment effect was different.

Because the protocol pre-specified 611 primary endpoint events were met earlier than expected, a staggered site closure was initiated, which did not affect the pre-specified duration of exposure (i.e. 42 months) for enrolled patients. The mean exposure to investigational drug was 3 years for either treatment group.

There was no adjustment of multiplicity for any of the efficacy endpoints. The statistically significant secondary endpoints are highlighted in **Table 10.** Expanded MACE, (i.e. time from randomization to the first occurrence of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, coronary revascularization, hospitalization for unstable angina pectoris, or hospitalization for heart failure), was experienced in 948 (20.3%) of patients randomized to liraglutide and 1062 (22.7%) of patients randomized to placebo. Based on a Cox proportional hazard model, liraglutide was statistically superior for expanded MACE with a 12% relative decrease for liraglutide compared to placebo (p=0.005). All the components of expanded MACE favored liraglutide over placebo, although a statistical difference was only seen for cardiovascular death.

Cardiovascular death was experienced in 219 (4.7%) of patients randomized to liraglutide and 278 (6%) patients randomized to placebo. Based on a Cox proportional hazard model, liraglutide was statistically superior for cardiovascular death with a 21.7% relative decrease for liraglutide compared to placebo (p=0.007).

All-cause mortality was lower for liraglutide than placebo. A total of 381 (8.2%) patients in the liraglutide and 447 (9.6%) of patients in the placebo group died. Based on a Cox proportional hazard model, liraglutide was statistically superior to placebo with a 15.3% relative decrease (p=0.017). The all cause death findings were primarily driven by cardiovascular deaths. Approximately 30% of the deaths in either treatment arm were due to unknown cause.

Changes in traditional CV risk factors during the trial included body weight, waist circumference, body mass index, blood pressure, lipids and HbA1c. There was a larger reduction in body weight (liraglutide-placebo difference of -2.3 Kg), body mass index (liraglutide- placebo difference of -0.8 kg/m^2), and waist circumference (liraglutide-placebo difference of -2 cm), at three years from the trial start. In addition, there was a larger decrease in systolic blood pressure with liraglutide than placebo (liraglutide-placebo difference of -1.2 mmHg) with a lower decrease in diastolic blood pressure (liraglutide-placebo difference of +0.59 mmHg). Changes in fasting lipids were clinically

similar between treatment groups while change in HbA1c from baseline to 3 years favored liraglutide (liraglutide – placebo of -0.4%).

Summary of microvascular endpoints

The microvascular endpoint in this trial was made up of a composite of nephropathy and retinopathy events (defined as need for retinal photocoagulation or treatment with intravitreal agents; vitreous hemorrhage; onset of diabetes related blindness; new or worsening nephropathy; need for continuous renal-replacement therapy in absence of acute reversible cause and death due to renal disease). A total of 355 (7.6%) patients randomized to liraglutide and 416 (8.9 %) patients randomized to placebo had a positively confirmed adjudicated microvascular event. The microvascular endpoint result was primarily driven by the renal component, specifically macroalbuminuria.

The trends in adjudicated confirmed first nephropathy and first retinopathy events were in opposite direction. With the exception of death due to renal disease, most of the first confirmed nephropathy events favored liraglutide over placebo while the first adjudicated confirmed retinopathy findings generally favored placebo over liraglutide; see **Table 10**. The nephropathy findings were mostly driven by new onset or persistent macro-albuminuria, which favored liraglutide over placebo (3.5% vs. 4.6% of liraglutide vs. placebo patients). Deaths due to renal events were higher (8 for liraglutide and 5 for placebo) in the liraglutide group as compared to placebo. However there were very few such events overall, and the ascertainment of causality for adjudicated deaths due to renal disease was limited by confounders in concomitant illnesses and narratives with limited details.

Assessments for renal safety including trends in estimated glomerular filtration rate (eGFR), trends in serum creatinine, shifts from baseline in eGFR and standard MedDRA Queries revealed either similarity or slight numerical imbalances without clear differences in trends between liraglutide and placebo.

Both vitreous hemorrhage and treatment with photocoagulation/intravitreal agents favored placebo, while diabetic related blindness was only identified in one patient (in the placebo group). Assessments of eye safety did not reveal any clear evidence of increased rates of blindness associated with liraglutide.

Table 10- Time to first EAC confirmed event –FAS- Sponsor's analyses

	Liraglutide		Placebo		Total		Lira/ placebo Hazard ratio	95% CI	Test for HR=1.0 two sided (unless specified)
	N (%)	R	N (%)	R	N (%)	R			
FAS	4668		4672						
PP	4657		4664						
Primary endpoint: MACE*	608 (13)	3.41	694 (14.9)	3.91	1302 (13.9)	3.66	0.868	[0.778; 0.968]	Test for HR≥1.3: <0.001 Test for HR≥1.0: 0.005 Test for HR=1: 0.011
Sensitivity analysis - MACE- PP	*493 (10.6)*	*3.30*	*564 (12.1)*	*3.85*	*1057 (11.3)*	*3.57*	*0.856*	*[0.758;0.966]*	*0.012*
Sensitivity analysis - MACE- on treatment	*414 (8.9)*	*2.85*	*482 (10.3)*	*3.4*	*896 (9.6)*	*3.12*	*0.834*	*[0.732;0.952]*	*0.007*
Sensitivity analysis - MACE on treatment plus 30 days	*469 (10.1)*	*3.13*	*549 (11.8)*	*3.76*	*1018 (10.9)*	*3.44*	*0.831*	*[0.734;0.940]*	*0.003*
Expanded MACE^	948 (20.3)	5.32	1062 (22.7)	5.99	2010 (21.5)	5.65	0.881	[0.807; 0.962]	0.005
Components of MACE and expanded MACE									
Cardiovascular death	219 (4.7)	1.23	278 (6)	1.57	497 (5.3)	1.40	0.783	[0.656;0.934]	0.007
Non-fatal stroke	159 (3.4)	0.89	177 (3.8)	1.00	336 (3.6)	0.94	0.894	[0.721;1.107]	0.303
Non-fatal MI	281 (6.0)	1.58	317 (6.8)	1.79	598 (6.4)	1.68	0.878	[0.747;1.031]	0.111
Hospitalization for unstable angina pectoris	122 (2.6)	0.68	124 (2.7)	0.70	246 (2.6)	0.69	0.980	[0.763;1.258]	0.872
Coronary revascularization	405 (8.7)	2.27	441 (9.4)	2.49	846 (9.1)	2.38	0.912	[0.797;1.044]	0.180
Hospitalization for heart failure	218 (4.7)	1.22	248 (5.3)	1.40	466 (5)	1.31	0.872	[0.727;1.046]	0.140
CV secondary endpoints									
All cause death	381 (8.2)	2.14	447 (9.6)	2.52	828 (8.9)	2.33	0.847	[0.739;0.971]	0.017
Non-cardiovascular death	162 (3.5)	0.91	169 (3.6)	0.95	331 (3.5)	0.93	0.952	[0.768;1.181]	0.656
Microvascular secondary endpoints									
Composite microvascular endpoint	355 (7.6)	1.99	416 (8.9)	2.34	771 (8.3)	2.17	0.841	[0.730;0.969]	0.016
Components of microvascular endpoint									
Nephropathy	268 (5.7)	1.50	337 (7.2)	1.90	605 (6.5)	1.70	0.782	[0.666;0.918]	0.003
Death due to renal disease	8 (0.2)	0.04	5 (0.1)	0.03	13 (0.1)	0.04	1.593	[0.521;4.869]	0.414
Need for continuous renal-replacement therapy	56 (1.2)	0.31	64 (1.4)	0.36	120 (1.3)	0.34	0.869	[0.607;1.244]	0.443
New onset of persistent macro-albuminuria	161 (3.5)	0.90	215 (4.6)	1.21	376 (4.0)	1.06	0.738	[0.602;0.905]	0.004
Doubling of creatinine	87 (1.9)	0.49	97 (2.1)	0.55	184 (2)	0.52	0.890	[0.667;1.189]	0.432
Retinopathy	106 (2.3)	0.59	92 (2)	0.52	198 (2.1)	0.56	1.149	[0.869;1.519]	0.330
Treatment with Photocoagulation/intravitreal agents	100 (2.1)	0.56	86 (1.8)	0.48	186 (2)	0.52	1.159	[0.869;1.546]	0.316

Diabetes related blindness	0 (0.00)	0	1 (0.0)	0.01	1 (0.0)	0	0.335	[0.004;30.847	0.635
Vitreous hemorrhage	32 (0.7)	0.18	22 (0.5)	0.12	54 (0.6)	0.15	1.454	[0.845;2.502]	0.177

FAS: Full analysis set. MACE: major adverse cardiovascular event, EAC: event adjudication committee, CI: confidence interval, HR: hazard ratio, N: number (%) percent of patients with a first EAC confirmed MACE between randomization date and follow up date. Events which occur before randomization date are not used for defining first event. NOTE: for this table, component events of MACE (and expanded MACE) do NOT sum to total number of MACE (exp. MACE).
*Contains the **first** MACE event which includes: cardiovascular death, non-fatal MI, non-fatal stroke
^ contains the **first** expanded MACE event, which includes: cardiovascular death, nonfatal MI, nonfatal stroke, coronary revascularization, hospitalization for unstable angina pectoris or hospitalization for heart failure
Source: CTR Table 14.2.83, page 783 and CTR table 14.2.88, page 788. Reviewer rounded percentages to the nearest 10^{th} decimal place. Highlighted cells are for statistically significant results.

6.1 Indication

Liraglutide is approved for the treatment of two different populations at two different dosing regimens:

- Liraglutide (under the trade name Victoza) at a maximally effective dose of 1.2-1.8 mg is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.
- Liraglutide (under the trade name Saxenda) at a maximally effective dose of 3 mg is indicated for chronic weight management in obese patients (body mass index ≥30 kg/m^2) or overweight patients (body mass index ≥27 kg/m^2) and ≥1 weight-related comorbidity.

The Sponsor aims to expand the indication in Victoza to:

- As an adjunct to standard treatment of cardiovascular risk factors to reduce the risk of major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke) in adults with type 2 diabetes mellitus and high cardiovascular risk.

6.1.1 Methods

My general review strategy for this review was to focus on the pre-specified primary and secondary endpoints; specifically focusing on time to first event analyses. For the cardiovascular safety endpoints section, my review includes *all* cardiovascular events, unless specified. Additional cardiovascular safety endpoints that I evaluated included: pulse, blood pressure, lipids, body weight, BMI, waist circumference and HbA1c.

As part of the evaluation of the cardiovascular endpoints, I performed an audit of a random sample of the adjudication packets. Overall the I agree with the EAC adudication of the cardiovascular events and hence did not re-adjudicate any of the cardiovascular events.

I used a similar approach to the cardiovascular safety evaluation, to evaluate the microvascular endpoints.

6.1.2 Demographics

This section will discuss baseline patient characteristics at the screening visit.

Overall, the patients randomized to liraglutide and placebo were well-matched with regards to demographic baseline characteristics. As shown in **Table 11**, the mean (SD) age of patients was 64 (7.2) years [range: 49- 91]. 54% of patients were 65 years old or younger and ~9% was older than 75 years of age. 64% were men. The population was made up of ~78% Whites, 10% Asians and ~8% Blacks. There were 12% patients with

Hispanic ethnicity. The distribution by region was highest for Europe, North America and "Rest of world", with ~7% of patients coming from Asia.

Table 11- Demographics - FAS

Demographic Variable	Liraglutide (n= 4668)	Placebo (n=4672)
Age, mean ± SD – yr.	64.2 (7.2)	64.4 (7.2)
<65 n (%)	2512 (53.8)	2499 (53.5)
65-74 n (%)	1738 (37.2)	1755 (37.6)
75-84 n (%)	401 (8.6)	393 (8.4)
≥85 n (%)	17 (0.4)	25 (0.5)
Female sex, n (%)	1657 (35.5)	1680 (36)
Race, no (%)		
White	3616 (77.5)	3622 (77.5)
Black/African American	370 (7.9)	407 (8.7)
Asian	471 (10.1)	465 (10)
American Indian or Alaskan Native	5 (0.1)	6 (0.1)
Native Hawaiian or other Pacific Islander	4 (<0.1)	4 (<0.1)
Other	202 (4.3)	168 (3.6)
Ethnic group (Hispanic), no. (%)	580 (12.4)	554 (11.9)
Region, no (%)		
Europe	1639 (35.1)	1657 (35.5)
North America	1401 (30)	1446 (31)
Asia	360 (7.7)	351 (7.5)
Rest of world	1268 (27.2)	1218 (26.1)

N: Number of subjects, %: Percentage of subjects, SD: Standard deviation, FAS: full analysis set, Region is defined as Europe, North America (US, Canada), Asia (China, Taiwan, Korea, India), and the Rest of the world (Brazil, Mexico, Australia, South Africa, Turkey, Russian Federation, United Arab Emirates.
Source: CTR, modified table 10-2, page 183

Table 12 shows the baseline concomitant illness and medical history of patients enrolled. The information was systematically collected in specific medical history forms regarding cardiovascular disease, diabetes complication and pancreas and gall bladder history. In addition to these forms, investigators could also report any other concomitant illnesses (listed as "concomitant illnesses" in **Table 12**). Therefore some of the information captured under this category may vary from other information in the table (i.e. hypertension ~25% under this category, but >90% in the cardiovascular disease form).

On average, patients were obese (mean BMI 32.5 kg/m^2) and had an average duration of diabetes of ~13 years. Cardiovascular history included hypertension for most patients (>90%), followed by a history of ischemic heart disease (>50%) and a history of myocardial infarction (in a third of patients). About18% of patients had a history of heart failure and slightly more than 10% of patients had a history of ischemic stroke. More than half of patients were previous smokers or were current smokers.

In regards to microvascular complications[54] present at baseline, diabetic nephropathy and diabetic neuropathy were common (~40% and ~35% respectively). About 20% of patients had diabetic retinopathy. The presence or absence of neuropathy and retinopathy was based on reported history alone. The presence or absence of nephropathy was corroborated with screening eGFR measurements. The average eGFR at baseline was similar when calculated by the MDRD or CKD-EPI formulas, with an average of ~80 ml/min/1.73m^2, with >60% of patients either having mild or moderate renal failure.

In regards to other comorbidities of interest, gallstone disease (~12%) was more common than cholecystitis (~7%) or pancreatitis (~3%). The average HbA1c for either group was 8.7%. The average lipid values were similar between treatment groups.

Cardiovascular drug therapies included anti-hypertensives (>90% of patients), antiplatelet agents (two-thirds of patients), and lipid lowering agents (three-quarters of patients).

Table 12- Baseline characteristics – FAS

Baseline characteristics	Liraglutide (n= 4668)	Placebo (n=4672)
BMI, kg/m^2 mean ± SD	32.5 (6.3)	32.5 (6.3)
Body weight, kg mean ± SD	91.9 (21.2)	91.6 (20.8)
Systolic blood pressure, mmHg, mean ± SD	135.9 (17.8)	135.9 (17.7)
Diastolic blood pressure, mmHg, mean ± SD	77.2 (10.3)	77.0 (10.1)
Heart rate (beats/minute), mean ± SD	72.7 (11.3)	72.5 (11.4)
Duration of diabetes, year(s), mean ± SD	12.8 (8.0)	12.9 (8.1)

[54] The information regarding microvascular complications was based on a specific CRF form; therefore, patients could have a history of nephropathy without meeting the more strict definition used for the chronic kidney failure evaluation of the selection criteria used in the trial.

Any Cardiovascular history n (%)	4588 (98.3)	4603 (98.5)
Hypertension	4261 (91.3)	4250 (91.0)
Ischemic heart disease	2542 (54.5)	2517 (53.9)
MI	1434 (30.7)	1373 (29.4)
PCI performed	1302 (27.9)	1266 (27.1)
Heart failure	835 (17.9)	832 (17.8)
CABG performed	782 (16.8)	749 (16.0)
Left ventricular diastolic dysfunction	782 (16.8)	799 (17.1)
Left ventricular systolic dysfunction	521 (11.2)	478 (10.2)
Ischemic stroke	512 (11.0)	526 (11.3)
Transient ischemic attack	257 (5.5)	310 (6.6)
Hemorrhagic stroke	53 (1.1)	50 (1.1)
Smoking, n (%)		
Previous smoker	2151 (46.1)	2189 (46.9)
Never smoked	1950 (41.8)	1920 (41.1)
Current smoker	567 (12.1)	563 (12.1)
Microvascular complications n (%)		
Diabetic nephropathy	1882 (40.3)	1917 (41.0)
Diabetic neuropathy	1614 (34.6)	1615 (34.6)
Diabetic retinopathy	978 (21.0)	899 (19.2)
Diabetic foot ulcer	208 (4.5)	196 (4.2)
eGFR, ml/min/1.73m^2 (MDRD), mean ± SD	80.2 (27.5)	80.6 (27.2)
Severe n (%)	117 (2.5)	107 (2.3)
Moderate n (%)	999 (21.4)	935 (20.0)
Mild n (%)	1932 (41.4)	1975 (42.3)
Normal n (%)	1620 (34.7)	1655 (35.4)
eGFR, ml/min/1.73m^2 (CKD-EPI), mean ± SD	78.9 (22.4)	79.3 (21.8)
Concomitant illnesses n (%)*		
Hyperlipidemia	1467 (31.4)	1475 (31.6)
Dyslipidemia	1309 (28.0)	1303 (27.9)
Hypertension	1182 (25.3)	1228 (26.3)
Obesity	837 (17.9)	804 (17.2)
Osteoarthritis	700 (15.0)	693 (14.8)
Pancreatitis n (%)	146 (3.1)	118 (2.5)
Gallstone disease n (%)	569 (12.2)	534 (11.4)
Cholecystitis n (%)	343 (7.3)	324 (6.9)
HbA1c (%), mean ± SD	8.7 (1.6)	8.7 (1.5)
LDL (mg/dL), mean ± SD	88.4 (36.6)	88.8 (36.2)
HDL (mg/dL), mean ± SD	44.7 (12.1)	44.9 (12.1)
Total Cholesterol (mg/dL), mean ± SD	168.1 (44.7)	168.5 (46.1)
Triglycerides (mg/dL), mean ± SD	184.7 (124.5)	184.3 (158.2)
Baseline diabetes medications, n (%)		
OAD only	2436 (52.2)	2375 (50.8)
Insulin only	361 (7.7)	377 (8.1)
Insulin +OAD	1677 (35.9)	1754 (37.5)
Not on insulin/OAD	194 (4.2)	166 (3.6)
Blood glucose lowering drugs (excluding insulin)	4113 (88.1)	4129 (88.4)
Metformin	3540(75.8)	3604(77.1)
SU	2370(50.8)	2363(50.6)
Alpha glucosidase inhibitors	139(3.0)	123(2.6)

TZD	296(6.3)	279(6.0)
DPP4 inhibitors	4(<0.1)	2(<0.1)
GLP1 receptor agonist	0	2(<0.1)
SGLT2 inhibitors	0	0
Glinides	178(3.8)	172(0.1)
Other	0	1(<0.1)
Insulin treatment at baseline	2038 (43.7)	2131(45.6)
Baseline CVD medications, n (%)		
Antihypertensive therapy	4329 (92.7)	4303 (92.1)
Beta blockers	2652 (56.8)	2529 (54.1)
Calcium channel blockers	1538 (32.9)	1479 (31.7)
ACE inhibitors	2417 (51.8)	2350 (50.3)
Angiotensin receptor blockers	1488 (31.9)	1486 (31.8)
Renin inhibitors	42 (0.9)	40 (0.9)
Others	468 (10.0)	454 (9.7)
Diuretics	1953 (41.8)	1953 (41.8)
Loop diuretics	824 (17.7)	837 (17.9)
Thiazides	829 (17.8)	788 (16.9)
Thiazide-like diuretics	325 (7.0)	355 (7.6)
Aldosterone antagonists	254 (5.4)	251 (5.4)
Lipid lowering drugs	3564 (76.3)	3515 (75.2)
Statins	3405 (72.9)	3336 (71.4)
Ezetemibe	165 (3.5)	169 (3.6)
Fibrates	412 (8.8)	432 (9.2)
Niacin	95 (2.0)	95 (2.0)
Other lipid lowering drugs	8 (0.2)	14 (0.3)
Platelet aggregation inhibitors	3205 (68.7)	3121 (66.8)
Acetylsalicylic acid (ASA)	2977 (63.8)	2899 (62.1)
Clopidogrel, Tioclopidine, pasugrel, Tigagrelor	720 (15.4)	745 (15.9)
Anti-thrombotic medication	314 (6.7)	327 (7.0)
Vitamin K antagonists	295 (6.3)	301 (6.4)
Direct thrombin inhibitors	17 (0.4)	12 (0.3)
Direct factor Xa inhibitors	0 (0.0)	1 (<0.1)
Heparin group	5 (0.1)	14 (0.3)

Source: CTR, modified table 10-3 page 184, table 10-9, page 189, Table 10-11, page 191; Table 10-16, page 196, table 10-14, page 194, table 10-17, page 197.
*showing concomitant illnesses affecting at least 15% of patients at screening. This information was obtained from the investigators reporting any other concomitant illness, and therefore this information was not systematically collected.
N: Number of subjects, SD: Standard deviation, BMI: body mass index; PCI: Percutaneous Coronary Intervention, NYHA: New York Heart Association, CABG: Coronary artery bypass graft surgery, ACE: Angiotensin-converting-enzyme, eGFR: estimated Glomerular Filtration Rate, MDRD: Modification of Diet in Renal Disease, CKD-EPI: Chronic Kidney Disease Epidemiology, FAS: full analysis set. Collaboration, Severe Renal Failure defined as subjects with eGFR < 30 ml/min/1.73 m^2 as per MDRD formula, Moderate renal failure defined as subjects with 30<= eGFR < 60 ml/min/1.73 m^2 as per MDRD formula, Mild renal failure defined as subjects with 60<= eGFR < 90 ml/min/1.73 m^2 as per MDRD formula, Normal renal function defined as subjects with eGFR >= 90 ml/min/1.73 m^2 as per MDRD formula. OAD: Oral antidiabetic drug

Reviewer's comment: The randomization of patients to liraglutide and placebo was overall balanced. The baseline characteristics of patients reflect the

intended population by the entry criteria, namely, patients with T2DM at relatively high risk for cardiovascular events`. In comparison to the demographic characteristics of EMPA-REG Outcome trial for empagliflozin, the population randomized in the LEADER trial was overall similar.[55]

Table 51[56] (in the Appendix of this review) and **Figure 6** show the patients who fulfilled the cardiovascular risk inclusion criteria. Overall, 81% of patients had established CV disease and had and age ≥50 years; while ~19% of patients had risk factors for CV disease and were ≥60 years of age. A quarter of the patients had chronic kidney disease (defined as eGFR<60mL/min/1.73m^2 per MDRD).

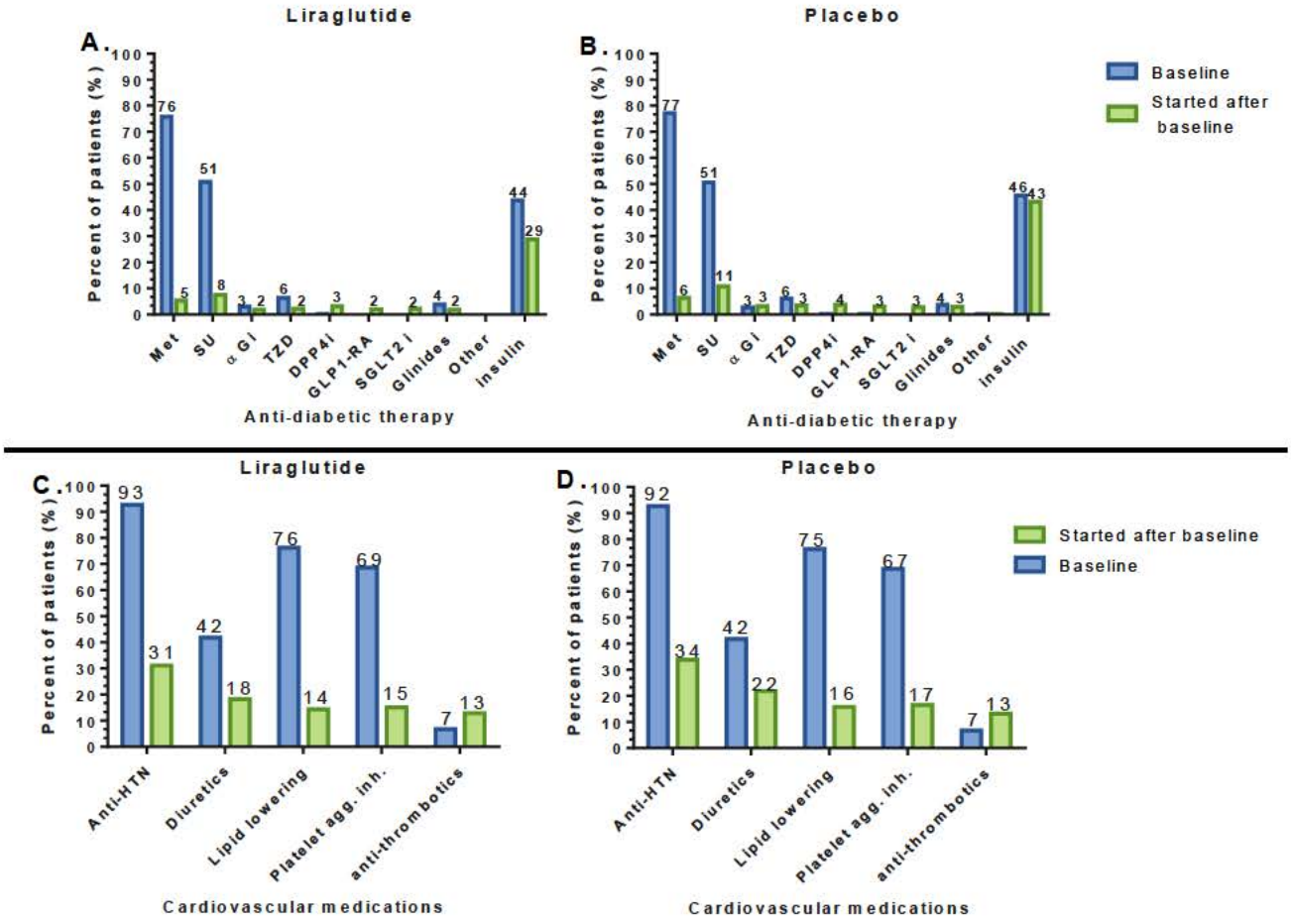
Use of both anti-diabetic and cardiovascular therapies at screening were balanced between liraglutide and placebo. In regards to antidiabetic therapies, 80% of patients were on blood glucose lowering drugs (excluding insulin) of which, metformin was the most common oral anti-diabetic drug (OAD) used (>three-quarters of patients). Notably, there were no patients taking SGLT2is, and only 1 patient in the placebo group was taking a GLP-1 receptor agonist. About 44% of patients were on some sort of insulin treatment at baseline. Only ~4 % of patients did not receive any antidiabetic treatment at baseline.

Figure 7 (**A and B**) shows the screening antidiabetic medications of patients (in blue) and the antidiabetic medications started after baseline (in green). When comparing by treatment group after baseline, there were generally more OADs started for the placebo arm than liraglutide arm. Only 2% - 3% of patients started a SGLT2i (a class to which empagliflozin, an OAD with a CV death reduction indication, belongs) after baseline. Insulin use at baseline was slightly lower for liraglutide than placebo; however, insulin was initiated after baseline in a higher percentage of patients for placebo than liraglutide (43% vs 29% respectively).

When evaluating the cardiovascular medications post baseline, there were a slightly higher number of patients on placebo who started a cardiovascular medication as compared to liraglutide with the exception of antithrombotics which were similar between treatment groups.

[55] Empa Reg demographics: 72% male, 72% white. Mean age 63%, 82% with diabetes>5 years, baseline HbA1c 8.1%76% had coronary artery disease (source Division Director review, page 8).
[56] It should be noted that many subjects met more than one sub-criterion and that subjects with both established cardiovascular disease and risk factors are only counted in the established cardiovascular disease group.

Figure 7 – Antidiabetic medications at baseline and started after baseline (A. Liraglutide; B placebo); Cardiovascular medications at baseline and started after baseline (C. Liraglutide; D. Placebo)



Met: metformin, SU: sulfonylurea, αGi: alpha glucosidase inhibitor; TZD: thiazolidinediones; DPP4i: dipeptidyl peptidase-4 inhibitor; GLP-1RA: glucagon-like receptor agonist, SGLT2i: sodium-glucose cotransporter-2 inhibitors; Anti-HTN: antihypertensives; platelet agg. Inh: platelet aggregate inhibitors.
Source: Reviewer graphed the data in table 10-18 and table 10-17 pages 197-198 of the CSR.
The term "started after baseline" covers initiation of concomitant medication registered at any time after randomization (visit 3).

6.1.3 Subject Disposition

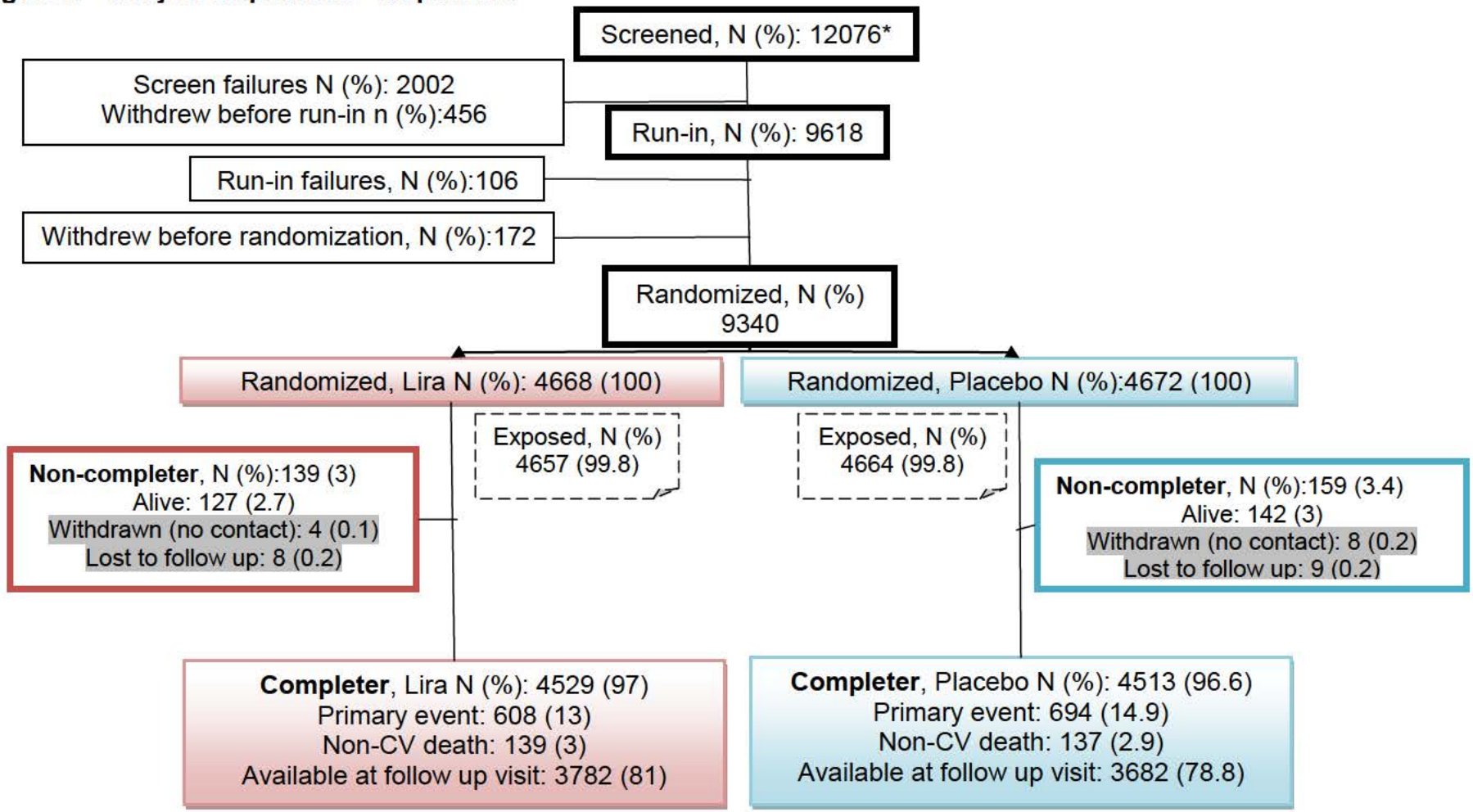
The figure below shows the patient disposition. In total 12,076 patients were screened. Between the screening period and randomization, 2736 patients were lost/ withdrawn. Most of the screen failures were due to not meeting inclusion criteria 5 (HbA1c≥ 7%)[57]

[57] Information obtained from table 14.1.7 in CTR.

9,340 patients were randomized 1:1 to liraglutide (4,668) or placebo (4,672). Over 99% patients were exposed to liraglutide or placebo during the trial.

Similar percentage of patients completed the trial, ~97% of patients randomized to liraglutide or placebo. Similar proportion of patients randomized to either treatment did not complete the trial (~3%).

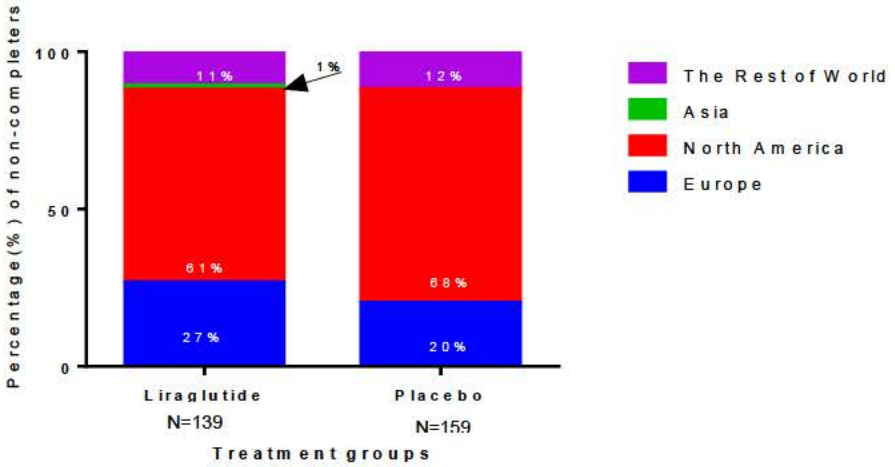
Figure 8 – Subject disposition – all patients



Unknown vital status. *Two subjects were screened twice, and one patient randomized twice for a total of 12078 screens. The number shown in the table reflects the actual number of patients screened. N: Number of subjects %: Proportion of subjects. Run-in: This is defined as the period between screening and randomization. Subjects who were in multiple categories before randomization were counted only once following this hierarchy: Screening failures > Withdrew before run-in > Run-in failures > Withdrew before randomization. Lost-to-follow-up was determined at the follow-up visit (visit16). Subjects, who withdrew but allowed contact, were included in the 'completed trial' category. The 'alive' category includes those subjects who were not available in person but for whom vital status was available. The 'available at follow-up visit' category includes subjects with whom personal contact could be established at the follow-up visit (visit 16). Subjects who were available at follow-up and with a primary event were counted as 'primary' event. Source: information in CTR Table 10-1, page 180.

When evaluating the non-completers by region of origin, the highest percentage was seen in North America, making up 61% and 68% of non-completers in liraglutide and placebo arms, respectively. The United States made up 60% of the total non-completers for liraglutide and 65% of the total non-completers for the placebo arm.

Figure 9 – Non-completers by region



Source: data graphed from CTR, table 14.1.3, page 498

Reviewer's comment: the large proportion of non-completers from the United States is similar between treatment arms and does not suggest that the lack of completion was due to a drug effect.

Treatment Exposure and observation time

Most randomized patients were exposed; only 19 patients were not exposed to investigational treatment (11 for liraglutide and 8 for placebo). The mean exposure to either study medication was approximately 3 years, see **Table 13**. The mean exposure time was slightly larger for liraglutide than placebo (3.11 years vs. 3.04 years, respectively). About 70% of patients were exposed for between 3-5 years.

Exploratory analyses by sex and age (data not shown) was consistent with the overall exposure results.

Table 13 – Exposure- FAS

Exposure category	Liraglutide (n= 4668)	Placebo (n=4672)	Total (N=9340
Total exposure, years	14502	14157	28659
Exposure			
N (%)	4657 (100)	4664 (100)	9321 (100)
Mean (SD)	3.11 (1.27)	3.04 (1.27)	3.07 (1.27)

Median	3.52	3.51	3.52
Min; Max	0.00 ; 5.01	0.00 ; 5.01	0.00 ; 5.01
Duration of exposure			
0-1 years	571 (12.3)	608 (13.0)	1179 (12.6)
1-2 years	318 (6.8)	410 (8.8)	728 (7.8)
2-3 years	357 (7.7)	412 (8.8)	769 (8.3)
3-4 years	2482 (53.3)	2363 (50.7)	4845 (52.0)
4-5 years	927 (19.9)	869 (18.6)	1796 (19.3)
5-6 years	2 (<0.1)	2 (<0.1)	4 (<0.1)

FAS; full analysis set; N: Number of subjects, %: Percentage of subjects, SD: Standard deviation, Exposure is defined as duration in trial excluding periods off treatment with investigational product. A total of 19 subjects were randomized but not exposed to investigational products.
Source: CTR, table 12-2, page 291.table 12-4, page 292

Both treatment groups were balanced when evaluating patient exposure by the duration of drug holidays. In either treatment group about 55% of patients who were exposed and alive at the end of the trial did not take a drug holiday. A quarter of patients in both treatment groups were off investigational drug for a period lasting 1 to 60 days. Only 7% of patients in both treatment groups had a drug holiday exceeding 120 days.

6.1.4 Analysis of Primary Endpoint(s)

The primary endpoint was the time from randomization to the **first** occurrence of MACE, defined as cardiovascular death, non-fatal myocardial infarction or non-fatal stroke in the time frame from randomization to visit 16 (last contact). As mentioned previously, the analysis of the primary endpoint was based on the full analysis set, which included all randomized patients, regardless of drug exposure. There were no patients that were excluded from the FAS.

Table 14 shows the first EAC confirmed events by treatment arms. In total 1302 (13.9%) patients experienced a MACE event. 13% (608 patients) randomized to liraglutide and 14.9% (694 patients) randomized to placebo experienced a MACE event. When considering the components of MACE by treatment arm, the liraglutide arm had slightly lower number of MACEs and lower percentage of patients for each individual component of MACE as compared to placebo.

Reviewer's comment: The lower incidence of MACE in the liraglutide group was also seen when considering the cases of EAC confirmed MACE after follow-up, which are not included in the primary analysis (7 and 13 cases for liraglutide and placebo, respectively).

Table 14 – First EAC- confirmed MACE- FAS

	Liraglutide			Placebo		
	N (%)	E	R	N	E	R
FAS	4668			4672		
PYO	17822			17741		
EAC confirmed 3 point MACE	608 (13)	608	3.41	694 (14.9)	694	3.91
Cardiovascular death	181 (3.9)	181	1.02	227 (4.9)	227	1.28
Non-fatal MI	275 (5.9)	275	1.54	304 (6.5)	304	1.71
Non-fatal stroke	152 (3.3)	152	0.85	163 (3.5)	163	0.92

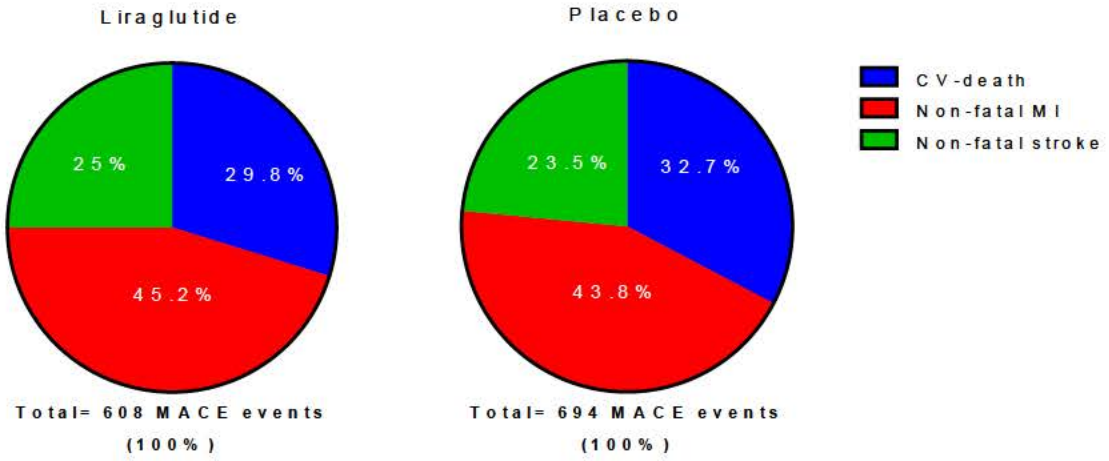
N: Number of subjects, %: Proportion of subjects, E: Number of events, FAS: Full analysis set.
PYO: Patient-years of observation, R: Event rate per 100 observation-years. MACE: major adverse cardiovascular event, EAC: event adjudication committee. Only first (index) events from randomization to follow-up are included.
Source: CTR Table 11-1, page 226

Reviewer's comment: The DMC minutes[58] notes that it was expected that 30% of recruited patients would be in the high risk CVD inclusion group, but actually 80% of the recruited patients were in this group. The inclusion of a higher risk group than expected may have resulted in the number of MACE events observed being double than what was expected.

The components of MACE in each treatment arm are shown by treatment in **Figure 10**. For both liraglutide and placebo, the largest component of MACE was contributed by non-fatal MI (accounting for 44-45% of MACE events), followed by CV-death (~30-33% of MACE events) and non-fatal stroke (24-25% of MACE events).

[58] Open DMC minutes dated May 11, 2012 \\cdsesub1\evsprod\NDA022341\0347\m5\53-clin-stud-rep\535-rep-effic-safety-stud\type-2-diabetes-cv-risk\5354-other-stud-rep\ex2211-3748-additional-information\16-1-01-dmc-mtg-min.pdf

Figure 10 – Percentage of the components of first MACE by treatment group

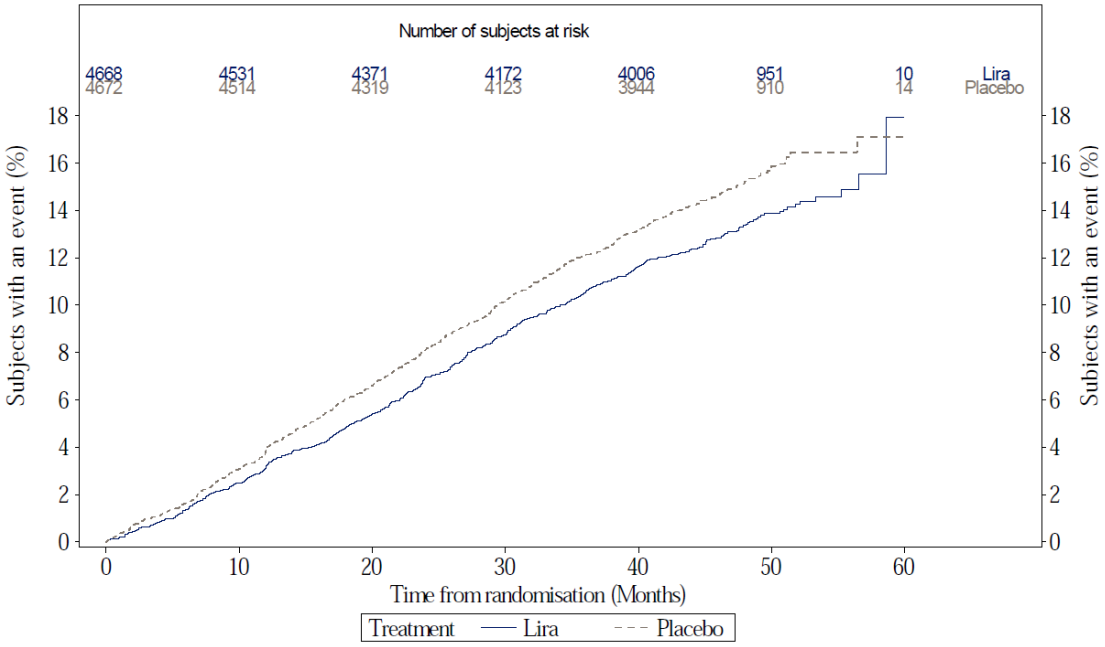


Source: CTR Table 11-1, page 226

Figure 11 shows the Kaplan-Meier plot of EAC-confirmed first MACE over time for liraglutide and placebo. Overall the risk of MACE was lower for liraglutide than for placebo for the entirety of the trial. Because of the staggered closedown on sites (as discussed in Amendment 39[59], after ~54 months of treatment, the progression of the curves were affected by single events.

59 see footnote **15** for details regarding the staggered close down of sites.

Figure 11 – Kaplan-Meier plot of time to first EAC confirmed MACE- FAS



Note: MACE is a composite of cardiovascular death, non-fatal myocardial infarction and non-fatal stroke
Abbreviations: FAS: full analysis set; MACE: major adverse cardiovascular event; EAC: event adjudication committee
Source: CTR figure 11-2, page 227

The additional 86 MACE cases in the placebo than the liraglutide group, resulted in a hazard ratio for time to first EAC-confirmed MACE of 0.87 [95% confidence interval; 0.78-0.97]. The results excluded the 30% excess increased cardiovascular risk for a post-marketing study, specified in the FDA Guidance[60] since the upper 95% CI was below 1.3 (non-inferiority p<0.001). Furthermore, the results were statistically significant for superiority (p=0.005) of liraglutide vs. placebo.

Reviewer's comment: Based on the results of LEADER, the Sponsor aims to add an indication of:

> **"Victoza is indicated as an adjunct to standard treatment of cardiovascular risk factors to reduce the risk of major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke) in adults with type 2 diabetes mellitus and high cardiovascular risk"**

The relative risk reduction of liraglutide is a 13% reduction in risk of MACE. This decrease is similar to the relative risk reduction of empagliflozin, the first ant-diabetic drug product labeled for a cardiovascular benefit: for three point MACE

[60] Guidance for Industry Diabetes Mellitus — Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes
http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm071627.pdf

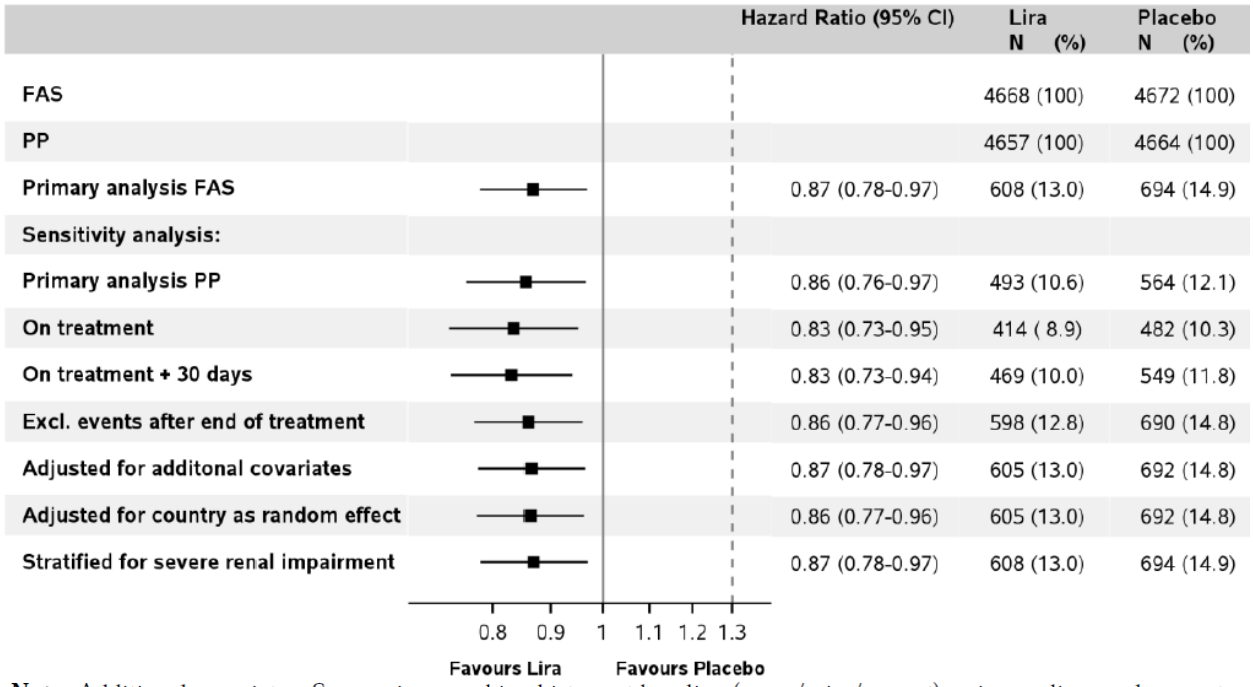
in the EMPA-REG OUTCOME study: 0.86 (0.74, 0.99, p=0.0382).[61] Of note the current indication of empagliflozin is "to reduce the risk of cardiovascular death in adult patients with type 2 diabetes mellitus and established cardiovascular disease". Empagliflozin does not have an indication for MACE in part because the Sponsor of EMPA-REG did not request this indication. FDA analysis revealed that the "differences in major adverse cardiovascular events in the EMPA-REG OUTCOME study were primarily driven by a large difference in occurrence of CV deaths between the groups."[62] In addition, the components of the MACE outcome of EMPA REG were not internally consistent (although the hazard ratios for CV death and non-fatal MI were less than 1, the hazard ratio for non-fatal stroke was >1).

Sensitivity analyses

The sensitivity analyses of the primary endpoint are shown in **Table 6.** Across multiple sensitivity analyses, the results were consistent with the results of the primary analysis, with a 95% CI below 1 and a hazard ratio ranging from 0.83 to 0.87.

[61] Table 3 in Jean-Marc Guettier's Division Director Review, page 11.
[62] Refer to Jean-Marc Guettier's Division Director Review, page 11

Figure 12 – Forest plot of primary analysis and sensitivity analyses



Note: Additional covariates: Sex, region, smoking history at baseline (never/prior/current), prior cardiovascular events at baseline (yes/no), antidiabetic therapy at baseline, age at baseline, diabetes duration at baseline, calculated eGFR-MDRD, where eGFR is the estimated glomerular filtration rate using the modification of diet in renal disease formula.

Abbreviations: FAS: full analysis set; PP: per protocol set; CI: confidence interval; %: proportion of subjects with an event; N: number of subjects.

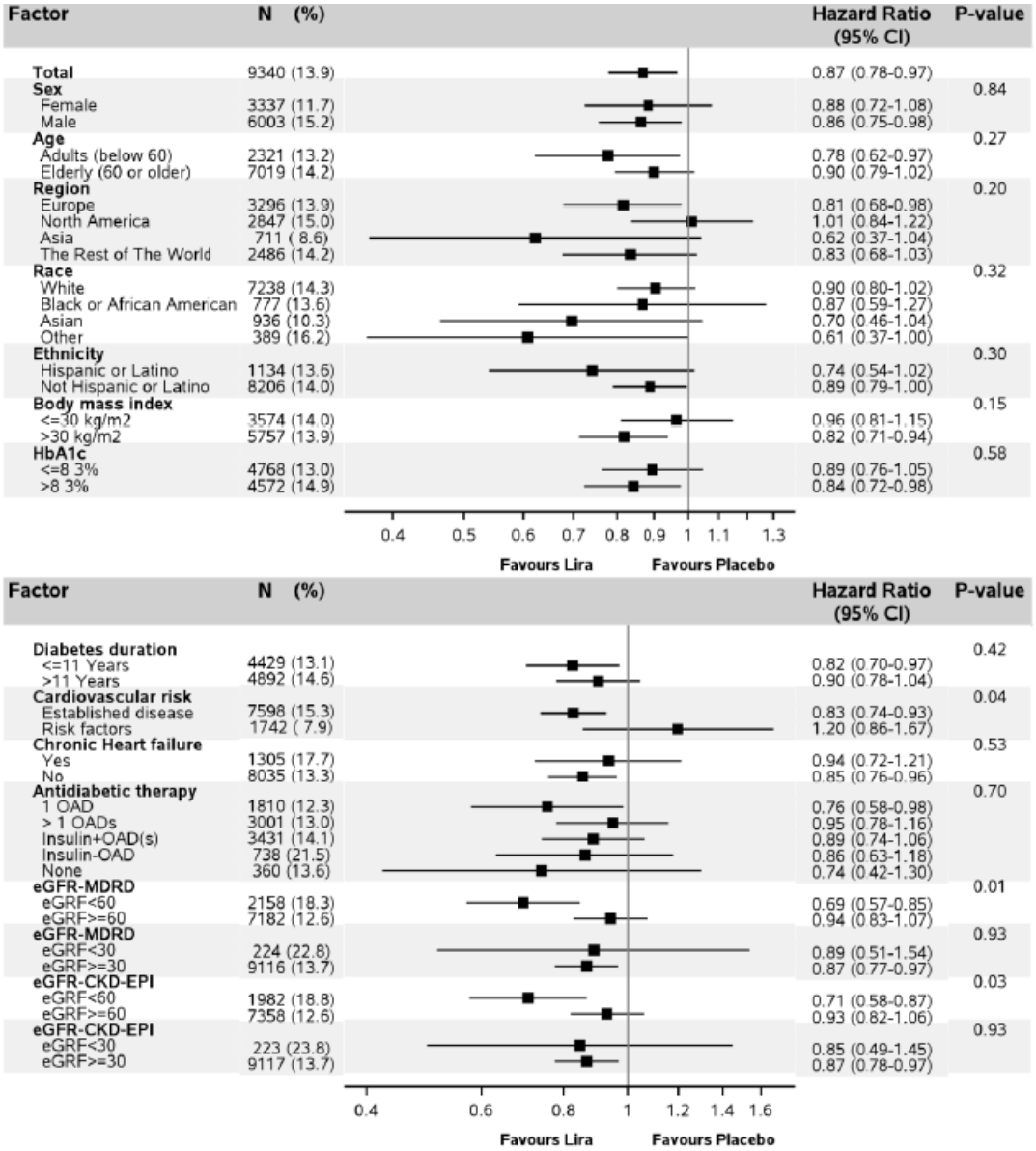
Source: CTR figure 11-3, page 229

Subgroup analyses

As pre-specified in the SAP, the Sponsor performed sub-group analyses. These analyses were performed without adjustments for multiplicity. Across the 37 subgroup analyses, all but 2 analyses had a hazard ratio below 1. Refer to the statistical review by Dr. Hamilton, for the FDA statistical analysis of subgroups.

As shown in **Figure 13**, the two subgroup analyses where the hazard ratios were above 1 were in patients from North America (hazard ratio 1.01), interaction p value 0.2 and in patients' ≥60 years of age with risk factors for cardiovascular disease- meeting inclusion criteria b (hazard ratio 1.20), interaction p value of 0.04. Further discussion of these two subgroups follows below.

Figure 13 – Forest plot of treatment contrast according to subgroups-FAS



Source: Clinical overview, figure 4-5, page 31

An analysis of the breakdown of the region 'North America' by *post hoc* evaluation showed that the hazard ratio estimate was 1.03 [0.84; 1.25] 95% CI for the US (with a p value for interaction of 0.048) and 0.80 [0.42; 1.52] 95% CI for Canada. The US population comprised 88% of the North America region. The Sponsor discussed *post hoc* analyses to evaluate differences to explain the findings. Demographic characteristics showed slight differences between the US population and the Non-US population. In particular patients in the US had a larger BMI, lower systolic, diastolic blood pressure, and total cholesterol, longer diabetes duration and lower mean eGFR (MDRD). Patients in the US also used more insulin, diuretics, lipid lowering drugs and

platelet aggregation inhibitors; see **Table 15**. Changes in HbA1c, changes in body weight and changes in systolic blood pressure are shown in **Table 16**. None of the interaction p values comparing these parameters by US and Non-US population was statistically significant.

Table 15 – Demographic characteristics of US vs. non-US population

	US population		Non-US population	
	Liraglutide (N = 1247)	Placebo (N = 1267)	Liraglutide (N = 3421)	Placebo (N = 3405)
Demographics and baseline characteristics				
Age (years)	64.5	64.5	64.1	64.3
Sex (%; females/males)	35.5/64.5	35.8/64.2	35.5/64.5	36.0/64.0
Body mass index (kg/m^2)	34.6	34.4	31.8	31.7
Systolic blood pressure (mmHg)	132.0	132.3	137.3	137.2
Diastolic blood pressure (mmHg)	74.2	74.1	78.3	78.0
Total cholesterol (mg/dL)	167.4	168.2	171.3	170.8
T2DM duration (years)	13.6	13.4	12.5	12.6
HbA_{1c} (%)	8.8	8.7	8.7	8.6
eGFR (mL/min/1.73 m^2) (MDRD)	76.4	77.2	81.6	81.8
Concomitant medication at baseline				
Antidiabetic medication – excl. insulin (%)	82.3	81.7	90.2	90.9
Insulin (%)	46.9	48.5	42.5	44.6
Antihypertensive therapy (%)	93.7	92.8	92.4	91.8
Diuretics (%)	47.9	42.9	39.6	41.4
Lipid lowering drugs (%)	82.8	79.9	74.0	73.5
Platelet aggregation inhibitors (%)	71.9	70.1	67.5	65.6
Anti-thrombotic medication (%)	8.3	6.6	6.0	6.8
Concomitant medication started exclusively after baseline				
Antidiabetic medication – excl. insulin (%)	22.6	30.9	21.3	28.4
Insulin (%)	31.8	41.0	27.7	44.0
Antihypertensive therapy (%)	30.5	32.0	31.3	34.4
Diuretics (%)	17.0	19.5	18.7	22.8
Lipid lowering drugs (%)	12.3	13.2	14.6	16.5
Platelet aggregation inhibitors (%)	13.2	13.4	15.7	17.7
Anti-thrombotic medication (%)	7.9	8.5	5.1	5.8

Full analysis set. Mean values for demographics and baseline characteristics are presented in table.

Abbreviations: eGFR: estimated glomerular filtration rate; HbA_{1c}: glycosylated hemoglobin; MDRD: modification of diet in renal disease; N: number of patients; T2DM: type 2 diabetes mellitus; US: United States.

Source: Novo briefing packet Appendix 5, table 1

Table 16 – Changes in HbA1c, body weight and systolic blood pressure from baseline to year 3 by US and non-US populations

	US population		Non-US population	
	Liraglutide (N = 1247)	Placebo (N = 1267)	Liraglutide (N = 3421)	Placebo (N = 3504)
HbA_{1c} (%)				
Baseline mean (SD)	8.8 (1.6)	8.7 (1.5)	8.7 (1.6)	8.6 (1.5)
Estimated mean change from baseline	-0.950	-0.649	-1.236	-0.808
ETD (liraglutide vs placebo) [95% CI]	-0.301 [-0.418; -0.183]		-0.429 [-0.495; -0.363]	
	p for interaction = 0.062			
Body weight (kg)				
Baseline mean (SD)	101.2 (22.3)	100.1 (21.8)	88.5 (19.7)	88.4 (19.4)
Estimated mean change from baseline	-3.522	-0.871	-2.456	-0.329
ETD (liraglutide vs placebo) [95% CI]	-2.651 [-3.207; -2.095]		-2.127 [-2.442; -1.811]	
	p for interaction = 0.108			
Systolic blood pressure (mmHg)				
Baseline mean (SD)	132.0 (18.0)	132.3 (16.9)	137.3 (17.5)	137.2 (17.8)
Estimated mean change from baseline	-0.026	0.188	-1.942	-0.424
ETD (liraglutide vs placebo) [95% CI]	-0.215 [-1.691; 1.262]		-1.518 [-2.338; -0.699]	
	p for interaction = 0.130			

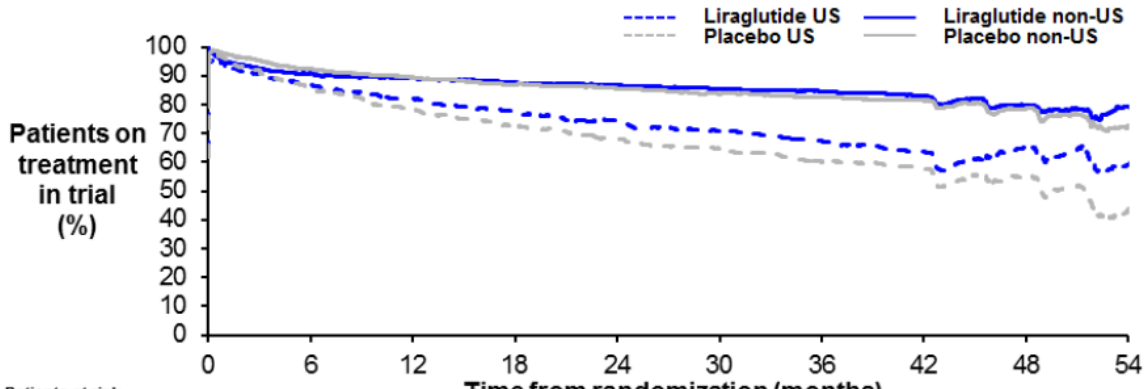
Full analysis set. Change from baseline to 3 year analyzed using MMRM with an unstructured covariance matrix. Treatment, sex, region and antidiabetic therapy at baseline are included as fixed effects and baseline HbA_{1c} or baseline body weight or systolic blood pressure and age as covariates, all nested within visit. The model also includes subgroup and the interaction between treatment and subgroup, both nested within visit.

Abbreviations: CI: confidence interval; ETD: estimated treatment difference; HbA_{1c}: glycosylated hemoglobin; MMRM: mixed model repeated measurement; N: number of patients; SD: standard deviation; US: United States.

Source: Novo briefing packet Appendix 5, table 2

The Sponsor states that a notable difference to explain the difference in findings is that exposure to trial product was lower for the US population (73%) than non-US population (87%); see **Figure 14** . It is also worth noting that 27% of randomized patients were from the US. Additional analyses by the Sponsor evaluated the rate of first MACE in placebo, which was similar for the US and non-US populations.

Figure 14 – Patients in the US vs. Non-US on treatment



Patients at risk										
US										
Liraglutide	1247	1235	1220	1205	1188	1167	1154	1126	483	166
Placebo	1267	1256	1243	1221	1209	1188	1173	1162	490	158
Non-US										
Liraglutide	3421	3395	3368	3341	3306	3263	3214	3182	1196	297
Placebo	3405	3385	3354	3314	3260	3210	3160	3100	1189	287

Source: Sponsor's Briefing Document, Figure 8

Reviewer's comments: The p value for interaction of 0.048 is marginal evidence that the size of the treatment effect may be different between the US and non-US subgroups. However there is not strong evidence that the direction of the treatment effect was different. These results could suggest a possible inconsistency in the effect for MACE across subgroups.

This interaction is worth noting, because approval of a cardiovascular benefit indication would be based on the assumption that the overall trial results are applicable to US patients and US standard of care.

In the June 20, 2017 Advisory Committee meeting, there was an extensive discussion about what these subgroup findings meant. Overall, the FDA did not agree that the Sponsor's on-treatment analysis were the most appropriate way to fully explain the US vs. Non-US differences. Therefore, the FDA was not prepared to endorse the concept that exposure could explain the US findings.

Some panel members found the lower adherence to therapy convincing, particularly in light of the Sponsor's presentation of the glycemic trends for the US vs. non-US, which were similar to the MACE findings, i.e. less effect in the US population. The majority of panel members, 17 out of 19 felt that there was substantial evidence that liraglutide reduces CV risk in patients with type 2 diabetes, the remaining members did not agree (refer to page 133). The majority of the panel struggled with the US vs. non-US subgroup findings.

The second subgroup with trends favoring placebo was the patients ≥60 years of age with risk factors for cardiovascular disease. This group had a HR: 1.20 [0.86; 1.67] 95% CI); with a test for interaction of *p*-value of 0.04. Approximately 19% of randomized

patients were in this subgroup; and this subgroup accounted for only ~10% of first MACE events.

Patients with CV risk factors and age ≥ 60 years included a baseline slightly larger proportion of females, slightly higher systolic blood pressure, slightly higher total cholesterol and slightly higher eGFR. At baseline, there were also fewer patients age ≥ 60 years on lipid lowering therapy, platelet aggregation inhibitor than patients with established cardiovascular disease [CVD] or CKD and age ≥ 50 years; see **Table 17**. **Table 18** shows the change in HbA1c, body weight and systolic blood pressure from baseline after 3 years. There were no statistically significant interaction p values comparing these parameters by patients with established CVD or CKD vs. patients with CV risk factors. The Sponsor states that these findings are likely due to the small composition of an imprecise estimate due to small size of the patients meeting criteria 3b.

Reviewer's comment: Similar to the US vs. Non-US subgroup, the 3a vs. 3b subgroup has a marginal p value for interaction, which again does not provide strong evidence that the direction of the treatment effect was different. This interaction is worth noting, however because the Sponsor seeks an indication for both primary and secondary cardiovascular disease prevention.

The Advisory Committee had an extensive discussion about this subgroup. During the discussion period, multiple members felt that the population with events were patients with established cardiovascular risk (i.e. 3a). Dr. Blaha (a cardiologist) noted that the inclusion criteria categories do not strictly describe patients in need of primary or secondary prevention. Dr. Rosenberg (a cardiologist) noted that the level of risk in each patient should be assessed, and that patients with higher risk will likely benefit more. Some members recommended that because the benefit was seen mainly in patients with establised CV disease that liraglutide be labeled for a benefit for this group only; refer to page 133.

Table 17 – Demographic characteristics of inclusion criteria 3a vs. 3b

	Inclusion criterion #3a: Established CVD or CKD		Inclusion criterion #3b: CV risk factors	
	Liraglutide (N = 3831)	Placebo (N = 3767)	Liraglutide (N = 837)	Placebo (N = 905)
Demographics and baseline characteristics				
Age (years)	63.8	64.0	65.0	65.0
Sex (%; females/males)	33.4/66.6	33.7/66.3	45.3/54.7	45.5/54.5
Body mass index (kg/m^2)	32.6	32.5	32.2	32.5
Systolic blood pressure (mmHg)	134.0	135.0	138.0	136.6
Diastolic blood pressure (mmHg)	77.0	76.7	78.5	78.0
Total cholesterol (mg/dL)	168.1	168.5	180.3	176.6
T2DM duration (years)	12.9	13.0	12.4	12.4
HbA_{1c} (%)	8.7	8.6	8.9	8.7
eGFR (mL/min/1.73 m^2) (MDRD)	78.0	78.5	90.5	89.2
Concomitant medication at baseline				
Antidiabetic medication – excl. insulin (%)	87.3	87.6	91.8	91.5
Insulin (%)	44.8	46.8	38.4	40.8
Antihypertensive therapy (%)	94.4	93.7	84.9	85.4
Diuretics (%)	42.8	43.8	37.3	33.6
Lipid lowering drugs (%)	80.0	79.1	59.9	59.3
Platelet aggregation inhibitors (%)	74.4	73.3	42.2	39.7
Anti-thrombotic medication (%)	7.2	7.5	3.8	3.4
Concomitant medication started exclusively after baseline				
Antidiabetic medication – excl. insulin (%)	21.6	28.6	22.1	30.9
Insulin (%)	29.3	43.4	26.5	42.7
Antihypertensive therapy (%)	30.4	33.3	34.2	35.6
Diuretics (%)	18.3	22.2	18.0	21.0
Lipid lowering drugs (%)	12.6	14.4	20.1	20.4
Platelet aggregation inhibitors (%)	14.4	15.8	17.8	19.8
Anti-thrombotic medication (%)	6.2	7.1	4.4	4.5

Full analysis set. Established CVD or CKD: patients enrolled based on the inclusion criterion #3a 'established cardiovascular disease or chronic kidney disease and age ≥ 50 years'. CV risk factors: patients enrolled based on the inclusion criterion #3b 'cardiovascular risk factors and age ≥ 60 years'. Mean values for demographics and baseline characteristics are presented in table.

Abbreviations: CKD: chronic kidney disease; CV: cardiovascular; CVD: cardiovascular disease; eGFR: estimated glomerular filtration rate; HbA_{1c}: glycosylated hemoglobin; MDRD: modification of diet in renal disease; N: number of patients; T2DM: type 2 diabetes mellitus.

Source: Novo briefing packet Appendix 5-table 4

Table 18 – Changes in HbA1c, body weight and systolic blood pressure from baseline to year 3 by inclusion criteria 3A vs.3b

	Inclusion criterion #3a: Established CVD or CKD		Inclusion criterion #3b: CV risk factors	
	Liraglutide (N = 3831)	Placebo (N = 3767)	Liraglutide (N = 837)	Placebo (N = 905)
HbA_{1c} (%)				
Baseline mean (SD)	8.7 (1.5)	8.6 (1.5)	8.9 (1.7)	8.7 (1.5)
Estimated mean change from baseline	-1.179	-0.768	-1.080	-0.753
ETD (liraglutide vs placebo) [95% CI]	-0.411 [-0.475; -0.347]		-0.326 [-0.457; -0.196]	
	p for interaction = 0.235			
Body weight (kg)				
Baseline mean (SD)	92.5 (21.1)	92.0 (20.6)	89.1 (21.4)	89.8 (21.2)
Estimated mean change from baseline	-2.889	-0.527	-2.066	-0.256
ETD (liraglutide vs placebo) [95% CI]	-2.362 [-2.668; -2.057]		-1.810 [-2.433; -1.187]	
	p for interaction = 0.119			
Systolic blood pressure (mmHg)				
Baseline mean (SD)	135.4 (17.9)	135.7 (18.0)	138.0 (16.9)	136.6 (16.5)
Estimated mean change from baseline	-1.553	-0.685	-0.959	1.481
ETD (liraglutide vs placebo) [95% CI]	-0.868 [-1.667; -0.070]		-2.441 [-4.058; -0.823]	
	p for interaction = 0.088			

Full analysis set. Established CVD or CKD: patients enrolled based on the inclusion criterion #3a 'established cardiovascular disease or chronic kidney disease and age ≥ 50 years'. CV risk factors: patients enrolled based on the inclusion criterion #3b 'cardiovascular risk factors and age ≥ 60 years'. Change from baseline to 3 year analyzed using MMRM with an unstructured covariance matrix. Treatment, sex, region and antidiabetic therapy at baseline are included as fixed effects and baseline HbA_{1c} or baseline body weight or systolic blood pressure and age as covariates, all nested within visit. The model also includes subgroup and the interaction between treatment and subgroup, both nested within visit.

Abbreviations: CI: confidence interval; CKD: chronic kidney disease; CV: cardiovascular; CVD: cardiovascular disease; ETD: estimated treatment difference; HbA_{1c}: glycosylated hemoglobin; MMRM: mixed model repeated measurement; N: number of patients; SD: standard deviation.

Source: Novo briefing packet Appendix 5- table 5

Discussion of the components of MACE

This section will discuss the individual components of MACE by evaluating both the time to event analyses for each component (i.e. time to first non-fatal myocardial infarction, time to first non-fatal stroke, and time to cardiovascular death), which were pre-specified as secondary endpoints in this trial. The discussion of these endpoints is carried out in this section (rather than in the secondary endpoints section), since understanding of the MACE components is necessary in an overall assessment of the primary endpoint.

In addition, in order to have a global understanding of the components of MACE, this section will also discuss the overall safety of the total findings (i.e. fatal/non-fatal, recurrent events) for myocardial infarction, stroke and CV death.

MI discussion
The EAC charter (**Table 44**) describes acute coronary syndrome (ACS) as a spectrum of conditions ranging from: unstable angina pectoris (UAP), non-ST elevation myocardial infarction (MI) and ST elevation MI. Myocardial infarction will be addressed in this section; unstable angina pectoris will be addressed in the secondary endpoints section of this document.

Changes to the EAC charter definition of myocardial infarction are described in **Table 42.** None of the changes to the EAC definition of myocardial infarction required re-adjudication of identified cases.[63]

Although the definitions for MI were generally in accordance with the 2010 FDA Standardized Definitions for Cardiovascular Outcomes Trials, the interpretation MI events was still somewhat open to interpretation by the EAC as described below.

The definition for acute MI stated that "The term "MI" should be used when there is evidence of myocardial necrosis in a clinical setting consistent with myocardial ischemia. MI may be adjudicated for an event that has characteristics of a MI but which does not meet the strict definition because biomarker or electrocardiographic results are not available." Although this definition may be clinically relevant it allows for a more liberal interpretation which may over-capture events under this definition. An example of this over-capture is illustrated in the narrative below:

> Subject ID (b) (6) is a 65 year old man with history of coronary artery disease, peripheral vascular disease who was admitted for new onset tachycardia and a syncopal episode in the past 1-2 months. Patient was documented as having atrial flutter with a 2:1 conduction alternating with atrial fibrillation. There was one reported troponin value of 0.04 (reference range 0.02-0.03 ng/mL) during hospitalization. There was no CK-MB performed. Patient underwent an echocardiogram with no regional wall motion abnormalities. The patient was discharged with plans for the patient to have an ablation procedure as an outpatient. The EAC adjudicators adjudicated this event as a symptomatic NSTEMI-Type 2 (comments: aflutter with small NSTEMI) and silent NSTEMI,

[63] Changes to the MI definition in the EAC charter included changes in version 2 (update definition based on cardiology organizations), version 4 (silent MI definition added to definition), version 5 (prior MI definition was removed from charter), version 7 (criteria for multiple assessment of ECGs when patient had one positive adjudicated MI was added and MI definition regarding ECG mm requirement for NSTEMI/STEMI was removed). Of note, the first MI was adjudicated on May 22, 2011 (after version 5 of the EAC charter).

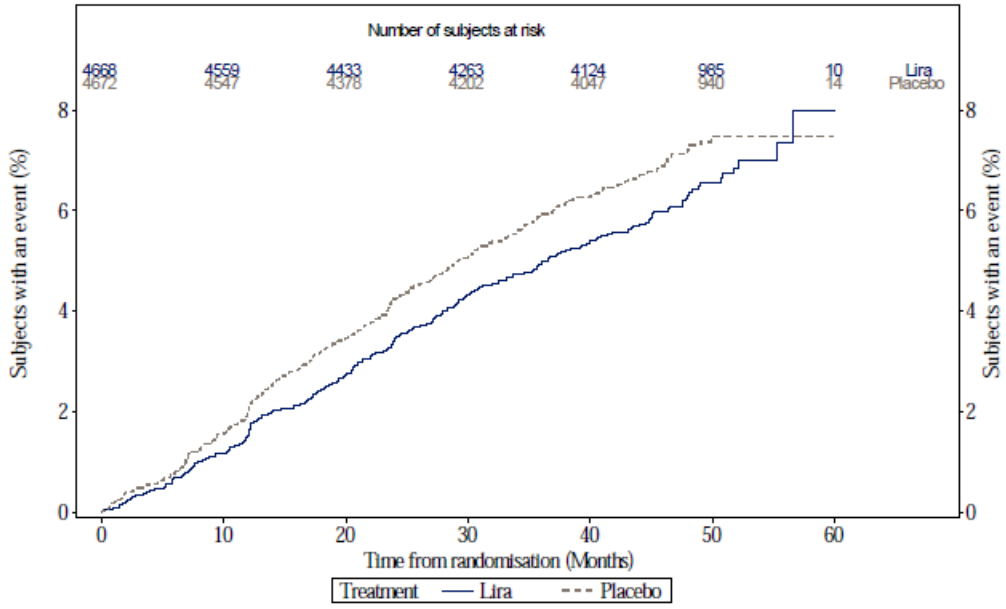
type 2 (comments: 2/2 AF). [64] Of note, the investigator reported this event as atrial fibrillation.

Reviewer's comment: the classification of the event in the narrative as a non-fatal MI is inconsistent with the overall clinical picture for this patient, and seems to be solely based on the single, mildly elevated troponin value. In an exploratory analysis of the adjudication dataset, there were few patients identified with mild troponin elevations and rhythm-related-investigator-reported adverse events that were classified as MI by the EAC. These few events are unlikely to overall change the trends in MI findings for LEADER.

Time to first non-fatal MI

There were a total of 598 non-fatal MIs identified in the analysis of time to first non-fatal MIs. The difference in non-fatal MIs between treatment arms was made up by an additional 36 events in the placebo group as compared to the liraglutide group. The Kaplan-Meier plot (**Figure 15**) shows that there was no significant difference between treatment arms; treatment hazard ratio based on the Cox regression model, was 0.88 [95% confidence interval; 0.75 -1.03].

Figure 15 – time to first EAC confirmed non-fatal myocardial infarction



Source: CSR Figure 11-7, page 238

[64] Of note, the event was brought to the reviewer's attention by OSI, who during the inspection noted that the investigator documentation was consistent with atrial fibrillation, while the EAC adjudication was for MI. Refer to the adjudication package: \\CDSESUB1\evsprod\NDA022341\0356\m5\53-clin-stud-rep\535-rep-effic-safety-stud\type-2-diabetes-cv-risk\5351-stud-rep-contr\study-report-ex2211-3748\832\patient-3748-832100-eac.pdf

Overall MI discussion

Figure 55 (in Appendix) shows the event flow for ACS event. Overall, half of the events sent for adjudication were confirmed by the EAC as ACS events. Of these confirmed events there were 828 first events of ACS and 233 recurrent events between randomization and visit 16.

Table 19 shows the EAC-confirmed acute MI events. In either treatment group, over 85% of myocardial infarction events were non STEMIs. Liraglutide had a slightly greater proportion of patients with STEMIs than placebo (13.4 vs. 9.3% respectively).

Over 95% of MIs were non-fatal with fewer fatal MIs for liraglutide than placebo (4.7% vs. 6.7%). There were also fewer patients experiencing a recurrent MI in the liraglutide than the placebo group (18.7% vs 19.5%).

When considering the magnitude of biomarker elevations, elevations tended to be lower for liraglutide than placebo, for elevations of 5-10 or >10 times the upper range limit.

Table 19 – EAC confirmed acute MI index events- FAS

	Liraglutide N (%)	Placebo N (%)
Number of events	359 (100.0)	421 (100.0)
STEMI	48 (13.4)	39 (9.3)
Non STEMI	311 (86.6)	382 (90.7)
Symptomatic MI	297 (82.7)	344 (81.7)
Silent MI	62 (17.3)	77 (18.3)
Type 1 (spontaneous)	280 (78.0)	324 (77.0)
Type 2 (secondary)	64 (17.8)	69 (16.4)
Type 3 (SCD due to suspected MI)	5 (1.4)	10 (2.4)
Type 4a (peri-PCI)	6 (1.7)	11 (2.6)
Type 4b (stent thrombosis)	4 (1.1)	7 (1.7)
Type 5 (peri-CABG)	0	0
Troponin available as biomarker	246 (68.5)	310 (73.6)
Only CK-MB available as biomarker	4 (1.1)	9 (2.1)
<1 times URL	1 (0.3)	2 (0.5)
1-3 times URL	62 (17.3)	68 (16.2)
>3-5 times URL	34 (9.5)	37 (8.8)
>5-10 times URL	23 (6.4)	40 (9.5)
>10 times URL	130 (36.2)	172 (40.9)
No biomarker	109 (30.4)	102 (24.2)
Non-fatal MI	342 (95.3)	393 (93.3)
Fatal MI	17 (4.7)	28 (6.7)
Recurrent MI	67 (18.7)	82 (19.5)

E: Number of events, %: Proportion of events. FAS: full analysis set. SCD: sudden cardiac death, PCI: Percutaneous coronary intervention, CABG: Coronary artery bypass graft, EAC: Event adjudication committee, STEMI: ST-elevation myocardial infarction, MI: Myocardial infarction, CK-MB: Creatine kinase, muscle and brain, URL: Upper range limit, ACS: acute coronary syndrome, Index events with EAC onset date from randomization date to follow-up are included.
Source: modified CTR Table 12-22, page 335

Silent MI discussion

As previously noted, LEADER included silent MIs in the definition of adjudicable myocardial infarction in version 4 of the EAC charter (before the adjudication of any events). Silent MIs were included in the non-fatal MI component of MACE. The Sponsor systematically collected ECGs at predefined visits, which were centrally read and reported to the EAC, if the event met criteria for adjudication. In addition to the ECG readings, the EAC charter also defined silent MIs by "Imaging evidence of a region of loss of viable myocardium that is thinned and fails to contract, in the absence of a nonischemic cause or autopsy evidence of a healed or healing MI."

The inclusion of silent MI in the non-fatal MI MACE component in LEADER contrasts with the approach in the recently approved cardiovascular outcomes trial, EMPA-REG trial for empagliflozin; where silent MIs were not part of the primary MACE endpoint.

As shown in **Table 19**, less than a quarter of events were silent MIs, with a slightly less proportion in the liraglutide than placebo (17.3% vs. 18.3%).In order to understand how silent MIs contributed to the overall MACE findings, I asked the Sponsor to perform an exploratory analysis of MACE *excluding* patients experiencing silent MI's from the primary endpoint. The result of the Sponsor's analysis was consistent with the primary MACE results (hazard ratio 0.858 [95% confidence interval 0.766; 0.961][65].

Non-fatal stroke

Cerebrovascular events were classified as a transient ischemic attack (TIA) or a stroke. Cerebrovascular events with duration of less than 24 hours were considered TIAs. Strokes were further characterized as: ischemic, hemorrhagic or undetermined, as per the EAC charter definitions (**Table 44** in appendix).

Previous history of ischemic stroke, hemorrhagic stroke or transient ischemic attack was seen in 11%, 1% and 6% of patients at baseline.

There were 2 changes to the EAC charter applicable to cerebrovascular events. Both changes occurred before the first event was adjudicated and did not require re-adjudication of any cerebrovascular event (see **Table 42** in appendix)**.** [66]

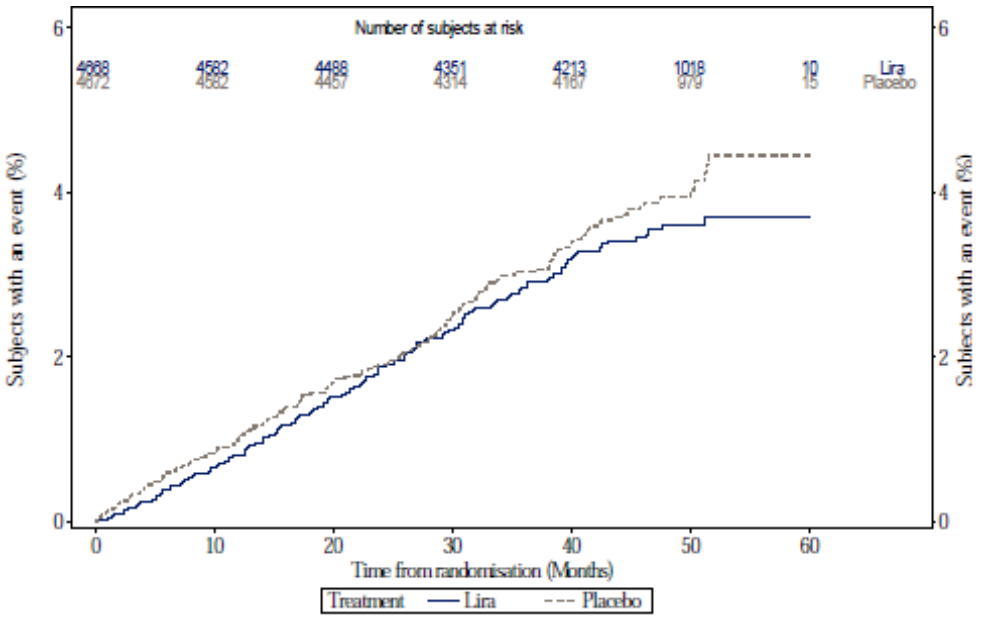
Time to first non-fatal stroke

There were a total of 336 non-fatal strokes identified in the analysis of time to first non-fatal stroke. The difference in non-fatal strokes between treatment arms was made up by an additional 18 non-fatal strokes in the placebo group as compared to the liraglutide group between randomization and the follow-up visit. The Kaplan-Meier plot (Figure 16) shows that there was no significant difference between treatment arms; treatment hazard ratio based on the Cox regression model, was 0.89 [95% confidence interval; 0.72 -1.11].

[65] refer to question 1 of information request located at : \\CDSESUB1\evsprod\NDA022341\0361\m1\us\resp-ir-20170307.pdf

[66] The first change was in version 2, which updated the stroke definition without any re-adjudication of events as this was done prior to the first patient visit. The second change was in version 5, which updated the number of neurologist reviewing events from 1 to 2

Figure 16 – time to first EAC confirmed non-fatal stroke



Source: CSR Figure 11-7, page 238

Overall stroke discussion

Figure 56 (in appendix) shows the event flow for stroke event. Over 80% of events sent for adjudication were confirmed by the EAC. Of these confirmed events there were 464 first events of cerebrovascular events and 73 recurrent events between randomization and visit 16. Of all events identified, regardless of treatment, three-quarters of events were due to stroke, with the remainder of events due to TIAs. Across categories, the incidence and event rates for cerebrovascular events tended to be lower for liraglutide when compared to placebo; see **Table 20**.

For either treatment group, most of the strokes were non-fatal. Ischemic strokes were the most common type of stroke followed by hemorrhagic strokes. Recurrent strokes were few in either treatment group.

Table 20 – EAC confirmed cerebrovascular index events- FAS

	Liraglutide			Placebo		
	N (%)	E	R	N	E	R
FAS	4668			4672		
PYO	17822			17741		
Number of events	213 (4.6)	245	1.37	251 (5.4)	292	1.65
Stroke	173 (3.7)	190	1.07	199 (4.3)	224	1.26
Ischemic stroke	147 (3.1)	161	0.90	166 (3.6)	186	1.05
Hemorrhagic stroke	20 (0.4)	20	0.11	26 (0.6)	26	0.15
Undetermined stroke	9 (0.2)	9	0.05	11 (0.2)	12	0.07
Non-fatal stroke	159 (3.4)	174	0.98	177 (3.8)	199	1.12
Fatal stroke	16 (0.3)	16	0.09	25 (0.5)	25	0.14
Recurrent stroke	15 (0.3)	17	0.10	21 (0.4)	25	0.14
Transient ischemic attack	48 (1.0)	55	0.31	60 (1.3)	68	0.38

N: Number of subjects, %: Proportion of subjects, E: Number of events, FAS: full analysis set; R: Event rate per 100 observation years. PYO: Patient years of observation, EAC: Event adjudication Committee Index events with EAC onset date from randomization date to follow-up are included. The index event is the event selected among multiple events if these were assessed and confirmed to be one and the same event.
Source: modified CTR Table 12-21, page 334

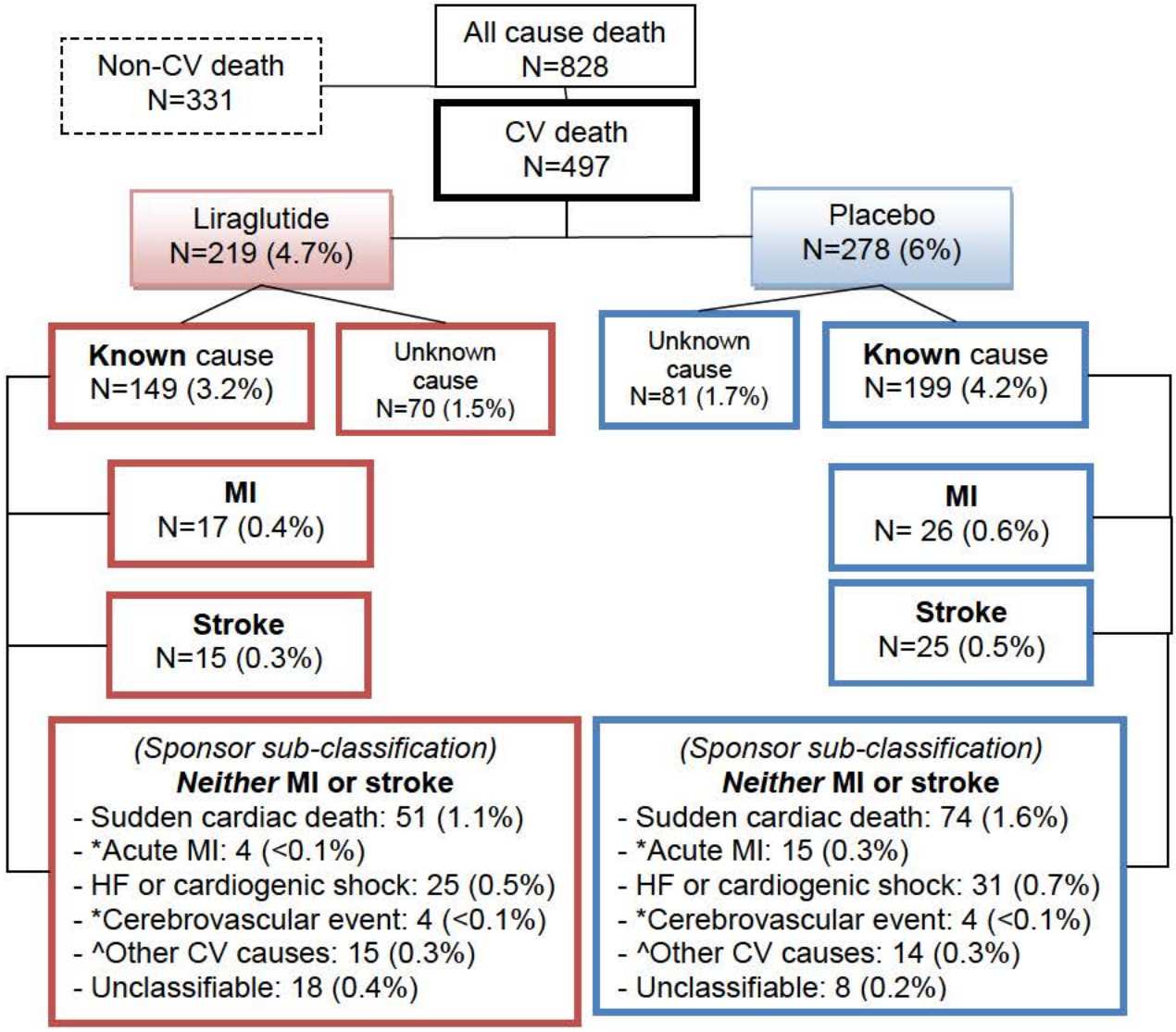
Cardiovascular death

The Sponsor presented the breakdown of cardiovascular death by MI, stroke and a post-database lock (DBL)-Sponsor sub-categorization according to the categories defined in the EAC Charter:[67] As a reminder, cardiovascular deaths were regarded as due to stroke or MI *only* if the EAC chair determined that the death was directly triggered by an MI or stroke within 30 days from death, during multiple event review; refer to Figure 45 in appendix.

Figure 17 shows the breakdown of EAC confirmed cardiovascular deaths in LEADER. Across categories of CV death, the number patients who died due to cardiovascular causes were less for liraglutide than placebo. There were a total of 497 cardiovascular deaths from randomization to Visit 16, with 4.7% vs. 6% of patients randomized to liraglutide and placebo respectively. The difference in cardiovascular deaths between treatment arms was made up by an additional 59 cardiovascular deaths in the placebo group as compared to the liraglutide group. For the known causes of death, the majority of EAC confirmed CV deaths (2.5% and 3.1% for liraglutide and placebo) were from other etiologies other than stroke or MI.

[67] Categories include: 'sudden cardiac death', 'death due to acute MI', 'death due to heart failure or cardiogenic shock', 'death due to cerebrovascular event', 'death due to other cardiovascular causes' and 'unclassifiable'. The category 'unclassifiable' was used when the two adjudicators did not enter a comparable cause of death (e.g. 'chronic heart failure' versus 'acute MI').

Figure 17- Flow of EAC-confirmed deaths between randomization and visit 16

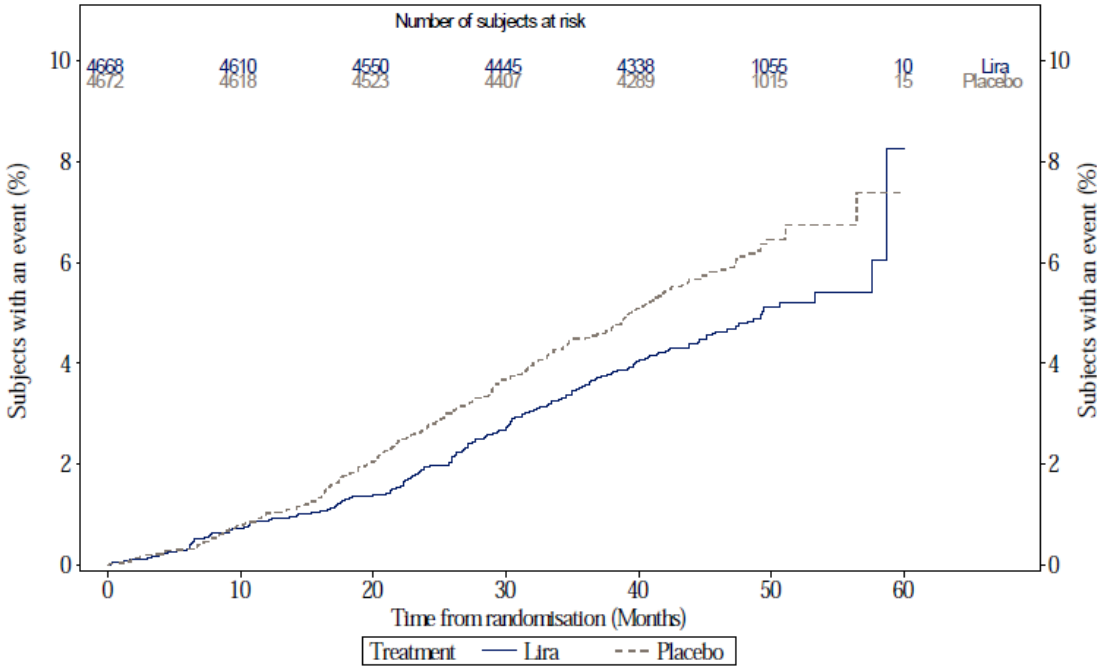


Source: module 5.3.5.4 sample charts figure 1-2, 1-1; percentages are calculated form the randomized number of patients. The total number of adjudicated deaths classified with 'unknown cause' includes 2 patients with "unknown cause, (ID (b)(6) and (b)(6) where the EAC chair during multiple event review linked the death to an EAC confirmed MI in these patients. In this figure, these 2 linked deaths are counted in unknown cause.
* For cardiovascular deaths, which had not been linked to another EAC-confirmed MI or stroke event during multiple events review, the information captured in the diagnosis (cause of death) field was reviewed and sub-categorized by Sponsor after DBL according to the cardiovascular death categories defined in the EAC Charter: 'sudden cardiac death', 'death due to acute MI', 'death due to heart failure or cardiogenic shock', 'death due to cerebrovascular event', 'death due to other cardiovascular causes' and 'unclassifiable'. The category 'unclassifiable' was used when the two adjudicators did not enter a comparable cause of death (e.g. 'chronic heart failure' versus 'acute MI').

^ Other CV causes included EAC identified vascular events such as: ruptured aortic aneurysm, thromboembolic disease, gangrene, pulmonary embolism, cardiac arrest and complications of vascular/cardiac surgery.

The time to CV death analysis revealed a hazard ratio, based on the Cox regression model of 0.78 with a 95% confidence interval: 0.66 -0.93. Figure 18 shows the curves starting to separate after month 10.

Figure 18 – time to EAC confirmed CV death



Source: CSR Figure 11-7, page 238

Reviewer's comment: Review of the cardiovascular death narratives often revealed concomitant illnesses which could have affected the cause of death, (i.e., heart failure, and cardiorespiratory arrest). Concomitant illnesses were present in both treatment groups; thus it is likely that although the *exact* classification of the event may be debatable (sudden cardiac death vs. heart failure, etc.), the overall classification of the event as "CV death" is not altered by my review.

The trends in cardiovascular death seem to be internally consistent with the overall death findings in LEADER. Therefore although the post-database lock classification of the death events by the Sponsor has the potential to be biased, the overall ascertainment of the cause of death (i.e., cardiovascular death or not) was done in a blinded, systematic manner which was not affected by post-hoc assessments.

Unknown cause of death

As shown in **Figure 17**, close to 30% of the cardiovascular deaths in either treatment arm were due to unknown cause, as defined in the EAC charter, "deaths for which there was no clearly documented non-vascular cause" and were considered cardiovascular deaths (see **Table 44**). These deaths of "unknown cause" made up roughly ~18% of all deaths in the LEADER program.

The available information regarding the unknown cause of deaths was collected by the Sponsor post hoc, see Table 21. Of the patient with unknown cause of death a third of patients had a death certificate with smaller percentages of patients having an autopsy or information available in registries.

Table 21 – post hoc classification of EAC confirmed deaths of unknown cause FAS

	Liraglutide			Placebo		
	N (%)	E	R	N	E	R
FAS	4668			4672		
PYO	17822			17741		
Patients with unknown cause of death	70 (1.50)	70	0.39	81 (1.73)	81	0.46
Inadequate medical information*	32 (0.69)	32	0.18	28 (0.60)	28	0.16
Death certificate	2 (0.04)	2	0.01	3 (0.06)	3	0.02
Autopsy	0	0	0	0	0	0
Limited medical information **	29 (0.62)	29	0.16	42 (0.90)	42	0.24
Death certificate	19 (0.41)	19	0.11	20 (0.43)	20	0.11
Autopsy	1 (0.02)	1	0.01	0	0	0
Only death certificate available	5 (0.11)	5	0.03	5 (0.11)	5	0.03
Only information from death registry available	4 (0.09)	4	0.02	6 (0.13)	6	0.03

N: Number of subjects, %: Proportion of subjects, E: Number of events, R: Event rate per 100 patient years of observation, EAC: event adjudication committee, FAS: full analysis set
*Inadequate medical information: No medical information related to cause of death and no or sparse information on medical history available
**Limited medical information: Limited medical information related to cause of death or medical history available
Classification is based on the information available in the source document packages provided to the EAC for the individual cases (deaths) including information from medical records, from the investigator and/or from subject´s family or relatives. Deaths from randomization to follow-up are included.
Source: Question 2 in information request dated March 21, 2017:
\\CDSESUB1\evsprod\NDA022341\0362\m1\us\resp-ir-20170314.pdf

Reviewer's comment: As discussed in the section titled: 6.1.3 Subject Disposition, **the unknown vital status for patients randomized to LEADER was low for patients who were non-completers, with only 29 (12 for liraglutide and 17 for placebo) patients with unknown vital status (making up 0.3% of all randomized patients).**

However the extent of fatal events with unknown cause makes up a large proportion of the total cardiovascular deaths (30%). Although this is a large proportions of the cardiovascular deaths, the findings are somewhat consistent with the extent of missing information seen in another cardiovascular outcomes trial (i.e. EMPA-REG OUTCOME had ~40% of fatal CV events that were 'not assessable', i.e. unknown cause).[68] The Sponsor was asked to provide analyses that excluded deaths with "unknown cause" from the primary and secondary analyses. Even when excluding these deaths, MACE, expanded MACE, cardiovascular death, and all cause death still statistically favored liraglutide. Refer to appendix, Table 53.

6.1.5 Analysis of Cardiovascular Secondary Endpoints(s)

This section will discuss the expanded MACE endpoint, which was pre-specified as a secondary endpoint. The following components of expanded MACE will be discussed in this section: time to first hospitalization for unstable angina pectoris, time to first hospitalization for heart failure, and time to first coronary revascularization.

The following secondary endpoints will not be discussed in this section as they were discussed as part of the MACE primary endpoint: time to first non-fatal MI, time to first non-fatal stroke, and time to cardiovascular death. Refer to section titled **Discussion of the components of MACE**, for a discussion on these topics.

Expanded MACE

The Sponsor defined expanded MACE as EAC-confirmed cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, coronary revascularization, hospitalization for unstable angina pectoris, or hospitalization for heart failure. Similar to the primary 3-point MACE endpoint, the expanded MACE included patients that contributed to the analysis once, with the first event.[69]

Table 22 shows the first EAC confirmed events by treatment arms for expanded MACE. In total 2010 (21.5%) of patients experienced an expanded MACE event [20.3% (948 patients) randomized to liraglutide and 22.7% (1062 patients) randomized to placebo]. When considering the components of the expanded MACE by treatment arm, the liraglutide arm had slightly lower percentage of patients for each individual component of the expanded MACE, with the exception of hospitalization for unstable angina pectoris, as compared to placebo.

[68] Source: Clinical review, dated November 4, 2016 (DARRTS), page 70
[69] In case several events in a single subject had the same date of onset the priority for classifying the first event was: cardiovascular death > non-fatal myocardial infarction > non-fatal stroke > hospitalization for UAP > hospitalization for heart failure > coronary revascularization.

Reviewer's comment: The lower incidence of expanded MACE in the liraglutide group was also seen when considering the cases occurring after follow-up, which are excluded from the expanded MACE analysis (19 and 27 cases for liraglutide and placebo).

Table 22 – First EAC- confirmed expanded MACE- FAS

	Liraglutide			Placebo		
	N (%)	E	R	N	E	R
FAS	4668			4672		
PYO	17822			17741		
EAC confirmed **expanded** MACE	948 (20.3)	948	5.32	1062 (22.7)	1062	5.99
Cardiovascular death	142 (3.0)	142	0.80	183 (3.9)	183	1.03
Non-fatal MI	238 (5.1)	238	1.34	257 (5.5)	257	1.45
Non-fatal stroke	140 (3.0)	140	0.79	152 (3.3)	152	0.86
Hospitalization for unstable angina pectoris	104 (2.2)	104	0.58	96 (2.1)	96	0.54
Hospitalization for heart failure	162 (3.5)	162	0.91	184 (3.9)	184	1.04
Coronary revascularization	162 (3.5)	162	0.91	190 (4.1)	190	1.07

N: Number of subjects, %: Proportion of subjects, E: Number of events, FAS: Full analysis set.
PYO: Patient years of observation, R: Event rate per 100 observation years. MACE: major cardiovascular event, EAC: event adjudication committee. Only first (index) events from randomization to follow-up are included. Heart failure and unstable angina pectoris (UAP) requires hospitalization. In case events have the same date of onset the priority is as follows for classifying the first event within subject: Death > non-fatal myocardial infarction > non-fatal stroke > UAP > Heart failure > Coronary revascularization
Source: CTR Table 11-5, page 233

The components of the expanded MACE in each treatment arm are shown by treatment in **Figure 10**. For both liraglutide and placebo, the largest component of expanded MACE was contributed by non-fatal MI (accounting for 24-25%). A greater percentage of the expanded MACE was attributed by cardiovascular death for placebo (17%) than for liraglutide (15%). Notably, a larger percentage of the expanded MACE events for liraglutide (11%) as compared to placebo (9%) were from hospitalization for unstable angina.

Figure 19 – Percentage of the components of first expanded MACE by treatment group

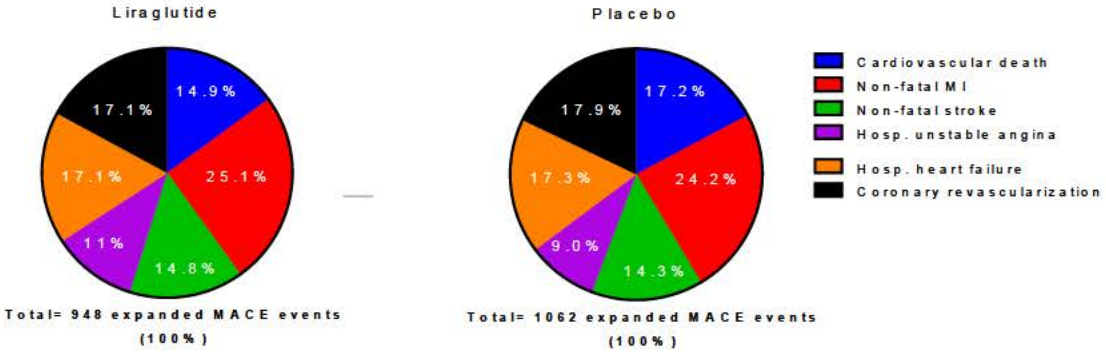
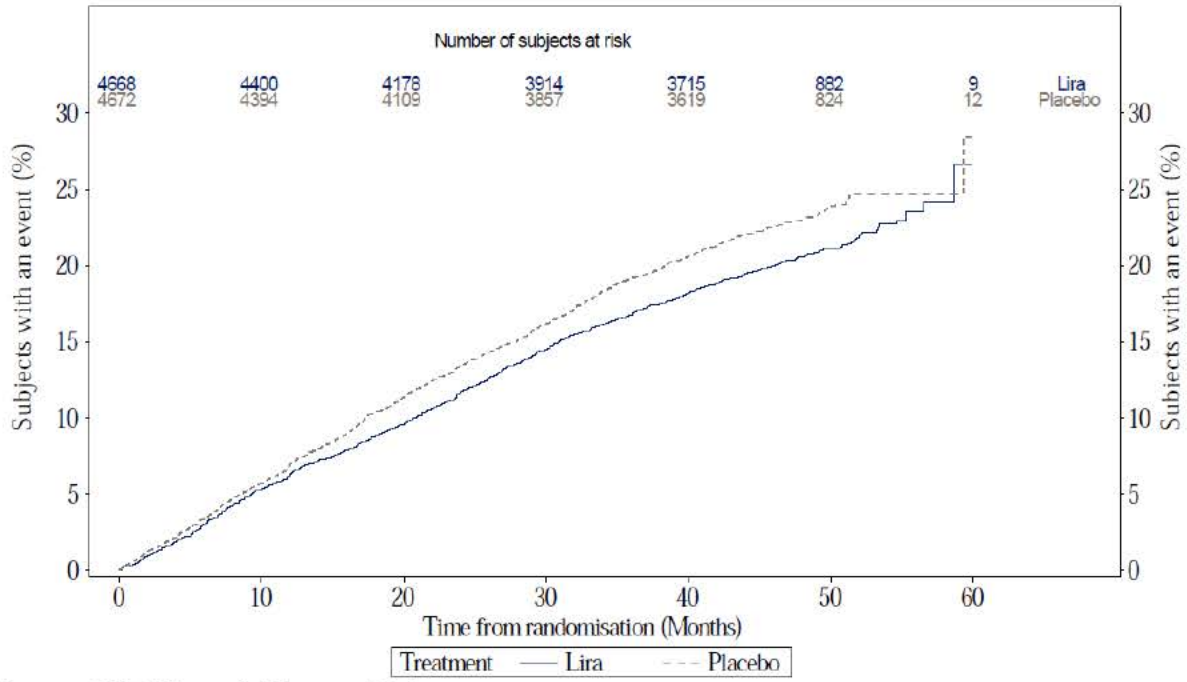


Figure 20 shows the Kaplan-Meier plot of EAC-confirmed first expanded MACE over time for liraglutide and placebo. Overall the occurrence of expanded MACE was lower for liraglutide than for placebo.

Figure 20 – Kaplan-Meier plot of time to first EAC confirmed expanded MACE-FAS



Source: CTR Figure 11-5, page 234

The hazard ratio for time to first expanded EAC-confirmed MACE, based on the Cox regression model, was 0.881 [95% confidence interval; 0.807-0.962] with a p value of 0.005. Adjustments for additional covariates at baseline resulted in similar results.[70]

Reviewer's comment: although the composite findings of expanded MACE favored liraglutide, this secondary endpoint although pre-specified, was not adjusted for multiplicity. In addition, the definitions for hospitalization for heart failure and hospitalization for unstable angina may have allowed a less specific detection of these events (see discussion below).

Individual components of the expanded composite cardiovascular endpoint

Similar to the approach used in the discussion of the components of MACE, this section will discuss the time to first event analyses and the overall safety (i.e. total events, including recurrent events) of the unique (i.e. not already discussed in the MACE section) components of expanded MACE: hospitalization for unstable angina, hospitalization for heart failure and coronary revascularization.

Table 23 shows the descriptive findings of the time to first individual event for expanded MACE. The table includes all first events with onset between randomization and follow-up. Coronary revascularization (9.1%) was the most frequent event followed by non-fatal MI (6.4%), cardiovascular death (5.3%), hospitalization for heart failure (5%), non-fatal stroke (3.6%) and hospitalization for unstable angina pectoris (2.6%). Overall, the proportion of patients experiencing any of the components was lower for liraglutide than placebo.

[70] 0.874 [0.8;0.954], (exploratory analyses) in a model adjusting for treatment, sex, region, smoking history at baseline (never/prior/current), prior cardiovascular events at baseline (yes/no) and antidiabetic therapy at baseline are included as fixed effects. Diabetes duration at baseline and calculated eGFR-MDRD at baseline and age at baseline are included as covariates, where eGFR-MDRD is the estimated glomerular filtration rate using the modification of diet in renal disease formula.

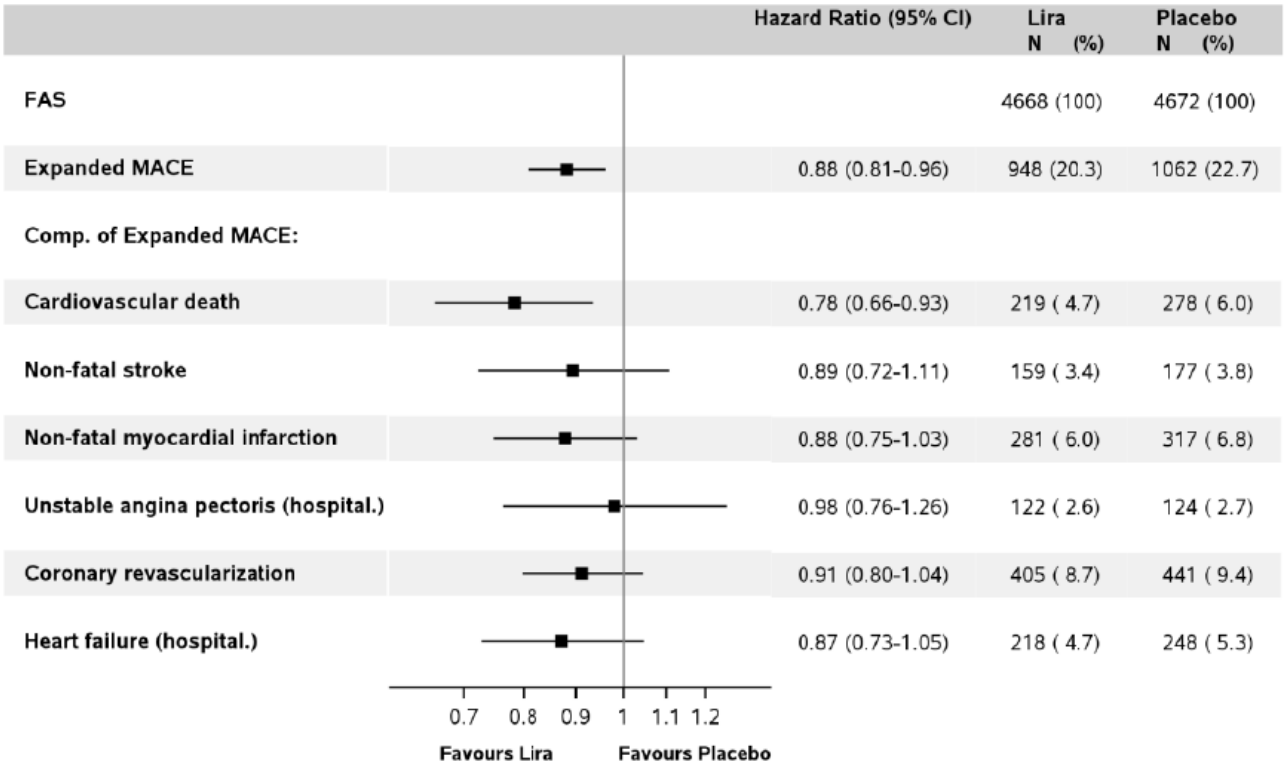
Table 23 – EAC- confirmed time to first component of expanded MACE - FAS

	Liraglutide			Placebo		
	N (%)	E	R	N	E	R
FAS	4668			4672		
PYO	17822			17741		
Cardiovascular death	219 (4.7)	219	1.23	278 (6.0)	278	1.57
Non-fatal MI	281 (6.0)	281	1.58	317 (6.8)	317	1.79
Non-fatal stroke	159 (3.4)	159	0.89	177 (3.8)	177	1.00
Hospitalization for unstable angina pectoris	122 (2.6)	122	0.68	124 (2.7)	124	0.70
Hospitalization for heart failure	218 (4.7)	218	1.22	248 (5.3)	248	1.40
Coronary revascularization	405 (8.7)	405	2.27	441 (9.4)	441	2.49

N: Number of subjects, %: Proportion of subjects, E: Number of events, FAS: Full analysis set.
MACE: major adverse cardiovascular event, EAC: event adjudication committee, PYO: Patient years of observation, R: Event rate per 100 observation years. Only (index) events after randomization are included. Heart failure and unstable angina pectoris requires hospitalization.
Source: CTR Table 11-7, page 235

The hazard ratio for each of the components of expanded EAC-confirmed MACE is shown in **Figure 21**. Although the analyses tended to favor liraglutide over placebo, the results were only statistically significant for cardiovascular death (refer to section titled **Cardiovascular death** for further discussion on this topic).

Figure 21- forest plot of treatment contrast for components of EAC-confirmed expanded MACE*



Abbreviations: CI: confidence interval; FAS: full analysis set; Lira: liraglutide; MACE: major adverse cardiovascular event; EAC: event adjudication committee; %: proportion of subjects with an event; N: number of subjects.

Source: CTR, Figure 11-6, page 236, *multiple events within a category of the individual components were counted only once

Hospitalization for unstable angina pectoris:

Per the EAC charter, hospitalization of unstable angina: was defined by clinical criteria as described in Table 44 in addition to 1.Hospitalization (including overnight stay on an inpatient unit- does not include chest pain observation units) within 48 hours of the most recent symptoms or 2. Coronary revascularization during an unscheduled visit to a healthcare facility or during an unplanned (or prolonged) hospitalization for the symptoms.

Reviewer's comment: the time frame of "hospitalization within 48 hours of most recent symptoms" in the definition of hospitalization for unstable angina is longer than the recommended time frame (by the Draft Definitions for CDISC 2014 or the 2010 CDISC definitions-- which were used to derive the EAC charter definitions)[71]

[71] Hicks KA, Hung H.M. James, Mahaffey KW, Mehran RW, Nissen SE, Stockbridge NL, Targum SL, Temple R on behalf of the Standardized Data Collection for Cardiovascular Trials Initiative. Standardized Definitions for Cardiovascular and Stroke Endpoint Events in Clinical Trials. Draft Definitions for CDISC,

of "unscheduled hospitalization within 24 hours of the most recent symptoms." In addition, the term "hospitalization" itself is not clearly defined in the EAC charter. While the CDISC definitions specify that hospitalization "is an admission to an inpatient unit or a visit to an emergency department that results in at least 24 hour stay (or a change in calendar date if the hospital admission or discharge times are not available)."

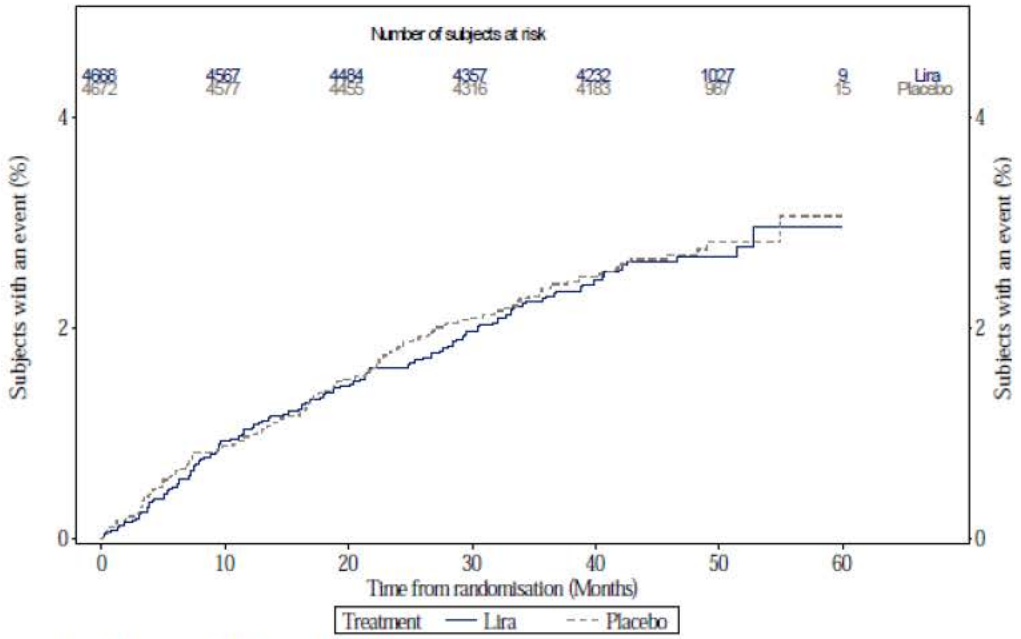
Therefore the EAC definitions used to capture hospitalization for unstable angina provided a more "loose interpretation" than what is typically recommended to capture these events.

Time to first Hospitalization for unstable angina pectoris

There were a total of 246 first hospitalizations for unstable angina pectoris events. The difference in hospitalization for unstable angina pectoris between treatment arms was made up by an additional 2 events in the placebo group as compared to the liraglutide group. The Kaplan-Meier plot (**Figure 22**) shows a point estimate close to 1 and no difference between treatment arms; treatment hazard ratio based on the Cox regression model, was 0.98 [95% confidence interval; 0.76 -1.26].

August 20, 2014.
https://www.cdisc.org/system/files/all/reference_material/application/pdf/Draft%20Definitions%20for%20CDISC%20July%203,%202014.pdf
Standardized Definitions for Endpoint Events in Cardiovascular Trials. FDA Center for Drug Evaluation and Research (CDER). Draft Version October 20, 2010.

Figure 22 – time to first EAC confirmed hospitalization for unstable angina pectoris



Source: CSR Figure 11-7, page 238

Overall hospitalization for unstable angina pectoris

An equal number of patients for were identified as having a hospitalization for unstable angina pectoris. There was also no notable difference in the number of patients who had a coronary revascularization as a result of the hospitalization; see **Table 24**. There were slightly more patients who had recurrent events in the liraglutide group than the placebo group (13.5% vs. 11.4%).

Table 24 – Hospitalization for EAC confirmed unstable angina pectoris- FAS

	Liraglutide N (%)	Placebo N (%)
Number of events	141 (100%)	140 (100%)
Hospitalization within 48 hours from most recent symptoms	137 (97.2%)	137 (97.9%)
Subject had coronary revascularization done*	104 (73.8)	105 (75%)
Recurrent events	19 (13.5%)	16 (11.4%)
E: Number of events, %: Proportion of events, *during unscheduled visit or during unplanned/prolonged visit. Source: CTR Table 12-23, page 337		

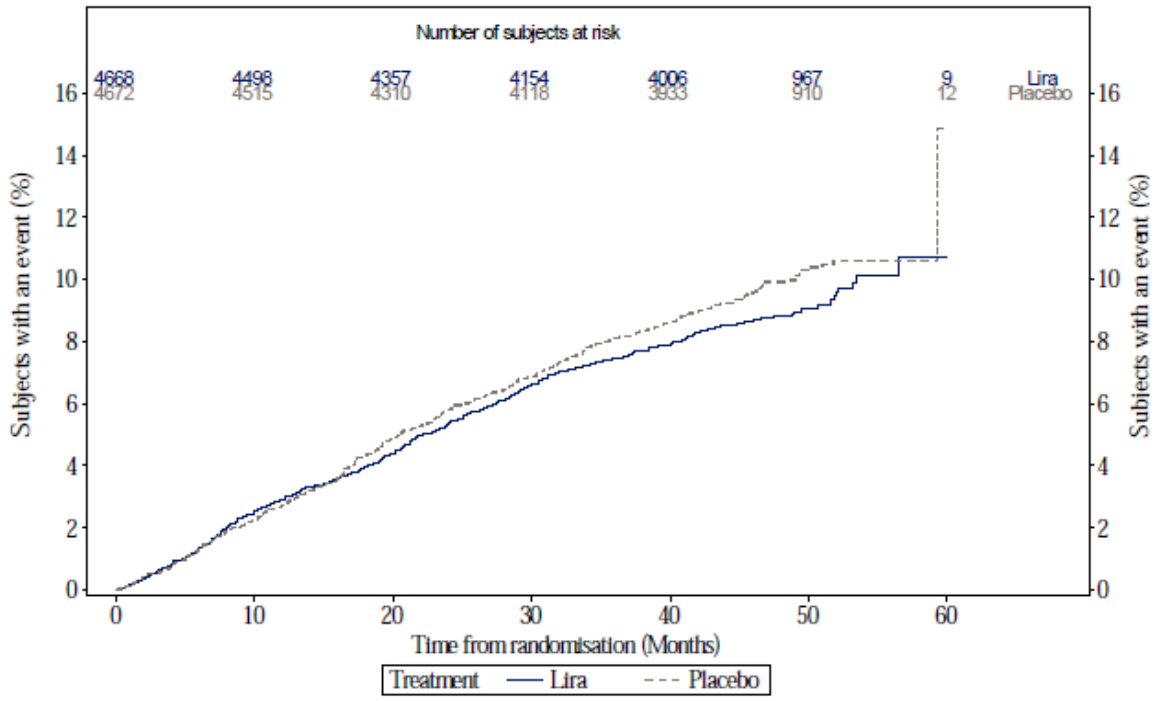
Coronary revascularization

Events meeting criteria for coronary revascularization were defined as either percutaneous coronary intervention or coronary artery bypass grafts, as per **Table 44** in appendix.

Time to first coronary revascularization

There were a total of 846 first coronary revascularizations events. The difference in coronary revascularization between treatment arms was made up by an additional 36 events in the placebo group as compared to the liraglutide group. The Kaplan-Meier plot (**Figure 23**) shows that there was no significant difference between treatment arms; treatment hazard ratio based on the Cox regression model, was 0.91 [95% confidence interval; 0.8 -1.04].

Figure 23 – time to first EAC confirmed coronary revascularization



Source: CSR Figure 11-7, page 239

Overall coronary revascularization

Figure 58 (in appendix) shows the event flow for coronary revascularization events. Over 95% of events sent for adjudication were confirmed by the EAC. Of these confirmed events there were 846 first events of coronary revascularization and 216 recurrent events between randomization and visit 16.

As shown in **Table 25**, around 9% of patients on liraglutide or placebo experienced coronary revascularization. The event adjusted rate was lower for liraglutide than placebo with a rate of 2.82 and 3.15 events per 100 observation years for liraglutide and placebo respectively.

Table 25 – EAC confirmed coronary revascularization index events - FAS

	Liraglutide			Placebo		
	N (%)	E	R	N	E	R
FAS	4668			4672		
PYO	17822			17741		
Number of events	405 (8.7)	503	2.82	441 (9.4)	559	3.15

N: Number of subjects, %: Proportion of subjects, E: Number of events, FAS: full analysis set;
R: Event rate per 100 observation years. PYO: Patient years of observation, EAC: Event adjudication committee. Index events with EAC-onset date from randomization date to follow-up are included.
The index event is the event selected among multiple events if these were assessed and confirmed to be one and the same event.
Source: modified CTR Table 12-27, page 348

Hospitalization for heart failure

Previous history of heart failure was seen in ~18% of patients at baseline. Events meeting criteria for hospitalization for heart failure had to meet all three criteria: required hospitalization >12 hours (or a date change if the time of admission/discharge was not available), clinical symptoms of heart failure, and additional/increase therapy[72], as per **Table 44** in appendix.

Reviewer's comment: The time frame for hospitalization for heart failure in LEADER is shorter than what is typically recommended by the CDISC definitions. The CDISC definitions define hospitalization as "the patient's length-of-stay in hospital extends for at least 24 hours (or a change in calendar date if the hospital admission and discharge times are unavailable)"[73] The shorter time frame of hospitalization in LEADER would likely allow a higher capture of events with a lower specificity.

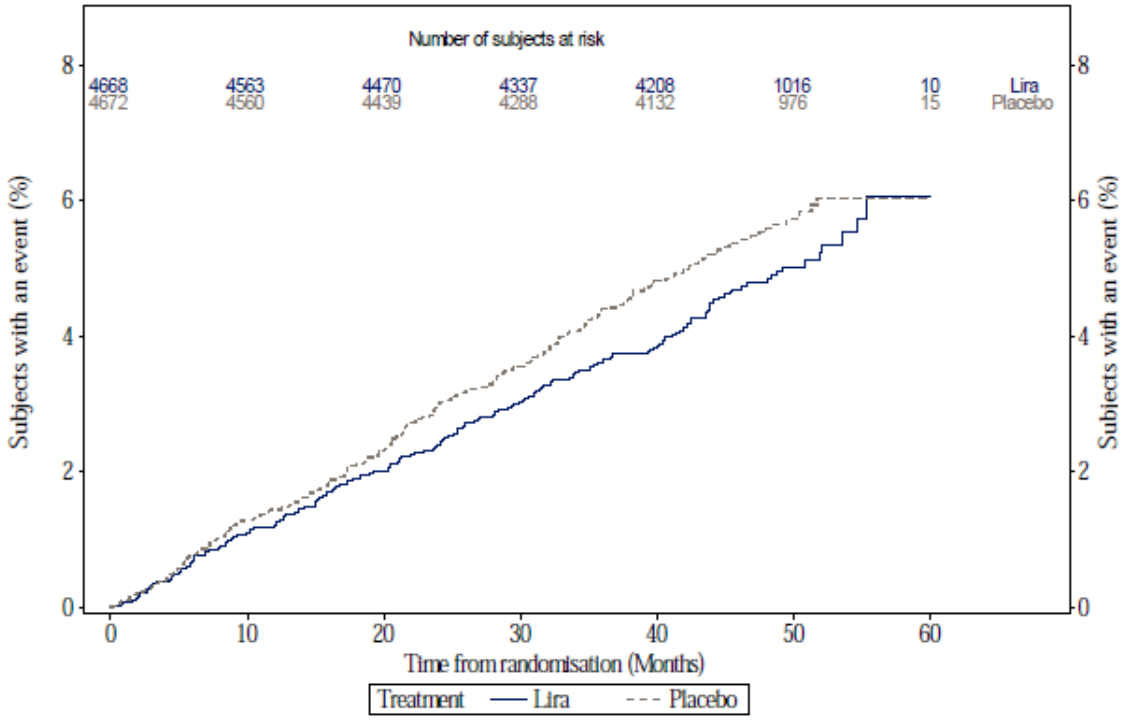
Time to first hospitalization for heart failure

[72] The increase in therapy includes the initiation of IV diuretic, inotrope or vasodilator therapy, up-titration of iv therapy if already on therapy, initiation of mechanical or surgical intervention or the use of ultrafiltration, hemofiltration or dialysis that is specifically directed at treatment of heart failure. Biomarkers were considered supportive.

[73] Hicks KA, Hung H.M. James, Mahaffey KW, Mehran RW, Nissen SE, Stockbridge NL, Targum SL, Temple R on behalf of the Standardized Data Collection for Cardiovascular Trials Initiative. Standardized Definitions for Cardiovascular and Stroke Endpoint Events in Clinical Trials. Draft Definitions for CDISC, August 20, 2014.
https://www.cdisc.org/system/files/all/reference_material/application/pdf/Draft%20Definitions%20for%20CDISC%20July%203,%202014.pdf

During the trial there were a total of 466 first hospitalizations for heart failure events. The difference in hospitalizations for heart failure between treatment arms was made up by an additional 30 events in the placebo group as compared to the liraglutide group. The Kaplan-Meier plot (**Table 23**) shows that there was no significant difference between treatment arms; treatment hazard ratio based on the Cox regression model, was 0.87 [95% confidence interval; 0.73 -1.05].

Figure 24 – time to first EAC confirmed hospitalization for heart failure



Source: CSR Figure 11-7, page 239

Overall coronary revascularization

Figure 57 (in appendix) shows the event flow for hospitalization for heart failure events. Over 60% of events sent for adjudication were confirmed by the EAC. Of these confirmed events there were 466 first events of cerebrovascular events and 265 recurrent events between randomization and visit 16. Close to 5% of patients on liraglutide or placebo experienced heart failure requiring hospitalization. However the number of events was higher for placebo, with an event adjusted rate of 1.92 and 2.19 events per 100 observation years for liraglutide and placebo respectively.

Table 26 – EAC confirmed heart failure index events requiring hospitalization-FAS

	Liraglutide			Placebo		
	N (%)	E	R	N	E	R
FAS	4668			4672		
PYO	17822			17741		
Number of events	218 (4.7)	342	1.92	248 (5.3)	389	2.19

%: Proportion of subjects, E: Number of events, EAC: event adjudication committee, FAS: full analysis set, N: Number of subjects, PYO: Patient years of observation, R: Event rate per 100 observation years Index events with EAC onset date from randomization date to follow-up are included. The index event is the event selected among multiple events if these were assessed and confirmed to be one and the same event.
Source: modified CTR Table 12-26, page 345

Death

Refer to **Figure 43** and **Figure 44**, in the Appendix for details regarding the adjudication of deaths. For a given patient the investigator could report more than one adverse event with fatal outcome. However for the purpose of adjudicating cause of death, the EAC was asked to evaluate the death of a patient as a whole and not the individual adverse event reported with fatal outcome. All deaths in randomized patients were sent for adjudication. The discussion in this section is based on the adjudication by the EAC, unless specified otherwise.

The cardiovascular sub-committee adjudicated all deaths for patients that were randomized[74]. Nine deaths occurred prior to randomization and were not adjudicated. In total 852 randomized patients died during the trial (391 in liraglutide, and 461 in placebo). Between randomization and visit 16, there were 828 deaths (which are included in the pertinent death analyses). An additional 24 deaths occurred in the period between follow-up and database lock (10 and 14 for liraglutide and placebo, respectively) [75]- these deaths are *not included* in the analyses of death discussed below.

EAC adjudicated overall death

All-cause mortality was a pre-specified secondary endpoint in LEADER.

There were a total of 828 deaths from randomization to visit 16. The difference in overall deaths between treatment arms was made up by an additional 66 deaths in the placebo group; see **Table 27**. For both treatment groups (58% and 62% for liraglutide and placebo respectively) the majority of deaths were from cardiovascular causes.

[74] Adjudicators identified events as either known or unknown. For known cases the adjudicator rated the likelihood that the death was classified as CV death: documented, probable/possible or unlikely. If the choice was unlikely then the adjudicator rated the likelihood of the death being a non-CV death using the same classifications.
[75] Of these deaths 11 were confirmed as CV deaths (liraglutide: 4 and placebo:7).

Table 27 – EAC-confirmed deaths from randomization to visit 16 - FAS

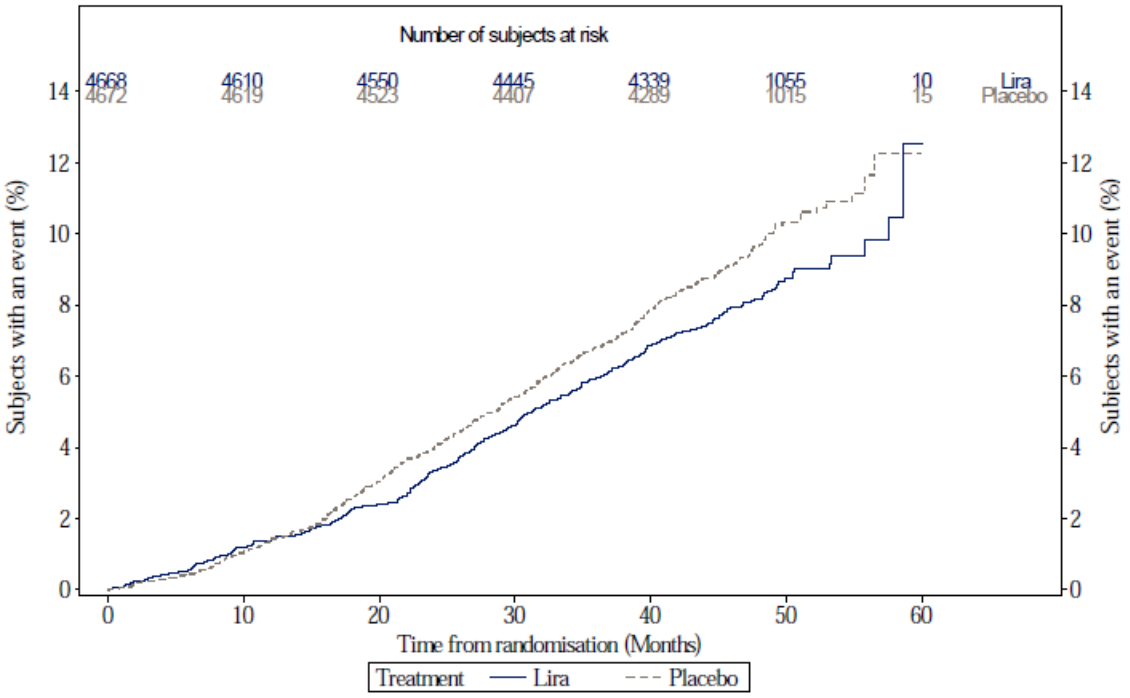
	Liraglutide			Placebo		
	N (%)	E	R	N	E	R
FAS	4668			4672		
PYO	17822			17741		
Total deaths	381 (8.2)	381	2.14	447 (9.6)	447	2.52
Cardiovascular deaths	219 (4.7)	219	1.23	278 (6)	278	1.57
Non-cardiovascular deaths	162 (3.5)	162	0.91	169 (3.6)	169	0.95

%: Proportion of subjects, E: Number of events, EAC: Event adjudication committee, FAS: full analysis set, N: Number of subjects, R: Event rate per 100 observation years, PYO: Patient years of observation.
Deaths with EAC onset date from randomization date to follow-up
Unknown cause of death is classified as CV death.
Source: modified CTR Table 12-13, page 315

The analysis of time to all-cause mortality (**Figure 25**) was similar between treatment arms until after month ~ 15 of the study. Then the death rate appeared lower for liraglutide than placebo. The time to all-cause death analysis comparing liraglutide to placebo favored liraglutide. The hazard ratio for time to EAC confirmed death based on the cox regression model was 0.847 [0.739; 0.971] p=0.017.[76] These findings appeared to be primarily driven by cardiovascular deaths.

[76] An analysis which adjusted for additional covariates at baseline had similar results: 0.84 [0.732; 0.963]

Figure 25 – Kaplan-Meier plot- time to EAC-confirmed all-cause death- FAS



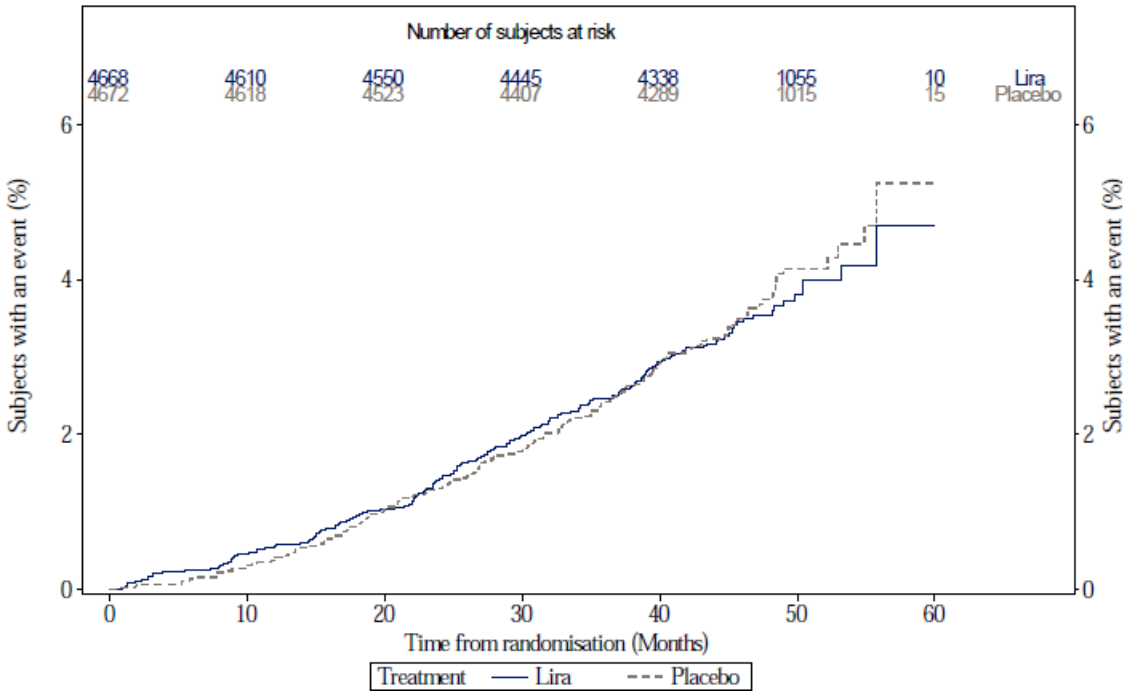
An exploratory evaluation of baseline characteristics of the patients who died was overall similar between treatment groups.[77]

Non-cardiovascular death

The Kaplan-Meier plot of time to non-cardiovascular deaths is shown in **Figure 26**. There were 331 non-cardiovascular deaths in LEADER. The proportion of non-cardiovascular deaths was similar between treatment groups; the difference in non-cardiovascular deaths was 7 additional deaths in the placebo group compared to the liraglutide group with a hazard ratio 0.952 [0.768; 1.181].

[77]Common characteristics included: older patients (most with ages 60-70), NYHA class II, on insulin +OADs, White, Male; See appendix for a descriptive graphical depiction of these characteristics (Error! Reference source not found. and Error! Reference source not found.).

Figure 26 – Kaplan-Meier plot- time to EAC confirmed non-cardiovascular deaths- FAS



Source: CSR figure 11-9, page 242

Table 52 (in the Appendix), shows the EAC-adjudicated non-cardiovascular deaths by MedDRA preferred term (PT) and System organ class (SOC). The most common system organ class (SOCs) were Neoplasms benign, malignant and unspecified (incl. cysts and polyps) and Infections and Infestations. For most preferred terms (PT) and SOCs there were small numerical imbalances between treatment arms. There was no obvious clustering of PT terms to suggest a clear trend for either treatment arm.

As specified in the EAC charter, medically qualified personnel at Novo Nordisk performed a *post hoc* classification of the non-cardiovascular deaths, according to organ system affected, as shown in **Table 28**. The Sponsor's analysis was overall consistent with the investigator reported PT and SOC analysis, and showed similar types of deaths between treatment groups. The higher number of observed 'renal deaths' in the liraglutide arm is discussed later in this review. Please refer to the safety review by Dr. Julie Golden for further information regarding non-cardiovascular deaths.

Table 28 – EAC-confirmed deaths reported with liraglutide and placebo- FAS

	Liraglutide N (%)	Placebo N (%)	Total N (%)
FAS	4668	4672	
PYO	17822	17741	
Total deaths	381 (8.2)	447 (9.6)	447
Unknown cause	70 (1.5)	81 (1.7)	151 (1.6)
Known cause of death	311 (6.7)	366 (7.8)	677 (7.2)
EAC confirmed MI	17 (0.4)	26 (0.6)	43 (0.5)
EAC confirmed stroke	15 (0.3)	25 (0.5)	40 (0.4)
Death not linked to EAC confirmed MI or stroke	117 (2.5)	146 (3.1)	263 (2.8)
Non-cardiovascular deaths (sponsor sub-classification)	162 (3.5)	169 (3.6)	169
Pulmonary	7 (0.1)	12 (0.3)	19 (0.2)
Renal causes	11 (0.2)	5 (0.1)	16 (0.2)
GI causes	4 (<0.1)	2 (<0.1)	6 (<0.1)
Infection	37 (0.8)	41 (0.9)	78 (0.8)
Non-infectious (e.g. SIRS)	1 (<0.1)	1 (<0.1)	2 (<0.1)
Malignancy	65 (1.4)	67 (1.4)	132 (1.4)
Hemorrhage (non-intracranial)	6 (0.1)	4 (<0.1)	10 (0.1)
Accidental/trauma	12 (0.3)	14 (0.3)	26 (0.3)
Suicide	1 (<0.1)	2 (<0.1)	3 (<0.1)
System organ failure (non-CV)	5 (0.1)	3 (<0.1)	8 (<0.1)
Non-CV surgery	2 (<0.1)	1 (<0.1)	3 (<0.1)
Other non-CV Death	3 (<0.1)	5 (0.1)	8 (<0.1)
Unclassifiable	8 (0.2)	12 (0.3)	20 (0.2)

N=Number of Subjects %=proportion of subjects, E=number of indexed events, FAS: Full analysis set EAC: Event adjudication committee. Events from randomization date to follow-up date are included. The total number of adjudicated deaths classified with 'unknown cause' includes 3 subjects ((b) (6)), where the EAC Chair during multiple events review had linked the deaths to an EAC-confirmed MI ((b) (6)) and stroke ((b) (6)) occurring within the same subject.
In this table, these 3 linked deaths are only counted in unknown cause. In other outputs only related to EAC-confirmed MI or stroke, these 3 EAC-confirmed MI or stroke events that were evaluated by the EAC Chair as precipitating the subjects death will be counted as 'fatal MI' or 'fatal stroke' as applicable.
Source: CSR, table 12-15, page 318

Traditional CV risk factors

This section of the review will focus on the traditional risk factors that contribute to cardiovascular disease. Since the end of treatment visit could take place any time between 42 and 60 months the Sponsor presented the results from change from

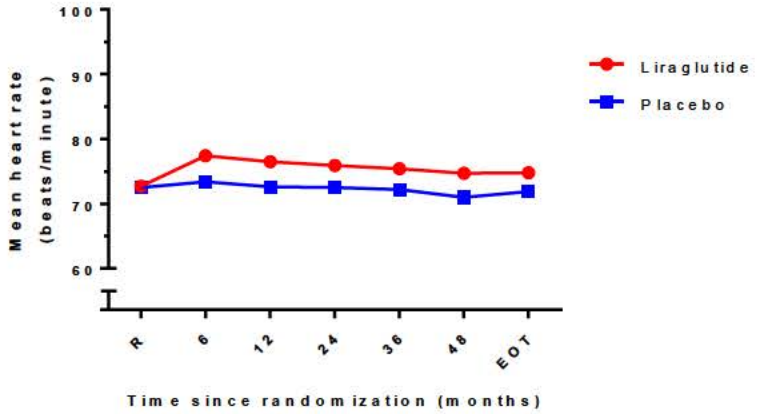
baseline to 3 years (2 years for waist circumference) therefore presenting a fixed treatment period for all patients.

Pulse

Liraglutide is labeled for having an increase from baseline in mean resting pulse of 2-3 beats per minute compared to placebo. In LEADER, heart rate was recorded every 6 months for the first year, after which it was measured yearly until the end of the trial. Heart rate was recorded over a period of 30 seconds or longer, after resting for 5 minutes in a sitting position.

Figure 27 shows the mean heart rate by visit in the trial. Both liraglutide and placebo had a similar baseline. After 6 months the mean heart rate increased for liraglutide and remained elevated as compared to placebo. In a pre-specified analysis of the change in heart rate from baseline to a 3 year assessment, the mean heart rate was statistically significantly higher in the liraglutide group compared to the placebo group (Lira-placebo treatment difference 2.98 beats/min [95% confidence interval 2.54;3.42] ; p<0.001).

Figure 27- Mean heart rate by visit -FAS



Source: reviewer graphed data from CTR table 14.2.271

I performed an exploratory evaluation of the SOC 'Cardiac disorders,' as identified by the investigator, in the adverse event dataset to evaluate the safety of cardiac arrhythmias. Overall the presence of cardiac arrhythmias was similar for both treatment

groups (refer to

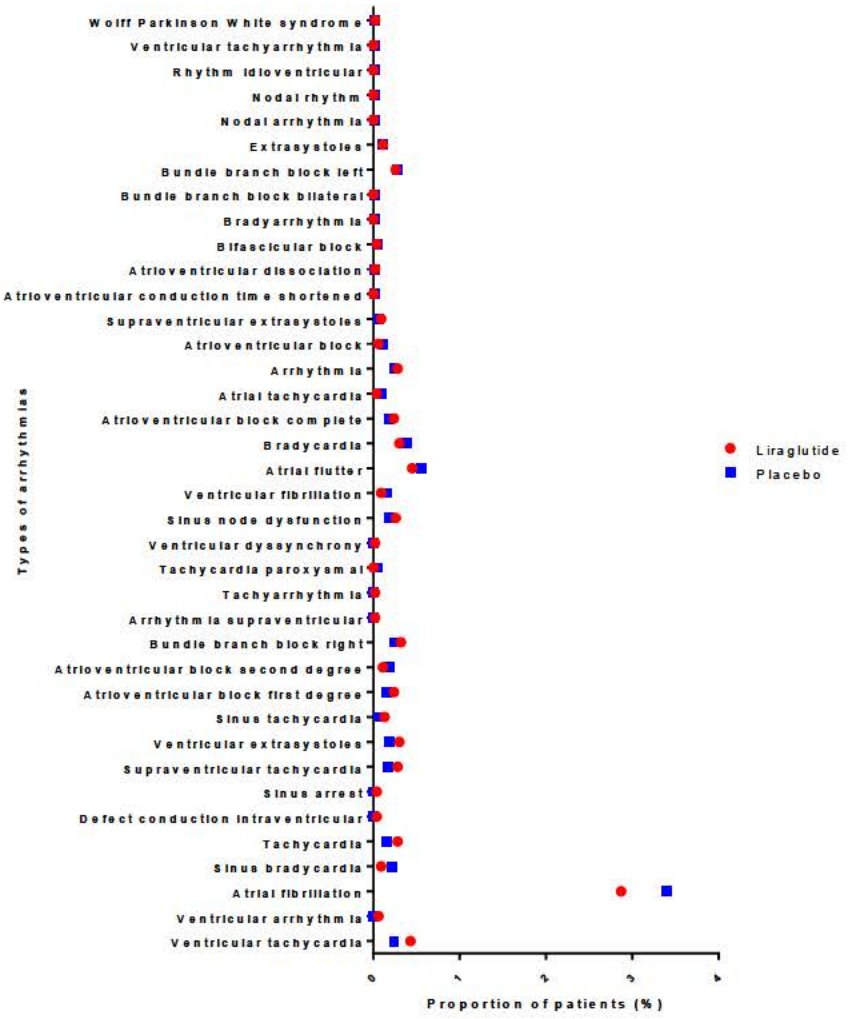
	Liraglutide N (%)	Placebo N (%)	Total N (%)	Lira/placebo Hazard ratio	95% CI	Test for HR=1.0 two sided
FAS	4668	4672	9340			
Primary endpoint: MACE*	546 (11.7)	624 (13.4)	1170 (12.5)	0.867	0.773, 0.973	0.015
Expanded MACE^	895 (19.2)	1000 (21.4)	1895 (20.3)	0.884	0.807, 0.967	0.007
Components of expanded MACE						
Cardiovascular death	149 (3.2)	197 (4.2)	346 (3.7)	0.752	0.608, 0.930	0.009
Non-fatal stroke	159 (3.4)	177 (3.8)	336 (3.6)	0.894	0.721, 1.107	0.303
Non-fatal MI	281 (6.0)	317 (6.8)	598 (6.4)	0.878	0.747, 1.031	0.111
Hospitalization for unstable angina pectoris	122 (2.6)	124 (2.7)	246 (2.6)	0.980	0.763, 1.258	0.872
Coronary revascularization	405 (8.7)	441 (9.4)	846 (9.1)	0.912	0.797, 1.044	0.180
Hospitalization for heart failure	218 (4.7)	248 (5.3)	466 (5.0)	0.872	0.727, 1.046	0.140
Other secondary endpoints						
All cause death	311 (6.7)	366 (7.8)	677 (7.2)	0.845	0.726, 0.983	0.029
Non-cardiovascular death	162 (3.5)	169 (3.6)	331 (3.5)	0.952	0.768, 1.181	0.656
Composite of hosp. for heart failure/all cause death (post hoc analysis)	481 (10.3)	549 (11.8)	1030 (11.0)	0.869	0.769, 0.982	0.024

FAS: Full analysis set. MACE: major adverse cardiovascular event, EAC: event adjudication committee, CI: confidence interval, CV: cardiovascular, hosp: hospitalization, HR: hazard ratio, N: number; (%) percent of patients with a first EAC confirmed event between randomization date and follow up date, MI: myocardial infarction. Events which occur before randomization date are not used for defining first event. NOTE: for this table, component events of MACE (and expanded MACE) do NOT sum to total number of MACE (exp. MACE).
*Contains the first MACE event which includes: cardiovascular death, non-fatal MI and non-fatal stroke
^contains the first expanded MACE event, which includes: cardiovascular death, nonfatal MI, nonfatal stroke, coronary revascularization, hospitalization for unstable angina pectoris or hospitalization for heart failure

Source: Question 1 in information request dated March 21, 2017: \\CDSESUB1\evsprod\NDA022341\0362\m1\us\resp-ir-20170314.pdf

Table 54 in the Appendix for a table showing arrhythmia events). A graph showing the proportion of patients by the types of arrhythmias is shown below.

Figure 28- Proportion of patients by types of arrhythmias



Source: graphed data from

	Liraglutide N (%)	Placebo N (%)	Total N (%)	Lira/placebo Hazard ratio	95% CI	Test for HR=1.0 two sided
FAS	4668	4672	9340			
Primary endpoint: MACE*	546 (11.7)	624 (13.4)	1170 (12.5)	0.867	0.773, 0.973	0.015
Expanded MACE^	895 (19.2)	1000 (21.4)	1895 (20.3)	0.884	0.807, 0.967	0.007
Components of expanded MACE						
Cardiovascular death	149 (3.2)	197 (4.2)	346 (3.7)	0.752	0.608, 0.930	0.009
Non-fatal stroke	159 (3.4)	177 (3.8)	336 (3.6)	0.894	0.721, 1.107	0.303
Non-fatal MI	281 (6.0)	317 (6.8)	598 (6.4)	0.878	0.747, 1.031	0.111
Hospitalization for unstable angina pectoris	122 (2.6)	124 (2.7)	246 (2.6)	0.980	0.763, 1.258	0.872
Coronary revascularization	405 (8.7)	441 (9.4)	846 (9.1)	0.912	0.797, 1.044	0.180
Hospitalization for heart failure	218 (4.7)	248 (5.3)	466 (5.0)	0.872	0.727, 1.046	0.140
Other secondary endpoints						
All cause death	311 (6.7)	366 (7.8)	677 (7.2)	0.845	0.726, 0.983	0.029
Non-cardiovascular death	162 (3.5)	169 (3.6)	331 (3.5)	0.952	0.768, 1.181	0.656
Composite of hosp. for heart failure/all cause death (post hoc analysis)	481 (10.3)	549 (11.8)	1030 (11.0)	0.869	0.769, 0.982	0.024

FAS: Full analysis set. MACE: major adverse cardiovascular event, EAC: event adjudication committee, CI: confidence interval, CV: cardiovascular, hosp: hospitalization, HR: hazard ratio, N: number; (%) percent of patients with a first EAC confirmed event between randomization date and follow up date, MI: myocardial infarction. Events which occur before randomization date are not used for defining first event. NOTE: for this table, component events of MACE (and expanded MACE) do NOT sum to total number of MACE (exp. MACE).
*Contains the first MACE event which includes: cardiovascular death, non-fatal MI and non-fatal stroke
^contains the first expanded MACE event, which includes: cardiovascular death, nonfatal MI, nonfatal stroke, coronary revascularization, hospitalization for unstable angina pectoris or hospitalization for heart failure

Source: Question 1 in information request dated March 21, 2017:
\\CDSESUB1\evsprod\NDA022341\0362\m1\us\resp-ir-20170314.pdf
Table 54

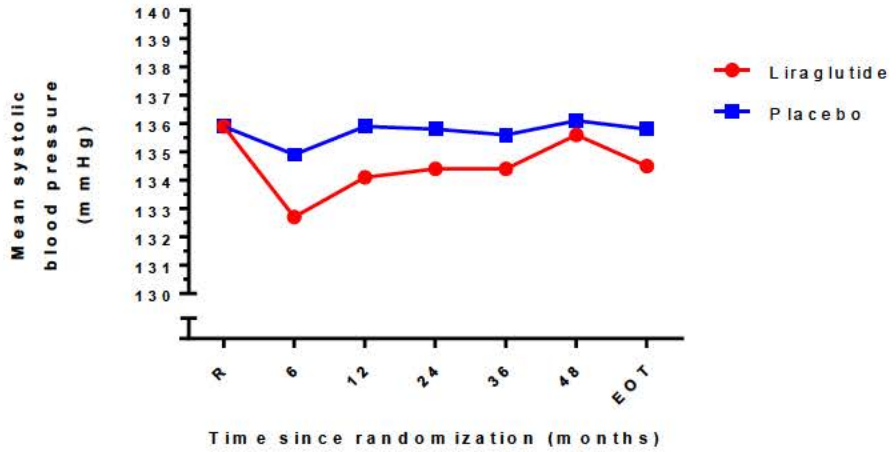
Blood Pressure

Blood pressure was recorded every 6 months for the first year, after which it was measured yearly until the end of the trial. Patients were told to avoid caffeine, smoking and exercise at least 30 minutes before the measurement. Two blood pressure measurements at intervals of at least two minutes were performed with no talking during measurements. Before the first measurement was taken, the subject was to sit for at least five minutes, with the legs uncrossed and his/her back and arm supported.

At baseline systolic and diastolic blood pressure was similar between treatment groups (mean systolic blood pressure 135.9 mmHg and diastolic blood pressure ~77 mmHg). Over 90% of patients had a history of hypertension and over 90% of patients were on antihypertensive therapy.

Figure 29 shows the mean systolic blood pressure over time. Both liraglutide and placebo had similar systolic blood pressure at the randomization visit. However liraglutide experienced a decrease in systolic blood pressure noted at month 6. Although the blood pressure decrease varied throughout the trial, the systolic blood pressure remained lower for liraglutide than placebo for any point in the trial.

Figure 29 – Mean systolic blood pressure by visit - FAS



Source: reviewer graphed mean values of CTR table 14.2.249

In a pre-specified analysis of the change in systolic blood pressure from baseline to a 3 year assessment, the mean systolic blood pressure was statistically significantly lower in the liraglutide group (adjusted mean decrease -1.4 mmHg) compared to the placebo group (adjusted mean decrease -0.2 mmHg) with a liraglutide -placebo treatment difference of -1.199 mmHg [95% confidence interval -1.916;-0.483]; p=0.001.

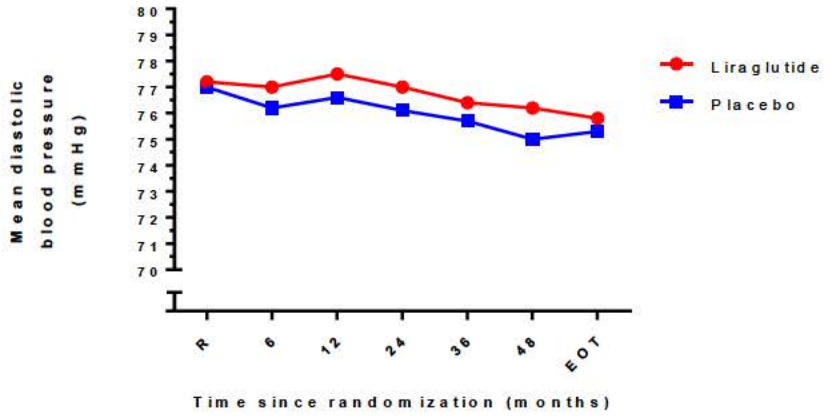
Reviewer's comment: Elevated systolic blood pressure has been associated with increased risk of cardiovascular disease. It is estimated that population reductions in systolic blood pressure would result in a reduction of cardiovascular mortality[78].

It is unclear if the persistently lower mean systolic blood pressure readings for liraglutide compared to placebo had an effect in the cardiovascular mortality seen in LEADER. Moreover, it does not appear that changes in antihypertensive therapy explained the difference in blood pressure. As Figure 7 **shows, slightly greater number of patients started anti-hypertensive therapy or diuretic therapy for placebo than liraglutide after baseline.**

Estimated mean diastolic blood pressure over time is shown in **Figure 30**. Both liraglutide and placebo had similar baseline values at randomization. Initially measures increased slightly for both groups until the first year, after which values decreased for both treatment arms. With the exception of the randomized visit, the measures for liraglutide diastolic blood pressure remained higher than placebo over time.

[78] A 2 mmHg reduction of systolic blood pressure may result in a 6%, 4% and 3% reduction of mortality from stroke, CHD and total mortality (see: Whelton PK et al. *JAMA* 2002;288:1884.)

Figure 30 – Mean diastolic blood pressure by visit - FAS



Source: reviewer graphed mean values of CTR table 14.2.260

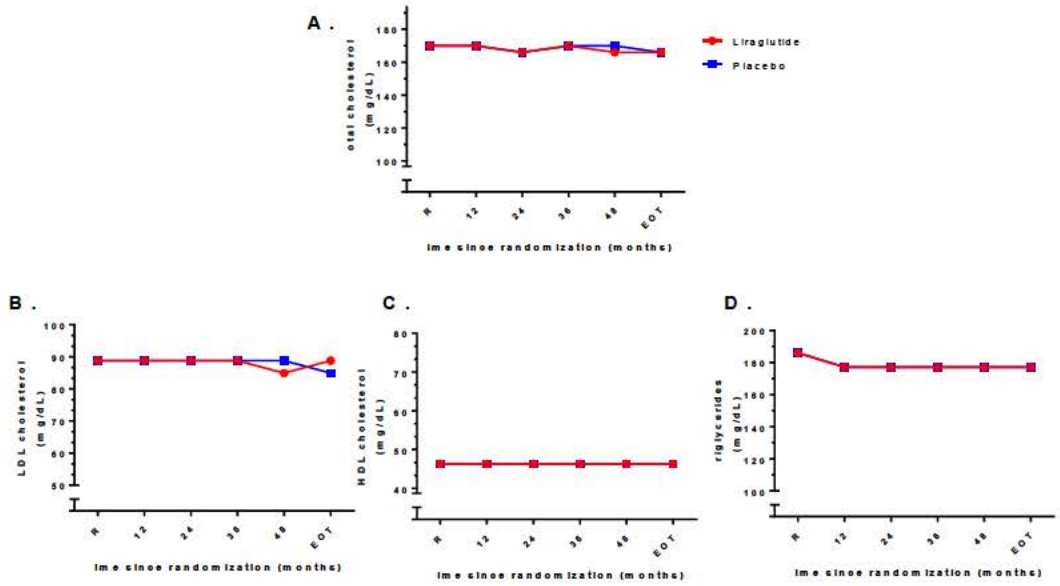
In a pre-specified analysis of the change in diastolic blood pressure from baseline to a 3 year assessment, there was a statistically significant smaller decrease in diastolic blood pressure with liraglutide (mean decrease of -0.8 mmHg) than placebo (mean decrease of -1.3 mmHg) with a Liraglutide -placebo treatment difference of +0.587 mmHg [95% confidence interval 0.187;0.987] ; p=0.004.

Lipids

Fasting lipid measurements were performed yearly during the study, after randomization. Across lipid measures, including LDL, HDL, total cholesterol and triglycerides, values were similar between liraglutide and placebo (refer to **Table 12**). Similar proportion of patients were using lipid lowering agents at baseline and similar proportion of patients started lipid lowering therapy after baseline (refer to **Figure 7**).

Figure 31 shows the mean lipid measures for liraglutide and placebo over time. Across different measures, there was no clear difference between treatment arms. Total, LDL and HDL cholesterol, tended to be stable from baseline; triglycerides decreased from baseline during the first year and remained stable for the remainder of the study.

Figure 31 – Mean lipid measures over time: A. total cholesterol; B. LDL cholesterol, C. HDL cholesterol; D. triglycerides - FAS



Source: reviewer graphed means from CTR, tables: 14.3.5.179, 14.3.5.161, 14.3.5.170, 14.3.5.188. The reviewer used the conversion of 1 mmol/l = 88.57396 mg/dl for triglycerides and 1 mmol/l = 38.66976 mg/dl for all other lipid measures

The reviewer discusses the *change* in lipid parameters from baseline to 3 years, in this review, since this analysis is clinically more informative; of note, the trial report shows the lipid analysis of the *ratio* of the 3 year visit to baseline in the body of the document.

When compared to baseline, at 3 years, there was a mean adjusted decrease in total cholesterol for liraglutide (-1.3 mg/dL), and a small adjusted increase for placebo (+0.3 mg/dL)[79]; there was a mean adjusted increased in HDL for both liraglutide (+1.5 mg/dL) and placebo (+1.2 mg/dL)[80]; there was a mean adjusted decrease in LDL for liraglutide (-1.5 mg/dL) and a slight adjusted increase for placebo (0.1 mg/dL)[81]; there was a slight decrease in triglycerides for both liraglutide (-7.9 mg/dL) and placebo (-6.4 mg/dL)[82].

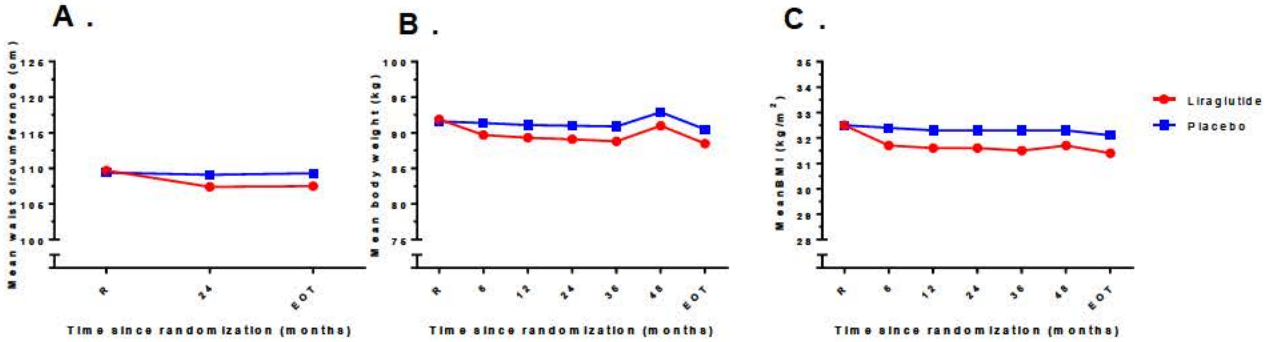
Body weight, BMI and waist circumference

[79] The treatment contrast in mmol/L was -0.042 [-0.085 ; 0.001] p=0.055 using MMRM FAS
[80] The treatment contrast in mmol/L was 0.009 [-0.001 ; 0.018] p=0.066 using MMRM FAS
[81] The treatment contrast in mmol/L was -0.041 [-0.077 ; -0.006] p=0.023 using MMRM FAS
[82] The treatment contrast in mmol/L was -0.017 [-0.071 ; 0.036] p=0.530 using MMRM FAS

Body weight and body mass index (BMI) were assessed at 6 and then yearly after randomization. Waist circumference was assessed at 24 and 60 months, after randomization.

Figure 32 shows the mean values over time for waist circumference, body weight and mean BMI. Overall, baseline values were similar between treatment groups. However after randomization, liraglutide values tended decrease and remain persistently lower than placebo for body weight, BMI and waist circumference.

Figure 32- A. mean waist circumference over time; B. mean body weight over time; C. mean BMI over time.



Source: tables: reviewer graphed means from CTR, tables 14.2.216, 14.2.238, and 14.2.227

A statistically significant reduction of body weight (pre-specified) and body mass index (*post-hoc)* was seen in the liraglutide group when compared to placebo after 3 years. Liraglutide had an adjusted mean decrease in weight of -2.7 kg vs. -0.5 kg for placebo with a liraglutide-placebo difference of ~2.3 kg favoring liraglutide. Similarly, liraglutide had an adjusted mean decrease in BMI of -0.96 kg/m^2 vs. -0.16 kg/m^2 for placebo, with a liraglutide-placebo difference of ~ 0.8 kg/m^2 favoring liraglutide.[83]

Changes in waist circumference also favored liraglutide. After 2 years, liraglutide had an adjusted mean decrease in waist circumference of -2 cm compared to placebo which had a decrease of -0.02 cm. The liraglutide-placebo difference was ~2 cm favoring liraglutide compared to placebo.[84]

Reviewer's comment: weight decrease with liraglutide when compared to placebo is labeled in section 14 of the Victoza label. The changes in body weight in

[83] For body weight change, the liraglutide-placebo treatment difference was -2.264 kg [95% confidence interval -2.539; -1.99], P<0.001, while the liraglutide-placebo treatment difference was -0.806 [95% confidence interval -0.903; -0.709], P<0.001.
[84] For body waist circumference the liraglutide-placebo treatment difference was -1.984cm [95% confidence interval -2.298; -1.669], P<0.001.

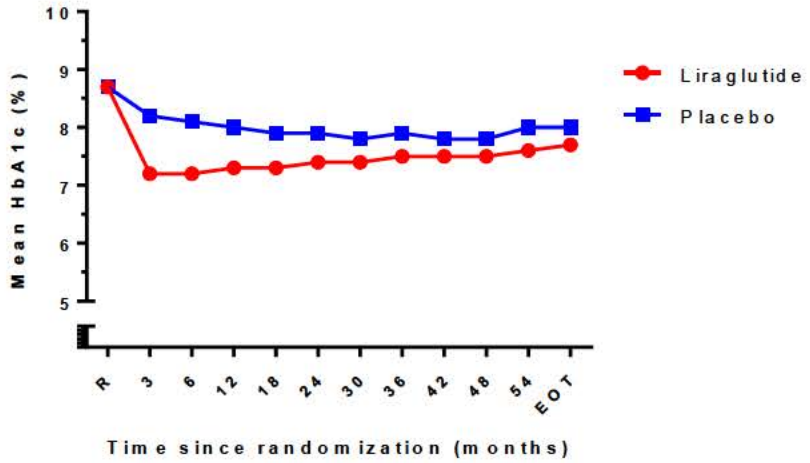
LEADER are consistent with the already labeled information in the Victoza label. It is unknown how weight loss may have influenced the cardiovascular findings in this study.

HbA1c

HbA1c was measured every 3 months for the first year and every 6 months subsequently. At baseline, HbA1c was the same between treatment groups, 8.7%. **Figure 33** shows that after randomization, the HbA1c decreased for both treatment groups. At 3 months of treatment there was a larger HbA1c decrease for liraglutide than placebo. After 3 months of treatment, the HbA1c for placebo tended to remain somewhat stable; while HbA1c tended to increase over time for liraglutide. Despite the HbA1c increase seen after month 3, the HbA1c for liraglutide remained persistently lower than placebo throughout the trial.

The change from baseline to month 36 for HbA1c was -1.2% for liraglutide and -0.8% for placebo-treated patients. The mean HbA1c was statistically significantly lower in the liraglutide group compared to the placebo group (Lira-placebo treatment difference -0.396 [95% confidence interval -0.453; -0.338]; p<0.001).

Figure 33 - Mean HbA1c by visit



Source: reviewer graphed CTR table 14.2.159

As previously noted, the trial did not withdraw patients due to treatment discontinuation. Both treatment groups were balanced when evaluating patient exposure by the duration of drug holidays (see section **Treatment Exposure and observation time**). Therefore, drug compliance, as captured by the trial, did not explain the differential findings.

As shown in **Figure 7**, although baseline medications tended to be similar, patients in the placebo group started more antidiabetic medications after baseline than in the

liraglutide group. Most notably, a larger percentage of patients on placebo started insulin after baseline (placebo vs. liraglutide: 43% vs. 29%, respectively). In a pre-specified analysis of time to first insulin initiation for patients who were insulin naïve at baseline, the Sponsor showed that the likelihood of insulin initiation was lower for liraglutide than placebo (liraglutide/placebo hazard ratio 0.522 [95% confidence interval 0.475; 0.574]).

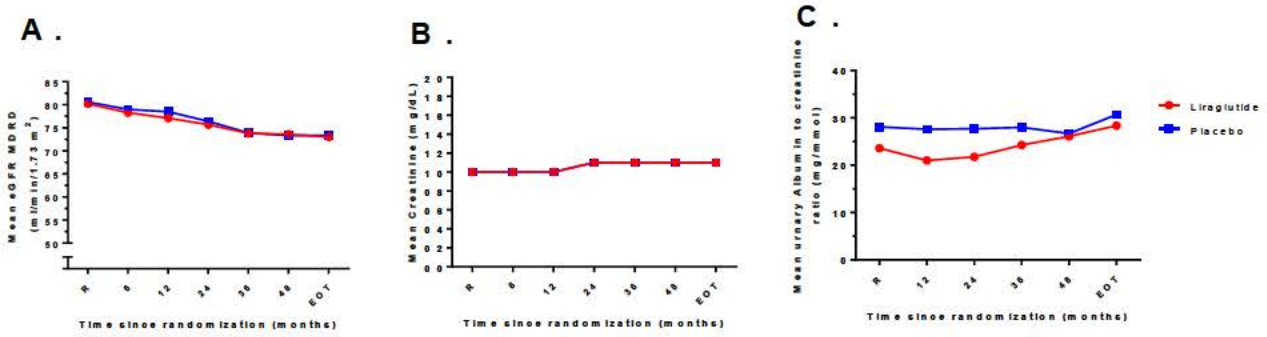
Reviewer's comments: It is unclear what factors may have influenced the difference in HbA1c between treatment arms. Although surprising, that even though more patients in the placebo group started insulin, which could be titrated to goal, there was still a difference in HbA1c between treatment groups; other CVOTs have shown similar trends.

General renal safety

Renal safety will be evaluated by a general assessment of renal safety (in this section) followed by an evaluation of the nephropathy efficacy endpoints (discussed in the following sections). The general renal safety will be assessed by exploring trends in renal laboratories over time, evaluating shifts in eGFR and by evaluating Standardized MedDRA Queries (SMQs) for acute and chronic renal failure.

At baseline, the average eGFR was 80 ml/min/1.73 m^2 (MDRD) and approximately 20% and 2% of patients had moderate or severe renal insufficiency as defined by eGFR MDRD. Throughout the course of the trial, the trends in eGFR, and creatinine were similar between liraglutide and placebo; see **Figure 34**. The trends in urinary albumin to creatinine ratio also tended to be similar between treatment groups with a lower baseline for liraglutide than placebo.

Figure 34 –A. mean eGFR MDRD over time, B. mean creatinine overtime, C. mean urinary albumin to creatinine ratio over time



Source: graphed results from CTR, table 14.2.346, CTR table 14.3.5.30 (creatinine), table 14.3.5.197 urinary albumin to creatinine ratio by visit

On May 18, 2011, the Victoza label was modified, based on a Prior Approval Supplement with postmarketing surveillance information, to include language regarding the risk of dehydration from nausea, vomiting, and diarrhea resulting in renal failure. Victoza has a Warnings and Precautions for renal impairment in the label that warns of postmarketing reports of renal impairment in association with nausea, vomiting diarrhea or dehydration, which may sometimes require hemodialysis.[85]

In a previous supplemental NDA submission (supplement 10)[86], the safety and efficacy of Victoza was evaluated in a double-blinded, placebo controlled trial evaluating a small population of patients with moderate renal impairment (30−59 mL/min/1.73 m^2 - using the modification of Diet in Renal Disease [MDRD] formula), over a 26 week period. In this supplement there were small shifts in eGFR worsening in the liraglutide group when compared to the placebo group, but these changes were primarily driven by a small number of patients and evaluation of outlier analyses (via shifts from baseline).The shifts identified in this prior supplement did not result in any patient requiring hemodialysis. A nephrology consult focused on renal adverse events and central tendency changes of serum creatinine, concluded that there was no identified safety signal in patients with moderate renal insufficiency using liraglutide up to a dose of 1.8 mg.

In line with the analyses performed in supplement 10, the reviewer asked the Sponsor to conduct an analysis of eGFR shifts (using the MDRD formula) in the LEADER trial. **Table 29** shows patients who had a shift in renal function from baseline to the lowest measured eGFR MDRD in the trial; **Table 30** shows the patients with a shift from baseline to the end of trial visit. Of note, the cells highlighted in pink show the categories in which liraglutide had a higher number of patients than placebo who down shifted (i.e. worsened) in eGFR.

Overall 2156 (46.2%) liraglutide-patients and 2130 (45.6%) placebo-patients experienced any downward shift of eGFR throughout the trial (see **Table 29**). When evaluating the eGFR at baseline to the end of trial (visit 15), the proportion of patients who experienced any downward shift was identical (26.6% of patients in either treatment arm).

In addition, outlier analyses of creatinine baseline to end of trial, was consistent with the eGFR findings. Overall, similar proportions of patients shifted from normal to a high creatinine values at the end of treatment (10.3% vs 10.9% for liraglutide and placebo respectively)[87].

Reviewer's comment: the trends in shifts of eGFR throughout the trial are similar to the trends observed in supplement 10, meaning there were small numerical

[85] Refer to Clinical reviewer Memo dated May 19, 2011 in DARRTS
[86] Refer to primary clinical review dated June 23, 2015
[87] Shift tables are not shown, refer to table 14.3.5.42 of the CTR

imbalances (i.e. slightly more patients in the liraglutide than placebo group had a decrease in eGFR at any point during the trial). However, unlike supplement 10, the shifts from baseline to the end of the trial were similar for both treatment groups. In addition, the shifts in eGFR do not suggest a clear benefit for liraglutide, when compared to placebo. 'Nephropathy' from a benefit perspective is further discussed below.

Table 29 -**Shift in renal function from baseline to post-baseline visit with lowest eGFR-MDRD value - FAS**

		MDRD eGFR at baseline											
		Liraglutide – 4668 patients						Placebo- 4672 patients					
MDRD eGFR shift from baseline	**MDRD eGFR**	**<15**	**15-<30**	**30-<45**	**45-<60**	**60-<90**	**90+**	**<15**	**15-<30**	**30-<45**	**45-<60**	**60-<90**	**90 +**
	<15	9 (0.2)	32 (0.7)	20 (0.4)	6 (0.1)	5 (0.1)	4 (0.1)	10 (0.2)	29 (0.6)	31 (0.7)	12 (0.3)	10 (0.2)	0
	15-<30	0	48 (1)	95 (2)	54 (1.2)	25 (0.5)	6 (0.1)	0	53 (1.1)	85 (1.8)	55 (1.2)	31 (0.7)	9 (0.2)
	30-<45	0	13 (0.3)	170 (3.6)	276 (5.9)	154 (3.3)	22 (0.5)	0	5 (0.1)	148 (3.2)	262 (5.6)	149 (3.2)	29 (0.6)
	45-<60	0	0	23 (0.5)	272 (5.8)	571 (12.2)	72 (1.5)	1 (0)	1 (0)	15 (0.3)	243 (5.2)	552(11.8)	86 (1.8)
	60-<90	1 (0)	1 (0)	7 (0.1)	33 (0.7)	1099 (23.5)	814 (17.4)	0	0	1 (0)	36 (0.8)	1141 (24.4)	790 (16.9)
	90+	0	1 (0)	0	1 (0)	33 (0.7)	651 (13.9)	0	0	0	2 (0)	35 (0.7)	685 (14.7)
	Missing	3 (0.1)	9 (0.2)	15 (0.3)	27 (0.6)	45 (1)	51 (1.1)	0	8 (0.2)	16 (0.3)	29 (0.6)	57 (1.2)	56 (1.2)
	total	13 (0.3)	104 (2.2)	330 (7.1)	669 (14.3)	1932 (41.4)	1620 (34.7)	11 (0.2)	96 (2.1)	296 (6.3)	639 (13.7)	1975 (42.3)	1655 (35.4)

N: Number of subjects, %: Proportion of subjects, eGFR-MDRD: Estimated glomerular filtration rate using the modification of diet in renal disease formula (ml/min/1.73m^2). FAS: full analysis set The shift from baseline is evaluated to the lowest eGFR-MDRD value at any scheduled or unscheduled post-baseline visit.

Table 30-Shift in renal function from baseline to visit 15 (end-of-trial visit) - FAS

		MDRD eGFR at baseline											
		Liraglutide – 4668 patients						Placebo- 4672 patients					
MDRD eGFR shift from baseline	**MDRD eGFR**	**<15**	**15-<30**	**30-<45**	**45-<60**	**60-<90**	**90+**	**<15**	**15-<30**	**30-<45**	**45-<60**	**60-<90**	**90 +**
	<15	6 (0.1)	25 (0.5)	16 (0.3)	4 (0.1)	2 (0)	3 (0.1)	5 (0.1)	13 (0.3)	23 (0.5)	7 (0.1)	6 (0.1)	0
	15-<30	0	25 (0.5)	45 (1)	33 (0.7)	18 (0.4)	4 (0.1)	0	24 (0.5)	40 (0.9)	30 (0.6)	15 (0.3)	6 (0.1)
	30-<45	0	12 (0.3)	105 (2.2)	157 (3.4)	71 (1.5)	9 (0.2)	1 (0)	12 (0.3)	83 (1.8)	146 (3.1)	87 (1.9)	14 (0.3)
	45-<60	0	3 (0.1)	40 (0.9)	246 (5.3)	327 (7)	39 (0.8)	1 (0)	1 (0)	31 (0.7)	169 (3.6)	331 (7.1)	45 (1.0)
	60-<90	1 (0)	1 (0)	10 (0.2)	77 (1.6)	1020 (21.9)	492 (10.5)	1 (0)	0	2 (0)	89 (1.9)	996 (21.3)	479 (10.3)
	90+	0	1 (0)	1 (0)	7 (0.1)	128 (2.7)	783 (16.8)	0	0	0	3 (0.1)	133 (2.8)	771 (16.5)
	Missing	6 (0.1)	37 (0.8)	113 (2.4)	145 (3.1)	366 (7.8)	290 (6.2)	3 (0.1)	46 (1)	117 (2.5)	195 (4.2)	407 (8.7)	340 (7.3)
	total	13 (0.3)	104 (2.2)	330 (7.1)	669 (14.3)	1932 (41.4)	1620 (34.7)	11 (0.2)	96 (2.1)	296 (6.3)	639 (13.7)	1975 (42.3)	1655 (35.4)

Lira: Liraglutide, N: Number of subjects, %: Proportion of subjects, eGFR-MDRD: Estimated glomerular filtration rate using the modification of diet in renal disease formula (ml/min/1.73m^2).

The reviewer performed additional analyses of SMQs for Acute renal failure and Chronic renal failure; the system organ class (AESOC) and preferred terms (AEDECOD) are shown in **Table 55** and **Table 56,** in the appendix.

For the acute renal failure SMQ analysis, although there were slight imbalances noted between treatment arms, (i.e. a larger number of patients experiencing PT acute kidney injury with liraglutide than placebo) the overall proportion of patients was small (3% vs. 2% for liraglutide vs. placebo respectively).

The analysis for chronic renal failure SMQ also revealed small numerical differences between treatment arms, with no clear trend favoring either treatment group, see **Table 56**.

An evaluation of SAEs for the system organ class: renal and urinary disorders, is shown in **Table 31.** Overall, across preferred terms there were small numerical imbalances (i.e., PT of 'acute kidney injury' 2.3% vs 2% for liraglutide and placebo), which were similar to the SMQ analyses (discussed above).

Table 31- Serious adverse events of the system organ class Renal and Urinary disorders- by preferred terms -FAS

	Liraglutide N = 4668			Placebo N = 4672		
	Events	*Number of subjects*	*Proportion (%)*	*Events*	*Number of subjects*	*Proportion (%)*
Renal and urinary disorders (SOC)	349	270	5.78	338	274	5.86
Acute kidney injury	124	108	2.31	105	94	2.01
Acute prerenal failure	1	1	0.02	1	1	0.02
Azotemia	3	3	0.06	2	2	0.04
Bladder diverticulum	0	0	0	1	1	0.02
Bladder dysplasia	1	1	0.02	0	0	0
Bladder hypertrophy	0	0	0	2	2	0.04
Bladder neck obstruction	2	2	0.04	0	0	0
Bladder outlet obstruction	0	0	0	1	1	0.02
Bladder prolapse	3	3	0.06	1	1	0.02
Bladder stenosis	1	1	0.02	0	0	0
Calculus bladder	1	1	0.02	0	0	0
Calculus ureteric	10	10	0.21	9	9	0.19
Calculus urinary	2	2	0.04	2	2	0.04
Chronic kidney disease	60	52	1.11	55	52	1.11
Diabetic nephropathy	7	6	0.13	11	11	0.24
Dysuria	1	1	0.02	3	3	0.06
Fibrillary glomerulonephritis	1	1	0.02	0	0	0
Focal segmental	0	0	0	1	1	0.02

glomerulosclerosis						
Glomerulonephritis membranous	2	1	0.02	0	0	0
Glomerulosclerosis	1	1	0.02	0	0	0
Hematuria	7	7	0.15	2	2	0.04
Hemorrhage urinary tract	2	1	0.02	0	0	0
Hydronephrosis	6	5	0.11	2	2	0.04
Mesangioproliferative glomerulonephritis	0	0	0	1	1	0.02
Microalbuminuria	1	1	0.02	0	0	0
Nephritis	1	1	0.02	0	0	0
Nephrolithiasis	27	26	0.56	22	21	0.45
Nephropathy	6	6	0.13	15	13	0.28
Nephropathy toxic	1	1	0.02	2	2	0.04
Nephrotic syndrome	2	2	0.04	1	1	0.02
Nocturia	0	0	0	1	1	0.02
Obstructive uropathy	2	2	0.04	0	0	0
Pelvi-ureteric obstruction	1	1	0.02	0	0	0
Polyuria	0	0	0	1	1	0.02
Proteinuria	2	2	0.04	3	3	0.06
Renal artery arteriosclerosis	0	0	0	1	1	0.02
Renal artery occlusion	0	0	0	1	1	0.02
Renal artery stenosis	2	2	0.04	3	3	0.06
Renal colic	3	3	0.06	1	1	0.02
Renal cyst	5	5	0.11	11	11	0.24
Renal failure	21	20	0.43	33	31	0.66
Renal hemorrhage	2	2	0.04	0	0	0
Renal impairment	14	14	0.3	10	10	0.21
Renal infarct	1	1	0.02	0	0	0
Renal injury	0	0	0	1	1	0.02
Renal pain	1	1	0.02	0	0	0
Renal tubular necrosis	1	1	0.02	5	5	0.11
Single functional kidney	1	1	0.02	0	0	0
Stress urinary incontinence	1	1	0.02	0	0	0
Tubulointerstitial nephritis	1	1	0.02	3	3	0.06
Ureteral necrosis	1	1	0.02	0	0	0
Ureteral polyp	0	0	0	1	1	0.02
Ureteric obstruction	1	1	0.02	0	0	0
Ureteric stenosis	1	1	0.02	0	0	0
Urethral stenosis	4	4	0.09	7	6	0.13
Urinary bladder polyp	0	0	0	2	2	0.04
Urinary incontinence	2	2	0.04	1	1	0.02
Urinary retention	8	8	0.17	13	12	0.26

Urinary tract obstruction	1	1	0.02	1	1	0.02

Source: MAED analysis of adsl xpt, adae.xpt, FASFL=y, AESER=Y, AEONTRFL=y and AESOC=renal and urinary disorders

Reviewer's comments: across multiple analyses the renal safety of liraglutide was overall similar to placebo.

6.1.6.2 Microvascular Disease Endpoints (Retinopathy and Nephropathy)

Multiple large-scale trials have shown that intensive glycemic therapy improves microvascular disease over time.[88]

In this review microvascular disease will be discussed by focusing on the following endpoints:

1. Microvascular composite endpoint
2. Nephropathy endpoint
3. Retinopathy endpoint

Microvascular composite endpoint

The microvascular endpoints in this trial included components of nephropathy and retinopathy. As shown in **Table 7**, the two microvascular endpoints included: time to randomization to first occurrence of a composite microvascular outcome and time from randomization to each individual component of the composite microvascular outcome for nephropathy (items 4-6 below) and retinopathy (items 1-3) outcomes separately.

This section will first address the composite microvascular endpoint, defined as:

1. Need for retinal photocoagulation or treatment with intravitreal agents
2. Vitreous hemorrhage
3. Onset of diabetes related blindness (Snellen visual acuity of 20/200 [6/60] or less, or visual field of <20 degrees in the better eye with best correction)
4. New or worsening nephropathy (defined as new onset of persistent urine albumin ≥300mg/g creatinine (macro-albuminuria) , or persistent doubling of serum creatinine level and eGFR ≤ 45 mL/min/1.73 m^2 per MDRD)
5. Need for continuous renal-replacement therapy in absence of acute reversible cause
6. Death due to renal disease

The methodology of EAC adjudication is shown in the appendix, **Figure 50** and **Figure 51.**

Reviewer's comment: The reviewer will focus on microvascular claims in section 14 of the label. The Sponsor proposes to label the following (b) (4)

[88] Intensive glycemic control in T1DM and T2DM trial shave shown improvements in microvascular disease: in type 2 diabetes: UKPDS, ADVANCE and ACCORD studies.

(b) (4)

None of these secondary claims were adjusted for multiplicity. Furthermore the analysis of the (b) (4) **was performed post hoc.**

Information regarding microvascular complications of diabetes (i.e. diabetic nephropathy, retinopathy and neuropathy, and diabetic foot ulcer) was recorded in the CRF at Visit1. There was no pre-specified ophthalmological evaluation of patients during the trial. Nephropathy events were captured in part by regular measurement of creatinine and urine albumin, as shown in **Table 9.**

Table 32 shows the first EAC confirmed microvascular events. In total 771 (8.3%) patients experienced a first EAC confirmed microvascular event. 7.6% (355 patients) randomized to liraglutide and 8.9% (416 patients) randomized to placebo experienced a first microvascular event. The overall composite endpoint numerically favored liraglutide over placebo. However, the trends in EAC confirmed first nephropathy and first retinopathy events were in opposition. With the exception of death due to renal disease, most of the first EAC confirmed nephropathy events favored liraglutide over placebo; while the first EAC confirmed retinopathy findings generally favored placebo over liraglutide.

Overall the composite microvascular endpoint findings appear to have been driven primarily by macroalbuminuria.

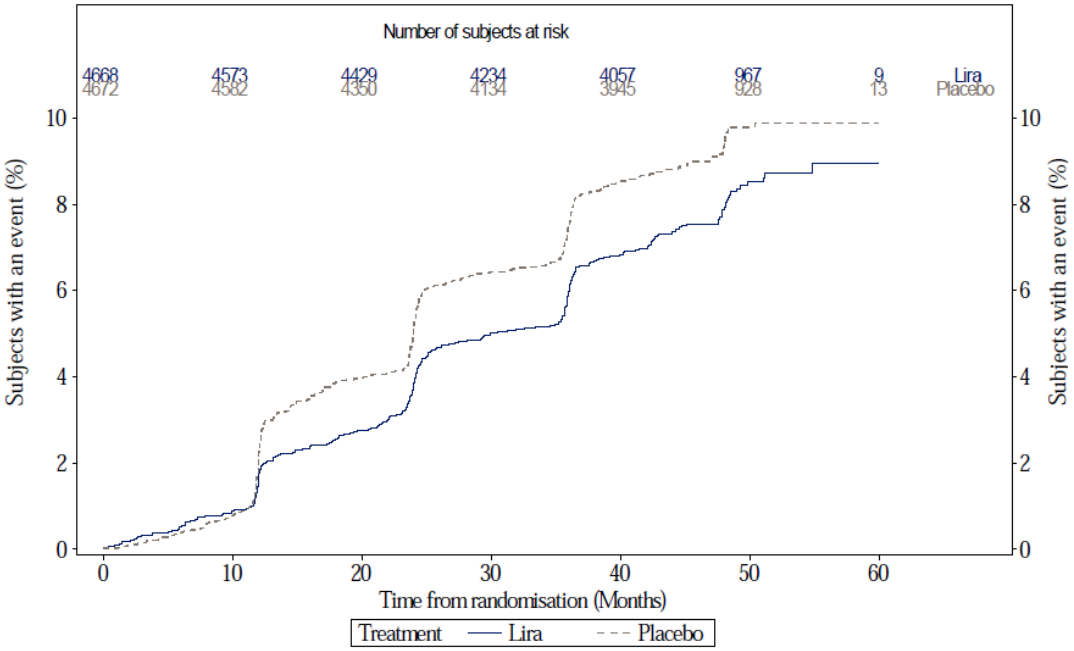
Table 32 – EAC confirmed microvascular events - FAS

	Liraglutide			Placebo		
	N (%)	E	R	N	E	R
FAS	4668			4672		
PYO	17822			17741		
EAC confirmed microvascular endpoint	355 (7.6)	355	1.99	416 (8.9)	416	2.34
EAC confirmed nephropathy	268 (5.7)	268	1.50	337 (7.2)	337	1.90
New onset of persistent macroalbuminuria	161 (3.4)	161	0.90	215 (4.6)	215	1.21
Persistent doubling of serum Creatinine*	87 (1.9)	87	0.49	97 (2.1)	97	0.55
Need for continuous renal-replacement therapy	56 (1.2)	56	0.31	64 (1.4)	64	0.36
Death due to renal disease	8 (0.2)	8	0.04	5 (0.1)	5	0.03
EAC confirmed retinopathy	106 (2.3)	106	0.59	92 (2.0)	92	0.52
Treatment with photocoagulation or intravitreal agents	100 (2.1)	100	0.56	86 (1.8)	86	0.48
Development of diabetes-related blindness	0 (0.0)	0	0	1 (0.0)	1	0.01
Vitreous hemorrhage	32 (0.7)	32	0.18	22 (0.5)	22	0.12

N: Number of subjects, %: Proportion of subjects, E: Number of events, PYO: Patient years of observation R: Event rate per 100 patient years of observation, EAC confirmed microvascular endpoint is a composite of EAC confirmed nephropathy and retinopathy. Only first (index) events after randomization and until follow-up are included. For sub groups the first event within each sub group is selected., *Persistent doubling of serum creatinine and eGFR <=45 ml/min/1.73 m2 per MDRD
Source: modified CTR Table 11-11, page 246

Figure 35 shows the Kaplan-Meier plot of EAC-confirmed first microvascular event over time for liraglutide and placebo. Overall the risk of microvascular events was lower for liraglutide than for placebo after 10 months.

Figure 35- Kaplan-Meier plot- time to first EAC-confirmed microvascular event- FAS



breviations: EAC: event adjudication committee; FAS: full analysis set; Lira: liraglutide.
Source: CSR Figure 11-12, page 248

The additional 61 microvascular cases in the placebo than the liraglutide group, resulted in a hazard ratio for time to first EAC-confirmed MACE of 0.84 [95% confidence interval; 0.73-0.969], p=0.016.

Reviewer's comments: the microvascular findings were primary driven by the nephropathy findings, and in particular by the macroalbuminuria findings. Therefore this endpoint does not provide an overall assessment of microvascular events.

An evaluation of all EAC confirmed microvascular events (first and recurrent events) from randomization to follow up was similar to the findings discussed above

Nephropathy endpoint

Time to first event discussion

As discussed earlier, the nephropathy endpoint was composed of two laboratory based assessments (new onset of persistent urine albumin ≥300mg/g creatinine [macro-albuminuria], or persistent doubling of serum creatinine level and eGFR ≤ 45 mL/min/1.73 m^2 per MDRD) and two clinical assessments (need for continuous renal-replacement therapy in absence of acute reversible cause and death due to renal disease).

After randomization, serum creatinine was measured by a central laboratory every 6 months for the first year, followed by yearly assessments until the end of trial. Urine laboratories were performed yearly. In order to confirm persistent macroalbuminuria or persistent doubling of serum creatinine, the protocol specified that a confirmatory measurement was to be performed within 12 weeks.

Reviewer's comment: Of note, the changes to the nephropathy definition occurred in amendment 8 of the protocol with the addition of the word "persistent". Also in version 8 of the EAC charter which changed macroalbuminuria from 300 mg/L to 300 mg albumin/g creatinine. This change in definition required re-adjudication of all nephropathy events previously adjudicated prior to update. Although these changes in the EAC charter required re-adjudication of events, the expected adjudication is not expected to be different between treatment arms in a double blinded trial.

There were also differences between the protocol and the EAC charter in the collection of spot vs. 24 hour urine and the timing of collection between the second urine sample. In an information request, the Sponsor was asked to clarify these differences. According to the Sponsor "Whereas the protocol specified that spot urine samples were to be collected at defined visits, the EAC Charter clarified that both a 24-hour urine collection and a spot urine collection were acceptable, to ensure that all available albuminuria measurements irrespective of collection method were taken into account during adjudication. Furthermore, in the EAC Charter the timing of the confirmatory albuminuria measurement was not restricted to within a 12-week period. This approach was implemented to ensure that a confirmatory measurement would not be disregarded during adjudication due to having been performed outside the protocol-specified 12-week period. The same approach was applied for blood samples to confirm 'persistent doubling of serum creatinine level and eGFR ≤ 45 ml/min/1.73 m2 per MDRD."[89]

The following additional observations/concerns apply to the Sponsor's proposed components of the nephropathy endpoint. These observations are in part credited to the nephrology consult performed by Dr. Kimberly Smith, who reviewed the renal findings of the EMPA-REG OUTCOME trial, which had similar renal endpoints.[90]

- **The required measurement of doubling of serum creatinine as "persistent" implies that this value is verified in at least 2 measures (rather than 1 measure). A persistent change in creatinine, as specified in LEADER, (despite the differences in protocol and EAC charter discussed above) is appropriate for the evaluation of the nephropathy endpoint as it is more likely to capture chronic, irreversible changes in renal function rather than acute, reversible changes.**

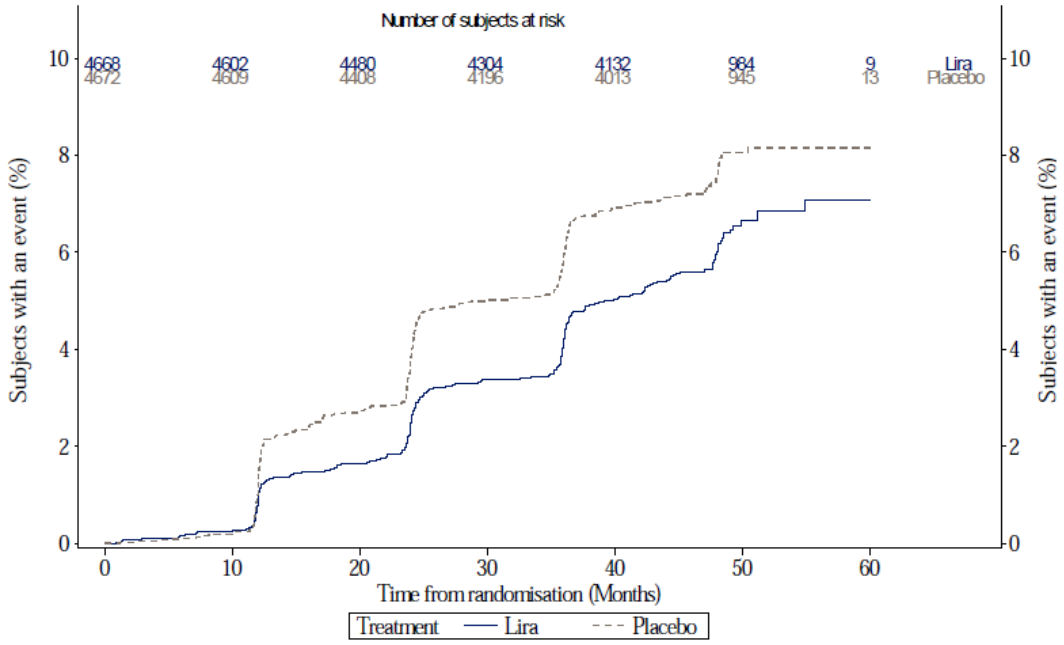
[89] see information request #3 : \\CDSESUB1\evsprod\NDA022341\0366\m1\us\resp-ir-20170327.pdf
[90] Dr. Smith's consult is located under NDA 204629; DARRTS dated April 29, 206.

- **As noted by Dr. Smith, in trials evaluating diabetic nephropathy, one component of the endpoint is often progression to end-stage disease, defined by initiation of chronic dialysis (i.e., dialysis that is ongoing after a specified period of time), renal transplant, or a sustained eGFR <15 mL/min/1.73m2. In the LEADER trial, although the hemodyalisis endpoint excludes acute reversible causes, there is no specific time point associated with the start of hemodialysis. Therefore, the possibility of including acute events is still a possibility.**
- **The EAC definitions for renal death did not provide adjudicators guidance on the identification of patients who died due to renal disease. The adjudication of "death due to renal disease" was based on the nephrologists' clinical judgement. As Dr. Smith notes, there is no obvious definition of renal death, it is generally defined as a death occurring after a patient refuses or a physician withholds renal replacement therapy (i.e., initiation of chronic dialysis or renal transplantation) or in cases where dialysis is unavailable. The definition often excludes deaths due to another primary process and/or when another cause is adjudicated (e.g., sepsis, end-stage heart failure, malignancy). Given the complexity in this definition, it is generally recommended that renal death be adjudicated with explicit rules for adjudication.**

Other concerns with the nephropathy endpoint are that the renal endpoints were not controlled by type 1 error and that the trial was not specifically designed to evaluate nephropathy, despite the enrollment of patients with moderate and severe renal impairment (see inclusion criteria in Table 3).

In version 3 of the SAP the Sponsor added time from randomization to the first occurrence of a composite nephropathy outcome. As shown in **Table 32**, the first EAC confirmed nephropathy events tended to favor liraglutide over placebo, with the exception of death due to renal disease. The Kaplan-Meier plot in **Figure 36** showed that EAC confirmed nephropathy events tended to be lower for liraglutide than placebo after month 10.

Figure 36 – Kaplan-Meier plot of time to EAC-confirmed nephropathy-FAS



Abbreviations: EAC: event adjudication committee; FAS: full analysis set; Lira: liraglutide.
Source: CTR figure 11-13, page 249

The additional 69 EAC confirmed first nephropathy events in the placebo than the liraglutide group, resulted in a hazard ratio for time to first EAC-confirmed nephropathy event of 0.78 [95% confidence interval; 0.67-0.92], p=0.003.

Of the individual components of the nephropathy endpoint, only the first EAC confirmed persistent macroalbuminuria events were significant for liraglutide when compared to placebo. The additional 54 events of persistent macroalbuminuria in placebo resulted in a hazard ratio of 0.738 [0.60; 0.91], nominal p=0.004. All other components of the nephropathy endpoint had a confidence interval crossing 1 and did not meet statistical significance (refer to **Table 10**). Note, however, that the Hazard Ratios should be considered exploratory.

The reviewer agrees with the overall EAC adjudication of nephropathy events after review of a sparse sample of narratives and adjudication packets for investigator reported MESI terms of: “proteinuria” and “diabetic nephropathy.”

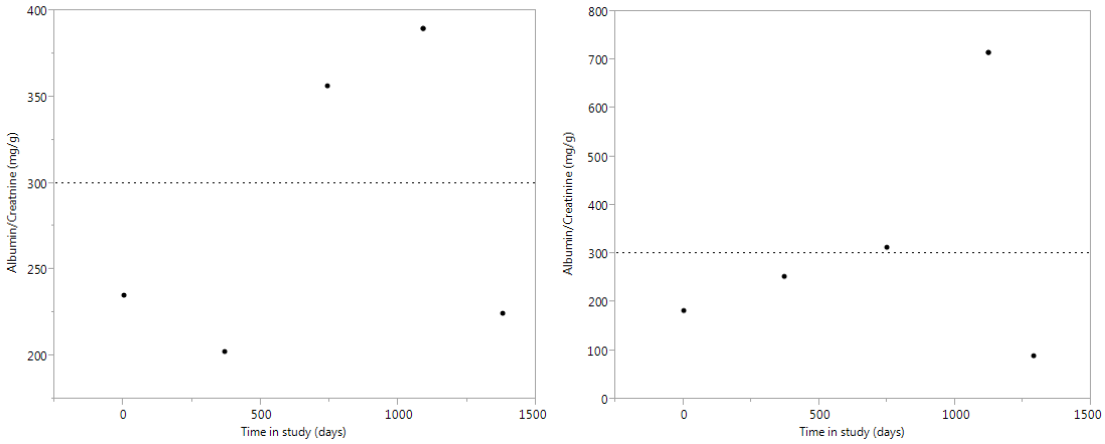
Reviewer’s comment: Although the overall nephropathy endpoint findings are favorable to liraglutide, there is no clear evidence of a benefit in the reduction of the overall complication of diabetes or progression of renal disease.

In addition, subject specific trends in macroalbuminuria raises questions regarding the “persistence of these findings.” Both patients in Figure 37, were adjudicated as meeting the macroalbuminuria criteria, by having an

albumin/creatinine ratio above the 300 mg/g. However, later in the trial the level of albuminuria no longer meets the macroalbuminuria definition (i.e. the albumin/creatinine ratio is below 300 mg/g) —therefore no longer staying "persistent."

Figure 37- Macroalbuminuria trends over time for patients adjudicated as meeting the "persistence" macroalbuminuria definition

A. Subject ID (b) (6) **B. Subject ID** (b) (6)

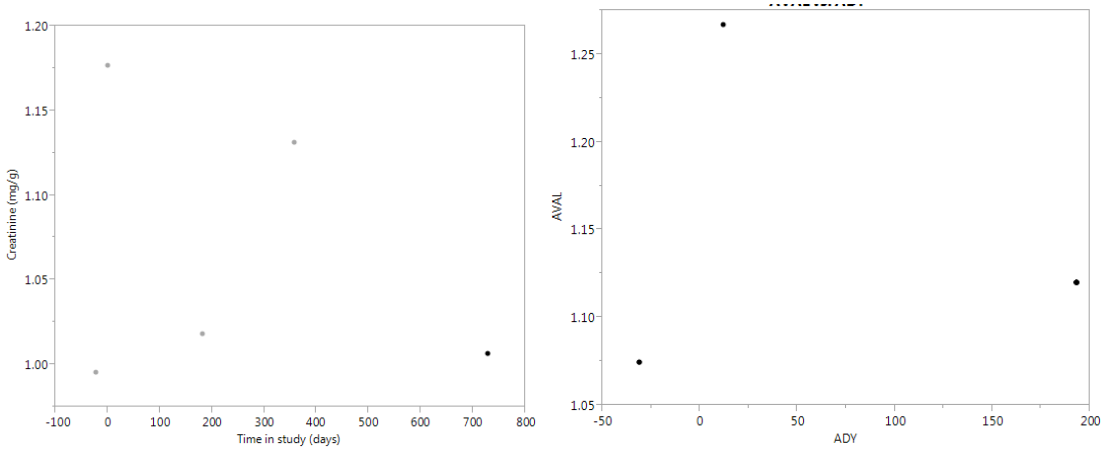


Source: reviewer generated graph of subjects form dataset adlbx.xpt selecting for albumin/creatinine conventional units and graphing variables ADY vs. AVAL

Similar to the macroalbuminuria findings discussed above, the reviewer evaluated subject level data of a sample of patients meeting the persistent doubling of creatinine and eGFR <=45 ml/min/1.73 m2 per MDRD definition. As seen in **Figure 38** there were patients identified as meeting this definition but not clearly showing a persistently elevated creatinine.

Figure 38- Example of patient adjudicated as meeting the persistent creatinine doubling and eGFR <=45 ml/min/1.73 m2 per MDRD

A. subject ID (b) (6) B. Subject ID (b) (6)



Source: reviewer generated graph of subjects form dataset adlb.xpt selecting for serum creatinine conventional units and graphing variables ADY vs. AVAL.

The reviewer reviewed all the identified cases of EAC confirmed events of "renal death" (see **Table 57** in appendix). Overall, most of the cases either had insufficient details or had confounding illnesses which may have contributed to the death. In two cases[91] (both for liraglutide) patients refused dialysis which resulted in death. These two cases show an association of worsening renal failure without renal replacement therapy resulting in death. The other cases are less clear regarding the lack of use of renal replacement therapy resulting death.

In addition to evaluation by the microvascular sub-committee, as noted previously, all deaths were adjudicated by the cardiovascular EAC subcommittee as either CV deaths or non-CV deaths. For most of the renal death cases (with the exception of 3 placebo and 1 liraglutide patients)[92], the adjudication of renal death by the microvascular subcommittee was similar to the adjudication of the cardiovascular subcommittee (in that the deaths were not classified as CV deaths).

Reviewer's comment: the adjudication of death due to renal causes was often associated with either insufficient information or confounding illnesses which made the attribution of causality difficult. The small numerical imbalance in death due to renal disease in favor of placebo is likely due to chance given the number of patients involved (8 for liraglutide and 5 for placebo), and the lack of clear evidence of causality.

Overall nephropathy events

[91] Subject ID (b) (6) and subject ID (b) (6)
[92] Subject ID (b) (6) (death adjudicated as probable CV death), subject ID (b) (6) (death adjudicated as known documented CV death), subject ID (b) (6) (Death adjudicated as unknown cause of death) and subject ID (b) (6) (as known, probable cardiovascular death (sudden cardiac death)

The evaluation of *all* EAC confirmed nephropathy index events (recurrent and first events), shown in **Table 33** were similar to the findings of the EAC confirmed first events discussed above.

Table 33 – EAC confirmed nephropathy index events - FAS

	Liraglutide			Placebo		
	N (%)	E	R	N	E	R
FAS	4668			4672		
PYO	17822			17741		
Number of events	268 (5.7)	299	1.68	337 (7.2)	369	2.08
New onset of persistent macroalbuminuria	161 (3.4)	164	0.92	215 (4.6)	221	1.25
Persistent doubling of serum creatinine*	87 (1.9)	98	0.55	97 (2.1)	111	0.63
Need for continuous renal-replacement therapy	56 (1.2)	61	0.34	64 (1.4)	68	0.38
Death due to renal disease	8 (0.2)	8	0.04	5 (0.1)	6	0.03

N: Number of subjects, %: Proportion of subjects, E: Number of events, R: Event rate per 100 observation years, PYO: Patient years of observation, EAC: Event adjudication committee, FAS: Full analysis set. Index events with EAC onset date from randomization date until follow-up are included. *Persistent doubling of serum creatinine level and eGFR <=45 ml/min/1.73 m2 per MDRD. The index event is the event selected among multiple events if these were assessed and confirmed to be one and the same event. For 1 subject in the placebo group (subject ID 894010), 2 investigator-reported nephropathy events (reported terms: 'chronic kidney disease stage 5' and 'death due to end stage kidney disease' [EOT Listing 14.3.2.21]) were adjudicated to have their onset on the same day. Each event was furthermore adjudicated to concomitantly fulfil the criteria 'death due to renal disease' and 'need for continuous renal replacement therapy' (EAC Listing 14.3.2.7), thus resulting in 2 reported events of 'death due to renal disease' for this subject. Source: CTR Table 12-29, page 353

When evaluating overall baseline risk factors for nephropathy, (see **Table 34**). Higher proportion of patients in the liraglutide and placebo group, that met the endpoint of nephropathy, had history of nephropathy, retinopathy, and higher HbA1c at baseline than the overall patients randomized in the trial.

Table 34 – Risk factors for nephropathy -FAS

	Patients with nephropathy		All patients	
	Liraglutide	Placebo	liraglutide	placebo
	N (%)	N (%)	N (%)	N (%)
Number of patients	268 (100)	337 (100)	4668 (100)	4672 (100)
Hyperfiltration at baseline	12 (4.5)	12 (3.6)	259 (5.5)	235 (5.0)
History of:				
nephropathy	192 (71.6)	241 (71.5)	1882 (40.3)	1917 (41.0)
retinopathy	79 (29.5)	99 (29.4)	978 (21.0)	899 (19.2)
hypertension	257 (95.9)	316 (93.8)	4261 (91.3)	4250 (91.0)
Duration of diabetes:				
≥5 to <10 years	46 (17.2)	64 (19.0)	1195 (25.6)	1216 (26.0)
≥10<15 years	78 (29.1)	83 (24.6)	1182 (25.3)	1099 (23.5)
≥15 years	121 (45.1)	158 (46.9)	1598 (34.2)	1654 (35.4)
HbA1c at baseline:				
≥8.5% to <10%	74 (27.6)	78 (23.1)	1289 (27.6)	1294 (27.7)
≥10% to <12%	57 (21.3)	75 (22.3)	698 (15.0)	654 (14.0)
≥12%	28 (10.4)	28 (8.3)	200 (4.3)	170 (3.6)

N: Number of subjects, %: Percentage of subjects, EAC: Event adjudication committee, eGFR: estimated glomerular filtration rate, FAS: Full analysis set, CRF: Case report form Med. history of nephropathy, retinopathy and hypertension is reported in specific forms in the CRF. Hyperfiltration at baseline is defined as baseline eGFR >= 125 mL/min per 1.73 m2.Source, CTR, table 12-30 page 354.

As mentioned previously, the Sponsor proposes to label a *post hoc* analysis of the (b) (4). This analysis showed a statistically significant difference in favor of liraglutide, with a treatment ratio of liraglutide/placebo of 0.809 [95% confidence interval of 0.758; 0.863].

Reviewer's comment: (b) (4) is discouraged due to potential bias. In addition, given the concerns with the definition of nephropathy (discussed previously), it is It is unclear the (b) (4) would be informative in the label.

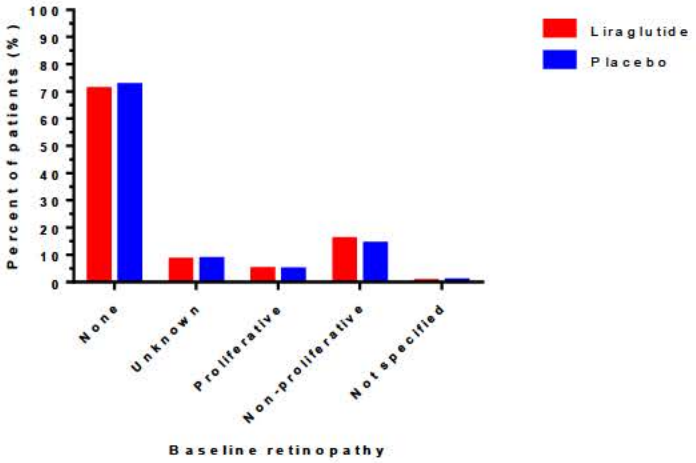
Retinopathy

For ease of the reader, the reviewer has included the baseline retinopathy findings in **Figure 39**. Of note, the figure is derived from an errata submitted by the Sponsor.[93] Over 70% of patients had no retinopathy at baseline, while approximately 20% of patients in either treatment arm had either proliferative, non-proliferative or retinopathy that was not specified at screening.

[93] The Sponsor informed the Division of an error in the CTR, which affected the FDA's briefing document. In short, the number of patients with 'unknonw' medical history of diabetic retinopathy was too high for both groups and the number of patietns with non was too low in both groups.

As noted previously, investigators in LEADER did *not* perform standard ophthalmological assessments (i.e. fundoscopy/fundusphotography) at any point during the trial.

Figure 39 – Baseline retinopathy status at screening



Source: errata submitted by the Sponsor

Reviewer's comments: Because retinopathy was not assessed systematically during the trial, the interpretation of the retinopathy findings is somewhat problematic. It is likely that some of the retinopathy findings in LEADER may have preceded the study, but not noted because of a lack of baseline assessments. Also, the lack of systematic ophthalmological assessments could have resulted in under-capture of events.

In order to evaluate broad trends in retinopathy, the reviewer evaluated the SOC of 'Eye disorders' for all reported events and SAEs. Admittedly, the events captured by this approach will not provide specific findings of just retinopathy; the approach will provide an overall safety evaluation of ophthalmological events.

Table 35 shows the most common preferred terms for the SOC of 'Eye disorders' for liraglutide and placebo (for the full listing, refer to **Table 58** in appendix). The events shown include EAC adjudicated and non-adjudicated events. Overall, the distribution of terms was similar between treatment arms; with 5.7% vs. 5.8% of patients on liraglutide and placebo affected, respectively. The most common preferred term for either group was diabetic 'retinopathy', affecting similar proportion of patients for liraglutide and placebo. 'Cataract' was the second most common preferred term with slightly less patients affected in the liraglutide group than the placebo group (1.5% vs. 1.7%, respectively). Vitreous hemorrhage was seen more commonly in the liraglutide group

(0.47%) than the placebo group (0.21%). However the overall numbers were low. The other categories were seen in 10 or less patients.

Table 35 – Most common preferred terms under the system organ class of Eye disorders- FAS

	Lira (N = 4668)			*Placebo (N = 4672)*		
Eye disorders SOC PT	*Events*	*Number of subjects*	*Proportion (%)*	*Events*	*Number of subjects*	*Proportion (%)*
Eye disorders (SOC)	372	267	5.72	364	273	5.84
Diabetic retinopathy	118	109	2.33	105	103	2.2
Cataract	84	71	1.52	92	79	1.69
Vitreous hemorrhage	25	22	0.47	11	10	0.21
Macular edema	11	9	0.19	11	10	0.21
Retinopathy	9	9	0.19	13	10	0.21
Diabetic retinal edema	9	8	0.17	9	8	0.17
Source: MAED analysis adsl.xpt, adae.xpt, where AESOC= Eye disorders and AEONTRFL=y FASFL=y						

Table 59 in the appendix shows the serious adverse events under the SOC of 'Eye disorders'. The preferred terms were similar to that of **Table 35**, although the overall number of events was smaller. Overall, there were too few events, in many cases, to differentiate between treatment groups.

The evaluation of *all* EAC confirmed retinopathy index events (recurrent and first events), is shown in
Table 36. Overall, there was a higher event adjusted rate of treatment with photocoagulation/intravitreal agents for liraglutide (0.65 events per 100 PYE) than placebo (0.56 events per 100 PYE). Similarly, the adjusted event rate for vitreous hemorrhage was higher for liraglutide (0.25 events per 100 PYE) than placebo (0.13 events per 100 PYE). The findings were overall similar to the findings of the EAC confirmed first events discussed later.

Table 36 – EAC confirmed retinopathy index events - FAS

	Liraglutide			Placebo		
	N (%)	E	R	N	E	R
FAS	4668			4672		
PYO	17822			17741		
Number of events	106 (2.3)	130	0.73	92 (2.0)	105	0.59
Treatment with photocoagulation/intravitreal agents	100 (2.1)	116	0.65	86 (1.8)	99	0.56
Vitreous hemorrhage	32 (0.7)	44	0.25	22 (0.5)	23	0.13
Development of diabetes related blindness	0	0	0	1 (0)	1	0.01
N: Number of subjects, %: Proportion of subjects, E: Number of events. PYO: Patient years of observation, EAC: Event adjudication committee, FAS: Full analysis set. Index events with EAC onset date from randomization date						

until follow-up are included. The index event is the event selected among multiple events if these were assessed and confirmed to be one and the same event.
Source: CTR, table 12-32, page 358

To assess the development of diabetes related blindness, the reviewer performed a broad exploratory analysis of all PT terms (adjudicated and non-adjudicated) consistent with vision loss. The preferred terms were chosen by the reviewer from the adverse event dataset under the SOC Eye disorder.[94] All the identified cases and narratives are shown in **Table 60** (in appendix); of note, some of the cases do not have narratives since the events were neither MESIs nor SAEs; of the cases with narratives, some are not consistent with possible blindness as a result of diabetes.

In this search, the reviewer identified three events in three separate patients,[95] which included the preferred term "blindness" but were not sent for adjudication. In information request[96] the Sponsor clarified that these events were identified by preferred term search and sent to ICON, which determined that the event did not meet criteria to be sent to adjudication.

Table 37 is a shortened list of **Table 60** and shows the cases which the reviewer considered possibly related to blindness from diabetes. In total 5 events in 5 patients were identified; 1 patient in the liraglutide group and 4 patients in the placebo group. Of note, all but one event (subject ID (b) (6) - placebo) were sent for adjudication. Only one event (subject ID (b) (6) placebo) was positively adjudicated as having diabetic retinopathy, and development of diabetes related blindness.

Table 37- Exploratory analysis of preferred terms suggestive of vision loss

			Ser.	Tx. arm	HBA1 base	Diab. dur. (yrs)	Day of AE	Narrative *Adjudicator's comments*
Preferred term	**subject ID#**	**Inv. reported term**	**Y/N**					
Blindness unilateral*	(b) (6)	VISION LOSS RIGHT EYE	N	Placebo	10.5	21.2	631	No narrative. *Of note, patient died (few details available- adjudicated as "unknown cause)."*
		DIABETIC RELATED BLINDNESS RIGHT EYE	Y	Liraglutide	12.9	18.1	358	63 year old woman with history of proliferative retinopathy since 2012 and nephropathy who presented with "diabetic related blindness, right eye." Patient presented with blurred vision and was suddenly unable to see with her right eye. No further information is available.

[94] The reviewer evaluated the preferred terms under the SOC Eye disorder and chose terms that would be consistent with vision loss. Specifically, the reviewer chose the following PT terms: "blindness unilateral", "diabetic blindness", "diplopia", "vision blurred", "visual acuity reduced", "visual impairment".
[95] Refer to **Table 60,** patient ID (b) (6)
[96] Refer to question 4 of information request \\CDSESUB1\evsprod\NDA022341\0372\m1\us\resp-ir-04282017.pdf

			Ser.	Tx. arm	HBA1 base	Diab. dur. (yrs)	Day of AE	Narrative *Adjudicator's comments*
Preferred term	**subject ID#**	**Inv. reported term**	**Y/N**					
								Adjudicators felt that since there is no report, it is unclear as to the etiology of the patient's blindness, and inability to determine what treatments and for what conditions the treatments were provided (event was not adjudicated as diabetic retinopathy)
Diabetic blindness	(b) (6)	RIGHT EYE DIABETIC BLINDNESS	Y	Placebo	5.9	25.7	782	73 year old male who developed "right eye diabetic blindness." Patient had previous eye cataract surgery in 2010, glaucoma since 2008, proliferative retinopathy since 2007 and right eye retinal detachment in 2010 with insertion of silicon oil insertion. On routine ocular echography (June 2013), patient was shown to have "external tractional retinal detachment applied to macula." On 02 Jul 2013, the patient had retinal cryotherapy and removal of silicon oil in right eye. On 01 Nov 2013 the patient developed right eye sight loss and was identified with severe diabetic retinopathy and diabetes related blindness. The patient was treated with ranibizumab. *One adjudicator felt this event was not a diabetic retinopathy AE, the second adjudicator felt this was an event met criteria for diabetic retinopathy with development of blindness with tractional RD. After reviewing each other's rationale, both adjudicators agreed that the event was consistent with diabetic retinopathy blindness.*
Diplopia	(b) (6)	BLURRING OF VISION	Y	Placebo	15.0	14.2	346	65 year old male who presented with "blurring vision" was hospitalized. There is no documentation of the tests performed. No documents were available from the hospitalization. The type of eye disease was reported as development of diabetes-related blindness. Patient awaited eye surgery. On 3 May 2014 the patient reported significant vision loss. No treatment was initiated. *Both adjudicators agreed that there was insufficient information to positively adjudicate*
Vision blurred	(b) (6)	DECREASED VISUAL ACUITY RIGHT EYE	N	Placebo	7.9	21.8	747	82 year old male with history of right cataract removal, right eye pars plana vitrectomy, left cataract, intermittent dizziness. Who presented with "decreased visual acuity right eye." Patient noted distortion with right eye and was sent to the ophthalmologist who noted the decrease in visual acuity. Results of photograph intravenous fluorescein angiography are not available. The type of eye disease reported is diabetes-related blindness. *A clinic note states that on slit lamp exam there was an epiretinal membrane in the right macula. There was not much apparent in regards to diabetic retinopathy. Patient underwent "right pars plana posterior vitrectomy, epiretinal membrane peeling" on June 5, 2015.*

			Ser.	Tx. arm	HBA1 base	Diab. dur. (yrs)	Day of AE	Narrative *Adjudicator's comments*
Preferred term	**subject ID#**	**Inv. reported term**	**Y/N**					
								Both adjudicators felt the case was not related to diabetic related retinopathy.
Inv.= investigator; Ser.= serious, tx.= treatment, base=baseline, Diab.= diabetes, Dur.= duration, yrs=years, AE= adverse events								

Reviewer's comment: Overall, the events associated with vision loss were few, with the majority of events lacking details related to the event. The reviewer agrees with the overall adjudication of the events. Despite the findings of higher diabetic retinopathy events (i.e. retinopathy endpoint), the exploratory analysis does not show evidence of increased rates of loss of vision associated with liraglutide.

When evaluating overall baseline risk factors for retinopathy, and comparing the patients with retinopathy to all the patients randomized, (see **Table 38**) there were a higher proportion of patients in the liraglutide and placebo group that had history of retinopathy, and had a higher HbA1c at baseline.

Table 38 – Risk factors for retinopathy -FAS

	Patients with retinopathy		All patients	
	Liraglutide	Placebo	Liraglutide	placebo
	N (%)	N (%)	N (%)	N (%)
Number of patients	106 (100)	92 (100)	4668 (100)	4672 (100)
History of retinopathy	68 (64.2)	62 (67.4)	978 (21.0)	899 (19.2)
Duration of diabetes:				
≥5 to <10 years	7 (6.6)	10 (10.9)	1195 (25.6)	1216 (26.0)
≥10 to <15 years	25 (23.6)	23 (25.0)	1182 (25.3)	1099 (23.5)
≥15 years	69 (65.1)	52 (56.5)	1598 (34.2)	1654 (35.4)
HbA1c at baseline:				
≥8.5% to <10%	28 (26.4)	34 (37.0)	1289 (27.6)	1294 (27.7)
≥10% to <12%	21 (19.8)	12 (13.0)	698 (15.0)	654 (14.0)
≥12%	12 (11.3)	3 (3.3)	200 (4.3)	170 (3.6)
N: Number of subjects, %: Percentage of subjects EAC: Event adjudication committee, FAS: Full analysis set Med. history of retinopathy is reported in specific forms in the CRF. Source, CTR, table 12-33 page 359.				

Retinopathy endpoint

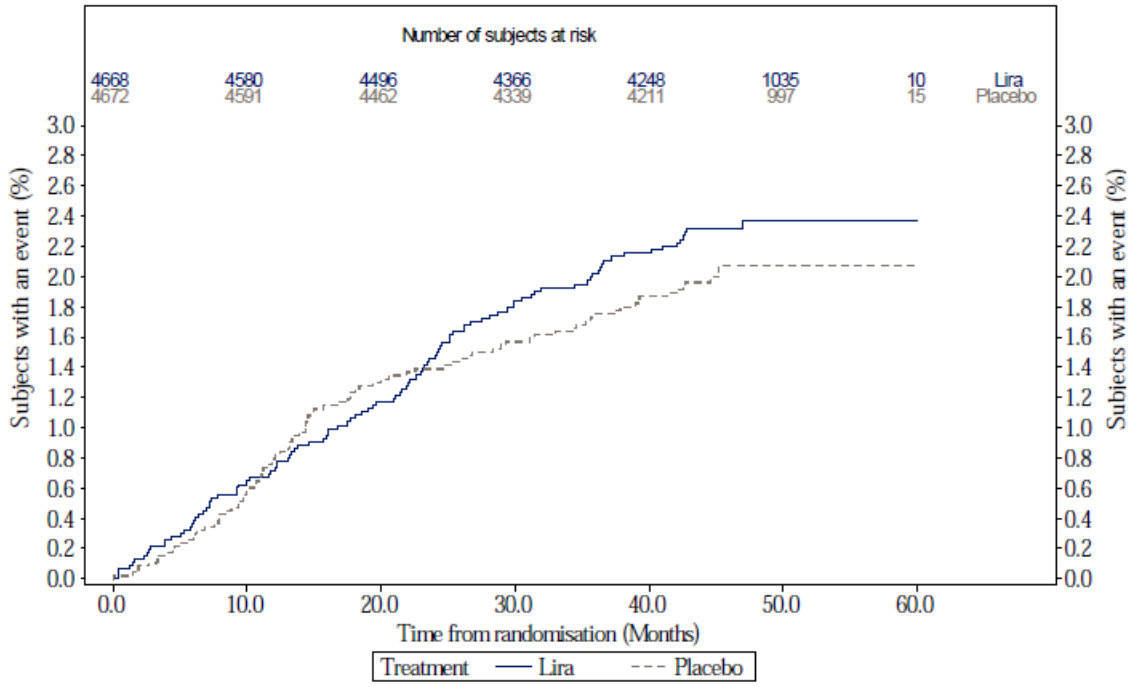
The retinopathy endpoint was composed of the following three criteria: need for retinal photocoagulation or treatment with intravitreal agents, vitreous hemorrhage, and onset

of diabetes related blindness (Snellen visual acuity of 20/200 [6/60] or less, or visual field of <20 degrees in the better eye with best correction).

Reviewer's comment: The definition of diabetes-related blindness was added in protocol amendment 20, where treatment with intravitreal agents was added, with corresponding changes in the EAC charter in Version 6 (see Table 50 **in appendix). The changes in retinopathy definition did not required re-adjudication of events and likely did not differentially affect the capture of events for either treatment group, but may have narrowed the capture of overall events of interest.**

Figure 40 shows the time to first EAC confirmed retinopathy event. The percent of patients with a retinopathy event was higher for liraglutide until ~month 12 at which point the curves cross and the proportion of patients with a retinopathy event is lower for liraglutide than placebo until month 23-25, when the proportion of patients is again higher for liraglutide than placebo. The analysis of time to first EAC confirmed retinopathy event had a hazard ratio of 1.149 [95% confidence interval 0.869; 1.519], P=0.33.

Figure 40- Kaplan-Meier plot of time to first EAC-confirmed retinopathy- FAS



Abbreviation: EAC: event adjudication committee; FAS: full analysis set; Lira: liraglutide.
Source: CTR, figure 11-15, page 253

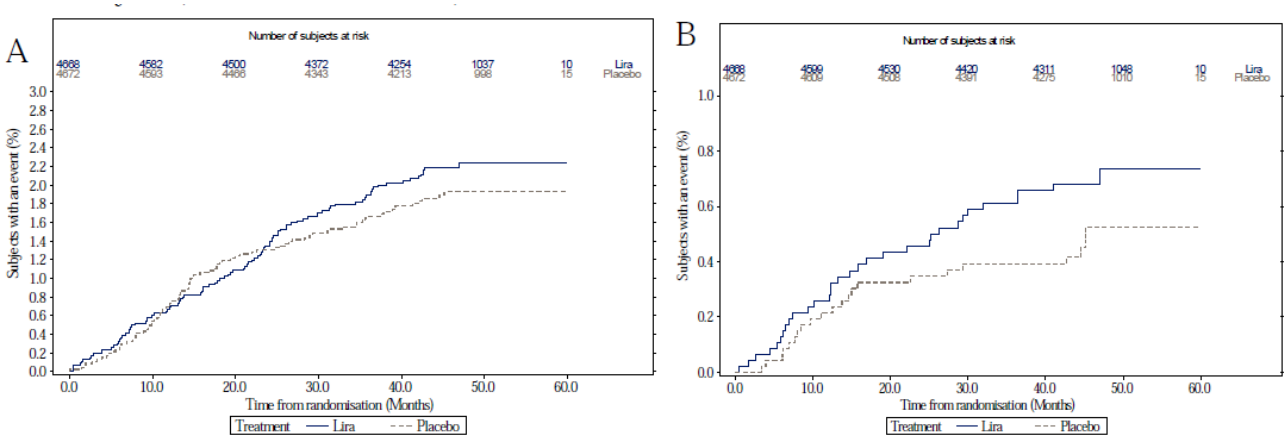
The analysis of individual retinopathy criteria is shown in **Table 32**. The proportion of patient who had a first treatment with photocoagulation or intravitreal agents was higher for liraglutide than placebo (2.1% vs. 1.8% respectively). The analysis of time to the

first EAC-confirmed event had a hazard ratio favoring placebo of 1.16 [95% confidence interval 0.869; 1.546], p=0.316.

Similar to the trends with photocoagulation or intravitreal agents, the proportion of patients who had a first vitreous hemorrhage event was higher for liraglutide than placebo (0.7% vs. 0.5%). The analysis of time to the first EAC-confirmed event had a hazard ratio favoring placebo of 1.454 [95% confidence interval 0.845; 2.502], p=0.177.

Figure 41 shows the time to first event of the individual retinopathy endpoint components (with the exception of diabetic related blindness, since there was only one event in the trial, in the placebo group).

Figure 41 –Kaplan-Meier plots of retinopathy event types-FAS –A: time to first EAC confirmed treatment with photocoagulation or intravitreal agents. B: Time to first EAC-confirmed vitreous hemorrhage



Note: The y-axes are adjusted to the proportion of subjects with events for each of the individual endpoints.
Abbreviations: EAC: event adjudication committee; FAS: full analysis set; Lira: liraglutide.

Source: CTR, figure 11-16, page 254

Reviewer's comments: In order to better understand the imbalance in retinopathy in LEADER, the Division of Metabolism and Endocrinologic Products consulted the Division of Transplant and Ophthalmology Products to opine in the interpretation of the retinopathy endpoints, and results, in light of the expected retinopathy findings in patients with type 2 diabetes mellitus. Please refer to the consult authored by Dr. Wiley Chambers.

Overall, the adjudicated retinopathy findings suggest there are higher retinopathy events for liraglutide than for placebo for the categories of photocoagulation/intravitreal agents and for vitreous hemorrhages. These findings are in light of the issues of missing baseline retinopathy data and lack of systematic assessment for retinopathy (discussed previously). It is unclear how

this missing data affected the observed findings. Nonetheless, the greater change in HbA1c from baseline for liraglutide (-1.2%) than for placebo (-0.8%), is consistent with the findings of early worsening retinopathy in the liraglutide group, as shown by previous trials in patients with type 1 diabetes and type 2 diabetes mellitus[97,98]

In interpreting these results, it is also worth noting that the population in LEADER is not the same as the population enrolled in other glycemic lowering trials, where often times history of retinopathy is an exclusion criterion (this was not an exclusion criteria in this trial).

9.1 Literature Review/References

These are cited throughout the document in footnotes.

9.2 Labeling Recommendations

Labeling recommendations and comments are present throughout the review.

9.3 Advisory Committee Meeting

The Endocrinologic and Metabolic Drugs Advisory Committee met on June 20, 2017 at the FDA White Oak Campus in Silver Spring, Maryland to discuss the efficacy and safety of NDA 22341, supplement 27 for liraglutide. This supplement was submitted by Novo Nordisk for the proposed additional indication of: as an adjunct to standard treatment of cardiovascular risk factors to reduce the risk of major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke) in adults with type 2 diabetes mellitus and high cardiovascular risk.

The Committee consisted of a patient representative, a consumer representative, an obesity and nutrition expert and endocrinologists, epidemiologists, biostatisticians, and cardiologists.

The following voting questions were discussed:

[97] Aiello, P. Diabetic Retinopathy and Other Ocular Findings in the Diabetes Control and Complications Trial/ Epidemiology of Diabetes Interventions and Complications Study. Diabetes Care 2014;37:17–23 and Diabetes Control and Complications Trial Research Group. Early worsening of diabetic retinopathy in the Diabetes Control and Complications Trial. Arch Ophthalmol 1998;116:874–886

[98] Varadhan L, Humphreys T, Walker AB, Varughese GI. The impact of improved glycaemic control with GLP-1 receptor agonist therapy on diabetic retinopathy. Diabetes research and clinical practice 2014;103:e37-9.

1. **VOTE:** Do the results of LEADER establish that use of liraglutide in patients with Type 2 Diabetes Mellitus (T2DM) is not associated with unacceptably high cardiovascular risk? **Provide the rationale for your vote.**
   Yes-19, No-0, abstain-0

Unanimously, all the committee members voted that YES, the results of LEADER establish the use of liraglutide in patients with type 2 diabetes mellitus and is not associated with unacceptably high cardiovascular risk.

Drs. Robbins (endocrinologist), Sannoff (oncologist), and Everett (cardiologist) stated that LEADER was well designed and that the results did not show unacceptably high risk.

The remaining members stated they agreed with the overall panel, or stated that there was nothing else to add.

2. **VOTE:** Does the LEADER trial provide the substantial evidence needed to establish that liraglutide 1.8 mg daily reduces cardiovascular risk in patients with T2DM? **Provide the rationale for your vote.**

   a. If yes, discuss the population for whom you believe this benefit applies.
   b. If no, comment on what additional data would be needed.

   Yes-17, No-2, abstain-0

Dr. Neaton- voted yes because he felt that the most influential finding in LEADER was the CV finding and the consistency of the results. The trial enrolled people at twice the risk of what the Sponsor expected.

Dr. Konstam- voted yes because he felt that the trial results were robust and substantiated. He felt that the CV mortality difference was the largest contributor to the findings. The population that benefited was the group with cardiovascular disease- it was unclear if the other subgroup contributed to the hazard benefit. Dr. Konstam was concerned with the US subpopulation findings, but felt that these results do not diminish the overall findings in LEADER.

Dr. Rosenberg- voted yes because of the consistent results from the components. Dr. Rosenberg felt that a level of substantial evidence has been provided. Nonetheless, he was concerned with the how to apply the LEADER results to the US population and questioned whether the US subgroup findings were related to adherence.

Dr. De Lemos- voted yes. He felt that the primary results were border line, but these were buttressed by the individual components. He felt that the burden for approval was lower because liraglutide is already approved. Dr. De Lemos felt strongly that liraglutide

did not show benefit in the lower CV risk group in the trial. Dr. De Lemos was less worried by the US subgroup findings, and felt that this finding was not plausible.

Dr. Wilson- voted yes. He felt that the inclusion criteria (3a and 3b) in the LEADER study did not clearly correspond to patients in need of primary and secondary prevention. Dr. Wilson wrestled with the question of which population benefited the most and concluded that patients with established atherosclerosis disease would benefit the most.

Dr. Fradkin- voted yes. Dr. Fradkin felt that the primary outcome was demonstrated in patients with established cardiovascular disease.

Dr. Budnitz- voted no. His rationale was that the proposed indication is for liraglutide as an adjunct to standard of care in the US. He worries about a slippery slope for approving an indication based on 1 trial when the US subgroup shows different results based on an interaction analysis. To resolve this concern, Dr. Budnitz would like to see either another international trial where the overall trial results are consistent with the US subgroup or a single trial in US.

Dr. Wang- voted yes. Dr. Wang felt that the trial highlights the heterogeneity of diabetes. Dr. Wang was interested in seeing a study dedicated to the prevention of cardiovascular disease in patients with diabetes.

Ms. Hallere- voted yes. Ms. Hallare agreed that the benefit applied to patients with renal disease and established cardiovascular disease.

Dr. Cho- voted yes. Dr. Cho felt that the indication should be for a reduction of MACE in patients with established cardiovascular disease or in patients with chronic kidney disease.

Dr. Burman- voted yes. Dr. Burman felt that MACE and CV deaths were different between liraglutide and placebo; whereas non-fatal mi and non-fatal strokes were not different. He noted that the FDA usually requires 2 or more trials with important endpoints for approval of an indication. LEADER is single trial, which meets a clinical important endpoint, therefore allowing the labeling of a single trial. In regards to adverse events, he felt that the evidence is inconclusive. Dr. Burman felt that it is important to have antidiabetic agents that reduce CV risk and to investigate the mechanism involved. He felt that the population studied was a high CV risk population.

Dr. Blaha- voted yes. Dr. Blaha felt that all patients with diabetes were at high cardiovascular risk. He was impressed with the hard outcomes in the trial, including the findings of all cause death. He did not think that an additional trial would alter the decision pathway. He had a hard time with his recommendation because of concerns about the subgroups.

Dr. Yanovski- voted yes- Dr. Yanovski felt that the reductions in MACE and CV mortality were statistically and clinically significant and seen in patients with established cardiovascular disease. She was less convinced by the results from the population with less risk.

Ms. Mc Call- voted yes. Ms. McCall felt that this drug was needed for the treatment of patients.

Dr. Sannoff- voted yes. Dr. Sannoff felt that the hazard ratio was unequivocally in favor of liraglutide; however the absolute risk reduction was small. As a comparative effectiveness researcher, Dr. Sannoff had concerns about the generalizability of the data. This concern stems from the large drop out in the run in period. Dr. Sannoff questions whether a large number of people will benefit from this therapy.

Dr. Robbins- voted yes. Dr. Robbins felt that although the subgroup analysis was interesting, he favored the primary outcome measure. Dr. Robbins felt that this trial was moving beyond just lowering blood glucose.

Dr. Everett- voted yes. Dr. Everett felt that LEADER evaluated important clinical benefits: CV endpoints, particularly mortality. This trial was a breakthrough for patients and physicians alike. Dr. Everett felt that LEADER was well conducted. The consistency of the effect of the study drug was reassuring, in particular, the CV and all-cause mortality results. Although small, the absolutely risk reduction is meaningful because for years treatment was based on a zero effect on CV risk and death.
Dr. Everett felt that the population where this drug should be used was in patients with CV disease or with important subclinical disease, such as known non-obstructive coronary disease, or chronic kidney disease.

Dr. Oakes- voted yes. Dr. Oaks recommended that the FDA look at the CV history in the patients in the trial. Dr. Oakes felt that the efficacy findings should note that these were driven by the non-US subgroup.

Dr. Allegra- voted no- Dr. Allegra was concerned by the subgroup analyses. Dr. Allegra felt that the US subgroup was very important, when considering the significant interaction in a considerable population of the randomized patients. Dr. Allegra was swayed by the fact that superiority was not seen in the US population, while superiority was seen other parts of the world. Dr. Allegra was not sure if it is important to understand why the US population is different than the rest of the world. Maybe the population was not exposed to the drug, or if there were differences in practice in the US. Dr. Allegra, as others, felt that this is a single trial. He would be convinced of the findings if he saw superiority in a trial conducted in the US, although he does not necessarily advocate this. He suggests that the labeling be clear about the findings in the US.

Appendices

Table 39 – Global Protocol amendments for LEADER

Date of amendment	*Category of change*	*Summary of change*
April 29, 2016	Original protocol approved	
December 6, 2010 (substantial amendment 08)	Safety/non-CV efficacy change	• Changes to action in exclusion, randomization and visit procedures in cases of measured calcitonin values ≥50 ng/L (changed from ≥100 ng/L) • Change creatinine sampling to include eGFR calculation. Also eGFR value will be calculated (visit 1 only) using the serum creatinine result and the MDRD formula • Actions taken in case of suspicion of acute hypersensitivity or immune-complex disease* • Specified actions taken in case a subject undergoes a thyroidectomy~ • Diabetic foot ulcer was to be recorded in history of diabetes complication • Changes to endpoints: o For the microvascular outcome the word *persistent* was added: as new or worsening nephropathy, defined as new onset of *persistent macroalbuminuria* or *persistent* doubling of serum creatinine level. To confirm persistent macroalbuminuria or persistent doubling of serum creatinine, a confirmatory measurement should be performed within 12 weeks. o The word any was added: *Any* confirmed calcitonin values ≥20 ng/L reported as MESI (Medical Even of Special Interest) during the trial • Instructions on waist circumference measurements were included • It was specified that sites would be informed of the centralized ECG evaluation if this abnormality represents an unreported SAE or MESI • Instructions on recording insulin dose were given^
	CV & prevention of missing data	• Specification of history of concomitant cardiovascular disease included: o i.e., myocardial infarction, disorders of rhythm or conduction, heart failure incl. NYHA class, ischemic heart disease incl. type, PCI and CABG, left ventricular systolic dysfunction, left ventricular diastolic dysfunction, hypertension, ischemic stroke, transient ischemic attack, hemorrhagic stroke, intracranial artery stenosis, carotid artery stenosis, peripheral arterial disease including >50% stenosis on angiography or other imaging) will be recorded in the CRF at visit 1 • From the section specifying what events were not AEs text was crossed out: Pre-planned procedures unless the condition for which the procedure was planned was worsened from the first trial related activity after the subject has signed the informed consent. ~~However revascularization procedure is a defined MESI and should be reported~~"
June 24, 2011 Substantial amendment 20	Safety/non-CV efficacy change	• Broadening of inclusion criteria allowing subjects on premixed insulin to participate in the trial (change suggested by steering committee) • The definition of the microvascular composite endpoint has been updated and the a definition of diabetes-related blindness was included (change suggested by the EAC)[£]
	CV & prevention of missing data	none
April 20, 2012 Substantial amendment 30	Safety/non-CV efficacy change	• Subjects withdrawn from randomized treatment due to violation of Exclusion criteria 2 and/or 3 (disallowed medication at or less than 3 months before screening) can be reintroduced on originally randomized treatment. The reintroduction should be planned in relation to a scheduled visit and there should

		be no change to the visit schedule following this. In order to avoid a potential carry-over effect of the disallowed medication and to ensure continual anti-diabetic treatment, reintroduction to randomized treatment will be executed after the following wash-out periods: 1 day for subjects on fast acting insulin or pramlintide 5 days for subjects on once daily GLP-1 analogues or DPP4-inhibitors 4 weeks for subjects on once weekly GLP-1 analogues • Changes to the recording of concomitant medication during hospitalization: only medication of specific relevance during hospitalization and concomitant medication at discharge were to be recorded.
	CV & prevention of missing data	None
February 21, 2013 Substantial amendment 34	Safety/non-CV efficacy change	• Inclusion criteria 3 updated: Subjects randomized in error due to not meeting the age criterion at screening could be reintroduced on originally randomized treatment as each subject reaches the required age. The reintroduction should be planned in relation to a scheduled visit and there should be no change to the subsequent visit schedule • Updates to the adverse event section to describe when certain types of AEs should be reported • All events confirmed or suspected to be a MESI must be reported. Additionally, in case the sponsor identifies potentially missed MESIs through predefined review of available data, the Investigator will be notified and asked to fill out the relevant AE, SIF and MESI forms in EDC. The Investigator may also be asked to provide source documents for these potential events. • Liraglutide background section updated based on the Investigator's Brochure • an additional SI/IC Form was offered, which will give permission to contact the family doctor at the time of completion of the trial, if the subject's participation in the trial has been stopped prematurely.
	CV & prevention of missing data	Removed text from protocol: ~~Sites will be informed of the central ECG evaluation in case this evaluation reveals an abnormal ECG reading. The evaluation result received from central ECG must be reviewed by the investigator. Any unreported clinical significant abnormalities must be reported as SAE or MESI by the investigator~~
May 19, 2014 Substantial - amendment 39	Safety/non-CV efficacy change	• Introducing a staggered close down of sites, which may result in some patients having a shorter time in trial compared to the original text of 3.5 to 5 years** • Follow-up visit (visit 16) applicable for all randomized subjects- this was done to allow a reasonable amount of time to capture adverse events emerging following discontinuation of trial treatment. The Sponsor notes that this visit may result in a slightly weaker antibody response. • Definition of neoplasms was expanded$^{\Omega}$ • Collection of information of concomitant medications are simplified, and protocol now allows patient's family to help fill out diaries.
	CV & prevention of missing data	• Revision of the statistical considerations section in the protocol, by simplifying language, to meet regulatory expectations and to align with the Statistical Programming Plan o Addition that sensitivity analysis will be performed using a per protocol approach and an approach where only first outcome event occurring on-treatment will contribute. o Added "renal function" was added to other covariates in the sensitivity analysis o Added "race, renal function, and chronic heart failure" for subgroup analyses • A subject will only be considered lost to follow-up in case vital status cannot be obtained at the end of the trial. Lost to follow-up cannot be determined before all of the following contacts have been attempted and documented in medical records: o to subjects: two phone calls and one written contact

- to primary physician and/or other health care professionals: calls until contact is established
- to relatives/next of kin: two phone calls and one written contact
- contacts to relevant public registries, if available.

- For patients withdrawing prematurely from the trial, the investigator must scrutinize public registries for relevant safety information as permitted to local regulations
- In order for the dataset to be as complete as possible, the end of trial follow up information can be collected until the trial database is locked
- Details of all concomitant illnesses and medication must be recorded at trial entry. Any changes in concomitant medication *during the trial concerning relevant concomitant medications such as medications taken to treat SAEs, MESIs, diabetes or cardiovascular related diseases (e.g. antihypertensive agents, lipid-lowering agents, aspirin and other antiplatelet agents)* must be recorded at each visit. *Dose adjustments (except for starting and stopping) will only need to be recorded if deemed relevant for the study outcome*

* Local testing for blood tryptase (total and/or mature tryptase) was recommended. If trial product was discontinued because of acute hypersensitivity, blood sampling for central assessment of anti-liraglutide antibodies and IgE-isotype of anti-liraglutide antibodies was to be conducted, at least seven days after trial product discontinuation. Information was to be sent to Novo Nordisk and will be included in the final MESI report. If immune complex disease was suspected, blood sample for complement levels C3 and C4 was to be done.
~ Patients will be asked to consent to be tested to identify germline RET gene mutation associated with MEN 2 syndrome. This RET gene mutation will be conducted in pts with pathology reports confirming C-cell abnormality (medullary carcinoma or c cell hyperplasia). For patients undergoing thyroidectomy (partial/total) for any reasons, pathology slides will be blindly, centrally reviewed (by pathologists with expertise in thyroid and c-cell pathology) in addition to routine exam at site level. The site pathology report and central pathology report will be reviewed by the EAC. Patients undergoing thyroidectomy will be consented to have thyroid tissue collected/stored in a tissue bank that will allow for future testing of C-cells such as RET Y1062 phosphorylation.
^ For all trial subjects receiving insulin (i.e., ongoing treatment with insulin at the screening visit or insulin introduced to treatment regimen after randomization), total daily dose of insulin administered on the day preceding each trial visit (if available) should be recorded in the concomitant medication form.
£diabetes-related blindness (defined as Snellen visual acuity of 20/20 [6/60] or less or visual field of less than 20 degrees in the better eye with best correction possible
** The event rate used to calculate the sample size in the original protocol has turned out to be higher than originally anticipated, and the expected number of primary outcome events to obtain the 90% power (611 events) is already achieved at the time of this protocol amendment. Consequently, the amended trial closure approach introduced with this protocol amendment will not negatively impact the statistical power of the primary analysis
Ω The definition of a neoplasm is deliberately broad including malignant as well as benign neoplasms, in situ neoplasms and neoplasms of uncertain or unknown behavior. The interpretation applied by the EAC of a neoplastic growth is "a clonal disorder that grows in an autonomous manner". The abnormality of clonal disorder and autonomous growth may not always be readily identified and this is the rationale for the very broad definition to be followed by the reporter of the event.

Table 40-Trial flowchart

	Screening	Run-in	Rand.	Treatment											End of treatment (EoT)	Follow-up
Visit Number	1	2	3[1]	4	5	6[2]	7[2]	8[2]	9[2]	10[2]	11[2]	12[2]	13[2]	14[2]	15	16
Months in relation to visit 3 (except visit 16)	- 4 to 5 w[4]	-2 to 3w	0	1	3	6	12	18	24	30	36	42	48	54	60	EoT + 30 days
Visit window, days				±3	±7	±7	±14	±14	±14	±14	±14	±14	±14	±14	±14	+ 7
SUBJECT RELATED INFORMATION/ASSESSMENTS																
Informed consent	X															
In/exclusion criteria	X		X													
Randomisation			X													
Randomisation Criteria			X													
Withdrawal Criteria				X	X	X	X	X	X	X	X	X	X	X		
Demography	X															
Concomitant illness/Medical history	X															
Diabetes History and Complications	X															
History of Concomitant Cardiovascular Disease	X															
History of Pancreatitis and Gallstone Disease	X															
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Height	X															
Attend visits fasting			X				X		X		X		X		X	
PRO: EQ-5D[6]			X				X		X		X		X		X	
Smoking habits	X															
End of trial															X	
End of trial follow-up																X
CLINICAL ASSESSMENTS																
HbA_{1c}	X		X		X	X	X	X	X	X	X	X	X	X	X	
Weight	X		X			X	X		X		X		X		X	
Waist circumference			X						X						X	
Fasting Lipids			X				X		X		X		X		X	
Vital signs	X		X			X	X		X		X		X		X	
Adverse Events[9]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Biochemistry[10]	X[11]		X			X	X		X		X		X		X	
Haematology			X						X						X	
Hormones	X						X		X		X		X		X	X[12]
Anti liraglutide antibodies[13]			X				X		X		X		X			X
Urinalysis[15]			X				X		X		X		X		X	
Pregnancy test[16] (if of childbearing potential)	X														X	
ECG			X				X		X		X		X		X	
Physical examination	X														X	
Hypoglycaemia[17]			X	X	X	X	X	X	X	X	X	X	X	X	X	
TRIAL MATERIAL																
Dispense subject ID card	X															
Instruct in trial product use		X	X													
Hand out directions for trial product use		X	X	X	X	X	X	X	X	X	X	X	X	X		
Dispense glucose meter			X													
Dispense diary		X	X	X	X	X	X	X	X	X	X	X	X	X		
Collect and review diary			X	X	X	X	X	X	X	X	X	X	X	X	X	
Dispense trial product[18]		X	X	X	X	X	X	X	X	X	X	X	X	X		
Trial product adjustment				X	X	X	X	X	X	X	X	X	X	X	X	
Drug accountability[19]			X	X	X	X	X	X	X	X	X	X	X	X	X	
IV/WRS call	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

[1] The investigator/designee contacted the subject by phone between Visits 3 and 4 to monitor the dose escalation (i.e., to investigate the subject's tolerance to the trial product and to ensure that dose escalation had been performed according to schedule)
[2] Trial product dispensing visits were conducted at the midpoint between treatment Visits 6 to 15 ± 14 days
[3] Footnote deleted *(in accordance with Amendment 39)*
[4] The run-in period was to be initiated maximum two weeks after screening
[5] Footnote deleted *(in accordance with Amendment 39)*

[6] Only applicable in a subset of subjects
[7] Footnote deleted *(in accordance with Amendment 39)*
[8] Footnote deleted *(in accordance with Amendment 39)*
[9] Only SAEs and MESIs were required to be reported. Non-serious AEs could be reported at investigator's discretion, if evaluated as related to trial product by Investigator
[10] Calcium (total), Potassium and Sodium only at Visits 3, 9 and 15
[11] Sampling for creatinine only (incl. eGFR calculation)
[12] Sampling was to be performed for subjects who demonstrated a calcitonin level greater than two times ULN at Visit 15 and who had levels below ULN at screening
[13] Only applicable in a subset of subjects
[14] Footnote deleted *(in accordance with Amendment 39)*
[15] Albumin to creatinine ratio
[16] Human chorionic gonadotropin. Urine-sticks pregnancy tests were to be performed for females of childbearing potential at any time during the trial, if a menstrual period was missed or as required by local law. The urine-sticks test was performed at the site
[17] Subjects were to record hypoglycaemic events from Visit 3
[18] Trial product was in addition to be dispensed every three months between Visits 6 to 15
[19] Drug accountability was in addition to be performed according to footnote 18
Only applicable for NL: Discuss continuation of trial participation at Visits 3, 5, 7, 9, 11 and 13
Source: CTR, Table 9-3

Trial conduct

This portion of the review highlights aspects of trial conduct that were implemented by the Sponsor to ensure the integrity of the trial findings.

Administrative structure:
LEADER had the monitoring committees listed in **Table 41.** The Data Monitoring Committee (DMC) and the external independent statistician were unblinded during the trial.

Table 41 –Committee groups in LEADER

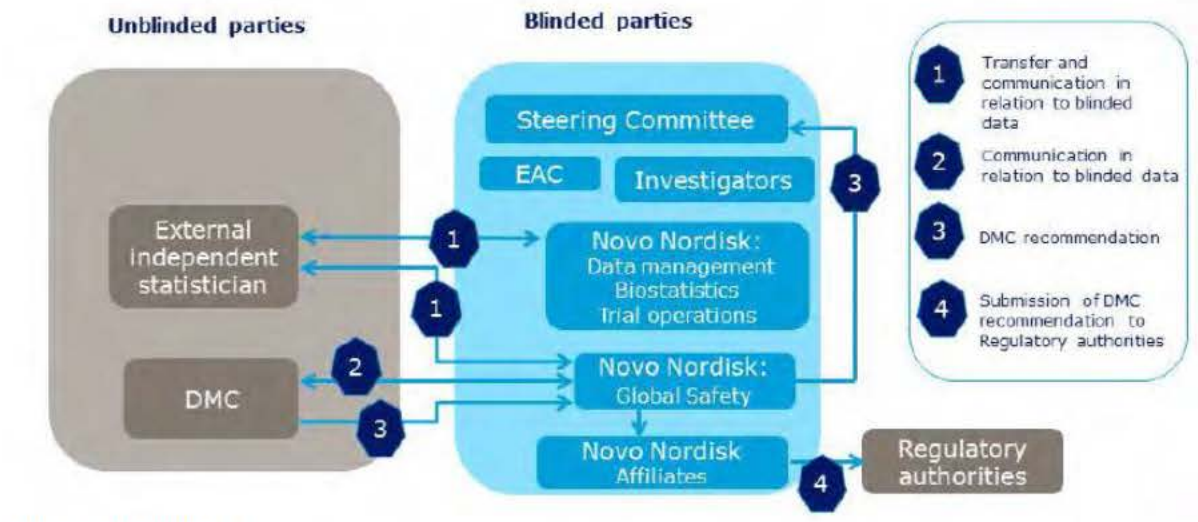
Blinded	Role
Steering Committee (STC)	Provided scientific and academic leadership for the trial. Members included members of Novo and cardiologists, endocrinologists (including diabetologists), gastroenterologists, nephrologists and statisticians with extensive experience in conducting CVOTs.
Event Adjudication Committee (EAC)	External, independent event adjudication committee contracted by independent company, ICON. The EAC was composed of cardiologists, neurologists, endocrinologists, gastroenterologists, oncologists, nephrologists and ophthalmologists. EAC adjudicated deaths, predefined MESIs, and the expanded composite cardiovascular endpoint (including death), components of the microvascular composite endpoint, neoplasms, and pancreatitis.
Calcitonin Monitoring Committee (CMC)	Independent committee made up of thyroid experts. The committee monitored calcitonin at regular intervals during the trial
Global Expert Panel	Was made up of principal investigators participating in the trial from different countries and designated Novo employees. The panel discussed and advised on global/local operational trial related issues

Internal Novo Nordisk Safety Committee	Committee performed ongoing safety surveillance of liraglutide from all sources (including clinical trials, post-marketing data) and recommended appropriate actions. The committee was blinded. The committee was chaired by Safety Surveillance (Novo) who received recommendations from the DMC regarding the LEADER trial.
Unblinded	**Role**
Data Monitoring Committee (DMC)	External independent DMC performed ongoing, independent evaluation of unblinded safety data, received from external, independent statistical consultant (Statistics Collaborative Inc). Members included cardiologists, endocrinologists, gastroenterologists and biostatisticians Provided recommendations to the internal Novo Nordisk A/S safety committee and to an independent Steering committee (STC).
External independent statistician	Provided unblinded analyses to the DMC for review of safety.

Transfer of data between blinded and unblinded parties

Figure 42 shows a schematic outlining the transfer of data between unblinded and blinded parties. Both the DMC and the External independent statistician were unblinded, with the other parties remaining blinded. Blinding was maintained until code break on 02 February 2016. The data was loaded into the clinical database on February 2 to February 5, 2016 and locked on 05 February 2016. There were no changes to any data between code break and database lock.

Figure 42 – Overview of transfer of data



Source: CTR figure 9-2

Breaking the blind for individual patients

Of note, the code for an individual patient could be broken in a medical emergency if knowing the identity of the treatment allocation influenced the treatment of the patient[99].

Semi-blinded reports of the data
There was no interim report for LEADER.
The FDA requested a semi-unblinded data for EAC-confirmed events of breast cancer (treatment A vs. B) was submitted to the FDA. The Sponsor's report states that few people from Novo Nordisk were involved in this report.

Important trial dates: Date of FPFV: 31 August 2010
First patient randomized: 22 September 2010
Last patient randomized 10 April 2012
Date of actual LPLV: December 2015
Report represents data as of: 05 February 2016
Date of code break: 02 February 2016
Date cut off for safety database (ARGUS) 01 February 2016
Data load to clinical database and locked 05 February 2016

EAC Charter Summary

This section is dedicated to the description of the EAC charter including the changes to the charter (i.e., via different versions), the EAC structure, and a discussion regarding the adjudication process for each of the adjudicated events in the trial.

Changes to the EAC charter
The final EAC charter (version 9) and the relevant portions of the previous versions of the EAC charter were reviewed by the reviewer. The changes to the EAC charter are shown in **Table 42**.

Table 42 – Changes to the EAC charter

Date of version EAC version #	Relevant changes to the EAC charter
May 13, 2010 Version 1	First version
June 1, 2010 Version 2	Update of MI[£] and stroke[¥] event definitions
June 25, 2010 Version 3	Editorial changes
Date of FPFV: 31 August 2010	
January 20, 2011 Version 4	- all nephropathy events will be reviewed by 2 nephrologists (prior 1 nephrologist and one ophthalmologist)*

[99] The sites were instructed to contact the Sponsor prior to breaking the code, if possible. If a code was broken, the person breaking the code was to record this break thru IV/WRS, which notified the Sponsor after code break. When a code was broken by a trial site, the treatment allocation was accessible to the investigator, the department responsible for Global Safety, Novo Nordisk and any other relevant party (e.g., the DMC).

	- MI event definition updated – Silent myocardial infarction definitions added
February 3, 2011 Version 5	- 2 neurologists (instead of 1) reviewed all neurological events - An automated function was added to the eCRF so that the EAC chair could perform an analysis of 'multiple events' occurring within the same patient, reported individually at similar time. This allowed EAC chair whether each event should remain as a single event or be combined into one or more events. - Event definition for prior MI was removed from charter.
First event evaluated by the EAC on 22 May 2011	
January 20, 2012 Version 6	- Update of retinopathy event definition (treatment with intra-vitreal agents was added)*. Definition of diabetes related blindness was added
December 20, 2013 Version 7	- Specified that EAC and ICON could identify events for adjudication - Option for "insufficient information" was added during PT review - 1 endocrinologist and 1 oncologist would review thyroid disease events/neoplasms - Description of process regarding multiple event assessment of ECGs where the patient already has 1 positively adjudicated MI was added[Ω] - Guidance for adjudication of neoplasms was added - Update to MI definition- specific ECG mm requirement for NSTEMI/STEMI was removed**
April 16, 2014 Version 8	- Nephropathy definition updated- macroalbuminuria changed from 300 mg/L to 300 mg albumin/g creatinine. Required re-adjudication of all nephropathy events previously adjudicated prior to update~
March 23, 2015 Version 9	- Appendix D added providing guidelines for adjudicating multiple events - Pancreatitis definitions updated (severity assessment according to Atlanta criteria). A total of 59 events were re-presented for adjudication - Neoplasm definition updated (tissue of origin). Re-classification/classification of neoplasm events with respect to tissue of origin was performed outside the EAC eCRF system

*No re-adjudication of events since it was decided in *October 2011* not to release any events for adjudication where subjects had been treated with intravitreal agents until the EAC retinopathy had been updated
**No ECGS were re-reviewed
~re-adjudication occurred from May 2014-September 2014
[£] MI was diagnosed based on any of the criteria, based on the redefinitions suggested by the European Society of Cardiology)/ACCF (American College of Cardiology Foundation)/AHA (American Heart Association)/WHF (World Heart Federation) task force.
[¥] micro-hemorrhages are defined. It is specified that the data collected on microhemorrhages will be exploratory and will not be part of the primary endpoint.
[Ω]A patient with a positively adjudicated myocardial infarction will likely be identified with new Q-waves in the following scheduled ECGs going for central reading. These ECGs sent for adjudication should, in the multiple events process, only be interpreted as new events if there is clear evidence of a new MI as compared to the already adjudicated one (eg. Different anatomical location).

Reviewer's comment: the changes to the EAC charter did not require the re-adjudication of cardiovascular events related to the primary endpoint; however

there was re-adjudication of events related to nephropathy and pancreatitis. A change to the charter that may have resulted in perhaps a greater capture of MI events was the removal of the millimeter requirement (version 7). Overall the changes with the EAC charter do not raise any concerns related to trial conduct.

The EAC was made up of 1 EAC chairman and 19 primary adjudicators. The subgroups of the EAC are shown in **Table 43.** Each case sent for adjudication was reviewed by two primary adjudicators, who individually evaluated the data. If there was disagreement between the adjudication between the two adjudicators after review of their documentation, the EAC Chair would determine the final adjudication of the event.

Table 43 – EAC subgroups and number of adjudicators

EAC subgroup	# of total adjudicators	Events reviewed
Cardiovascular*	3 cardiologists 3 neurologists	Cardiovascular events Neurological events
Microvascular	3 nephrologists 2 ophthalmologists	Nephropathy events Retinopathy events
Pancreatitis	3 gastroenterologists	Pancreatitis events
Neoplasm*	3 oncologists 2 endocrinologists	Oncologists reviewed neoplasm events, excluding thyroid neoplasm**
**In case of thyroid disease resulting in a thyroidectomy, and or thyroid neoplasm, the Adjudicators will be 1 endocrinologist and 1 oncologist. In cases where thyroidectomy was performed, the Primary Adjudicators will review both the local pathology report and the report of a central (external) pathologist who has reviewed the pathology specimen independently. If the specimen is unavailable, the Primary Adjudicators will review only the local pathology report *adjudicated ALL deaths		

The adjudication of events could be based on: complete,[100] incomplete[101] or insufficient[102] information. The EAC Chair reviewed events that were not adjudicated with complete information.

The event definition and classifications used to adjudicate events are shown in **Table 44**. Per the Sponsor, the cardiovascular events definitions are based on FDA requirements[103].

[100] The event package had all source data the site was able to submit with sufficiently detailed and or/meticulous documentation, but not necessarily all recommended source documentation
[101] Source documentation was incomplete, but contained sufficient in-depth information for an assessment to be reached
[102] Adjudication assessment could not be made due to insufficient source documentation. Only the EAC chair was able to decide if the information as insufficient for classification
[103] Standardized Definitions for Cardiovascular Outcomes Trials: Draft Recommendations. Division of Metabolism and Endocrinology Products. Center for Drug Evaluation and Research (CDER). July 22, 2009. And Standardized Definitions for Endpoint Events in Cardiovascular Trials. FDA Center for Drug Evaluation and Research (CDER). Draft Version October 20, 2010

Table 44- Definitions used for EAC adjudication of events

Event	Definition
Acute Coronary Syndrome	Acute Coronary Syndrome (ACS) conditions range from unstable angina pectoris (UAP) to non-ST elevation myocardial infarction (MI) (NSTEMI—subendocardial or nontransmural) and ST elevation MI (STEMI—transmural). **Criteria for STEMI**: New ST segment elevation is present in 2 or more contiguous leads on the 12-lead ECG[5] **Criteria for NSTEMI:** ST segment elevation is absent in 2 or more contiguous leads on the 12-lead ECG[5] In patients with abnormal biomarkers, it is recognized that lesser ECG abnormalities may represent an ischemic response and may be accepted under the category of abnormal ECG findings.
Acute Myocardial Infarction (Subcategory of ACS)	The term "MI" should be used when there is evidence of myocardial necrosis in a clinical setting consistent with myocardial ischemia. MI may be adjudicated for an event that has characteristics of a MI but which does not meet the strict definition because biomarker or electrocardiographic results are not available. MI is diagnosed based on any of the following criteria, based on the redefinitions suggested by the ESC (European Society of Cardiology)/ACCF (American College of Cardiology Foundation)/AHA (American Heart Association)/WHF (World Heart Federation) task force.[4] Under these conditions, any one of the following criteria meets the diagnosis for AMI: **Spontaneous MI:** Detection of rise and/or fall of cardiac biomarkers (preferably troponin) with at least 1 value above the 99th percentile of the upper reference limit (URL) together with evidence of myocardial ischemia with at least 1 of the following: Symptoms of ischemia ECG changes indicative of new ischemia (new ST-T changes or new left bundle branch block [LBBB]) [5] Development of pathological Q waves in the ECG[6] Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality

[4] Thygesen K, et al. "Universal Definition of Myocardial Infarction." J Am Coll Cardiol 2007 Nov 27; 50 (22): 2173-95.

[5] ECG manifestations of acute myocardial ischemia (in absence of left ventricular hypertrophy (LVH) and left bundle branch block (LBBB): 1) ST elevation New ST elevation at the J-point in two contiguous leads with the cut-off points: $\geq$ 0.2 mV in men or $\geq$ 0.15 mV in women in leads V2-V3 and/or $\geq$ 0.1 mV in other leads. 2) ST depression and T-wave changes New horizontal or down-sloping ST depression $\geq$ 0.05 mV in two contiguous leads; and/or T inversion $\geq$ 0.1 mV in two contiguous leads with prominent R-wave or R/S ratio > 1.

[6] Pathological Q waves: 1) Any Q-wave in leads V2-V3 $\geq$ 0.02 seconds or QS complex in leads V2 and V3 Q-wave $\geq$ 0.03 seconds and $\geq$ 0.1 mV deep or QS complex in leads I, II, aVL, aVF, or V4-V6 in any two leads of a contiguous lead grouping (I, aVL, V6; V4-V6; II, III, and aVF).

Event	Definition
	CK-MB and troponin are preferred, but CK may be used in the absence of CK-MB and troponin. **Sudden, Unexpected Cardiac Death.** Sudden, unexpected cardiac death, involving cardiac arrest, often with symptoms suggestive of myocardial ischemia, and accompanied by presumably new ST elevation, or new LBBB, and/or evidence of fresh thrombus by coronary angiography and/or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood. **Percutaneous Coronary Intervention-Related Myocardial Infarction**. For percutaneous coronary interventions (PCI) in patients with normal baseline troponin values, elevations of cardiac biomarkers above the 99th percentile URL are indicative of peri-procedural myocardial necrosis. By convention, increases of biomarkers greater than 3 x 99th percentile URL have been designated as defining PCI-related MI. A subtype related to a documented stent thrombosis is recognized. If the cardiac biomarker is elevated prior to PCI, a ≥ 20% increase of the value in the second cardiac biomarker sample within 24 hours of the PCI and documentation that cardiac biomarker values were decreasing (two samples at least 6 hours apart) prior to the suspected recurrent MI is also consistent with PCI-related myocardial infarction. Symptoms of cardiac ischemia are not required. **Coronary Artery Bypass Grafting-Related Myocardial Infarction**. For coronary artery bypass grafting (CABG) in patients with normal baseline troponin values, elevations of cardiac biomarkers above the 99th percentile URL are indicative of peri-procedural myocardial necrosis. By convention, increases of biomarkers greater than 5 x 99th percentile URL plus either new pathological Q waves or new LBBB, or angiographically documented new graft or native coronary artery occlusion, or imaging evidence of new loss of viable myocardium have been designated as defining CABG-related MI. If the cardiac biomarker is elevated prior to CABG, a ≥ 20% increase of the value in the second cardiac biomarker sample within 72 hours of CABG and documentation that cardiac biomarker values were decreasing (two samples at least 6 hours apart) prior to the suspected recurrent MI plus either new pathological Q waves in at least 2 contiguous leads on the electrocardiogram or new LBBB, angiographically documented new graft or native coronary artery occlusion, or imaging evidence of new loss of viable myocardium is consistent with a periprocedural myocardial infarction after CABG. Symptoms of cardiac ischemia are not required **Silent Myocardial Infarction** Silent MI is defined by the following: 1. No evidence of acute myocardial infarction **AND** 2. Any one of the following criteria: • New pathological Q-waves. A confirmatory ECG is recommended if there have been no clinical symptoms or history of myocardial infarction. • Imaging evidence of a region of loss of viable myocardium that is thinned and fails to contract, in the absence of a non-ischemic cause • Autopsy evidence of a healed or healing MI

Event	Definition
Clinical Classification of Different Types of MI	For EAC adjudication the following classifications of MI will be identified. In addition to classification, the EAC Adjudicators will identify ranges of URL values. Type 1: Spontaneous MI related to ischemia due to a primary coronary event such as plaque fissuring or rupturing. Type 2: MI secondary to ischemia due to imbalance between oxygen demand and supplies, eg. coronary spasm. Type 3: Sudden cardiac death with symptoms of myocardial ischemia, accompanied by new ST elevation or LBBB, or verified coronary thrombus by angiography, but death occurring before blood samples could be obtained. Type 4a: MI associated with PCI; 4b: stent thrombosis documented by angiography or autopsy Type 5: MI associated with CABG.
Unstable Angina Pectoris requiring hospitalization (Subcategory of ACS)	UAP is defined as cardiac ischemic events that do not fulfill the criteria of acute MI (NSTEMI or STEMI). If neither of these conditions is present by the criteria above in the MI sections of this document, then UAP may be present. The symptoms in UAP are often of shorter duration and/or are relapsing and represent a significant worsening of the patient's baseline symptoms to an extent as being the primary cause of unplanned hospitalization. For UAP to be present, NSTEMI and STEMI cannot be present. Severe recurrent ischemia (UAP) is defined as ischemic discomfort or equivalent meeting the following criteria in the absence of MI criteria: 1) No elevation in cardiac biomarkers (cardiac biomarkers are negative for myocardial necrosis) AND 2) Clinical presentation lasting at least 10 minutes at rest, or repeated episodes at rest lasting ≥ 5 minutes, or an accelerating pattern of ischemic discomfort (episodes that are more frequent, severe, longer in duration, and precipitated by minimal exertion), considered to be myocardial ischemia upon final diagnosis. Rest angina *or* New-onset (< 2 months) severe angina (Canadian Cardiovascular Society Grading Scale* (or CCS classification system) classification severity ≥ III) *or* Increasing angina (in intensity, duration, and/or frequency) with an increase in severity of at least 1 CCS class to at least CCS class III AND 3) At least one of the following additional criteria for coronary artery disease and/or ischemia: New or worsening ST or T wave changes on ECG. ECG changes should satisfy the following criteria for acute myocardial ischemia in the absence of LVH and LBBB: ST elevation New transient (known to be < 20 minutes) ST elevation at the J-point in two contiguous leads with the cut-off points: ≥ 0.2 mV in men or ≥ 0.15 mV in women in leads V2-V3 and/or ≥ 0.1 mV in other leads ST depression and T-wave changes New horizontal or down-sloping ST depression ≥ 0.05 mV in two contiguous leads; and/or T inversion ≥ 0.1 mV in two contiguous leads with prominent R-wave or R/S ratio > 1. Evidence of ischemia on stress testing with cardiac imaging Evidence of ischemia on stress testing without cardiac imaging but with angiographic evidence of ≥ 70% lesion and/or thrombus in an epicardial coronary artery *or* initiation/increased dosing of antianginal therapy. Angiographic evidence of ≥ 70% lesion and/or thrombus in an epicardial coronary artery AND 4. Requiring an unscheduled visit to a healthcare facility and overnight admission (does not include chest pain observation units During adjudication, it should then be noted if the event required: 1) Hospitalization (including an overnight stay on an inpatient unit) within 48 hours of the most recent symptoms. 2) Coronary revascularization during an unscheduled visit to a healthcare facility or during an unplanned (or prolonged) hospitalization for the symptoms.

Event	Definition
Heart Failure Requiring Hospitalization	Heart failure (HF) requiring hospitalization is defined as an event that meets the following criteria: Requires hospitalization defined as an admission to an inpatient unit or a visit to an emergency department that results in at least a 12 hour stay (or a date change if the time of admission/discharge is not available). AND Clinical manifestations of heart failure including at least one of the following: New or worsening dyspnea orthopnea paroxysmal nocturnal dyspnea edema pulmonary basilar crackles jugular venous distension new or worsening third heart sound or gallop rhythm, or radiological evidence of worsening heart failure. AND Additional/Increased therapy Initiation of intravenous diuretic, inotrope, or vasodilator therapy Uptitration of intravenous therapy, if already on therapy Initiation of mechanical or surgical intervention (mechanical circulatory support, heart transplantation or ventricular pacing to improve cardiac function), or the use of ultrafiltration, hemofiltration, or dialysis that is specifically directed at treatment of heart failure. Biomarker results (e.g., brain natriuretic peptide) consistent with congestive heart failure will be supportive of this diagnosis.

Event	Definition
Cerebrovascular Events (Stroke and TIA)	Stroke is an acute episode of neurological dysfunction attributed to a vascular cause and determined to *not* be due to a readily identifiable cause, such as a tumor or seizure with residual symptoms at least 24 hours after onset, or leading to death. Stroke is documented by imaging (eg, CT or MRI scan). Evidence obtained from autopsy can also confirm the diagnosis. Findings on lumbar puncture can also be supportive to the diagnosis. Ischemic cerebrovascular events lasting less than 24 hours will not be considered stroke and will be considered transient ischemic attacks, and will be identified as such in the eCRF. Micro-hemorrhages are defined as rounded <5-10 mm foci of susceptibility artifact on gradient-echo (T2*) MRI sequences. These appear hypointense without signal characteristics of acute or subacute hemorrhage and are distinct from other causes of signal loss on gradient echo (T2*) MRI sequences (e.g. vascular flow voids, leptomeningeal hemasidarosis, or non-hemorrhagic subcortical mineralization). (NB: When found in the setting of acute or subacute stroke symptoms, hemosiderin alone [micro-hemorrhages] without MR signal changes consistent with acute or subacute stroke should be considered incidental and not the cause of the stroke symptoms.) While data pertaining to the occurrence of micro-hemorrhages will be collected as exploratory data, the occurrence of micro-hemorrhage will not be included in the primary endpoint.
Classification of Cerebrovascular Events (Stroke and TIA)	**A. Transient Ischemic Attack** Transient ischemic attack (TIA) is defined as a transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia, without acute infarction. **B. Ischemic Stroke** Ischemic stroke is defined as an acute episode of focal cerebral, spinal, or retinal dysfunction caused by an infarction of central nervous system tissue that results from a thrombus or embolus impairing central nervous system perfusion (not due to hemorrhage) and is documented by imaging. Evidence of ischemic stroke obtained from autopsy can also confirm the diagnosis. Findings on lumbar puncture can be supportive to the diagnosis. **C. Hemorrhagic stroke** Hemorrhagic stroke is defined as an acute episode of focal or global cerebral, spinal, or retinal dysfunction caused by a nontraumatic intraparenchymal, intraventricular, or subarachnoid hemorrhage with documentation of cerebral hemorrhage on imaging (eg, CT or MRI scan), ie, intraparenchymal, intraparenchymal with penetration into the ventricles, intraventricular, or subarachnoidal hemorrhage. Subdural and epidural bleedings are not included. Evidence of hemorrhagic stroke obtained from autopsy can also confirm the diagnosis. Findings on lumbar puncture can be supportive to the diagnosis. **D. Undetermined Stroke** Undetermined stroke is defined as a stroke with insufficient information to allow categorization as B or C. **Stroke Disability** Stroke disability should be classified using the modified Rankin Scale[7] (www.strokecenter.org/trials/scales/rankin.html)

Event	Definition
Coronary Revascularization	**Percutaneous Coronary Intervention (PCI):** Placement of an angioplasty guide wire, balloon, or other device (e.g., stent, atherectomy catheter, brachytherapy delivery device, or thrombectomy catheter) into a native coronary artery or coronary artery bypass graft for the purpose of mechanical coronary revascularization. In the assessment of the severity of coronary lesions with the use of intravascular ultrasound, CFR, or FFR, insertion of a guide wire will NOT be considered PCI. **Coronary Artery Bypass Grafting (CABG):** Surgical placement of an artery, vein, or other conduit that connects the aorta or one of its branches (e.g., internal mammary artery) to a coronary artery distal to a coronary stenosis.
Death	**Mortality from CV Causes** CV mortality includes sudden cardiac death, death due to acute myocardial infarction, death due to heart failure, death due to stroke, and death due to other cardiovascular causes, as well as deaths for which there was no clearly documented non-vascular cause. **Sudden Cardiac Death**: refers to death that occurs unexpectedly in a previously stable patient and includes the following deaths: a. Witnessed and instantaneous without new or worsening symptoms b. Witnessed within 60 minutes of the onset of new or worsening cardiac symptoms c. Witnessed and attributed to an identified arrhythmia (eg, captured on an ECG recording or witnessed on a monitor by either a medic or paramedic) d. Subjects unsuccessfully resuscitated from cardiac arrest or successfully resuscitated from cardiac arrest but who die within 24 hours without identification of a non-cardiac etiology e. Unwitnessed death or other causes of death (information regarding the patient's clinical status within the week preceding death should be provided) **Death due to Acute MI**: death occurring up to 30 days after a documented acute MI (verified either by the diagnostic criteria outlined for acute MI or by autopsy findings showing recent MI or recent coronary thrombus) and where there is no conclusive evidence of another cause of death. If death occurs before biochemical confirmation of myocardial necrosis can be obtained,

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Scale	Disability
0	No symptoms at all
1	No significant disability despite symptoms; able to carry out all usual duties and activities
2	Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance
3	Moderate disability; requiring some help, but able to walk without assistance
4	Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Severe disability; bedridden, incontinent and requiring constant nursing care and attention
6	Dead

Event	Definition
Death continued	adjudication should be based on clinical presentation and ECG evidence. Death due to a MI that occurs as a direct consequence of a cardiovascular investigation/procedure/operation will be classified as death due to other cardiovascular cause. **Death due to Heart Failure or Cardiogenic Shock**: refers to death occurring in the context of clinically worsening symptoms and/or signs of heart failure without evidence of another cause of death. New or worsening signs and/or symptoms of congestive heart failure (CHF) include any of the following: a. New or increasing symptoms and/or signs of heart failure requiring the initiation of, or an increase in, treatment directed at heart failure or occurring in a patient already receiving maximal therapy for heart failure b. Heart failure symptoms or signs requiring continuous intravenous therapy or oxygen administration c. Confinement to bed predominantly due to heart failure symptoms d. Pulmonary edema sufficient to cause tachypnea and distress not occurring in the context of an acute MI or as the consequence of an arrhythmia occurring in the absence of worsening heart failure e. Cardiogenic shock not occurring in the context of an acute MI or as the consequence of an arrhythmia occurring in the absence of worsening heart failure. Cardiogenic shock is defined as systolic blood pressure (SBP) < 90 mm Hg for greater than 1 hour, not responsive to fluid resuscitation and/or heart rate correction, and felt to be secondary to cardiac dysfunction and associated with at least one of the following signs of hypo-perfusion: Cool, clammy skin or Oliguria (urine output < 30 mL/hour) or Altered sensorium or Cardiac index < 2.2 L/min/m^2 Cardiogenic shock can also be defined as SBP ≥ 90 mm Hg as a result of positive inotropic or vasopressor agents alone and/or with mechanical support in less than 1 hour. The outcome of cardiogenic shock will be based on CEC assessment and must occur after randomization. Episodes of cardiogenic shock occurring before and continuing after randomization will not be part of the study endpoint. This category will include sudden death occurring during an admission for worsening heart failure. **Death due to Cerebrovascular Event:** (intracranial hemorrhage or non-hemorrhagic stroke): refers to death occurring up to 30 days after a suspected stroke based on clinical signs and symptoms as well as neuroimaging and/or autopsy, and where there is no conclusive evidence of another cause of death. The FDA Stroke Team Definition of Death due to Stroke can also refer to death occurring up to 30 days after a stroke that is either due to the stroke or caused by a complication of the stroke. **Death due to Other Cardiovascular Causes** Death must be due to a fully documented cardiovascular cause not included in the above categories (eg, dysrhythmia, pulmonary embolism, or cardiovascular intervention). **Non-Cardiovascular Death** Non-cardiovascular death is defined as any death not covered by cardiac death or vascular death and will be categorized into following groups: pulmonary causes, renal causes, gastrointestinal causes, infection (includes sepsis), non-infectious (e.g., systemic inflammatory response syndrome

Event	Definition
Death continued	(SIRS)), malignancy (i.e., new malignancy, worsening of prior malignancy), hemorrhage- not intracranial, accidental/trauma, suicide, non-cardiovascular system organ failure (e.g., hepatic failure), non-cardiovascular surgery, other non-cardiovascular. **Presumed Cardiovascular Death** All deaths not attributed to the categories of cardiovascular death and not attributed to a non-cardiovascular cause, are presumed cardiovascular deaths and as such are part of the cardiovascular mortality endpoint. **Classification of Death Events** Causes of death events will be initially identified as either "Known" or "Unknown." If classified as Unknown, no further adjudication of the event will be performed. If Known is selected, the Adjudicator will then be prompted to rate the likelihood that the death can be classified as a CV death event, by making one of the following selections for CV-Related Death: 1) Documented, 2) Probable/Possible, or 3) Unlikely. If "Documented" or "Probable/Possible" is selected, the death event will be classified as CV-related. If "Unlikely" is selected or if cause of death is not suspected to be CV related, the Adjudicator will rate the likelihood that the death event was a non-CV death event by making one of the following selections for Non-CV-Related Death: 1) Documented, 2) Probable/Possible, or 3) Unlikely. The definitions of classifications are as follows: • **Documented**—There is documented evidence for classification • **Probable/Possible**— There is good reason and sufficient documentation and/or it is conceivable and cannot be dismissed • **Unlikely—**The event is most likely related to an alternative cause other than a cardiovascular cause (eg, medical history relevant for cancer) For operational purposes, in case of doubt the EAC members are encouraged to consider the definitions at the end of this spectrum of definitions
Pancreatitis	Pancreatitis is an inflammatory process of the pancreas. Two of following diagnostic criteria meets the diagnosis of acute pancreatitis: severe acute upper abdominal pain elevated blood levels of pancreatic enzymes (lipase, amylase) 3xURL characteristic imaging finding (ultrasound, CT, MRI) Chronic pancreatitis will be defined by characteristic imaging finding (ultrasound, CT, MRI) with abnormal pancreatic function tests or characteristic histological findings. Events of acute pancreatitis will be further classified according to degree of severity based on revised Atlanta criteria[8]. • Mild acute pancreatitis (no organ failure and no local or systemic complications) • Moderately severe acute pancreatitis (organ failure that resolves within 48 h (transient organ failure) and/or local or systemic complications without persistent organ failure) • Severe acute pancreatitis (persistent organ failure (>48 h) (single/multiple organs))

[88] Banks PA, et al. "Classification of acute pancreatitis -2012: revision of the Atlanta classification and definitions by international consensus" Gut 2013;62:102-111

Event	Definition
Neoplasm*	Neoplasm is defined as an abnormal growth of tissue. All neoplasms will be captured. Neoplasms will be classified according to the tissue of origin, the organ system and to the malignancy status: • Benign • Malignant • Pre-malignant/Carcinoma in situ/borderline • Unclassified
Thyroid disease requiring thyroidectomy and/or thyroid neoplasms	All thyroid disease requiring thyroidectomy, including partial thyroidectomy (e.g. lobectomy, partial lobectomy) and all thyroid neoplasms will be adjudicated. Medullary carcinoma of the thyroid (MTC) is defined as a distinct thyroid carcinoma that originates in the calcitonin producing parafollicular C cells of the thyroid gland. Thyroid neoplasms deriving from the C cells will be classified according to the pathology report, as: • C-cell hyperplasia • Medullary microcarcinoma (carcinoma *in situ)* • Medullary carcinoma.
Nephropathy	A new onset of persistent macroalbuminuria, or persistent doubling of serum creatinine level and creatinine clearance per MDRD $\leq$45 mL/min/1.73m^2, or the need for continuous renal-replacement therapy (in the absence of an acute reversible cause) or death due to renal disease. Macroalbuminuria is defined either as a 24 hour urine collection above 300 mg, or as an elevated ratio in a spot sample above 300 mg albumin / g creatinine. To confirm persistent macroalbuminuria or persistent doubling of serum creatinine, a confirmatory measurement should be performed.
Diabetic Retinopathy	Diabetic retinopathy defined as need for retinal photocoagulation or treatment with intravitreal agents or vitreous haemorrhage or diabetes-related-blindness (defined as Snellen visual acuity of 20/200 [6/60] or less or visual field of less than 20 degrees, in the better eye with best correction possible).
* Additional guidance for adjudicating neoplasms is available in Appendix C.	

In addition to the systematic definitions which were followed by the EAC, there was additional guidance regarding adjudication of neoplasms and cause of death **(Table 45** and **Table 46**[104] respectively).

[104] Of note, all fatal MESI events were to be adjudicated twice, both at the (non-fatal) MESI category (i.e. pancreatitis) and also as the fatal MESI event. If the event is not a MESI, then it should be only adjudicated as a fatal event.

Table 45- Guidance for adjudication of neoplasms

Definition of neoplasm	The EAC interprets neoplastic growth as clonal disorders that grow in an autonomous manner. The abnormality of clonal disorder may not always be identified nor can autonomous growth always be determined but both are fundamental aspects of neoplastic growth.
Adjudication of neoplasms	a. A pathologic diagnosis, either by histology or cytology, is of foremost importance. b. If pathologic diagnosis is not available, citation wherein there is extensive disease present on imaging and markedly abnormal tumor markers, (e.g. skeletal lesions with markedly elevated prostate specific antigen) will be considered. c. If the principal investigator submits a Clinical Narrative or if there is other dated source documentation that describes a diagnosis of neoplasm but the original report is unavailable, then, it will be accepted as diagnostic of a neoplasm. d. Entries solely in the NN clinical eCRF are not considered source documentation and are not acceptable documentation of a neoplasm. e. A radiologic appearance of tumors alone is generally not acceptable as diagnostic of a neoplasm, even if it was treated as such (with exception to c). Visualization of a lesion on endoscopy or scans does not represent a neoplastic growth unless proven histologically (with exception to c).

Adjudication of deaths

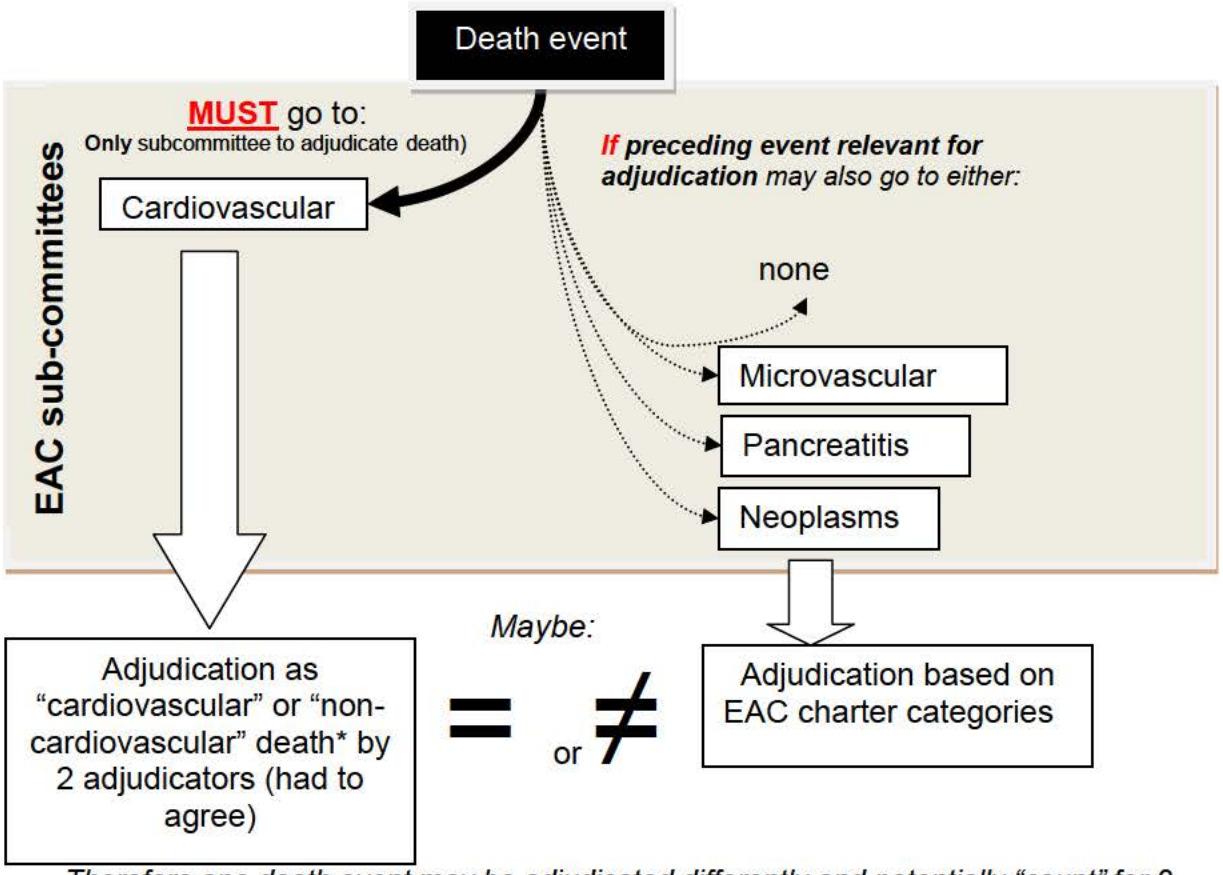
The reviewer will discuss the following in this section: 1. the committees involved in the adjudication of death, 2. the process of adjudicating known and unknown deaths; and 3. the types of cardiovascular and non-cardiovascular deaths adjudicated.

Committees involved in adjudication of death events

All fatal events were adjudicated in the 'death adjudication queue' by the EAC cardiovascular subcommittee to identify potential cardiovascular deaths. If the event preceding the fatal event did not meet criteria for adjudication, only the death would be adjudicated. For example, for a neoplasm event reported with fatal outcome, it was adjudicated in 2 queues: 'neoplasm' and 'death' queues. No reconciliation was made for the adjudication outcomes for fatal events that were evaluated twice in two separate adjudication queues. Therefore, potentially, if each sub-committee adjudicated the event differently, then one death event could count for two separate endpoints; refer to **Figure 43** for a schema of adjudication of death.

The EAC also adjudicated the onset dates and dates of death for all adjudicated events.

Figure 43- Adjudication of deaths by sub-committees



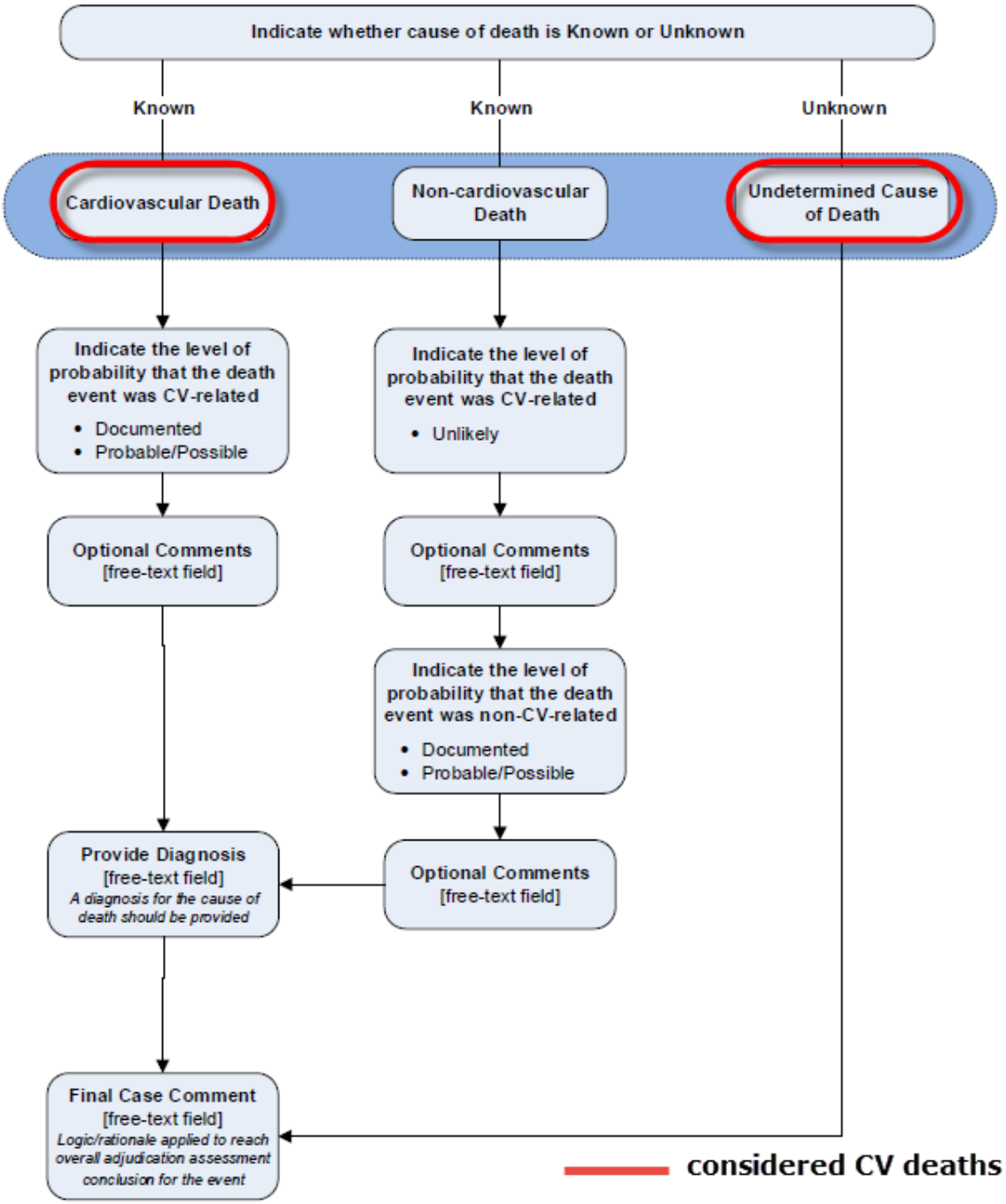
Therefore one death event may be adjudicated differently and potentially "count" for 2 different endpoints

*Of note the EAC-confirmed non-cardiovascular events were counted by the classification of the relevant non-cardiovascular EAC subcommittee, according to the categories in the EAC charter

The process of adjudicating known and unknown deaths

Figure 44 shows the cardiovascular sub-committee's logic flow for adjudicating death events. Death was known or unknown. If the cause of death was unknown, no further assessment was performed. Deaths that were unknown were considered cardiovascular deaths, and part of the cardiovascular mortality endpoint (shown in red outline).

Figure 44- Death event adjudication flow chart



Source: 16-1-13 Event adjudication SRS flowcharts, modified by adding red lines.
\\cdsesub1\evsprod\NDA022341\0347\m5\53-clin-stud-rep\535-rep-effic-safety-stud\type-2-diabetes-cv-risk\5351-stud-rep-contr\study-report-ex2211-3748\16-1-13-special-committee-documents-3748.pdf

Types of cardiovascular and non-cardiovascular deaths

Table 47 shows the guidelines for adjudicating death provided to the EAC. Cardiovascular death included the following categories: sudden cardiac death, death due to MI, death due to heart failure/cardiogenic shock, death due to cerebrovascular event and death due to other cardiovascular causes. Three of these cardiovascular deaths had a time association with the event: death due to MI (death occurring ≤30 days), death due to stroke (death occurring ≤30 days) and death due to sudden death (death occurring ≤24 hours after patient was seen by family).

The EAC was required to assign the most likely cause of death based on clinical judgment, and not strict criteria as was done for other adjudicated events. For example, death due to MI did not have to meet all the criteria required to confirm an MI.

For cardiovascular deaths, which were not linked to another CV event during multiple events review (discussed in the next section), the cause of death field was reviewed and sub-categorized by the Sponsor after database lock according to the cardiovascular death categories defined by the EAC Charter: 'sudden cardiac death', 'death due to acute MI', 'death due to heart failure or cardiogenic shock', death duet to cerebrovascular event', 'death due to other cardiovascular causes' and unclassifiable'. The category 'unclassifiable' was used when the two adjudicators did not enter a comparable cause of death (i.e. chronic heart failure, vs acute MI).

The causes of deaths provided by the adjudicators were classified by the Sponsor after DBL according to the non-cardiovascular death categories in the EAC charter (see **Table 44**).

Table 46- Guidelines for adjudicating death

	Event	Specific time criteria?	Definition
CV death	MI	Death ≤30 days after MI*	Any death after MI (verified by diagnostic criteria for acute MI or autopsy findings) OR Death from PCI/CABG to treat **complication** resulting from MI AND where there is no conclusive evidence of another cause of death.
	CV procedures	no	Death from elective coronary procedure to treat myocardial ischemia OR Death due to MI occurring as direct consequence of CV investigation/procedure
	Sudden death	For unwitnessed death, patient seen ≤24 hours	Unexpected death **NOT** following MI **Death witnessed and** a. occurring without new or worsening symptoms or b. within **60 minutes** of the onset of new or worsening cv symptoms, unless the symptoms suggest acute MI or c. attributed to an identified arrhythmia~ d. Death after unsuccessful resuscitation from cv arrest e. Death after successful resuscitation from cv arrest & without identification of a specific cardiac or non-cardiac etiology f. **Unwitnessed** death in patient seen alive & clinically stable ≤24 hrs. prior to being found dead without any evidence supporting a specific non-cardiovascular cause of death
	Heart failure	No	Death associated with worsening **symptoms/signs** of heart failure regardless of HF etiology without evidence of another cause of death. Death can have various etiologies (incl. single or recurrent MI, ischemic or non-ischemic cardiomyopathy, hypertension, or valvular disease)
	Stroke	Death ≤30 days after stroke*	Death occurring up to 30 days after suspected stroke and where there is no conclusive evidence of an alternative cause of death. Death after a stroke that is either a direct consequence of the stroke or a complication of the stroke. Acute stroke should be verified to the extent possible by the diagnostic criteria outlined for stroke.
	CV hemorrhage		Death related to hemorrhage such as a non-stroke intracranial hemorrhage, non-procedural or non-traumatic vascular rupture (e.g., aortic aneurysm), or hemorrhage causing cardiac tamponade
	Other CV causes	No	CV death not included in the above categories but with a specific, known

			cause (e.g., pulmonary embolism or peripheral arterial disease).
Non-CV death	Any death that is not thought to be due to CV	No	Classification includes:: •Pulmonary • Renal • Gastrointestinal • Infection (includes sepsis) • Non-infectious (e.g., systemic inflammatory response syndrome (SIRS)) • Malignancy • Hemorrhage that is neither cardiovascular bleeding or a stroke • accidental/ trauma • Suicide • non-cardiovascular system organ failure (hepatic failure) • Non-CV procedure or surgery • Other non-CV
Undetermined cause of death	--	Patient not seen >24 hours	Death not attributable to one of the above categories. i.e., Patient found dead in bed but was not seen by family for several days. **Considered cardiovascular death for the statistical analysis**

MI: myocardial infarction, CV: cardiovascular, HF: heart failure, PE: pulmonary embolus, PAD: peripheral artery disease
* where there is no conclusive evidence of another cause of death.
~ e.g. Captured on an electrocardiographic (ECG) recording, witnessed on a monitor, or unwitnessed but found on implantable cardioverter defibrillator
Categories specified in the EAC appendix, and not part of the EAC definitions in Table 44

Adjudication of multiple events

The Sponsor uses the terms "multiple events" in the EAC charter to refer to the classification of multiple events[105] in a single patient. The EAC Chair had the responsibility to determine if multiple adjudicated events constituted one event or multiple separate events. As a general rule, the same events occurring in one visit counted as one event (i.e. multiple stents in one visit =1 event; see **Table 47**), with the exception of neoplasms (as described in **Table 48**).

Figure 45 shows the EAC's general approach at adjudicating multiple events. All the adjudicated events could undergo Multiple Event Review by the EAC chair. For non-fatal scenarios, the EAC chair selected an index event, [106] based on clinical importance (i.e. the event that led to the chain of events), when multiple events were grouped. This index event, only, was included in the statistical analyses and summaries of EAC-confirmed events; the other "duplicate" events were disregarded.

Below are a few examples of how the "multiple events" approach worked:

- **A patient diagnosed with an MI with subsequent ECG showing q-waves-** The ECGs sent for adjudication, should only be interpreted as new events if there is was clear evidence of a new MI as compared to the already adjudicated one (e.g., different anatomical location).
- **A patient with EAC confirmed MI(s) or stroke(s) in a patient with an EAC-confirmed CV-death** – The EAC Chair evaluated whether any of the events precipitated the CV death by directly triggering it. In such a case the EAC Chair linked the EAC-confirmed MI and/or stroke event to the CV death. Hence, EAC-confirmed MI and stroke events will only be counted as 'fatal MI' and 'fatal stroke' if the event precipitated the CV-death.

Index events were further categorized as 'first events' and 'recurrent events'. Recurrent events were index events occurring in a patient who had already had a previous index event. In the time-to event analyses, only the 'first events' were included.

[105] This guidance was provided in Appendix D of the EAC charter added in version 7 of the EAC charter.
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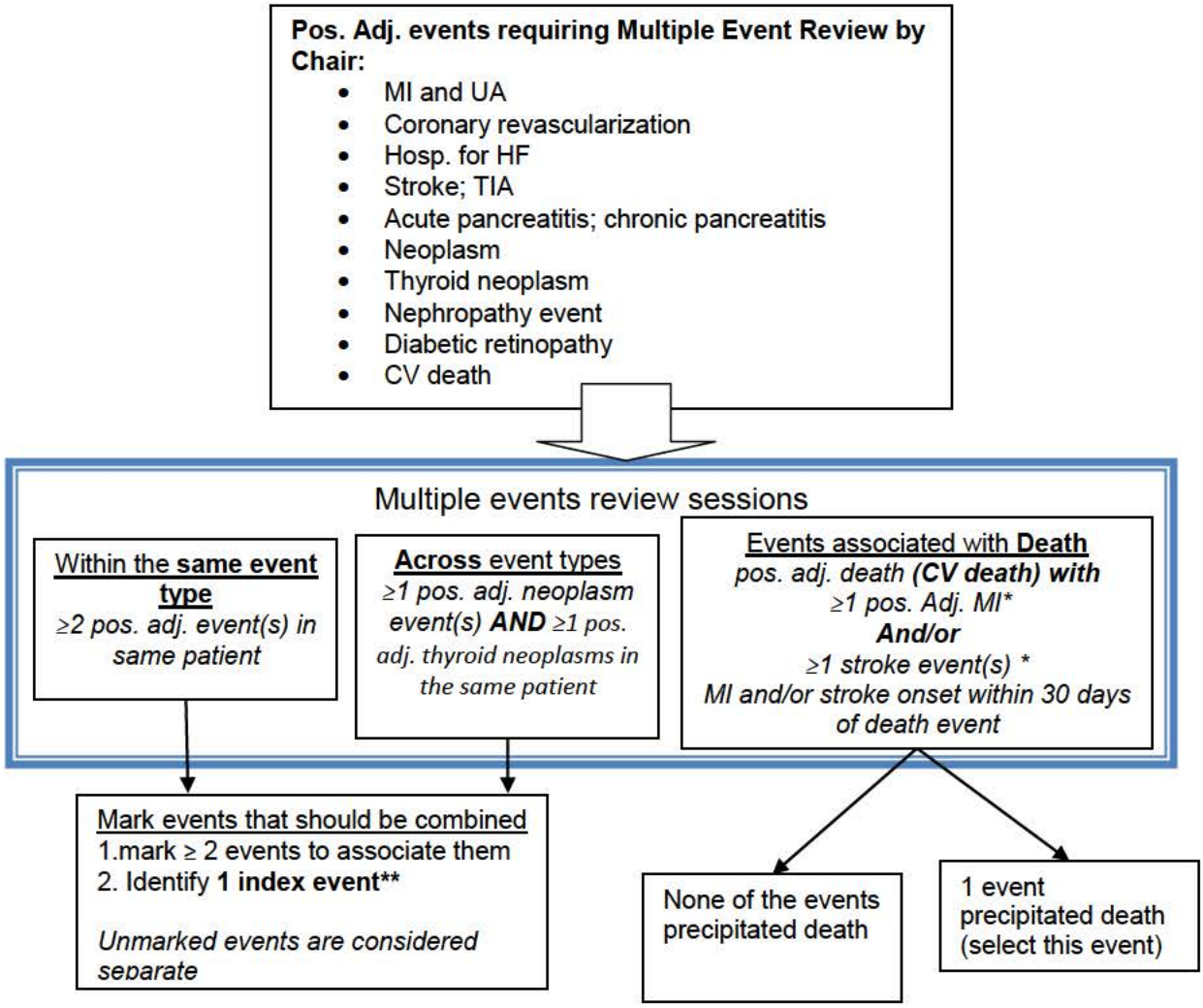
Figure 45 – Multiple Events Assessment Logic Flow



*Event occurring in the same patient
** The first event that leads to the other medical events in the group.
Pos.=positive, Adj.= adjudicated, MI= myocardial infarction, CV= cardiovascular, revasc.= revascularization, hosp.= hospitalization, HF= heart failure; UA= unstable angina
Source: 16-1-13 Event adjudication SRS flowcharts \\cdsesub1\evsprod\NDA022341\0347\m5\53-clin-stud-rep\535-rep-effic-safety-stud\type-2-diabetes-cv-risk\5351-stud-rep-contr\study-report-ex2211-3748\16-1-13-special-committee-documents-3748.pdf

Table 47- Guidelines for adjudicating multiple cardiovascular events

Procedure	CABG	PCI	Hybrid PCI and CABG	UA and MI	UA and PCI	Peri-procedural MI
Possible scenario	CABG ≥1 territories*	stent ≥1 vessel*	PCI to totally occluded vessel +CABG Or failed PCI+ urgent CABG	Intermittent chest pain + MI **within** 48 hours	PCI +normal baseline cTn (UA)	baseline cTN elevated and stable or falling at time of PCI
Number of procedure event for adjudication	1 event (CABG)	1 event (PCI)	1 event (hybrid procedure)	1 event (MI)	1 event (PCI)	1 event (PCI)
How event could count as a second event	Return to operating room at a subsequent time to treat same/new lesion	Recurrence of symptom w/same or 2nd blockage treated in **unplanned** procedure *A 2nd **elective** procedure to treat 2nd blockage **or** elective catherization with no revascularization prior to CABG **does not count***	None	Chest pain >48 hours from MI (code as one event of UA and one event of MI)	Post PCI: cTN 3x 99th percentile <48 hrs. of PCI **and either:** i) prolonged ischemia (20 min) shown by chest pain ii) ischemic ST changes or new pathological Q waves iii) angiographic evidence of flow limiting complication** iv) imaging of new loss of viable myocardium or new regional wall motion abnormality code as 2nd event of PCI-related MI (type 4a)	baseline cTN elevated and stable or falling at time of PCI + Rise of 20%in biomarkers Code as 2nd event of PCI related MI (type 4a)~

***it is possible that a non-culprit or "bystander" or an additional contributing area was treated.**
**** such as loss of patency of a side branch, persistent slow-flow or no-reflow or embolization**
~ If baseline cTn are elevated and rising, it is not possible to diagnose a post PCI MI unless the patient began procedure with an open artery and had a persistently closed artery at end of case.
PCI: percutaneous intervention, MI: myocardial infarction, CABG: coronary artery bypass, UA: unstable angina, cTN,

Table 48- Guidelines for adjudicating multiple non-cardiovascular events

Event	retinopathy	Benign & malignant growths	Nephropathy	TIA Ischemic stroke and hemorrhagic conversion
Possible scenario	≥1 laser procedures in one visit	Multiple benign growths of the skin /colon or thyroid excised in one procedure OR Malignant carcinoma + anatomically contiguous carcinoma in situ of same cell lineage	Continuous sustained rise in Cr over time unless the rise is punctuated by improvements in renal function OR Cr doubled	Imaging that suggests necrosis or hemorrhage during a TIA= stroke (not TIA) Conversion of ischemic stroke to hemorrhagic stroke
Number of procedure event for adjudication	1 event	1 event	1 event	1 event
How event could count as a second event	Return to operating room at a subsequent time to treat same/new lesion	If: 2nd visit for excision of more benign growths OR **Benign** growth + **malignant** growth excised OR 2nd visit when malignant growth is removed OR Malignant tumor + 2nd tumor of the same lineage in situ but not anatomically contiguous removed	If sustained rise in Cr requires hemodialysis, code as 2 events OR Cr fourfold increase over baseline OR New macroalbuminuria +doubling of CR on same day OR New macroalbuminuria +hemodialysis on same day OR Multiple events: new microalbuminuria, new doubling of Cr and new initiation of HD	TIA followed by stroke (ischemic/hemorrhagic) *Incidental findings of micro-hemorrhages are not considered events*
TIA: transient ischemic attack (transient symptoms that resolve within 24 hours)				

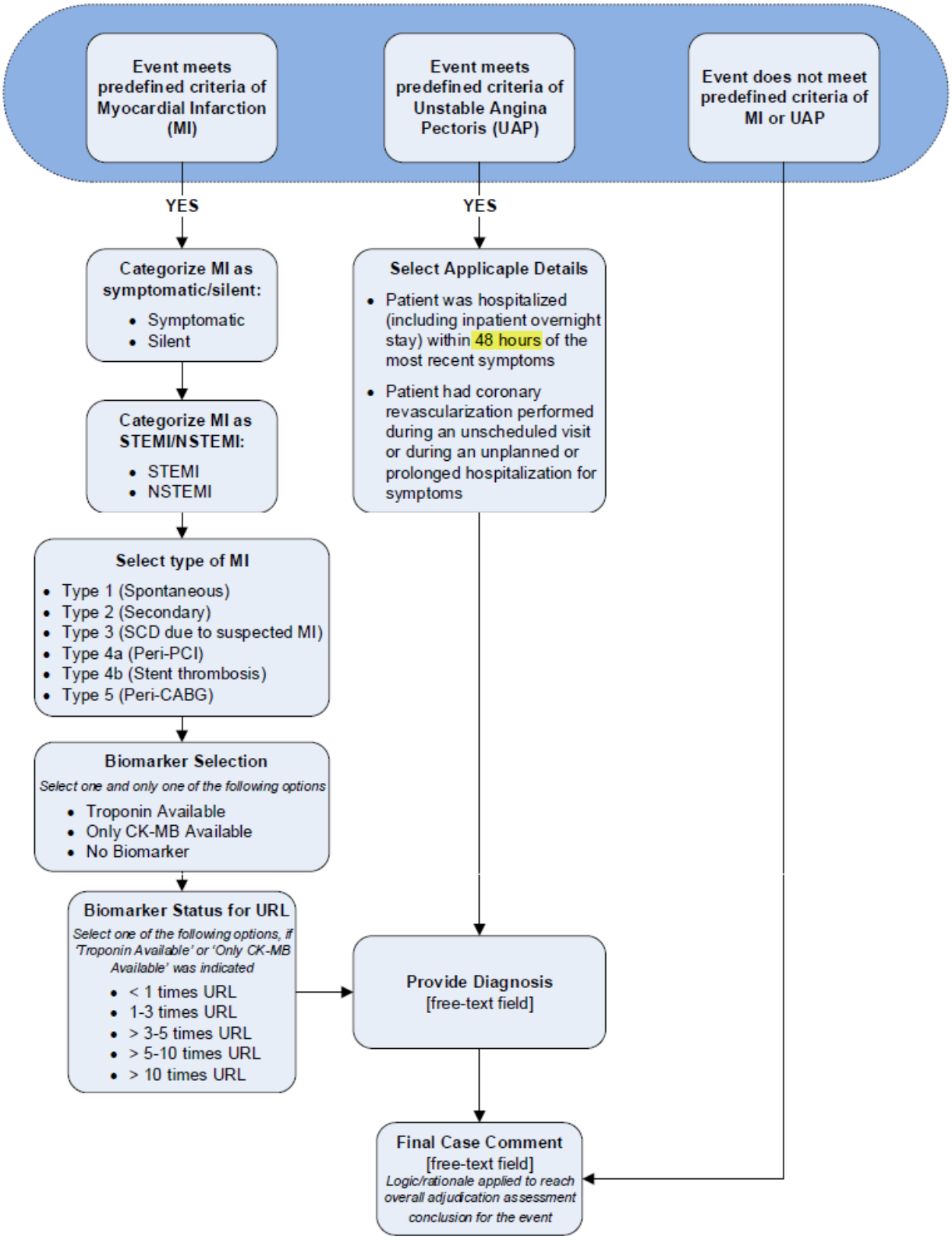
Adjudication of cardiovascular (non-fatal events)

MIs (both silent and symptomatic) were identified by investigator reports, central ECG readings, by ICON/EAC and by Sponsor derived MedDRA searches. MIs were classified according to categories of MI type based on evaluation of biomarkers, ECG, imaging or autopsy findings; see **Table 44** and **Figure 46.** For UA, in addition to meeting the criteria in **Table 44,** patients were classified as being hospitalized within 48 hours from most recent symptoms and/or undergoing unplanned cardiac catherization.

Stroke was classified as ischemic stroke, hemorrhagic stroke or undetermined stroke; see **Table 44** and **Figure 47.** Stroke could be documented by imaging and/or autopsy. An ischemic cerebrovascular event lasting less than 24 hours was considered a TIA.

The EAC evaluated coronary revascularization procedures to see if the procedure met the pre-defined criteria for coronary revascularization (see **Table 44** for definition)

Figure 46- ACS adjudication flow chart



Source: 16-1-13 Event adjudication SRS flowcharts

Figure 47- cerebrovascular event adjudication flow chart

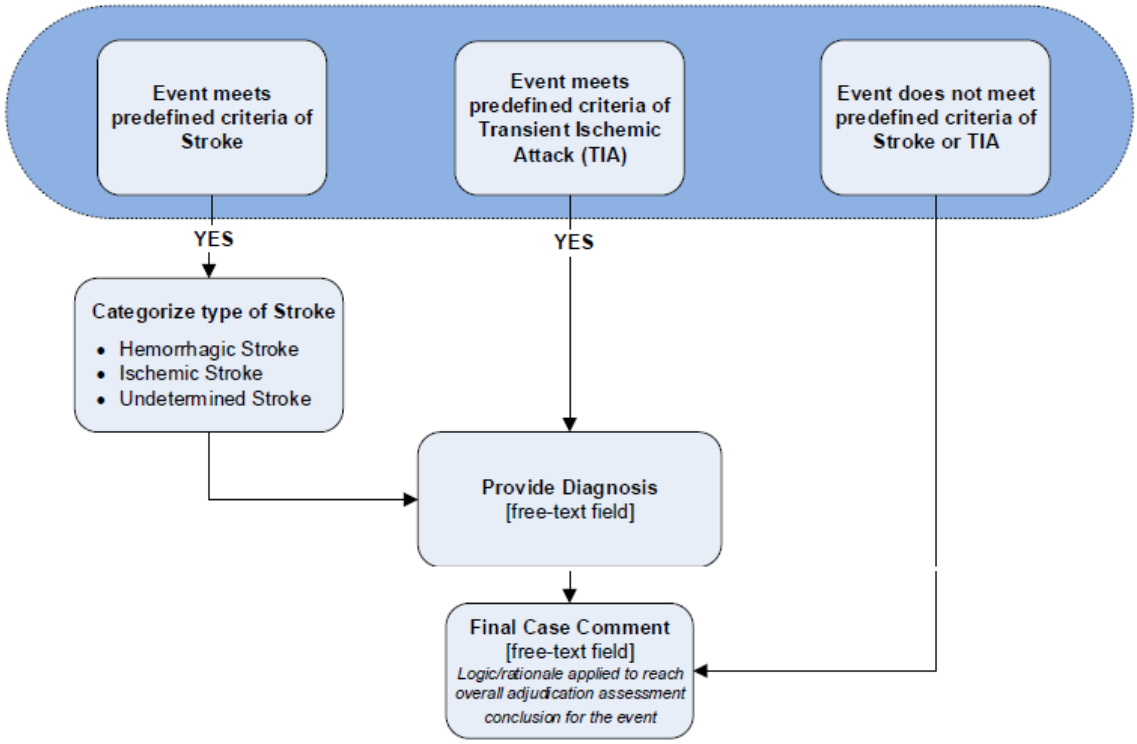
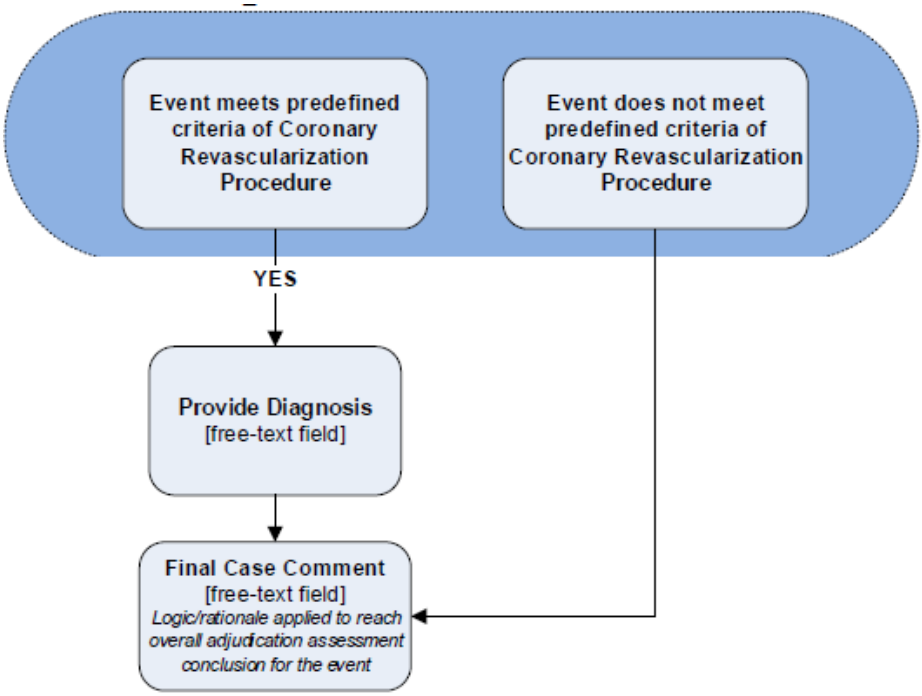
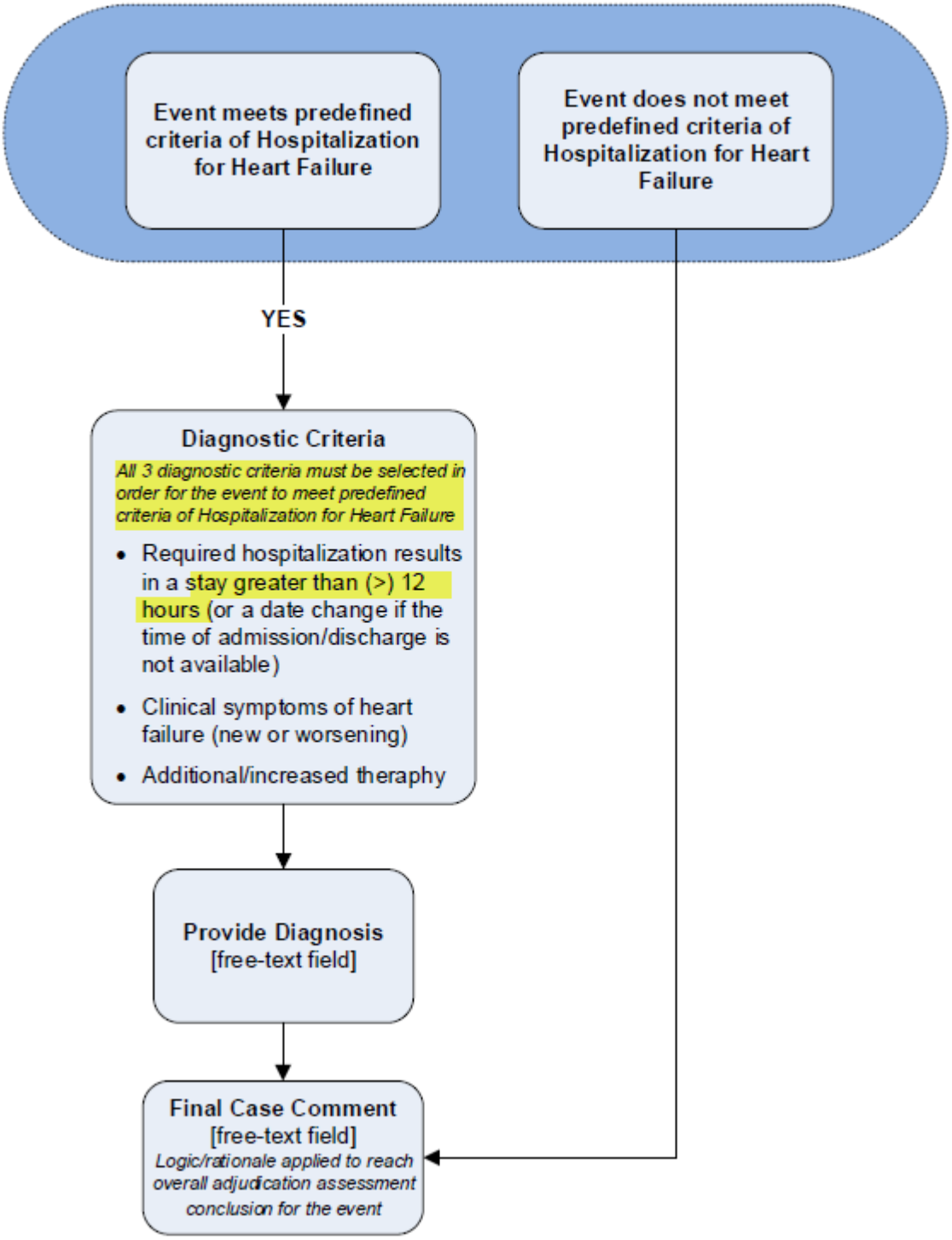


Figure 48- coronary revascularization procedure event adjudication flow chart



Source: 16-1-13 Event adjudication SRS flowcharts

Figure 49- Hospitalization of heart failure event adjudication flow chart

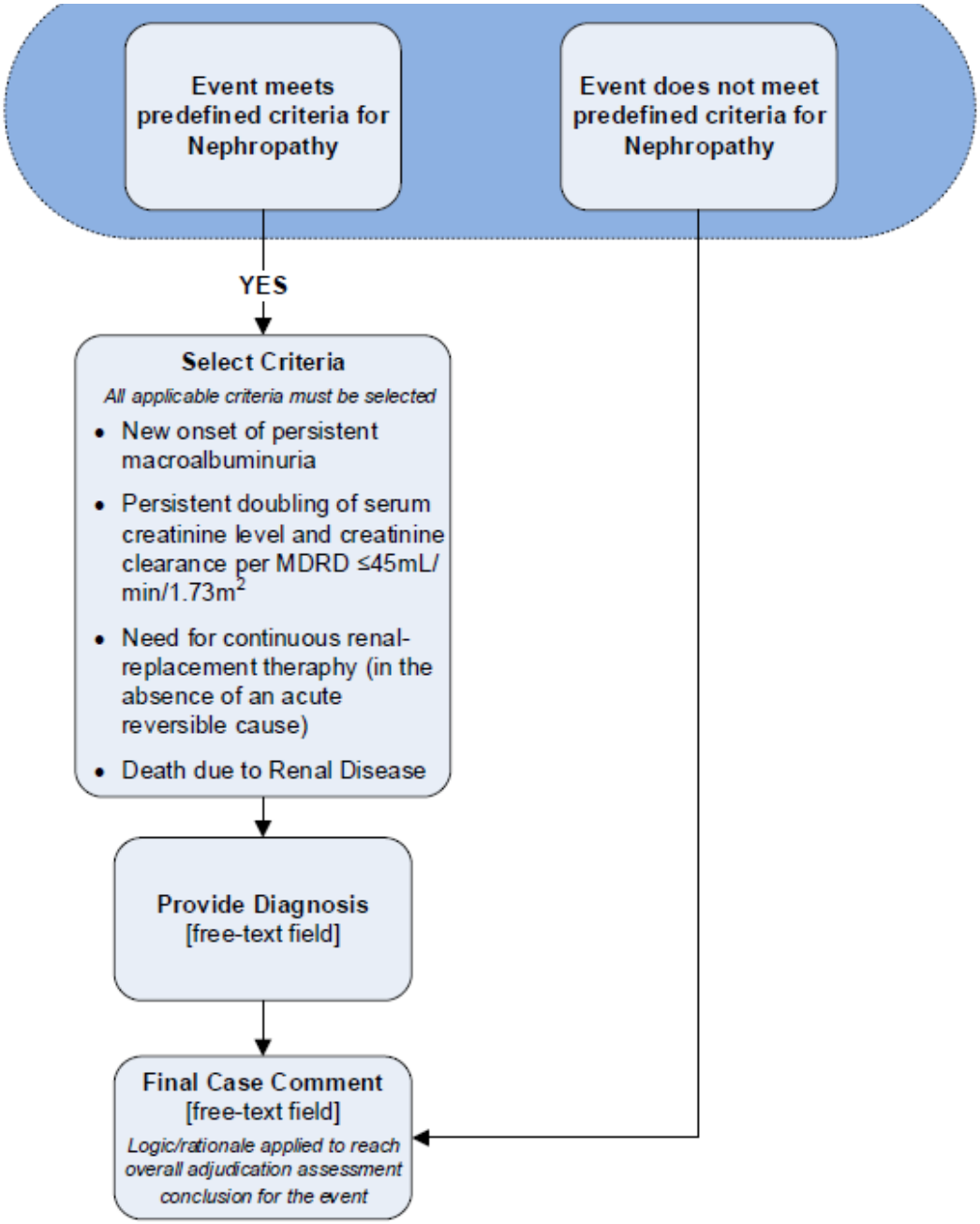


Source: 16-1-13 Event adjudication SRS flowcharts

EAC evaluation of microvascular events

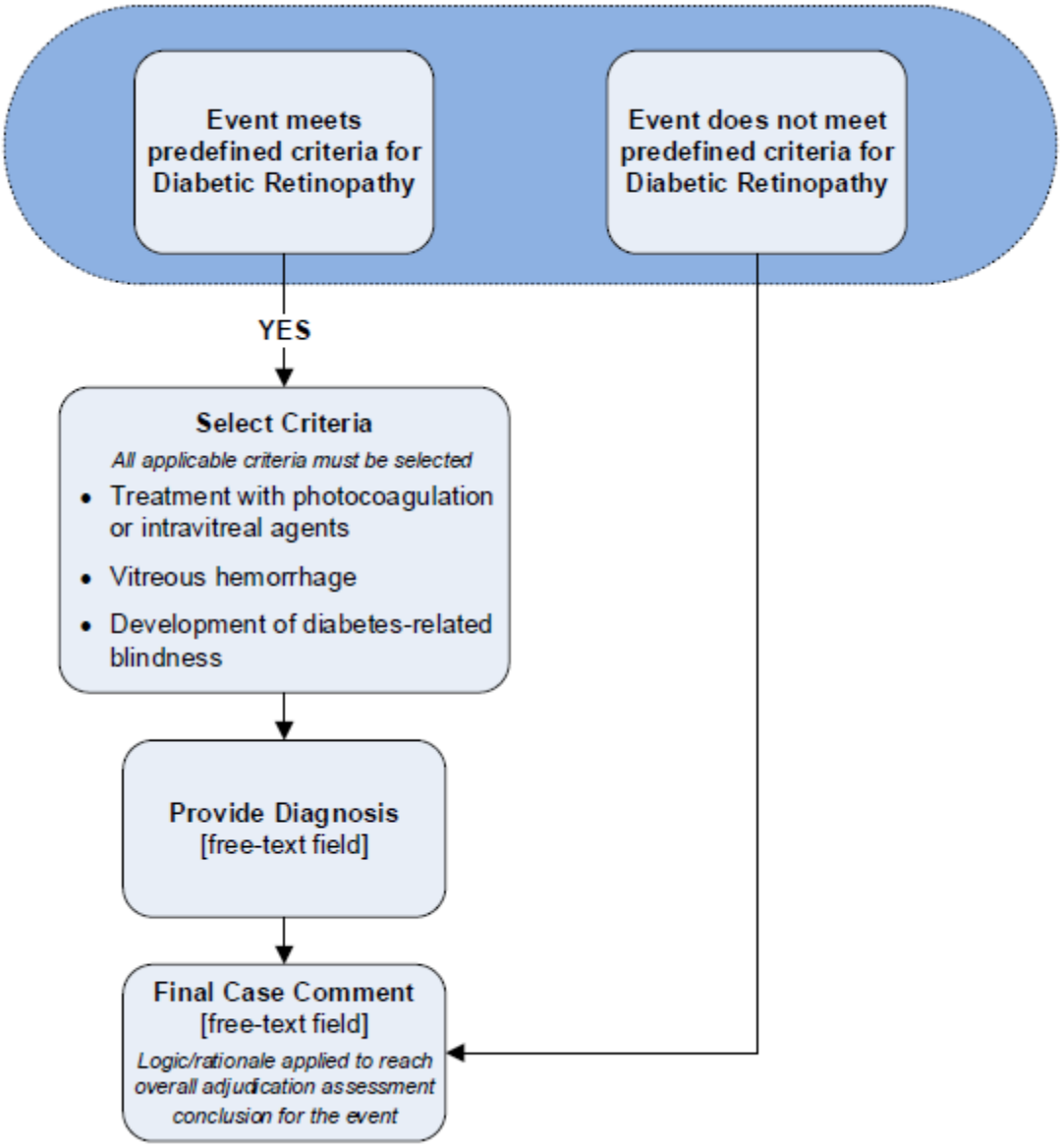
The EAC evaluated microvascular events as per **Figure 50** and **Figure 51**. For the microvascular events, meeting only 1 pertinent criterion was sufficient for adjudication. For microvascular events, one event could fulfil one or more of the specified criteria as the EAC was to select all criteria applicable for a specific event. For example, an EAC-confirmed event of retinopathy could concomitantly fulfil both the criteria 'treatment with photocoagulation or intravitreal agents' and 'vitreous hemorrhage'. In this example, the event would count once in time to first retinopathy endpoint, and once in each of the analyses with the individual criteria.

Figure 50- Nephropathy event adjudication flow chart



Source: 16-1-13 Event adjudication SRS flowcharts

Figure 51- Diabetic retinopathy event adjudication flow chart

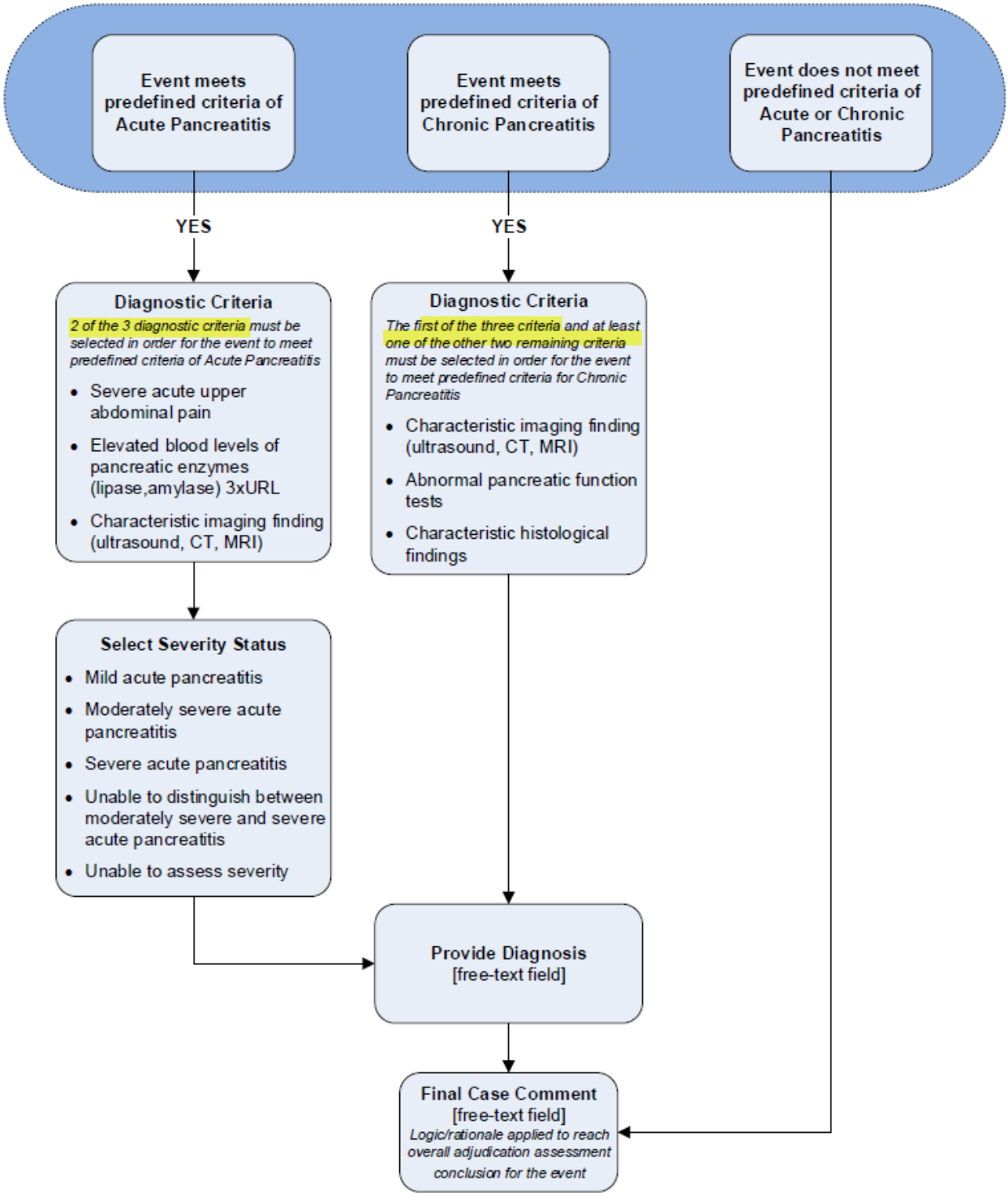


Source: 16-1-13 Event adjudication SRS flowcharts

EAC evaluation of pancreatitis

The EAC classified pancreatitis as acute or chronic pancreatitis (an event could not meet both criteria). Acute pancreatitis had to meet 2 of 3 criteria (either severe acute, upper abdominal pain, 3X upper reference limit of pancreatic enzymes or characteristic imaging); while chronic pancreatitis had to meet at least imaging criteria.

Figure 52- Pancreatitis event adjudication flow chart



Source: 16-1-13 Event adjudication SRS flowcharts

EAC evaluation of neoplasms

The EAC interpreted neoplastic growth as clonal disorders that grow in an autonomous manner. To ensure that all neoplasms were captured, the investigator was asked to report all types of neoplasms using a broader definition than applied by the EAC. The EAC's adjudication of the neoplasms could be based on: diagnostic test results, pathology reports, specialist consultations, related imaging reports and/or biomarkers. However, for adjudication of any neoplastic event, the pathologic diagnosis (i.e. histology or cytology) was considered the most important for confirmation.

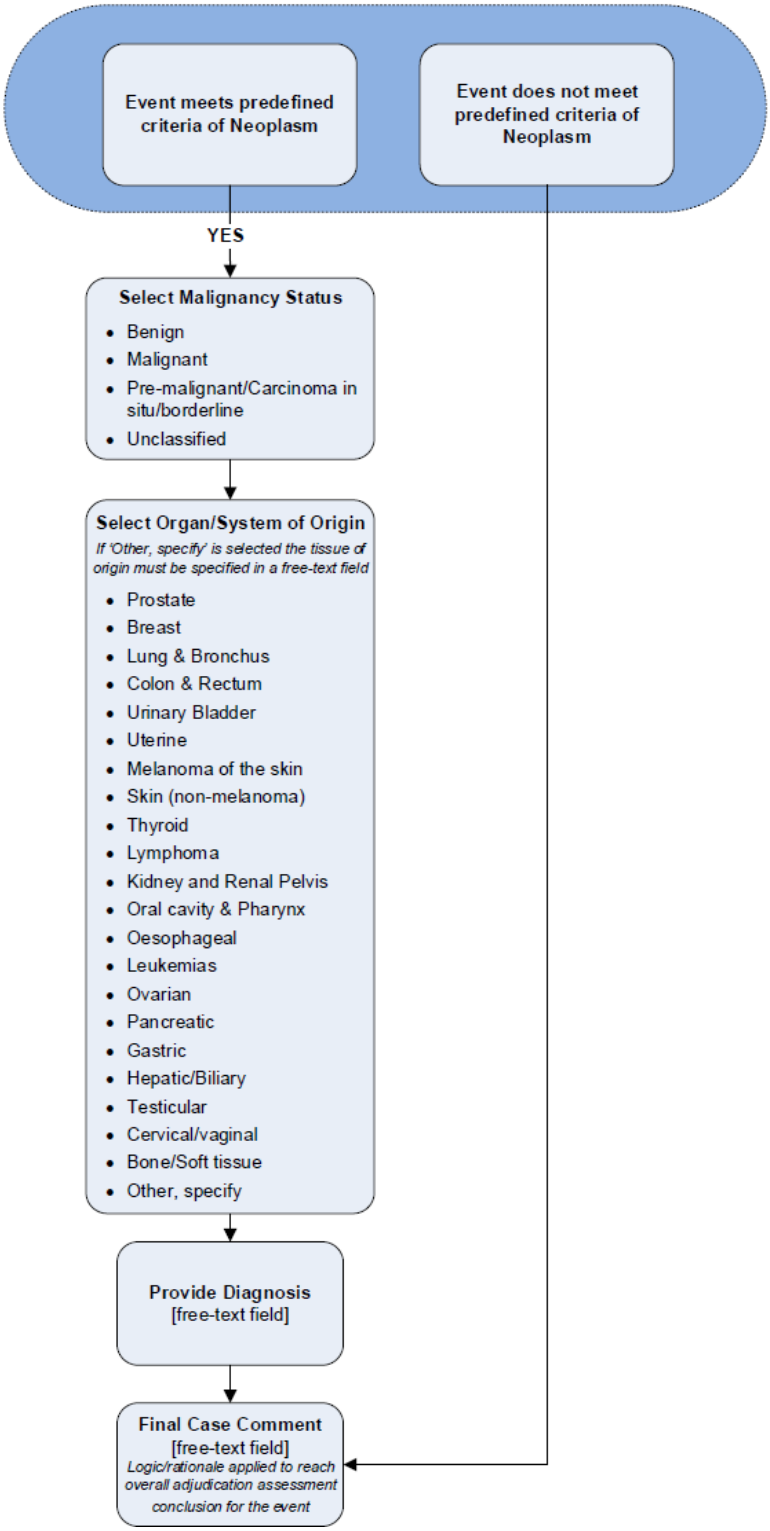
Thyroid neoplasms and thyroid disease requiring thyroidectomy were adjudicated. For thyroid neoplasms, operative reports and relevant laboratory findings (i.e. tumor markers) were also used as diagnostic criteria, see **Figure 54**.

The EAC classified neoplasms according to the organ affected/tissue of origin and malignancy status, as shown in **Figure 53.**

In addition to investigator-identified cases, the Sponsor conducted 2 searches for additional cases of missed neoplasms:

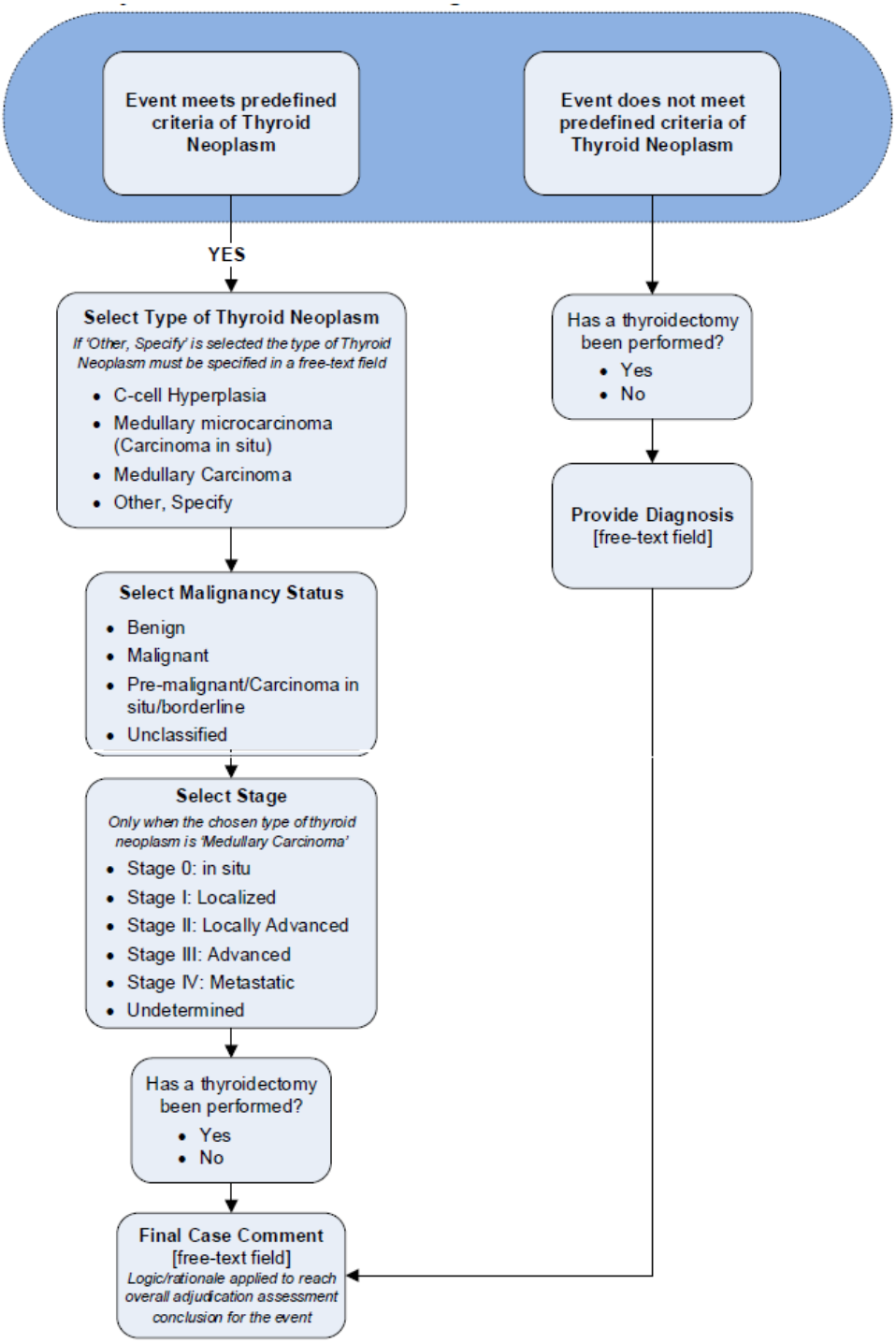
1. *Post-hoc,* MedDRA searches for all types of malignant neoplasms and for pre-selected neoplasms of malignant breast, pancreatic, prostrate, and thyroid neoplasms and malignant ad all colorectal neoplasms in all SAEs and non-serious MESIs. *Ad hoc* MedDRA searches for malignant neoplasm types for which imbalances between treatment groups were seen for adjudicated data.
2. After data base lock, SMQ search of malignant tumors *not confirmed* by the EAC as malignant neoplasm. The Sponsor conducted case reviews of the subject source data documents of the data package provided to the EAC for the individual subjects identified by the search.

Figure 53- Neoplasm event adjudication flow chart



Source: 16-1-13 Event adjudication SRS flowcharts

Figure 54- Thyroidectomy and/or thyroid neoplasm event adjudication flow chart



Source: 16-1-13 Event adjudication SRS flowcharts
\\cdsesub1\evsprod\NDA022341\0347\m5\53-clin-stud-rep\535-rep-effic-safety-stud\type-2-diabetes-cv-risk\5351-stud-rep-contr\study-report-ex2211-3748\16-1-13-special-committee-documents-3748.pdf

CMC Charter summary

The calcitonin monitoring committee (CMC) was to evaluate longitudinal changes in calcitonin, focusing on patients with persistently high levels of calcitonin while participating in particular trials.[107]

The CMC was to monitor calcitonin concentration values and other clinical information to provide recommendations to the site to coordinate necessary follow-up for the affected patients.[108]

Table 49 –Recommended action based on calcitonin level

	<20 ng/L	≥20 and <50 ng/L	≥50 and <100 ng/L	≥100
Evaluate factors leading to calcitonin elevation + calcitonin sampling q3 months	X	X		
Refer patient to thyroid specialist			X	X
Ultrasound +pentagastrin stimulation test (Europe), if + undergo surgery. In US ultrasound and FNA may be done			X	X
-if c-cell neoplasia is diagnosed, family hx of MTC or MEN 2 will be evoked and RET protooncogene analysis should be done				X
Continue drug?	Yes	Yes	Yes**	No
** if levels fluctuate around 50 ng/L without progressive rise -if level >50, discontinue drug				

Electrocardiogram Review charter

All electrocardiograms (ECGs) were reviewed centrally in LEADER. One cardiologist reviewed each 12-Lead ECG, presented by study time point. All historical, as well as the most proximate preceding ECG, were presented to allow a serial comparison at every time point in an effort to identify any new abnormalities since the last ECG(s). As appropriate, the cardiologist provided a classification of the ECG abnormality in the custom-designed ECG eCRF.

The criteria used to evaluate the ECG are shown below:

[107] LEADER, SCALE, and DUAL following trials Novo Nordisk A/S liraglutide trials LEADER® (EX2211-3748), SCALE™ (NN8022-1922, NN8022-1839, NN8022-3970), and DUAL™ (NN9068-3697, NN9068-3912, NN9068-3851, NN9068-3951, NN9068-3952, NN9068-4119, NN9068-4056) and semaglutide trial NN9924 Oral GLP-1(NN9924-3790)

[108] Patients with calcitonin>10 ng/L who were screen failures, were to be referred to a thyroid specialist and patients with calcitonin ≥50 ng/L were not to be randomized.

1. Rhythm
    a. Sinus
    b. Atrial fibrillation
    c. Other, please specify
2. Does the ECG indicate any of the following: (Select one or more) (Yes or No)
    a. Ischemia (ST changes)
    b. Infarction (eg. Q waves or ST elevation)
        i. If Yes to Infarction, location:
            1. Anterior
            2. Inferior
            3. Lateral
            4. Posterior
            5. LBBB and cannot assess location of infarction
    c. Left Bundle Branch Block (LBBB)?
    d. None of the Above
3. Other Abnormalities (Yes or No)
    a. If Yes (select all that apply):
        i. Arrhythmia (Follow-up timepoints only)
        ii. LVH
        iii. Other
4. Overall Conclusion (select ONLY ONE of the following):
    a. Normal ECG or ECG with clinically-insignificant findings (Baseline only)
    b. Normal ECG or Non-Significant Changes (Follow-up time point only)
    c. ECG findings suggestive of MI (eg, Q wave or ST elevation) - (Baseline only)
    d. New findings suggestive of MI (eg, Q Wave or ST elevation) - (Follow-up timepoint only)
    e. Other significant abnormal ECG findings (Baseline only)
    f. Other new significant abnormal ECG findings (Follow-up timepoint only)

A q wave was considered significant if:

- It was greater than 1 box in width (longer than 0.04 msec) OR is larger than ¼ of the R wave.
- Any Q wave in V2-V3 ≥0.02 sec or presence of QS complex in V2 and V3.Q wave ≥0.03 sec and ≥0.1 mV deep or presence of QS complexes in leads I, II, aVL, aVF or V4-V5-V6 in any two leads of a contiguous lead grouping (I, aVL, V6; V4-V5-V6, II, III and aVF). The same criteria are used for supplemental leads V7-V8-V9, and for the Cabrera frontal plane leads.
- R wave ≥0.04 sec in V1-V2 and R/S >1 with a concordant positive T wave in the absence of a conduction defect.

Table 50 – Time course of changes to patient flow, protocol, SAP and data handling

	2010			2011					2012						2013						2014						2015				2016			
Numerical month in a year	5 6 7	8 9 10		11 12 1	2 3 4	5 6 7	8 9 10	11 12 1	2 3 4			5 6 7	8 9 10	11 12 1	2 3 4	5 6 7	8 9 10	11 12 1	2 3 4	5 6 7		8 9 10	11 12 1	2 3 4	5 6 7	8 9 10	11 12 1		2 3 4				
Patient flow: R: 1st patient randomized **FPFV:** first patient first visit **LPR:** last patient randomized **LPLV:** last patient last visit		FPFV	R						LPR																					LPLV				
Protocol changes **A:** amendment number				A8		A20				A30					A34						A39												
SAP changes **V:** version														V2									V3										
Data handling **CB:** Code break **DL:** Database lock																																CB	DL
EAC charter changes	V1 V2 V3			V4	V5	1st EAC Adj. Event		V6											V7	V8					V9								
	-Update of MI, stroke definitions -silent MI added for adjudication -CRF updated so EAC chair could ID multiple events and combine -remove definition of prior MI						Retinopathy definition update										-Description of multiple event assessment of ECGs where the patient already has 1 pos. adjudicated MI was added -Update MI definition- ECG mm requirement for NSTEMI/STEMI was removed (no re-review) -guidance for adj. of neoplasms **-nephropathy def. update**								-Guidelines for adj. Multiple events added **-pancreatitis def. updated** **-neoplasm definition update**										

Table 51 – Total number of patients fulfilling the inclusion criteria by CV risk – FAS

	Liraglutide N=4668	Placebo N=4672
Subjects with established CV disease Age ≥ 50 years	3831 (82.1)	3767 (80.6)
a) prior myocardial infarction	1464 (31.4)	1400 (30.0)
b) prior stroke or prior transient ischemic attack	730 (15.6)	777 (16.6)
c) prior arterial revascularization	1835 (39.3)	1803 (38.6)
d) >50% stenosis on angiography	1188 (25.4)	1191 (25.5)
e) documented history of symptomatic coronary heart disease	412 (8.8)	406 (8.7)
f) documented asymptomatic cardiac ischemia	1241 (26.6)	1231 (26.3)
g) chronic heart failure NYHA II or III	653 (14.0)	652 (14.0)
h) chronic kidney failure	1185 (25.4)	1122 (24.0)
Subjects with risk factors for CV disease Age ≥60 years#	837 (17.9)	905 (19.4)
i) microalbuminuria or proteinuria	501 (10.7)	558 (11.9)
j) hypertension and left ventricular hypertrophy	248 (5.3)	251 (5.4)
k) left ventricular systolic or diastolic dysfunction	203 (4.3)	191 (4.1)
l)ankle/brachial index <0.9	110 (2.4)	116 (2.5)

N: Number of subjects, %: Proportion of subjects, CV: Cardiovascular, FAS: full analysis set.
NYHA: New York Heart Association, According to inclusion criteria no 3 in the protocol subjects are either to have age>=50 and at least one of the conditions a) to h) or age>=60 and at least one of the conditions i) to l),
#: 16 subjects who did not satisfy the inclusion criteria a) to l) have been categorized as risk factors for CV disease category. Information taken from Cardiovascular History and Complications form. It should be noted that many subjects met more than one sub-criterion and that subjects with both established cardiovascular disease and risk factors are only counted in the established cardiovascular disease group.
Source: CTR, table 10-8, page 188

Demographic characteristics for patients who experienced a primary MACE event:

Table 52- Non-cardiovascular deaths by SOC and PT terms- FAS

System Organ Class	Preferred Term	Liraglutide N (%)	Placebo N (%)	All N (%)
		4672	4668	9340
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	All	58 (1.2)	57 (1.2)	115 (1.2)
	Pancreatic carcinoma	3 (0.1)	4 (0.1)	7 (0.1)
	Lung neoplasm malignant	2 (0)	4 (0.1)	6 (0.1)
	Cholangiocarcinoma	3 (0.1)	1 (0)	4 (0)
	Hepatic cancer	3 (0.1)	1 (0)	4 (0)
	Lung cancer metastatic	2 (0)	2 (0)	4 (0)
	Non-small cell lung cancer	2 (0)	2 (0)	4 (0)
	Pancreatic carcinoma metastatic	2 (0)	2 (0)	4 (0)
	Adenocarcinoma of colon	2 (0)	1 (0)	3 (0)
	Adenocarcinoma pancreas	2 (0)	1 (0)	3 (0)
	Bronchial carcinoma	1 (0)	2 (0)	3 (0)

	Hepatocellular carcinoma	2 (0)	1 (0)	3 (0)
	Lung adenocarcinoma metastatic	1 (0)	2 (0)	3 (0)
	Plasma cell myeloma	1 (0)	2 (0)	3 (0)
	Small cell lung cancer metastatic	2 (0)	1 (0)	3 (0)
	Squamous cell carcinoma of lung	0 (0)	3 (0.1)	3 (0)
	Adenocarcinoma	0 (0)	2 (0)	2 (0)
	Adenocarcinoma gastric	1 (0)	1 (0)	2 (0)
	Glioblastoma	2 (0)	0 (0)	2 (0)
	Lung adenocarcinoma	2 (0)	0 (0)	2 (0)
	Metastases to central nervous system	2 (0)	0 (0)	2 (0)
	Metastases to peritoneum	1 (0)	1 (0)	2 (0)
	Metastatic squamous cell carcinoma	0 (0)	2 (0)	2 (0)
	Non-small cell lung cancer metastatic	1 (0)	1 (0)	2 (0)
	Esophageal adenocarcinoma	2 (0)	0 (0)	2 (0)
	Rectal cancer	1 (0)	1 (0)	2 (0)
	Rectal cancer metastatic	1 (0)	1 (0)	2 (0)
	Bladder neoplasm	0 (0)	1 (0)	1 (0)
	Central nervous system lymphoma	1 (0)	0 (0)	1 (0)
	Cerebellar tumor	0 (0)	1 (0)	1 (0)
	Chondrosarcoma metastatic	0 (0)	1 (0)	1 (0)
	Chronic myelomonocytic leukemia	0 (0)	1 (0)	1 (0)
	Colon cancer metastatic	1 (0)	0 (0)	1 (0)
	Gastric cancer	0 (0)	1 (0)	1 (0)
	Gastrointestinal stromal tumor	0 (0)	1 (0)	1 (0)
	Glioblastoma multiforme	1 (0)	0 (0)	1 (0)
	Intraductal papillary mucinous neoplasm	0 (0)	1 (0)	1 (0)
	Laryngeal squamous cell carcinoma	0 (0)	1 (0)	1 (0)
	Lung adenocarcinoma stage IV	0 (0)	1 (0)	1 (0)
	Lung carcinoma cell type unspecified stage III	1 (0)	0 (0)	1 (0)
	Lung squamous cell carcinoma stage IV	1 (0)	0 (0)	1 (0)
	Malignant melanoma	1 (0)	0 (0)	1 (0)
	Metastases to lung	1 (0)	0 (0)	1 (0)
	Metastatic neoplasm	1 (0)	0 (0)	1 (0)
	Metastatic renal cell carcinoma	0 (0)	1 (0)	1 (0)
	Myelodysplastic syndrome	0 (0)	1 (0)	1 (0)
	Neoplasm skin	1 (0)	0 (0)	1 (0)
	Neuroendocrine carcinoma	0 (0)	1 (0)	1 (0)

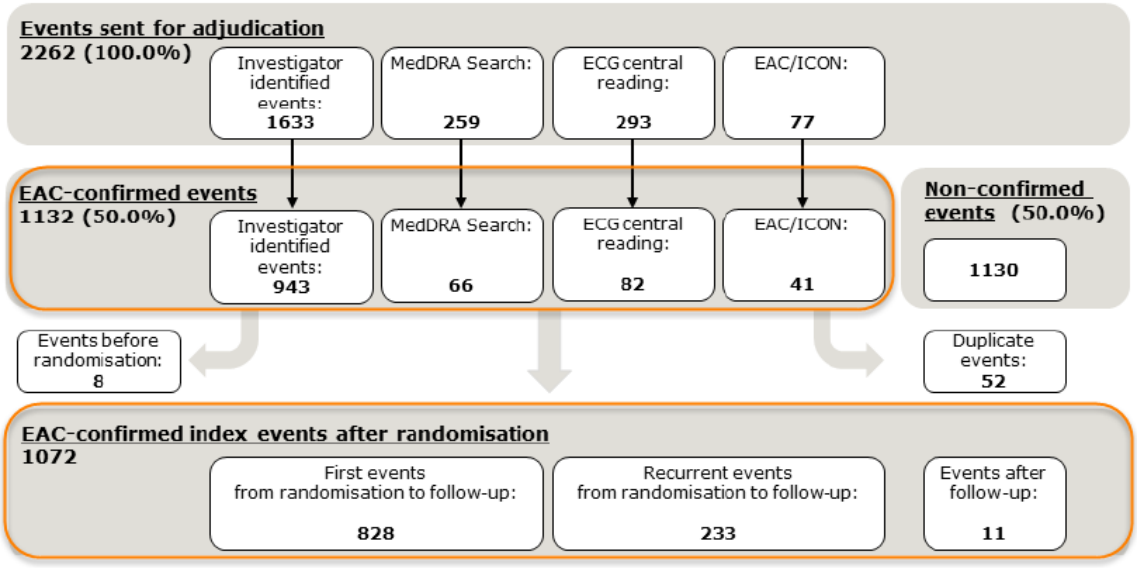
	of the skin			
	Non-Hodgkin's lymphoma	0 (0)	1 (0)	1 (0)
	Esophageal adenocarcinoma metastatic	1 (0)	0 (0)	1 (0)
	Esophageal cancer metastatic	0 (0)	1 (0)	1 (0)
	Esophageal squamous cell carcinoma stage IV	0 (0)	1 (0)	1 (0)
	Oropharyngeal cancer stage IV	1 (0)	0 (0)	1 (0)
	Ovarian cancer metastatic	0 (0)	1 (0)	1 (0)
	Pancreatic neoplasm	1 (0)	0 (0)	1 (0)
	Phyllodes tumour	0 (0)	1 (0)	1 (0)
	Pleural mesothelioma	1 (0)	0 (0)	1 (0)
	Prostate cancer metastatic	0 (0)	1 (0)	1 (0)
	Small cell lung cancer	0 (0)	1 (0)	1 (0)
	Small intestine carcinoma	1 (0)	0 (0)	1 (0)
	Small intestine carcinoma metastatic	1 (0)	0 (0)	1 (0)
	Squamous cell carcinoma	1 (0)	0 (0)	1 (0)
	Transitional cell carcinoma metastatic	1 (0)	0 (0)	1 (0)
Infections and infestations	All	28 (0.6)	35 (0.7)	63 (0.7)
	Pneumonia	11 (0.2)	8 (0.2)	19 (0.2)
	Sepsis	5 (0.1)	6 (0.1)	11 (0.1)
	Septic shock	0 (0)	5 (0.1)	5 (0.1)
	Bronchopneumonia	1 (0)	2 (0)	3 (0)
	Bronchitis	0 (0)	2 (0)	2 (0)
	Urosepsis	1 (0)	1 (0)	2 (0)
	Abdominal abscess	1 (0)	0 (0)	1 (0)
	Device related infection	0 (0)	1 (0)	1 (0)
	Diverticulitis	1 (0)	0 (0)	1 (0)
	Gangrene	0 (0)	1 (0)	1 (0)
	Infectious colitis	1 (0)	0 (0)	1 (0)
	Infective exacerbation of chronic obstructive airways disease	1 (0)	0 (0)	1 (0)
	Liver abscess	1 (0)	0 (0)	1 (0)
	Lobar pneumonia	1 (0)	0 (0)	1 (0)
	Localized infection	0 (0)	1 (0)	1 (0)
	Lung infection	0 (0)	1 (0)	1 (0)
	Meningitis	0 (0)	1 (0)	1 (0)
	Necrotising fasciitis	1 (0)	0 (0)	1 (0)
	Peritonitis	1 (0)	0 (0)	1 (0)
	Pneumonia viral	1 (0)	0 (0)	1 (0)
	Pyelonephritis	0 (0)	1 (0)	1 (0)
	Pyelonephritis acute	1 (0)	0 (0)	1 (0)
	Staphylococcal bacteremia	0 (0)	1 (0)	1 (0)
	Staphylococcal infection	0 (0)	1 (0)	1 (0)
	Tracheobronchitis	0 (0)	1 (0)	1 (0)
	Urinary tract infection	0 (0)	1 (0)	1 (0)
	Zygomycosis	0 (0)	1 (0)	1 (0)

Respiratory, thoracic and mediastinal disorders	All	16 (0.3)	14 (0.3)	30 (0.3)
	Respiratory failure	4 (0.1)	4 (0.1)	8 (0.1)
	Chronic obstructive pulmonary disease	2 (0)	3 (0.1)	5 (0.1)
	Pneumonia aspiration	2 (0)	1 (0)	3 (0)
	Respiratory distress	3 (0.1)	0 (0)	3 (0)
	Acute respiratory failure	2 (0)	0 (0)	2 (0)
	Asphyxia	0 (0)	2 (0)	2 (0)
	Acute respiratory distress syndrome	1 (0)	0 (0)	1 (0)
	Aspiration	1 (0)	0 (0)	1 (0)
	Asthma	0 (0)	1 (0)	1 (0)
	Emphysema	0 (0)	1 (0)	1 (0)
	Hypoxia	0 (0)	1 (0)	1 (0)
	Pleural effusion	0 (0)	1 (0)	1 (0)
	Pulmonary fibrosis	1 (0)	0 (0)	1 (0)
Cardiac disorders	All	10 (0.2)	12 (0.3)	22 (0.2)
	Cardiac arrest	2 (0)	4 (0.1)	6 (0.1)
	Cardiac failure	1 (0)	2 (0)	3 (0)
	Cardio-respiratory arrest	1 (0)	1 (0)	2 (0)
	Cardiogenic shock	2 (0)	0 (0)	2 (0)
	Cardiopulmonary failure	0 (0)	2 (0)	2 (0)
	Myocardial infarction	2 (0)	0 (0)	2 (0)
	Acute myocardial infarction	0 (0)	1 (0)	1 (0)
	Angina unstable	1 (0)	0 (0)	1 (0)
	Atrial fibrillation	0 (0)	1 (0)	1 (0)
	Cardiac failure chronic	1 (0)	0 (0)	1 (0)
	Cardiac failure congestive	0 (0)	1 (0)	1 (0)
Renal and urinary disorders	All	14 (0.3)	7 (0.1)	21 (0.2)
	Chronic kidney disease	7 (0.1)	4 (0.1)	11 (0.1)
	Acute kidney injury	2 (0)	2 (0)	4 (0)
	Renal failure	3 (0.1)	0 (0)	3 (0)
	Azotaemia	1 (0)	0 (0)	1 (0)
	Hematuria	1 (0)	0 (0)	1 (0)
	Urinary bladder polyp	0 (0)	1 (0)	1 (0)
Injury, poisoning and procedural complications	All	8 (0.2)	12 (0.3)	20 (0.2)
	Road traffic accident	3 (0.1)	4 (0.1)	7 (0.1)
	Fall	2 (0)	3 (0.1)	5 (0.1)
	Subdural hematoma	0 (0)	2 (0)	2 (0)
	Carbon monoxide poisoning	1 (0)	0 (0)	1 (0)
	Chest injury	1 (0)	0 (0)	1 (0)
	Fibula fracture	0 (0)	1 (0)	1 (0)
	Gunshot wound	0 (0)	1 (0)	1 (0)
	Head injury	1 (0)	0 (0)	1 (0)
	Respiratory fume inhalation disorder	0 (0)	1 (0)	1 (0)
General disorders and	All	4 (0.1)	11 (0.2)	15 (0.2)

administration site conditions				
	Death	3 (0.1)	3 (0.1)	6 (0.1)
	Multi-organ failure	1 (0)	4 (0.1)	5 (0.1)
	Sudden death	0 (0)	2 (0)	2 (0)
	General physical health deterioration	0 (0)	1 (0)	1 (0)
	Sudden cardiac death	0 (0)	1 (0)	1 (0)
Nervous system disorders	All	6 (0.1)	5 (0.1)	11 (0.1)
	Cerebrovascular accident	2 (0)	1 (0)	3 (0)
	Hemorrhage intracranial	1 (0)	1 (0)	2 (0)
	Encephalopathy	0 (0)	1 (0)	1 (0)
	Hepatic encephalopathy	1 (0)	0 (0)	1 (0)
	Hypoglycemic unconsciousness	0 (0)	1 (0)	1 (0)
	Ischemic stroke	0 (0)	1 (0)	1 (0)
	Multiple system atrophy	1 (0)	0 (0)	1 (0)
	Parkinson's disease	1 (0)	0 (0)	1 (0)
Gastrointestinal disorders	All	4 (0.1)	4 (0.1)	8 (0.1)
	Gastrointestinal hemorrhage	1 (0)	2 (0)	3 (0)
	Intestinal ischemia	1 (0)	1 (0)	2 (0)
	Intestinal infarction	1 (0)	0 (0)	1 (0)
	Retroperitoneal hemorrhage	0 (0)	1 (0)	1 (0)
	Upper gastrointestinal hemorrhage	1 (0)	0 (0)	1 (0)
Hepatobiliary disorders	All	5 (0.1)	3 (0.1)	8 (0.1)
	Cholecystitis acute	1 (0)	1 (0)	2 (0)
	Chronic hepatic failure	0 (0)	2 (0)	2 (0)
	Cholecystitis	1 (0)	0 (0)	1 (0)
	Cirrhosis alcoholic	1 (0)	0 (0)	1 (0)
	Hepatic failure	1 (0)	0 (0)	1 (0)
	Hepatic steatosis	1 (0)	0 (0)	1 (0)
Metabolism and nutrition disorders	All	2 (0)	3 (0.1)	5 (0.1)
	Dehydration	0 (0)	1 (0)	1 (0)
	Diabetes mellitus inadequate control	0 (0)	1 (0)	1 (0)
	Failure to thrive	1 (0)	0 (0)	1 (0)
	Hyperkalemia	1 (0)	0 (0)	1 (0)
	Metabolic acidosis	0 (0)	1 (0)	1 (0)
Psychiatric disorders	All	1 (0)	4 (0.1)	5 (0.1)
	Completed suicide	1 (0)	3 (0.1)	4 (0)
	Delirium	0 (0)	1 (0)	1 (0)
Skin and subcutaneous tissue disorders	All	1 (0)	1 (0)	2 (0)
	Diabetic foot	0 (0)	1 (0)	1 (0)
	Skin ulcer	1 (0)	0 (0)	1 (0)
Surgical and medical procedures	All	1 (0)	0 (0)	1 (0)

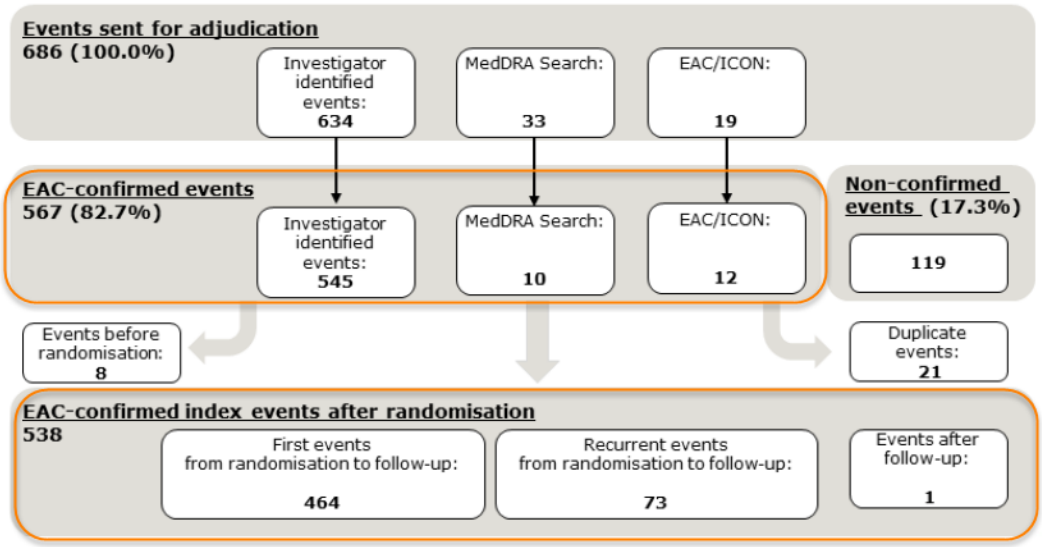
	Peripheral artery stent insertion	1 (0)	0 (0)	1 (0)
Vascular disorders	All	0 (0)	1 (0)	1 (0)
	Hypovolemic shock	0 (0)	1 (0)	1 (0)
All	All	158 (3.4)	169 (3.6)	327 (3.5)
Source: ADADJ.xpt ADMEVC='DEATH', MCRITYN = 'N', AEONTRFL="Y" Although there were 331 patients who died from non-CV death, PT and SOC terms were missing from 4 patients randomized to the liraglutide arm. Therefore there is only 158 patients for the liraglutide arm in this table, while there are 162 patients who were adjudicated to die from non-cardiovascular causes in this arm.				

Figure 55 - Adjudication flow for acute coronary syndrome



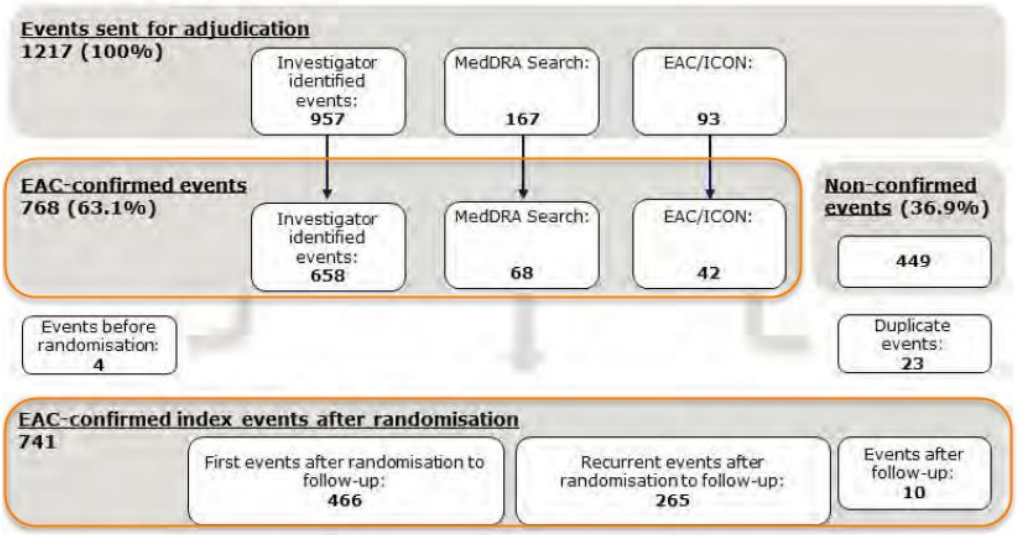
Note: Full analysis set. Non-confirmed events include a total of 6 events, where the EAC was unable to adjudicate the event due to insufficient information.
Abbreviations: EAC: event adjudication committee; ECG: electrocardiogram; ICON: adjudication vendor (contract research organisation); MedDRA: Medical Dictionary for Regulatory Activities.
Source: CSR, Figure 12-14, page 333

Figure 56 - Adjudication flow for cerebrovascular events



Note: Full analysis set.
Abbreviations: EAC: event adjudication committee; ICON: adjudication vendor (contract research organisation); MedDRA: Medical Dictionary for Regulatory Activities.
Source: CSR, Figure 12-17, page 339

Figure 57 - Adjudication flow for heart failure requiring hospitalization events

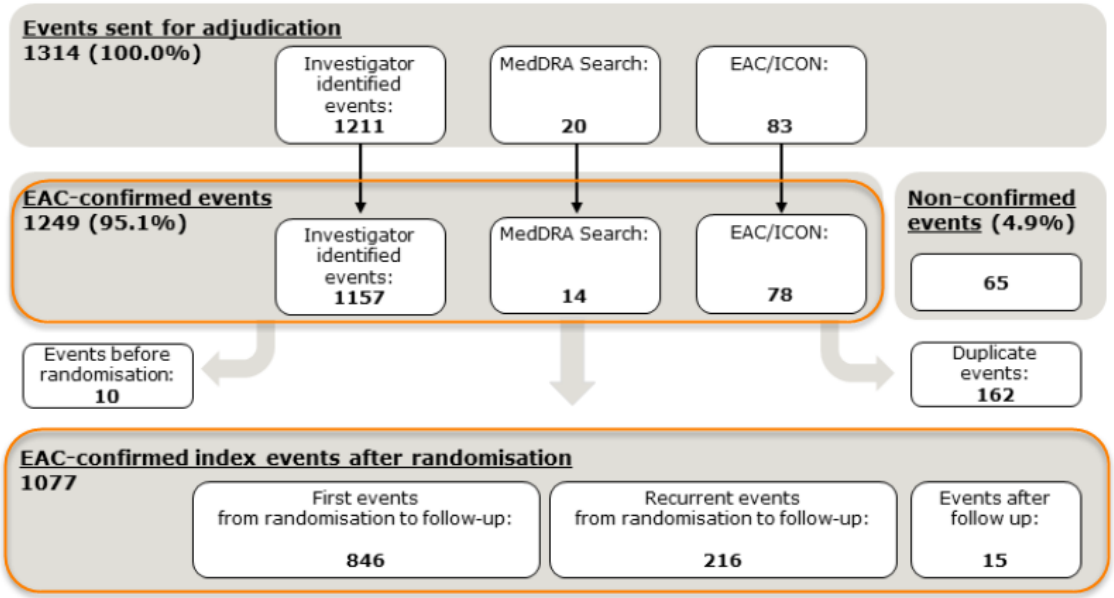


Note: Full analysis set. Non-confirmed events include 4 events where the EAC was unable to adjudicate the event due to insufficient information. Events with EAC onset date from randomisation and onwards are included (of these, 10 events had onset from follow-up visit to DBL and were not included in the statistical analyses of events).

Abbreviations: EAC: event adjudication committee; ICON: adjudication vendor (contract research organisation); MedDRA: Medical Dictionary for Regulatory Activities.

CTR: Figure 12-20, page 344

Figure 58 - Adjudication flow for coronary revascularization



Note: Full analysis set. Non-confirmed events include a total of 1 event, where the EAC was unable to adjudicate the event due to insufficient information. **Abbreviations:** EAC: event adjudication committee; ICON: adjudication vendor (contract research organisation); MedDRA: Medical Dictionary for Regulatory Activities.

Source: CTR, figure 12-22, page 347

Table 53 – Time to EAC confirmed MACE; expanded MACE, components of expanded MACE, all-cause mortality, non-CV death and the composite

hospitalization for heart failrue for all cause death excluding deaths classified as 'unknown'

	Liraglutide N (%)	Placebo N (%)	Total N (%)	Lira/placebo Hazard ratio	95% CI	Test for HR=1.0 two sided
FAS	4668	4672	9340			
Primary endpoint: MACE*	546 (11.7)	624 (13.4)	1170 (12.5)	0.867	0.773, 0.973	0.015
Expanded MACE^	895 (19.2)	1000 (21.4)	1895 (20.3)	0.884	0.807, 0.967	0.007
Components of expanded MACE						
Cardiovascular death	149 (3.2)	197 (4.2)	346 (3.7)	0.752	0.608, 0.930	0.009
Non-fatal stroke	159 (3.4)	177 (3.8)	336 (3.6)	0.894	0.721, 1.107	0.303
Non-fatal MI	281 (6.0)	317 (6.8)	598 (6.4)	0.878	0.747, 1.031	0.111
Hospitalization for unstable angina pectoris	122 (2.6)	124 (2.7)	246 (2.6)	0.980	0.763, 1.258	0.872
Coronary revascularization	405 (8.7)	441 (9.4)	846 (9.1)	0.912	0.797, 1.044	0.180
Hospitalization for heart failure	218 (4.7)	248 (5.3)	466 (5.0)	0.872	0.727, 1.046	0.140
Other secondary endpoints						
All cause death	311 (6.7)	366 (7.8)	677 (7.2)	0.845	0.726, 0.983	0.029
Non-cardiovascular death	162 (3.5)	169 (3.6)	331 (3.5)	0.952	0.768, 1.181	0.656
Composite of hosp. for heart failure/all cause death (post hoc analysis)	481 (10.3)	549 (11.8)	1030 (11.0)	0.869	0.769, 0.982	0.024

FAS: Full analysis set. MACE: major adverse cardiovascular event, EAC: event adjudication committee, CI: confidence interval, CV: cardiovascular, hosp: hospitalization, HR: hazard ratio, N: number; (%) percent of patients with a first EAC confirmed event between randomization date and follow up date, MI: myocardial infarction. Events which occur before randomization date are not used for defining first event. NOTE: for this table, component events of MACE (and expanded MACE) do NOT sum to total number of MACE (exp. MACE).
*Contains the first MACE event which includes: cardiovascular death, non-fatal MI and non-fatal stroke
^contains the first expanded MACE event, which includes: cardiovascular death, nonfatal MI, nonfatal stroke, coronary revascularization, hospitalization for unstable angina pectoris or hospitalization for heart failure

Source: Question 1 in information request dated March 21, 2017:
\\CDSESUB1\evsprod\NDA022341\0362\m1\us\resp-ir-20170314.pdf

Table 54 – Exploratory analysis of arrhythmia-related preferred terms identified in the adverse event dataset

	Lira (N = 4668)			*Placebo (N = 4672)*		
PT	*Events*	*Number of subjects*	*Proportion (%)*	*Events*	*Number of subjects*	*Proportion (%)*
Ventricular arrhythmia	3	3	0.06	0	0	0
Defect conduction intraventricular	2	2	0.04	0	0	0
Sinus arrest	2	2	0.04	0	0	0
Arrhythmia supraventricular	1	1	0.02	0	0	0
Tachyarrhythmia	1	1	0.02	0	0	0
Ventricular dyssynchrony	1	1	0.02	0	0	0
Sinus tachycardia	6	6	0.13	3	3	0.06
Tachycardia	14	13	0.28	7	7	0.15
Ventricular tachycardia	31	20	0.43	14	11	0.24
Supraventricular tachycardia	13	13	0.28	10	8	0.17
Atrioventricular block first degree	11	11	0.24	7	7	0.15
Ventricular extrasystoles	16	14	0.3	9	9	0.19
Bundle branch block right	15	15	0.32	12	11	0.24
Sinus node dysfunction	12	12	0.26	9	9	0.19
Supraventricular extrasystoles	4	4	0.09	3	3	0.06
Atrioventricular block complete	11	11	0.24	9	9	0.19
Arrhythmia	14	13	0.28	11	11	0.24

Atrioventricular dissociation	1	1	0.02	1	1	0.02
Bifascicular block	2	2	0.04	2	2	0.04
Extrasystoles	5	5	0.11	5	5	0.11
Wolff-Parkinson-White syndrome	1	1	0.02	1	1	0.02
Bundle branch block left	13	12	0.26	13	13	0.28
Atrial fibrillation	164	134	2.87	188	159	3.4
Atrial flutter	24	21	0.45	28	26	0.56
Bradycardia	14	14	0.3	19	18	0.39
Atrioventricular block	3	3	0.06	5	5	0.11
Ventricular fibrillation	4	4	0.09	7	7	0.15
Atrioventricular block second degree	5	5	0.11	9	9	0.19
Atrial tachycardia	2	2	0.04	4	4	0.09
Sinus bradycardia	4	4	0.09	11	10	0.21
Atrioventricular conduction time shortened	0	0	0	1	1	0.02
Bradyarrhythmia	0	0	0	1	1	0.02
Bundle branch block bilateral	0	0	0	1	1	0.02
Nodal arrhythmia	0	0	0	1	1	0.02
Nodal rhythm	0	0	0	1	1	0.02
Rhythm idioventricular	0	0	0	1	1	0.02
Ventricular tachyarrhythmia	0	0	0	1	1	0.02
Tachycardia paroxysmal	0	0	0	2	2	0.04

Source: adae.xpt, where AEONTRFL-y and AEBODSYS= 'cardiac disorders', MedDRA version 18

Table 55- patients identified as meeting SMQ of acute renal failure

AESOC	AEDECOD	Liraglutide n=4668		Placebo n=4672		All n=9340	
		Subjects N	Proportion (%)	Subjects N	Proportion (%)	Subjects N	Proportion (%)
Renal and urinary disorders	Acute kidney injury	127	3	114	2	241	9340
	Proteinuria	75	2	113	2	188	2
	Renal failure	31	1	55	1	86	1
	Renal impairment	29	1	20	0	49	1
	Renal tubular necrosis	1	0	5	0	6	0
	Albuminuria	3	0	2	0	5	0
	Azotaemia	3	0	2	0	5	0
	Nephropathy toxic	2	0	3	0	5	0
	Tubulointerstitial nephritis	2	0	3	0	5	0
	Acute prerenal failure	1	0	2	0	3	0

	Oliguria	1	0	1	0	2	0
	Nephritis	1	0	0	0	1	0
	All	276	6	320	7	596	6
Investigations	Blood creatinine increased	39	1	35	1	74	1
	Glomerular filtration rate decreased	5	0	1	0	6	0
	Blood urea increased	1	0	1	0	2	0
	Creatinine renal clearance decreased	0	0	2	0	2	0
	Protein urine present	2	0	0	0	2	0
	Urine output decreased	0	0	1	0	1	0
	All	47	1	40	1	87	1
All	All	323	7	360	8	683	7
Source: MAED data set of SMQs, with selection of AEONFL, FAS, SMQ acute renal failure							

Table 56- Patients identified as meeting SMQ of chronic renal failure

AESOC	AEDECOD	Liraglutide N=4668		Placebo N=4672		All N=9340	
		Subjects N	Proportion (%)	Subjects N	Proportion (%)	Subjects N	Proportion (%)
Renal and urinary disorders	Proteinuria	75	2	113	2	188	2
	Chronic kidney disease	87	2	88	2	175	2
	Microalbuminuria	52	1	58	1	110	1
	Diabetic nephropathy	39	1	55	1	94	1
	Renal failure	31	1	55	1	86	1
	Nephropathy	28	1	40	1	68	1
	Albuminuria	3	0	2	0	5	0
	Azotaemia	3	0	2	0	5	0
	Nephropathy toxic	2	0	3	0	5	0
	Tubulointerstitial nephritis	2	0	3	0	5	0
	Nephrotic syndrome	3	0	1	0	4	0
	Fibrillary glomerulonephritis	1	0	0	0	1	0
	Focal segmental glomerulosclerosis	0	0	1	0	1	0
	Glomerulonephritis membranous	1	0	0	0	1	0
	Glomerulosclerosis	1	0	0	0	1	0
	Intercapillary glomerulosclerosis	0	0	1	0	1	0
	Leukocyturia	0	0	1	0	1	0
	Mesangioproliferative	0	0	1	0	1	0

	glomerulonephritis						
	Renal atrophy	0	0	1	0	1	0
	All	328	7	425	9	753	8
Investigations	Blood creatinine increased	39	1	35	1	74	1
	Urine albumin/creatinine ratio increased	15	0	12	0	27	0
	Albumin urine present	9	0	5	0	14	0
	Blood potassium increased	10	0	3	0	13	0
	Glomerular filtration rate decreased	5	0	1	0	6	0
	Blood urea increased	1	0	1	0	2	0
	Creatinine renal clearance decreased	0	0	2	0	2	0
	Protein urine present	2	0	0	0	2	0
	Urine output decreased	0	0	1	0	1	0
	All	81	2	60	1	141	2
Metabolism and nutrition disorders	Hyperkalemia	23	0	34	1	57	1
	Hyponatremia	7	0	10	0	17	0
	Metabolic acidosis	2	0	3	0	5	0
	Hypoalbuminemia	1	0	3	0	4	0
	Hypocalcaemia	2	0	1	0	3	0
	Hypervolemia	2	0	0	0	2	0
	Hyperphosphatemia	1	0	0	0	1	0
	All	38	1	51	1	89	1
Cardiac disorders	Pericarditis	1	0	6	0	7	0
	Pericarditis uremic	1	0	1	0	2	0
	All	2	0	7	0	9	0
Nervous system disorders	Encephalopathy	3	0	3	0	6	0
	Uremic encephalopathy	2	0	0	0	2	0
	All	5	0	3	0	8	0
Blood and lymphatic system disorders	Normochromic normocytic anemia	2	0	3	0	5	0
	Hemorrhagic diathesis	0	0	1	0	1	0
	Nephrogenic anemia	0	0	1	0	1	0
	All	2	0	5	0	7	0
Endocrine disorders	Hyperparathyroidism secondary	1	0	2	0	3	0
	Hyperparathyroidism	1	0	1	0	2	0
	All	2	0	3	0	5	0
Musculoskeletal and connective tissue disorders	Bone cyst	1	0	2	0	3	0
	All	1	0	2	0	3	0

Injury, poisoning and procedural complications	Dialysis related complication	1	0	0	0	1	0
	All	1	0	0	0	1	0
Vascular disorders	Vascular calcification	0	0	1	0	1	0
	All	0	0	1	0	1	0
All	All	460	10	557	12	1017	11
Source: MAED data set of SMQs, with selection of AEONFL, FAS, SMQ chronic renal failure							

Table 57 – EAC adjudicated death due to renal disease

Subject ID	Investigator reported term	Preferred term	Baseline eGFR MDRD	Treatment	Trial day	Narrative
(b) (6)	None	None	Mild (EGFR<90)	Liraglutide	1363	64 year old male seen in the emergency department for pulmonary edema. Patient was treated with IV fluids and CPAP and elevated troponin. ER note states that there was acute on chronic renal failure observed that worsened with a clinical presentation of oliguria and almost anuria. Patient was intubated and was started on pressors due to hypotension. Patient was started on dialysis due to significant pulmonary congestion and anuria and electrolyte deterioration. Patient continued with hypotension despite pressors and died.
	ACUTE RENAL FAILURE	Acute kidney injury	Severe (EGFR<30)	Liraglutide	38	66 year old woman with worsening creatinine from Sept 2011 (Cr 1.95 mg/dL) to 2.41 mg/dL (23 Dec 2011) and patient noting swelling of face, body, limbs with decreased urine output, and dyspnea. Patient was advised to have dialysis but refused. Creatinine increased to 5.7 mg/dL (31 Dec 2011). Patient became anuric and was bedridden, and died. No autopsy was performed.
	ACUTE RENAL FAILURE	Acute kidney injury	Moderate (EGFR<60)	Liraglutide	222	66 year old male was admitted to the hospital with acute renal failure. Patient's condition deteriorated while in the hospital and the patient died. On the death certificate it was reported that patient died a natural death due to renal failure. Unable to obtain medical records.
	CAUSE FOR DEATH IN THE DEATH CERTIFICATE SHOWS NATURAL CAUSES	Death	Moderate (EGFR<60)	Liraglutide	991	68 year old woman who a month prior to death was hospitalized due to kidney problems, swollen legs, body pain and shortness of breath and was started on Lasix. Patient passed away, no autopsy was performed. Death certificate states the patient died of natural causes.
	RENAL TERMINAL	Chronic	Severe	Liraglutide	1267	56 year old male who was hospitalized due to

Subject ID	Investigator reported term	Preferred term	Baseline eGFR MDRD	Treatment	Trial day	Narrative
	FAILURE	kidney disease	(EGFR<30)			"renal terminal failure." The patient refused renal replacement therapy and had uremic symptoms. The cause of death was reported as uremic syndrome.
(b) (6)	WORSENING OF CHRONIC RENAL FAILURE	Chronic kidney disease	Severe (EGFR<30)	Liraglutide	762	78 year old male with elevated creatinine of 5.07 mg/dL (range 0.67-1.17) who presented with community acquired pneumonia 2 weeks later. Patient was hospitalized due to vomiting and diarrhea. Patient had dyspnea, orthopnea and edema. Lasix and ceftriaxone was started. Patient as started on pressors due to hypotension. Patient developed cardiac arrest and died. No autopsy was performed.
	DEATH FROM CHRONIC RENAL FAILURE	Chronic kidney disease	Severe (EGFR<30)	Liraglutide	509	67 year old woman with history of chronic renal failure on peritoneal dialysis with previous events of peritonitis (treated with antibiotics), was reported as dying at home. In the days prior to the event the patient had fatigue, weakness, anorexia and anuria. No autopsy was performed. The cause of death was chronic renal failure.
	UREMIC SYNDROME	Azotaemia	Moderate (EGFR<60)	Liraglutide	653	64 year old woman who was hospitalized due to pedal edema, dyspnea and was on ventilator (details were unknown by the family). Seven days later the patient died. The cause of death was reported as uremic syndrome due to chronic renal failure. Autopsy was not performed.
	None	None	Moderate (EGFR<60)	Placebo	719	Patient was hospitalized for implantable cardiac device not firing for an episode of ventricular tachycardia. Patient was discharged and readmitted 2 weeks later due to chest pain and palpitations. Patient was admitted to the hospital and discharged. The patient was readmitted and died. The cause of death was asystolic cardiac arrest due to acute hyperkalemia, acute renal failure, vascular disease, type 2 diabetes mellitus, and left ventricular systolic dysfunction.
	WORSENING OF CHRONIC RENAL FAILURE	Chronic kidney disease	Severe (EGFR<30)	Placebo	856	72 year old woman who was hospitalized for a stroke. During hospitalization, worsening renal failure was noted and patient was advised to start renal replacement therapy, but patient refused. Patient subsequently had a myocardial infarction. Patient died, and death certificate was reported acute myocardial infarction which was considered secondary to chronic renal failure. Hypertension and diabetes were also mentioned as cause of death.
	CHRONIC KIDNEY DISEASE STAGE 5	Chronic kidney disease	Severe (EGFR<30)	Placebo	749	72 year old male who passed away in nursing home due to end stage renal disease. No further details available.
	DEATH DUE TO	Chronic	Severe	Placebo	749	

Subject ID	Investigator reported term	Preferred term	Baseline eGFR MDRD	Treatment	Trial day	Narrative
	END STAGE RENAL DISEASE	kidney disease	(EGFR<30)			
(b) (6)	CUTE RENAL AILURE	Acute kidney injury	Severe (EGFR<30)	Placebo	356	83 year old female experienced acute renal failure and bradycardia and was admitted to the hospital. Patient had recent hospitalizations for urinary tract infection. Patient had increased weakness and difficulty taking care of herself. Patient was hospitalized and was noted to have a peak creatinine of 5.3 mg/dL, elevated CK, elevated LFTs, elevated brain natriuretic peptide. Patient was given gentle IV fluids. Patient died during hospitalization and cause of death in death certificate was documented as acute renal failure, chronic renal failure, diabetes mellitus type II. Other significant conditions contributing to death, but not resulting in underlying cause were atrial fibrillation with bradycardia, asthma and dilated cardiomyopathy. No autopsy was performed.
	ND STAGE ENAL DISEASE	Chronic kidney disease	Severe (EGFR<30)	Placebo	873	72 year old woman who was previously hospitalized due to worsening renal failure, end stage renal disease (started on dialysis), and aortic valve endocarditis. Patient was noted to be unresponsive in asystole. The death certificate states the cause of death as end stage renal disease. No autopsy was performed.

*Events were identified by EAC, not investigator; therefore there are no available investigator terms nor PT terms.

Table 58 – Preferred terms under the system organ class of Eye disorders- FAS

	Lira (N = 4669)			*Placebo (N = 4672)*		
Eye disorders SOC PT	*Events*	*Number of subjects*	*Proportion (%)*	*Events*	*Number of subjects*	*Proportion (%)*
Eye disorders (SOC)	372	267	5.72	364	273	5.84
Diabetic retinopathy	118	109	2.33	105	103	2.2
Cataract	84	71	1.52	92	79	1.69
Vitreous hemorrhage	25	22	0.47	11	10	0.21
Macular edema	11	9	0.19	11	10	0.21
Retinopathy	9	9	0.19	13	10	0.21
Diabetic retinal edema	9	8	0.17	9	8	0.17
Glaucoma	5	5	0.11	8	8	0.17
Diplopia	4	4	0.09	4	4	0.09
Retinal vein occlusion	5	4	0.09	3	3	0.06
Retinopathy hemorrhagic	4	4	0.09	1	1	0.02
Retinopathy hypertensive	4	4	0.09	8	8	0.17
Retinopathy proliferative	4	4	0.09	5	4	0.09
Vision blurred	4	4	0.09	9	9	0.19
Age-related macular	3	3	0.06	1	1	0.02

degeneration						
Dry eye	3	3	0.06	4	4	0.09
Macular fibrosis	3	3	0.06	4	4	0.09
Retinal artery occlusion	3	3	0.06	3	3	0.06
Retinal detachment	6	3	0.06	1	1	0.02
Retinal hemorrhage	3	3	0.06	2	2	0.04
Vitreous detachment	3	3	0.06	1	1	0.02
Amaurosis	2	2	0.04	0	0	0
Arteriosclerotic retinopathy	2	2	0.04	3	3	0.06
Astigmatism	2	2	0.04	0	0	0
Blindness unilateral	2	2	0.04	1	1	0.02
Chorioretinopathy	2	2	0.04	0	0	0
Conjunctivitis allergic	2	2	0.04	1	1	0.02
Eye hemorrhage	2	2	0.04	3	3	0.06
Eye pain	2	2	0.04	0	0	0
Eyelid edema	2	2	0.04	0	0	0
Lacrimation increased	2	2	0.04	0	0	0
Maculopathy	2	2	0.04	3	3	0.06
Optic ischemic neuropathy	2	2	0.04	4	3	0.06
Retinal aneurysm	2	2	0.04	1	1	0.02
Retinal infarction	2	2	0.04	0	0	0
Visual acuity reduced	2	2	0.04	2	2	0.04
Visual impairment	2	2	0.04	0	0	0
Vitreous adhesions	2	2	0.04	0	0	0
Aphakia	1	1	0.02	0	0	0
Autoimmune uveitis	1	1	0.02	0	0	0
Blepharitis	1	1	0.02	0	0	0
Cataract diabetic	2	1	0.02	0	0	0
Cataract nuclear	1	1	0.02	1	1	0.02
Conjunctival bleb	1	1	0.02	0	0	0
Conjunctival hemorrhage	1	1	0.02	2	1	0.02
Conjunctival irritation	1	1	0.02	0	0	0
Cystoid macular edema	1	1	0.02	1	1	0.02
Diabetic blindness	1	1	0.02	1	1	0.02
Dry age-related macular degeneration	1	1	0.02	0	0	0
Eyelid ptosis	1	1	0.02	0	0	0
Iridocyclitis	1	1	0.02	0	0	0
Lens disorder	1	1	0.02	0	0	0
Macular degeneration	1	1	0.02	4	4	0.09
Macular pigmentation	1	1	0.02	0	0	0
Macular rupture	1	1	0.02	0	0	0
Open angle glaucoma	1	1	0.02	4	4	0.09
Papilloedema	1	1	0.02	0	0	0

Retinal artery embolism	1	1	0.02	1	1	0.02
Retinal degeneration	2	1	0.02	2	2	0.04
Retinal edema	1	1	0.02	0	0	0
Retinal vein thrombosis	1	1	0.02	0	0	0
Ulcerative keratitis	1	1	0.02	0	0	0
Uveitis	1	1	0.02	0	0	0
Vitreous floaters	1	1	0.02	2	2	0.04
Angle closure glaucoma	0	0	0	1	1	0.02
Blepharochalasis	0	0	0	1	1	0.02
Cataract cortical	0	0	0	2	2	0.04
Cataract subcapsular	0	0	0	1	1	0.02
Corneal erosion	0	0	0	1	1	0.02
Dacryostenosis acquired	0	0	0	2	2	0.04
Detachment of macular retinal pigment epithelium	0	0	0	1	1	0.02
Ectropion	0	0	0	1	1	0.02
Episcleritis	0	0	0	1	1	0.02
Exfoliation syndrome	0	0	0	1	1	0.02
Eye pruritus	0	0	0	1	1	0.02
Eye swelling	0	0	0	1	1	0.02
Eyelid cyst	0	0	0	2	1	0.02
Iritis	0	0	0	1	1	0.02
Keratopathy	0	0	0	1	1	0.02
Neovascular age-related macular degeneration	0	0	0	1	1	0.02
Ocular hyperaemia	0	0	0	1	1	0.02
Ocular hypertension	0	0	0	2	2	0.04
Ophthalmoplegia	0	0	0	1	1	0.02
Optic atrophy	0	0	0	1	1	0.02
Optic nerve infarction	0	0	0	1	1	0.02
Pterygium	0	0	0	1	1	0.02
Retinal dystrophy	0	0	0	1	1	0.02
Retinal vascular occlusion	0	0	0	1	1	0.02
Retinoschisis	0	0	0	1	1	0.02
Scleral hemorrhage	0	0	0	1	1	0.02
Trichiasis	0	0	0	1	1	0.02
Vitreous degeneration	0	0	0	1	1	0.02
Xerophthalmia	0	0	0	1	1	0.02

Source: MAED analysis adsl.xpt, adae.xpt, where AESOC= Eye disorders and AEONTRFL=y

Table 59 – Preferred terms of Serious Adverse events under the system organ class of Eye disorders- FAS

	Lira (N = 4668)	*Placebo (N = 4672)*

PT	*Events*	*Number of subjects*	*Proportion (%)*	*Events*	*Number of subjects*	*Proportion (%)*
Cataract	29	24	0.51	35	32	0.68
Diabetic retinopathy	9	9	0.19	15	15	0.32
Vitreous haemorrhage	6	6	0.13	5	5	0.11
Retinal vein occlusion	4	3	0.06	0	0	0
Amaurosis	2	2	0.04	0	0	0
Blindness unilateral	2	2	0.04	0	0	0
Macular fibrosis	2	2	0.04	4	4	0.09
Retinal artery occlusion	2	2	0.04	1	1	0.02
Retinal detachment	2	2	0.04	0	0	0
Retinal infarction	2	2	0.04	0	0	0
Retinopathy	2	2	0.04	5	4	0.09
Vitreous adhesions	2	2	0.04	0	0	0
Aphakia	1	1	0.02	0	0	0
Autoimmune uveitis	1	1	0.02	0	0	0
Blepharitis	1	1	0.02	0	0	0
Diabetic blindness	1	1	0.02	1	1	0.02
Diabetic retinal edema	1	1	0.02	0	0	0
Diplopia	1	1	0.02	0	0	0
Eyelid ptosis	1	1	0.02	0	0	0
Glaucoma	1	1	0.02	3	3	0.06
Iridocyclitis	1	1	0.02	0	0	0
Macular edema	1	1	0.02	1	1	0.02
Macular rupture	1	1	0.02	0	0	0
Open angle glaucoma	1	1	0.02	1	1	0.02
Optic ischemic neuropathy	1	1	0.02	3	3	0.06
Papilloedema	1	1	0.02	0	0	0
Retinal aneurysm	1	1	0.02	0	0	0
Retinal degeneration	1	1	0.02	1	1	0.02
Retinal vein thrombosis	1	1	0.02	0	0	0
Retinopathy hemorrhagic	1	1	0.02	0	0	0
Ulcerative keratitis	1	1	0.02	0	0	0
Vision blurred	1	1	0.02	3	3	0.06
Visual impairment	1	1	0.02	0	0	0
Angle closure glaucoma	0	0	0	1	1	0.02
Corneal erosion	0	0	0	1	1	0.02
Eye haemorrhage	0	0	0	1	1	0.02
Iritis	0	0	0	1	1	0.02
Optic nerve infarction	0	0	0	1	1	0.02
Retinal artery embolism	0	0	0	1	1	0.02
Retinal haemorrhage	0	0	0	1	1	0.02
Retinal vascular occlusion	0	0	0	1	1	0.02

Retinopathy proliferative	0	0	0	1	1	0.02

Table 60 – Exploratory analysis of PT terms related to vision loss

Preferred term	SUBJ ID (b) (6)	Inv. Reported term	Serious	Treatment arm	Sent for Adj	Leading to Discont	HBA1 base	Diabetes dur. (yrs)	Day of AE	Narrative
			Y/N		Y/N	Y/N				
Blindness unilateral		LINDNESS OF HE RIGHT EYE	Y	Liraglutide	N	N	7.8	41.8	585	91 year old woman with history of bilateral cataracts, glaucoma, left amblyopia who developed unilateral blindness of the right eye. Per the narrative, the patient "presented with right eye blindness due to glaucoma and ectopia lentis of left eye." The patient was hospitalized and Phacoemulsification of ectopis lentis without implantation and anterior vitrectomy of left eye was performed.
		ISION LOSS IGHT EYE	N	Placebo	N	N	10.5	21.2	631	No narrative. In formation request, he sponsor provided the following 'Per PI response: as per telephonic conversation with subject, he has not visited a physician. Subject has also expressed that he is no longer willing to participate in the study and is withdrawing consent.'
		ONOCULAR ISION LOSS, IGHT EYE	Y	Liraglutide	N	N	11.7	2.6	230	57 year old male with history of stroke who developed "monocular vision loss, right eye." Patient had dizziness and vomiting and right blurred vision. The pa ient was hospitalized and was ruled out for TIA with CT and MRI. Patient was diagnosed with monocular vision loss. The patient was discharged with ophthalmological follow up. Discharge sequelae reported as 'rapidly progressing cataract." Pa ient had an eye exam ~2 weeks after discharge which was normal except for bilateral cataracts
Diabetic blindness		IABETIC ELATED LINDNESS , IGHT EYE	Y	Liraglutide	Y	N	12.9	18.1	358	63 year old woman with history of proliferative retinopathy since 2012 and nephropathy who presented with "diabetic related blindness, right eye." Patient presented with blurred vision and was suddenly unable to see with her right eye. No further information is available.
		IGHT EYE IABETIC LINDNESS	Y	Placebo	Y	N	5.9	25.7	782	73 year old male who developed "right eye diabetic blindness." Pa ient had previous eye cataract surgery in 2010, glaucoma since 2008, proliferative retinopathy since 2007 and right eye retinal detachment in 2010 with insertion of silicon oil insertion. On routine ocular echography (June 2013), patient was shown to have "external tractional retinal detachment applied to macula." On 02 Jul 2013, the patient had retinal cryotherapy and removal of silicon oil in right eye. On 01 Nov 2013 the pa ient developed right eye sight loss and was identified with severe diabetic retinopathy and diabetes related blindness. The patient was treated with ranibizumab.
Diplopia		OUBLE VISION EFT EYE	N	Liraglutide	N	Y	8.9	1.9	9	57 year old woman with history of pupil paralysis of right eye was seen in a routine clinic visit and reported she had a CT of the brain 4 days prior due to double vision. CT scan did not show any pathological findings. No further details available. Event occurred 8 days after starting treatment.
		IPLOPIA	N	Placebo	N	N	7.7	20.9	140	No narrative
		ORIZONTAL IPLOPIA	N	Placebo	N	N	7.4	3.5	1110	No narrative
		OUBLE VISION N LEFT EYE	N	Placebo	N	N	7.3	23.1	1073	No narrative
		ILATERAL OUBLE VISON	Y	Liraglutide	N	Y	7.2	13.9	3	74 year old male with history of non-proliferative diabetic retinopathy reported bilateral double vision and he trial drug was discontinued. The patient was admitted to the hospital for bilateral eyelid ptosis. Patient underwent imaging, and tensilon test which was without improvement. Patient was discharged. Patient showed slow improvement and no evidence of myasthenia gravis, sarcoidosis or borrelia.
		IPLOPIA	N	Liraglutide	N	N	8.8	17.2	235	No narrative
		OUBLE VISION	N	Liraglutide	N	N	7.9	10.9	1309	No narrative
		OUBLE VISION	N	Placebo	N	N	10.0	9.4	626	No narrative
Vision blurred		LURRING OF ISION	Y	Placebo	Y	N	15.0	14.2	346	65 year old male who presented with "blurring vision" was hospitalized. There is no documentation of the tests performed. No documents were available from the hospitalization. The type of eye disease was reported as development of diabetes-related blindness. Patient awaited eye surgery. On 3 May 2014 the patient reported significant vision loss. No treatment was initiated.
		IGHT EYE LURRED ISION	Y	Liraglutide	N	N	8.5	19.1	612	70 year old male with history of cataracts and non-proliferative retinopathy, was diagnosed with "right eye blurred vision" and right arm paresthesia. He had CT scan /MRI of brain without acute findings. Patient was discharged.

Preferred term	SUBJ ID (b) (6)	Inv. Reported term	Serious Y/N	Treatment arm	Sent for Adj Y/N	Leading to Discont Y/N	HBA1 base	Diabetes dur. (yrs)	Day of AE	Narrative
		BLUERED VISION	N	Placebo	N	N	9.5	11.2	621	No narrative
		TWO EPISODES OF TRANSIENT BLURRED VISION	Y	Placebo	N	Y	7.2	16.9	1001	70 year old male with two episodes of transient blurred vision which resulted in hospitalization. Imaging did not reveal etiology of event. The only finding was low blood pressure 126/60. The vent resolved. The test drug was temporarily withdrawn and reintroduced, and the blurry vision did not return
		BLURRED VISION	N	Liraglutide	N	N	7.6	8.2	600	No narrative
		LYRICA INDUCED BLURRED VISION	N	Liraglutide	N	N	8.3	4.9	535	No narrative
		BLURRED VISION	N	Placebo	N	N	7.7	12.2	1248	No narrative
		BLURRED VISION	N	Placebo	N	N	8.400	17.5	309	No narrative
		BLURRED VISION	N	Placebo	N	N	9.4	15.0	65	No narrative
		BLURRY VISION	N	Placebo	N	N	7.9	16.8	60	No narrative
		BLURRED VISION LEFT EYE	N	Placebo	N	Y	8.6	6.3	10	No narrative
		BLURRED VISION	N	Liraglutide	N	N	8.4	19.9	1449	No narrative
		BLURRED VISION	Y	Placebo	N	N	8.6	1.5	397	65 year old male who presented with unstable angina and chest pain, blurry vision and elevated blood pressure. Patient had an acute myocardial infarc ion. No further details pertaining to the blurry vision are present.
Visual acuity reduced		LASER EYE PROCEDURE (L) FOR REDUCED VISION	N	Liraglutide	N	N	10.1	21.0	465	No narrative
		WORSENING OF ACUITY VISUAL DECREASE	N	Liraglutide	N	Y	10.9	11.9	46	63 year old woman with history of cataracts presented with worsening of anxious depression and worsening of vision and cognitive deficit. Visual symptoms included hyperopia, myopia, excessive tearing and photophobia
		DECREASED VISUAL ACUITY RIGHT EYE	N	Placebo	Y	N	7.9	21.8	747	82 year old male with history of right cataract removal, right eye pars plana vitrectomy, left cataract, intermittent dizziness. Who presented with "decreased visual acuity right eye." Patient noted distortion with right eye and was sent to the oph halmologist who noted the decrease in visual acuity. Results of photograph intravenous fluorescein angiography are not available. The type of eye disease reported is diabetes-related blindness. Patient is reported awaiting surgery.
		DECREASED VISION	N	Placebo	N	N	9.0	16.7	961	No narrative
Visual impairment		WAVY LINES IN VISION	N	Liraglutide	N	N	6.7	3.7	944	No narrative
		VISUAL DISTURBANCE	Y	Liraglutide	N	N	8.3	9.5	278	76 year old male with history of glaucoma, itchy eyes who presented to the hospital with pain, swelling and redness of the left foot and calf area for 2-3 days. Patient was diagnosed with cellulitis and treated with IV

			Serious	Treatment arm	Sent for Adj	Leading to Discont	HBA1 base	Diabetes dur. (yrs)	Day of AE	Narrative
Preferred term	SUBJ ID	Inv. Reported term	Y/N		Y/N	Y/N				
		LEFT EYE FOR 10 MINUTES								antibiotics. The patient was diagnosed with dementia during hospitaliza ion and had a visual disturbance in the left eye at some point in the hospitalization which the patient was evaluated by neurology and ophthalmology with no pathology found.

Financial disclosures

Covered Clinical Study (Name and/or Number): LEADER, EX2211-3748

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 2019		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 11		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 58		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 58 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 15 (of which none had disclosable information, per the Sponsor)		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from applicant)

In total there were 58 investigators with disclosable financial interests (27 investigators in the U.S. and 31 outside the U.S.). Table 61 and Table 62 list investigators with payments of ≥$100,000; with 18 investigators are listed outside the U.S and 14 investigators in the U.S. There were 3 sites (all outside the U.S.) with investigators reporting over $1 million in disclosable interests.

Table 61 - Investigators with disclosable financial interests outside the U.S.

Site No.	Name of Investigator	Trial Site Role (Principal or sub-investigator)	Disclosable financial interest	Explanation	No. of Subjects Entered Treatment (Randomized subjects)
(b) (6)			$3,177,361	From 2006-2013 for honorarium/fees consultation fees	43
			$199,109	From 2010-2015 – Lecture, advisory board	25
			$2,231,911	From 2010-2016 - Collaboration payment	39
			$2,231,911	From 2010-2016 Collaboration payment	39
			$1,653,846	2010 Institutional grant	39
			$ 2,231,911	Collaboration payment	39

(b) (6)	$2,231,911	From 2010-2016 Collaboration payment	39
	$2,231,911	From 2010-2016 Infrastructure funding	12
	$2,510,900	From 2010-2016- Infrastructure funding/research support	12
	$2,51,900	From 2010-2016- Infrastructure funding/research support	12
	$2,510,900	From 2010-2016- Infrastructure funding/research support	12
	$2,510,900	From 2010-2016- Infrastructure funding/research support	12
	$319,233	2011 - Research grant	22
	$319,233	2011 - Research grant	22
	$319,233	2011 - Research grant	22
	$319,233	2011 - Research grant	22
	$319,233	2011 - Research grant	22
	$362,814	2010- Research funding	17

˜ the investigator disclosures are different from that reported by the Sponsor in the table and amount to $1,124,000.
*The detailed financial disclosures for site (b) (6) is the same for all investigators, that in collaboration payment to (b) (6) (b) (6) to: (b) (6) facility and staff (b) (6) and to work together with Novo Nordisk to establish the (b) (4) and also for emerging new interests such as metabolism m and endocrinology (starting on April 2006 £200,000).
^detailed financial information states that the department receives infrastructure funding as a (b) (6) from Novo Nordisk to the tune of £200,000 per year.
**research grant reported for (b) (6) by all investigators
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Table 62 - Investigators with disclosable financial interests in the U.S.

Site No.	Name of Investigator	Trial Site Role (Principal or sub-investigator)	Disclosable financial interest	Explanation	No. of Subjects Entered Treatment (Randomized subjects)
(b) (6)			110,850	Honorarium/Fees 03/2011- 04/2016	30
			281,760	Honorarium/Fees 10/2011-03/2016	12
			$148,210	Honorarium/Fees 04/2011-10/2015	12
			$116,380	Honorarium/Fees 05/2011-02/2016	5
			179,980	Honorarium/Fees 04/2011-04/2016	14
			$115,820	Honorarium/Fees 10/2013-04/2016	33
			$115,580	Honorarium/Fees 02/2011-11/2014	(b) (6)

(b) (6)	$304,590	Honorarium/Fees 02/2011-04/2016	25
	$183,610	Honorarium/Fees 02/2011-05/2016	14
	$104,910	Honorarium/Fees 03/2011-04/2016	45
	$220,880	Honorarium/Fees 03/2011-05/2016	22
	$192,445	Honorarium/Fees 04/2011-04/2016	48
	$281,760	Honorarium/Fees 10/2011-03/2016	23
	$190,449	Honorarium/Fees 04/2011-04/2016	13

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/s/

TANIA A CONDARCO
07/14/2017

LISA B YANOFF
07/14/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: May 22, 2017

FROM: Shannon Sullivan, MD, PhD, Medical Officer, Division of Metabolism and Endocrinology Products (DMEP)

To: File (sNDA 22341, Liraglutide)

SUBJECT: Safety review of thyroid cancer incidence in the LEADER trial

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Executive Summary

This review summarizes cases of elevated serum calcitonin, C-cell hyperplasia, and thyroid neoplasm in subjects randomized to liraglutide compared to placebo in the "Liraglutide Effect and Action in Diabetes: Evaluation of cardiovascular outcomes Results" (LEADER) trial. The LEADER trial was conducted to fulfill a post-marketing requirement (PMR) upon approval of liraglutide as an adjunct to diet and exercise in the management of Type 2 Diabetes Mellitus (T2DM), with a primary objective of evaluating major cardiovascular adverse events (AEs) and other AEs of interest, including long-term effects of liraglutide on risk of C-cell hyperplasia and thyroid cancer, specifically the risk for medullary thyroid cancer (MTC).

No cases of MTC were observed in liraglutide-randomized subjects and one case of MTC occurred in a placebo-randomized subject, suggesting no increased risk of MTC due to liraglutide treatment. There were few thyroid cancer events of other cell type. Calcitonin assessments were unremarkable. However, caution should be exercised in drawing definitive conclusions due to the limited number of cases of thyroid neoplasms observed in LEADER and the long-latency of thyroid cancer.

Backgroud

Liraglutide was approved on January 25, 2010, for treatment of T2DM (Victoza, Novo Nordisk, NDA 22341). A higher dose formulation of liraglutide was approved in December, 2014, for weight management (Saxenda, NDA 206321). Since approval, the Victoza and Saxenda labels have carried Boxed warnings regarding risk of thyroid C-cell tumors, as shown below for the Victoza label (the Saxenda label is very similar):

- **Liraglutide causes thyroid C-cell tumors at clinically relevant exposures in rodents. It is unknown whether Victoza causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans, as human relevance could not be determined by clinical or nonclinical studies (5.1)**.
- **Victoza is contraindicated in subjects with a personal or family history of MTC or in subjects with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2) (5.1).**

However, despite additional human experience with liraglutide since the drug's initial approval, the relevance of animal findings to humans remains unknown to date.

In addition to the monitoring of AEs related to C-cell hyperplasia and thyroid cancer required in the LEADER trial, several additional post-marketing requirements (PMRs) and surveillance studies have been initiated in order to help elucidate the true potential risk of C-cell hyperplasia and MTC in humans exposed to GLP-1 receptor analogs as a class, including liraglutide (**Table 1**).

First, the Liraglutide Safety and Surveillance Program using the Optum Research Database was established by the FDA as a PMR after approval of Victoza in 2010 (PMR 1583-6). This program was a 5-year, prospective observational cohort safety surveillance study in which one of the primary outcomes was events of thyroid cancer, specifically MTC. Final study results were reported to the FDA in July 2016, and a thorough review of these data by the Office of Surveillance and Epidemiology/Office of Pharmacovigilance and Epidemiology/ Division of Epidemiology (OSE/OPE/DEPI) (refer to CONSULT REV-SAFETY-05 (Epidemiology Review), dated December 9, 2016 in DARRTS) concluded that in an average follow-up time of 500 days, rates of thyroid cancer in users of liraglutide compared with any and all comparator diabetes drugs were not statistically significantly different. Rate ratios ranged from 1.0 (95% CI, 0.6-1.8) when liraglutide was compared with metformin to 1.7 (95% CI, 1.0-2.8) when liraglutide was compared with all comparator drugs, compared with all comparator drugs except exenatide (95% CI, 1.0-2.8), and compared with exenatide alone (95% CI, 0.7-3.8). *However, a major limitation of this study is a lack of data regarding the specific subtypes of thyroid cancer that occurred*. Given that MTC is relatively rare, accounting for only ~4% of all thyroid cancer cases in the U.S. (Kloos et al., 2009), and that the most common sub-type of thyroid cancer, papillary thyroid cancer (PTC), is easily treated and not related to C-cell hyperplasia, it is likely that most of the thyroid cancer cases observed were of papillary origin. The rates of specific subtypes of thyroid cancer will need to be determined to identify a potential safety signal between liraglutide use in humans and risk of MTC.

Second, after approval of multiple GLP-1 analog formulations, the FDA issued a PMR to all sponsors of long-acting GLP-1 receptor agonists to participate in a MTC case series registry (PMR 1583-7 (Victoza, Novo Nordisk, January 2010), PMR 1860-5 (Bydureon, Amlyn, January 2012), PMR #2 (Tanzeum, GlaxoSmithKline, May 2014), PMR 2781-3 (Trulicity, Eli Lilly, September 2014), and PMR 2802-6 (Saxenda, Novo Nordisk, December 2014)). To satisfy these PMRs, the sponsors formed the MTC Registry Consortium, whose members include Novo Nordisk (liraglutide for treatment of T2DM (Victoza) and for weight loss management (Saxenda), AstraZeneca (exenatide extended release (Bydureon), GlaxoSmithKline (albiglutide (Tanzeum), and Eli Lily (dulaglutide (Trulicity)). The MTC Registry Consortium is monitoring the annual incidence of MTC in the U.S. using data from the North American Association of Central Cancer Registries (NAACCR) prior to and after the introduction of GLP-1 analogs into the U.S. market, and by establishing a nation-wide MTC Registry. An interim report from the MTC Registry Consortium was submitted to the FDA in March 2016 and was reviewed by OSE/OPE/DEPI (refer to REV-SURVEPI-05 (Epidemiology review), dated June 19, 2016 in DARRTS). From NAACCR data, the OSE/OPE/DEPI review concluded that since introduction of GLP-1 receptor analogs into the U.S. market in 2010, the age-adjusted annual incidence rate of MTC has been similar to or lower than the projected incidence rates based on a comparator baseline period of nine years prior to consumer use of any GLP-1 analog product in the U.S. (January 1, 2001 to December 31, 2009). These data were limited, however, by a short duration of follow-up to evaluate for malignancy, as NAACCR provided only data through 2012, providing a total

duration of only 2 years since approval of the first GLP-1 analog. From the MTC Registry data, only three subjects of 1,559 MTC cases (0.2%) in the registry reported exposure to a GLP-1 receptor agonist; however, the registry has been limited thus far by a very low capture rate of only ~35% of all MTC cases based on the total number of cases reported in the NAACCR database.

Third, during review of the NDA for Saxenda (NDA 206321), DMEP reviewed all post-marketing cases of MTC in subjects randomized to liraglutide that had been reported to the FDA Adverse Event Reporting System (FAERS) since initial approval of liraglutide for diabetes management in 2010 (Refer to REV-CLINICAL-21 (primary review), dated September 26, 2014 in DARRTS). From this review, a total of 13 case reports of MTC were reported to the Agency from 2010 to 2014. The reviewer concluded that given the low number of reported MTC cases, the relatively short duration of exposure prior to diagnosis, and the paucity of clinical information in the majority of case reports to assess baseline risk, "no firm conclusion regarding causal relationship of MTC with liraglutide can be drawn from these cases."

Finally, a Tracked Safety Issue (TSI #894) was established in April 2010 to track cases of any thyroid tumors in subjects using any approved long-acting GLP-1 agonist, and is ongoing. Overall, despite the accumulating data provided by the post-marketing data described above, there is still insufficient information to determine the true risk of C-cell hyperplasia or MTC in subjects exposed to long-acting GLP-1 analogs, including liraglutide.

Table 1. **Post-marketing Studies Assessing the Risk of Medullary Thyroid Cancer in Humans Exposed to GLP-1 Receptor Agonists.**

PMR	Sponsor/Product(s)	Database(s) explored	Description	Major Findings
PMR 1583-9: LEADER trial TSI 894	**Novo Nordisk**: Liraglutide (Victoza (NDA 22341) and Saxenda (NDA 206321))	Post-marketing surveillance of calcitonin elevations, C-cell hyperplasia, and thyroid cancer (classified by sub-type) in 9,340 diabetics randomized to liraglutide vs placebo.	Placebo-controlled, randomized trial in 9,340 subjects with T2DM and high cardiovascular disease risk. Subjects were randomized to liraglutide or placebo in addition to standard-of-care therapy (duration of exposure, 3.5- 5 years) in order to evaluate the primary outcome: the first occurrence of 3 component MACE (CV death, non-fatal MI, or non-fatal stroke). Secondary outcome measures included calcitonin elevation, thyroid C-cell hyperplasia, and thyroid cancer.	
PMR 1583-6: Liraglutide Safety and Surveillance Program TSI 894	**Novo Nordisk**: Liraglutide (Victoza, NDA 22341)	Optum Research Database	5-year, prospective observational cohort safety surveillance study	No increased incidence of thyroid cancer (any subtype) in users of liraglutide compared to users of comparator diabetes drugs [*Note, thyroid cancer subtypes were not*

				reported.]
PMR 1583-7 (Victoza, Novo Nordisk) PMR 1860-5 (Bydureon, Amlyn) PMR #2 (Tanzeum, GlaxoSmithKline) PMR 2781-3 (Trulicity, Eli Lilly) PMR 2802-6 (Saxenda, Novo Nordisk): MTC Registry Consortium TSI 894	**Novo Nordisk**: Liraglutide (Victoza (NDA 22341) and Saxenda (NDA 206321)) **AstraZeneca**: exenatide extended release (Bydureon, NDA 22200) **GlaxoSmithKline**: albiglutide (Tanzeum, BLA 125431) **Eli Lily**: Dulaglutide (Trulicity, BLA 125469)	1) North American Association of Central Cancer Registries (NAACCR) 2) National MTC Registry	1) Monitoring for at least 15 years the annual incidence of MTC after the introduction of GLP-1 analogs into the U.S. market compared to annual incidence rates prior to GLP-1 analog use using NAACCR data 2) Identification for at least 15 years cases of MTC in subjects exposed to GLP-1 analogs by reviewing State Cancer Registry case reports, then contacting each patient by telephone to determine if he/she was exposed to a GLP-1 analog, and confirming positive cases by contacting treating physicians	1) Annual incidence rates of MTC were similar to or lower than expected after GLP-1 analog introduction into the U.S. market compared to prior to GLP-1 analog introduction 2) 0.2% (3 of 1,559) of MTC cases reported ever use of a GLP-1 analog, thus no safety signal has been identified
Clinical Review of post-marketing cases of MTC reported to FAERS between 2010 and 2014 (part of original NDA review for Saxenda)	**Novo Nordisk**: Liraglutide (Victoza (NDA 22341) and Saxenda (NDA 206321))	FAERS database	Review of all post-marketing cases of MTC in subjects randomized to liraglutide reported to FAERS from 2010 to 2014	13 MTC cases were reported. No conclusion regarding causal relationship between liraglutide and MTC could be drawn due to limited data.

LEADER Trial

LEADER was a multicenter, multinational, randomized, double-blind, placebo-controlled trial in 9,340 subjects with T2DM and high risk of cardiovascular disease to assess the effects of liraglutide compared to placebo for at least 3.5 years and up to 5 years on the incidence of cardiovascular events (primary outcome) and other AEs of interest. Subjects were randomized 1:1 to liraglutide or placebo in addition to standard-of-care therapy, with the option of adding glucose-lowering or cardiovascular medications to achieve guideline targets for glycemic control, blood pressure, and lipids on an individualized basis. Median follow-up for all subjects enrolled in LEADER was 3.8 years.

Serious AEs (SAEs) and pre-specified Medical Events of Special Interest (MESIs) were collected. Thyroid neoplasms and calcitonin values ≥20 ng/L (as a potential marker for C-cell hyperplasia) were considered as MESIs.

An independent external calcitonin monitoring committee (CMC) consisting of endocrinologists assessed all confirmed calcitonin levels ≥20 ng/L and provided clinical advice to investigators regarding further investigation and treatment of subjects.

An External (independent) Adjudication Sub-committee (EAC) consisting of one endocrinologist and one oncologist performed ongoing adjudication and assessment of all thyroid neoplasms. After EAC confirmation, all malignant and pre-malignant thyroid

neoplasms were also confirmed by a blinded external endocrinologist reviewer to allow for further characterization (but not re-adjudication) of EAC-confirmed thyroid neoplasms. Thyroid neoplasm classifications were based on EAC-confirmed cytology or pathology reports.

A summary of the source data provided to the EAC and to the external endocrinologist reviewer is shown below.

Thyroid Neoplasm and Thyroid Disease Resulting in Thyroidectomy	• Admission History and Physical (if applicable) • Oncology/Endocrinology/Otolaryngology Specialist Consult records • Laboratory results (eg, thyroid hormones, calcitonin, Pentagastrin stimulation test, genetic testing, etc) • Imaging reports (ultrasound, CT, MRI, nuclear thyroid scan, etc) • Surgical procedure report • Pathology/cytology report • Pathology report from external pathologist • Hospital Discharge Summary If the patient died from this event: • Autopsy (if performed) • Death Certificate

Calcitionin

Elevated serum calcitonin is a potential biochemical marker of C-cell neoplasia, especially levels ≥50 ng/L (Costante et al., 2007). In LEADER, serum calcitonin was measured using a chemiluminescent immunometric assay performed by a central laboratory (ICONPLC, Dublin, Ireland). The lower limit of quantification (LLQ) was 2.0 ng/L, and the upper limit of normal (ULN) was 8.4 ng/L in men and 5.0 ng/L in women. Calcitonin levels ≥20 ng/L were considered elevated. Serum calcitonin was measured fasting at baseline and at study visits 1, 7, 9, 11, 13, and 15 in all participants (visit 1 occurred 4-5 weeks prior to the start of study drug, and visits 7, 9, 11, and 13 occurred 12, 24, 36, and 48 months after the start of study drug, respectively; visit 15 was an end of treatment visit that occurred 42 months + 90 days after the last subject was randomized, thus timing of visit 15 was variable for each study subject). As a precautionary measure, subjects who had calcitonin values ≥2x the upper limit of normal (ULN) at visit 15 and calcitonin levels below the ULN at screening were scheduled to have another blood calcitonin test after an off-drug follow-up period at visit 16.

Per the enrollment criteria for LEADER, baseline calcitonin was ≤50 ng/L in all subjects. At baseline, 2.8% of women and 21.3% of men had calcitonin levels above sex-specific normal reference values of 5.0 ng/L and 8.4 ng/L, respectively. A similar proportion of subjects had calcitonin values ≥ULN at baseline in both treatment groups in male subjects (liraglutide: 21.5%; placebo: 22.0%) and female subjects (liraglutide: 3.2%; placebo: 2.7%). In both sexes, lower eGFR, higher BMI, and smoking were associated with higher baseline calcitonin levels, as expected (d'Herbomez et al., 2007; Daniels et al., 2015).

The proportion of subjects with post-baseline calcitonin levels ≥20 ng/L at any study visit was similar in the liraglutide and placebo groups (3.1% vs 3.0%, respectively). On AE reporting, 'blood calcitonin increased' was reported at a slightly lower frequency and rate in the liraglutide group (0.9%, 0.24 events per 100 PYO) compared with the placebo group (1.1%, 0.31 events per 100 PYO). In both treatment groups, median calcitonin levels were

stable throughout the trial, with a slight overall decrease in males from 3.9 ng/L at screening to 2.5 ng/L at treatment end and no change in females from screening (1.0 ng/L) to treatment end (**Figure 1 and Figure 2**). Among male subjects meeting criteria for a visit 16 calcitonin level (130 subjects in the liraglutide group and 149 subjects in the placebo group), the median calcitonin value at visit 16 was 5.9 ng/L in the liraglutide group and 7.8 ng/L in the placebo group. Among females meeting criteria for a visit 16 calcitonin check (62 subjects in liraglutide group and 65 subjects in the placebo group), median calcitonin at visit 16 was 1.0 ng/L in both groups. Study drug was discontinued in one liraglutide-randomized patient (Subject (b) (6) described below) and two placebo-randomized subjects due to increased serum calcitonin.

Calcitonin elevations above 50 ng/L are considered a more sensitive biochemical marker of potential C-cell hyperplasia compared to calcitonin levels ≥20 < 50 ng/L (Costante et al., 2007). There was no difference in the number of subjects with any post-baseline calcitonin ≥50 ng/L between the liraglutide and placebo groups (Liraglutide: n=16, 0.34% *vs* placebo: n=17, 0.36%). Of note, all subjects in the LEADER trial with any post-baseline calcitonin ≥50 ng/L were male, consistent with known sex differences in calcitonin levels in which levels are higher in men compared to women (d'Herbomez et al., 2007). This reviewer also compared the mean nadir and peak calcitonin levels among the subjects with any post-baseline calcitonin ≥50 ng/L between the liraglutide and placebo groups. Although mean nadir and peak calcitonin levels in the small subgroup of subjects with any post-baseline calcitonin value ≥50 ng/L were higher in the liraglutide group, there were no statistically significant between-group differences in either nadir or peak calcitonin levels in this sub-population (**Table 2**).

Table 2. Mean (±SD) nadir and peak calcitonin levels among LEADER subjects with any post-baseline calcitonin ≥50 ng/L.

Treatment	Subjects with post-baseline calcitonin ≥50 ng/L (N, %)	Nadir Calcitonin, ng/L (mean, SD)	Peak Calcitonin, ng/L (mean, SD)
Liraglutide	16, 0.34%	52±34	95±69
Placebo	17, 0.36%	39±11	62±15
p-value[1]		0.15	0.06

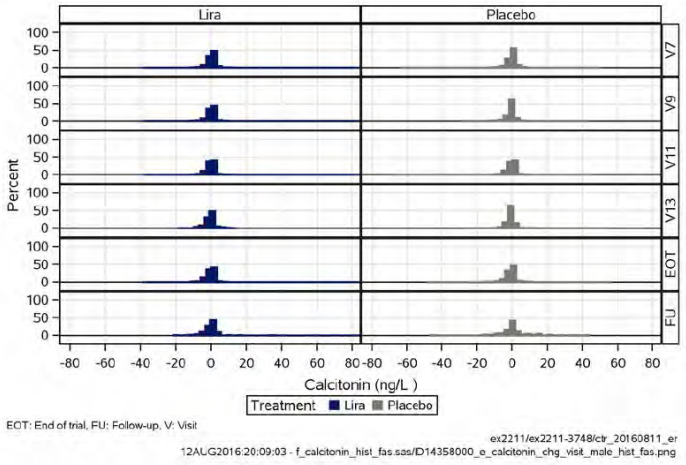
[1]2-tailed student's T-test, P<0.05 considered significant

Only 1 subject (ID (b) (6), liraglutide group) had consistent increases in calcitonin over time; all other subjects with calcitonin elevations during the study period exhibited fluctuating levels without consistent increases. Subject (b) (6) was a 67 year-old Indian male non-smoker with no history of histamine H2-receptor antagonist or proton pump inhibitor use, medications known to increase serum calcitonin levels (Toledo et al., 2009). His baseline calcitonin was 19.2 ng/L in September 2011 and increased to 70.4 ng/L by September 2012. Study drug was discontinued in November 2012, and neck ultrasound and sestamibi scan were performed. Both imaging studies were normal, with no evidence of thyroid nodules or parathyroid gland hyperplasia. One month after discontinuing study drug, his calcitonin continued to increase, reaching 258 ng/L in November 2012. Three years after stopping study drug, the patient's calcitonin had further increased to 280 ng/L.

One female subject in the liraglutide group had persistently elevated calcitonin >20 ng/L; however, her calcitonin was elevated at baseline and never exceeded 50 ng/L.

In conclusion, safety data from the LEADER trial provide no indication of a liraglutide effect on serum calcitonin levels.

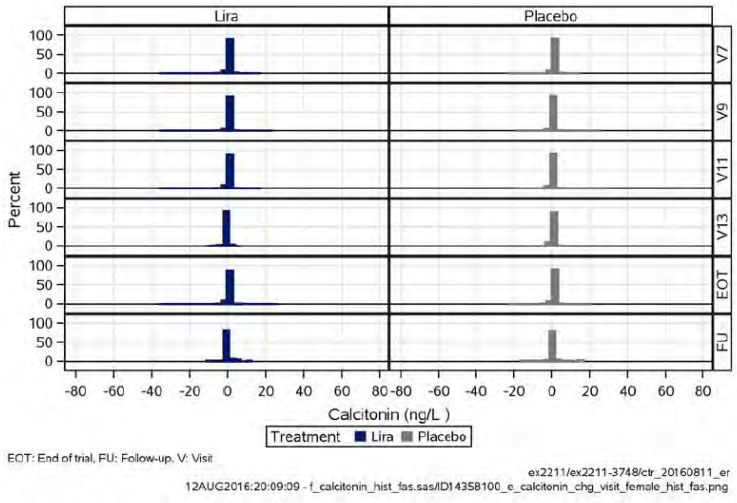
Figure 1. Calcitonin levels change from baseline by visit and treatment—males[1]



14.3.5.258 Calcitonin measurements by visit and treatment - change from baseline - males - histogram - full analysis set

[1]Source: Figure 14.3.5.258, NDA 22341

Figure 2. Calcitonin levels change from baseline by visit and treatment—females[2]



14.3.5.259 Calcitonin measurements by visit and treatment - change from baseline - females - histogram - full analysis set

[2]Source: Figure 14.3.5.259, NDA 22341

Thyroid neoplasms

New thyroid neoplasms were classified as either benign, pre-malignant, or malignant, and further sub-typed as either i.) C-cell hyperplasia, ii.) medullary microcarcinoma (carcinoma *in situ*), iii.) medullary carcinoma, or iv.) other.

Seven subjects (0.15%) in the liraglutide group had events of thyroid neoplasm, compared to three subjects (0.06%) in the placebo group (**Table 3)**. There were no notable differences in demographic or baseline characteristics between liraglutide- and placebo-randomized

subjects with events of thyroid neoplasms (data not shown). Malignant or pre-malignant thyroid neoplasms were observed in 5 liraglutide-randomized subjects, compared to 4 placebo-randomized subjects. Two subjects in the liraglutide group had benign thyroid neoplasms, compared to no subject in the placebo group.

The majority of malignant thyroid neoplasms in the liraglutide group occurred within the first 12 months of the trial (4 of 5 events) and 1 event occurred after month 40. All malignant thyroid neoplasms in the placebo group, including one event of MTC (discussed below) occurred after month 16 (**Figure 4**).

With regard to the types of malignant thyroid neoplasms observed, five events of papillary thyroid cancer (PTC) occurred in 5 subjects in the liraglutide group, compared to 4 events of PTC in 3 subjects in the placebo group (**Table 3**). There were *no cases of MTC in liraglutide-randomized subjects*, compared to 1 case of MTC in 1 placebo-randomized subject (Subject (b) (6)). Subject (b) (6) was a 72-year old male who underwent right hemi-thyroidectomy for removal of two thyroid nodules that were suspicious for follicular thyroid cancer on fine needle aspiration (FNA). Pathology from the right hemi-thyroidectomy revealed a 2 mm focus of medullary carcinoma without local metastases (pT1pN0pMx). Completion left thyroidectomy with central lymph node dissection was performed and pathology revealed a 1 cm focus of follicular variant PTC and 2 foci (~1 mm) of medullary microcarcinoma in a background of C-cell hyperplasia (pT1aN0Mx). Genetic testing for multiple endocrine neoplasia type 2 and familial medullary thyroid cancer was negative. Of note, this patient had a mildly elevated serum calcitonin, up to 25.4 ng/L prior to thyroidectomy, which declined to the normal range after the right hemi-thyroidectomy.

There were no on-treatment events of isolated C-cell hyperplasia (**Table 3**). One placebo-randomized subject (Subject (b) (6), described above) was found to have MTC on a background of C-cell hyperplasia per surgical pathology report. One liraglutide-randomized subject (Subject (b) (6) with a confirmed malignant thyroid neoplasm (classified as 'other' and of papillary origin) during the trial had one focus of C-cell hyperplasia *prior to randomization* to study treatment. Another liraglutide-randomized subject (Subject (b) (6)) had an AE of "possible C-cell hyperplasia" that was NOT confirmed by the EAC. Subject (b) (6) was a 72 year-old white male randomized to liraglutide with a reported history of "elevated calcitonin" (no level provided) in December 2011, prior to randomization to study drug. This subject had been previously referred to an endocrinologist for evaluation of his elevated calcitonin, and a thyroid ultrasound performed in February 2011 showed a "mildly enlarged thyroid gland without suspicious dominant nodule and a small cystic area in the upper right thyroid." The endocrinologist recommended no further evaluation at that time and repeat surveillance neck ultrasound in 1 year. Based on the presence of the right thyroid cyst and the patient's past history of "elevated calcitonin," an AE of "possible C-cell hyperplasia" was recorded by the investigator. However, based on the lack of any evidence to confirm C-cell hyperplasia in this case, the EAC did not confirm this as an adjudicated AE of C-cell hyperplasia. This reviewer agrees with the EAC's assessment that in this case, there is no evidence that an AE of C-cell hyperplasia occurred. In support of this assessment, this patient did not have any serum calcitonin levels >20 ng/L during the entirety of the study.

Table 3. Thyroid Neoplasms in Liraglutide-randomized vs Placebo-randomized Subjects[1]

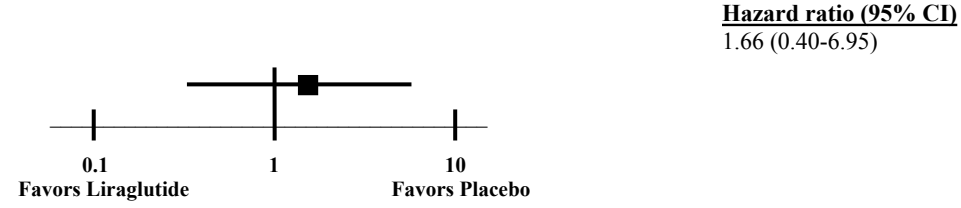
Type of Neoplasm	Number of subjects, N Proportion of subjects, % [N, (%)] Liraglutide (N=4,668 subjects)	Number of subjects, N Proportion of subjects, % [N, (%)] Placebo (N=4,672 subjects)
Total	7 (0.15%)	3 (0.06%)
Benign	2 (0.04%)	0 (0.0%)
Pre-malignant	0 (0.0%)	1 (0.02%)
Malignant	5 (0.11%)	3 (0.06%)
Sub-type		
C-cell hyperplasia	0 (0.0%)	0 (0.0%)
Medullary micro-carinoma (in situ)	0 (0.0%)	1 (0.02%)*
Medullary carcinoma	0 (0.0%)	1 (0.02%)*
Papillary thyroid cancer	5 (0.11%)	3 (0.06%)*
Thyroidectomy performed (i.e., pathology report available)	6	3
Total	7 (0.15%)	3 (0.06%)

[1]Source: Table 12-45, NDA 22341

*1event of medullary carcinoma, 2 events of medullary microcarcinoma, and 1 event of PTC occurred in a single patient in the placebo group.

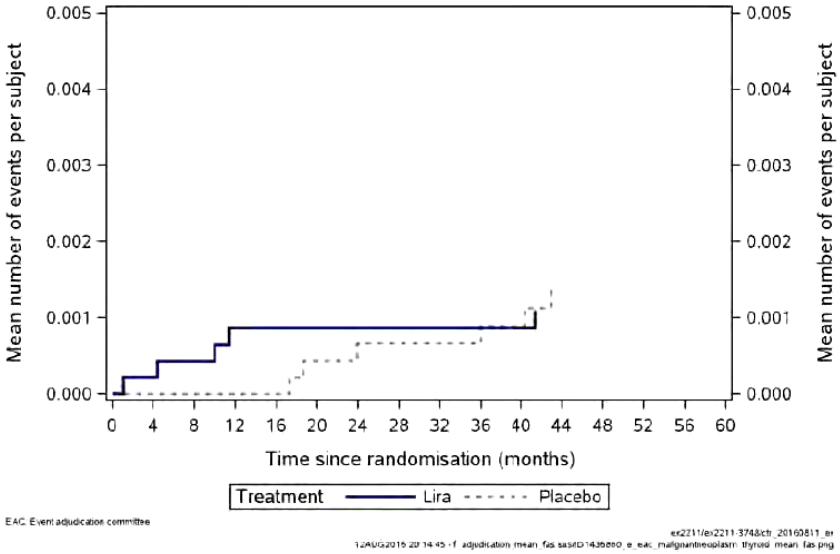
Regarding events of malignant thyroid neoplasms, the hazard ratio (HR) for malignant thyroid neoplasm in liraglutide- versus placebo-randomized subjects, derived from a Cox model with treatment as the only covariate, was 1.66 (95% CI: 0.40-6.95). According to the Sponsor, this non-significant hazard ratio indicates *no increased risk of malignant thyroid neoplasm associated with liraglutide use* (**Figure 3**).

Figure 3. Hazard Ratio for Malignant Thyroid Neoplasm in Liraglutide-randomized vs Placebo-randomized Subjects[1]



[1]Source: Figure 5-2, NDA 22341

Figure 4. Malignant thyroid neoplasm events by time since randomization[1]



14.3.1.124 EAC confirmed malignant thyroid neoplasm index events - mean number of events - plot - full analysis set

[1]**Source: Figure 14.3.1.124, NDA 22341**

Conclusions

Data from the LEADER trial do not demonstrate an increased risk of thyroid neoplasm overall, C-cell hyperplasia, or MTC in subjects randomized to liraglutide compared to placebo. Mild elevations in serum calcitonin levels (≥20 ng/L) were seen equally as frequently in the liraglutide and placebo groups (~3%), and no cases of C-cell hyperplasia or cases of MTC were seen in any subject in the liraglutide group during the trial period. Medullary thyroid cancer was seen in only one study subject, who was randomized to placebo.

Limitations to these data include small overall rates of any thyroid neoplasms in the study population (0.1% of subjects in the both the liraglutide and placebo groups) and relatively short duration of follow up (median 3.8 years) to observe an increased incidence in thyroid cancer event rates, given the generally slow-growing nature of thyroid malignancies. As noted by FDA reviewers at the time of approval of Victoza, because the background rate for medullary thyroid carcinoma is very low, a clinical trial, even a large trial such as LEADER, was not expected to have meaningful power to rule out an increased risk for medullary thyroid carcinoma with liraglutide unless this risk is substantial, and by extension, a clinical trial is not expected to have meaningful power to detect patients with an increase in calcitonin that is caused by medullary thyroid carcinoma or by a pre-neoplastic lesion that is destined to become medullary thyroid carcinoma. Evaluation of thyroid tumors in patients using liraglutide or any approved long-acting GLP-1 agonist is ongoing through post-marketing requirements, including epidemiologic studies and cardiovascular outcome trials (CVOTs) for other long-acting GLP-1 agonists.

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/s/

SHANNON D SULLIVAN
05/22/2017

MARINA ZEMSKOVA
05/22/2017

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022341Orig1s027

PHARMACOLOGY REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	22341
Supporting document/s:	1724 / 10.25.16 / Efficacy supplement S027 (LEADER trial), (b) (4) request 1729 / 11.01.16 / Efficacy supplement S027, Pediatric Study Plan (PSP)
Applicant's letter date:	25 October 2016
CDER stamp date:	25 October 2016
Product:	Victoza (liraglutide for injection)
Indication:	Approved as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM) Proposed as an adjunct to standard treatment of cardiovascular risk factors to reduce the risk of major adverse cardiovascular events (MACE) in adults with T2DM and high cardiovascular risk
Applicant:	Novo Nordisk Inc., PO Box 846 Plainsboro, NJ 08536
Review Division:	Metabolism and Endocrinology Products
Reviewer:	Anthony Parola, PhD
Supervisor/Team Leader:	Lee Elmore, PhD
Division Director:	Jean-Marc Guettier, MD
Project Manager:	Marisa Petruccelli

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1 Executive Summary

1.1 Introduction

Liraglutide, an active pharmaceutical ingredient in 3 approved products from Novo Nordisk, is a long-acting lipidated peptide glucagon-like peptide 1 (GLP-1) receptor agonist formulated as a solution for subcutaneous injection. Liraglutide (6 mg/mL solution) was first approved as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM) in January 2010 under NDA 22341 for Victoza at doses of 1.2 or 1.8 mg/day. Approval of Victoza included a postmarketing requirement for the sponsor to evaluate cardiovascular safety in a clinical study in patients with T2DM.

Victoza NDA 22341 efficacy supplement S027 (supporting document 1724) received 25 October 2016 from Novo Nordisk included a report for clinical study EX2211-3748 titled "Liraglutide Effect and Action in Diabetes: Evaluation of cardiovascular outcome results (LEADER®)" intended to fulfill post marketing requirement (PMR) 1583-9 evaluating the effects of Victoza on the incidence of major adverse cardiovascular events (MACE) in patients with T2DM and to support a new indication for Victoza as an adjunct to standard treatment of cardiovascular risk factors to reduce the risk of MACE in adults with T2DM and high cardiovascular risk. The sponsor requested (b) (4) for the efficacy supplement because the sponsor believes (b) (4) To support the new indication, the sponsor proposed (b) (4)

Efficacy supplement S027 requested a waiver for pediatric studies in patients less than 18 years old with T2DM and high cardiovascular risk because the condition is rare in that patient population. A Pediatric Study Plan (PSP) for the new indication (supporting document 1729 received 1 November 2016) requested a partial waiver from conducting pediatric studies for pediatric patients with T2DM less than 10 years old and a full waiver for pediatric patients with T2DM and high cardiovascular risk less than 18 years old. No new nonclinical information was submitted to support a waiver for clinical studies of liraglutide in pediatric patients with T2DM and high cardiovascular risk.

The current approved label for Victoza is not compliant with the Pregnancy and Lactation Labeling Rule (PLLR) because Victoza was approved prior to PLLR implementation. The proposed Victoza label submitted in efficacy supplement S027 revises sections "8.1 Pregnancy" and "8.3 Nursing Mothers" to comply with the PLLR and the revisions were based on premarketing and postmarketing pharmacovigilance data and previously reviewed nonclinical data.

1.2 Brief Discussion of Nonclinical Findings

Effects of Liraglutide in Mouse Models of Atherosclerosis

In 2 genetically modified mouse models of diet-induced atherosclerosis, liraglutide reduced the progression of aortic atherosclerotic plaques induced by a Western diet, but liraglutide did not affect regression of established plaques.

Effects of liraglutide on diet-induced atherosclerotic plaques were evaluated in a 3-part study in female apolipoprotein E-deficient (ApoE KO) mice. In part 1, ApoE KO mice were fed an atherogenic Western diet during 15 weeks of treatment with 0 (vehicle) or 1 mg/kg/day liraglutide. Compared to the vehicle group, liraglutide decreased body weight 18.8% in week 11, decreased aorta intima thickness in week 14, and decreased aortic plaque area in week 15.

Part 2 comparing effects of liraglutide in ApoE KO mice fed a western diet to a compound (identified as 0247-0000-001, also called 0247) of unknown pharmacologic activity that caused body weight loss showed anti-atherosclerotic effects of liraglutide were not secondary to lower body weight. In ApoE KO mice fed a western diet during 12 weeks of treatment with 0 (vehicle), 1 mg/kg/day liraglutide, or 0.2 or 0.8 mg/kg/day 0247, liraglutide decreased body weight gain and aortic plaque area without affecting total cholesterol levels compared to the vehicle control group while both doses of 0247 caused body weight loss without affecting diet-induced aortic plaque area or total cholesterol. Liraglutide had no effect on regression of established diet-induced aortic plaques. In part 3, female ApoE KO mice were fed a western diet to establish aortic plaques prior to being fed a normal rodent diet during 6 weeks of treatment with 0 (vehicle) or 0.6 mg/kg/day liraglutide (administered in equally divided doses of 0.3 mg/kg/injection). Liraglutide decreased body weight gain, decreased body weight, and reduced the atherogenicity of the plasma lipid profile (reduced total cholesterol 31.2%, reduced very low density lipoprotein cholesterol (VLDL-C) 35.7%, reduced low density lipoprotein cholesterol (LDL-C) 30.6% and increased high density lipoprotein cholesterol (HDL-C) 100%), but without affecting aortic plaque area. Compared to dietary intervention alone, liraglutide significantly altered expression of genes involved in the inflammatory process related to leukocyte recruitment (downregulated Ccr2, Cxcl12, Cx3cr1), leukocyte adhesion (downregulated Cx3cr1, Itga3, Thy1), lipid signaling (downregulated Ptgir), and fibrinolysis (downregulated Plat). However, the contribution of liraglutide-related changes in gene expression in aorta to any anti-atherosclerotic effects was confounded by the absence of an effect of liraglutide on regression of established aortic plaques in ApoE KO mice.

In male LDL receptor deficient (Ldlr KO) mice fed an atherogenic Western diet for 15 weeks beginning 2 weeks after starting treatment with vehicle or 1 mg/kg/day liraglutide, liraglutide decreased body weight gain 73.7% during treatment, reduced body weight 30.0% by the end of treatment, reduced atherogenicity of the plasma lipid profile (reduced total cholesterol 54.9%, reduced VLDL 62.9%, reduced LDL 49.6% and increased HDL 84.2%), and reduced the area of aortic plaques by 78.5%. All vehicle-treated Ldlr KO mice developed aortic plaques, but liraglutide prevented the formation of aortic plaques in 46.7% of Ldlr KO mice. Some liraglutide changes in aortic mRNA levels were consistent with anti-inflammatory effects (decreased Il1rn, Il6, Mmp12, and Mmp13 and increased Acta2), improved glucose homeostasis in the vasculature (increased Irs1 and Insr), and changes in plaque composition (increased smooth muscle Acta2 and Tag1n), but in the absence of GLP-1 receptor expression in aorta, mRNA level changes in aorta may be secondary to the less atherogenic lipid profile in liraglutide-treated Ldlr KO mice.

Human relevance of liraglutide-related decreased progression of atherosclerotic plaques in genetically modified mouse models of diet-induced atherosclerosis is confounded by:

1. The absence of effects of liraglutide on established plaques in ApoE KO mice, particularly since established atherosclerotic disease would have been expected to be present in subjects in the liraglutide cardiovascular outcomes, study EX2211-3748.

2. The absence of evidence levels of mRNAs consistent with anti-inflammatory effects are modified by liraglutide in ApoE KO mice under conditions that demonstrate effects of liraglutide on plaque regression.

3. An apparent correspondence between total cholesterol and LDL cholesterol lowering effects and reduced aortic plaque formation and progression in liraglutide-treated Ldlr KO mice compared to minimal total cholesterol and LDL cholesterol effects of liraglutide in humans.

Nonclinical Information for PLLR Compliance

No new nonclinical studies were submitted to support the proposed changes to the Victoza label to comply with the Pregnancy and Lactation Labeling Rule (PLLR). Nonclinical information in sections “8.1 Pregnancy” and “8.2 Lactation” in the current Victoza label are included in the proposed label intended to comply with PLLR (see Appendix 1). According to the label for Victoza:

Female rats given subcutaneous doses of 0.1, 0.25 and 1.0 mg/kg/day liraglutide beginning 2 weeks before mating through gestation day 17 had estimated systemic exposures 0.8-, 3-, and 11-times the human exposure at the MRHD based on plasma AUC comparison. The number of early embryonic deaths in the 1 mg/kg/day group increased slightly. Fetal abnormalities and variations in kidneys and blood vessels, irregular ossification of the skull, and a more complete state of ossification occurred at all doses. Mottled liver and minimally kinked ribs occurred at the highest dose. The incidence of fetal malformations in liraglutide-treated groups exceeding concurrent and historical controls were misshapen oropharynx and/or narrowed opening into larynx at 0.1 mg/kg/day and umbilical hernia at 0.1 and 0.25 mg/kg/day.

Pregnant rabbits given subcutaneous doses of 0.01, 0.025 and 0.05 mg/kg/day liraglutide from gestation day 6 through day 18 inclusive, had estimated systemic exposures less than the human exposure at the MRHD of 1.8 mg/day at all doses, based on plasma AUC. Liraglutide decreased fetal weight and dose-dependently increased the incidence of total major fetal abnormalities at all doses. The incidence of malformations exceeded concurrent and historical controls at 0.01 mg/kg/day (kidneys, scapula), ≥ 0.01 mg/kg/day (eyes, forelimb), 0.025 mg/kg/day (brain, tail and sacral vertebrae, major blood vessels and heart, umbilicus), ≥ 0.025 mg/kg/day (sternum) and at 0.05 mg/kg/day (parietal bones, major blood vessels). Irregular ossification and/or skeletal abnormalities occurred in the skull and jaw, vertebrae and ribs, sternum, pelvis, tail, and scapula; and dose-dependent minor skeletal variations were observed. Visceral abnormalities occurred in blood vessels, lung, liver, and esophagus. Bilobed or bifurcated gallbladder was seen in all treatment groups, but not in the control group.

In pregnant female rats given subcutaneous doses of 0.1, 0.25 and 1.0 mg/kg/day liraglutide from gestation day 6 through weaning or termination of nursing on lactation day 24, estimated systemic exposures were 0.8-, 3-, and 11-times human exposure at the MRHD of 1.8 mg/day, based on plasma AUC. A slight delay in parturition was observed in the majority of treated rats. Group mean body weight of neonatal rats from liraglutide-treated dams was lower than neonatal rats from control group dams. Bloody scabs and agitated behavior occurred in male rats descended from dams treated with 1 mg/kg/day liraglutide. Group mean body weight from birth to postpartum day 14 trended lower in F2 generation rats descended from liraglutide-treated rats compared to F2 generation rats descended from controls, but differences did not reach statistical significance for any group.”

Toxicity Study of Liraglutide in Juvenile Rats Supporting Pediatric Clinical Studies

No new nonclinical studies were submitted to support a waiver for pediatric studies of Victoza for the new indication as an adjunct to standard treatment of cardiovascular risk factors to reduce the risk of MACE in patients with T2DM and high cardiovascular risk. The sponsor is requesting a full waiver for pediatric studies for this indication for liraglutide because the condition is rare in children.

In a definitive study of 0.05, 0.25, or 1 mg/kg/day liraglutide in juvenile rats treated from postnatal days (PNDs) 21 to 90, systemic exposures were 0.5-, 3.6-, and 11.3-times the exposure in pediatric patients with T2DM, respectively, at the maximum recommended human dose (MRHD) of 1.8 mg/day liraglutide based on plasma liraglutide area under the curve (AUC) comparison. This study included vehicle control groups. Body weight 8.4% to 12.5% lower in males and 5.0% to 5.4% lower in females at ≥0.25 mg/kg/day liraglutide with corresponding 4% to 7% decreased food consumption in males at ≥0.25 mg/kg/day, but not in females at any liraglutide dose, were considered pharmacological effects. Ulna length was statistically significantly 2% shorter in males and 1% shorter in females at ≥0.25 mg/kg/day liraglutide. Liraglutide had no effect on motor activity in males, but in females, rearing was increased 49% and 30% in 0.25 and 1 mg/kg/day liraglutide groups in week 8. In males, the onset of balano-preputial separation was delayed 1.1 to 1.6 days at ≥0.25 mg/kg/day liraglutide and completion was delayed 2.9 days at 1 mg/kg/day, and the delay was attributed to decreased body weight gain, at least in part. In females, vaginal opening was delayed 4.8 to 7.8 days and relative weight of ovaries (normalized to body weight) was decreased 13.5% to 15.0% at ≥0.25 mg/kg/day while a higher incidence of slightly prolonged estrous cycle occurred at 1 mg/kg/day (0% and 45% in 0 and 1 mg/kg/day liraglutide groups, respectively), but delayed sexual maturation in females was not related to decreased body weight gain. Reversible hypertrophy in the Brunner's gland of duodenum considered adaptive occurred in males at ≥0.05 mg/kg/day liraglutide and in females at 0.05 and 1 mg/kg/day. The no observed adverse effect level (NOAEL) was 0.05 mg/kg/day liraglutide due to slightly shorter length of ulna and delayed sexual maturation in males and females and increased motor activity in females at 0.25 and 1 mg/kg/day liraglutide. After at least a 4 week recovery period, liraglutide treated rats were mated with untreated rats. Prior treatment of paternal or maternal rats with liraglutide had no effect on fertility or survival, clinical signs, body weight gain, body weight, or macroscopic pathology of offspring. Prior treatment of maternal female rats with 1 mg/kg/day liraglutide reduced the number of implantations per uterus (16.4 and 14.8 implantations in females treated with 0 and 1 mg/kg/day liraglutide, respectively), decreased the litter size (14.9 and 13.3 pups/litter born to females treated with 0 and 1 mg/kg/day liraglutide, respectively), and increased the percentage of male offspring (48.1% and 57.2% males in litters born to dams treated with 0 or 1 mg/kg/day liraglutide, respectively).

1.3 Recommendations

1.3.1 Approvability

Victoza was approved in January 2010.

No nonclinical studies were required for approval of efficacy supplement S027 indicating Victoza as an adjunct to standard treatment of cardiovascular risk factors to reduce the risk of MACE in adults with T2DM and high cardiovascular risk. Labeling recommendations based on studies evaluating anti-atherosclerotic effects of liraglutide in genetically modified mouse models of diet-induced atherosclerosis are included in this review in section "1.3.3 Labeling", below.

A pivotal toxicity study of liraglutide in juvenile rats supports clinical studies of liraglutide in pediatric patients with T2DM at least 10 years old, but the sponsor is requesting a full waiver for studies evaluating the use of Victoza in pediatric patients with T2DM and high cardiovascular

risk less than 18 years old because high cardiovascular risk is rare in pediatric patients with T2DM.

No new nonclinical clinical studies were requested or required for modifying the Victoza label to comply with the PLLR and labeling recommendations for sections “8.1 Pregnancy” and “8.3 Lactation” are included in this review in section “1.3.3 Labeling”, below.

1.3.2 Additional Non Clinical Recommendations

Internal

Seventy-one liraglutide-exposed pregnancies in women with diabetes mellitus (DM) with known outcomes were reported by the sponsor (69 up to May 2016 and 2 in June 2016). Fourteen of these pregnancies were terminated and fetal abnormalities were reported in 5 of the terminated pregnancies. Fetal abnormalities were also reported in 2 live births, 1 stillbirth, and 1 ongoing pregnancy. Of the 57 liraglutide-exposed pregnancies in women with DM with known outcomes that were not terminated, there were 25 cases of fetal loss including 21 spontaneous abortions and 4 stillbirths. In liraglutide-exposed pregnancies in women with DM, the apparent rate of birth defects was 12.7% (9/71), above the rate of 5% - 10% in women with pregestational diabetes with HbA1c >7, and the apparent rate of fetal loss was 43.9% (25/57), above the rate of 20 – 25% in women with HbA1c >10. Increased incidences of fetal malformations and fetal loss in liraglutide-exposed pregnancies in women with DM are consistent with increased incidences of malformations in fetuses from pregnant rats and rabbits treated with liraglutide during organogenesis and an increased incidence of early embryonic deaths in maternal rats treated with liraglutide 2 weeks prior to mating through organogenesis. Consider including outcomes from liraglutide-exposed pregnancies in women with DM in the label for Victoza.

Efficacy supplement S027 requests a waiver for studies of liraglutide in pediatric patients less than 18 years old and a PSP requests a partial waiver from conducting pediatric studies for pediatric patients with T2DM less than 10 years old and a full waiver for pediatric patients with T2DM and high cardiovascular risk less than 18 years old. A definitive toxicity study of liraglutide in juvenile rats was completed to support clinical studies of liraglutide in pediatric patients with T2DM at least 10 years old and obese pediatric patients at least 7 years old, and the sponsor did not propose any new nonclinical studies to support the waivers requested in the PSP. There were no finding in toxicity studies of liraglutide in juvenile rats (report 212291) that precludes the use of liraglutide in clinical studies in pediatric patients ≥10 years old with T2DM or obese pediatric patients ≥7 years old.

1.3.3 Labeling

PLLR Compliance

Appendix 1 shows the sponsor’s proposed label for Victoza NDA 22341 efficacy supplements S027 that includes sponsor changes tracked from the current label intended to comply with PLLR by modifying sections “8.1 Pregnancy” and “8.2 Lactation”. The reviewer recommended modifications to the sponsor’s proposed label are shown in section “11 Integrated Summary and Safety Evaluation” (below). The following proposed verbiage in the Victoza label is recommended to comply with the PLLR.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

(b) (4)

2 Drug Information

2.1 Drug

Proprietary Name: Victoza, Saxenda
CAS Registry Number: 204656-20-2
Generic Name: liraglutide
Code Name: NNC 90-1170, NNC 0090-0000-1170, NN2211, glipacyl
Chemical Name: Arg^{34}Lys^{26}-(N-ε-(γ-Glu-(N-α-hexadecanoyl)))-GLP-1[7-37]
Molecular Formula/Molecular Weight: $C_{172}H_{265}N_{43}O_{51}$ / 3751.2 Daltons
Structure or Biochemical Description:

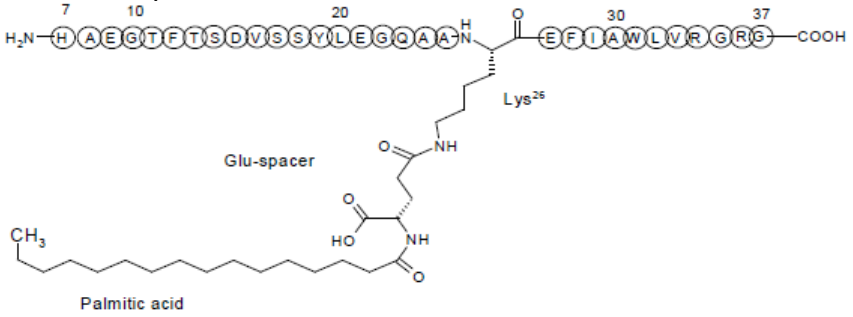


Figure 1 Molecular structure of liraglutide
One-letter amino acid codes are used in this figure.

[SD1 Module 2.6 Nonclinical Written and Tabulated Summaries Introduction P6]

Pharmacologic Class: glucagon-like peptide-1 (GLP-1) receptor agonist

2.2 Relevant INDs, NDAs, BLAs and DMFs

Liraglutide NDAs from Novo Nordisk

NDA 22341: Victoza®, up to 1.8 mg/day liraglutide for the treatment of T2DM (approved January 2010)
NDA 206321: Saxenda®, up to 3 mg/day liraglutide for weight management in obese and overweight adults (approved December 2014)
NDA 208583: Xultophy® 100/3.6, up to 50 units insulin degludec / 1.8 mg liraglutide for the treatment of T2DM (approved November 2016)

Liraglutide INDs from Novo Nordisk
IND 61040: treatment of type 2 diabetes mellitus (T2DM) (opened October 2000)
IND 73206: treatment of obesity in adults (opened September 2008)
IND 77460: nasal delivery for diabetes (terminated October 2015)
IND 109121: liraglutide and insulin degludec for the treatment of T2DM (opened January 2011)
(b) (4)
IND 115945: treatment of type 1 diabetes mellitus (T1DM) (inactive March 2016)
IND 121763: NNC9204-0530 and liraglutide for the treatment of obesity (opened June 2014)
(b) (4)

2.3 Drug Formulation

Victoza is a clear, colorless or almost colorless solution of 6 mg/mL liraglutide in a glass cartridge provided in a pre-filled Flexpen injector. The glass cartridge contains 3 mL of 6 mg/mL liraglutide and the inactive ingredients 1.42 mg/mL disodium phosphate dihydrate, 14 mg/mL propylene glycol, and 5.5 mg/mL phenol in water for injection. The Victoza Flexpen is capable of delivering up to 1.8 mg liraglutide (0.3 mL) in a single subcutaneous injection, the maximum recommended human dose (MRHD) for the treatment of T2DM.

2.6 Proposed Clinical Population and Dosing Regimen

Victoza (6 mg/mL liraglutide solution) for subcutaneous injection is approved as an adjunct to diet and exercise for the treatment of T2DM in adults at doses of 1.2 or 1.8 mg/day liraglutide. To improve gastrointestinal tolerability, the starting dose is 0.6 mg/day liraglutide for at least 1 week, and the dose should be escalated at a maximum rate of 0.6 mg/day/week up to the maintenance dose of 1.2 or 1.8 mg/day liraglutide. Liraglutide can be subcutaneously injected in the abdomen, thigh, or upper arm once a day any time of day without regard to meals.

Novo Nordisk is seeking a new indication for the same doses of Victoza as an adjunct to standard treatment of cardiovascular risk factors to reduce the risk of MACE in adults with T2DM and high cardiovascular risk based on completed cardiovascular outcomes trial EX2211-3748.

2.7 Regulatory Background

Liraglutide (6 mg/mL solution for subcutaneous injection) was investigated for the treatment of type 2 diabetes mellitus (T2DM) under IND 61040 opened in November 2000 and approved as an adjunct for diet and exercise to improve glycemic control in adults with T2DM under NDA 22341 for Victoza in January 2010. A higher dose of 3 mg/day liraglutide using the same formulation (6 mg/mL) was approved as an adjunct to a reduced calorie diet and increased physical activity for chronic weight management in obese adults (initial body mass index (BMI) $\geq$30 kg/m^2) or overweight adults (initial BMI $\geq$27 kg/m^2) with at least 1 weight-related comorbidity in December 2014 under NDA 206321 for Saxenda. Xultophy, a product combining 100 mg/mL insulin degludec with 3.6 mg/mL liraglutide, was approved as an adjunct to diet and exercise to improve glycemic control in adults with T2DM in November 2016 under NDA 208583.

Approval of Victoza included postmarketing requirement (PMR) 1583-9, a clinical study evaluating the effects of Victoza on the incidence of MACE in patients with T2DM and assess long-term effects of Victoza on specific adverse events of interest including potential biomarkers

of medullary thyroid carcinoma, pancreatitis, renal safety, serious hypoglycemia, immunological reactions, and neoplasms. NDA 22341 supporting document 1724 received 25 October 2016 included a final report for study EX2211-3748 titled "Liraglutide Effect and Action in Diabetes: Evaluation of cardiovascular outcome results (LEADER®)" intended to fulfill PMR 1583-9 and support efficacy supplement S027.

Efficacy supplement S027 proposes to indicate Victoza as an adjunct to standard treatment of cardiovascular risk factors to reduce the risk of MACE in adults with T2DM and high cardiovascular risk, based on results from the LEADER clinical study. The sponsor requested (b) (4) because the sponsor believes (b) (4) and requested a waiver for clinical studies in pediatric patients less than 18 years old with T2DM and high cardiovascular risk because the condition is rare. A Pediatric Study Plan (supporting document 1729 received 1 November 2016) requested a partial waiver from conducting pediatric studies for pediatric patients with T2DM less than 10 years old and a full waiver for pediatric patients with T2DM and high cardiovascular risk less than 18 years old. A definitive toxicity study of liraglutide in juvenile rats was completed to support clinical studies of liraglutide in pediatric patients with T2DM at least 10 years old and obese pediatric patients at least 7 years old, and the sponsor did not propose any new nonclinical studies to support the waivers requested in the PSP.

Efficacy supplement S027 included reports of 2 nonclinical pharmacology studies evaluating the effects of liraglutide in mouse models of atherosclerosis (b) (4)

The proposed label submitted with S027 also includes revised labeling intended to comply with the Pregnancy and Lactation Labeling Rule (PLLR). Two products from Novo Nordisk containing liraglutide include PLLR compliant labeling: Saxenda, a product for weight management of overweight and obese adults containing the same formulation of 6 mg/mL liraglutide as Victoza, and Xultophy, a combination product containing liraglutide and insulin degludec approved for the treatment of T2DM. Victoza and Xultophy are both indicated for the treatment of T2DM, therefore information about the use of liraglutide in pregnancy and lactation in the revised Victoza label should be based on the PLLR compliant Xultophy label (see Appendix 3).

A meeting of the Endocrinologic and Metabolic Advisory Committee to discuss the safety and efficacy findings from the LEADER clinical study is scheduled for 20 June 2017. Nonclinical information submitted for consideration in the FDA's background package for this advisory committee meeting is appended (Appendix 4).

3 Studies Submitted

3.1 Studies Reviewed

NDA 22341 supporting document 1724 received 25 October 2016

Primary Pharmacology

- Effect on atherosclerotic plaques in ApoE knock-out mice treated with liraglutide (report (b) (4) 140701, non-GLP)

- NN2211: Effect on atherosclerotic plaques in LDL receptor knock-out mice treated with liraglutide (report (b) (4) 141102, non-GLP)

3.2 Studies Not Reviewed

None

3.3 Previous Reviews Referenced

Victoza NDA 22341 Nonclinical Reviews
July 10, 2009 review of pivotal safety and toxicology studies

Saxenda NDA 206321 Nonclinical Reviews
May 20, 2015 review of toxicity studies or liraglutide in juvenile rats
February 19, 2016 memorandum regarding response to nonclinical information requests from review of toxicity studies of liraglutide in juvenile rats
February 17, 2017 review for PLLR compliance

Liraglutide for Weight Management IND 73206 Reviews
March 2, 2016 memorandum including revised NOAEL in the pivotal toxicity study of liraglutide in juvenile rats

Xultophy Label
16 November 2016 PLLR compliant label information for liraglutide

Saxenda Label
PLLR compliant label approved 26 April 2017

4 Pharmacology

4.1 Primary Pharmacology

Study title: Effect on atherosclerotic plaques in ApoE knock-out mice treated with liraglutide (report (b) (4) 140701, non-GLP)

Key Study Findings

- Liraglutide reduced the progression of aortic plaques induced by a western diet before and during treatment in female apolipoprotein E (ApoE) deficient mice (ApoE KO).
  - In part 1 (substudy (b) (4) 140701), ApoE KO mice fed a western diet during treatment with 0 (vehicle) or 1 mg/kg/day liraglutide, liraglutide decreased body weight 18.8% on day 77, decreased aorta intima thickness in week 14, and decreased aortic plaque area in week 15.
- Liraglutide reduced the area of aortic plaques induced by a western diet only during treatment (fed standard rodent chow before treatment) in female ApoE KO mice.
  - In part 2 (substudy (b) (4) 141101), although the sponsor states liraglutide prevents initiation of diet-induced aortic plaques, since atherosclerotic plaque formation in ApoE KO mice occurred on a standard rodent diet and plaques occurred in the liraglutide-treated group, liraglutide reduced progression of aortic plaques, but it did not prevent their formation.
  - Comparing effects of liraglutide in ApoE KO mice fed a western diet to a compound (identified as 0247-0000-001, also called 0247) of unknown pharmacologic activity that caused body weight loss showed anti-atherosclerotic effects of liraglutide were not secondary to lower body weight. In ApoE KO mice fed a western diet during 12 weeks of

treatment with 0 (vehicle), 1 mg/kg/day liraglutide, or 0.2 or 0.8 mg/kg/day 0247, liraglutide decreased body weight gain and aortic plaque area without affecting total cholesterol levels compared to the vehicle control group while both doses of 0247 caused body weight loss without affecting diet-induced aortic plaque area or total cholesterol.

- Liraglutide had no effect on regression of established diet-induced aortic plaques in female ApoE KO mice.
  - In part 3 (substudy (b) (4) 131001), 0.6 mg/kg/day liraglutide had no effect on aortic plaque area in female ApoE KO mice fed a western diet to establish aortic plaques prior to being fed a normal rodent during 6 weeks of treatment. Liraglutide decreased body weight gain, decreased body weight, and reduced the atherogenicity of the plasma lipid profile (reduced total cholesterol 31.2%, reduced VLDL 35.7%, reduced LDL 30.6% and increased HDL 100%), but without affecting aortic plaque area.
  - Compared to dietary intervetion alone, liraglutide significantly altered expression of genes involved in the inflammatory process related to leukocyte recruitment (downregulated Ccr2, Cxcl12, Cx3cr1) and adhesion (downregulated Cx3cr1, Itga3, Thy1), lipid signaling (downregulated Ptgir), and fibrinolysis (downregulated Plat). However, the contribution of liraglutide-related changes in gene expression in aorta to any anti-atherosclerotic effects is confounded by the absence of an effect of liraglutide on regression of established aortic plaques in ApoE KO mice.
- Study issues were:
  - In substudy (b) (4) 140701, the treatment period was 15 weeks and body weights were recorded daily, but the last body weights reported were day 77 (week 11), not day 105 (week 15).
  - The identity of the active comparator (0247-0000-0001) in substudy (b) (4) 140701 causing weight loss is unknown, so it may have GLP-1 receptor agonist activity related to weight loss, but without affecting progression of atherosclerotic plaques.
  - The contribution of liraglutide-related changes in gene expression in aorta to any anti-atherosclerotic effects is confounded by the absence of an effect of liraglutide on regression of established aortic plaques in ApoE KO mice.
  - Since aortic plaques occur in ApoE KO mice fed a normal rodent diet and aortic plaques formed in ApoE KO mice fed a standard rodent diet prior to starting treatment and a western diet during treatment, the efficacy of liraglutide to prevent plaque formation cannot be assessed in substudy (b) (4) 141101.

Summary and Conclusions

Effects of liraglutide on prevention and regression of atherosclerotic plaques were evaluated in a 3 part study in female apolipoprotein E (ApoE) deficient mice (ApoE KO).

In the first part evaluating effects of liraglutide on prevention of atherosclerotic plaques (study (b) (4) 140701), ApoE KO mice (9 – 12 weeks old) were fed a western diet (WD, diet D12079B from Research Diets (NJ) enriched in fat, carbohydrates, and cholesterol) and treated with 0 (vehicle; 50 mM phosphate, 70 mM NaCl, 0.05% polysorbate 80, pH 7.4) or 1 mg/kg/day liraglutide (0.2 mg/mL) by subcutaneous injection (5 mL/kg) once a day (n = 13 -15/group) or fed a regular rodent diet (RD, diet Altromin #1324, Brogaarden, Denmark) and treated with vehicle (n = 5) for 15 weeks. Dose groups are summarized in Table 1, below. To improve tolerability, the dose of liraglutide was escalated from 0.3 mg/kg on day 0 to 0.6 mg/kg on day 1 and finally to the maintenance dose of 1 mg/kg/day on day 2. Study parameters were body weight (daily), aortic intima thickness (assessed in isoflurane anesthetized mice by ultra sound imaging of the sinus aorta in week 14 after denuding the upper part of the thorax), and en face quantification of plaque lesion area in a predefined piece of the aortic arch (without staining).

Approximately 24 hours after the last dose, mice were anesthetized (fentanyl, fluanisone, and midazolam) and perfused with ice cold saline prior to excising a section of the aorta from the heart to the 8th rib, trimming the excess fat, cutting it open longitudinally, placing it on glass plates, imaging with a microscope "en face", and analyzing plaque area with Visiomorph software (Visiopharm A/S).

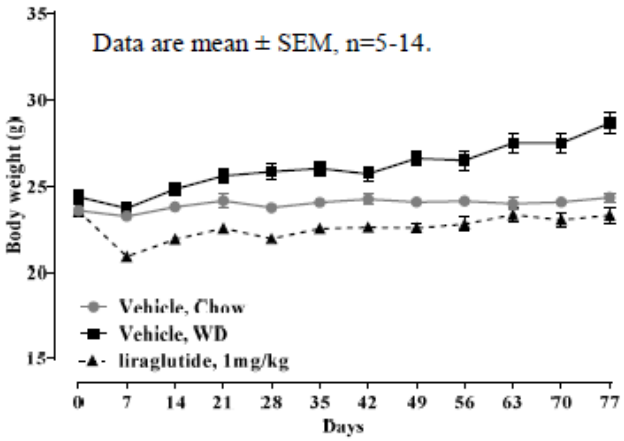
Table 1 Overview of dosing groups in the 3 different studies

Study no	Group no	Treatment	Diet	Number of animals
Gura140701	1	Vehicle	Chow (Altromin #1324)	5
	2	Vehicle	Western Diet (D12079B)	15
	3	Liraglutide, 1mg/kg	Western Diet (D12079B)	14

[P13]

In WD-fed ApoE KO mice, mean body weight in the liraglutide group was statistically significantly lower than the vehicle control group from day 7 to day 77 (Figure 2, below). On day 77, mean body weight in the liraglutide group (23.3 g) was 18.8% lower compared to the vehicle control group (28.7 g).

Figure 2 Body weight as function of time

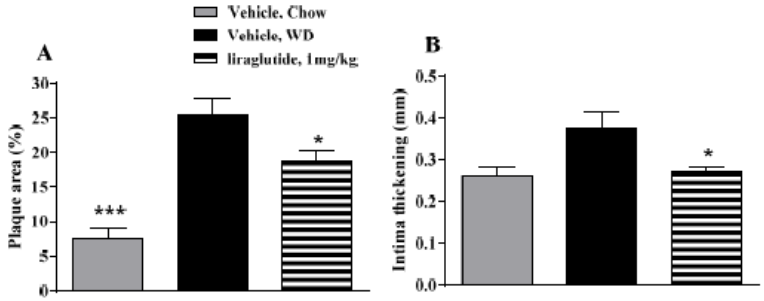


[P20]

Reviewer note: Figure 2 shows body weight up to day 77, but treatment was continued to week 15 (approximately day 105).

Aorta intima thickness was similar in vehicle-treated ApoE KO mice groups fed a RD or WD (Figure 1B, below). In female ApoE KO mice fed a WD, liraglutide decreased aorta intima thickness in week 14 (Figure 1B, below). In vehicle-treated female ApoE KO mice, Aortic plaque lesion area was statistically significantly lower in ApoE KO mice the fed a RD compared to the group fed a WD (Figure 1A, below). In ApoE KO mice fed a WD, liraglutide decreased aortic plaque lesion area (Figure 1A, below).

Figure 1 Aortic plaque lesions.



Plaque lesion area (A) and intima thickening by ultra sound imaging (B).
Data are mean±SEM, n=5-14. *p<0.05, ***p<0.0001 vs Vehicle, WD.

[P19]

In the second part evaluating effects of liraglutide on prevention of atherosclerotic plaques (study (b) (4) 141101), female ApoE KO mice (9 – 12 weeks old), were fed a RD during liraglutide dose escalation (using the same regimen as in study (b) (4) 140701), then switched to a WD and treated with 0 (vehicle), 1 mg/kg/day liraglutide (0.2 mg/mL), or 0.2 or 0.8 mg/kg/day 0247-0000-0001 (referred to as 0247) by subcutaneous injection (5 mL/kg) once a day (n = 13 - 15/group) or fed a RD and treated with vehicle (n = 6) for 12 weeks. Dose groups are summarized in Table 1, below. Study parameters were body weight (daily), terminal orbital sinus blood sample (K_3EDTA treated) for determining plasma triglycerides, cholesterol, and lipoprotein fractions, and en face quantification of plaque lesion area in a predefined piece of the aortic arch (without staining).

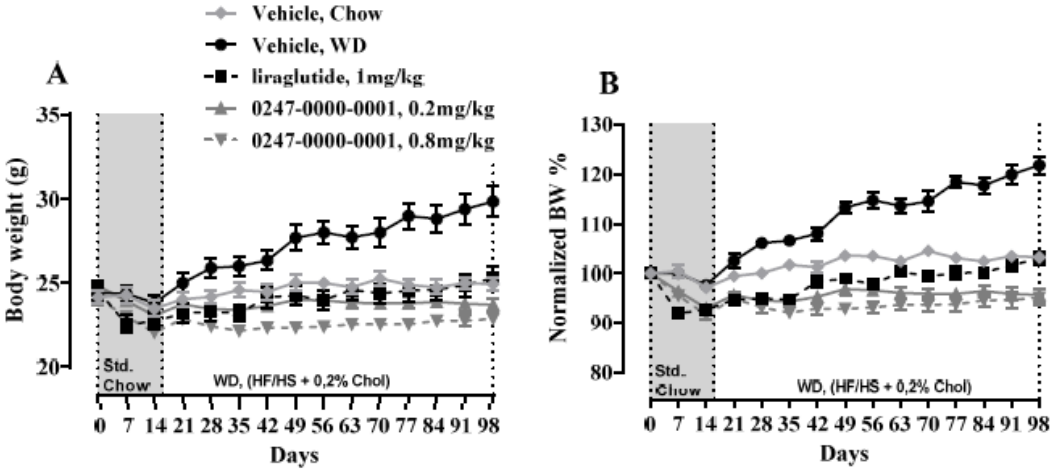
Table 1 Overview of dosing groups in the 3 different studies

Study no	Group no	Treatment	Diet	Number of animals
Gura141101	1	Vehicle	Chow (Altromin #1324)	6
	2	Vehicle	Western Diet (D12079B)	13
	3	Liraglutide, 1mg/kg	Western Diet (D12079B)	14
	4	0247-0000-0001, 0.2 mg/kg	Western Diet (D12079B)	14
	5	0247-0000-0001, 0.8 mg/kg	Western Diet (D12079B)	15

[P13]

Body weight on day 98 was higher in ApoE KO mice fed a WD compared to the RD (Figure 4A and 4B). In ApoE KO mice fed a WD, body weight gain during the treatment period was lower in the liraglutide group (gained 3% of initial body weight) compared to the vehicle control group (gained 22% of initial body weight). WD-fed ApoE KO mice treated with 0247 lost weight. In WD-fed ApoE KO mice treated with 0.2 or 0.8 mg/kg/day 0247, body weight at the end of treatment was 5% lower than their initial body weight.

Figure 4 Body weight



Body weight during the time course (A), and normalized body weight (B). Data are mean±SEM, n=5-15.

[P22]

In vehicle-treated ApoE KO mice, total cholesterol was increased in mice fed a WD compared to RD-fed mice in weeks 8 and 14 (Table 2, below), but there were no diet-dependent differences in plasma triglyceride levels (Table 3, below). In ApoE KO mice fed a WD, liraglutide had no effect on total cholesterol, but plasma triglycerides were lower compared to the vehicle control group in week 8, but not in week 14. The active comparator 0247 that decreased body weight did not lower plasma total cholesterol or triglycerides in WD-fed ApoE KO mice.

Table 2 Plasma T-Chol

		Vehicle, Chow	Vehicle, WD	Liraglutide, 1mg/kg	0247-0000-0001, 0.2 mg/kg	0247-0000-0001, 0.8 mg/kg
Weeks:	2	10,4±0.5	9.5±0.4	5,7±0.2	11,2±0.3	11,5±0.4
	8	11,6±0.6	31.1±0.9	27,2±1.9	39,0±1.3	33,9±1.7
	14	10,5±0.7	28.2±1.3	25,7±2.1	38,4±0.7***	29,3±2.2

Data are mean ± SEM, n=5-15. One-Way ANOVA at each time point, Dunnett's post-hoc analysis for comparison between groups, ***p<0.0001 vs. Vehicle WD

[P21]

Table 3 Plasma TG

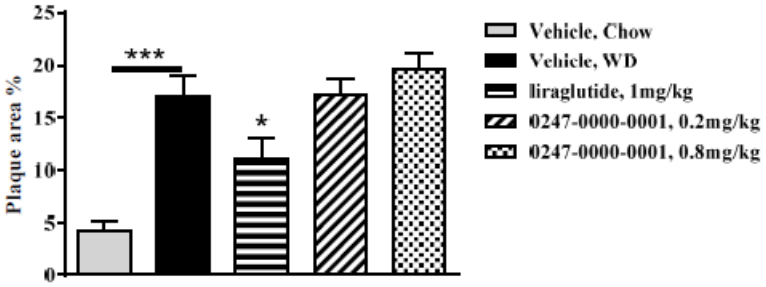
		Vehicle, Chow	Vehicle, WD	Liraglutide, 1mg/kg	0247-0000-0001, 0.2mg/kg	0247-0000-0001, 0.8mg/kg
Weeks:	2	1,7±0.15	1,6±0.07	1,5±0.11	1,5±0.08	1,4±0.08
	8	1,6±0.16	1,7±0.06	1,2±0.05***	1,6±0.07	1,4±0.07
	14	0,9±0.10	1,2±0.08	1,0±0.07	1,3±0.07	1,1±0.07

Data are mean ± SEM, n=5-15. One-Way ANOVA at each time point, Dunnett's post-hoc analysis for comparison between groups, ***p<0.0001 vs. Vehicle WD

[P21]

In vehicle-treated ApoE KO mice, aortic plaque lesion area in the RD-fed group was statistically significantly lower compared to the WD-fed group (Figure 3, below). In WD-fed ApoE KO mice, liraglutide decreased aortic plaque lesion area, but 0.2 or 0.8 mg/kg/day 0247 had no effect (Figure 3, below).

Figure 3 Aortic plaque lesions as assessed by the "en face" method



Data are mean ± SEM, n=5-15, One Way ANOVA, Dunnett's post-hoc analysis for comparison between groups,

*p<0.05; ***p<0.0001 vs. Vehicle, WD

[P20]

In the third part of the study evaluating effects of liraglutide on regression of established atherosclerotic plaques (study (b) (4) 131001), female ApoE KO mice (9 – 12 weeks old) were fed a WD for 10 weeks to establish atherosclerotic plaques prior to switching to a RD and initiating treatment with 0 (vehicle) or 0.6 mg/kg/day liraglutide (administered in equally divided doses twice a day, 2 x 0.3 mg/kg/injection) for 6 weeks (n = 14 – 17/group). A diet control group was fed a RD for 10 weeks prior to treatment with vehicle (0 mg/kg/day) for 6 weeks (n = 8). Dose groups are summarized in Table 1, below. To improve tolerability, the dose of liraglutide was escalated from 0.1 mg/kg/injection on day 0 to 0.2 mg/kg/injection on day 1 and finally to the maintenance dose of 0.3 mg/kg/injection on day 2. Study parameters were body weight (weekly), terminal orbital sinus blood sample (K_3EDTA treated) for determining plasma liraglutide (a non-validated method with a 200 pM lower limit of quantitation), triglycerides, cholesterol, and lipoprotein fractions, and approximately 24 hours after the last dose, en face quantification of plaque lesion area in a predefined piece of the aortic arch (without staining). A piece of aorta was snap frozen in liquid N_2 and stored at -80C for mRNA analysis (Nanostring analysis of 275 genes using GEN2 nCounter PrepStation and Digital Analyzer with nSolver Analysis software 2.5).

Table 1 Overview of dosing groups in the 3 different studies

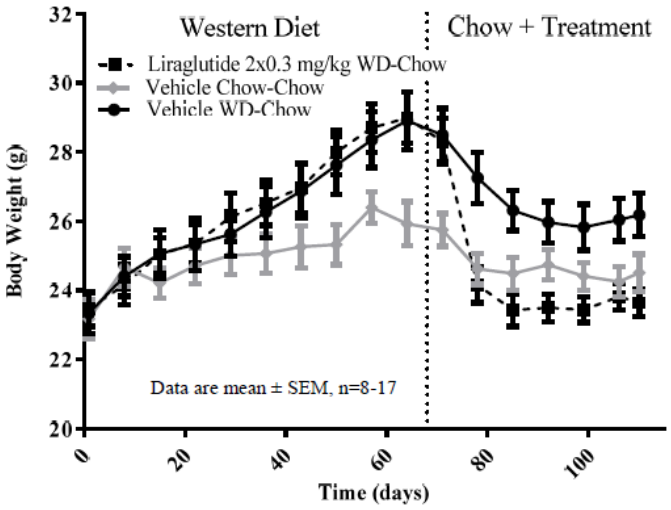
Study no	Group no	Treatment	Diet	Number of animals
BidR131001	1	Vehicle	Chow-Chow (Altromin #1324)	8
	2	Vehicle	Western Diet - (D12079B) -Chow (Altromin#1324)	17
	3	Liraglutide 2 x 0.3 mg/kg	Western Diet - (D12079B) -Chow (Altromin#1324)	14

[P13]

Body weight at the end of the 10 week period of diet induced atherosclerosis was higher in ApoE KO mice fed a WD (29 g) compared to RD-fed mice (26 g) due to higher body weight gain in WD groups (6 g during the 10 week period in WD groups compared to 3 g in the RD group) (Figure 5, below). During the 6 week treatment period, all groups were fed a RD. At the end of the 6 week treatment period in mice switched from a WD to a RD (WD/RD), body weight was lower in the liraglutide group (23.6 g) compared to the vehicle control group (26.2 g). At the end

of treatment in vehicle control groups, body weight of ApoE mice fed a RD before and during treatment (24.5 g) was lower compared to the WD/RD group (26.2 g).

Figure 5 Body weight as function of time



[P23]

In ApoE KO mice switched from a WD to a RD during treatment, plasma lipid parameters were less atherogenic in the liraglutide group compared to the vehicle group due to 31.2% lower total cholesterol, 30.6% lower LDL-C, 35.7% lower VLDL-C, and 100% higher HLD-C along with 35.7% lower triglycerides (Table 4, below).

Table 4 Plasma lipid levels at termination

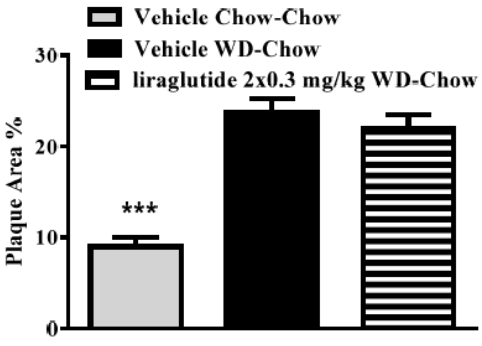
Group	Triglyceride, mM	Total Cholesterol, mM	HDL-cholesterol, mM	LDL-cholesterol, mM	VLDL-cholesterol, mM
1. vehicle (Chow-Chow)	1.3±0.1	9.4±0.4	0.14±0.03	4.2±0.2	5.0± 0.3
2. vehicle (WD-Chow)	1.4±0.1	9.3±0.3	0.20±0.02	4.9±0.2	4.2±0.2
3. liraglutide (WD-chow)	0.9±0.1***	6.4±0.2***	0.40±0.05**	3.4±0.1***	2.7±0.2***

Data are mean±SEM, n=8-17, ***p<0.0001, **p<0.001 Students t-test (gr 2 vs gr 3)

[P24]

At the end of treatment in vehicle control groups, aortic plaque lesion area in ApoE KO mice fed a RD before and during treatment was lower compared to the group that switched from a WD to a RD (Figure 6). In WD/RD ApoE KO mice, liraglutide had no effect on aortic plaque lesion area (Figure 6). Plasma liraglutide concentration at termination was 88 nM.

Figure 6 Aortic plaque lesion area as assessed by the "en face" method



Data are mean ± SEM, n=8-17, One Way ANOVA, Tukeys post-hoc analysis for comparison between groups, ***p<0.0001

[P24]

Relative mRNA levels from 275 genes in aorta were determined using nanostring nCounter analysis. Principle component analysis determined dietary treatment (RD only versus WD/RD) accounted for variance in gene expression, but liraglutide treatment resulted in relatively minor changes in addition to dietary changes in the WD/RD group. Table 5 shows in vehicle treated ApoE KO mice, 41 genes were significantly regulated in the WD/RD group compared to the RD only group (Diet Effect in Table 5). In WD/RD ApoE KO mice, liraglutide treatment altered expression of an additional 20 genes (20 more genes compared to the larger effect of dietary change on 41 genes, and 5 of the 20 genes were nominally significantly regulated by dietary intervention) (Treatment Effect in Table 5).

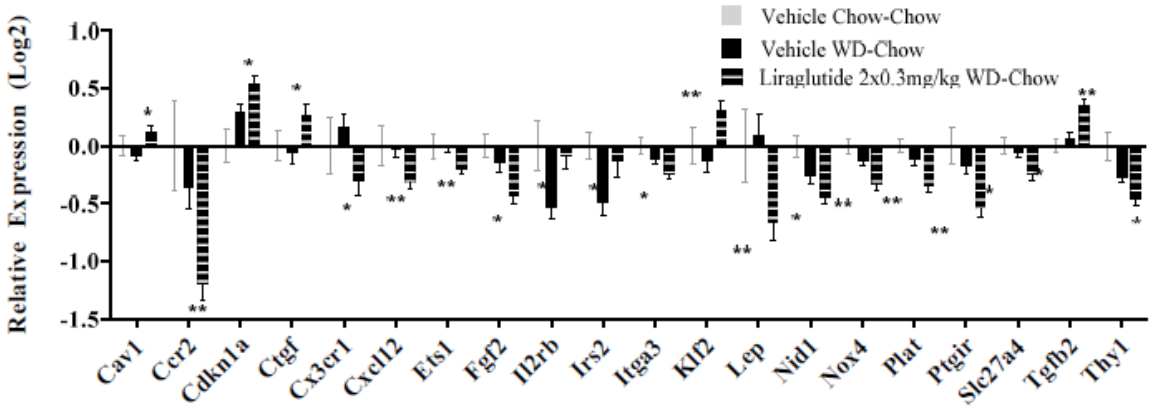
Table 5 Group wise comparison for number of genes nominal significantly regulated.

Comparisons	Number of genes nominal significantly regulated (p<0.05)
Diet Effect	
Chow-Chow compared to WD-Chow	41
Treatment Effect	
Liraglutide compared to WD-Chow	20

[P26]

Figure 8 shows relative mRNA levels from 20 genes considered regulated by liraglutide (caveolin 1 (Cav1), chemokine (C-C) receptor 2 (Ccr2), cyclin-dependent kinase inhibitor 1A (Cdkn1a), connective tissue growth factor (Ctgf), chemokine (C-X3-C) receptor 1 (Cx3cr1), chemokine (C-X-C motif ligand 12 (Cxcl12), E26 avian leukemia oncogene 1, 5' domain (Ets1), fibroblast growth factor 2 (Fgf2), interleukin 2 receptor beta chain (Il2rb), insulin receptor substrate 2 (Irs2), integrin alpha 3 (Itga3), Kruppel-like factor 2 (Klf2), leptin (Lep), nidogen 1 (Nid1), NADPH oxidase 4 (Nox4), tissue plasmogen activator (Plat), prostaglandin I receptor (Ptgir), solute carrier family 27 member 4 (Slc27a4), transforming growth factor beta 2 (Tgfb2), and thymus cell anitgen 1 theta (Thy1)). GLP-1 receptor mRNA levels were below the limit of detection in all groups. Compared to dietary intervetion alone, liraglutide significantly altered expression of genes involved in the inflammatory process related to leukocyte recruitment (downregulated Ccr2, Cxcl12, Cx3cr1) and adhesion (downregulated Cx3cr1, Itga3, Thy1), lipid signaling (downregulated Ptgir), and fibrinolysis (downregulated Plat).

Figure 8 Liraglutide effects on mRNA expression.



Data are mean ± SEM, n=8-16, Unpaired t-test comparing Vehicle WD-Chow with Liraglutide 2x0.3mg/kg WD-Chow, **p<0.01; *p<0.05

[P27]

Study title: NN2211: Effect on atherosclerotic plaques in LDL receptor knock-out mice treated with liraglutide (report (b) (4) 141102, non-GLP)

Key Study Findings

- In male LDL receptor deficient (Ldlr KO) mice fed an atherogenic western diet for 15 weeks beginning 2 weeks after starting treatment with vehicle or 1 mg/kg/day liraglutide, liraglutide decreased body weight gain during treatment by 73.8%, reduced body weight 30.0% by the end of treatment, reduced the atherogenicity of the plasma lipid profile (reduced total cholesterol 54.9%, reduced VLDL 62.9%, reduced LDL 49.6% and increased HDL 84.2%), and reduced the area of aortic plaques by 78.5%.
  - Some liraglutide changes in aortic mRNA levels of were consistent with anti-inflammatory effects, improved glucose homeostasis in the vasculature, and changes in plaque composition, but in the absence of GLP-1 receptor expression in aorta, mRNA level changes in aorta may be secondary to the less atherogenic lipid profile in liraglutide-treated Ldlr KO mice.

Summary and Conclusions

Effects of liraglutide on prevention of atherosclerotic plaques were evaluated in a study in male low density lipoprotein receptor (Ldlr) deficient mice (Ldlr KO).

In a 17 week study, male Ldlr KO mice (20 vehicle control and 15 liraglutide treated, 10 – 11 weeks old) were subcutaneously injected once a day with 0 (vehicle; 20 mM phosphate, 130 mM NaCl, 0.05% polysorbate 80, pH 7.4) or 1 mg/kg/day liraglutide (see Table 1, below). To improve tolerability, the dose of liraglutide was escalated from 0.3 mg/kg on day 0 to 0.6 mg/kg on day 1 and finally to the maintenance dose of 1 mg/kg/day from day 2 to the end of treatment (week 17). Mice were fed a standard rodent diet (RD, diet Altromin #1324, Brogaarden, Denmark) for the first 2 weeks of treatment, and then switched to an atherogenic western diet (WD, diet D12079B from Research Diets, NJ enriched in fat, carbohydrates, and cholesterol) until the end of the study. Study parameters were body weight (daily), terminal orbital sinus blood sample (K_3EDTA treated) for determining plasma triglycerides, total cholesterol, and lipoprotein fractions (very low density lipoprotein (VLDL), low density lipoprotein

(LDL), and high density lipoprotein (HDL) cholesterol), plaque lesion area in the aortic arch, and aortic arch mRNA levels (275 genes comprising markers of inflammation, atherosclerosis, injury, and connective tissue disorders). Approximately 24 hours after the last dose, mice were anesthetized (isoflurane/N_2O) and perfused with ice cold saline prior to excising a section of the aorta from the heart to the 8th rib, trimming the excess fat, cutting it open longitudinally, placing it on glass plates, and imaging it with a microscope "en face" without staining. Plaques were analyzed with Visiomorph software (Visiopharm A/S). A piece of aorta was snap frozen in liquid N_2 and stored at -80C for mRNA analysis (Nanostring analysis of 275 genes using GEN2 nCounter PrepStation and Digital Analyzer with nSolver Analysis software 2.5).

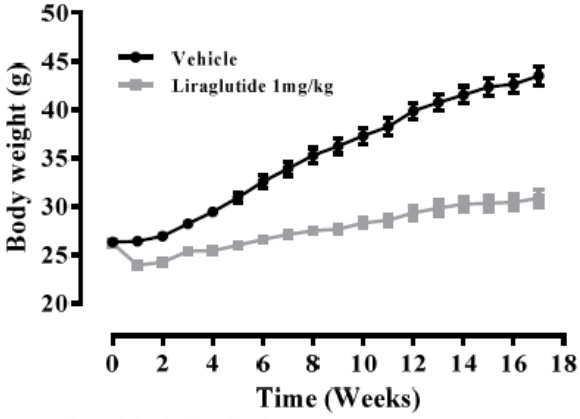
Table 1 Overview of dosing solutions and volumes during the full dose period

Group	Compound/ treatment	Formulation batch numbers	Dose (mg/kg)	Dosing Volume (ml/kg)	Dosing solution conc. (mg/ml)
1	vehicle	-	-	5	-
2	liraglutide	14A, 15A, 16A, 17A, 18A, 37A, 38A	1	5	0.2

[P9]

Liraglutide decreased body weight and body weight gain in WD-fed Ldlr KO mice. By the end of treatment, mean body weight in the liraglutide group (30.9 g) was 30.0% lower compared to vehicle control group (43.5 g) due to 73.7% lower body weight gain in the liraglutide group (Figure 4, below).

Figure 4 Body weight.

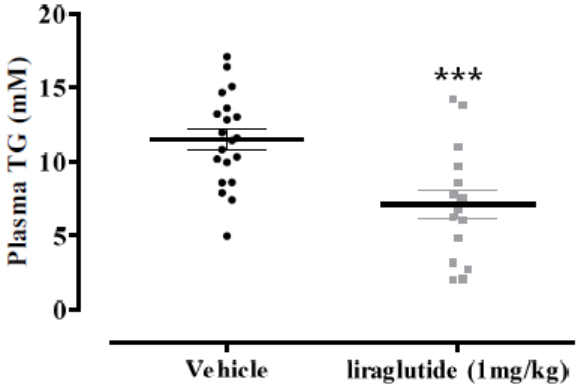


Body weight during the time course.
Data are mean±SEM, n=15-20. ***p<0.0001 vs Vehicle.

[P16]

Liraglutide-related changes in the lipid profile were consistent with reduced atherogenicity (decreased total cholesterol, VLDL, and LDL and increased HDL). Plasma lipid parameters at the end of treatment were lower in the liraglutide group compared to the vehicle group including 38.3% lower triglycerides (Figure 2).

Figure 2 Terminal plasma TG.

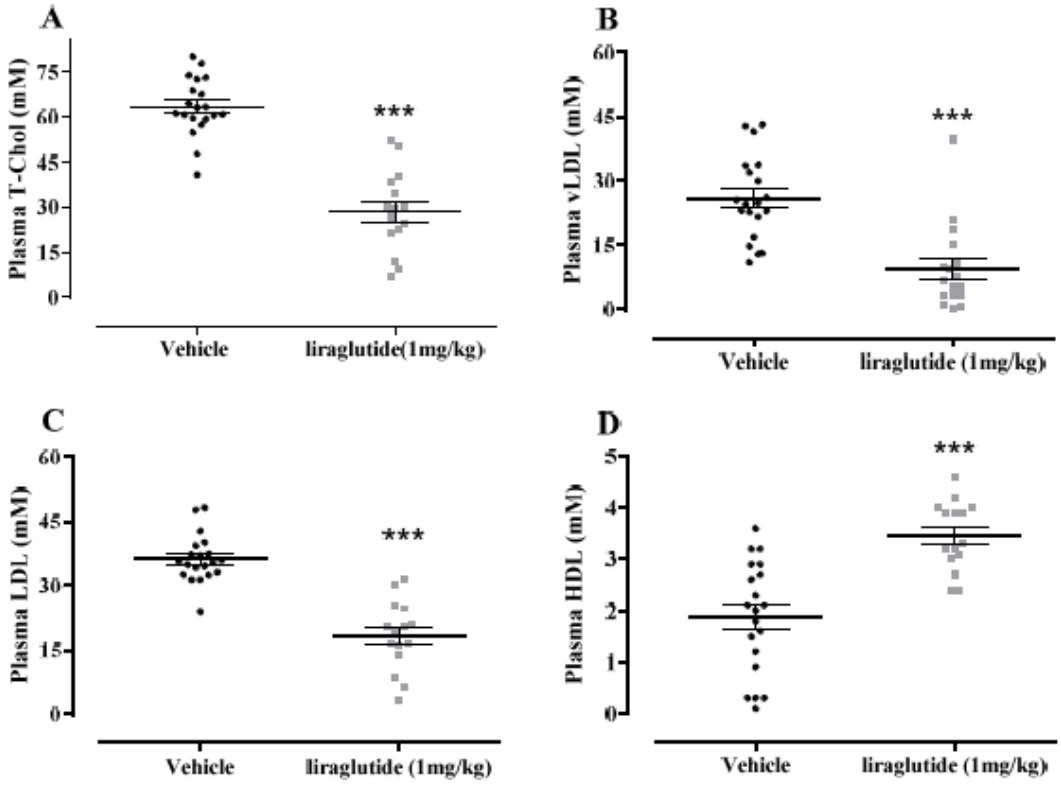


Data are mean±SEM, n=15-20. ***p<0.0001 vs vehicle.

[P14]

Compared to the vehicle control group, total cholesterol was 54.9% lower in the liraglutide group due to 49.6% lower LDL and 62.9% lower VLDL (Figure 3A - C, below). Compared to the vehicle control group, HLD-C was 84.2% higher in the liraglutide group (Figure 3D, below).

Figure 3 Terminal cholesterol lipoproteins.



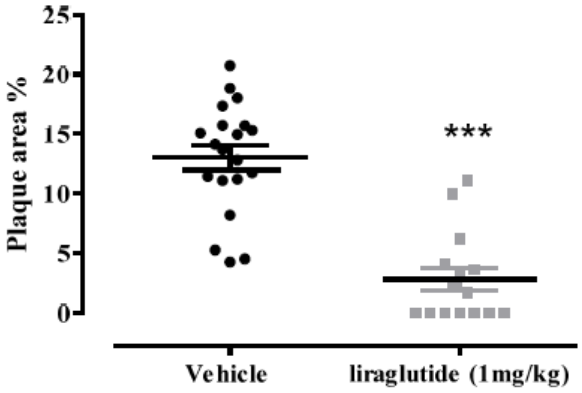
Plasma T-Chol (A), Plasma vLDL (B), Plasma LDL (C) and Plasma HDL (D).
Data are mean±SEM, n=15-20. ***p<0.0001 vs Vehicle.

[P15]

Consistent with an improved plasma lipid profile, liraglutide reduced the area of aortic atherosclerotic plaques. Aortic plaques occurred in all vehicle-treated Ldlr KO mice and 8/15

(53.3%) of liraglutide-treated mice. Aortic plaque area in the liraglutide group (2.8% of area) was 78.5% lower compared to the vehicle control group (13% of area) (Figure 1, below).

Figure 1 Aortic plaque lesions.



Data are mean±SEM, n=15-20. ***p<0.0001 vs Vehicle

[P14]

Relative mRNA levels (gene expression) of 275 genes in aorta were determined using nanostring nCounter analysis. Principle component analysis determined liraglutide caused changes in expression of some mRNAs (greater than the variance within the dataset). Liraglutide differentially regulated (upregulated or downregulated) mRNA levels from 123 genes (Table 3, below).

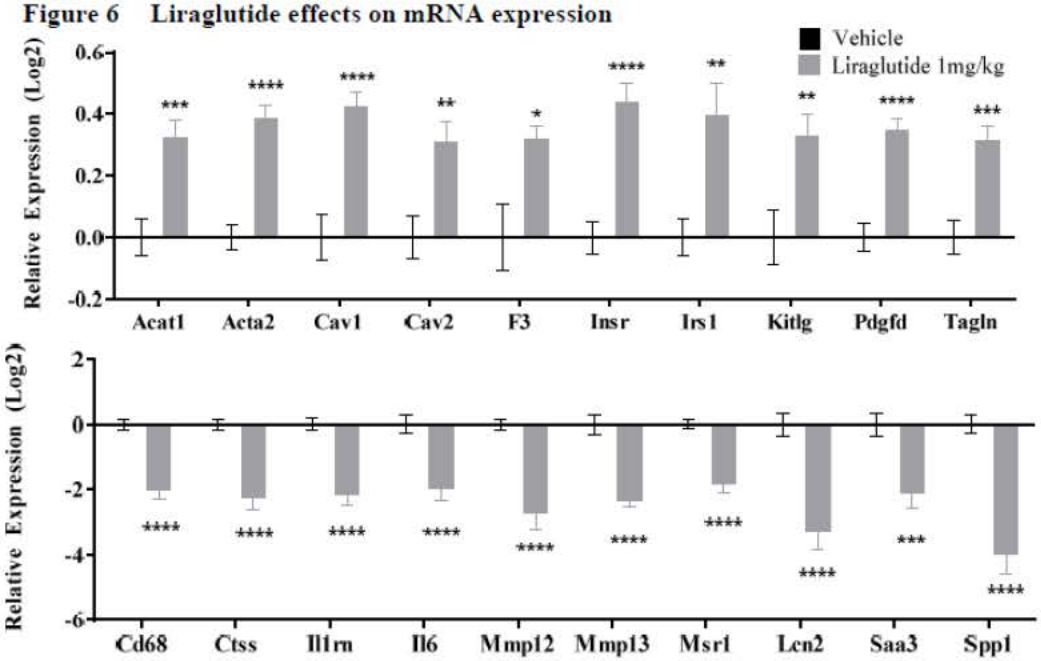
Table 3 Number of genes nominal significantly regulated by liraglutide.

Comparison	Number of genes nominal significantly regulated ($p<0.05$)
Liraglutide Effect	123

[P17]

Figure 6 shows relative mRNA levels of 20 genes considered regulated by liraglutide. Ten aortic mRNA levels with the highest magnitude of upregulation by liraglutide were acetyl-CoA acetyltransferase 1 (Acat1), smooth muscle aortic alpha-actin (Acta2), caveolin 1 (Cav1), caveolin 2 (Cav2), coagulation factor III (F3), insulin receptor (Insr), insulin receptor substrate 1 (Irs1), KIT ligand (Kitlg), platelet-derived growth factor (Pdgfd) and transgelin (Tagln). Ten aortic mRNA levels with the highest magnitude of down-regulation by liraglutide were CD68 (Cd68), cathepsin (Ctss), interleukin 1 receptor antagonist (Il1rn), interleukin 6 (Il6), matrix metallopeptidase 12 (Mmp12), matrix metallopeptidase 13 (Mmp13), macrophage scavenger receptor 1 (Msr1), lipocalcin 2 (Lcn2), serum amyloid A3 (Saa3), and secreted phosphoprotein 1 (Spp1). GLP-1 receptor mRNA was below the limit of detection in aorta from both groups.

Figure 6 Liraglutide effects on mRNA expression



Data are means ± SEM; Statistics: unpaired t-test; * p<0.05; **p<0.01; ***p<0.001; ****p<0.0001

[P18]

According to the sponsor, based on changes in aorta mRNA levels, liraglutide may have anti-inflammatory effects by decreasing leukocyte recruitment (decreased Il1rn and Il6) and leukocyte extravasation (increased Acta2 and decreased Mmp12 and Mmp13). Increased smooth muscle cell Acta2 and Tag1n mRNA levels suggest changes in plaque composition relevant to advanced lesion formation. Increased mRNA levels for insulin receptor and insulin receptor substrate-1 suggest improvements in glucose homeostasis and insulin signaling in the vasculature. Liraglutide induced reductions in osteopontin (Spp1) and interleukin-6 (Il6) aortic mRNA in Ldlr KO mice suggest human relevance for these findings because osteopontin is associated with coronary atherosclerosis and cardivascular disease and interleukin-6 is a potential predictive biomarker for cardiovascular disease in patients with T2DM.

11 Integrated Summary and Safety Evaluation

Victoza efficacy supplement S027 (included in supporting document 1724) proposes to add an indication for the use of Victoza as an adjunct to standard treatment of cardiovascular risk factors to reduce the risk of MACE in adults with T2DM and high cardiovascular risk, based on results from the LEADER clinical study. In the efficacy supplement, the sponsor proposed [redacted] (b) (4) revised section 8 of the Victoza label to comply with the Pregnancy and Lactation Labeling Rule (PLLR) based on existing nonclinical data and updated human data submitted to support a PLLR compliant label for Xultophy, a combination product containing liraglutide and insulin degludec approved under NDA 208583 in November 2016, and requested a waiver for studies of liraglutide in pediatric patients with T2DM and high cardiovascular risk because the condition is rare and submitted a PSP.

Proposed Changes to Victoza Label (b) (4)

In the proposed amended label submitted in efficacy supplement S027, the sponsor added the following statement (b) (4) to support the proposed new indication for Victoza:

(b) (4)

Sponsor Rationale

The sponsor evaluated effects of liraglutide in 2 rodent models of atherosclerosis induced by high fat western diets: female apolipoprotein E (ApoE) deficient mice (ApoE KO) and male low density lipoprotein receptor (Ldlr) deficient mice (Ldlr KO). In female ApoE KO mice, liraglutide decreased aortic plaque lesion size, decreased aorta intima thickness, and reduced aorta inflammation, and based on the absence of anti-atherosclerotic effects of a comparator drug that caused body weight loss, anti-atherosclerotic effects of liraglutide were not dependent on decreased body weight gain. In ApoE KO mice with established aortic plaques, liraglutide had no effect on plaque size, but liraglutide had an anti-inflammatory effect in aorta detected by changes for mRNAs from genes involved in leukocyte recruitment, adhesion, and migration and extracellular matrix protein turnover. In male Ldlr KO mice, liraglutide decreased aortic plaques along with significantly reducing body weight gain, plasma triglycerides, very low density lipoproteins, and low density lipoproteins and increasing high density lipoproteins. Liraglutide decreased mRNA expression changes in aorta induced by a western diet including mRNAs encoding proteins associated with leukocyte recruitment, adhesion, and migration.

The sponsor provided their rationale (b) (4) (b) (4) "2.4.5 Integrated Overview and Conclusions" in the document titled "Non-clinical Overview – Addendum" submitted in module 2.4 of efficacy supplement S027. The sponsor states GLP-1 receptor (GLP1R) agonists lower systolic blood pressure and increase heart rate, and based on literature reports, GLP1R agonists are cardioprotective, reduce atherosclerosis, increase plaque stability, and attenuate platelet function. ApoE KO and Ldlr KO mice are widely used to study atherosclerosis. GLP-1Rs are expressed in heart, vasculature, immune system, and kidneys. These receptors may mediate, directly or indirectly, cardiovascular and microvascular effects of GLP-1. Genome-wide association studies identified 5 interaction networks involved in coronary artery disease, and the 4 most important networks were linked to lipid metabolism and inflammation and a glucose lowering GLP-1R variant was protective for coronary artery disease. The sponsor asserts their nonclinical data showing liraglutide attenuates atherosclerosis and reduces inflammation in mouse models of atherosclerosis (b) (4) for major adverse cardiovascular event (MACE) risk reduction observed in study 3748 (the LEADER clinical trial), and MACE risk reduction is in addition to effects of liraglutide to lower blood glucose, body weight, and blood pressure.

Reviewer Assessment

Based on results from clinical study EX2211-3748 titled "Liraglutide Effect and Action in Diabetes: Evaluation of cardiovascular outcome Results (LEADER®)" that enrolled 9,340 patients, Novo Nordisk is seeking approval for a new indication for the use of Victoza as an adjunct to standard treatment of cardiovascular risk factors to reduce the risk of MACE

(cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke) in adults with T2DM and high cardiovascular risk.

MACEs are cardiovascular death (death due to acute myocardial infarction, heart failure, stroke, sudden cardiac death (unexpected death not following an acute MI), or other cardiovascular causes (i.e., dysrhythmia unrelated to sudden cardiac death, pulmonary embolism)), nonfatal myocardial infarction, or nonfatal stroke. A primary cause of MACE is macrovascular disease (coronary artery disease and cerebrovascular disease) due to arterial atherosclerotic plaques and thrombi that reduce and occlude blood flow to the heart and brain. The pathogenesis of atherosclerosis, a highly complex process, is shown in Figure 1 (from Rader and Daugherty, Nature. 2008 Feb 21;451(7181):904-13). Major risk factors for atherosclerotic cardiovascular disease are advanced age, increased total serum cholesterol, non-HDL-C, and LDL-C, low HDL-C, diabetes melliuts, hypertension, chronic kidney disease, cigarette smoking, and a family history of atherosclerotic cardiovascular disease (Jellinger et al, Endocr Pract. 2017 Feb 3. doi: 10.4158/EP171764.GL). A large scale gene-coronary artery disease association analysis showed genes affecting lipid metabolism (particularly LDL-C), blood pressure, and inflammation, but not diabetes mellitus, were key factors in the pathogenesis of atherosclerosis (CARDIoGRAMplusC4D Consortium, Nat Genet. 2013 Jan;45(1):25-33). However, a study of human genetic variation suggests a link between GLP-1 receptor signaling and cardiovascular disease risk reduction. A low frequency missense mutation in the GLP-1 receptor gene (GLP1R), Ala316Thr in a single nucleotide polymorph designated rs 10305492, was associated with lower fasting glucose, a decreased risk of developing T2DM, and a lower risk of coronary artery disease that was independent of any changes in blood pressure or body mass index (Scott et al, Sci Transl Med. 2016 Jun 1;8(341):341ra76). In the absence of characterizing the pharmacological signaling properties of the Ala316Thr GLP-1 receptor variant, the effect of the mutation on GLP-1 receptor signaling is unknown (Drucker Cell Metab. 2016 Jul 12;24(1):15-30).

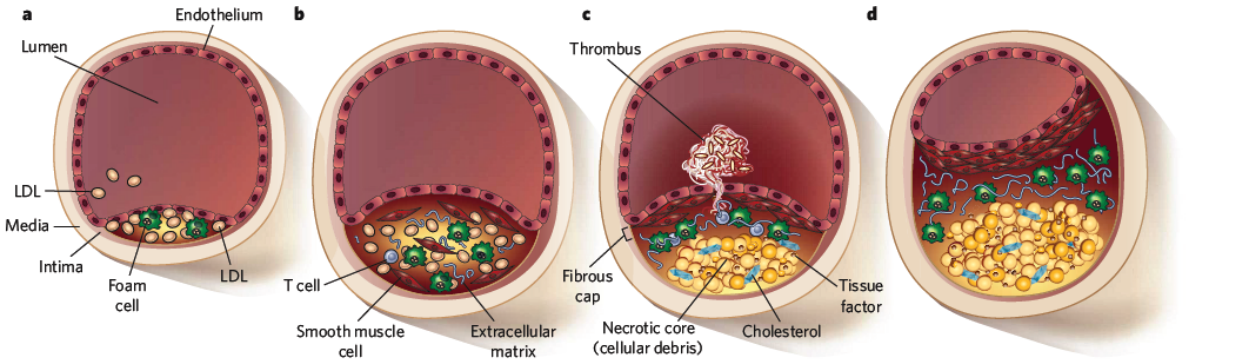


Figure 1 | Initiation and progression of atherosclerosis. Atherosclerosis occurs at sites in the arterial tree where laminar flow is disrupted. A lesion begins as a fatty streak (**a**) and can develop into an intermediate lesion (**b**), and then into a lesion that is vulnerable to rupture (**c**) and, finally, into an advanced obstructive lesion (**d**). A more detailed description of this process follows. **a**, Atherogenic lipoproteins such as low-density lipoproteins (LDLs) enter the intima, where they are modified by oxidation or enzymatic activity and aggregate within the extracellular intimal space, thereby increasing their phagocytosis by macrophages. Unregulated uptake of atherogenic lipoproteins by macrophages leads to the generation of foam cells, which are laden with lipid. The accumulation of foam cells leads to the formation of fatty streaks, which are often present in the aorta of children, the coronary arteries of adolescents, and other peripheral vessels of young adults. Although they cause no clinical pathology, fatty streaks are widely considered to be the initial lesion leading to the development of complex atherosclerotic lesions. **b**, Vascular smooth muscle cells — either recruited from the media into the intima or proliferating within the intima — contribute to this process by secreting large amounts of extracellular-matrix components, such as collagen. The presence of these increases the retention and aggregation of atherogenic lipoproteins. In addition to monocytes, other types of leukocyte, particularly T cells, are recruited to atherosclerotic lesions and help to perpetuate a state of chronic inflammation. As the plaque grows, compensatory remodelling takes place, such that the size of the lumen is preserved while its overall diameter increases. **c**, Foam cells eventually die, resulting in the release of cellular debris and crystalline cholesterol. In addition, smooth muscle cells form a fibrous cap beneath the endothelium, and this walls off the plaque from the blood. This process contributes to the formation of a necrotic core within the plaque and further promotes the recruitment of inflammatory cells. This non-obstructive plaque can rupture or the endothelium can erode, resulting in the exposure of thrombogenic material, including tissue factor, and the formation of a thrombus in the lumen. If the thrombus is large enough, it blocks the artery, which causes an acute coronary syndrome or myocardial infarction (heart attack). **d**, Ultimately, if the plaque does not rupture and the lesion continues to grow, the lesion can encroach on the lumen and result in clinically obstructive disease.

[Rader and Daugherty, Nature. 2008 Feb 21;451(7181):904-13]

The liraglutide cardiovascular outcomes trial (clinical study EX2211-3748) enrolled adults at least 50 years old with T2DM and a history of cardiovascular disease likely due to established atherosclerosis. Compared to placebo after 3 years of treatment, changes in endpoints related to potential effectiveness of liraglutide to lower cardiovascular risk were statistically significantly reductions in HbA1c (-0.396%), body weight (-2.26 kg), systolic blood pressure (-1.199 mm Hg), total cholesterol (-1.2%), and LDL cholesterol (-2.3%), and a statistically significant increase in HDL cholesterol (0.9%). The incidence of MACE in the liraglutide group (4.12 events per 100 patient years of observation (PYO)) was 15.9% lower compared to the incidence in the placebo group (4.90 events per 100 PYO), and it is not known if magnitude of the reduction in MACE in the liraglutide group compared to placebo is attributable to small reductions in total or LDL cholesterol or systolic blood pressure.

Endpoints related to effectiveness: Change from baseline to 3 years – MMRM – FAS

	Change from baseline (estimated means)		Treatment contrast: Lira vs placebo		
	Lira	**Placebo**	**ETD**	**95% CI**	**p-value**
HbA_{1c} (%)	-1.161	-0.765	-0.396	[-0.453; -0.338]	<0.001
Body weight (kg)	-2.736	-0.472	-2.264	[-2.539; -1.990]	<0.001
SBP (mmHg)	-1.444	-0.245	-1.199	[-1.916; -0.483]	0.001
DBP (mmHg)	-0.787	-1.374	0.587	[0.187; 0.987]	0.004
	Ratio to baseline (estimated means)		**Treatment contrast: Lira vs placebo**		
	Lira	**Placebo**	**ETR**	**95% CI**	**p-value**
Total cholesterol (mmol/L)	0.990	1.002	0.988	[0.979; 0.997]	0.012
HDL cholesterol (mmol/L)	1.032	1.022	1.009	[1.002; 1.017]	0.013
LDL cholesterol (mmol/L)	0.974	0.998	0.977	[0.962; 0.992]	0.003
Triglycerides (mmol/L)	0.961	0.975	0.985	[0.968; 1.003]	0.103

CI: confidence interval; DBP: diastolic blood pressure; ETD: estimated treatment difference; ETR: estimated treatment ratio; FAS: full analysis set; Lira: liraglutide; SBP: systolic blood pressure. MMRM: mixed model for repeated measures.

[SD1724 Report EX2211-3748 synopsis P10]

In 2 models of diet-induced atherosclerosis in genetically modified mouse, liraglutide reduced the area of aortic atherosclerotic plaques induced by a western diet, but it did not affect regression of established plaques. Liraglutide decreased western diet-induced body weight gain, body weight, and aortic plaque in ApoE KO mice, but without decreasing total cholesterol. A compound of unknown pharmacologic activity that caused body weight loss (presumably by a GLP-1 receptor independent mechanism, identified as 0247-0000-001) did not decrease aortic plaque area induced by a western diet in ApoE KO mice indicating effects of liraglutide on atherosclerotic plaque progression were not secondary to weight loss. In ApoE KO mice with established aortic plaques, liraglutide decreased body weight gain, decreased body weight, and reduced the atherogenicity of the plasma lipid profile (reduced total cholesterol 31.2%, reduced VLDL 35.7%, reduced LDL 30.6% and increased HDL 100%), but liraglutide did cause aortic plaques regression. Although liraglutide significantly altered expression of genes involved in the inflammatory process related to leukocyte recruitment (downregulated Ccr2, Cxcl12, Cx3cr1), leukocyte adhesion (downregulated Cx3cr1, Itga3, Thy1), lipid signaling (downregulated Ptgir), and fibrinolysis (downregulated Plat), the contribution of liraglutide-related changes in gene expression in aorta to any anti-atherosclerotic effects are confounded by the absence of an effect of liraglutide on regression of established aortic plaques in ApoE KO mice. Liraglutide did not prevent the formation of aortic plaques in ApoE KO mice, which can occur in ApoE mice fed

a standard diet. In male LDL receptor deficient (Ldlr KO) mice fed an atherogenic Western diet for 15 weeks beginning 2 weeks after starting treatment with vehicle or 1 mg/kg/day liraglutide, liraglutide decreased body weight gain during treatment, reduced body weight by the end of treatment, reduced atherogenicity of the plasma lipid profile (decreased total cholesterol 54.9%, decreased VLDL 62.9%, decreased LDL 49.6% and increased HDL 84.2%), reduced the area of aortic plaques by 78.5%, and decreased the incidence of Ldlr KO mice with aortic plaques by 46.7%. Some liraglutide changes in aortic mRNA levels were consistent with anti-inflammatory effects (decreased Il1rn, Il6, Mmp12, and Mmp13 and increased Acta2), improved glucose homeostasis in the vasculature (increased Irs1 and Insr), and changes in plaque composition (increased smooth muscle Acta2 and Tag1n), but in the absence of GLP-1 receptor expression in aorta, mRNA level changes in aorta may be secondary to the less atherogenic lipid profile in liraglutide-treated Ldlr KO mice. Human relevance of liraglutide-related decreased initiation or progression of diet-induced atherosclerotic plaques in genetically modified mouse models was confounded by:

1. The absence of effects of liraglutide on established plaques in ApoE KO mice, particularly since established atherosclerotic disease would have been expected to be present in subjects in CVOT EX2211-3748.

2. The absence of evidence levels of mRNAs consistent with anti-inflammatory are modified by liraglutide in ApoE KO mice under conditions that demonstrate effects of liraglutide on plaque regression.

3. An apparent correspondence between total cholesterol and LDL cholesterol lowering effects and reduced plaque initiation and progression in liraglutide-treated Ldlr KO mice compared to minimal effects of liraglutide on total cholesterol and LDL cholesterol in humans.

A search of the indications section in the Facts and Comparisons electronic drug database and DailyMed website showed the following drugs are indicated to reduce the risk of cardiovascular death:

- LDL cholesterol lowering: HMG CoA reductase inhibitors simvastatin and pravastatin
- Anti-hypertensives: the angiotensin-converting enzyme (ACE) inhibitor ramipril (Altace) and angiotensin II receptor blockers candesartan (Atacand) and telmisartan (Micardis)

- Anti-platelet drugs: platelet $P2Y_{12}$ receptor antagonists clopidogrel, prasugrel, and ticagrelor, cyclooxygenase inhibitor aspirin, platelet aggregation inhibitor tirofiban, and protease-activated receptor-1 (PAR-1) antagonist vorapaxar

- Oral anti-diabetes drug: sodium glucose co-transport 2 inhibitor empagliflozin

Searching (b) (4) approved drug labels in the DailyMed website (b) (4) :

(b) (4)

(b) (4)

To date, the only anti-diabetic drug indicated to reduce the risk of cardiovascular death in adult patients with T2DM and established cardiovascular disease is Jardiance (empagliflozin), an orally bioavailable small molecule sodium-glucose co-transporter 2 (SGLT2) inhibitor. A (b) (4)

Reviewer Modifications to the Sponsor Proposed Changes to Label (b) (4) (b) (4)

The sponsor proposed changes (b) (4) are not acceptable. Reviewer recommended changes to the sponsor proposed modifications are shown below (sponsor modifications in yellow, reviewer modifications in red).

(b) (4)

Victoza Label PLLR Conversion

Supporting Information

Novo Nordisk submitted a document titled "NDA 22341: Supporting Information for Pregnancy Labeling and Lactation Rule" that summarized and reviewed reports concerning liragluitde exposure during pregnancy and lactation and effects on fertililty in adults from the Novo Nordisk pharmacovigilance database, including information from a previously submitted document for liraglutide containing information up to May 2016 to support PLLR compliant labeling of Xultophy, new liraglutide information from Novo Nordisk's pharmacovigilance database from June 2016, and published literature.

Information submitted to support PLLR compliant labeling for liraglutide in Xultophy was reviewed by Dr. Carol Kasten, a Medical Officer in the Division of Pediatric and Maternal Health. Based on outcomes reported for 109 lirglutide-exposed pregnancies through 31 May 2016 from Novo Nordisk's pharmacovigilance database, there were 48.6% (53/109) live births, 29.4% (32/109) spontaneous aborations, 1.8% (2/109) ectopic pregnancies, 1.8% (2/109) stillbirths, and 18.3% (20/109) elective abortions. Nine total congenital abnormalities were reported in 3.8% (2/53) live births, 50% (1/2) of stillbirths, and 30% (6/20) of elective abortions. Case review of congential abnormalities concluded a relation to liraglutide exposure could not be exclueded for 6 of 9 cases (univentricular heart, stillbirth with placental insufficiency and poor maternal disease control, exencephaly, rare genetic brain damage disease, fetal death at 6 weeks, and hydrocephalus). The review concluded the incidence of birth defects in liraglutide-exposed pregnancies (5.5% (6/109)) was high compared to non-diabetic women (2% to 4% of the general population (draft Guidance for Industry titled "Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products —Content and Format (December 2014))), but within the expected range of 6% to 10% in women with diabetes mellitus. The rate of spontaneous abortions in liraglutide-exposed pregnancies (29.4%) was higher than the the incidence expected in the U.S. general population (15% to 20%), but a higher risk of adverse pregnancy outcomes in women with diabetes was noted. Potential safety signals of increased incidences of spontaneous abortion and birth defects in liraglutide-exposed pregnancies were attributed to maternal disease and not drug exposure.

Dr. Kasten's review noted liraglutide concentration in the milk of lactating rats was reported to be half the concentration in plasma, but animal data may not predict drug levels in human milk. Because of the increased risk of thyroid C-cell tumors in animals following prenatal exposure to liragultide, women treated with Xultophy should be advised not to breastfeed during treatment. The current label for Xultophy does not include the recommendation to discontinue breastfeeding while being treated with Xultophy. Dr. Kasten identified 1 published case report of adverse effects of liraglutide on male fertility in a 35 year old man with a history of primary infertility that developed decreased sperm count and non-motile sperm within 5 months of starting treatment with liraglutide with full recovery 5 months after discontinuing liraglutide treatment. This single report was not considered sufficient to warrant labeling with respect to effects of liraglutide on fertility in men.

The sponsor submitted a revised analysis of the effects of liraglutide on pregnancy, lactation, and fertility in humans to the Saxenda NDA in the document titled "NDA 22341: Supporting Information for Pregnancy Labeling and Lactation Rule" that included additional information from Novo Nordisk's pharmacovigilance database from June 2016 and an updated literature search. The sponsor reported 111 liraglutide exposed pregnancies with known outcomes (Table 2-1, below) up to May 2016. This information was previously reveiwed by Dr. Kasten. Of the 111 liraglutide exposed pregnancies with known outcomes up to the end of May 2016, 69 (62.2%) occurred in patients with diabetes mellitus (DM, type 1 or type 2). Out of the 69 liraglutide-exposed pregnancies in women with DM in Table 2-1, 14 were terminated and 5 of the terminated pregnancies reported fetal abnormalities (termination with fetal defects of osteogenesis imperfecta, fetal malformation, congenital brain damage, congenital hydrocephalus, and fetal death). Of the 55 remaining liraglutide-exposed pregnancies in women

with DM, there were 24 cases of fetal loss, including 20 spontaneous abortions and 4 stillbirths (including 1 with congential abormalities of placental insufficiency, cardiac hypertrophy, and microsomia). Two additional cases of Victoza-exposed pregnancies with known outcomes were reported in the sponsor's pharmacovigilance database in June 2016; one spontaneous abortion and a fetus with a cleft palate and cleft lip identifed in a fetal scan at an unknown week of pregnancy. In liraglutide-exposed pregnancies in women presumed to have DM, the apparent rate of birth defects was 9/71 (12.7%), above the rate of 2% - 4% in the US general population and above the rate of 5% - 10% in women with pregestational diabetes with HbA1c >7, and the apparent rate of fetal loss was 25/57 (43.9%), above the rate of 15 – 20% in the US general population and above the rate of 20 – 25% in women with HbA1c >10. No cases concerning the use of liraglutide in lactating women were reported in clinical studies of liraglutide, but 2 cases of the use of Victoza in lactating women were reported in the sponsor's safety database. One of these women used Victoza throughout pregnancy and breastfeeding with no adverse effects reported. No additional cases concerning the use of liraglutide in lactating women or effects of liraglutide on fertility in men or women were identified in the sponsor's pharmacovigilance database from June 2016. In clinical study EX2211-3748, 2 serious advserse events on fertility were mild hematospermia in 1 subject (recovered) and severe testicular necrosis in a second subject (recovered). The sponsor concludes reports on the use of liraglutide in pregnant and lactating women and information concerning effects of liraglutide on men and women are limited, and the sponsor will continue monitoring as part of routine pharmacovigilence. Please refer to Dr. Julie Golden's clinical safety review for a definitive assesment of Victoza-exposed pregnancies in humans.

Table 2–1 Pregnancy cases with available fetal outcome

Fetal outcome	Total N (%)	Source			
		Clinical trials N (%)	Other solicited N (%)	Spontaneous N (%)	Literature N (%)
Total	111 (100%)	60 (100%)	11 (100%)	39 (100%)	1 (100%)
Live birth without CA	51 (45.9 %)	30 (50.0%)	4 (36.4%)	16 (41.0%)	1 (100%)
Live birth with CA	2 (1.8%)	0 (0%)	0 (0%)	2 (5.0%)	0 (0%)
Fetal loss[a]	38 (34.2 %)	19 (31.7 %)	4 (36.4%)	15 (38.7%)	0 (0%)
Spontaneous abortion	*32 (28.8%)*	*16 (26.7%)*	*4 (36.4%)*	*12 (30.8%)*	*0 (0%)*
Ectopic pregnancy	*2 (1.8%)*	*2 (3.3%)*	*0 (0%)*	*0 (0%)*	*0 (0%)*
Stillbirth	*2 (1.8%)*	*1 (1.6%)*	*0 (0%)*	*1 (2.6%)*	*0 (0%)*
Stillbirth with fetal defects	*1 (0.9 %)*	*0 (0%)*	*0 (0%)*	*1 (2.6%)*	*0 (0%)*
Stillbirth without fetal defects	*1 (0.9 %)*	*0 (0%)*	*0 (0%)*	*1 (2.6%)*	*0 (0%)*
Termination	20 (18.0 %)	11 (18.3 %)	3 (27.3%)	6 (15.4 %)	0 (0%)
with fetal defects	*6 (5.4%)*	*1 (1.6%)*	*0 (0%)*	*5 (12.9 %)*	*0 (0%)*
without fetal defects	*2 (1.8%)*	*2 (3.3%)*	*0 (0%)*	*0 (0%)*	*0 (0%)*
termination (without reasons)	*12 (10.8%)*	*8 (13.3 %)*	*3 (27.3%)*	*1 (2.6%)*	*0 (0%)*

Notes: [a] Fetal loss includes still birth, spontaneous abortion and ectopic pregnancy. **Abbreviations:** CA = congenital anomalies; N = number of cases.

[SD1724 Supporting Information for PLLR P10]

Increased incidence of fetal malformations and fetal loss in Victoza-exposed pregnancies are consistent with increased incidences of fetal malformations in pregnant rats and pregnant rabbits exposed to liraglutide during organogenesis and the slightly increased

incidence of early embryonic deaths in maternal rats treated 2 weeks prior to mating through organogenesis with 1 mg/kg/day liraglutide, a dose that reduced body weight gain and food consuption of maternal rats and yeilded sysstemic exposures in maternal rats 11-times human exposure, based on AUC comparison.

Recommended Modifications to Sponsor Proposed Victoza Label for PLLR Compliance

Sponsor proposed modifications to the current Victoza label for PLLR compliance are shown in Appendix 1 (purple text). The reviewer proposed recommendations, shown below (red text and comments are mine, yellow text and comments are the sponsors) were incorporated into the sponsor's modified label.

The sponsor proposed changes to section "8.1 Pregnancy" to comply to the PLLR are acceptable. The proposed summary of risk information based on animal data is consistent with the corresponding information for liraglutide in the Xultophy label. Increased incidences of fetal malformations and fetal loss in liraglutide-exposed pregnancies in women with DM are consistent with increased incidences of malformations in fetuses from pregnant rats and rabbits at clinically relevant liraglutide exposures during organogenesis and the increased incidence of of early embryonic deaths in pregnant rats treated 2 weeks prior to mating through organogenesis with 1 mg/kg/day liraglutide, a dose that yeilded systemic exposures in maternal rats 11-times human exposure. Changes to section "8.2 Lactation" are recommended by the reviewer to be consistent with information about liraglutide in the correponding section of the approved Xultophy label.

Nonclinical Support for the PSP

A Pediatric Study Plan (PSP) for the new indication (supporting document 1729 received 1 November 2016) requested a partial waiver from conducting pediatric studies for pediatric patients with T2DM less than 10 years old and a full waiver for pediatric patients with T2DM and high cardiovascular risk less than 18 years old. No new nonclinical information was submitted to support a waiver for clinical studies of liraglutide in pediatric patients with T2DM and high cardiovascular risk. A definitive toxicity study of liraglutide in juvenile rats was completed to support clinical studies of liraglutide in pediatric patients with T2DM at least 10 years old and obese pediatric patients at least 7 years old, and the sponsor did not propose any new nonclinical studies to support the waivers requested in the PSP. There were no finding in toxicity studies of liraglutide in juvenile rats (report 212291) that precludes the use of liraglutide in clinical studies in pediatric patients ≥10 years old with T2DM or obese pediatric patients ≥7 years old.

8 page of Draft Labeling have been Withheld in Full immediately following this page.

Appendix 4: Nonclinical Information Submitted for Consideration for the 20 June 2017 Meeting of the Endocrinologic and Metabolic Drugs Advisory Committee Background Package (editorial contributions from Drs. Lee Elmore, Todd Bourcier, and Lisa Yanoff)

NONCLINICAL SUMMARY

Introduction

Liraglutide is a lipidated glucagon-like peptide 1 (GLP-1) analog with prolonged GLP-1 receptor agonist activity after subcutaneous injection (Figure 1, below). Liraglutide was approved as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM) under New Drug Application (NDA) 22341 for Victoza in January 2010. Two safety concerns were identified prior to approval of Victoza: 1) a potential risk of medullary thyroid carcinoma (MTC), identified in rodent carcinogenicity studies, and 2) pancreatitis, identified in clinical studies of liraglutide and pharmacovigilance data for exenatide, a shorter-acting GLP-1 receptor agonist approved in 2005, and sitagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor approved for the treatment of T2DM in 2006 (Parks and Rosebraugh 2010).

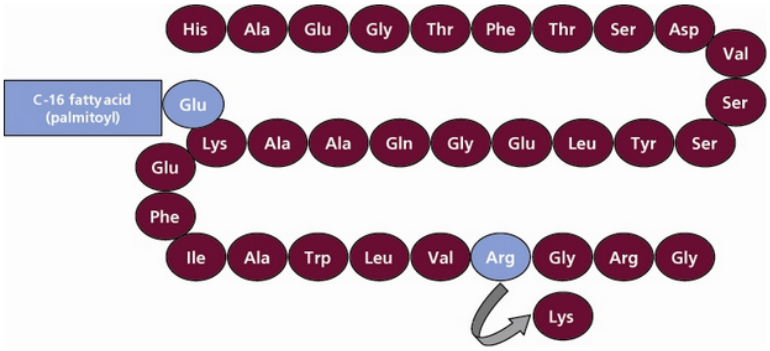


Figure 1 Structural Formula of liraglutide

[Prescribing Information for Victoza issued 21 April 2016]

Risks of MTC and pancreatitis from liraglutide treatment are attributed to its GLP-1 receptor agonist activity, and these risks are not unique to liraglutide. A boxed warning about the potential risk of MTC based on unknown human relevance of drug-related thyroid C-cell tumors in rodents is included in labels for products containing long-acting GLP-1 receptor agonists liraglutide (Victoza, Saxenda, and Xultophy), dulaglutide (Trulicity), and albiglutide (Tanzeum) and an extended-release formulation of the shorter-acting GLP-1 receptor agonist exenatide (Bydureon), but this warning is not included in product labels for products containing the shorter-acting GLP-1 receptor agonists exenatide (Byetta) or lixisenatide (Adlyxin and Soliqua). The risk of acute pancreatitis is included in product labels for all GLP-1 receptor agonists. Table 1 (below) lists approved single active ingredient GLP-1 receptor agonist products for the treatment of T2DM and indicates if the label includes a warning about the risk of pancreatitis, a boxed warning about the potential risk of MTC, and multiples of human exposure for GLP-1 receptor agonists at the lowest observed adverse effect level (LOAEL) for thyroid C-cell tumors in carcinogenicity studies in mice or rats.

Table 1. Summary of Labeling for the Risk of Pancreatitis , Potential Risk of Medullary Thyroid Carcinoma (MTC), and Rodent C-cell Tumorigenicity for Approved GLP-1 Receptor Agonists

Product	GLP-1 Receptor Agonist	Pancreatitis Warning in Label	Potential Risk of MTC		
			Boxed Warning in Label	Multiple of Human Exposure at C-cell Tumor LOAEL[1]	
				Mice	Rats
Byetta	exenatide	+	-	>95 (-)	≥5 (+)
Victoza	liraglutide[2]	+	+	≥10 (+)	≥0.5 (+)
Bydureon	extended release exenatide	+	+	ND	≥2 (+)
Trulicity	dulaglutide[3]	+	+	(-)[4]	≥7 (+)
Tanzeum	albiglutide[5]	+	+	ND	ND
Adlyxin	lixisenatide[6]	+	-	>180 (+)	≥15 (+)

[1]Lowest observed adverse effect level in carcinogenicity study (lowest dose causing a drug-related C-cell tumor in either sex). Exposure multiple and carcinogenicity study outcome as positive (+) or negative (-). ND = not determined (no study)

[2]Liraglutide is also an active pharmaceutical ingredient in Saxenda, the same formulation of liraglutide for weight management, and Xultophy, a combination of liraglutide and insulin degludec for the treatment of type 2 diabetes mellitus.

[3]Trulicity is the only GLP-1 receptor agonist to include information about effects on exocrine pancreas in a rat model of type 2 diabetes in the label.

[4]No exposure multiples in the label. Dulaglutide did not induced C-cell hyperplasia or tumors in Tg rasH2 transgenic mice treated with up to 3 mg/kg subcutaneously injected twice a week.

[5]Rodent carcinogenicity studies were not feasible due to immunogenicity of albiglutide in mice and rats.

[6]Lixisenatide is also an active pharmaceutical ingredient in Soliqua, a combination of lixisenatide and insulin glargine for the treatment of type 2 diabetes mellitus.

To further assess human risks of MTC and pancreatitis, Victoza approval included two nonclinical postmarketing requirements (PMRs) evaluating liraglutide's effects on thyroid C-cells (PMRs 1583-3 and 1583-5) and one evaluating liraglutide's effects on the exocrine pancreas (PMR 1583-4).

Thyroid C-cell Tumors

The Victoza label includes a boxed warning that liraglutide causes dose-dependent and treatment-duration-dependent thyroid C-cell tumors at clinically relevant exposures in both genders of mice and rats and human relevance of liraglutide-induced rodent thyroid C-cell tumors is unknown. Based on C-cell tumorigenicity of liraglutide in rodents, Victoza is contraindicated in patients with a personal or family history of MTC or patients with multiple endocrine neoplasia syndrome type 2 (MEN2) and it is not recommended as first-line therapy for patients with T2DM inadequately controlled on diet and exercise. The following description of

C-cell tumorigenicity of liraglutide in rodents is included in section "13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility" of the Victoza label.

> *"A 104-week carcinogenicity study was conducted in male and female CD-1 mice at doses of 0.03, 0.2, 1.0, and 3.0 mg/kg/day liraglutide administered by bolus subcutaneous injection yielding systemic exposures 0.2-, 2-, 10- and 45-times the human exposure, respectively, at the MRHD [maximum recommended human dose] of 1.8 mg/day based on plasma AUC comparison. A dose-related increase in benign thyroid C-cell adenomas was seen in the 1.0 and the 3.0 mg/kg/day groups with incidences of 13% and 19% in males and 6% and 20% in females, respectively. C-cell adenomas did not occur in control groups or 0.03 and 0.2 mg/kg/day groups. Treatment-related malignant C-cell carcinomas occurred in 3% of females in the 3.0 mg/kg/day group. Thyroid C-cell tumors are rare findings during carcinogenicity testing in mice.*
>
> *A 104-week carcinogenicity study was conducted in male and female Sprague Dawley rats at doses of 0.075, 0.25 and 0.75 mg/kg/day liraglutide administered by bolus subcutaneous injection with exposures 0.5-, 2- and 8-times the human exposure, respectively, resulting from the MRHD based on plasma AUC comparison. A treatment-related increase in benign thyroid C-cell adenomas was seen in males in 0.25 and 0.75 mg/kg/day liraglutide groups with incidences of 12%, 16%, 42%, and 46% and in all female liraglutide-treated groups with incidences of 10%, 27%, 33%, and 56% in 0 (control), 0.075, 0.25, and 0.75 mg/kg/day groups, respectively. A treatment-related increase in malignant thyroid C-cell carcinomas was observed in all male liraglutide-treated groups with incidences of 2%, 8%, 6%, and 14% and in females at 0.25 and 0.75 mg/kg/day with incidences of 0%, 0%, 4%, and 6% in 0 (control), 0.075, 0.25, and 0.75 mg/kg/day groups, respectively. Thyroid C-cell carcinomas are rare findings during carcinogenicity testing in rats."*

The mechanism of liraglutide-induced rodent C-cell tumors and human relevance are unknown, but C-cell tumorigenicity of GLP-1 receptor agonists is associated with prolonged GLP-1 receptor activation from long-acting GLP-1 receptor agonists or extended release formulations of shorter-acting GLP-1 receptor agonists. Although mechanistic studies from Novo Nordisk and some published data suggest GLP-1 receptor agonists induce calcitonin secretion and upregulation of calcitonin mRNA in C-cells, C-cell proliferation, and C-cell tumors in rodents, but not in primates, data are insufficient to support a conclusion regarding this potential mechanism. The strongest evidence supporting this mechanism comes from studies in mice showing liraglutide increased plasma calcitonin after the first dose, increased C-cell focal hyperplasia after about 4 weeks of treatment, and induced C-cell tumors after more than 52 weeks of treatment. However, repeat dose toxicity studies and mechanistic studies of liraglutide in rats do not support this mechanism because liraglutide did not persistently increase plasma calcitonin levels above age-related increases, rats less than 8 months old (middle-aged) are insensitive to liraglutide induced C-cell focal hyperplasia or tumors, and C-cell adenoma induced by 30 weeks of liraglutide treatment initiated when rats were young adults was not preceded by an increased incidence of C-cell focal hyperplasia. Plasma calcitonin was not a biomarker for liraglutide-induced C-cell tumors in rats. Dulaglutide, a long-acting GLP-1 receptor agonist that caused C-cell tumors in rats at clinically relevant exposures in a 2 year carcinogenicity study,

induced C-cell focal hyperplasia in rats after 52 weeks of treatment, but without inducing diffuse C-cell hyperplasia and without increasing calcitonin secretion or C-cell mass (Byrd 2015). In rodents, C-cell diffuse hyperplasia is considered a physiologic response while C-cell focal hyperplasia is considered a pre-neoplastic lesion distinguished from C-cell adenoma only by the smaller size of focal hyperplasia. Because of the long latency of liraglutide-induced C-cell tumors in rodents, which occur only after drug exposure for more than 25% of their lifespan, it is unlikely the duration of liraglutide exposure in repeat dose toxicity studies in monkeys or clinical studies in humans will be sufficient to evaluate relevance of liraglutide-induced rodent C-cell tumors to primates.

Victoza approval included two nonclinical postmarketing requirements (PMRs) to further assess human risks of liraglutide-induced rodent C-cell tumors: PMR 1583-3, a 2-year study in mice to determine if 26 weeks of liraglutide treatment (transient exposure) increases the lifetime risk of thyroid C-cell tumors, and PMR 1583-5, a 13-week mouse study to determine if liraglutide-induced C-cell focal hyperplasia depended on activation of the GLP-1 receptor or REarranged during-Transfection (RET) proto-oncogene.

PMR 1583-3 Evaluating the Lifetime Risk of C-cell Tumors in Mice Transiently Exposed to Liraglutide

In female mice, C-cell focal hyperplasia induced by 9 weeks of liraglutide treatment was not fully reversed after a 15-week recovery period. In a repeat subcutaneous dose study of up to 5 mg/kg/day liraglutide in CD-1 mice treated for up to 9 weeks evaluating reversibility of drug-induced thyroid C-cell focal hyperplasia, C-cell hyperplasia persisted in 31.3% (5/16) of females treated with the high dose of 5 mg/kg/day liraglutide after a 6-week recovery period and in 6.3% (1/16) of high dose females after a 15-week recovery period. These results suggested that transient exposure to liraglutide may cause persistent proliferative changes in C-cells of female mice. A potential mechanism for persistent effects from transient GLP-1 receptor agonist exposure was demonstrated for pancreatic beta cells in rats. Intrauterine growth retarded rats develop adult onset insulin resistance and diabetes at 15 to 26 weeks of age, but a short duration of treatment with exenatide during the neonatal period prevents adult-onset diabetes by normalizing pancreatic beta cell proliferation rates and increasing pancreatic beta cell mass via an epigenetic mechanism (Stoffers 2003, Pinney 2011).

To fulfill the requirements of PMR 1583-3, the risk of developing C-cell tumors after transient exposure to liraglutide was assessed in a 104-week study in CD-1 mice exposed to 0 (vehicle), 0.2, 1, or 3 mg/kg/day liraglutide for 26 weeks, approximately 25% of their total lifespan. Three doses of liraglutide were selected based on results from a lifetime carcinogenicity study: 0.2 mg/kg/day, a dose that caused C-cell focal hyperplasia, but not tumors, 1 mg/kg/day, a dose that caused C-cell focal hyperplasia and adenoma, but not carcinoma, and 3 mg/kg/day, a dose that caused C-cell focal hyperplasia, adenoma, and carcinoma. The 26 week treatment duration was expected to cause preneoplastic C-cell focal hyperplasia, but not tumors. At the end of the 26 week treatment period, plasma calcitonin was 6.4- to 14.1-fold higher compared to the vehicle control group in males at ≥0.2 mg/kg/day liraglutide and 3.5- to 4.0-fold higher in females at ≥1 mg/kg/day and the incidence of thyroid C-cell focal hyperplasia was 0%, 4.3%, 8.3%, and 22.7% in males and 0%, 8.3%, 0%, and 31.8% in females in 0, 0.2, 1, and 3 mg/kg/day liraglutide

groups, respectively, but C-cell tumors did not occur in any group. By the end of a 78 week recovery period, plasma calcitonin was 1.5- to 1.8-fold higher than the control group in males previously treated with ≥0.2 mg/kg/day liraglutide, but not in females previously treated with liraglutide. The incidence of C-cell focal hyperplasia in males previously treated with 3 mg/kg/day liraglutide (3.8% (3/78)) exceeded the incidence in the concurrent and laboratory historical control groups (2.7% (2/75) and 0% (0/940), respectively), and C-cell focal hyperplasia did not occur in any female group. Benign C-cell adenoma occurred in 1.3% (1/78) of females previously treated with 3 mg/kg/day liraglutide, and the incidence in the 3 mg/kg/day recovery group exceeded the incidence in concurrent and historical control groups (0% (0/77) and 0% (0/931), respectively). Despite the rarity of C-cell focal hyperplasia, adenomas, and carcinomas in lifetime carcinogenicity study control groups in CD-1 mice (laboratory historical control incidences of 0%, 0%, and 0% in 940 males, respectively, and 0.2%, 0%, and 0% in 931 females, respectively), a relation between liraglutide and C-cell proliferative lesions occurring during the 78 week recovery period was confounded by the finding of C-cell focal hyperplasia in 2.7% of control group males. Tertiary review of study results by the Executive Carcinogenicity Assessment Committee in FDA's Center for Drug Evaluation and Research concluded that due to the low incidence of proliferative C-cell lesions in male and female high dose recovery group mice and in concurrent control group male mice, a clear relationship to liraglutide treatment was not established for proliferative C-cell lesions in high dose recovery groups. Results from this study were not published.

PMR 1583-5 Evaluating GLP-1 Receptor and RET Dependence of Liraglutide-Induced C-cell Hyperplasia in Mice

Human relevance of liraglutide-induced rodent thyroid C-cell tumors was not determined by nonclinical or clinical studies prior to approval of Victoza. C-cell proliferative effects of liraglutide in rodents were suspected to be GLP-1 receptor mediated, in part because both exenatide and liraglutide caused rodent C-cell tumors and GLP-1 receptors were localized on C-cells in mice and rats. Although some studies show human C-cells don't express GLP-1 receptors, other studies show they do. In one study using human tissues, GLP-1 receptors were detected in C-cells from 33% of normal thyroid tissue, 91% of MTCs, and all samples of reactive C-cell hyperplasia or C-cell hyperplasia due to germline mutations in RET (Gier 2012). GLP-1 receptors were also detected in 18% of human papillary thyroid cancers (Gier 2012). It is not clear that GLP-1 receptors on C-cells mediate GLP-1 receptor agonist induced proliferation. In vitro in rat MTC 6-23 cells, a C-cell line, liraglutide, exenatide, and GLP-1 increased calcitonin secretion, but not cell proliferation. In humans, activating mutations in the RET proto-oncogene are the most common cause of sporadic and hereditary MTC, a human C-cell tumor. Oncogenic activating mutations in RET resulting in phosphorylation of tyrosine 1062 (Y1062) occur in nearly all hereditary MTCs and in approximately 50% of sporadic MTCs, but the age of onset and clinical aggressiveness of MTC varies with RET genotype. Although liraglutide caused rodent C-cell tumors by a nongenotoxic mechanism, and it is unlikely to cause activating mutations in RET, there were reports that G-protein coupled receptors can modulate RET signaling (Song 2010, Gomes 2009), and potentially affect RET-mediated cell proliferation. Dependence of liraglutide-induced thyroid C-cell focal hyperplasia on the GLP-1 receptor and RET was evaluated in wild-type and genetically engineered GLP-1 receptor-deficient (GLP-1rKO) CD-1 mice.

In a 13-week study evaluating GLP-1 receptor dependence and RET-dependence of liraglutide-induced thyroid C-cell hyperplasia in wild-type and GLP-1rKO mice, liraglutide-induced thyroid C-cell diffuse hyperplasia was GLP-1 receptor dependent because it occurred in liraglutide-treated wild-type mice, but not in liraglutide-treated GLP-1rKO mice. RET was not activated (Y1062 was not phosphorylated) in normal or hyperplastic C-cells in liraglutide-treated wild-type mice. Evaluation of cell signaling pathways potentially downstream from RET activation indicated liraglutide did not activate mitogen activated protein kinase kinases (MEK1/2), but it did activate ribosomal protein S6. Ribosomal protein S6 activation can mediate cell growth or cell proliferation. Because liraglutide activated ribosomal protein S6 in both normal and hyperplastic C-cells in mice and because C-cell hyperplasia in this study was characterized as diffuse and not focal, a link between liraglutide-induced GLP-1 receptor-mediated ribosomal S6 protein activation and C-cell tumorigenesis was not established. In all previous studies of liraglutide in mice from the sponsor, liraglutide-induced C-cell hyperplasia was characterized as focal, not diffuse. Results from this study were published (Madsen 2012). This study satisfied the requirements of PMR 1583-5 and supported the following statement added to section "13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility" section of the Victoza label:

> "*Studies in mice demonstrated that liraglutide-induced C-cell proliferation was dependent on the GLP-1 receptor and that liraglutide did not cause activation of the REarranged during Transfection (RET) proto-oncogene in thyroid C-cells*."

Because human relevance of GLP-1 receptor agonist induced rodent thyroid C-cell tumors has not been determined, participation in a MTC Cancer Registry is a post marketing requirement for all manufacturers of long-acting GLP-1 receptor agonists, including Victoza (PMR 1583-7). Approval of Victoza also required Novo Nordisk to conduct a 5 year prospective epidemiological study using a large healthcare claims database to determine the incidence of thyroid cancer among patients with T2DM exposed to Victoza (PMR 1583-6). However, due to the latency of liraglutide-induced thyroid C-cell tumors in rodents, a potential association between liraglutide and thyroid cancer in humans may require long-term epidemiological studies (Andersen 2013).

Pancreatitis and Pancreatic Cancer

The Victoza label includes a warning about the risk of pancreatitis based on human data, specifically an imbalance in the incidence of pancreatitis during clinical studies that did not favor Victoza, and after approval, spontaneous postmarketing reports. Treatment with Victoza should be discontinued if pancreatitis is suspected, and not restarted if pancreatitis is confirmed. In addition to the concern for GLP-1 receptor agonist-related pancreatitis, acute pancreatitis has the potential to progress to chronic pancreatitis and pancreatic cancer (Andersen 2013). The nonclinical program for Victoza did not identify liraglutide-related adverse effects on the exocrine pancreas. In the nonclinical drug development program for liraglutide using normoglycemic animals, there were no dose or treatment-duration-dependent adverse effects in the pancreas of mice or rats treated for up to 2 years or monkeys treated for up to 1 year.

Victoza approval included a nonclinical postmarketing requirement to further investigate the potential for liraglutide to induce pancreatitis: PMR 1583-4, a 3-month study of the effects of liraglutide on the exocrine pancreas in a rodent model of T2DM.

PMR 1583-4 Evaluating Effects of Liraglutide on Exocrine Pancreas in a Rat Model of T2DM

To fulfill PMR 1583-4, effects of liraglutide on the exocrine pancreas were characterized in a 3-month repeat subcutaneous dose toxicity study of 0 (vehicle), 0.4, or 1 mg/kg/day liraglutide administered once a day or 1 mg/kg/day administered twice a day (0.5 mg/kg/injection) to male and female diabetic Zucker Diabetic Fatty (ZDF) *fa/fa* rats, models of T2DM characterized by hyperphagia, obesity, hyperlipidemia, insulin resistance, and fasting hyperglycemia. Both male and female ZDF *fa/fa* rats are homozygous recessive for mutations resulting in a defective leptin receptor, but males and females differ in dietary requirements to induce diabetes. Male ZDF *fa/fa* rats become diabetic on a normal rodent diet while female ZDF *fa/fa* rats only become diabetic on a high fat diet. In this study, males were maintained on a normal rodent diet while females were fed a high fat diet for at least 6 weeks prior to switching to a normal rodent diet during week 4 of the study to minimize mortality due to prolonged consumption of the high fat diet. Liraglutide was pharmacologically active in diabetic ZDF *fa/fa* rats, decreasing food and water consumption, decreasing body weight gain, lowering non-fasting plasma glucose, and lowering HbA1c in males and females. Increased pancreas beta cell mass in liraglutide-treated diabetic females, but not in liraglutide-treated diabetic males, was consistent with greater glucose lowering efficacy in females. Increased beta cell mass in liraglutide-treated females was attributed to improved cell survival and/or increased cell size because it occurred in the absence of increased beta cell proliferation. Liraglutide had no adverse effects on the exocrine pancreas of diabetic ZDF *fa/fa* rats. At several time points during the 12-week treatment period, liraglutide increased plasma amylase in male and female diabetic rats, but without increasing plasma lipase or plasma triglycerides and without evidence of treatment-related macroscopic or microscopic pathology findings in the exocrine pancreas. In diabetic male rats, liraglutide had no effect on pancreas weight. In diabetic females, liraglutide significantly decreased pancreas weight, but decreased pancreas weight lacked correlative adverse findings in the exocrine or endocrine pancreas. Liraglutide did not affect exocrine cell mass (acinar cells or ductal) or exocrine cell proliferation in diabetic male or female rats. Results of this study were published (Vrang 2012).

Other Assessments of the Effects of Incretin-based Drugs on the Exocrine Pancreas

Marketed incretin-based drugs include DPP-4 inhibitors and GLP-1 receptor agonists. To evaluate models for identifying pancreatic toxicity of incretin-based drugs, FDA independently conducted studies in ZDF rats, C57Bl/6 mice fed a high fat diet, and chemically-induced pancreatitis in mice. Sitagliptin, a DPP-4 inhibitor, or exenatide, a GLP-1 receptor agonist, had no adverse effects on pancreas in ZDF rats or chemically induced pancreatitis in mice. In male C57BL/6 mice, exocrine pancreatic injury induced by 6 weeks of treatment with 200 mg/kg sitagliptin (oral gavage once a day) or 3 mcg/kg exenatide (subcutaneous injection once a day) included acinar cell injury (autophagy, apoptosis, necrosis, and atrophy), vascular injury, interstitial edema and inflammation, fat necrosis, and duct changes (dilatation, inflammation, and fibrosis) that could be exacerbated by a high fat diet that also inducing partial insulin resistance (Rouse 2014A). A second study evaluated the time course and dose-dependence of exenatide-

induced pancreatic injury in mice. In male C57BL/6 mice treated with 3, 10, or 30 mcg/kg exenatide (subcutaneously injected once a day) for 3, 6, or 12 weeks, exenatide-related adverse effects on the exocrine pancreas were dose-dependent and treatment-duration-dependent and characterized by acinar cell injury and cell adaptations (hypertrophy, hyperplasia, and proliferation / regeneration), along with inflammation resulting in secondary injury in blood vessels, ducts, and adipose (Rouse 2014B). Exenatide-related histiological changes in the pancreas in mice were exacerbated by a high fat diet, potentially due to oxidative stress from increased lipid metabolism. Because of uncertain human relevance of pancreatic injury by incretin-based drugs in C57BL/6 mice, the value of these studies for predicting human safety is unknown.

An evaluation of nonclinical assessments supporting marketing applications for incretin-based drugs by the FDA and the European Medicines Agency that included more than 250 toxicology studies conducted in approximately 18,000 healthy animals (15,480 rodents and 2,475 non-rodent mammals) showed no overt pancreatic toxicity or pancreatitis (Egan 2014). In life-time rodent carcinogenicity studies, there were no incretin-based drug-related pancreatic tumors in mice or rats, even at high multiples of human exposure. FDA also required sponsors of marketed incretin-based drugs to evaluate pancreatic toxicity in 3-month studies in rodent models of T2DM, and no drug-related adverse effects were reported, including the study of liraglutide in ZDF rats conducted by Novo Nordisk to satisfy a nonclinical postmarketing requirement. In the absence of overt pancreatic injury from incretin-based therapies in healthy animals or rodent models of T2DM, the FDA no longer routinely requires sponsors developing incretin-based therapies to perform dedicated pancreatic safety studies in rodents.

Risks of developing pancreatic ductal adenocarcinoma from treatment of diabetes were discussed by representatives of academia, industry, and government at a 2013 workshop on Pancreatitis-Diabetes-Pancreatic Cancer sponsored by the National Institute of Diabetes and Digestive and Kidney Disease and the National Cancer Institute. Despite concerns raised by reports in the medical literature and lay press about the risk of pancreatic cancer in patients treated with GLP-1 receptor agonists or DPP-4 inhibitors, there was no evidence of drug-related pancreatitis or pancreatic cancer in animal studies of incretin-acting drugs submitted to FDA and FDA had not seen a convincing signal between the use of incretin-acting drugs and pancreatic cancer in humans, but FDA continues to monitor and evaluate new information (Andersen 2013).

Conclusions

Liraglutide and 4 other GLP-1 receptor agonists are approved and widely used for the treatment of T2DM in adults, and liraglutide is approved for weight management in overweight adults with at least 1 weight-related comorbidity or obese adults. Based on unknown human relevance of liraglutide-induced rodent thyroid C-cell tumors in mice and rats at clinically relevant exposures, the label for Victoza includes a boxed warning about the potential risk of MTC, Victoza is contraindicated in patients with a personal or family history of MTC or patients with MEN2, and Victoza is not recommended as a first-line therapy for T2DM. Since approval of Victoza in 2010, human relevance of GLP-1 receptor agonist-induced rodent C-cell tumors has not been determined, and although there is no conclusive evidence liraglutide or other GLP-1 receptor agonists cause MTC in humans, the latency of GLP-1 receptor agonist-induced rodent C-cell

tumors suggests the duration of exposure in humans to date may be insufficient to elicit or detect it. The warning about the risk of pancreatitis in the Victoza label is based on an increased incidence of pancreatitis in clinical studies of liraglutide and postmarketing reports, but the relation to drug exposure for this risk is confounded by a higher disease-associated risk of pancreatitis in patients with T2DM and the absence of drug-related pancreatitis or pancreatic cancer in studies of liraglutide in normoglycemic mice, rats, and monkeys or diabetic rats. Human relevance of liraglutide-induced rodent thyroid C-cell tumors and the relation to liraglutide treatment for pancreatitis or pancreatic cancer in humans is being evaluated using human data, therefore additional mechanistic studies of approved GLP-1 receptor agonists in animals are likely to be of limited value for labeling or regulatory decisions.

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/s/

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06/01/2017

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06/01/2017

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022341Orig1s027

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

ADDENDUM

CLINICAL STUDIES

NDA #:	NDA 22341
Supplement #:	027
Drug Name:	Victoza (liraglutide injection)
Indications:	Adjunct to standard treatment of cardiovascular risk factors to reduce the risk of major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke) in adults with type 2 diabetes mellitus and high cardiovascular risk
Applicant:	Novo Nordisk Inc.
Dates:	Stamp date: 10/25/2016 PDUFA date: 8/25/2017
Review Priority:	Standard
Biometrics Division:	Division of Biometrics II
Statistical Reviewer:	Kiya Hamilton, Ph.D.
	Yun Wang, Ph.D., Acting Team Leader
Concurring Reviewers:	Mark Rothmann, PhD, Deputy Division Director
Medical Division:	Division of Metabolism and Endocrinology Products
Clinical Team:	Tania Condarco, M.D., Reviewer
	Lisa Yanoff, M.D., Team Leader
Project Manager:	Marisa Petruccelli

Keywords: Cardiovascular Outcome, MACE

LIST OF TABLES

This is an addendum to the statistical review of Victoza (liraglutide injection). The Division sent two information requests (IR) requesting the applicant to conducted analyses further investigating the region-based subgroup analyses.

Accounting for treatment discontinuation

The purpose of the first IR was to determine the liraglutide versus placebo hazard ratio that was consistent with a given dichotomous distribution for treatment discontinuation by 42 months. The selected distribution was the distribution observed in the trial for the US population. All data are used regardless of region. Subjects in the LEADER trial were scheduled to have a minimum treatment period of 42 months unless the subject died. The US made up 27% of the population in the study. The rate of subjects who prematurely discontinued from study treatment was double in the US compared to non-US subjects (Table 1).

The first IR dated July 19, 2017 sent by the Division is as follows:

> We would like you to determine an estimate of the hazard ratio in the setting of the treatment discontinuation observed in the U.S. where treatment discontinuation is the only effect modifier.
>
> We propose performing the following simulation:
>
> Divide the overall collection of subjects and their respective data into four groups by treatment group and whether a treatment discontinuation occurred during the first 42 months. For a single replication, draw a random sample of size
>
> W from the group randomized to liraglutide who discontinued treatment during the first 42 months,
>
> X from the group randomized to liraglutide who did not discontinue treatment during the first 42 months,
>
> Y from the group randomized to placebo who discontinued treatment during the first 42 months, and
>
> Z from the group randomized to placebo who did not discontinue treatment during the first 42 months
>
> where W is the number of subjects in the US who were randomized to liraglutide and discontinued treatment during the first 42 months, X is the number of subjects in the US who were randomized to liraglutide and did not discontinue treatment during the first 42 months, Y is the number of subjects in the US who were randomized to placebo and discontinued treatment during the first 42 months, and Z is the number of subjects in the US who were randomized to placebo and did not discontinue treatment during the first 42 months.

From those data, then determine the liraglutide vs. placebo hazard ratio. Perform 1000 such simulation, each time retaining the liraglutide vs. placebo hazard ratio. Finally, determine (1) the median among those simulated hazard ratios and (2) what proportion of these simulated liraglutide vs. placebo hazard ratios were above the observed liraglutide vs. placebo hazard ratio for the US subgroup.

The following is the response from the applicant:

Based on the request above, a simulation of 1000 replications was performed where each replication was based on random sampling with replacement from the total trial population. The sampling was stratified by treatment and premature treatment discontinuation with sample sizes for the 4 strata matching those in the US subpopulation:

- W=486 from the group randomized to liraglutide who discontinued treatment prematurely
- X=761 from the group randomized to liraglutide who did not discontinue treatment prematurely
- Y=549 from the group randomized to placebo who discontinued treatment prematurely
- Z=718 from the group randomized to placebo who did not discontinue treatment prematurely, as presented in Table 1.

A subject was considered to have discontinued treatment prematurely if the treatment discontinuation occurred during the first 42 months after randomization. However, if a subject died or had a MACE one day after treatment discontinuation or earlier, the subject was considered as *not* having discontinued prematurely. The date of treatment discontinuation is captured as the last day on drug on the End of Trial form.

Table 1 Premature treatment discontinuation - US and non-US subpopulations - summary - FAS

	US Subjects		Non-US Subjects	
	Lira N (%)	Placebo N (%)	Lira N (%)	Placebo N (%)
Did not discontinue prematurely	761 (61.0)	718 (56.7)	2719 (79.5)	2679 (78.7)
Discontinued prematurely	486 (39.0)	549 (43.3)	702 (20.5)	726 (21.3)

FAS: full analysis set, Lira: liraglutide, N: number of subjects, %: Percentage of subjects

For each replicated dataset, the liraglutide vs placebo hazard ratio was estimated using the same Cox regression model as in the primary analysis. The median among the 1000 simulated hazard ratios was 0.878 and 7.1% of these were greater than the observed hazard ratio for the US subpopulation (Table 2).

Reviewer's Notes:
From Table 2, 0.878 is the hazard ratio based on all data that is consistent with the treatment discontinuation observed in the US subpopulation. The probability is approximately 7.1% to observe a hazard ratio greater than 1.026 in a random subset of size equal to the US

subpopulation and has the same treatment discontinuation distribution observed in US population.

Table 2 Time to first EAC confirmed MACE for US subjects accounting for premature treatment discontinuation - statistical analysis - FAS

	Value
Observed HR for US Subjects	1.026
Median Simulated HR	0.878
Proportion of Simulated HRs> Observed HR for US Subjects	7.1

FAS: full analysis set, Lira: Liraglutide, EAC: event adjudication committee, MACE: major cardiovascular event, HR: hazard ratio of lira versus placebo. The simulation uses 1000 replications where each replication is based on a random sample from the total trial population. The sampling is performed with replacement and is stratified by treatment and early treatment discontinuation with sample sizes for the four strata matching those observed in US.
Hazard ratios are calculated using a Cox proportional hazards model with treatment as a factor. MACEs which occur before randomization date are not used for defining first event. Subjects without an event are censored at time of last contact (phone or visit).

The applicant stated that:

> This definition of premature treatment discontinuation as discontinuing at any time before 42 months after randomization can be regarded as one way of assessing treatment adherence, although it does not account for the timing of treatment discontinuation, e.g. whether a subject discontinued after one month or after 40 months, or whether a subject had drug holidays. The mean proportion of time on trial drug was lower in the US (0.73) than in the non-US subpopulation (0.87) and considering the exposure distribution by region, the number of days in the lowest quartile of exposure was substantially lower in the North American region (556 days) compared to the other regions (Asia: 1274 days, Europe: 1097 days, and the rest of the world: 1139 days). This was also consistent with the slightly smaller reduction in HbA_{1c} observed over time in the US vs non-US subpopulation. The difference in hazard ratios between the US and non-US subpopulations was not explained by the current analysis of 'premature discontinuation', Table 2. However, this result does not exclude either differences in exposure between US and non-US subpopulations, or a chance finding, as possible explanations.

Reviewers Notes:
The median hazard ratio (HR=0.878) from simulation for time to first EAC confirmed MACE based on the treatment discontinuation observed in the US is only a little larger than the observed overall hazard ratio (HR=0.87). Thus, premature discontinuation on its own does not explain the difference between the hazard ratios observed for the non-US (HR=0.81) and US subgroups (HR=1.026). The fact that the probability is approximately 7.1% that a random subset of the size equal to the US subpopulation that has the treatment discontinuation observed in US population

provides a liraglutide versus placebo hazard ratio greater than 1.026 means that after accounting for the treatment discontinuation observing a hazard ratio of 1.026 within the US subgroup may be due to chance.

Shrinkage Estimation

The variability of the sample treatment effects seen across regions is the sum of the variability of the true underlying treatment effects and the within subgroup variability in estimating a subgroup-specific treatment effect. Bayesian hierarchical modeling produces shrinkage estimates of the regional treatment effects that exhibit variability in the true underlying subgroup treatment effects that is consistent with the data. In other words, the within region variability is removed when determining the estimates. Treatment effects are regarded as exchangeable, which allows the treatment effects to be different and related. Relative to separate analyses of subgroups, shrinkage estimates tend to be more precise and provide narrower confidence/credible intervals. In the second information request we asked the applicant to perform an analysis which uses shrinkage estimation to determine estimated treatment effects for the regions North America, Europe, Asia, and the Rest of the World. We stated that the underlying treatment effects for those four regions should be regarded as exchangeable. These four regions were selected as they were the regions the applicant pre-specified to analyze. The applicant's response is as follows:

> As requested, an analysis which uses shrinkage estimation as described by Quan et al. (1) has been prepared to estimate the treatment effects for the regions North America, Europe, Asia, and the rest of the world. In this analysis, the underlying treatment effect for those four regions has been regarded as exchangeable; that is, region is not considered to provide any *a priori* knowledge about the direction or magnitude of the treatment effect. The results of the analysis are presented in Table 1 together with the original results based on Cox regression.

Table 3: Applicant's Analysis: Time to First EAC Confirmed MACE by Region - Original Results and Results Based on Shrinkage Estimation - Full Analysis Set

Region	Original results	Shrinkage estimates
	HR (95% CI)	HR (95% CI)
Asia	0.622 (0.372, 1.040)	0.686 (0.589, 0.799)
Europe	0.815 (0.678, 0.979)	0.823 (0.693, 0.976)
North America	1.010 (0.835, 1.220)	0.980 (0.826, 1.162)
The Rest Of The World	0.833 (0.676, 1.027)	0.838 (0.708, 0.993)

MACE: Major cardiovascular event, EAC: Event adjudication committee, CI: confidence interval, HR: Hazard ratio

Reviewer's Notes:

The shrinkage estimation method which the applicant applied is not an appropriate or valid way to do shrinkage estimation. The procedure is centered on the estimation of a parameter that is not a study parameter. In the Quan, et. al. paper, δ is not a study parameter, but is instead a modeling parameter. As it is not a study parameter, we are not interested in its estimation or any inference about that parameter. A purpose of shrinkage estimation is to remove the within subgroup variability and obtain estimates that have variability fairly similar to the estimated between subgroup variability in the underlying/true treatment effects. The applicant's estimated effects,

based on log-hazard ratios have variability (sample variance = 0.0250) more than three times the estimated between-subgroup variability (0.0075) in the underlying log-hazard ratios from a random effects model. Clearly, the applicant's estimates did not satisfy this criterion. Per the authors' notation we are interested in the estimation, hypotheses and inference involving $\sum_{i=1}^{s}(N_i/N)\delta_i$ (and also in δ_1, δ_2, δ_3, and δ_4) the overall treatment effect from a study, not in δ (which is mislabeled as "the overall treatment effect"). We are also interested in $E\left(\hat{\delta}-\sum_{i=1}^{s}(N_i/N)\delta_i\right)^2$, not in $E\left(\hat{\delta}-\delta\right)^2$. Additionally, as Asia, Europe, North America, and the Rest of the World are mutually exclusive and collectively exhaustive, it does not make sense to try to make an inference about some region that was not studied. In addition, the subgroup treatment effects are exchangeable if any ordering of them is considered equally likely a priori. It is not true that exchangeability means "not considered to provide any *a priori* knowledge about the direction or magnitude of the treatment effect." Table 4 shows the results from our analysis on shrinkage estimation. See the Appendix for the OpenBugs code.

Table 4 Statistical Reviewer's Analysis: Time to First EAC Confirmed MACE by Region - Original Results and Results Based on Shrinkage Estimation - Full Analysis Set

	Sample estimate		Bayes Shrinkage estimate	
Region	HR	95% CI	HR	95% CI
Asia	0.622	(0.372, 1.040)	0.803	(0.591, 1.089)
Europe	0.815	(0.678, 0.979)	0.836	(0.715, 0.978)
North America	1.010	(0.835, 1.220)	0.936	(0.786, 1.115)
The Rest of the World	0.833	(0.676, 1.027)	0.847	(0.716, 1.003)

Source: Statistical Reviewer's Analysis

Reviewer's Notes:
Based on our analyses, the best estimate of the liraglutide versus placebo hazard ratio within North America is 0.936 and the difference between 0.936 and 1.01 would be regarded as due to chance (as the random deviation from the truth). The shrinkage estimates are consistent with a smaller treatment effect in North America than in the other regions. There is no qualitative interaction between treatment and region.

Acknowledgements:
We would like to thank Drs. James Travis and Gene Pennello for help in running programs on shrinkage estimation.

Appendix

Normal-normal hierarchical model on MEANS and PRECISIONS using sample estimates sest of the log hazard ratios and variances s2 model

```
model
{
for(s in 1:S) {
   prec.sest[s] <- 1/s2.sest[s]
         sest[s]~dnorm(mu[s], prec.sest[s])
         mu[s]~dnorm(mu0, prec.mu)
         prob[s] <- step(opc - mu[s]);
}
  tau2.mu0 <- 1/var.mu0
  mu0~dnorm(0, tau2.mu0)
prec.mu~dgamma(.001,.001)
tau2.mu <- 1/prec.mu
  }
```

Data

```
list(S=4, sest=c(-0.475, -0.205,0.01,-0.183), s2.sest=c(0.0688, 0.0088, 0.0094, 0.0114 ),
var.mu0=16, opc=0)
```

Inits

```
list(mu0=0, prec.mu=1)
```

References:

Quan H, Li M, Shih WJ, Ouyang SP, Chen J, Zhang J, Zhao PL. Empirical shrinkage estimator for consistency assessment of treatment effects in multi-regional clinical trials. Statistics in Medicine. 2013; 32(10):1691-706.

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08/23/2017

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA #:	NDA 22341
Supplement #:	027
Drug Name:	Victoza (liraglutide injection)
Indications:	Adjunct to standard treatment of cardiovascular risk factors to reduce the risk of major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke) in adults with type 2 diabetes mellitus and high cardiovascular risk
Applicant:	Novo Nordisk Inc.
Dates:	Stamp date: 10/25/2016 PDUFA date: 8/25/2017
Review Priority:	Standard
Biometrics Division:	Division of Biometrics II
Statistical Reviewer:	Kiya Hamilton, Ph.D. Yun Wang, Ph.D., Acting Team Leader
Concurring Reviewers:	
Medical Division:	Division of Metabolism and Endocrinology Product
Clinical Team:	Tania Condarco, M.D., Reviewer Lisa Yanoff, M.D., Team Leader
Project Manager:	Marisa Petruccelli

Keywords: Cardiovascular Outcome, MACE

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1 EXECUTIVE SUMMARY

Novo Nordisk submitted a supplemental new drug application (sNDA) to fulfill the FDA post marketing requirement, as well as, to obtain an additional efficacy claim for the already marketed Victoza. The applicant proposes adding the results of the "Liraglutide Effect and Action in Diabetes: Evaluation of cardiovascular outcome Results," better known as the LEADER study to the Victoza label. The primary objective of this study was to assess the effect of treatment with liraglutide compared to placebo for at least 3.5 years and up to 5 years on the incidence of cardiovascular events in adults with type 2 diabetes mellitus (T2DM) that are at high risk for cardiovascular events.

The LEADER study was conducted to demonstrate that the treatment with liraglutide will not result in an unacceptable increase in cardiovascular risk. The primary endpoint was time to first major adverse cardiovascular events (MACE), which consisted of three components: cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke. Data from the study were used to rule out a 30% or greater increased risk in the time to first MACE, using a non-inferiority test. Non-inferiority of Victoza compared to placebo was established in this study with a hazard ratio and 95% confidence interval of 0.87 (0.78, 0.97) for the primary endpoint, time to first MACE. Superiority was also achieved because the upper bound for the hazard ratio was less than 1. Of the three components that make up the MACE endpoint, the hazard ratio and 95% confidence interval were: 0.78 (0.66, 0.93) for time to first cardiovascular death, 0.88 (0.75, 1.03) for time to first non-fatal MI, and 0.89 (0.72, 1.11) for time to first non-fatal stroke.

Overall, the study showed a treatment benefit of Victoza for adults with T2DM that are at high risk for cardiovascular events, with the proportion of subjects experiencing a MACE event being lower in the liraglutide group compared to placebo. This was due to a large disparity in the number of cardiovascular deaths between liraglutide and placebo.

An advisory committee was held for this submission on June 20, 2017. The panel voted 19 to 0 in favor of the LEADER study having adequately achieved its original safety objective demonstrating there was not an unacceptable increase in cardiovascular risk. The vote was 17 to 2 in favor of the LEADER study providing substantial evidence needed to establish that liraglutide 1.8 mg daily reduces cardiovascular risk in subjects with T2DM.

2 INTRODUCTION

2.1 Overview

2.1.1 Class and Indication

Novo Nordisk submitted their post marketing final report for Victoza (liraglutide) injection. Victoza was approved on January 25, 2010 as an adjunct therapy to diet and exercise to improve glycemic control in adults with T2DM. This approval came with a post marketing requirement (1583-9) for Novo Nordisk to conduct a randomized, double-blind, controlled study evaluating the effect of Victoza on the incidence of major adverse cardiovascular events in subjects with T2DM. The applicant requested (b) (4), which was not granted by the Division of Metabolism and Endocrinology Products (DMEP).

2.1.2 History of Drug Development

There were some interactions between Novo Nordisk and DMEP regarding the post marketing study of Victoza under NDA 022341. Pertinent parts of the communications and interactions relevant to the statistical review are summarized herein.

There was a Type C pre-sNDA meeting held on June 29, 2016 to discuss the specific format and content requirements for the LEADER supplement. The Division had the following statistical comments:

1. Each analysis dataset should include the treatment assignments, baseline assessments, and key demographic variables. The analysis datasets should include all variables needed for conducting all primary, secondary, and sensitivity analyses included in the study report. For endpoints that include imputations, both observed and imputed variables should be included and clearly identified. If any subjects were enrolled in more than one study, include a unique subject ID that permits subjects to be tracked across multiple studies.
2. The SAS programs that are used to create the derived datasets for the efficacy endpoints and the SAS programs that are used for efficacy data analysis should be included in the submission.
    - Please submit one SAS program for each analysis.
    - Please submit code used for analysis only and omit code used for generating tables and figures.
3. Please provide the location of the SAS dataset, the names of the variables used and the programs used to get every new value that will be appearing in the label.

The applicant stated that they would schedule a technical walkthrough of the statistical and clinical datasets to take place after the submission of this supplement.

2.1.3 Studies Reviewed

This review will focus on the results from study EX2211-3748 (hereafter referred to as 3748).

2.2 Data Sources

The submission of sNDA 022341 was received on October 25, 2016. The study reports including protocols, statistical analysis plan, and all referenced literature were submitted by the applicant to the Agency. The data and final study report for the electronic submission were archived under the network path location \\CDSESUB1\evsprod\NDA022341\0347.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

In general, the submitted data are acceptable in terms of quality and integrity. I was able to reproduce the primary and secondary endpoint analyses for the clinical study submitted.

3.2 Evaluation of Efficacy

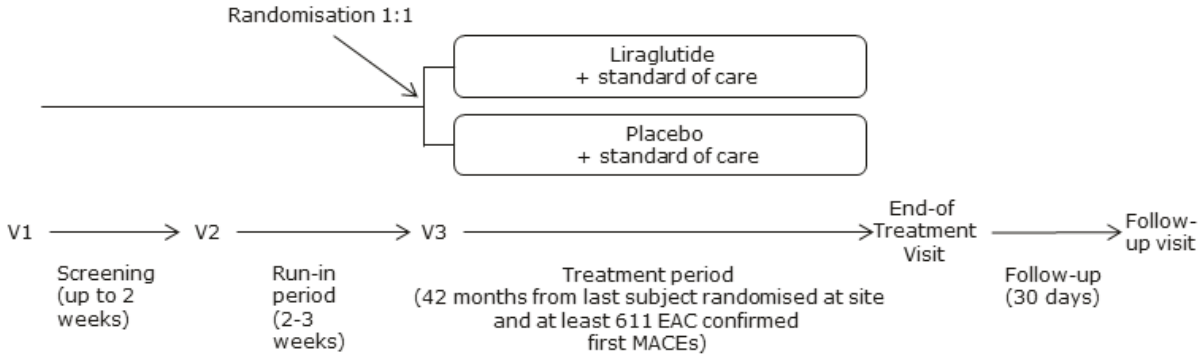
3.2.1 Study Design and Endpoints

The LEADER study was a long term, multi-center, multi-national, randomized, double-blind, placebo-controlled study to determine the effect and safety of liraglutide on cardiovascular outcomes. A total of 9340 subjects with T2DM who were at a high risk of cardiovascular events were randomized 1:1 to receive either liraglutide or placebo in addition to standard of care therapy.

The study consisted of 410 sites in 32 countries. The duration of this study was driven by both the number of events and treatment period. The study ended when all subjects had had a minimum treatment period of 42 months (plus a follow-up period of 30 days) and at least 611 event adjudication committee (EAC) confirmed MACE events were recorded. The study included a recruitment period of 18 months, resulting in a maximum treatment period of 60 months.

There was a screening visit (up to 2 weeks), a run-in period (2-3 weeks), a treatment period (42 months), and a follow-up period (30 days). Figure 1 below shows the schematic of the study design.

Figure 1: Study Design



Source: Clinical Study Report Protocol EX2211-3748 Figure 9-1, page 94

All subjects were started on 0.6 mg of liraglutide or the equivalence of placebo. The dose was escalated to 1.2 mg after one week followed by another dose escalation to 1.8 mg after one additional week. The dose escalation period could be extended based on the subject's tolerance to the study drug. If the maximum dose was not tolerated or otherwise associated with unacceptable AEs, reduction in dose was allowed.

The primary endpoint was time from randomization to first occurrence of a composite cardiovascular outcome, MACE: cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke. MACE stands for major adverse cardiovascular event. The secondary time-to-event endpoints were:

- time from randomization to first occurrence of an expanded composite cardiovascular outcome, defined as either cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, coronary revascularization, hospitalization for unstable angina pectoris, or hospitalization for heart failure
- time from randomization to all-cause death
- time from randomization to non-cardiovascular death
- time from randomization to each individual component of the expanded composite cardiovascular outcome
- time from randomization to first occurrence of a composite microvascular outcome, defined as any one of the following:
    - need for retinal photocoagulation or treatment with intravitreal agents
    - vitreous hemorrhage
    - onset of diabetes-related blindness (defined as Snellen visual acuity of 20/200 [6/60] or less, or visual field of <20 degrees in the better eye with best correction possible)
    - new or worsening nephropathy (defined as new onset of persistent urine albumin ≥300 mg/g creatinine (macro-albuminuria), or persistent doubling of serum creatinine level and eGFR ≤ 45 mL/min/1.73 m2 per MDRD
    - need for continuous renal replacement therapy in the absence of an acute reversible cause
    - death due to renal disease

- time from randomization to each individual component of the composite microvascular outcome and to the retinopathy and nephropathy composite outcomes separately.

Note the applicant did not control for multiplicity of the secondary endpoints.

3.2.2 Statistical Methodologies

All analyses were performed using the full analysis set (FAS), which was defined as all randomized subjects. The applicant's pre-specified analysis of the primary endpoint, time from randomization to first occurrence of MACE, was performed using a Cox proportional regression model including treatment group as a factor. Cox proportional hazards regression was used to test non-inferiority (NI) of liraglutide vs. placebo in the primary endpoint against a NI margin of 1.3 to rule out a 30% increase in cardiovascular risk. If NI was achieved for the primary endpoint, meaning the upper bound of the 95% CI was below 1.3, a test for superiority was performed with the upper bound of the 95% CI below 1.00.

The applicant conducted a few pre-specified additional analyses on the primary endpoint. A per-protocol (PP) analysis was performed, where PP was defined as all subjects who took at least one dose of the investigational product and these subjects were considered exposed until the accumulated number of days of no exposure to investigational drugs exceeded 120 days. Subjects were allowed to go on and off treatment during the study, thus the applicant performed two on-treatment analyses, where the focus was only on events occurring on randomized treatment. One analysis included subjects on randomized treatment and the second analysis was for subjects who were no later than 30 days into an off-treatment period (on randomized treatment + 30 days). The primary analysis was also repeated excluding the 30 days ascertainment period following end of treatment. A Cox regression analysis was performed that included additional covariates sex, region, baseline age (continuous), diabetes duration (continuous), prior cardiovascular events at baseline (yes/no), antidiabetic medication at baseline (none/1 OAD/>1 OAD/Insulin +/- OAD), smoking history (never/prior/current), and eGFR (continuous) at screening.

The secondary time-to-event endpoints were analyzed using a Cox regression model with treatment as a factor. Additional covariates were included similar to the primary analysis. No adjustments for multiple endpoints were pre-specified by the applicant.

Missing data was low for this study (3.2%). The applicant did not impute missing data. However, they did tipping point analyses to assess the possible impact of missing values on treatment effect.

3.2.3 Subject Disposition, Demographic and Baseline Characteristics

The summary of the subject disposition in the LEADER study is given in Table 1. Approximately 3% of the subjects failed to complete the study. The main reason for failure to complete study was that the subject was alive, but could not be determined if the subject had had a non-fatal MI or a non-fatal stroke.

Table 1 Subject Disposition

	Lira N = 4668 n (%)	Placebo N = 4672 n (%)	Total N = 9340 n (%)
FAS	4668 (100)	4672 (100)	9340 (100)
Exposed	4657 (99.8)	4664 (99.8)	9321 (99.8)
Not exposed	11 (0.2)	8 (0.2)	19 (0.2)
Did not complete study	139 (3)	159 (3.4)	298 (3.2)
Alive	127 (2.7)	142 (3.0)	269 (2.9)
Withdrawn- does not allow contact	4 (0.1)	8 (0.2)	12 (0.1)
Lost-to-follow up	8 (0.2)	9 (0.2)	17 (0.2)
Completed study	4529 (97)	4513 (96.6)	9042 (96.8)
Primary event	608 (13)	694 (14.9)	1302 (13.9)
Non-cardiovascular death	139 (3)	137 (2.9)	276 (3)
Available at follow-up visit (visit 16)	3782 (81)	3682 (78.8)	7464 (79.9)

Source: Full Clinical Study Report-Protocol Number EX2211-3748 Table 10-1, page 180
Notes: Column header Lira: liraglutide

Baseline demographics for all randomized subjects in the study are shown in Table 2. The subjects' mean age was approximately 64 years old and the majority of the subjects were white males. Baseline characteristics were generally well-balanced across the treatment groups.

Table 2 Demographics and Baseline Characteristics - FAS

	Lira N = 4668 n (%)	Placebo N = 4672 n (%)	Total N = 9340 n (%)
Age (years) at screening			
Mean (SD)	64.2 (7.2)	64.4 (7.2)	64.3 (7.2)
Median (Min, Max)	64 (50, 91)	64 (49, 91)	64 (49, 91)
Sex			
Female	1657 (35.5)	1680 (36)	3337 (35.7
Male	3011 (64.5)	2992 (64)	6003 (64.3)
Region			
Europe	1639 (35.1)	1657 (35.5)	3296 (35.3)
North America	1401 (30)	1446 (31)	2847 (30.5)
Asia	360 (7.7)	351 (7.5)	711 (7.6)
Rest of the world	1268 (27.2)	1218 (26.1)	2486 (26.6)
Ethnicity			
Hispanic or Latino	580 (12.4)	554 (11.9)	1134 (12.1)
Not Hispanic or Latino	4088 (87.6)	4118 (88.1)	8206 (87.9)
Race			
White	3616 (77.5)	3622 (77.5)	7238 (77.5)
Black or African American	370 (7.9)	407 (8.7)	777 (8.3)
Asian	471 (10.1)	465 (10)	936 (10)
America Indian or Alaska Native	5 (0.1)	6 (0.1)	11 (0.1)
Native Hawaiian or Other Pacific Islander	4 (<0.1)	4 (<0.1)	8 (<0.1)
Other	202 (4.3)	168 (3.6)	370 (4)
BMI (kg/m^2)			
Mean (SD)	32.5 (6.3)	32.5 (6.3)	32.5 (6.3)
HbA_{1c} (%)			
Mean (SD)	8.7 (1.6)	8.7 (1.5)	8.7 (1.5)
Diabetes Duration (years)			
Mean (SD)	12.8 (8.0)	12.9 (8.1)	12.8 (8.0)

Source: Full Clinical Study Report-Protocol Number EX2211-3748 Table 10-2, page 183 and Table 10-3, page 184
Notes: Column header Lira: liraglutide
N: Number of subjects

3.2.4 Results and Conclusions

This section will discuss the results for the primary and selected secondary endpoints. The pre-specified primary analysis for the primary endpoint, time to first MACE event, is shown in Table

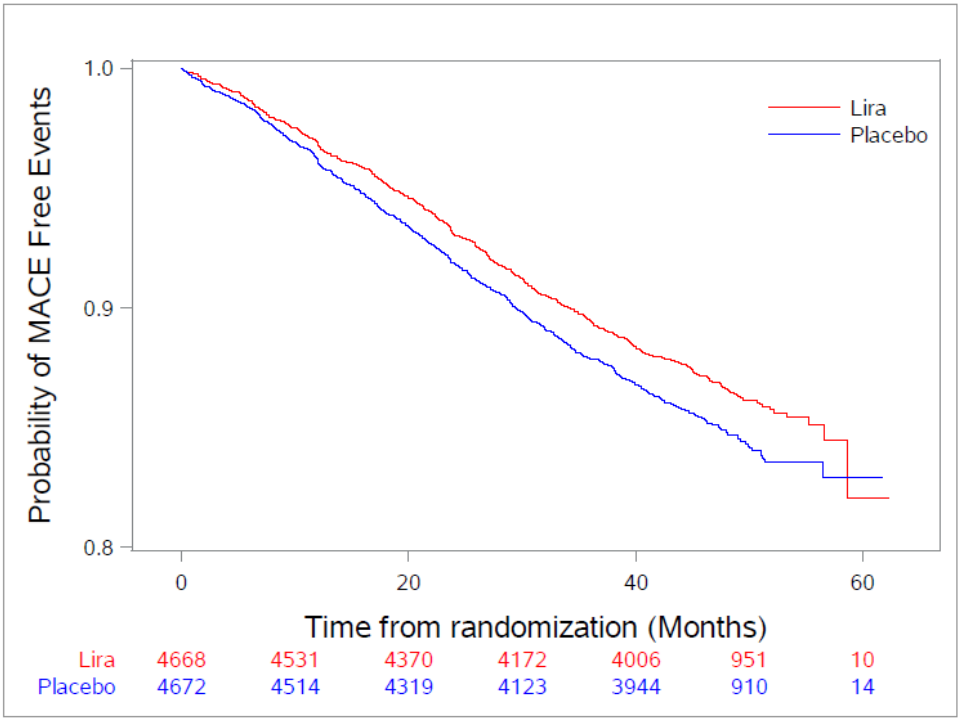
3. It can be seen that that the upper bound of the 95% CI is less than 1.3 which rules out a 30% risk increase for this endpoint. The hazard ratio of 0.87 results in a 13% relative risk reduction of a MACE event occurring in the liraglutide group over placebo. Superiority of liraglutide over placebo was also achieved for the primary MACE endpoint because the upper bound of the 95% CI of 0.97 is less than 1.0. Figure 2 shows the estimated Kaplan-Meier curve for time to first MACE by treatment groups. About 97% of the subjects completed this study. No missing data imputations were conducted.

Table 3 Primary Analysis- Time to First MACE- FAS

Treatment	FAS	First Events n	First Events Prop. (%)	Hazard Ratio	95% CI	P-value HR>=1.3 One-sided	P-value HR>=1.0 One-sided
Lira	4668	608	(13.02)				
Placebo	4672	694	(14.85)				
Lira/Placebo				0.87	0.78, 0.97	<0.0001	0.0054

Source: Full Clinical Study Report-Protocol Number EX2211-3748 Table 11-2, page 227 and Table 11-3, page 228
HR: hazard ratio; CI: confidence interval;
HR < 1.0 indicates treatment benefit of liraglutide

Figure 2: Reviewer Kaplan-Meier Plot Time to First EAC-Confirmed MACE - FAS



Source: Statistical Reviewer's Analysis

Tables 4 through 8 show the results of the pre-specified additional analyses for the primary endpoint. Tables 4 through 7 show the results of the additional analyses in relation to exposure to study drug. The results for the primary endpoint in the PP set concur with the primary analysis using the FAS set (Table 4).

Table 4 Additional Analysis – Time to First Confirmed MACE - Per Protocol

		First events			
Treatment	**FAS**	n	Prop (%)	**Hazard ratio**	**95 % CI**
Lira	4657	493	10.6		
Placebo	4664	564	12.1		
Lira/Placebo				0.86	0.76, 0.97

Source: Full Clinical Study Report-Protocol Number EX2211-3748 Table 14.2.33 page 733

Table 5 and Table 6 show the results for additional analyses for on-treatment analyses. On-treatment was defined as all subjects who took at least one dose of the study product, but who had an event that occurred on randomized treatment. The applicant stated that the first MACE occurring in a treatment period for each subject would contribute to these analyses irrespective of whether the subject in question had an earlier MACE that occurred in an off-treatment period. The results for subjects, who had a MACE event while on treatment, show a slightly lower hazard ratio compared to that of the primary endpoint (Table 5). For those subjects who had a MACE event occur while on treatment and no later than 30 days into an off-treatment period (on treatment plus 30 days), the hazard ratio was also slightly smaller than that of the primary endpoint (Table 6). However, both of these analyses do support the primary analysis.

Table 5 Additional Analysis – Time to First Confirmed MACE - On-Treatment (FAS)

		First events			
Treatment	**FAS**	n	Prop (%)	**Hazard ratio**	**95 % CI**
Lira	4668	414	8.9		
Placebo	4672	482	10.3		
Lira/Placebo				0.83	0.73, 0.95

Source: Full Clinical Study Report-Protocol Number EX2211-3748 Table 14.2.34 page 734

Table 6 Additional Analysis – Time to First Confirmed MACE - On-Treatment plus 30 days (FAS)

		First events			
Treatment	**FAS**	n	Prop (%)	**Hazard ratio**	**95 % CI**
Lira	4668	469	10.1		
Placebo	4672	549	11.8		
Lira/Placebo				0.83	0.73, 0.94

Source: Full Clinical Study Report-Protocol Number EX2211-3748 Table 14.2.35 page 735

Table 7 shows the results for all excluded MACE events that occurred after the end of treatment visit (visit 15). This result was similar to that of the primary analysis.

Table 7 Additional Analysis – Time to First Confirmed MACE - Excluding Events after End of Treatment

		First events			
Treatment	FAS	n	Prop (%)	Hazard ratio	95 % CI
Lira	4668	598	12.8		
Placebo	4672	690	14.8		
Lira/Placebo				0.86	0.77, 0.96

Source: Full Clinical Study Report-Protocol Number EX2211-3748 Table 14.2.36 page 736

The results for the additional analysis of adding additional covariates to the model were similar to the primary analysis results (Table 8). The additional covariates were sex, region, baseline age (continuous), diabetes duration (continuous), prior cardiovascular events at baseline (yes/no), antidiabetic medication at baseline (none/1 OAD/>1 OAD/Insulin +/- OAD), smoking history (never/prior/current), and eGFR (continuous) at screening.

Table 8 Additional Analysis – Time to First Confirmed MACE- Adjusted for Additional Covariates at Baseline

		First events			
Treatment	FAS	N	Prop (%)	Hazard ratio	95 % CI
Lira	4668	605	13.0		
Placebo	4672	692	14.8		
Lira/Placebo				0.87	0.78, 0.96

Source: Full Clinical Study Report-Protocol Number EX2211-3748 Table 14.2.37 page 737

None of the secondary endpoints or MACE related endpoints was pre-specified in the testing hierarchy; however, there are some endpoints of interest that will be discussed. These endpoints are used as exploratory endpoints to support the primary endpoint. Table 9 shows the results for the secondary endpoint, time to first occurrence of an expanded MACE, defined as EAC-confirmed cardiovascular death (CV), non-fatal myocardial infarction, non-fatal stroke, coronary revascularization, hospitalization for unstable angina pectoris, or hospitalization for heart failure. Subjects were allowed to contributed only once to this analysis with their first event. If a subject had more than one event on the same day of onset, the applicant defined the priority classification for first event as: cardiovascular death > non-fatal myocardial infarction > non-fatal stroke > hospitalization for UAP > hospitalization for heart failure > coronary revascularization. Recurrent events were not counted in the analyses. Numerically time to experiencing an expanded MACE event was lower in the liraglutide group than the placebo group.

Table 9 Secondary Analysis-Time to first EAC-Confirmed Expanded MACE- FAS

		First events			
Treatment	FAS	n	Prop (%)	Hazard ratio	95 % CI
Lira	4668	948	20.3		
Placebo	4672	1062	23		
Lira/Placebo				0.88	0.81, 0.96

Source: Full Clinical Study Report-Protocol Number EX2211-3748 Table 11-6, page 234

Table 10 shows the number of first events for three of the MACE related endpoints, CV death (a component of MACE), total MI, total stroke, and all-cause death. Numerically, more events occurred in the placebo group for each endpoint. Most events that occurred were of total MI.

Table 10 MACE Related Endpoints of First Events - FAS

	Lira N = 4668 n (%)	Placebo N = 4672 n (%)
Cardiovascular death	219 (4.7)	278 (6.0)
Total MI	292 (6.3)	339 (7.3)
Total stroke	173 (3.7)	199 (4.3)

Source: Statistical Reviewer's Analysis

Table 11 shows the results for CV death. The time to first CV death showed a numerical treatment benefit for liraglutide over placebo. There were fewer subjects that had a CV death in the liraglutide group compared to placebo, with a 22% decrease in CV death risk for liraglutide compared to those on placebo. When adjusted for additional covariates (sex, region, baseline age (continuous), diabetes duration (continuous), prior cardiovascular events at baseline (yes/no), antidiabetic medication at baseline (none/1 OAD/>1 OAD/Insulin +/- OAD), smoking history (never/prior/current), and eGFR (continuous) at screening) the results were similar to those just having treatment in the model (results not shown).

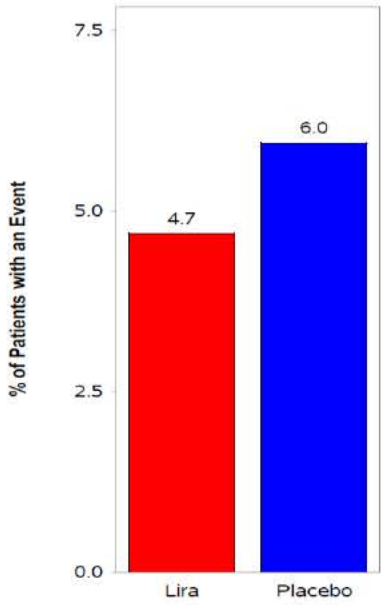
Table 11 Secondary Analysis-Time to First Cardiovascular Death- FAS

		First events			
Treatment	**FAS**	n	Prop (%)	**Hazard ratio**	**95 % CI**
Lira	4668	219	4.7		
Placebo	4672	278	6.0		
Lira/Placebo				0.78	0.66, 0.93

Source: Full Clinical Study Report-Protocol Number EX2211-3748 Table 14.2.58 page 758

Figure 3 shows the proportion of patients with CV death events in each treatment group. Of the components of MACE, this component had the largest difference between the treatment groups in the number of patients experiencing an event.

Figure 3: Proportion of Subjects with CV Death Events



Source: Statistical Reviewer's Analysis

Table 12 shows the results for total MI. Total MI is the sum of fatal MI and non-fatal MI. Numerically the risks of experiencing a total MI were lower for liraglutide subjects compared to those on placebo. The hazard ratio of 0.85 corresponds to a 15% relative risk reduction of a total MI occurring in the liraglutide group compared to placebo. However, the upper limit of the 95% CI was equal to1, but the trend is still in the same direction as MACE.

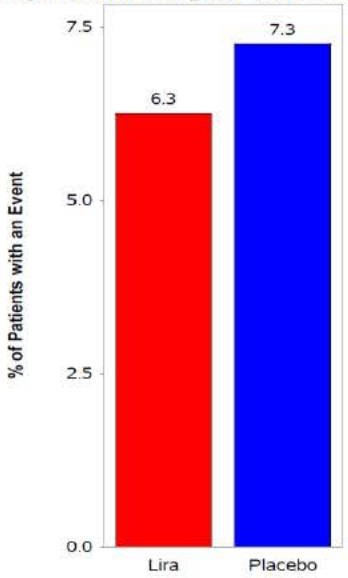
Table 12 Time to First Total MI- FAS

		First events			
Treatment	**FAS**	**n**	**Prop (%)**	**Hazard ratio**	**95 % CI**
Lira	4668	292	6.3		
Placebo	4672	339	7.3		
Lira/Placebo				0.85	0.73, 1.00

Source: Statistical Reviewer's Analysis

Figure 4 shows the proportion of subjects who experienced an MI during the trial in each treatment group. There were more events of MI than there were of CV deaths.

Figure 4: Proportion of Subjects with Total MI Events



Source: Statistical Reviewer's Analysis

Table 13 shows the results for total stroke. Total stroke is made up of fatal stroke and non-fatal stroke. Numerically the risks of experiencing total stroke were lower for liraglutide subjects compared to those on placebo. The hazard ratio of 0.87 reflects a 13 % relative risk reduction of total stroke occurring in the liraglutide group compared to placebo. However, the upper limit of the 95% CI was greater than 1, but the trend is still in the same direction.

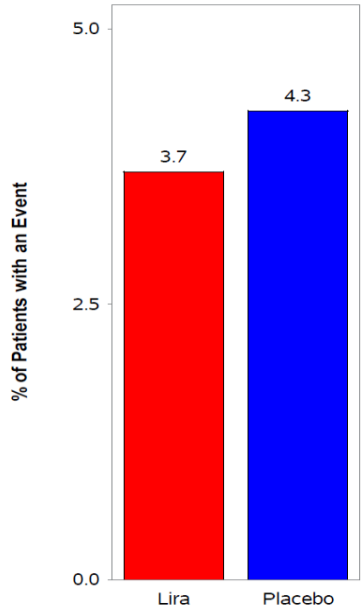
Table 13 Secondary Analysis-Time to First Total Stroke - FAS

		First events			
Treatment	**FAS**	n	Prop (%)	**Hazard ratio**	**95 % CI**
Lira	4668	173	3.7		
Placebo	4672	199	4.3		
Lira/Placebo				0.87	0.71, 1.06

Source: Statistical Reviewer's Analysis

Figure 5 shows the proportion of subjects who experienced a stroke. Total stroke had the smallest number of event compared to CV death and total MI.

Figure 5: Proportion of Subjects with Total Stroke Events



Source: Statistical Reviewer's Analysis

The number of subjects experiencing MACE and the results for CV death, non CV deaths and all-cause deaths are shown in Table 14. MACE and CV death were included for comparison. The upper bound for the 95% CI for non CV death was greater than 1, showing that there was no difference between liraglutide and placebo for this endpoint. All-cause death was made up of CV death and non CV death. The difference in all-cause death was driven by the difference in CV death.

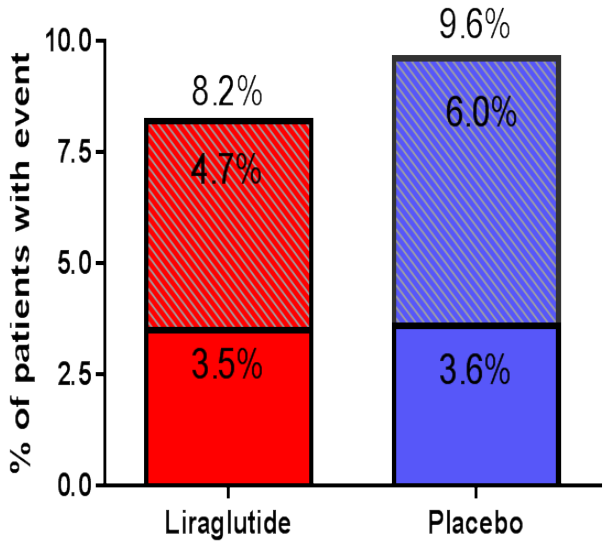
Table 14 Confirmed Deaths - FAS

	Lira N=4668 n (%)	Placebo N=4672 n (%)	Hazard Ratio (95% CI)
MACE	608 (13.0)	694 (14.9)	0.87 (0.78, 0.97)
CV Death	219 (4.7%)	278 (6.0%)	0.78 (0.66, 0.93)
Non CV Death	162 (3.5%)	169 (3.6%)	0.95 (0.76, 1.18)
All-Cause Death	381 (8.2%)	447 (9.6%)	0.85 (0.74, 0.97)

Source: Statistical Reviewer's analysis
CI: confidence interval;
Hazard Ratio < 1.0 indicates treatment benefit of liraglutide

Figure 6 shows the proportion of subjects with all-cause death events. The shaded region represents the proportion of subjects experiencing a CV death. The solid region represents the proportion of subjects experiencing a non CV death. The percent above each bar shows the total all-cause death for each treatment group.

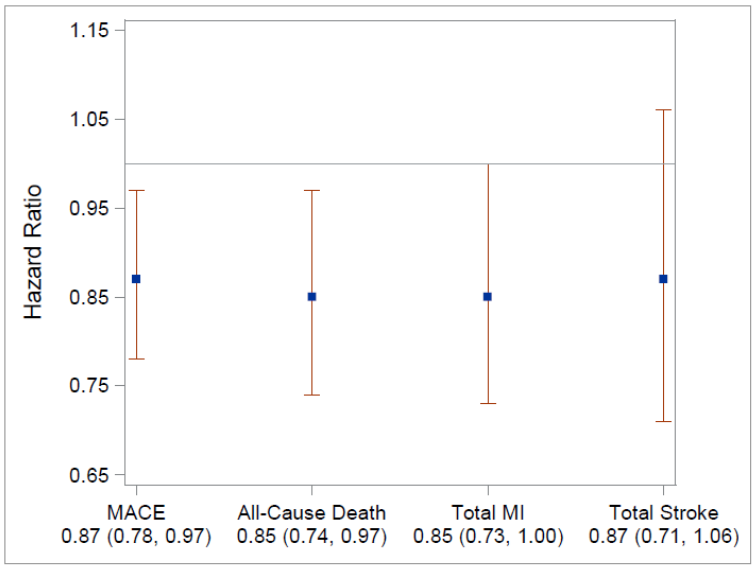
Figure 6: Proportion of Subjects with All-Cause Death Events



Source: Statistical Reviewer's analysis

The hazard ratios of MACE, all-cause death, total MI, and total stroke are presented together, Figure 7. The same Cox proportional hazards model from the primary analysis was used to estimate the hazard ratios and 95% confidence intervals for MACE and its related endpoints. The hazard ratios of the related endpoints fall in line with the hazard ratio of MACE, which supports the primary endpoint. However, the hazard ratios for total MI and total stroke have upper bounds that are at or greater than 1.

Figure 7: MACE and MACE Related Outcomes



Source: Statistical Reviewer's analysis

The total number of subject-years of follow-up until censoring or MACE event was approximately 17,822 years for liraglutide and 17,741 years for placebo. Estimated incidence based on this follow-up is shown in Table 15. The incidence rates were also estimated for CV death, non-fatal MI, non-fatal stroke, all-cause deaths, and non CV deaths.

Table 15 Estimated Raw Incidence per 100 Subject Years - FAS

	Lira N=4668	Placebo N=4672
MACE	3.41	3.91
CV Death	1.23	1.57
Non-fatal MI	1.58	1.79
Non-fatal Stroke	0.89	1.00
All-Cause Deaths	2.14	2.52
Non CV Death	0.91	0.95

Source: Statistical Reviewer's analysis

3.3 Evaluation of Safety

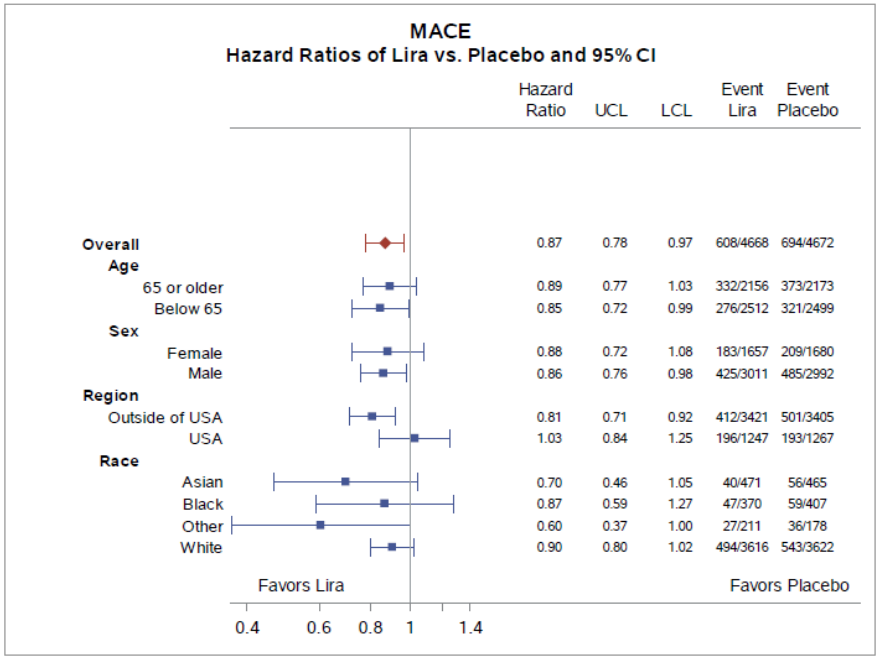
Safety evaluations for this submission will be evaluated by the Medical Reviewer, Tania Condarco, M.D. Refer to her review for more details regarding the safety findings of liraglutide.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Subgroup analyses were performed on the primary efficacy endpoint by age (<65, ≥65), sex (Male, Female), region (Outside the USA, USA), and race (Asian, Black, Other, White). The subgroup analyses were performed using the FAS population. Figure 8 summarizes the efficacy

results in these subgroups. The point estimate of the hazard ratio for the subgroup of USA was greater than 1. This trend was in the opposite direction from the primary endpoint. The nominal p value for the test of interaction between region (USA vs. Non-USA) and treatment was 0.048, which suggests there may be some quantitative difference in treatment effects for USA and non-USA subgroups. The sponsor did some exploratory analyses and proposed short duration of treatment due to worse treatment adherence may be the cause for the observed difference in treatment effects for USA and non-USA subgroups.

Figure 8: Subgroup Analyses - FAS



Source: Statistical Reviewer's analysis
UCL: Upper confidence limit; LCL: Lower confidence limit;
Hazard Ratio < 1.0 indicates treatment benefit of liraglutide

By design, the LEADER trial was enriched for patients at high risk for cardiovascular disease. Subjects eligible for enrolment were to be at high risk for cardiovascular events according to inclusion criterion #3a (established cardiovascular disease [CVD] or CKD and age ≥ 50 years) and inclusion criterion #3b (CV risk factors and age ≥ 60 years). Another subgroup that triggered extensive discussion during AC meeting on June 20th was cardiovascular history defined by inclusion criteria 3a versus 3b.

Table 16 Subgroup analysis by cardiovascular history - FAS

Factor	FAS	Liraglutide			Placebo			Hazard ratio (95% CI)	Interaction p-value
	N	N	Events	%	N	Events	%		
Cardiovascular history[a]									0.04
Established CVD or CKD and age ≥ 50 years	7598	3831	536	14.0	3767	629	16.7	0.83 (0.74; 0.93)	
CV risk factors and age ≥ 60 years	1742	837	72	8.6	905	65	7.2	1.20 (0.86; 1.67)	

Source: Sponsor's LEADER AC briefing document Figure 7 on page 45

The point estimate of the hazard ratio for the subgroup of inclusion criteria 3b (CV risk factors and age ≥ 60 years) was greater than 1. This trend was in the opposite direction from the primary

endpoint. The nominal p value for the test of interaction between cardiovascular history (inclusion criteria 3a versus 3b) and treatment was 0.04, which suggests there may be some quantitative difference in treatment effects for subgroups of inclusion 3a vs 3b.

The sponsor performed post hoc on-treatment sensitivity analyses of patients enrolled based on the inclusion criterion #3b. The on-treatment analysis did not result in higher estimated hazard ratios compared to the primary subgroup analysis. The patient group enrolled based on the inclusion criterion #3b (CV risk factors and age ≥ 60 years) accounted for only ~19% of the patients in the trial (1,742 out of 9,340 patients) and, consistent with a group with less advanced disease, for only ~10% of all first MACEs (137 out of 1,302 first MACEs). Thus, the sponsor proposed that observed effect of liraglutide in this subgroup may be related to the imprecision in the point estimate.

Reviewer's comment:

- The results we are seeing here for the subgroups of USA and inclusion criteria 3b could be due to chance. The test for interaction in both subgroups provides marginal evidence that there may be some quantitative but not qualitative difference in observed treatment effects for these subgroups.
- Weighed with the results of the primary MACE and its components, and all-cause death for overall population, we think the LEADER study supports the claim that Victoza reduce cardiovascular risk for the overall population studied in LEADER, i.e. adults with T2DM that are at high risk for cardiovascular events.

5 SUMMARY AND CONCLUSION

5.1 Statistical Issues

There were no statistical issues identified during the course of this review that would preclude approval. Missing data was low, 3.2%. In the briefing document for the AC meeting the applicant submitted the results for two the tipping point analyses to evaluate the potential impact of missing data on the result of the primary analysis. The Division sent an information request (IR) requesting details of these tipping point analyses. The first tipping point analysis for the primary endpoint was for those that were lost to follow-up. The events were added consecutively on the day after last visit for the 12 subjects with unknown vital status at follow-up in the liraglutide group until either all subjects lost to follow-up were added or until the treatment effect was no longer statistically significant. They stated that no events were added among the 17 subjects in the placebo group. After all 12 patients had been added to the liraglutide group, the result remained statistically significant in favor of liraglutide (estimated HR and 95% CI: 0.89 (0.79, 0.99). In the second tipping point analysis for the primary endpoint, the applicant included all non-completers in the liraglutide group (i.e. subjects who were alive at follow-up, but for whom it was unknown if they had experienced a non-fatal MI or a non-fatal stroke, plus subjects with unknown vital status at follow-up) were added in a step-wise manner under the assumption that they had had a non-fatal MI or a non-fatal stroke the day after last visit. Of the 139 non-completers in the liraglutide group only 21 subjects would have needed to have an event before

the hazard ratio was no longer statistically significant compared to none of the 159 non-completers in the placebo group, (estimated hazard ratio and 95% CI: 0.90 (0.81, 1.0)).

5.2 Conclusions and Recommendations

The primary objective of this study was to show non-inferiority of liraglutide when compared to placebo in cardiovascular outcomes as measured by the primary endpoint, time to first MACE (CV death, non-fatal MI, and non-fatal stroke). The non-inferiority was achieved for the primary endpoint because the 95% upper bound of 0.97 was below the NI margin of 1.3. The pre-specified testing hierarchy allowed for claiming superiority for the primary endpoint if the same 95% upper bound was below 1. The superiority was achieved as well in this study. The secondary endpoints, expanded MACE (CV death, non-fatal MI, and non-fatal stroke coronary revascularization, hospitalization for unstable angina pectoris, or hospitalization for heart failure), all-cause death, non CV death, and the individual components of expanded MACE were used to support the primary objective. There were no pre-specified multiplicity adjustments made for testing secondary endpoints by the applicant. The differences between the two treatment arms for the primary endpoint, time to first MACE, are largely due to differences in the CV death component (Figure 2). This large difference in the CV death also resulted in the difference in all-cause death which is made up of CV death and non CV death.

5.3 Labeling and Recommendations

Based on the review of the submitted data, the following are proposed edits to the label in section 14.

- The forest plot, Figure 6, should be removed
- None of the secondary endpoints were adjusted for multiplicity, thus they should not appear in the label
- Results for endpoints such as microvascular events, nephropathy event, retinopathy event, and urinary albumin/creatinine ratio were not part of the primary or secondary endpoints, nor were they adjusted for in the testing hierarchy, (b) (4) (b) (4)

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/s/

KIYA HAMILTON
07/17/2017

YUN WANG
07/17/2017

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022341Orig1s027

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY MEMO

NDA	022341 (S027)
Submission Date	10/25/2016
Brand Name	VICTOZA
Generic Name	Liraglutide
Clinical Pharmacology Reviewer	Jianmeng Chen, M.D., Ph.D.
Clinical Pharmacology Team Leader	Manoj Khurana, Ph.D.
OCP Division	Clinical Pharmacology II
OND Division	DMEP
Sponsor/Authorized Applicant	Novo Nordisk
Submission Type; Code	Efficacy Supplement
Formulation; Strength(s)	6 mg/mL solution in a pre-filled, multi-dose pen that delivers doses of 0.6 mg, 1.2 mg, or 1.8 mg.
Approved Indication	Type 2 diabetes mellitus
Proposed Indication	Adjunct to standard treatment of cardiovascular risk factors to reduce the risk of major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke) in adults with type 2 diabetes mellitus and high cardiovascular risk.
Dosage Regimen	Initiate with 0.6 mg SC qd for one week, then increase to 1.2 mg SC qd. May titrate up to 1.8 mg SC qd.

1. Executive Summary

1.1 Recommendations

There is no new clinical pharmacology information submitted in this efficacy supplement S027 of the NDA 022341. The acceptability of the claims and indication for cardiovascular benefit is deferred to the review by clinical and statistical review disciplines.

1.2 Phase IV Commitments

None.

1.3 Summary of Clinical Pharmacology Findings

Background

Victoza (liraglutide) injection is a glucagon-like-peptide-1 (GLP-1) receptor agonist that was approved on January 25, 2010, as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. One of the post-marketing requirements for Victoza included PMR 1583-9: A randomized, double-blind, controlled trial evaluating the effect of Victoza (liraglutide) injection on the incidence of major adverse cardiovascular events in patients with type 2 diabetes mellitus. Liraglutide is also marketed as Saxenda (NDA206321, approved on Dec 23, 2014) for the treatment of obese patients and overweight adults with at least one weight-related comorbidity. The sponsor is not seeking the cardiovascular benefit indication for Saxenda in this submission.

Current Submission

This submission contains the clinical trial report of the "Liraglutide Effect and Action in Diabetes: Evaluation of cardiovascular outcome Results" (LEADER) trial, intended to fulfill PMR 1583-9 and to support an efficacy supplement for a new indication and revised labeling. The sponsor also provided the safety updates in this efficacy supplement.

An Advisory Committee meeting was held on Jun 20, 2017, and voted 17-2 in support of this NDA supplement for liraglutide (Victoza) to reduce the risk of major adverse cardiovascular events in adults with type 2 diabetes and established cardiovascular disease. See clinical review for the summary of AC discussion.

- The Advisory Committee voted 19-0 in favor of Victoza® on the question: "Do the results of LEADER establish that use of Victoza® in patients with type 2 diabetes is not associated with excess cardiovascular risk?"

- The Advisory Committee voted 17-2 in favor of Victoza® on the question: "Does the LEADER trial provide the substantial evidence needed to establish that Victoza® (liraglutide 1.8 mg) reduces cardiovascular risk in patients with type 2 diabetes?"

There is no new clinical pharmacology information in this submission. No changes are proposed for relevant clinical pharmacology sections in the proposed label with this submission. The acceptability of the claims and indication for CV benefit is deferred to the review by clinical and statistical review disciplines.

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/s/

JIANMENG CHEN
07/14/2017

MANOJ KHURANA
07/14/2017