CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

203314Orig1s008

Trade Name: **TRESIBA**

Generic Name: Insulin Degludec

Sponsor: Novo Nordisk Inc.

Approval Date: 03/26/2018

Indications: TRESIBA is a long-acting human insulin analog indicated to improve glycemic control in patients 1 year of age and older with diabetes mellitus.

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APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 203314/S-008

SUPPLEMENT APPROVAL
FULFILLMENT OF POSTMARKETING REQUIREMENT

Novo Nordisk Inc.
Attention: Nina Liang, Ph.D.
Associate Director, Regulatory Affairs
800 Scudders Mill Rd.
Plainsboro, NJ 08536

Dear Dr. Liang:

Please refer to your Supplemental New Drug Application (sNDA) dated and received May 26, 2017, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Tresiba (insulin degludec) injection, 100 units/mL and 200 units/mL.

This Prior Approval supplemental new drug application proposes the following change: addition of clinical data to the prescribing information from the cardiovascular outcomes trial, EX1250-4080 (DEVOTE), *A trial comparing cardiovascular safety of insulin degludec versus insulin glargine in subjects with type 2 diabetes at high risk of cardiovascular events.*

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 with the minor editorial revisions listed below.

1. Line numbering was removed.
2. The revision date was added under the heading Recent Major Changes.
3. The revision date was added at the end of the highlights section.

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, text for the patient package insert, 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 (which includes new salts and new fixed combinations), 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 in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your supplemental 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 September 25, 2015, approval letter.

2954-2 Conduct a randomized, double-blind, active-controlled trial evaluating the effect of Tresiba (insulin degludec injection) on the incidence of major adverse cardiovascular events (MACE) in subjects with type 2 diabetes mellitus. The primary objective of the trial should be to demonstrate that the upper bound of the 2-sided 95% confidence interval for the estimated risk ratio comparing the incidence of adjudicated MACE (non-fatal myocardial infarction, non-fatal stroke, cardiovascular death) observed with Tresiba to that observed in the comparator group is less than 1.3.

We have reviewed your supplemental application, as amended, and conclude that the above requirement was fulfilled.

We remind you that there is a postmarketing commitment listed in the September 25, 2015, approval letter that is 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 Callie Cappel-Lynch, Regulatory Project Manager, at (301) 796-8436.

Sincerely,

{See appended electronic signature page}

Mary Thanh Hai, M.D.
Deputy Director
Office of Drug Evaluation II
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURES:
Prescribing Information
Patient Package Insert (previously approved December 16, 2016)
Instructions for Use (U-100) (previously approved December 16, 2016)
Instructions for Use (U-200) (previously approved December 16, 2016)

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

/s/

MARY T THANH HAI
03/26/2018

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 TRESIBA safely and effectively. See full prescribing information for TRESIBA.

TRESIBA® (insulin degludec injection), for subcutaneous use
Initial U.S. Approval: 2015

---------- **RECENT MAJOR CHANGES**----------
Dosage and Administration (2) 03/2018

----------**INDICATIONS AND USAGE**----------
TRESIBA is a long-acting human insulin analog indicated to improve glycemic control in patients 1 year of age and older with diabetes mellitus (1).

Limitations of Use:
Not recommended for treating diabetic ketoacidosis.

Not recommended for pediatric patients requiring less than 5 units of TRESIBA

----------**DOSAGE AND ADMINISTRATION**----------
- See Full Prescribing Information for important administration instructions (2.1).
- Rotate injection sites to reduce the risk of lipodystrophy (2.1).
- In adults, inject subcutaneously once daily at any time of day (2.2).
- In pediatric patients inject subcutaneously once daily at the same time every day (2.2).
- Individualize dose based on type of diabetes, metabolic needs, blood glucose monitoring results and glycemic control goal (2.2).
- The recommended days between dose increases is 3 to 4 days (2.2)
- See Full Prescribing Information for recommended starting dose in insulin naïve patients and patients already on insulin therapy (2.3, 2.4).

----------**DOSAGE FORMS AND STRENGTHS**----------
TRESIBA injection is available in the following package sizes:
- 100 units/mL (U-100): 3 mL FlexTouch® (3).
- 200 units/mL (U-200): 3 mL FlexTouch® (3).

----------**CONTRAINDICATIONS**----------
- During episodes of hypoglycemia (4).
- Hypersensitivity to TRESIBA or one of its excipients (4).

----------**WARNINGS AND PRECAUTIONS**----------
- *Never share* a TRESIBA FlexTouch pen between patients, even if the needle is changed (5.1).
- *Hyper- or hypoglycemia with changes in insulin regimen* Carry out under close medical supervision and increase frequency of blood glucose monitoring (5.2).
- *Hypoglycemia* May be life-threatening. Increase monitoring with changes to: insulin dosage, co-administered glucose lowering medications, meal pattern, physical activity; and in patients with renal impairment or hepatic impairment or hypoglycemia unawareness (5.3, 5.4, 6 1).
- *Hypoglycemia due to medication errors* Accidental mix-ups between insulin products can occur. Instruct patients to check insulin labels before injection. DO NOT transfer TRESIBA into a syringe for administration as overdosage and severe hypoglycemia can result (5.4).
- *Hypersensitivity reactions* Severe, life-threatening, generalized allergy, including anaphylaxis, can occur. Discontinue TRESIBA, monitor and treat if indicated (5.5).
- *Hypokalemia* May be life-threatening. Monitor potassium levels in patients at risk for hypokalemia and treat if indicated (5.6).
- *Fluid retention and heart failure with concomitant use of Thiazolidinediones (TZDs)* Observe for signs and symptoms of heart failure; consider dosage reduction or discontinuation if heart failure occurs (5.7).

----------**ADVERSE REACTIONS**----------
Adverse reactions commonly associated with TRESIBA are:
- hypoglycemia, allergic reactions, injection site reactions, lipodystrophy, pruritus, rash, edema and weight gain (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Novo Nordisk at 1-800-727-6500 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------**DRUG INTERACTIONS**----------
- *Drugs that may increase the risk of hypoglycemia* antidiabetic agents, ACE inhibitors, angiotensin II receptor blocking agents, disopyramide, fibrates, fluoxetine, monoamine oxidase inhibitors, pentoxifylline, pramlintide, propoxyphene, salicylates, somatostatin analog (e.g., octreotide),and sulfonamide antibiotics(7).
- *Drugs that may decrease the blood glucose lowering effect* atypical antipsychotics, corticosteroids, danazol, diuretics, estrogens, glucagon, isoniazid, niacin, oral contraceptives, phenothiazines, progestogens (e.g., in oral contraceptives), protease inhibitors, somatropin, sympathomimetic agents (e.g., albuterol, epinephrine, terbutaline), and thyroid hormones (7)
- *Drugs that may increase or decrease the blood glucose lowering effect* Alcohol, beta-blockers, clonidine, lithium salts, and pentamidine (7)
- *Drugs that may blunt the signs and symptoms of hypoglycemia*: beta-blockers, clonidine, guanethidine, and reserpine (7)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 03/2018

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

TRESIBA is indicated to improve glycemic control in patients 1 year of age and older with diabetes mellitus.

Limitations of Use

- Not recommended for the treatment of diabetic ketoacidosis
- Not recommended for pediatric patients requiring less than 5 units of TRESIBA

2 DOSAGE AND ADMINISTRATION

2.1 Important Administration Instructions

- Always check insulin labels before administration *[see Warnings and Precautions (5.4)]*.
- Inspect visually for particulate matter and discoloration. Only use TRESIBA if the solution appears clear and colorless.
- Inject TRESIBA subcutaneously into the thigh, upper arm, or abdomen.
- Rotate injection sites within the same region from one injection to the next to reduce the risk of lipodystrophy *[see Adverse Reactions (6.1)]*.
- Use TRESIBA with caution in patients with visual impairment that may rely on audible clicks to dial their dose.
- DO NOT administer TRESIBA intravenously or in an insulin infusion pump.
- DO NOT dilute or mix TRESIBA with any other insulin products or solutions.
- DO NOT transfer TRESIBA from the TRESIBA pen into a syringe for administration *[see Warnings and Precautions (5.4)]*.

2.2 General Dosing Instructions

- TRESIBA is available in 2 disposable prefilled pens:
    - TRESIBA U-100 contains 300 units of TRESIBA U-100. It delivers doses in 1 unit increments and can deliver up to 80 units in a single injection.
    - TRESIBA U-200 contains 600 units of TRESIBA U-200. It delivers doses in 2 unit increments and can deliver up to 160 units in a single injection.
- DO NOT perform dose conversion when using the TRESIBA U-100 or U-200 pens. The dose window shows the number of insulin units to be delivered and no conversion is needed.
- In adults, inject TRESIBA subcutaneously once-daily at any time of day.
- In pediatric patients inject TRESIBA subcutaneously once-daily at the same time every day.
- Individualize and titrate the dose of TRESIBA based on the patient's metabolic needs, blood glucose monitoring results, and glycemic control goal.
- The recommended days between dose increases are 3 to 4 days.
- Dose adjustments may be needed with changes in physical activity, changes in meal patterns (i.e., macronutrient content or timing of food intake), changes in renal or hepatic function or during acute illness to minimize the risk of hypoglycemia or hyperglycemia *[see Warnings and Precautions (5.3)]*.

- For adult patients, instruct patients who miss a dose of TRESIBA to inject their daily dose during waking hours upon discovering the missed dose. Instruct patients to ensure that at least 8 hours have elapsed between consecutive TRESIBA injections.
- For pediatric patients, instruct patients who miss a dose of TRESIBA to contact their healthcare provider for guidance and to monitor blood glucose levels more frequently until the next scheduled TRESIBA dose.

2.3 Starting Dose in Insulin Naïve Patients

Type 1 Diabetes Mellitus:

The recommended starting dose of TRESIBA in insulin naïve patients with type 1 diabetes is approximately one-third to one-half of the total daily insulin dose. The remainder of the total daily insulin dose should be administered as a short-acting insulin and divided between each daily meal. As a general rule, 0.2 to 0.4 units of insulin per kilogram of body weight can be used to calculate the initial total daily insulin dose in insulin naïve patients with type 1 diabetes.

Type 2 Diabetes Mellitus:

The recommended starting dose of TRESIBA in insulin naïve patients with type 2 diabetes mellitus is 10 units once daily.

2.4 Starting Dose in Patients Already on Insulin Therapy

Adults with Type 1 or Type 2 Diabetes Mellitus:

Start TRESIBA at the same unit dose as the total daily long or intermediate-acting insulin unit dose.

Pediatric Patients 1 Year of Age and Older with Type 1 or Type 2 Diabetes Mellitus:

Start TRESIBA at 80% of the total daily long or intermediate-acting insulin unit dose to minimize the risk of hypoglycemia *[see Warnings and Precautions (5.2)]*.

3 DOSAGE FORMS AND STRENGTHS

Injection: TRESIBA is available as a clear and colorless solution:

- 100 units/mL (U-100): 3 mL FlexTouch disposable prefilled pen
- 200 units/mL (U-200): 3 mL FlexTouch disposable prefilled pen

4 CONTRAINDICATIONS

TRESIBA is contraindicated:

- During episodes of hypoglycemia *[see Warnings and Precautions (5.3)]*.
- In patients with hypersensitivity to TRESIBA or one of its excipients *[see Warnings and Precautions (5.5)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Never Share a TRESIBA FlexTouch Pen Between Patients

TRESIBA FlexTouch disposable prefilled pens should never be shared between patients, even if the needle is changed. Sharing poses a risk for transmission of blood-borne pathogens.

5.2 Hyperglycemia or Hypoglycemia with Changes in Insulin Regimen

Changes in insulin, manufacturer, type, or method of administration may affect glycemic control and predispose to hypoglycemia or hyperglycemia. These changes should be made cautiously and only under medical supervision and the frequency of blood glucose monitoring should be increased. For patients with type 2 diabetes, adjustments in concomitant anti-diabetic treatment may be needed. When converting from other insulin therapies to TRESIBA follow dosing recommendations *[see Dosage and Administration (2.4)]*.

5.3 Hypoglycemia

Hypoglycemia is the most common adverse reaction of insulin, including TRESIBA *[see Adverse Reactions (6.1)]*. Severe hypoglycemia can cause seizures, may be life-threatening or cause death. Hypoglycemia can impair concentration ability and reaction time; this may place an individual and others at risk in situations where these abilities are important (e.g., driving or operating other machinery). TRESIBA, or any insulin, should not be used during episodes of hypoglycemia *[see Contraindications (4)]*.

Hypoglycemia can happen suddenly and symptoms may differ in each individual and change over time in the same individual. Symptomatic awareness of hypoglycemia may be less pronounced in patients with longstanding diabetes, in patients with diabetic nerve disease, in patients using medications that block the sympathetic nervous system (e.g., beta-blockers) *[see Drug Interactions (7)]*, or in patients who experience recurrent hypoglycemia.

Risk Factors for Hypoglycemia

The risk of hypoglycemia generally increases with intensity of glycemic control. The risk of hypoglycemia after an injection is related to the duration of action of the insulin *[see Clinical Pharmacology (12.2)]* and, in general, is highest when the glucose lowering effect of the insulin is maximal. As with all insulin preparations, the glucose lowering effect time course of TRESIBA may vary among different individuals or at different times in the same individual and depends on many conditions, including the area of injection as well as the injection site blood supply and temperature.

Other factors which may increase the risk of hypoglycemia include changes in meal pattern (e.g., macronutrient content or timing of meals), changes in level of physical activity, or changes to co-administered medication *[see Drug Interactions (7)]*. Patients with renal or hepatic impairment may be at higher risk of hypoglycemia *[see Use in Specific Populations (8.6, 8.7)]*.

Risk Mitigation Strategies for Hypoglycemia

Patients and caregivers must be educated to recognize and manage hypoglycemia. Self-monitoring of blood glucose plays an essential role in the prevention and management of

hypoglycemia. In patients at higher risk for hypoglycemia and patients who have reduced symptomatic awareness of hypoglycemia, increased frequency of blood glucose monitoring is recommended.

5.4 Hypoglycemia Due to Medication Errors

Accidental mix-ups between basal insulin products and other insulins, particularly rapid-acting insulins, have been reported. To avoid medication errors between TRESIBA and other insulins, instruct patients to always check the insulin label before each injection.

To avoid dosing errors and potential overdose, never use a syringe to remove TRESIBA from the TRESIBA pen into a syringe *[see Dosage and Administration (2.1) and Warnings and Precautions (5.3)]*.

5.5 Hypersensitivity and Allergic Reactions

Severe, life-threatening, generalized allergy, including anaphylaxis, can occur with insulin products, including TRESIBA. If hypersensitivity reactions occur, discontinue TRESIBA; treat per standard of care and monitor until symptoms and signs resolve. TRESIBA is contraindicated in patients who have had hypersensitivity reactions to insulin degludec or one of the excipients *[see Contraindications (4)]*.

5.6 Hypokalemia

All insulin products, including TRESIBA, cause a shift in potassium from the extracellular to intracellular space, possibly leading to hypokalemia. Untreated hypokalemia may cause respiratory paralysis, ventricular arrhythmia, and death. Monitor potassium levels in patients at risk for hypokalemia if indicated (e.g., patients using potassium-lowering medications, patients taking medications sensitive to serum potassium concentrations).

5.7 Fluid Retention and Congestive Heart Failure with Concomitant Use of a PPAR Gamma Agonist

Thiazolidinediones (TZDs), which are peroxisome proliferator-activated receptor (PPAR)-gamma agonists can cause dose related fluid retention, particularly when used in combination with insulin. Fluid retention may lead to or exacerbate congestive heart failure. Patients treated with insulin, including TRESIBA and a PPAR-gamma agonist should be observed for signs and symptoms of congestive heart failure. If congestive heart failure develops, it should be managed according to current standards of care and discontinuation or dose reduction of the PPAR-gamma agonist must be considered.

6 ADVERSE REACTIONS

The following adverse reactions are also discussed elsewhere:

- Hypoglycemia *[see Warnings and Precautions (5.3)]*
- Medication errors *[see Warnings and Precautions (5.4)]*
- Hypersensitivity and allergic reactions *[see Warnings and Precautions (5.5)]*
- Hypokalemia *[see Warnings and Precautions (5.6)]*

6.1 Clinical Trial 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.

The safety of TRESIBA in subjects with type 1 diabetes or type 2 diabetes was evaluated in nine trials of 6-12 month duration in adults and in one trial of 12-month duration in pediatric patients 1 year of age and older with type 1 diabetes. The cardiovascular safety of TRESIBA was evaluated in one double-blinded, event-driven trial of 2-year median duration in patients with type 2 diabetes at high risk of cardiovascular events *[see Clinical Studies (14)]*.

The data in Table 1 reflect the exposure of 1102 adults with type 1 diabetes to TRESIBA with a mean exposure duration to TRESIBA of 34 weeks in three open-label trials. The mean age was 43 years and 1% were older than 75 years. Fifty-seven percent were male, 81% were White, 2% were Black or African American and 4% were Hispanic. The mean body mass index (BMI) was 26 kg/m^2. The mean duration of diabetes was 18 years and the mean HbA_{1c} at baseline was 7.8%. A history of neuropathy, ophthalmopathy, nephropathy and cardiovascular disease at baseline was reported in 11%, 16%, 7% and 0.5% respectively. The mean eGFR at baseline was 87 mL/min/1.73 m^2 and 7% of the patients had an eGFR less than 60 mL/min/1.73 m^2.

The data in Table 2 reflect the exposure of 2713 adults with type 2 diabetes to TRESIBA with a mean exposure duration to TRESIBA of 36 weeks in six open-label trials. The mean age was 58 years and 3% were older than 75 years. Fifty-eight percent were male, 71% were White, 7% were Black or African American and 13% were Hispanic. The mean BMI was 30 kg/m^2. The mean duration of diabetes was 11 years and the mean HbA_{1c} at baseline was 8.3%. A history of neuropathy, ophthalmopathy, nephropathy and cardiovascular disease at baseline was reported for 14%, 10%, 6% and 0.6% of participants respectively. At baseline, the mean eGFR was 83 mL/min/1.73 m^2 and 9% had an eGFR less than 60 mL/min/1.73 m^2.

Common adverse reactions (excluding hypoglycemia) occurring in TRESIBA treated subjects during clinical trials in adult patients with type 1 diabetes mellitus and adults with type 2 diabetes mellitus are listed in Table 1 and Table 2, respectively. Common adverse reactions were defined as reactions occurring in ≥5% of the population studied. Hypoglycemia is not shown in these tables but discussed in a dedicated subsection below.

174 pediatric patients 1 year of age and older with type 1 diabetes were exposed to TRESIBA with a mean exposure to TRESIBA of 48 weeks. The mean age was 10 years: 25% were ages 1-5 years, 40% were ages 6-11 years, and 35% were ages 12-17 years. 55.2% were male, 78.2% were White, 2.9% were Black or African American and 4% were Hispanic. The mean body mass index (BMI) was 18.7 kg/m^2. The mean duration of diabetes was 3.9 years and the mean HbA_{1c} at baseline was 8.2%. Common adverse reactions in TRESIBA treated pediatric patients with type 1 diabetes mellitus were similar to the adverse reactions listed in Table 1.

Table 1: Adverse Reactions Occurring in ≥5% of TRESIBA-Treated Adult Patients with Type 1 Diabetes Mellitus

Adverse Reaction	TRESIBA (n=1102)
Nasopharyngitis	23.9 %
Upper respiratory tract infection	11.9 %
Headache	11.8 %
Sinusitis	5.1 %
Gastroenteritis	5.1 %

Table 2: Adverse Reactions Occurring in ≥5% of TRESIBA-Treated Adult Patients with Type 2 Diabetes Mellitus

Adverse Reaction	TRESIBA (n=2713)
Nasopharyngitis	12.9 %
Headache	8.8 %
Upper respiratory tract infection	8.4 %
Diarrhea	6.3 %

Hypoglycemia

Hypoglycemia is the most commonly observed adverse reaction in patients using insulin, including TRESIBA *[see Warnings and Precautions (5.3)]*. The rates of reported hypoglycemia depend on the definition of hypoglycemia used, diabetes type, insulin dose, intensity of glucose control, background therapies, and other intrinsic and extrinsic patient factors. For these reasons, comparing rates of hypoglycemia in clinical trials for TRESIBA with the incidence of hypoglycemia for other products may be misleading and also, may not be representative of hypoglycemia rates that will occur in clinical practice.

In the open-label adult clinical trials of patients with type 1 and type 2 diabetes, and in the open-label pediatric clinical trial of patients with type 1 diabetes, percentages of adult and pediatric patients with type 1 diabetes randomized to TRESIBA who experienced at least one episode of hypoglycemia in clinical trials *[see Clinical Studies (14)]* and adults with type 2 diabetes are shown in Tables 3 and 4, respectively.

Severe hypoglycemia in the open-label trials with adult patients was defined as an episode requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions. Severe hypoglycemia in the pediatric trial was defined as an altered mental status where the child could not assist in his own care, was semiconscious or unconscious, or in a coma ± convulsions and may require parenteral therapy (glucagon or intravenous glucose). A Novo Nordisk hypoglycemia episode was defined as a severe hypoglycemia episode or an episode where a laboratory or a self-measured glucose calibrated to plasma was less than 56

mg/dL or where a whole blood glucose was less than 50 mg/dL (i.e., with or without the presence of hypoglycemic symptoms).

Table 3: **Percent (%) of Type 1 Diabetes Patients Experiencing at Least One Episode of Severe Hypoglycemia or Novo Nordisk Hypoglycemia[§] on TRESIBA in Open-Label Adult and Pediatric Clinical Trials**

	Study A Adults + insulin aspart 52 weeks	**Study B Adults + insulin aspart 26 weeks**	**Study C Adults + insulin aspart 26 weeks**		**Study J Pediatrics + insulin aspart 52 weeks**
	TRESIBA (N=472)	**TRESIBA (N=301)**	**TRESIBA at the same time each day (N=165)**	**TRESIBA at alternating times (N=164)**	**TRESIBA (N=174)**
Severe hypoglycemia[*]					
Percent of patients	12.3%	10.6%	12.7%	10.4%	17.8%
Novo Nordisk hypoglycemia[§]					
Percent of patients	95.6%	93.0%	99.4%	93.9%	98.3%

[*]Severe hypoglycemia in pediatric patients: an episode with altered mental status, where the child could not assist in his own care, was semiconscious or unconscious, or in a coma ± convulsions and may require parenteral therapy (glucagon or intravenous glucose).
[§]Novo Nordisk hypoglycemia**:** a severe hypoglycemia episode or an episode where a laboratory or a self-measured glucose calibrated to plasma was less than 56 mg/dL or where a whole blood glucose was less than 50 mg/dL (i.e., with or without the presence of hypoglycemic symptoms).

Table 4: Percent (%) of Patients with Type 2 Diabetes Experiencing at Least One Episode of Severe Hypoglycemia or Novo Nordisk Hypoglycemia[§] on TRESIBA in Open-Label Adult Clinical Trials

	Study D + 1-2 OADs* insulin naïve 52 weeks	Study E + 1-2 OADs* insulin naïve 26 weeks	Study F ± 1-3 OADs* insulin naïve 26 weeks	Study G T2DM ± 0-3 OADs* 26 weeks		Study H T2DM ± 0-2 OADs* + insulin aspart 52 weeks	Study I T2DM ± 1-2 OADs* insulin naïve 26 weeks
	TRESIBA **(N=766)**	**TRESIBA** **(N=228)**	**TRESIBA** **(N=284)**	**TRESIBA** **(N=226)**	**TRESIBA (alternating time)** **(N=230)**	**TRESIBA** **(N=753)**	**TRESIBA** **(N=226)**
Severe Hypoglycemia							
Percent of patients	0.3%	0	0	0.9%	0.4%	4.5%	0.4%
Novo Nordisk Hypoglycemia[§]							
Percent of patients	46.5%	28.5%	50%	43.8%	50.9%	80.9%	42.5%

*OAD: oral antidiabetic agent, [§]Novo Nordisk hypoglycemia**:** a severe hypoglycemia episode or an episode where a laboratory or a self-measured glucose calibrated to plasma was less than 56 mg/dL or where a whole blood glucose was less than 50 mg/dL (i.e., with or without the presence of hypoglycemic symptoms).

Allergic Reactions

Severe, life-threatening, generalized allergy, including anaphylaxis, generalized skin reactions, angioedema, bronchospasm, hypotension, and shock may occur with any insulin, including TRESIBA and may be life threatening *[see Warnings and Precautions (5.5)]*. Hypersensitivity (manifested with swelling of tongue and lips, diarrhea, nausea, tiredness, and itching) and urticaria were reported in 0.9% of patients treated with TRESIBA.

Lipodystrophy

Long-term use of insulin, including TRESIBA, can cause lipodystrophy at the site of repeated insulin injections. Lipodystrophy includes lipohypertrophy (thickening of adipose tissue) and lipoatrophy (thinning of adipose tissue) and may affect insulin absorption *[see Dosage and Administration (2.1)]*. In the clinical program, lipodystrophy, lipohypertrophy, or lipoatrophy was reported in 0.3% of patients treated with TRESIBA.

Injection Site Reactions

Patients taking TRESIBA may experience injection site reactions, including injection site hematoma, pain, hemorrhage, erythema, nodules, swelling, discoloration, pruritus, warmth, and injection site mass. In the clinical program, injection site reactions occurred in 3.8% of patients treated with TRESIBA.

Weight Gain

Weight gain can occur with insulin therapy, including TRESIBA, and has been attributed to the anabolic effects of insulin. In the clinical program after 52 weeks of treatment, patients with type 1 diabetes treated with TRESIBA gained an average of 1.8 kg and patients with type 2 diabetes treated with TRESIBA gained an average of 3.0 kg.

Peripheral Edema

Insulin, including TRESIBA, may cause sodium retention and edema. In the clinical program, peripheral edema occurred in 0.9% of patients with type 1 diabetes mellitus and 3.0% of patients with type 2 diabetes mellitus treated with TRESIBA.

6.2 Immunogenicity

As with all therapeutic proteins, insulin administration may cause anti-insulin antibodies to form. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay and may be influenced by several factors such as: assay methodology, sample handling, timing of sample collection, concomitant medication, and underlying disease. For these reasons, comparison of the incidence of antibodies to TRESIBA with the incidence of antibodies in other studies or to other products may be misleading.

In studies of adult type 1 diabetes patients, 95.9% of patients who received TRESIBA once daily were positive for anti-insulin antibodies (AIA) at least once during the studies, including 89.7%

that were positive at baseline. In studies of type 2 diabetes patients, 31.5% of patients who received TRESIBA once daily were positive for AIA at least once during the studies, including 14.5% that were positive at baseline. The antibody incidence rates for type 2 diabetes may be underreported due to potential assay interference by endogenous insulin in samples in these patients.

The incidence of anti-insulin degludec antibodies has not been established.

7 DRUG INTERACTIONS

Table 5 includes clinically significant drug interactions with TRESIBA.

Table 5: Clinically Significant Drug Interactions with TRESIBA

Drugs That May Increase the Risk of Hypoglycemia	
Drugs:	Antidiabetic agents, ACE inhibitors, angiotensin II receptor blocking agents, disopyramide, fibrates, fluoxetine, monoamine oxidase inhibitors, pentoxifylline, pramlintide, propoxyphene, salicylates, somatostatin analogs (e.g., octreotide), and sulfonamide antibiotics, GLP-1 receptor agonists, DPP-4 inhibitors, SGLT-2 inhibitors.
Intervention:	Dose reductions and increased frequency of glucose monitoring may be required when TRESIBA is co-administered with these drugs.
Drugs That May Decrease the Blood Glucose Lowering Effect of TRESIBA	
Drugs:	Atypical antipsychotics (e.g., olanzapine and clozapine), corticosteroids, danazol, diuretics, estrogens, glucagon, isoniazid, niacin, oral contraceptives, phenothiazines, progestogens (e.g., in oral contraceptives), protease inhibitors, somatropin, sympathomimetic agents (e.g., albuterol, epinephrine, terbutaline), and thyroid hormones.
Intervention:	Dose increases and increased frequency of glucose monitoring may be required when TRESIBA is co-administered with these drugs.
Drugs That May Increase or Decrease the Blood Glucose Lowering Effect of TRESIBA	
Drugs:	Alcohol, beta-blockers, clonidine, and lithium salts. Pentamidine may cause hypoglycemia, which may sometimes be followed by hyperglycemia.
Intervention:	Dose adjustment and increased frequency of glucose monitoring may be required when TRESIBA is co-administered with these drugs.
Drugs That May Blunt Signs and Symptoms of Hypoglycemia	
Drugs:	Beta-blockers, clonidine, guanethidine, and reserpine
Intervention:	Increased frequency of glucose monitoring may be required when TRESIBA is co-administered with these drugs.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data with TRESIBA or insulin degludec in pregnant women to inform a drug-associated risk for major birth defects and miscarriage. There are risks to the mother and fetus associated with poorly controlled diabetes in pregnancy *[see Clinical Considerations]*.

Rats and rabbits were exposed to insulin degludec in animal reproduction studies during organogenesis. Pre-and post-implantation losses and visceral/skeletal abnormalities were observed in rats at doses 5 times (rat) and at 10 times (rabbit) the human exposure at a dose of 0.75 U/kg/day. These effects were similar to those observed in rats administered human insulin (NPH) *[see Data]*.

The estimated background risk of major birth defects is 6-10% in women with pre-gestational diabetes with a HbA1c >7 and has been reported to be as high as 20-25% in women with a HbA1c >10. The estimated background risk of miscarriage for the indicated population is unknown. 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. Poorly controlled diabetes increases the fetal risk for major birth defects, still birth, and macrosomia related morbidity.

Data

Animal Data

Insulin degludec was investigated in studies covering fertility, embryo-fetal development and pre- and post-natal development in rats and during the period of embryo-fetal development in rabbits. Human insulin (NPH insulin) was included as comparator. In these studies insulin degludec caused pre- and post-implantation losses and visceral/skeletal abnormalities when given subcutaneously at up to 21 U/kg/day in rats and 3.3 U/kg/day in rabbits, resulting in 5 times (rat) and 10 times (rabbit) the human exposure (AUC) at a human subcutaneous dose of 0.75 U/kg/day. Overall, the effects of insulin degludec were similar to those observed with human insulin, which were probably secondary to maternal hypoglycemia.

8.2 Lactation

Risk Summary

There are no data on the presence of insulin degludec in human milk, the effects on the breastfed infant, or the effects on milk production. Insulin degludec is present in rat milk [*see Data*]. The developmental and health benefits of breastfeeding should be considered along with the mother's

clinical need for TRESIBA and any potential adverse effects on the breastfed infant from TRESIBA or from the underlying maternal condition.

Data

In lactating rats, insulin degludec was present in milk at a concentration lower than that in plasma.

8.4 Pediatric Use

The safety and effectiveness of TRESIBA to improve glycemic control in type 1 and type 2 diabetes mellitus have been established in pediatric patients 1 year of age and older. The safety and effectiveness of TRESIBA have not been established in pediatric patients less than 1 year old.

The use of TRESIBA in pediatric patients 1 year of age and older with type 1 and type 2 diabetes mellitus is supported by evidence from an adequate and well-controlled study and a pharmacokinetic study (studies included pediatric patients 1 year of age and older with type 1 diabetes mellitus) *[see Clinical Pharmacology (12.3) and Clinical Studies (14.2)]*. The use of TRESIBA in pediatric patients 1 year of age and older with type 2 diabetes mellitus is also supported by evidence from adequate and well-controlled studies in adults with type 2 diabetes mellitus *[see Clinical Studies (14.3)]*.

In pediatric patients 1 year of age and older already on insulin therapy, start TRESIBA at a reduced dose to minimize the risk of hypoglycemia *[see Dosage and Administration (2.4)]*.

8.5 Geriatric Use

In controlled clinical studies *[see Clinical Studies (14)]* a total of 77 (7%) of the 1102 TRESIBA -treated patients with type 1 diabetes were 65 years or older and 9 (1%) were 75 years or older. A total of 670 (25%) of the 2713 TRESIBA-treated patients with type 2 diabetes were 65 years or older and 80 (3%) were 75 years or older. Differences in safety or effectiveness were not suggested in subgroup analyses comparing subjects older than 65 years to younger subjects.

In the safety outcomes trial (DEVOTE), a total of 1983 (52%) of the 3818 TRESIBA-treated patients with type 2 diabetes were 65 years or older and 381 (10%) were 75 years or older. Differences in safety or effectiveness were not observed in these subgroup analyses.

Nevertheless, greater caution should be exercised when TRESIBA is administered to geriatric patients since greater sensitivity of some older individuals to the effects of TRESIBA cannot be ruled out. The initial dosing, dose increments, and maintenance dosage should be conservative to avoid hypoglycemia. Hypoglycemia may be more difficult to recognize in the elderly.

8.6 Renal Impairment

In clinical studies *[see Clinical Studies (14)]* a total of 75 (7%) of the 1102 TRESIBA-treated patients with type 1 diabetes had an eGFR less than 60 mL/min/1.73 m^2 and 1 (0.1%) had an eGFR less than 30 mL/min/1.73 m^2. A total of 250 (9%) of the 2713 TRESIBA-treated patients with type 2 diabetes had an eGFR less than 60 mL/min/1.73 m^2 and no subjects had an eGFR

less than 30 mL/min/1.73 m^2.

In the safety outcomes trial (DEVOTE), a total of 1429 (37.4%) of the 3818 TRESIBA-treated patients with type 2 diabetes had an eGFR less than 60 mL/min/1.73 m^2, and 108 (2.8%) subjects had an eGFR less than 30 mL/min/1.73 m^2. Differences in safety or effectiveness were not observed in the subgroup analyses.

No clinically relevant difference in the pharmacokinetics of TRESIBA was identified in a study comparing healthy subjects and subjects with renal impairment including subjects with end stage renal disease *[see Clinical Pharmacology (12.3)]*. However, as with all insulin products, glucose monitoring should be intensified and the TRESIBA dosage adjusted on an individual basis in patients with renal impairment.

8.7 Hepatic Impairment

No difference in the pharmacokinetics of TRESIBA was identified in a study comparing healthy subjects and subjects with hepatic impairment (mild, moderate, and severe hepatic impairment) *[see Clinical Pharmacology (12.3)]*. However, as with all insulin products, glucose monitoring should be intensified and the TRESIBA dosage adjusted on an individual basis in patients with hepatic impairment.

10 OVERDOSAGE

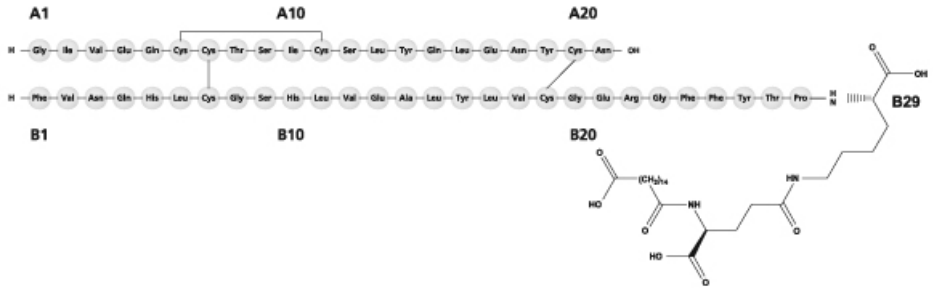
An excess of insulin relative to food intake, energy expenditure, or both may lead to severe and sometimes prolonged and life-threatening hypoglycemia and hypokalemia *[see Warnings and Precautions (5.3, 5.6)]*. Mild episodes of hypoglycemia usually can be treated with oral glucose. Adjustments in drug dosage, meal patterns, or exercise may be needed. More severe episodes of hypoglycemia with coma, seizure, or neurologic impairment may be treated with intramuscular/subcutaneous glucagon or concentrated intravenous glucose. After apparent clinical recovery from hypoglycemia, continued observation and additional carbohydrate intake may be necessary to avoid reoccurrence of hypoglycemia. Hypokalemia must be corrected appropriately.

11 DESCRIPTION

TRESIBA (insulin degludec injection) is a long-acting basal human insulin analog for subcutaneous injection. Insulin degludec is produced by a process that includes expression of recombinant DNA in *Saccharomyces cerevisiae* followed by chemical modification.

Insulin degludec differs from human insulin in that the amino acid threonine in position B30 has been omitted and a side-chain consisting of glutamic acid and a C16 fatty acid has been attached (chemical name: LysB29(Nε-hexadecandioyl-γ-Glu) des(B30) human insulin). Insulin degludec has a molecular formula of $C_{274}H_{411}N_{65}O_{81}S_6$ and a molecular weight of 6103.97. It has the following structure:

Figure 1: Structural Formula of TRESIBA



TRESIBA is a sterile, aqueous, clear, and colorless solution that contains insulin degludec 100 units/mL (U-100) or 200 units/mL (U-200).

Inactive ingredients for the 100 units/mL are glycerol 19.6 mg/mL, phenol 1.50 mg/mL, metacresol 1.72 mg/mL, zinc 32.7 mcg/mL and water for injection.

Inactive ingredients for the 200 units/mL are glycerol 19.6 mg/mL, phenol 1.50 mg/mL, metacresol 1.72 mg/mL, zinc 71.9 mcg/mL and water for injection.

TRESIBA has a pH of approximately 7.6. Hydrochloric acid or sodium hydroxide may be added to adjust pH.

12 CLINICAL PHARMACOLOGY

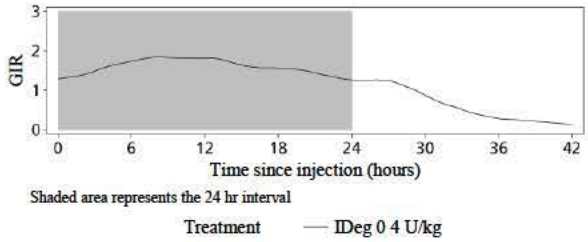
12.1 Mechanism of Action

The primary activity of insulin, including TRESIBA, is regulation of glucose metabolism. Insulin and its analogs lower blood glucose by stimulating peripheral glucose uptake, especially by skeletal muscle and fat, and by inhibiting hepatic glucose production. Insulin also inhibits lipolysis and proteolysis, and enhances protein synthesis. TRESIBA forms multi-hexamers when injected into the subcutaneous tissue resulting in a subcutaneous insulin degludec depot. The protracted time action profile of TRESIBA is predominantly due to delayed absorption of insulin degludec from the subcutaneous tissue to the systemic circulation and to a lesser extent due to binding of insulin-degludec to circulating albumin.

12.2 Pharmacodynamics

The glucose-lowering effect of TRESIBA after 8 days of once-daily dosing was measured in a euglycemic glucose clamp study enrolling 21 patients with type 1 diabetes. Figure 2 shows the pharmacodynamic effect of TRESIBA over time following 8 once-daily subcutaneous injections of 0.4 U/kg of TRESIBA in patients with type 1 diabetes.

Figure 2: Mean GIR Profile for 0.4 units/kg Dose of TRESIBA (Steady State) in Patients with Type 1 Diabetes Mellitus



The mean maximum glucose lowering effect (GIR_{max}) of a 0.4 units/kg dose of TRESIBA was 2.0 mg/kg/min, which was observed at a median of 12 hours post-dose. The glucose lowering effect of TRESIBA lasted at least 42 hours after the last of 8 once-daily injections.

In patients with type 1 diabetes mellitus, the steady-state, within subjects, day-to-day variability in total glucose lowering effect was 20% with TRESIBA (within-subject coefficient of variation for $AUC_{GIR,\tau,SS}$).

The total glucose-lowering effect of TRESIBA over 24 hours measured in a euglycemic clamp study after 8 days of once-daily administration in patients with type 1 diabetes increases approximately in proportion to the dose for doses between 0.4 units/kg to 0.8 units/kg.

The total glucose-lowering effect of 0.4 units/kg of TRESIBA U-100 and 0.4 units/kg of TRESIBA U-200, administered at the same dose, and assessed over 24 hours in a euglycemic clamp study after 8 days of once-daily injection was comparable.

12.3 Pharmacokinetics

Absorption

In patients with type 1 diabetes, after 8 days of once daily subcutaneous dosing with 0.4 units/kg of TRESIBA, maximum degludec concentrations of 4472 pmol/L were attained at a median of 9 hours (t_{max}). After the first dose of TRESIBA, median onset of appearance was around one hour.

Total insulin degludec concentration (i.e., exposure) increased in a dose proportional manner after subcutaneous administration of 0.4 units/kg to 0.8 units/kg TRESIBA. Total and maximum insulin degludec exposure at steady state are comparable between TRESIBA U-100 and TRESIBA U-200 when each is administered at the same units/kg dose.

Insulin degludec concentration reach steady state levels after 3-4 days of TRESIBA administration *[see Dosage and Administration (2.2)]*.

Distribution

The affinity of insulin degludec to serum albumin corresponds to a plasma protein binding of >99% in human plasma. The results of the *in vitro* protein binding studies demonstrate that there is no clinically relevant interaction between insulin degludec and other protein bound drugs.

Elimination

The half-life after subcutaneous administration is determined primarily by the rate of absorption from the subcutaneous tissue. On average, the half-life at steady state is approximately 25 hours

independent of dose. Degradation of TRESIBA is similar to that of insulin human; all metabolites formed are inactive. The mean apparent clearance of insulin degludec is 0.03 L/kg (2.1 L/h in 70 kg individual) after single subcutaneous dose of 0.4 units/kg.

Specific Populations

Pediatrics-

Population pharmacokinetic analysis was conducted for TRESIBA using data from 199 pediatric subjects (1 to <18 years of age) with type 1 diabetes. Body weight was a significant covariate affecting the clearance of TRESIBA. After adjusting for body weight, the total exposure of TRESIBA at steady state was independent of age.

Geriatrics-

Pharmacokinetic and pharmacodynamic response of TRESIBA was compared in 13 younger adult (18−35 years) and 14 geriatric (≥65 years) subjects with type 1 diabetes following two 6-day periods of once-daily subcutaneous dosing with 0.4 units/kg dose of TRESIBA or insulin glargine. On average, the pharmacokinetic and pharmacodynamic properties of TRESIBA at steady-state were similar in younger adult and geriatric subjects, albeit with greater between subject variability among the geriatric subjects.

Gender-

The effect of gender on the pharmacokinetics of TRESIBA was examined in an across-trial analysis of the pharmacokinetic and pharmacodynamic studies conducted using unit/kg doses of TRESIBA. Overall, there were no clinically relevant differences in the pharmacokinetic properties of insulin degludec between female and male subjects.

Obesity-

The effect of BMI on the pharmacokinetics of TRESIBA was explored in a cross-trial analysis of pharmacokinetic and pharmacodynamic studies conducted using unit/kg doses of TRESIBA. For subjects with type 1 diabetes, no relationship between exposure of TRESIBA and BMI was observed. For subjects with type 1 and type 2 diabetes a trend for decrease in glucose-lowering effect of TRESIBA with increasing BMI was observed.

Race and Ethnicity-

TRESIBA has been studied in a pharmacokinetic and pharmacodynamic study in Black or African American subjects not of Hispanic or Latino origin (n=18), White subjects of Hispanic or Latino origin (n=22) and White subjects not of Hispanic or Latino origin (n=23) with type 2 diabetes mellitus conducted using unit/kg doses of TRESIBA. There were no statistically significant differences in the pharmacokinetic and pharmacodynamic properties of TRESIBA between the racial and ethnic groups investigated.

Pregnancy-

The effect of pregnancy on the pharmacokinetics and pharmacodynamics of TRESIBA has not been studied *[see Use in Specific Populations (8.1)]*.

Renal Impairment-

TRESIBA pharmacokinetics was studied in 32 subjects (n=4-8/group) with normal or impaired renal function/end-stage renal disease following administration of a single subcutaneous dose (0.4 units/kg) of TRESIBA. Renal function was defined using creatinine clearance (Cl_{cr}) as follows: ≥90 mL/min (normal), 60-89 mL/min (mild), 30-59 mL/min (moderate) and <30 mL/min (severe). Subjects requiring dialysis were classified as having end-stage renal disease (ESRD). Total ($AUC_{IDeg,0\text{-}120h,SD}$) and peak exposure of TRESIBA were on average about 10-25% and 13-27% higher, respectively in subjects with mild to severe renal impairment except subjects with ESRD who showed similar exposure as compared to subjects with normal renal function. No systematic trend was noted for this increase in exposure across different renal impairment subgroups. Hemodialysis did not affect clearance of TRESIBA ($CL/F_{IDeg,SD}$) in subjects with ESRD *[see Use in Specific Populations (8.6)]*.

Hepatic Impairment-
TRESIBA has been studied in a pharmacokinetic study in 24 subjects (n=6/group) with normal or impaired hepatic function (mild, moderate, and severe hepatic impairment) following administration of a single subcutaneous dose (0.4 units/kg) of TRESIBA. Hepatic function was defined using Child-Pugh Scores ranging from 5 (mild hepatic impairment) to 15 (severe hepatic impairment). No differences in the pharmacokinetics of TRESIBA were identified between healthy subjects and subjects with hepatic impairment *[see Use in Specific Populations (8.7)]*.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Standard 2-year carcinogenicity studies in animals have not been performed to evaluate the carcinogenic potential of insulin degludec. In a 52-week study including human insulin (NPH insulin) as comparator (6.7 units/kg/day), Sprague-Dawley rats were dosed subcutaneously with insulin degludec at 3.3, 6.7, and 10 units/kg/day, resulting in 5 times the human exposure (AUC) when compared to a human subcutaneous dose of 0.75 units/kg/day. Human insulin was dosed at 6.7 units/kg/day. No treatment-related increases in incidences of hyperplasia, benign or malignant tumors were recorded in female mammary glands from rats dosed with insulin degludec and no treatment related changes in the female mammary gland cell proliferation were found using BrdU incorporation. Further, no treatment related changes in the occurrence of hyperplastic or neoplastic lesions were seen in other tissues in animals dosed with insulin degludec when compared to vehicle or human insulin.

Genotoxicity testing of insulin degludec was not performed.

In a combined fertility and embryo-fetal study in male and female rats, treatment with insulin degludec up to 21 units/kg/day (approximately 5 times the human subcutaneous dose of 0.75 units/kg/day, based on units/body surface area) prior to mating and in female rats during gestation had no effect on mating performance and fertility.

14 CLINICAL STUDIES

The efficacy of TRESIBA administered once-daily either at the same time each day or at any time each day in patients with type 1 diabetes and used in combination with a mealtime insulin was evaluated in three randomized, open-label, treat-to-target, active-controlled trials in adults

and one randomized, open-label, treat-to-target, active-controlled trial in pediatric patients 1 year of age and older. The efficacy of TRESIBA administered once-daily either at the same time each day or at any time each day in adult patients with type 2 diabetes and used in combination with a mealtime insulin or in combination with common oral anti-diabetic agents was evaluated in six randomized, open-label, treat-to-target active-controlled trials.

Adult patients treated with TRESIBA achieved levels of glycemic control similar to those achieved with LANTUS (insulin glargine 100 units/mL) and LEVEMIR (insulin detemir) and achieved statistically significant improvements compared to sitagliptin.

14.1 Type 1 Diabetes – Adult

TRESIBA Administered at the Same Time Each Day in Combination with a Rapid-Acting Insulin Analog at Mealtimes in Adult Patients

Study A

The efficacy of TRESIBA was evaluated in a 52-week randomized, open-label, multicenter trial in 629 patients with type 1 diabetes mellitus (Study A). Patients were randomized to TRESIBA once-daily with the evening meal or insulin glargine U-100 once-daily according to the approved labeling. Insulin aspart was administered before each meal in both treatment arms.

The mean age of the trial population was 43 years and mean duration of diabetes was 18.9 years. 58.5% were male. 93% were White, 1.9% Black or African American. 5.1% were Hispanic. 8.6% of patients had eGFR<60 mL/min/1.73m^2. The mean BMI was approximately 26.3 kg/m^2.

At week 52, the difference in HbA_{1c} reduction from baseline between TRESIBA and insulin glargine U-100 was -0.01% with a 95% confidence interval of [-0.14%; 0.11%] and met the pre-specified non-inferiority margin (0.4%). See Table 6, Study A.

Study B

The efficacy of TRESIBA was evaluated in a 26-week randomized, open-label, multicenter trial in 455 patients with type 1 diabetes mellitus (Study B). Patients were randomized to TRESIBA or insulin detemir once-daily in the evening. After 8 weeks, insulin detemir could be dosed twice-daily. 67.1% used insulin detemir once daily at end of trial. 32.9% used insulin detemir twice daily at end of trial. Insulin aspart was administered before each meal in both treatment arms.

The mean age of the trial population was 41.3 years and mean duration of diabetes was 13.9 years. 51.9% were male. 44.6% were White, 0.4% Black or African American. 4.4% were Hispanic. 4.4% of patients had eGFR<60 mL/min/1.73m^2. The mean BMI was approximately 23.9 kg/m^2.

At week 26, the difference in HbA_{1c} reduction from baseline between TRESIBA and insulin detemir was -0.09% with a 95% confidence interval of [-0.23%; 0.05%] and met the pre-specified non-inferiority margin (0.4%). See Table 6, Study B.

Table 6: Results at Week 52 in a Trial Comparing TRESIBA to Insulin Glargine U-100 (Study A) and Week 26 in a Trial Comparing TRESIBA to Insulin Detemir (Study B) in Adult Patients with Type 1 Diabetes Mellitus Receiving Insulin Aspart at Mealtimes

	Study A		**Study B**	
	TRESIBA + Insulin aspart	**Insulin glargine U-100 + Insulin aspart**	**TRESIBA + Insulin aspart**	**Insulin detemir + Insulin aspart**
N	**472**	**157**	**302**	**153**
HbA_{1c} (%)				
Baseline	7.7	7.7	8.0	8.0
End of trial	7.3	7.3	7.3	7.3
Adjusted mean change from baseline*	-0.36	-0.34	-0.71	-0.61
Estimated treatment difference [95%CI] TRESIBA - basal insulin U-100	-0.01 [-0.14;0.11]		-0.09 [-0.23;0.05]	
Proportion Achieving HbA_{1c} < 7% at Trial End	39.8%	42.7%	41.1%	37.3%
FPG (mg/dL)				
Baseline	165	174	178	171
End of trial	141	149	131	161
Adjusted mean change from baseline	-27.6	-21.6	-43.3	-13.5
Daily basal insulin dose				
Baseline mean	28 U	26 U	22 U	22 U
Mean dose at end of study	29 U[1]	31 U[1]	25 U[2]	29 U[2]
Daily bolus insulin dose				
Baseline mean	29 U	29 U	28 U	31 U
Mean dose at end of study	32 U[1]	35 U[1]	36 U[2]	41 U[2]

[1]At Week 52

[2]At Week 26

*The change from baseline to end of treatment visit in HbA_{1c} was analysed using ANOVA with treatment, region, sex, and anti-diabetic treatment at screening as fixed effects, and age and baseline HbA_{1c} as covariates.
In Study A, there were 14.8% of subjects in the TRESIBA and 11.5% Insulin glargine arms for whom data was missing at the time of the HbA_{1c} measurement.
In Study B, there were 6.3% of subjects in the TRESIBA and 9.8% Insulin detemir arms for whom data was missing at the time of the HbA_{1c} measurement.

Study C: TRESIBA Administered at the Same Time Each Day or at Any Time Each Day in Combination with a Rapid-Acting Insulin Analog at Mealtimes in Adult Patients

The efficacy of TRESIBA was evaluated in a 26-week randomized, open-label, multicenter trial in 493 patients with type 1 diabetes mellitus. Patients were randomized to TRESIBA injected once-daily at the same time each day (with the main evening meal), to TRESIBA injected once daily at any time each day or to insulin glargine U-100 injected once-daily according to the approved labeling. The any time each day TRESIBA arm was designed to simulate a worst-case scenario injection schedule of alternating short and long, once daily, dosing intervals (i.e., alternating intervals of 8 to 40 hours between doses). TRESIBA in this arm was dosed in the morning on Monday, Wednesday, and Friday and in the evening on Tuesday, Thursday, Saturday, and Sunday. Insulin aspart was administered before each meal in all treatment arms.

The mean age of the trial population was 43.7 years and mean duration of diabetes was 18.5 years. 57.6% were male. 97.6% were White, 1.8% Black or African American. 3.4% were Hispanic. 7.4% of patients had eGFR<60 mL/min/1.73m^2. The mean BMI was approximately 26.7 kg/m^2.

At week 26, the difference in HbA_{1c} reduction from baseline between TRESIBA administered at alternating times and insulin glargine U-100 was 0.17% with a 95% confidence interval of [0.04%; 0.30%] and met the pre-specified non-inferiority margin (0.4%). See Table 7.

Table 7: Results at Week 26 in a Trial Comparing TRESIBA Dosed Once Daily at the Same and at Alternating Times Each Day to Insulin Glargine U-100 in Adult Patients with Type 1 Diabetes Mellitus Receiving Insulin Aspart at Mealtimes

	TRESIBA at the same time each day + Insulin aspart	**TRESIBA at alternating times + Insulin aspart**	**Insulin glargine U-100 + Insulin aspart**
N	165	164	164
HbA_{1c} (%)			
Baseline	7.7	7.7	7.7
End of trial	7.3	7.3	7.1
Adjusted mean change from baseline*	-0.41	-0.40	-0.57
Estimated treatment difference [95%CI] TRESIBA alternating - Insulin glargine U-100		0.17 [0.04;0.30]	
Proportion Achieving HbA_{1c} < 7% at Trial End	37.0%	37.2%	40.9%
FPG (mg/dL)			
Baseline	179	173	175
End of trial	133	149	151
Adjusted mean change from	-41.8	-24.7	-23.9

baseline			
Daily basal insulin dose			
Baseline mean	28 U	29 U	29 U
Mean dose at end of study	32 U	36 U	35 U
Daily bolus insulin dose			
Baseline mean	29 U	33 U	32 U
Mean dose at end of study	27 U	30 U	35 U

*The change from baseline to end of treatment visit in HbA_{1c} was analysed using ANOVA with treatment, region, sex, and anti-diabetic treatment at screening as fixed effects, and age and baseline HbA_{1c} as covariates. In Study C, there were 15.8% and 15.9% of subjects in the TRESIBA (same time and alternating times respectively) and 7.9% Insulin glargine arms for whom data was missing at the time of the HbA_{1c} measurement.

14.2 Type 1 Diabetes – Pediatric Patients 1 Year of Age and Older

Study J: TRESIBA Administered at the Same Time Each Day in Combination with a Rapid-Acting Insulin Analog at Mealtimes in Pediatric Patients 1 Year of Age and Older

The efficacy of TRESIBA was evaluated in a 26-week, randomized, open label, multicenter trial in 350 patients with type 1 diabetes mellitus (Study J). Patients were randomized to TRESIBA once-daily or insulin detemir once or twice-daily. Subjects on a twice-daily insulin detemir regimen were dosed at breakfast and in the evening either with the main evening meal or at bedtime. Insulin aspart was administered before each main meal in both treatment arms. At end of trial, 36% used insulin detemir once daily and 64% used insulin detemir twice daily.

The mean age of the trial population was 10 years; 24% were ages 1-5 years; 39% were ages 6-11 years and 36% were ages 12-17 years. The mean duration of diabetes was 4 years. 55.4% were male. 74.6% were White, 2.9% Black or African American. 2.9% were Hispanic. The mean z-score for body weight was 0.31.

At week 26, the difference in HbA_{1c} reduction from baseline between TRESIBA and insulin detemir was 0.15% with a 95% confidence interval of [-0.03%; 0.33%] and met the pre-specified non-inferiority margin (0.4%). See Table 8.

Table 8: Results at Week 26 in a Trial Comparing TRESIBA to Insulin Detemir in Pediatric Patients 1 Year of Age and Older with Type 1 Diabetes Mellitus Receiving Insulin Aspart at Mealtimes

	TRESIBA+ Insulin aspart	**Insulin detemir + Insulin aspart**
N	174	176
HbA_{1c} (%)		
Baseline	8.2	8.0
End of 26 weeks	8.0	7.7
Adjusted mean change from baseline after 26 weeks ±	-0.19	-0.34
Estimated treatment		

difference [95%CI] TRESIBA v. Insulin detemir	0.15 [-0.03; 0.33]	
FPG (mg/dL)		
Baseline	162	151
End of 26 weeks	150	160
Adjusted mean change from baseline after 26 weeks	52.0	59.6
Daily basal insulin dose		
Baseline mean	15 U (0.37 U/kg)	16 U (0.41 U/kg)
Mean dose after 26 weeks	16 U (0.37 U/kg)	22 U (0.51 U/kg)
Daily bolus insulin dose		
Baseline mean	20 U (0.50 U/kg)	20 U (0.52 U/kg)
Mean dose after 26 weeks	23 U (0.56 U/kg)	22 U (0.57 U/kg)

[±]The change from baseline to end of treatment visit in HbA_{1c} was analysed using ANOVA with missing data imputed by multiple imputation carrying forward the baseline value and adding the error term, with treatment, region, sex, and age group as fixed factors, and baseline HbA_{1c} as covariate.
In Study J, there were 2.9% of subjects in TRESIBA and 6.3% Insulin detemir arms for whom data was missing at the 26-week HbA_{1c} measurement.

14.3 Type 2 Diabetes – Adult

Study D: TRESIBA Administered at the Same Time Each Day as an Add-on to Metformin with or without a DPP-4 Inhibitor in Insulin Naïve Adult Patients

The efficacy of TRESIBA was evaluated in a 52-week randomized, open-label, multicenter trial that enrolled 1030 insulin naïve patients with type 2 diabetes mellitus inadequately controlled on one or more oral antidiabetic agents (OADs). Patients were randomized to TRESIBA once-daily with the evening meal or insulin glargine U-100 once-daily according to the approved labeling. Metformin alone (82.5%) or in combination with a DPP-4 inhibitor (17.5%) was used as background therapy in both treatment arms.

The mean age of the trial population was 59.1 years and mean duration of diabetes was 9.2 years. 61.9% were male. 88.4% were White, 7.1% Black or African American. 17.2% were Hispanic. 9.6% of patients had eGFR<60 mL/min/1.73m^2. The mean BMI was approximately 31.1 kg/m^2.

At week 52, the difference in HbA_{1c} reduction from baseline between TRESIBA and insulin glargine U-100 was 0.09% with a 95% confidence interval of [-0.04%; 0.22%] and met the pre-specified non-inferiority margin (0.4%); See Table 9.

Table 9: Results at Week 52 in a Trial Comparing TRESIBA to Insulin Glargine U-100 in Adult Patients with Type 2 Diabetes Mellitus on OAD(s)*

	TRESIBA + OAD(s)*	**Insulin glargine U-100 + OAD(s)***
N	**773**	**257**
HbA_{1c} (%)		

Baseline	8.2	8.2
End of trial	7.1	7.0
Adjusted mean change from baseline**	-1.06	-1.15
Estimated treatment difference [95%CI] TRESIBA - Insulin glargine U-100	0.09 [-0.04;0.22]	
Proportion Achieving HbA_{1c} < 7% at Trial End	51.7%	54.1%
FPG (mg/dL)		
Baseline	174	174
End of trial	106	115
Adjusted mean change from baseline	-68.0	-60.2
Daily insulin dose		
Baseline mean (starting dose)	10 U	10 U
Mean dose after 52 weeks	56 U	58 U

*OAD: oral antidiabetic agent

**The change from baseline to end of treatment visit in HbA_{1c} was analysed using ANOVA with treatment, region, sex, and anti-diabetic treatment at screening as fixed effects, and age and baseline HbA_{1c} as covariates. In Study D, there were 20.6% of subjects in the TRESIBA and 22.2% Insulin glargine arms for whom data was missing at the time of the HbA_{1c} measurement.

Study E: TRESIBA U-200 Administered at the Same Time Each Day as an Add-on to Metformin with or without a DPP-4 Inhibitor in Insulin Naïve Adult Patients

The efficacy of TRESIBA U-200 was evaluated in a 26-week randomized, open-label, multicenter trial in 457 insulin naïve patients with type 2 diabetes mellitus inadequately controlled on one or more oral antidiabetic agents (OADs) at baseline. Patients were randomized to TRESIBA U-200 once-daily with the evening meal or insulin glargine U-100 once-daily according to the approved labeling. Both treatment arms were receiving metformin alone (84%) or in combination with a DPP-4 inhibitor (16%) as background therapy.

The mean age of the trial population was 57.5 years and mean duration of diabetes was 8.2 years. 53.2% were male. 78.3% were White, 13.8% Black or African American. 7.9% were Hispanic. 7.5% of patients had eGFR <60 mL/min/1.73m^2. The mean BMI was approximately 32.4 kg/m^2.

At week 26, the difference in HbA_{1c} reduction from baseline between TRESIBA U-200 and insulin glargine U-100 was 0.04% with a 95% confidence interval of [-0.11%; 0.19%] and met the pre-specified non-inferiority margin (0.4%). See Table 10.

Table 10: Results at Week 26 in a Trial Comparing TRESIBA U-200 to Insulin Glargine U-100 in Adult Patients with Type 2 Diabetes Mellitus on OAD(s)*

	TRESIBA U-200 + Met ± DPP-4	**Insulin glargine U-100 + Met ± DPP-4**
N	**228**	**229**
HbA_{1c} (%)		
Baseline	8.3	8.2
End of trial	7.0	6.9
Adjusted mean change from baseline**	-1.18	-1.22
Estimated treatment difference [95%CI] TRESIBA - Insulin glargine U-100	0.04 [-0.11;0.19]	
Proportion Achieving HbA_{1c} < 7% at Trial End	52.2%	55.9%
FPG (mg/dL)		
Baseline	172	174
End of trial	106	113
Adjusted mean change from baseline	-71.1	-63.5
Daily insulin dose		
Baseline mean	10 U	10 U
Mean dose after 26 weeks	59 U	62 U

*OAD: oral antidiabetic agent

**The change from baseline to end of treatment visit in HbA_{1c} was analysed using ANOVA with treatment, region, sex, and anti-diabetic treatment at screening as fixed effects, and age and baseline HbA_{1c} as covariates. In Study E, there were 12.3% of subjects in the TRESIBA and 12.7% Insulin glargine arms for whom data was missing at the time of the HbA_{1c} measurement.

Study F: TRESIBA Administered at the Same Time Each Day in Insulin Naïve Adult Patients as an Add-on to One or More of the Following Oral Agents: Metformin, Sulfonylurea, Glinides or Alpha-Glucosidase Inhibitors

The efficacy of TRESIBA was evaluated in a 26-week randomized, open-label, multicenter trial in Asia in 435 insulin naïve patients with type 2 diabetes mellitus inadequately controlled on one or more oral antidiabetic agents (OADs) at baseline. Patients were randomized to TRESIBA once-daily in the evening or insulin glargine U-100 once-daily according to the approved labeling. Pre-trial oral antidiabetes agents were continued as background therapy except for DPP-4 inhibitors or thiazolidinediones in both treatment arms.

The mean age of the trial population was 58.6 years and mean duration of diabetes was 11.6 years. 53.6% were male. All patients were Asian. 10.9% of patients had eGFR<60 mL/min/1.73m^2. The mean BMI was approximately 25.0 kg/m^2.

At week 26, the difference in HbA_{1c} reduction from baseline between TRESIBA and insulin glargine U-100 was 0.11% with a 95% confidence interval of [-0.03%; 0.24%] and met the pre-specified non-inferiority margin (0.4%). See Table 11.

Table 11: Results at Week 26 in a Trial Comparing TRESIBA to Insulin Glargine U-100 in Adult Patients with Type 2 Diabetes Mellitus on OAD(s)*

	TRESIBA + OAD(s)*	**Insulin glargine U-100 + OAD(s)***
N	**289**	**146**
HbA_{1c} (%)		
Baseline	8.4	8.5
End of trial	7.2	7.1
Adjusted mean change from baseline**	-1.42	-1.52
Estimated treatment difference [95%CI] TRESIBA - Insulin glargine U-100	0.11 [-0.03 ; 0.24]	
Proportion Achieving HbA_{1c} < 7% at Trial End	40.8%	48.6%
FPG (mg/dL)		
Baseline	152	156
End of trial	100	102
Adjusted mean change from baseline	-54.6	-53.0
Daily insulin dose		
Baseline mean (starting dose)	9 U	9 U
Mean dose after 26 weeks	19 U	24 U

*OAD: oral antidiabetic agent

**The change from baseline to end of treatment visit in HbA_{1c} was analysed using ANOVA with treatment, region, sex, and anti-diabetic treatment at screening as fixed effects, and age and baseline HbA_{1c} as covariates. In Study F, there were 10% of subjects in the TRESIBA and 6.8% Insulin glargine arms for whom data was missing at the time of the HbA_{1c} measurement.

Study G: *TRESIBA Administered at the Same Time Each Day or Any Time Each Day as an Add-on to One and up to Three of the Following Oral Agents: Metformin, Sulfonylurea or Glinides or Pioglitazone in Adult Patients*

The efficacy of TRESIBA was evaluated in a 26-week randomized, open-label, multicenter trial in 687 patients with type 2 diabetes mellitus inadequately controlled on basal insulin alone, oral antidiabetic agents (OADs) alone or both basal insulin and OAD. Patients were randomized to TRESIBA injected once-daily at the same time each day (with the main evening meal), to TRESIBA injected once daily at any time each day or to insulin glargine U-100 injected once-daily according to the approved labeling. The any time each day TRESIBA arm was designed to simulate a worst-case scenario injection schedule of alternating short and long, once daily,

dosing intervals (i.e., alternating intervals of 8 to 40 hours between doses). TRESIBA in this arm was dosed in the morning on Monday, Wednesday, and Friday and in the evening on Tuesday, Thursday, Saturday, and Sunday. Up to three of the following oral antidiabetes agents (metformin, sulfonylureas, glinides or thiazolidinediones) were administered as background therapy in both treatment arms.

The mean age of the trial population was 56.4 years and mean duration of diabetes was 10.6 years. 53.9% were male. 66.7% were White, 2.5% Black or African American. 10.6% were Hispanic. 5.8% of patients had eGFR<60 mL/min/1.73m^2. The mean BMI was approximately 29.6 kg/m^2.

At week 26, the difference in HbA_{1c} reduction from baseline between TRESIBA at alternating times and insulin glargine U-100 was 0.04% with a 95% confidence interval of [-0.12%; 0.20%]. This comparison met the pre-specified non-inferiority margin (0.4%). See Table 12.

Table 12: Results at Week 26 in a Trial Comparing TRESIBA at Same and Alternating Times to Insulin Glargine U-100 in Adult Patients with Type 2 Diabetes Mellitus on OAD(s)*

	TRESIBA at the same time each day ± OAD(s)*	**TRESIBA at alternating times ± OAD(s)***	**Insulin glargine U-100 ± OAD(s)***
N	**228**	**229**	**230**
HbA_{1c} (%)			
Baseline	8.4	8.5	8.4
End of trial	7.3	7.2	7.1
Adjusted mean change from baseline**	-1.03	-1.17	-1.21
Estimated treatment difference [95%CI] TRESIBA alternating-Insulin glargine U-100		0.04 [-0.12;0.20]	
Estimated treatment difference TRESIBA alternating – TRESIBA same	-0.13		
Proportion Achieving HbA_{1c} < 7% at Trial End	40.8%	38.9%	43.9%
FPG (mg/dL)			
Baseline	158	162	163
End of trial	105	105	112
Adjusted mean change from baseline	-54.2	-55.0	-47.5
Daily insulin dose			
Baseline mean	21 U	19 U	19 U
Mean dose after 26 weeks	45 U	46 U	44 U

*OAD: oral antidiabetic agent

**The change from baseline to end of treatment visit in HbA_{1c} was analysed using ANOVA with treatment, region, sex, and anti-diabetic treatment at screening as fixed effects, and age and baseline HbA_{1c} as covariates. In Study G, there were 11.4% subjects for TRESIBA (both same time and alternating times) and 11.7% Insulin glargine arms for whom data was missing at the time of the HbA_{1c} measurement.

Study H: TRESIBA Administered at the Same Time Each Day in Combination with a Rapid-Acting Insulin Analog at Mealtimes in Adult Patients

The efficacy of TRESIBA was evaluated in a 52-week randomized, open-label, multicenter trial in 992 patients with type 2 diabetes mellitus inadequately controlled on premix insulin, bolus insulin alone, basal insulin alone, oral antidiabetic agents (OADs) alone or any combination thereof. Patients were randomized to TRESIBA once-daily with the main evening meal or insulin glargine U-100 once-daily according to the approved labeling. Insulin aspart was administered before each meal in both treatment arms. Up to two of the following oral antidiabetes agents (metformin or pioglitazone) were used as background therapy in both treatment arms.

The mean age of the trial population was 58.9 years and mean duration of diabetes was 13.5 years. 54.2% were male. 82.9% were White, 9.5% Black or African American. 12.0% were Hispanic. 12.4% of patients had eGFR<60 mL/min/1.73m^2. The mean BMI was approximately 32.2 kg/m^2.

At week 52, the difference in HbA_{1c} reduction from baseline between TRESIBA and insulin glargine U-100 was 0.08% with a 95% confidence interval of [-0.05%; 0.21%] and met the pre-specified non-inferiority margin (0.4%). See Table 13.

Table 13: Results at Week 52 in a Trial Comparing TRESIBA to Insulin Glargine U-100 in Adult Patients with Type 2 Diabetes Mellitus Receiving Insulin Aspart at Mealtimes and OADs*

	TRESIBA + Insulin aspart ± OAD(s)*	**Insulin glargine U-100 + Insulin aspart ± OAD(s)***
N	**744**	**248**
HbA_{1c} (%)		
Baseline	8.3	8.4
End of trial	7.1	7.1
Adjusted mean change from baseline**	-1.10	-1.18
Estimated treatment difference [95%CI] TRESIBA - Insulin glargine U-100	0.08 [-0.05;0.21]	
Proportion Achieving HbA_{1c} < 7% at Trial End	49.5%	50.0%
FPG (mg/dL)		
Baseline	166	166

End of trial	122	127
Adjusted mean change from baseline	-40.6	-35.3
Daily basal insulin dose		
Baseline mean	42 U	41 U
Mean dose after 52 weeks	74 U	67 U
Daily bolus insulin dose		
Baseline mean	33 U	33 U
Mean dose after 52 weeks	70 U	73 U

*OAD: oral antidiabetic agent

**The change from baseline to end of treatment visit in HbA_{1c} was analysed using ANOVA with treatment, region, sex, and anti-diabetic treatment at screening as fixed effects, and age and baseline HbA_{1c} as covariates.

In Study H, there were 16.1% of subjects in the TRESIBA and 14.5% Insulin glargine arms for whom data was missing at the time of the HbA_{1c} measurement.

Study I: TRESIBA Administered at Any Time Each Day as an Add-on to One or Two of the Following Oral Agents: Metformin, Sulfonylurea, or Pioglitazone in Adult Patients

The efficacy of TRESIBA was evaluated in a 26-week randomized, open-label, multicenter trial in 447 patients with type 2 diabetes mellitus inadequately controlled on one or more oral antidiabetic agent (OADs) at baseline. Patients were randomized to TRESIBA once-daily at any time of day or sitagliptin once-daily according to the approved labeling. One or two of the following oral antidiabetes agents (metformin, sulfonylurea or pioglitazone) were also administered in both treatment arms.

The mean age of the trial population was 55.7 years and mean duration of diabetes was 7.7 years. 58.6% were male. 61.3% were White, 7.6% Black or African American. 21.0% were Hispanic. 6% of patients had eGFR<60 mL/min/1.73m^2. The mean BMI was approximately 30.4 kg/m^2.

At the end of 26 weeks, TRESIBA provided greater reduction in mean HbA_{1c} compared to sitagliptin ($p < 0.001$). See Table 14.

Table 14: Results at Week 26 in a Trial Comparing TRESIBA to Sitagliptin in Adult Patients with Type 2 Diabetes Mellitus on OADs*

	TRESIBA + OAD(s)*	**Sitagliptin + OAD(s)***
N	**225**	**222**
HbA_{1c} (%)		
Baseline	8.8	9.0
End of trial	7.2	7.7
Adjusted mean change from baseline**	-1.52	-1.09
Estimated treatment difference [95%CI] TRESIBA - Sitagliptin	-0.43 [-0.61;-0.24][1]	
Proportion Achieving	40.9%	27.9%

HbA_{1c} < 7% at Trial End		
FPG (mg/dL)		
Baseline	170	179
End of trial	112	154
Adjusted mean change from baseline	-61.4	-22.3
Daily insulin dose		
Baseline mean	10 U	N/A
Mean dose after 26 weeks	43 U	N/A

*OAD: oral antidiabetic agent

**The change from baseline to end of treatment visit in HbA_{1c} was analysed using ANOVA with treatment, region, sex, and anti-diabetic treatment at screening as fixed effects, and age and baseline HbA_{1c} as covariates.

In Study I, there were 20.9% of subjects in the TRESIBA and 22.5% Sitagliptin arms for whom data was missing at the time of the HbA_{1c} measurement.

[1]p <0.001; 1-sided p-value evaluated at 2.5% level for superiority

14.4 Safety Outcomes Trial

DEVOTE (NCT01959529) Cardiovascular Outcomes Trial of TRESIBA Administered Once-Daily Between Dinner and Bedtime in Combination with Standard of Care in Subjects with Type 2 Diabetes and Atherosclerotic Cardiovascular Disease

DEVOTE was a multi-center, multi-national, randomized, double-blinded, active-controlled, treat-to-target, event-driven trial. 7,637 patients with inadequately controlled type 2 diabetes and atherosclerotic cardiovascular disease were randomized to either TRESIBA or insulin glargine U-100. Each was administered once-daily between dinner and bedtime in addition to standard of care for diabetes and cardiovascular disease for a median duration of 2 years.

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 (85% of the enrolled population) or were 60 years of age or older and had other specified risk factors for cardiovascular disease (15% of the enrolled population).

At baseline, demographic and disease characteristics were balanced between treatment groups. The mean age of the trial population was 65 years and the mean duration of diabetes was 16.4 years. The population was 62.6% male, 75.6% White 10.9% Black or African American, 10.2% Asian. 14.9% had Hispanic ethnicity. The mean HbA1c was 8.4% and the mean BMI was 33.6 kg/m^2. The baseline mean estimated glomular filtration rate (eGFR) was 68 mL/min/1.73m^2. 41% of patients had eGFR 60-90 mL/min/1.73m^2; 35% of patients had eGFR 30 to 60 mL/min/1.73 m^2 and 3% of patients had eGFR <30 mL/min/1.73 m^2. Previous history of severe hypoglycemia was not captured in the trial.

At baseline, patients treated their diabetes with oral antidiabetic drugs (72%) and with an insulin regimen (84%). Types of insulins included long acting insulin (60%), intermediate acting insulin (14%) short acting insulin (37%) and premixed insulin (10%). 16% of patients were insulin

naive. The most common background oral antidiabetic drugs used at baseline were metformin (60%), sulfonylureas (29%) and DPP-4 inhibitors (12%).

During the trial, investigators could modify anti-diabetic and cardiovascular medications to achieve local standard of care treatment targets for lipids and blood pressure.

Cardiovascular Outcomes *- Patients with T2DM and Atherosclerotic CVD*

The incidence of major cardiovascular events with TRESIBA was evaluated in DEVOTE. Subjects treated with TRESIBA had a similar incidence of major adverse cardiovascular events (MACE) when compared to those treated with insulin glargine U-100.

The primary endpoint in DEVOTE was time from randomization to the first occurrence of a 3-component major adverse cardiovascular event (MACE): cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke. The study was designed to exclude a pre-specified risk margin of 1.3 for the hazard ratio of MACE comparing TRESIBA to insulin glargine U-100. The primary outcome at end of trial was available for 98.2% of participants in each treatment group.

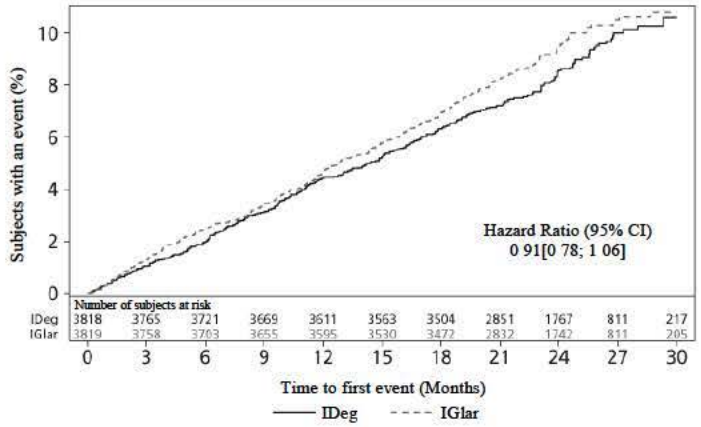
The time to first occurrence of MACE with TRESIBA as compared to insulin glargine U-100 was non-inferior (HR: 0.91; 95% CI [0.78;1.06]; see Figure 3). The results of the primary composite MACE endpoint and a summary of its individual components are shown in Table 15.

Table 15: Analysis of the Composite 3-point MACE and Individual Cardiovascular Endpoints in DEVOTE

	TRESIBA		**Insulin glargine U-100**		
N	**3818**		**3819**		
	Number of Patients (%)	**Rate per 100 PYO***	**Number of Patients (%)**	**Rate per 100 PYO***	**Hazard Ratio (95% CI)**
Composite of first event of CV death, non-fatal MI, or non-fatal stroke (3-Point MACE)	325 (8.5)	4.41	356 (9.3)	4.86	0.91 [0.78; 1.06]
CV death	136 (3.6)	1.85	142 (3.7)	1.94	
Non-fatal MI	144 (3.8)	1.95	169 (4.4)	2.31	
Non-fatal stroke	71(1.9)	0.96	79(2.1)	1.08	

* PYO = patient-years of observation until first MACE, death, or trial discontinuation

Figure 3: Cumulative Event Probability for Time to First MACE in DEVOTE



Hypoglycemia Outcomes *- Patients with T2DM and Atherosclerotic CVD*

The pre-specified secondary endpoints of event and incidence rates of severe hypoglycemia were sequentially tested.

Severe hypoglycemia was defined as an episode requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions and during which plasma glucose concentration may not have been available, but where neurological recovery following the return of plasma glucose to normal was considered sufficient evidence that the event was induced by a low plasma glucose concentration.

The incidence of severe hypoglycemia was lower in the TRESIBA group as compared to the insulin glargine U-100 group (Table 16). Glycemic control between the two groups was similar at baseline and throughout the trial.

Table 16: Severe Hypoglycemic Episodes in Patients Treated with TRESIBA or Insulin Glargine U-100 in DEVOTE

	TRESIBA	**Insulin glargine U-100**
N	**3818**	**3819**
Severe Hypoglycemia		
Percent of patients with events	4.9%	6.6%
Estimated odds ratio [95%CI] TRESIBA/Insulin glargine U-100	0.73 [0.60; 0.89]*	
Events per 100 Patient Years of Observation	3.70	6.25
Estimated rate ratio [95%CI] TRESIBA/Insulin glargine U-100	0.60 [0.48; 0.76]*	

* Test for superiority evaluated at 5% level for significance, (2-sided p<0.001)

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

TRESIBA is available as a clear and colorless solution in the following package sizes (see Table 17).

Table 17 Presentations of TRESIBA

TRESIBA	Total volume	Concentration	Total units available in presentation	NDC number	Max dose per injection	Dose increment	Package Size
U-100 FlexTouch	3 mL	100 units/mL	300 Units	0169-2660-15	80 Units	1 Unit	5 pens/pack
U-200 FlexTouch	3 mL	200 units/mL	600 Units	0169-2550-13	160 Units	2 Unit	3 pens/pack

16.2 Recommended Storage

Unused TRESIBA should be stored in a refrigerator (36ºF to 46ºF [2ºC to 8ºC]). Do not store in the freezer or directly adjacent to the refrigerator cooling element. Do not freeze. Do not use TRESIBA if it has been frozen.

The storage conditions are summarized in Table 18:

Table 18: Storage Conditions for TRESIBA FlexTouch

	Not in-use (unopened)		In-use (opened)	
	Refrigerated (36ºF to 46ºF [2ºC to 8ºC])	**Room Temperature (below 86ºF [30ºC])**	**Room Temperature (below 86ºF [30ºC])**	**Refrigerated (36ºF to 46ºF [2ºC to 8ºC])**
3 mL TRESIBA U-100 FlexTouch	Until expiration date	56 days (8 weeks)	56 days (8 weeks)	56 days (8 weeks)
3 mL TRESIBA U-200 FlexTouch	Until expiration date	56 days (8 weeks)	56 days (8 weeks)	56 days (8 weeks)

17 PATIENT COUNSELING INFORMATION

Advise the patient and/or caregiver to read the FDA-approved patient labeling (Patient Information and Instructions for Use).

Never Share a TRESIBA FlexTouch Pen Between Patients

Advise patients that they should never share a TRESIBA FlexTouch, pen device with another person, even if the needle is changed, because doing so carries a risk for transmission of blood-borne pathogens *[see Warnings and Precautions (5.1)]*.

Hyperglycemia or Hypoglycemia

Inform patients that hypoglycemia is the most common adverse reaction with insulin. Inform patients of the symptoms of hypoglycemia. Inform patients that the ability to concentrate and react may be impaired as a result of hypoglycemia. This may present a risk in situations where these abilities are especially important, such as driving or operating other machinery. Advise

patients who have frequent hypoglycemia or reduced or absent warning signs of hypoglycemia to use caution when driving or operating machinery.

Advise patients that changes in insulin regimen can predispose to hyper- or hypoglycemia.
Advise patients that changes in insulin regimen should be made under close medical supervision *[see Warnings and Precautions (5.2)]*.

Medication Errors
Inform patients to always check the insulin label before each injection *[see Warnings and Precautions (5.4)]*. Inform patients that the dose counter of TRESIBA FlexTouch pen shows the number of units of TRESIBA to be injected. NO dose re-calculation is required *[see Dosage and Administration (2.2)]*. Instruct Patients to never use a syringe to remove TRESIBA from the FlexTouch disposable insulin prefilled pen.

Women of Reproductive Potential
Advise patients to inform their health care professional if they are pregnant or are contemplating pregnancy.

Rx Only

Date of Issue: XX/201X
Version: X

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

Manufactured by:
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1-800-727-6500

www.novonordisk-us.com

Patient Information
TRESIBA® (tre–SI-bah)
(insulin degludec injection)

Do not share your TRESIBA FlexTouch insulin delivery device with other people, even if the needle has changed. You may give other people a serious infection, or get a serious infection from them.

What is TRESIBA?

- TRESIBA is a man-made insulin that is used to control high blood sugar in adults and children who are 1 year of age and older with diabetes mellitus.
- TRESIBA is not for people with diabetic ketoacidosis (increased ketones in the blood or urine).
- TRESIBA is not for children who need less than 5 units of TRESIBA each day.
- It is not known if TRESIBA is safe and effective in children under 1 year of age.
- TRESIBA is available in 2 concentrations: The 100 units/mL pen can be injected from 1 to 80 units in a single injection, in increments of 1 unit. The 200 units/mL pen can be injected from 2 to 160 units in a single injection, in increments of 2 units.

Who should not take TRESIBA?
Do not take TRESIBA if you:

- are having an episode of low blood sugar (hypoglycemia).
- have an allergy to TRESIBA or any of the ingredients in TRESIBA.

Before taking TRESIBA, tell your healthcare provider about all your medical conditions including, if you are:

- pregnant, planning to become pregnant, or are breastfeeding.
- taking new prescription or over-the-counter medicines, vitamins, or herbal supplements.

Before you start taking TRESIBA, talk to your healthcare provider about low blood sugar and how to manage it.

How should I take TRESIBA?

- **Read the Instructions for Use** that come with your TRESIBA.
- Take TRESIBA exactly as your healthcare provider tells you to.
- **Do not do any conversion of your dose. The dose counter always shows the selected dose in units.** Both the 100 units/mL and 200 units/mL TRESIBA FlexTouch pens are made to deliver your insulin dose in units.
- Know the type and strength of insulin you take. **Do not** change the type of insulin you take unless your healthcare provider tells you to. The amount of insulin and the best time for you to take your insulin may need to change if you take different types of insulin.
- Adults: If you miss or are delayed in taking your dose of TRESIBA:
  - Take your dose as soon as you remember then continue with your regular dosing schedule.
  - Make sure there are at least **8** hours between your doses.
- If children miss a dose of TRESIBA:
  - Call the healthcare provider for information and instructions about checking blood sugar levels more often until the next scheduled dose of TRESIBA.
- **Check your blood sugar levels.** Ask your healthcare provider what your blood sugars should be and when you should check your blood sugar levels.
- **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.
- **Never** inject TRESIBA into a vein or muscle.
- **Never** use a syringe to remove TRESIBA from the FlexTouch pen.

What should I avoid while taking TRESIBA?
While taking TRESIBA do not:

- Drive or operate heavy machinery, until you know how TRESIBA affects you.
- Drink alcohol or use prescription or over-the-counter medicines that contain alcohol.

What are the possible side effects of TRESIBA?
TRESIBA may cause serious side effects that can lead to death, including:

- **Low blood sugar (hypoglycemia).** Signs and symptoms that may indicate low blood sugar include:
  - dizziness or light-headedness
  - sweating
  - confusion
  - fast heartbeat
  - blurred vision
  - slurred speech
  - shakiness
  - anxiety, irritability, or mood changes
  - hunger
  - headache
- **Low potassium in your blood (hypokalemia).**
- **Heart failure.** Taking certain diabetes pills called thiazolidinediones or "TZDs" with TRESIBA may cause heart failure in some people. This can happen even if you have never had heart failure or heart problems before. If you already have heart failure, it may get worse while you take TZDs with TRESIBA. Your healthcare provider should monitor you closely while you are taking TZDs with TRESIBA. Tell your healthcare provider if you have any new or worse symptoms of heart failure including shortness of breath, tiredness, swelling of your ankles or feet and sudden weight gain. Treatment with TZDs and TRESIBA may need to be adjusted or stopped by your healthcare provider if you have new or worse heart failure.

Your insulin dose may need to change because of:

- change in level of physical activity or exercise
- increased stress
- change in diet

- weight gain or loss
- illness

Common side effects of TRESIBA may include:

- serious allergic reactions (whole body reactions), reactions at the injection site, skin thickening or pits at the injection site (lipodystrophy), itching, rash, swelling of your hands and feet, and weight gain.

Get emergency medical help if you have:

- trouble breathing, shortness of breath, fast heartbeat, swelling of your face, tongue, or throat, sweating, extreme drowsiness, dizziness, confusion.

These are not all the possible side effects of TRESIBA. 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 TRESIBA.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. You can ask your pharmacist or healthcare provider for information about TRESIBA that is written for health professionals. Do not use TRESIBA for a condition for which it was not prescribed. Do not give TRESIBA to other people, even if they have the same symptoms that you have. It may harm them.

What are the ingredients in TRESIBA?

Active Ingredient: insulin degludec

Inactive Ingredients: zinc, metacresol, glycerol, phenol, and water for injection. Hydrochloric acid or sodium hydroxide may be added.

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

For more information, go to www.novonordisk-us.com or call 1-800-727-6500.

This Patient Informa ion has been approved by the U.S. Food and Drug Administration **Revised: 12/2016**

Instructions for Use

TRESIBA® (tre-SI-bah) FlexTouch® Pen 100 units/mL

(insulin degludec injection)

- **Do not share your TRESIBA FlexTouch Pen with other people, even if the needle is changed. You may give other people a serious infection, or get a serious infection from them.**
- **TRESIBA FlexTouch Pen 100 units/mL ("Pen") is a prefilled disposable pen** containing 300 units of TRESIBA (insulin degludec injection) 100 units/mL insulin. You can inject from 1 to 80 units in a single injection. The units can be increased by 1 unit at a time.
- **This Pen is not recommended for use by the blind or visually impaired without the assistance of a person trained in the proper use of the product.**

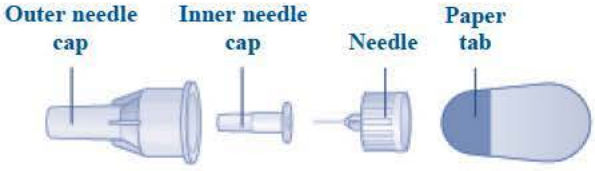
Supplies you will need to give your TRESIBA injection:

- TRESIBA FlexTouch Pen
- a new NovoFine or NovoTwist needle
- alcohol swab
- a sharps container for throwing away used Pens and needles. **See "After your injection" at the end of these instructions.**

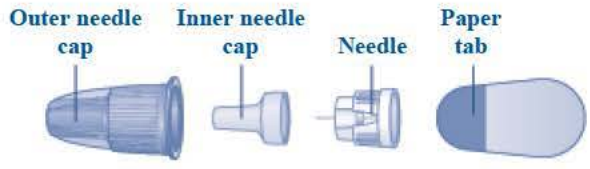
Preparing your TRESIBA FlexTouch Pen:

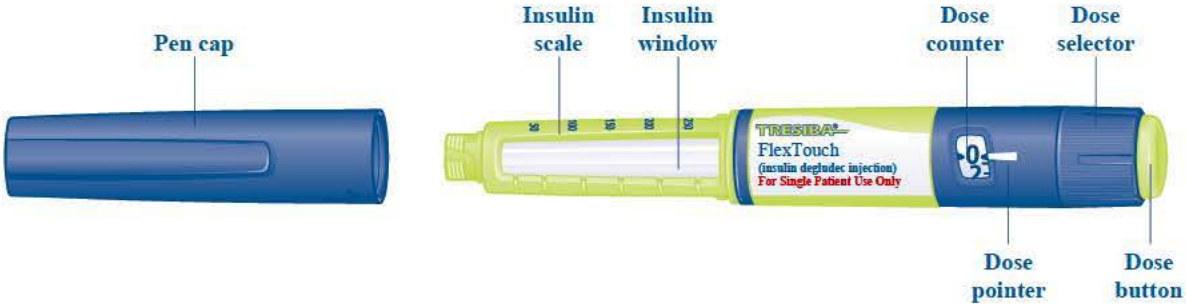
- Wash your hands with soap and water.
- **Before you start to prepare your injection, check the TRESIBA FlexTouch Pen label to make sure you are taking the right type of insulin. This is especially important if you take more than 1 type of insulin.**
- TRESIBA should look clear and colorless. **Do not** use TRESIBA if it is cloudy or colored.
- **Do not** use TRESIBA past the expiration date printed on the label or 56 days after you start using the Pen.
- **Always use a new needle for each injection to help ensure sterility and prevent blocked needles. Do not reuse or share needles with another person. You may give other people a serious infection, or get a serious infection from them.**

NovoFine®



NovoTwist®

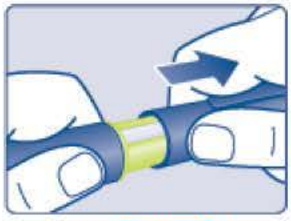




(Figure A)

Step 1:

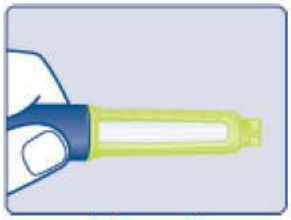
• Pull Pen cap straight off (See Figure B).



(Figure B)

Step 2:

• **Check the liquid in the Pen** (See Figure C). TRESIBA should look clear and colorless. **Do not** use it if it looks cloudy or colored.

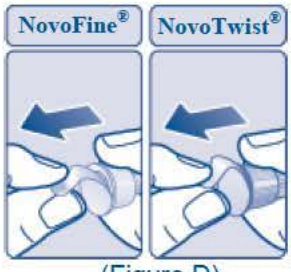


(Figure C)

Step 3:

• **Select a new needle.**

• Pull off the paper tab from the outer needle cap (See Figure D).



(Figure D)

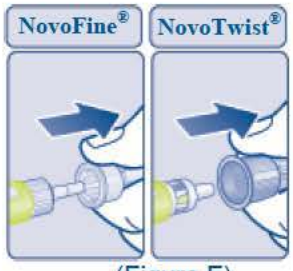
Step 4:

• Push the capped needle straight onto the Pen and twist the needle on until it is tight (See Figure E).

(Figure E)

Step 5:

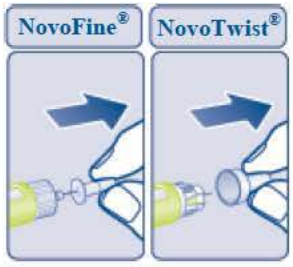
• Pull off the outer needle cap. **Do not** throw it away (See Figure F).



(Figure F)

Step 6:

• Pull off the inner needle cap and throw it away (See Figure G).



(Figure G)

Priming your TRESIBA FlexTouch Pen:

Step 7:

• Turn the dose selector to **select 2 units** (See Figure H).

(Figure H)

Step 8:

• Hold the Pen with the needle pointing up. Tap the top of the Pen gently a few times to let any air bubbles rise to the top (See Figure I).

(Figure I)

Step 9:

• **Hold the Pen with the needle pointing up.** Press and hold in the dose button until the dose counter shows "0". The "0" must line up with the dose pointer.

• A drop of insulin should be seen at the needle tip (See Figure J).

o If you **do not** see a drop of insulin, repeat steps 7 to 9, no more than 6 times.

o If you **still do not** see a drop of insulin, change the needle and repeat steps 7 to 9.

(Figure J)

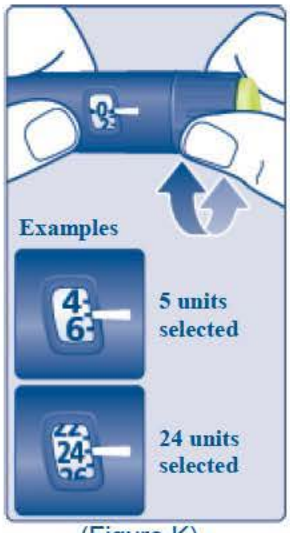
Selecting your dose:

Step 10:

TRESIBA FlexTouch Pen 100 units/mL is made to deliver the number of insulin units that your healthcare provider prescribed. **Do not perform any dose conversion.**

Check to make sure the dose selector is set at 0.

- **Turn the dose selector to select the number of units you need to inject.** The dose pointer should line up with your dose (See Figure K).
  - o If you select the wrong dose, you can turn the dose selector forwards or backwards to the correct dose.
  - o The **even** numbers are printed on the dial.
  - o The **odd** numbers are shown as lines.



(Figure K)

• The TRESIBA FlexTouch Pen insulin scale will show you how much insulin is left in your Pen (See Figure L).

(Figure L)

- **To see how much insulin is left in your TRESIBA FlexTouch Pen:**
    - Turn the dose selector until it stops. The dose counter will line up with the number of units of insulin that is left in your Pen. If the dose counter shows 80, there are **at least 80** units left in your Pen.
    - If the dose counter shows **less than 80,** the number shown in the dose counter is the number of units left in your Pen.

Giving your injection:

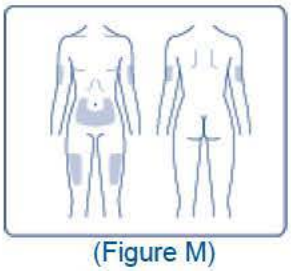
• Inject your TRESIBA exactly as your healthcare provider has shown you. Your healthcare provider should tell you if you need to pinch the skin before injecting.

• TRESIBA can be injected under the skin (subcutaneously) of your upper legs (thighs), upper arms, or stomach area (abdomen).

• Change (rotate) your injection sites within the area you choose for each dose. **Do not** use the same injection site for each injection.

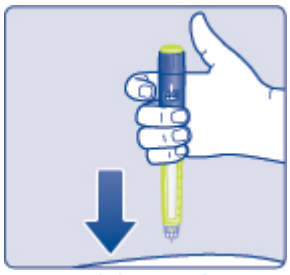
Step 11:

• Choose your injection site and wipe the skin with an alcohol swab (See Figure M). Let the injection site dry before you inject your dose.


(Figure M)

Step 12:

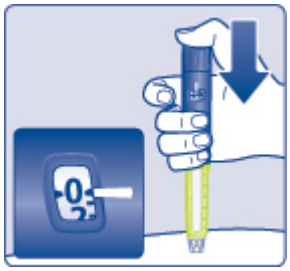
- **Insert the needle into your skin** (See Figure N).
  - o **Make sure you can see the dose counter. Do not** cover it with your fingers, this can stop your injection.



(Figure N)

Step 13:

- **Press and hold down the dose button until the dose counter shows "0"** (See Figure O).
  - o The "0" must line up with the dose pointer. You may then hear or feel a click.



(Figure O)

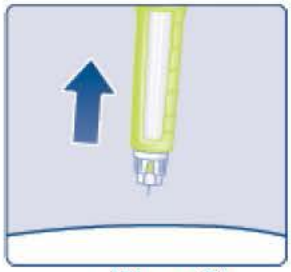
- **Keep the needle in your skin after** the dose counter has returned to "0" and **slowly count to 6** (See Figure P).
  - o **When the dose counter returns to "0", you will not get your full dose until 6 seconds later.**
  - o **If the needle is removed before you count to 6, you may see a stream of insulin coming from the needle tip.**
  - o **If you see a stream of insulin coming from the needle tip you will not get your full dose. If this happens you should check your blood sugar levels more often because you may need more insulin.**

(Figure P)

Step 14:

- **Pull the needle out of your skin** (See Figure Q).

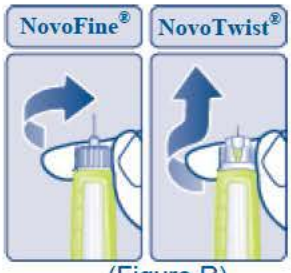
  o If you see blood after you take the needle out of your skin, press the injection site lightly with a piece of gauze or an alcohol swab. **Do not** rub the area.


(Figure Q)

Step 15:

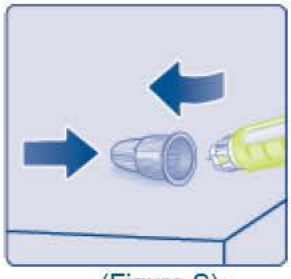
- **Carefully remove the needle from the Pen and throw it away** (See Figure R).

  o **Do not** recap the needle. Recapping the needle can lead to needle stick injury.



(Figure R)

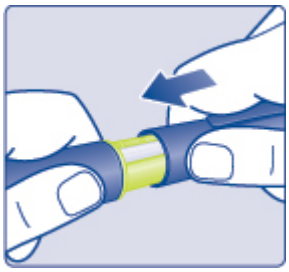
- If you **do not** have a sharps container, carefully slip the needle into the outer needle cap (See Figure S). Safely remove the needle and throw it away as soon as you can.


(Figure S)

- **Do not** store the Pen with the needle attached. Storing without the needle attached helps prevent leaking, blocking of the needle, and air from entering the Pen.

Step 16:

- Replace the Pen cap by pushing it straight on (See Figure T).



(Figure T)

After your injection:

- Put your used TRESIBA FlexTouch 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 needles or syringes with another person. 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.

How should I store my TRESIBA FlexTouch Pen?

Before use:

- Store unused TRESIBA FlexTouch Pens in the refrigerator at 36ºF to 46ºF (2°C to 8°C).
- **Do not** freeze TRESIBA. **Do not** use TRESIBA if it has been frozen.
- Unused Pens may be used until the expiration date printed on the label, if kept in the refrigerator.

Pen in use:

- Store the Pen you are currently using in the refrigerator between 36ºF to 46ºF (2ºC to 8ºC) or keep at room temperature below 86ºF (30ºC).

- Keep TRESIBA away from heat or light.
- The TRESIBA FlexTouch Pen you are using should be thrown away after 56 days if it is refrigerated or kept at room temperature, even if it still has insulin left in it and the expiration date has not passed.

General Information about the safe and effective use of TRESIBA.

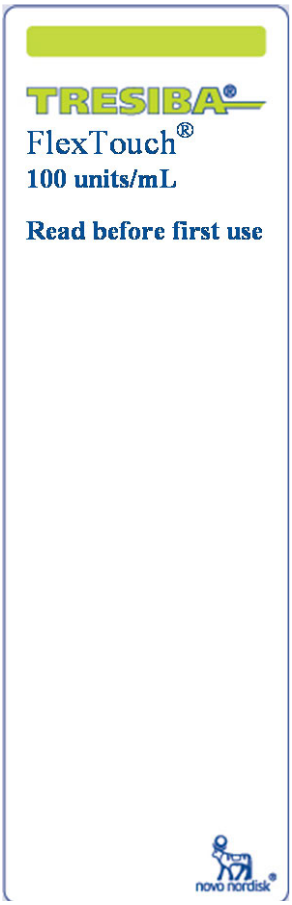
- **Keep TRESIBA FlexTouch Pens and needles out of the reach of children.**
- **Always** use a new needle for each injection.
- **Do not** share TRESIBA FlexTouch Pens or needles with other people. You may give other people a serious infection, or get a serious infection from them.

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

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

Revised: 12/2016

For more information go to **www.TRESIBA.com**



Instructions for Use

TRESIBA® (tre-SI-bah) FlexTouch® Pen 200 units/mL

(insulin degludec injection)

- **Do not share your TRESIBA FlexTouch Pen with other people, even if the needle is changed. You may give other people a serious infection, or get a serious infection from them.**
- **TRESIBA FlexTouch Pen 200 units/mL ("Pen") is a prefilled disposable pen** containing 600 units of TRESIBA (insulin degludec injection) 200 units/mL insulin. You can inject from 2 to 160 units in a single injection. The units can be increased by 2 units at a time.
- **This Pen is not recommended for use by the blind or visually impaired without the assistance of a person trained in the proper use of the product.**

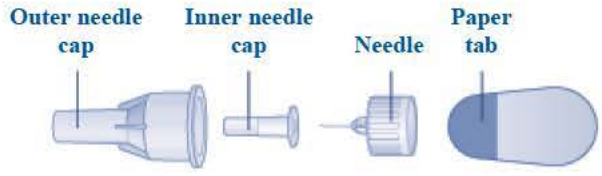
Supplies you will need to give your TRESIBA injection:

- TRESIBA FlexTouch Pen
- a new NovoFine or NovoTwist needle
- alcohol swab
- a sharps container for throwing away used Pens and needles. **See "After your injection" at the end of these instructions.**

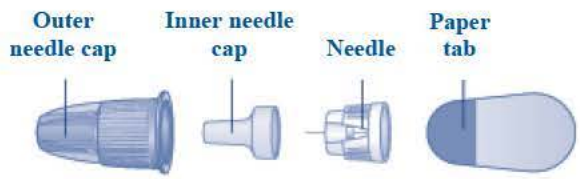
Preparing your TRESIBA FlexTouch Pen:

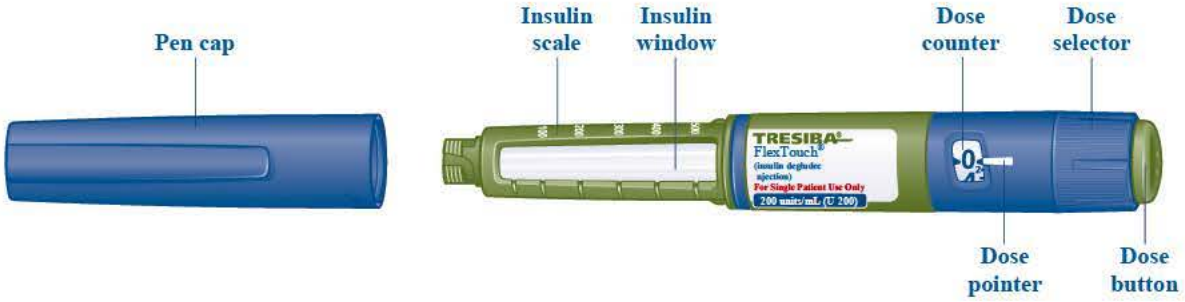
- Wash your hands with soap and water.
- **Before you start to prepare your injection, check the TRESIBA FlexTouch Pen label to make sure you are taking the right type of insulin. This is especially important if you take more than 1 type of insulin.**
- TRESIBA should look clear and colorless. **Do not** use TRESIBA if it is cloudy or colored.
- **Do not** use TRESIBA past the expiration date printed on the label or 56 days after you start using the Pen.
- **Always use a new needle for each injection to help ensure sterility and prevent blocked needles. Do not reuse or share needles with another person. You may give other people a serious infection, or get a serious infection from them.**

NovoFine®



NovoTwist®

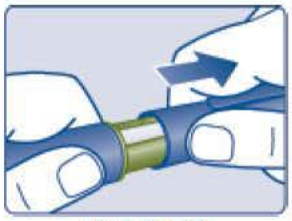




(Figure A)

Step 1:

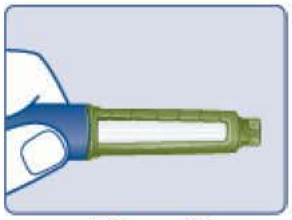
- Pull Pen cap straight off (See Figure B).



(Figure B)

Step 2:

- **Check the liquid in the Pen** (See Figure C). TRESIBA should look clear and colorless. **Do not** use it if it looks cloudy or colored.



(Figure C)

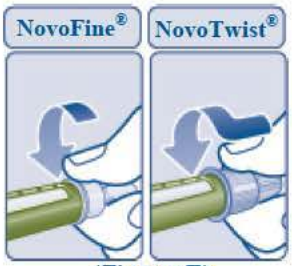
Step 3:

- **Select a new needle.**
- Pull off the paper tab from the outer needle cap (See Figure D).

(Figure D)

Step 4:

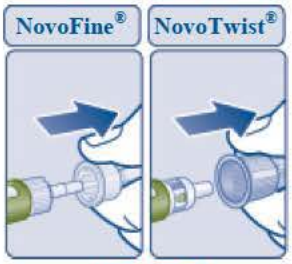
- Push the capped needle straight onto the Pen and twist the needle on until it is tight (See Figure E).



(Figure E)

Step 5:

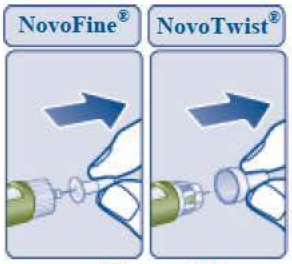
- Pull off the outer needle cap. **Do not** throw it away (See Figure F).



(Figure F)

Step 6:

- Pull off the inner needle cap and throw it away (See Figure G).



(Figure G)

Priming your TRESIBA FlexTouch Pen:

Step 7:

- Turn the dose selector to **select 2 units** (See Figure H).

(Figure H)

Step 8:

- Hold the Pen with the needle pointing up. Tap the top of the Pen gently a few times to let any air bubbles rise to the top (See Figure I).


(Figure I)

Step 9:

- **Hold the Pen with the needle pointing up.** Press and hold in the dose button until the dose counter shows "0". The "0" must line up with the dose pointer.
- A drop of insulin should be seen at the needle tip (See Figure J).
  - If you **do not** see a drop of insulin, repeat steps 7 to 9, no more than 6 times.
  - If you **still do not** see a drop of insulin, change the needle and repeat steps 7 to 9.


(Figure J)

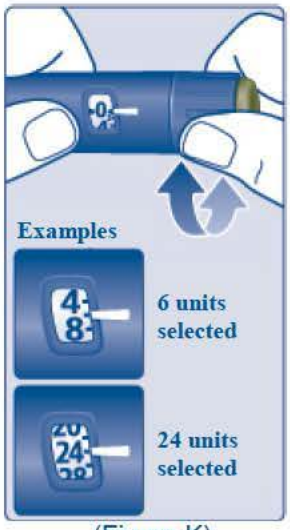
Selecting your dose:

Step 10:

TRESIBA FlexTouch Pen 200 units/mL is made to deliver the number of insulin units that your healthcare provider prescribed. **Do not perform any dose conversion.**

Check to make sure the dose selector is set at 0.

- **Turn the dose selector to select the number of units you need to inject.** The dose pointer should line up with your dose (See Figure K).
  - If you select the wrong dose, you can turn the dose selector forwards or backwards to the correct dose.
  - Each line on the dial is an even number.



(Figure K)

- The TRESIBA FlexTouch Pen insulin scale will show you how much insulin is left in your Pen (See Figure L).

(Figure L)

- **To see how much insulin is left in your TRESIBA FlexTouch Pen:**

- Turn the dose selector until it stops. The dose counter will line up with the number of units of insulin that is left in your Pen. If the dose counter shows 160, there are **at least 160** units left in your Pen.

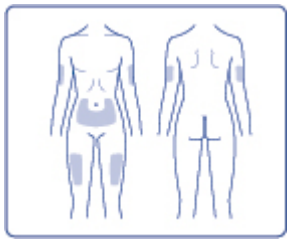
- If the dose counter shows **less than 160,** the number shown in the dose counter is the number of units left in your Pen.

Giving your injection:

- Inject your TRESIBA exactly as your healthcare provider has shown you. Your healthcare provider should tell you if you need to pinch the skin before injecting.
- TRESIBA can be injected under the skin (subcutaneously) of your upper legs (thighs), upper arms, or stomach area (abdomen).
- Change (rotate) your injection sites within the area you choose for each dose. **Do not** use the same injection site for each injection.

Step 11:

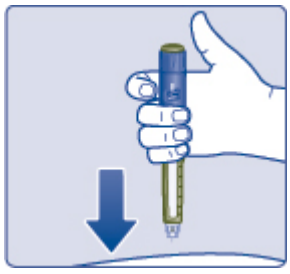
- Choose your injection site and wipe the skin with an alcohol swab (See Figure M). Let the injection site dry before you inject your dose.



(Figure M)

Step 12:

- **Insert the needle into your skin** (See Figure N).
  - **Make sure you can see the dose counter. Do not** cover it with your fingers, this can stop your injection.



(Figure N)

Step 13:

- **Press and hold down the dose button until the dose counter shows "0"** (See Figure O).
  - The "0" must line up with the dose pointer. You may then hear or feel a click.

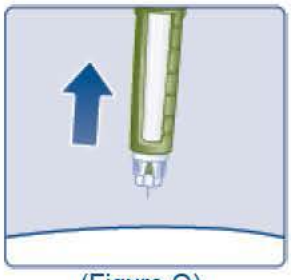
(Figure O)

- **Keep the needle in your skin after** the dose counter has returned to "0" and **slowly count to 6** (See Figure P).
    - **When the dose counter returns to "0", you will not get your full dose until 6 seconds later.**
    - **If the needle is removed before you count to 6, you may see a stream of insulin coming from the needle tip.**
    - **If you see a stream of insulin coming from the needle tip you will not get your full dose. If this happens you should check your blood sugar levels more often because you may need more insulin.**

(Figure P)

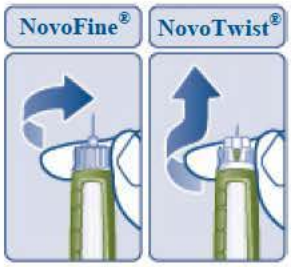
Step 14:

- **Pull the needle out of your skin** (See Figure Q).
    - If you see blood after you take the needle out of your skin, press the injection site lightly with a piece of gauze or an alcohol swab. **Do not** rub the area.


(Figure Q)

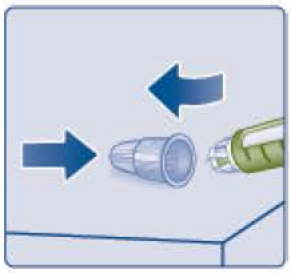
Step 15:

- **Carefully remove the needle from the Pen and throw it away** (See Figure R).
    - **Do not** recap the needle. Recapping the needle can lead to needle stick injury.



(Figure R)

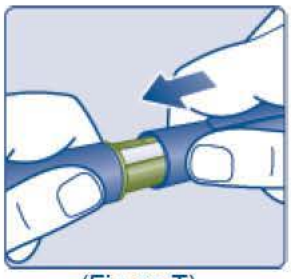
- If you **do not** have a sharps container, carefully slip the needle into the outer needle cap (See Figure S). Safely remove the needle and throw it away as soon as you can.


(Figure S)

  - **Do not** store the Pen with the needle attached. Storing without the needle attached helps prevent leaking, blocking of the needle, and air from entering the Pen.

Step 16:

- Replace the Pen cap by pushing it straight on (See Figure T).


(Figure T)

After your injection:

- Put your used TRESIBA FlexTouch 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 needles or syringes with another person. 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.

How should I store my TRESIBA FlexTouch Pen?

Before use:

- Store unused TRESIBA FlexTouch Pens in the refrigerator at 36°F to 46°F (2°C to 8°C).
- **Do not** freeze TRESIBA. **Do not** use TRESIBA if it has been frozen.
- Unused Pens may be used until the expiration date printed on the label, if kept in the refrigerator.

Pen in use:

- Store the Pen you are currently using in the refrigerator between 36°F to 46°F (2°C to 8°C) or keep at room temperature below 86°F (30°C).
- Keep TRESIBA away from heat or light.
- The TRESIBA FlexTouch Pen you are using should be thrown away after 56 days if it is refrigerated or kept at room temperature, even if it still has insulin left in it and the expiration date has not passed.

General Information about the safe and effective use of TRESIBA.

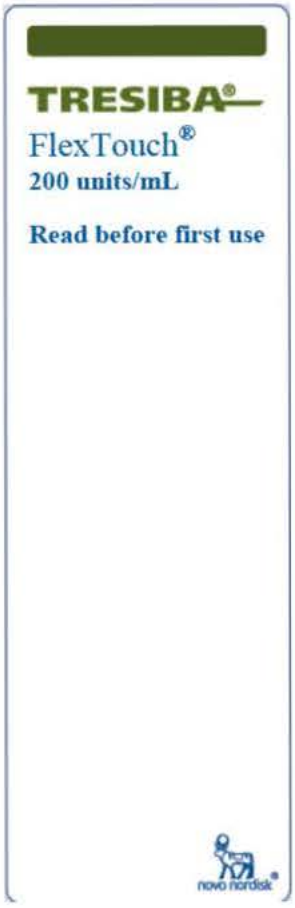
- **Keep TRESIBA FlexTouch Pens and needles out of the reach of children.**
- **Always** use a new needle for each injection.
- **Do not** share TRESIBA FlexTouch Pens or needles with other people. You may give other people a serious infection, or get a serious infection from them.

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

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

Revised: 12/2016

For more information go to **www.TRESIBA.com**


TRESIBA®
FlexTouch®
200 units/mL
Read before first use
novo nordisk®

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203314Orig1s008

CROSS DISCIPLINE TEAM LEADER REVIEW

Division Summary Memo for Regulatory Action and CDTL review

Date	March 23, 2018
From	Patrick Archdeacon, MD
Subject	Division of Metabolism and Endocrinology Products (DMEP) Summary Memo for Regulatory Action
NDA # / Sequence #:	203314 / S0135
Applicant	Novo Nordisk
Date of Submission Receipt	May 26, 2017
PDUFA Goal Date	March 26, 2018
Proprietary Name / Established (USAN) names	Tresiba Insulin degludec injection
Dosage forms / Strength	Tresiba U-100 Individualized dose for sc injection once daily 100 units/mL
Proposed Indication	(b) (4)
Recommended Action	Approval

1. Introduction

This document contains the 'Summary Basis for Regulatory Action' memo for sNDA 2033314/S0135 [prior approval supplement (PAS) containing clinical data from EX1250-4080 (DEVOTE); Supplement 8] for Tresiba (insulin degludec injection; NDA 203-314). DEVOTE was a randomized, double-blind, active-controlled trial evaluating the effect of insulin degludec on the incidence of major adverse cardiovascular events (MACE) in subjects with type 2 diabetes mellitus (T2DM) relative to the effect of insulin glargine. Tresiba was approved on September 2015 based on an interim analysis of DEVOTE with a postmarketing requirement (PMR; 2954-2) to complete DEVOTE and exclude a 30% increase in the incidence of MACE attributable to exposure to insulin degludec relative to exposure to insulin glargine. In addition to the primary outcome of MACE, DEVOTE evaluated two additional pre-specified secondary endpoints: 1) the total number of adjudicated severe hypoglycemic events, 2) the number of patients experiencing at least one episode of severe hypoglycemia.

The clinical data contained in the PAS has been determined to satisfy PMR 2954-2 and also to support the addition of new labeling for Tresiba to describe the superiority of insulin degludec relative to insulin glargine observed with regards to the incidence of severe hypoglycemia in patients with type 2 diabetes (T2D), as demonstrated in DEVOTE. No new labeling regarding hypoglycemia in patients with type 1 diabetes (T1D) is supported by the data in the PAS. (b) (4)

(b) (4)

The reader is referred to Section 11 and Section 12 of this Summary Memo for details about the new labeling, including the determination to report the pattern of hypoglycemic events observed in the DEVOTE trial but not to extrapolate broadly the findings to populations not studied in DEVOTE.

Simultaneously with the addition of new labeling on the basis of the PAS, new language to address a safety risk associated with visual impairment is also being added to the Tresiba labeling. (b) (4)

The reader is referred to the multiple discipline reviews for a more comprehensive review and detailed discussion of this prior approval supplement for Tresiba. For the sake of completeness, the reader is also referred to the DMEPA review addressing the safety signal related to visual impairment. This memo references the following documents/sources:

Subject	Author	Date
Clinical Efficacy and Safety Review (DMEP)	Dr. Tania Condarco	February 20, 2018
Statistical review (DBII)	Dr. Kiya Hamilton	February 16, 2018
Statistical review (DBVII)	Dr. Eugenio Andraca-Carrera	February 9, 2018
Office of Scientific Investigation (OSI)	Dr. Cynthia Kleppinger	February 9, 2018
Office of Prescription Drug Promotion (OPDP)	Ankur Kalola	March 5, 2018
Division of Medication Error Prevention and Analysis (DMEPA)	Ariane Conrad and Hina Mehta	November 17, 2017

2. Background

Tresiba (insulin degludec or IDeg) has been approved for marketing in the US since September of 2015. It is indicated to improve glycemic control in patients 1 year of age and older with diabetes mellitus. Insulin degludec is a recombinant, long-acting, once-daily insulin analog; it differs from human insulin by the deletion of the threonine amino acid at position B30 and the conjugation of hexadecanedioic acid via a glutamic acid spacer to the amino acid lysine at position B29. The addition of the hexadecanedioic acid results in the formation of multi-hexamers after subcutaneous injection, thereby forming a depot of insulin in the subcutaneous tissue. Insulin degludec monomers gradually separate, leave the depot, and enter into the circulation. The result is a slow delivery of insulin degludec to the patient such that a consistent concentration of drug is maintained.

Regulatory History

The Applicant originally submitted the insulin degludec New Drug Application (NDA) on September 29, 2011. During the review of the NDA, the Division of Metabolism and Endocrinology Products (DMEP) identified a safety signal generated by a pre-specified meta-analysis of cardiovascular risk associated with insulin degludec. While insulin products are not typically subject to the formal cardiovascular risk assessment that the Agency has required of non-insulin antihyperglycemic agents since 2008, a meta-analysis of sixteen trials from the degludec and degludec/aspart programs suggested the possibility that degludec products could increase the risk of cardiovascular event – including cardiovascular death, myocardial infarction, stroke, and unstable angina – by 10% relative to active comparators. These data were presented at an Advisory Committee meeting held on November 8, 2012; the committee unanimously voted that the signal merited evaluation by a dedicated cardiovascular outcome trial (CVOT). On February 8, 2013, DMEP issued a Complete Response (CR) Letter that included a request for a CVOT to assess the cardiovascular safety of insulin degludec, based on the composite endpoint of major adverse cardiovascular events (MACE) including

cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke. Specifically, the CR letter stated "you will need to submit additional clinical trial data from a dedicated, double-blind, cardiovascular outcomes trial using glargine as the comparator. The trial should be powered to exclude an excess cardiovascular risk based on a composite of cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke (MACE), not MACE+. The risk margin to exclude that is necessary for approval should be discussed with the Agency at an End-of-Review meeting. At a minimum, the resubmission must include enough MACE events to definitively exclude a hazard of 80% with a reassuring point estimate." At an April 4, 2013 meeting between the Agency and the Applicant, the design of the CVOT was discussed. The requirements for the trial were summarized in the meeting minutes as follows: "While we will accept for resubmission and potentially approve your product based on an interim analysis excluding a CV risk margin of 1.8, assuming a reassuring point estimate and no other countervailing safety signals identified in the resubmission, you will be required to exclude an excess hazard of 30% postmarketing."

The Applicant designed and conducted the DEVOTE trial to address the deficiency that resulted from the MACE signal observed in the original submission accordingly. On the basis of an interim analysis of data from DEVOTE that met the standard of excluding a hazard ratio (HR) greater than 1.8, insulin degludec (under the trade name of Tresiba) and insulin degludec/aspart were approved for marketing on September 25, 2015. While the Agency approved insulin degludec based on the results of the interim analysis, it also issued Post-Marketing Requirement (PMR) #2954-2, requiring the Applicant to "conduct a randomized, double-blind, active-controlled trial evaluating the effect of Tresiba (insulin degludec injection) on the incidence of major cardiovascular events (MACE) in subjects with type 2 diabetes mellitus. The primary objective of the trial should be to demonstrate that the upper bound of the 2-sided 95% confidence interval for the estimated risk ratio comparing the incidence of adjudicated MACE (non-fatal myocardial infarction, non-fatal stroke, cardiovascular death) observed with Tresiba to that observed in the comparator group is less than 1.3." In order to ensure sufficient power to exclude the required hazard ratio, the DEVOTE trial was designed to continue until 633 MACE events were collected and confirmed. The May 26, 2017 PAS submission includes the final results of DEVOTE, including the data related to MACE events in 681 subjects.

Hypoglycemia was also a topic at the initial November 8, 2012 Advisory Committee meeting and of the original NDA review. While the Applicant had argued that the unique PK/PD characteristics of insulin degludec (avoiding the peaks and troughs typically associated with insulin products) should mitigate events of hypoglycemia, the Applicant was informed that a hypoglycemia risk reduction claim would require additional demonstration of a meaningful risk reduction over other available once-daily basal insulins. Though the original NDA submission included some clinical data addressing hypoglycemia, those data were deemed insufficient to establish a benefit due to several deficiencies [including the reliance on open-label trials, lack of consistent trends across different definitions of hypoglycemia (i.e., "Novo confirmed hypoglycemia", "nocturnal confirmed hypoglycemia", "severe hypoglycemia", and "documented hypoglycemia") and different patient populations (i.e., T1D and T2D)].

In response to the deficiencies related to the claim of a benefit related to hypoglycemia cited in the February 8, 2013 CR letter, the Applicant incorporated secondary endpoints into the design of DEVOTE to show that the use of insulin degludec resulted in fewer hypoglycemia events compared to the use of insulin glargine in patients with T2D. The secondary endpoints related to hypoglycemia were statistically powered and relied on the America Diabetes Association definition of severe hypoglycemia: an episode requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions and during which plasma glucose concentration may not have been available, but where neurological recovery following the return of plasma glucose to normal was considered sufficient evidence that the event was induced by a low plasma glucose concentration. (b) (4)

(b) (4)

The current action, therefore, addresses hypoglycemia only in the context of T2D.

3. CMC/Device

The PAS did not include any new data related to CMC or device issues.

4. Nonclinical Pharmacology/Toxicology

The PAS did not include any new nonclinical data.

5. Clinical Pharmacology/Biopharmaceutics

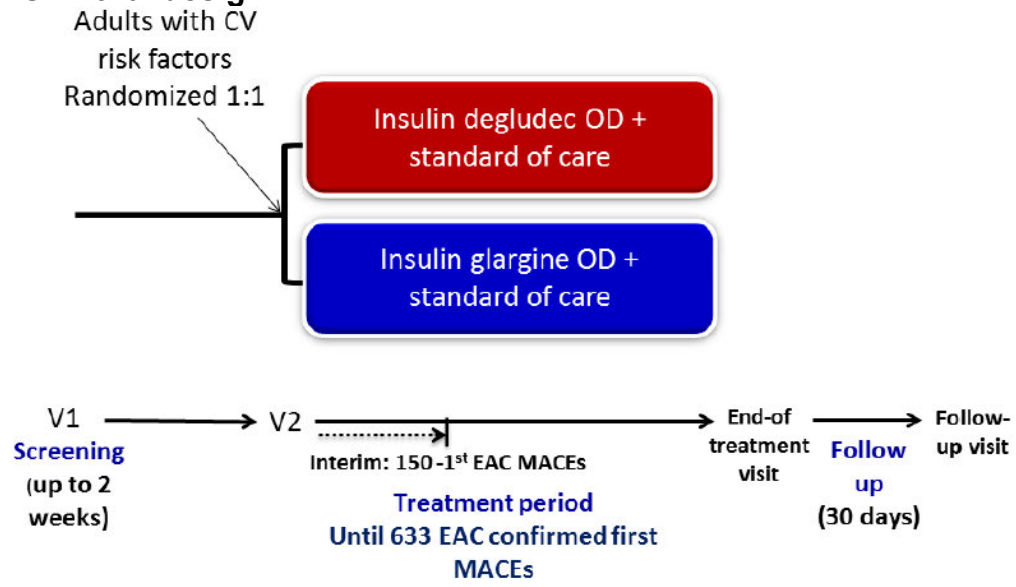
The PAS did not raise any new clinical pharmacology issues.

6. Clinical/Statistical- Efficacy

The clinical [Dr Condarco from the Division of Metabolism and Endocrinology Products (DMEP)] and both statistical review teams [Dr Andraca-Carrera and Dr Mark Levenson from Division from the Division of Biometrics VII (DBVII), who evaluated the MACE data; Dr Kiya Hamilton and Dr Yun Wang from the Division of Biometrics II (DBII), who evaluated the hypoglycemia data] did not identify any issues from their analyses of the primary and secondary endpoints of the DEVOTE trial that would preclude approval of the PAS. All of the teams recommended approval of the supplement, pending agreement on new labeling language.

As previously described, DEVOTE compared the cardiovascular safety of insulin degludec to insulin glargine; its secondary objectives included assessments of the effect of insulin degludec relative to insulin glargine on markers of glycemic control (including comparisons of outcomes related to hypoglycemia that were allocated statistical power). It was an event driven, multi-center, double-blinded, randomized control trial comparing insulin degludec (U100) to insulin glargine (U100) added to standard of care in patients with type 2 diabetes at high risk of cardiovascular events.

Figure 1: DEVOTE trial design



Abbreviations: CV: cardiovascular; EAC: event adjudication committee; MACE: Major adverse cardiovascular event; OD: daily; V1: screening visit; V2: randomization and start of treatment

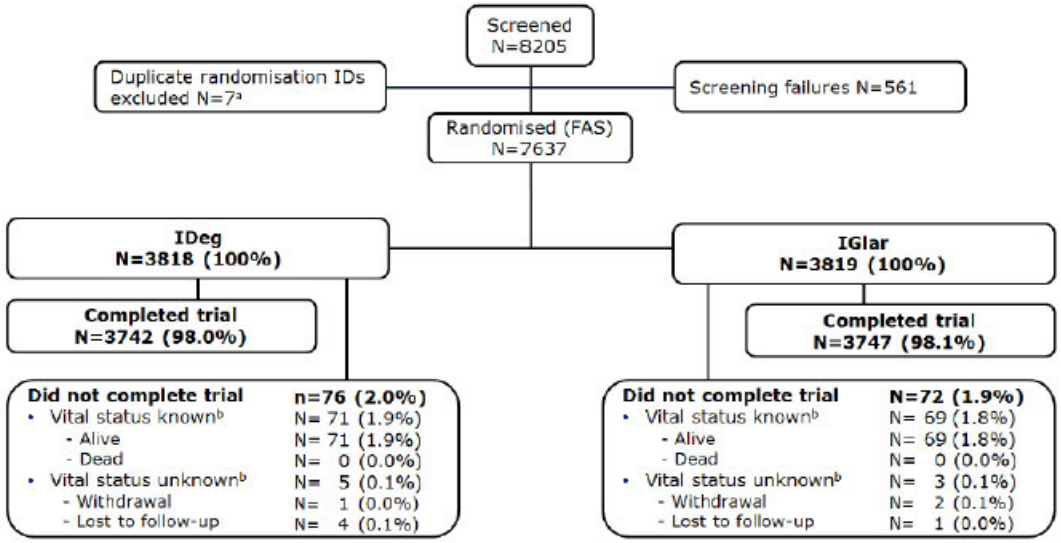
Source: Figure 9-1, DEVOTE Clinical Study Report

The trial recruited patients with poorly controlled blood glucose or who needed basal insulin at enrollment and who had either a previously established history of cardiovascular disease or risk factors for cardiovascular disease. After enrolling 1500 patients who met the criteria of "age ≥ 60 with cardiovascular risk factors", further enrollment of such patients were stopped, to ensure that a substantial fraction of the total trial population of 7500 patients would have more advanced cardiovascular disease. Enrolled subjects required a minimum of 20 units of insulin a day, to ensure adequate exposure to the investigational products. The trial used a "treat-to-target" strategy targeting an HbA1c<7%.

The trial period included a screening period, a randomization visit, an estimated treatment period of up to 59 months, and a 30-day post-treatment follow-up period. Subjects were scheduled to visit the site every month for the first six months, then every three months for the rest of the trial, in addition to monthly phone contacts. These contacts were used to assess the occurrence of outcomes, adherence to study medication, and changes in concomitant therapies.

DEVOTE initiated in October 2013 and completed its last study visit in October 2016. A total of 8205 subjects were screened; 7637 were randomized to a study treatment (3818 were randomized to insulin degludec and 3819 were randomized to insulin glargine) and comprised the Full Analysis Set (FAS) population. Among the FAS population, 98.1% of subjects completed the trial. Among those subjects who did not complete the trial, 10 out of 76 subjects randomized to insulin degludec and 4 out of 72 subjects randomized to insulin glargine experienced a non-fatal MACE prior to trial discontinuation. That is, 66 subjects randomized to insulin degludec and 68 subjects randomized to insulin glargine (total 132 randomized subjects) withdrew or were lost to follow up prior to experience a MACE. The Applicant was able to determine final vital status for all but 8 of these 132 subjects (5 randomized to insulin degludec and 3 randomized to insulin glargine).

Figure 2: Disposition of Subjects in DEVOTE



Source: DBVII statistical review

Table 1: Demographics and Baseline Characteristics of FAS

	IDeg N = 3818	IGlar N = 3819	Total N = 7637
Age (years) *			
Mean (SD)	64.9 (7.3)	65.0 (7.5)	65.0 (7.4)
Sex			
Female	1422 (37.2)	1437 (37.6)	2859 (37.4)
Male	2396 (62.8)	2382 (62.4)	4778 (62.6)
Region			
Europe	438 (11.5)	437 (11.4)	875 (11.5)
North America	2625 (68.8)	2646 (69.3)	5271 (69.0)
South America	304 (8.0)	281 (7.4)	585 (7.7)
Asia excluding India	151 (4.0)	141 (3.7)	292 (3.8)
India	168 (4.4)	189 (4.9)	357 (4.7)
Africa	132 (3.5)	125 (3.3)	257 (3.4)
Ethnicity			
Hispanic or Latino	582 (15.2)	555 (14.5)	1137 (14.9)
Not Hispanic or Latino	3235(84.7)	3263 (85.4)	6498 (85.1)
Unknown	1 (0.0)	1 (0.0)	2 (0.0)
Race			
White	2903 (76.0)	2872 (75.2)	5755 (75.6)
Black or African American	401 (10.5)	431 (11.3)	832 (10.9)
Asian	391 (10.2)	385 (10.1)	776 (10.2)
America Indian or Alaska Native	17 (0.4)	13 (0.3)	30 (0.4)
Native Hawaiian or Other Pacific Islander	11 (0.3)	13 (0.3)	24 (0.3)
Other	94 (2.5)	104 (2.7)	198 (206)
Unknown	1 (0)	1 (0)	2(0)
BMI (kg/m^2)			
Mean (SD)	33.6 (6.8)	33.6 (6.8)	33.6 (6.8)
HbA$_{1c}$ (%)			
Mean (SD)	8.4 (1.6)	8.4 (1.7)	8.4 (1.7)
Diabetes Duration (years)			
Mean (SD)	16.6 (8.8)	16.2 (8.9)	16.4 (8.9)

N: Number of subjects; * Including 3 subjects with age < 50 years
Source: DBII review

The median on-treatment follow-up time was similar in both treatment arms (678 days on insulin degludec and 677 days in insulin glargine). The distribution of exposure time was also similar across treatment arms.

The primary and secondary endpoints were tested in a pre-defined hierarchical sequence: in the hierarchy, it was necessary to fulfill each test criteria of an endpoint to proceed to the next step.

- Step 1: Non-inferiority of insulin degludec relative to insulin glargine for the primary endpoint of 3-point MACE
- Step 2: Superiority of insulin degludec vs insulin glargine for the number of EAC-confirmed hypoglycemic episodes
- Step 3: Superiority of insulin degludec vs insulin glargine for the occurrence of at least one EAC-confirmed severe hypoglycemic episode within a patient

The alpha level for the statistical tests was not adjusted because the statistical results of the interim analysis did not affect the continuation of the trial or the statistical tests and the results of the full trial.

MACE

Dr. Andraca-Carrera of DBVII conducted the statistical evaluation of the data for the primary objective of DEVOTE (to show that the hazard ratio of MACE associated with insulin degludec relative to insulin glargine does not exceed the pre-specified risk margin of 1.3). Dr. Andraca-Carrerra concluded that the DEVOTE trial met this primary objective and that insulin degludec is not associated with an unacceptable increase risk of MACE compared to insulin glargine.

Conduct of the trial was to continue until at least 633 first event adjudication committee (EAC)-confirmed MACE events accrued; at study close, a total of 681 subjects had experienced at least one adjudicated primary MACE events. The primary analysis of MACE was conducted in the FAS population, following the intention-to-treat (ITT) principle. Sensitivity analyses were conducted in the FAS population censoring subjects at time of treatment discontinuation and also in the FAS population censoring subjects at time of treatment discontinuation + 30 days.

The pre-specified primary analysis of time to first MACE used a Cox proportional hazards regression model with study treatment as the only covariate. Non-inferiority of insulin degludec relative to insulin glargine was considered confirmed if the upper bound of the two-side 95% CI for the HR was smaller than 1.3.

Subjects randomized to insulin degludec experienced numerically fewer MACE, including numerically fewer events in each MACE category (CV deaths, non-fatal MIs, and non-fatal strokes), than subjects randomized to insulin glargine. The estimated HR based on the pre-specified Cox proportional hazards model was 0.91 with corresponding 95% CI (0.78, 1.06).

Table 2: Primary Analysis of MACE in DEVOTE trial

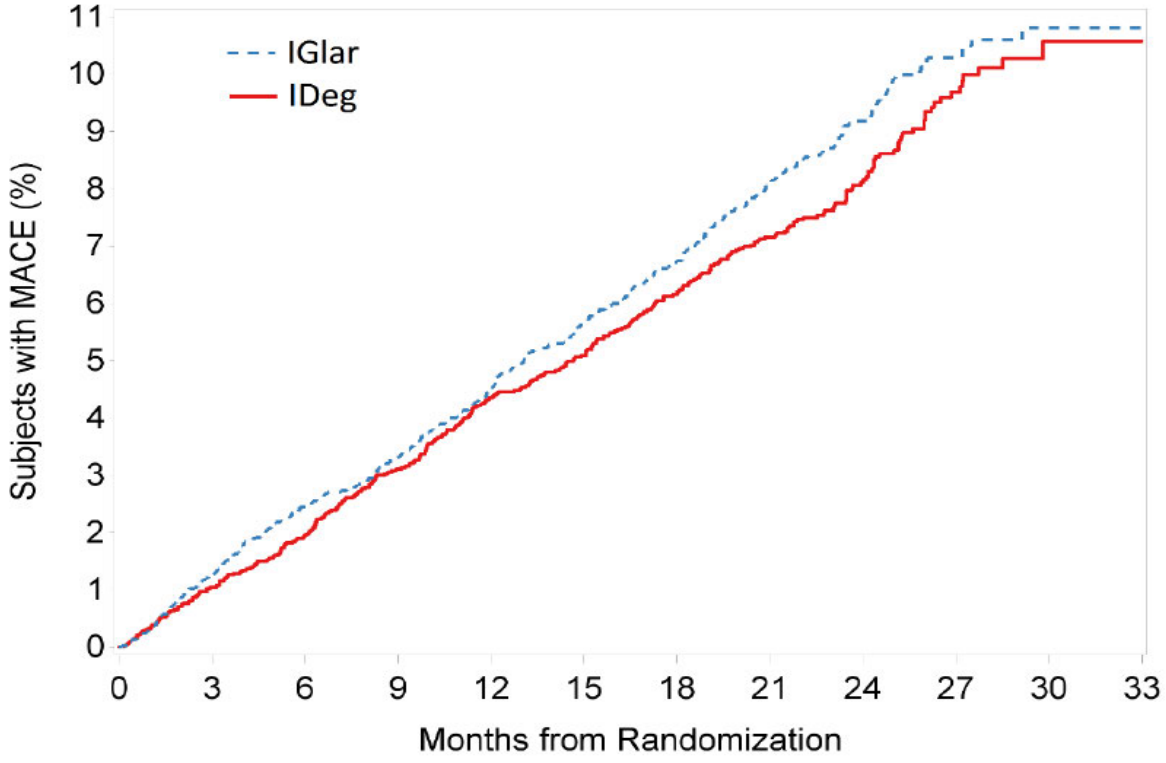
	IDeg N=3818 PY[1]=7366	**IGlar** N=3819 PY[1]=7326	**Hazard Ratio (95% CI)**
MACE	325 [4.4]	356 [4.9]	0.91 (0.78, 1.06)
Cardiovascular death	136	142	
Non-fatal MI	144	169	
Non-fatal Stroke	71	79	

[1]Patient-Years based on time to first MACE in the FAS population censored at the time of MACE, death, or trial discontinuation
[ ] incidence rate per 100 person-years based on first observed MACE event

Source: DBVII statistical review

The cumulative probability of experiencing MACE numerically favored insulin degludec compared to insulin glargine at all time points after randomization, though the differences between the two curves was not statistically significant.

Figure 3: Cumulative Probability of MACE by Treatment Arm - FAS Population



Source: DBVII statistical review

The sensitivity analyses, censoring events that were observed after discontinuation of the study treatments, returned results consistent with the primary MACE analysis.

Table 3: Analyses of MACE - FAS Population, On-Treatment Censoring

Censoring Scheme	IDeg N=3818 PY[1]=6725	IGlar N=3819 PY[1]=6643	Hazard Ratio (95% CI)
On-treatment	241 [3.6]	273 [4.1]	0.87 (0.73, 1.04)
On-treatment + 30 days	294 [4.2]	319 [4.6]	0.91 (0.78, 1.07)

[1]Patient-Years based on time to first MACE in the FAS population censored at the time of treatment discontinuation

Source: DBVII statistical review

A tipping point analysis was also conducted to evaluate the potential impact of missing data from the 66 subjects randomize to insulin degludec and 68 subjects randomize to insulin glargine who withdrew from the trial or were lost to follow-up prior to experiencing a MACE. The analysis showed that even if all 66 subjects randomized to insulin degludec and no subjects randomized to insulin glargine were imputed to have experienced a MACE, the estimated hazard ratio would be 1.09 and the corresponding 95% CI would be (0.95, 1.26) – still meeting the pre-specified risk margin of 1.3.

Similarly, Dr. Andraca-Carrera conducted subgroup analyses according to sex (male or female), race (white, Asian, or black), age (≤ 65 years or > 65 years), country (USA or non-USA), HbA1c (< 8% or ≥ 8%), renal function (normal/mild impairment or moderate/sever impairment), previous insulin use (yes or no), diabetes duration (≤ 15 years or > 15 years), and statin use (yes or no). The point estimate of the hazard ratio favored insulin degludec over insulin glargine for every subgroup analyzed with the single exception of the non-statin user subgroup. The non-statin user subgroup was a relatively small (798 patients randomized to insulin degludec and 836 patients randomized to insulin glargine) with a wide CI that overlapped 1: the point estimate was 1.12 with corresponding CI (0.81, 1.57).

CDTL comment: The sensitivity analyses, the tipping point analysis, and the subgroup analyses demonstrate the robustness of the primary analysis of MACE.

Hypoglycemia

Dr. Hamilton of DBII conducted the statistical evaluation of the data for the secondary objective of DEVOTE related to assessing the effect of insulin degludec relative to insulin glargine on markers of glycemic control, including the two statistically powered secondary endpoints based on observations of severe hypoglycemic events previously described. Specifically, these secondary endpoints were the number of EAC-confirmed severe hypoglycemic events and the number of patients who experienced at least one EAC-confirmed hypoglycemic event. Dr. Hamilton concluded that superiority was achieved for insulin degludec with regards to both of these endpoints and that no statistical issues were identified that would preclude approval of the PAS.

The evaluation of the hypoglycemia endpoints was conducted using the data from the FAS. The number of EAC-confirmed severe hypoglycemic episodes was analyzed using a negative binomial regression model with log-link function and logarithm of the observation times as offset. The occurrence of at least one EAC-confirmed severe hypoglycemic episode within a patient was analyzed using a logistic regression model with log-link function. The pre-specified analyses established that statistically fewer overall EAC-confirmed severe hypoglycemic events were observed in patients randomized to insulin degludec compared to insulin glargine (280 vs 472) and that statistically fewer patients randomized to insulin degludec compared to insulin glargine experienced at least one EAC-confirmed severe hypoglycemic event (187 vs 252); these conclusions were further supported by the additional analyses. For the first of these two endpoints, the estimated relative risk is 0.6 with 95% CI (0.48, 0.76); for the second of these two endpoints, the estimated relative risk is 0.73 with 95% CI (0.60, 0.89).

Table 4: EAC-Confirmed Severe Hypoglycemic Events FAS

	IDeg				IGlar			
	N	(%)	E	R	N	(%)	E	R
Number of Subjects	3818				3819			
PYO	7568				7558			
EAC confirmed events	187	(4.9)	280	3.70	252	(6.6)	472	6.25

Source: DBII statistical review

To evaluate the robustness of these analyses, the FDA statistical review also included additional statistical models and on-treatment analyses to evaluate the collected data and also considered tipping point analyses to examine the potential impact of missing data. All of these approaches providing support to the conclusions arrived at with the pre-specified analyses. Similarly, subgroup analyses according to age, sex, region, and race were conducted – the findings of these evaluations were also consistent. In all subgroups, the point estimate favored insulin degludec over insulin glargine, with the sole exception of the "Asian race" subgroup (for which the point estimate was 1.21 favoring insulin glargine with wide confidence intervals due to the relatively small size of this subgroup).

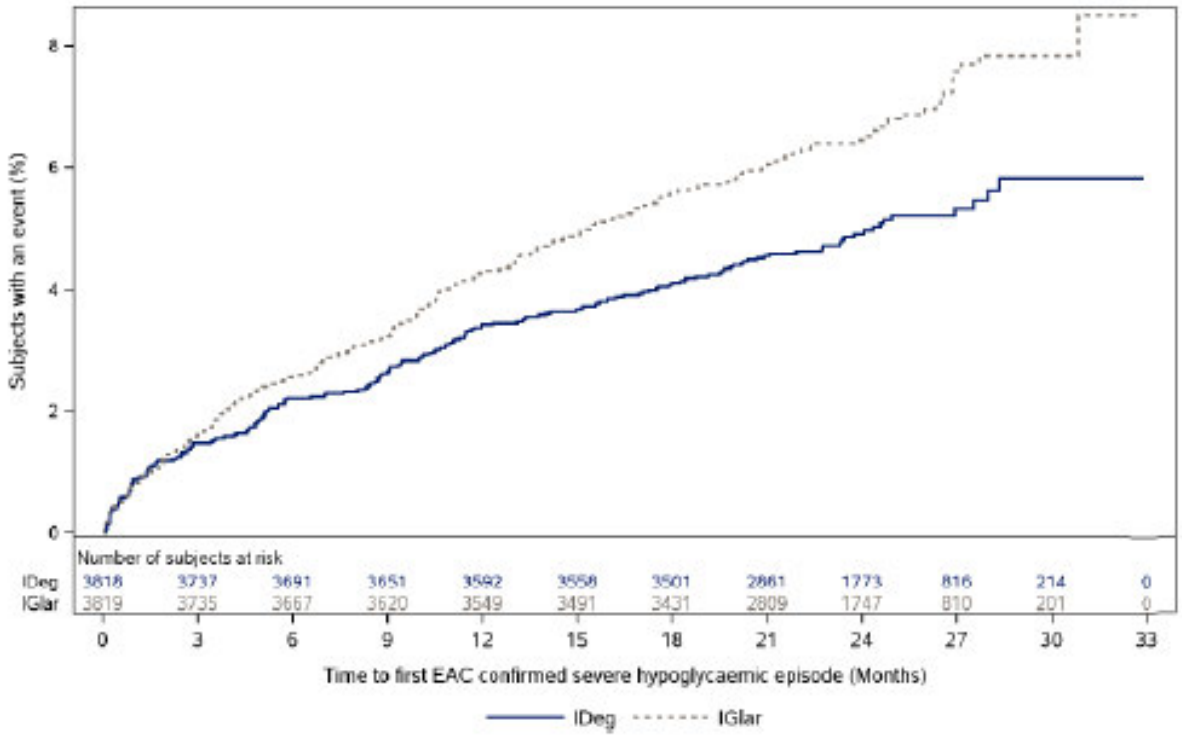
CDTL comment: [redacted] (b) (4)

Clinical review of MACE and severe hypoglycemia events

Dr. Condarco from DMEP also reviewed the outcome data related to MACE and severe hypoglycemia events. Her findings were consistent with those of the statistical reviewers. In addition, her review discussed the clinical context of these outcomes and provided important insights into the nature of the clinical events, particularly the events of severe hypoglycemia.

Dr. Condarco conducted a Kaplan-Meier analysis of time to first EAC-confirmed severe hypoglycemic event. The exploratory analysis suggested that a difference with regards to incidence of severe hypoglycemia was detectable starting around month 3 and increased thereafter.

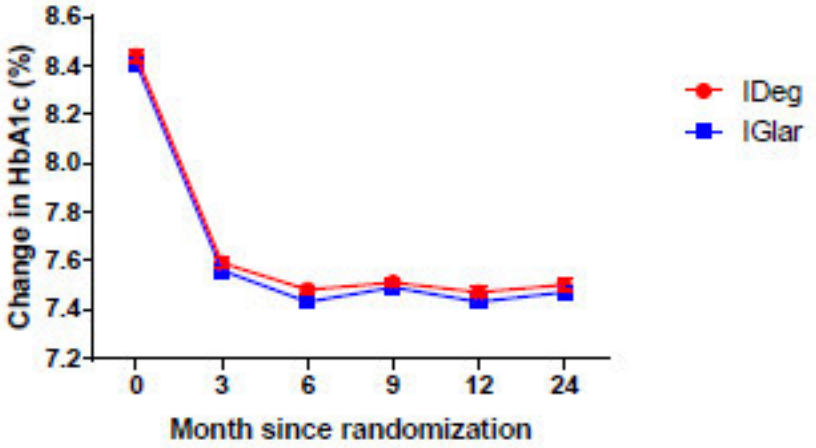
Figure 4: Time to first EAC-confirmed severe hypoglycemic event - FAS



Source: DMEP clinical review

Dr. Condarco also considered clinical data related to glycemic control to understand whether difference in incidence of hypoglycemia was explained by differences in efficacy and/or dose of the investigational products. The longitudinal HbA1c, fasting plasma glucose, and self-monitored plasma glucose data all indicated that the two treatment arms exhibited similar glycemic control. In addition, the data on insulin titration and insulin dose supports that both treatment arms used the investigational products in a similar fashion.

Figure 5: HbA1c over time - FAS



Time	0	3	6	9	12	24
IDeg (N)	3774	3656	3608	3535	3525	2458
IGlar (N)	3776	3640	3562	3516	3500	2424

Source: DMEP clinical review

Table 5: Titration targets at baseline for randomized patients

	Standard titration goal 71-90 mg/dL		Titration goal of 126 mg/dL		Other titration goal	
	IDeg	IGlar	IDeg	IGlar	IDeg	IGlar
N (%)	3153 (82.5)	3154 (82.5)	133 (3.5)	132 (3.5)	532 (13.9)	533 (13.9)

Source: DMEP clinical review

Table 6: Insulin doses at baseline and 24 months

Insulin dose analysis	Tx	N FAS	n	Baseline Mean insulin dose (SD)	N	24 month LS Mean dose (SD)	Change from baseline LS Mean insulin dose (SE)	LS Mean difference in insulin dose ^	Treatment difference (95% CI)	p-value*
BASAL INSULIN DOSE (Units)										
All randomized patients	IDeg IGlar	3818 3819	3717 3694	41.3 (30.4) 40.4 (30.3)	3717 3695	65.1(0.74) 61.9 (0.74)	24.4 (0.74) 21.1 (0.74)	3.2	[1.2; 5.3]	0.002
Patients also using bolus	IDeg IGlar	3818 3819	2308 2348	48.4 (31.6) 47.2 (31.7)	2311 2338	72.3 (1.00) 67.5 (0.99)	24.8 (1.00) 20.0 (0.99)	4.8	[2.0; 7.6]	<0.001
Patients NOT using bolus	IDeg IGlar	3818 3819	1416 1375	29.9 (24.3) 28.9 (23.7)	1406 1357	53.0 (1.06) 52.5 (1.08)	23.7 (1.06) 23.2 (1.08)	0.5	[-2.5; 3.5]	0.739
BOLUS INSULIN DOSE (Units)										
Patients using bolus	IDeg IGlar	3818 3819	1709 1719	42.5 (38.1) 39.9 (33.9)	2265 2292	61.6 (1.25) 65.0 (1.25)	28.7 (1.25) 32.1 (1.25)	-3.4	[-6.9; 0.0]	0.052
TOTAL INSULIN DOSE (Units)										
All randomized patients (with or without bolus)	IDeg IGlar	3818 3819	3734 3731	60.7 (54.1) 58.7 (50.7)	3717 3695	100.6 (1.27) 100.1 (1.27)	41.5 (1.27) 41.1 (1.27)	0.5	[-3.1; 4.0]	0.801
Patients also using bolus	IDeg IGlar	3818 3819	2317 2356	79.5 (58.4) 76.1 (54.1)	2311 2338	129.1 (1.88) 127.8 (1.87)	52.5 (1.88) 51.2 (1.87)	1.3	[-3.9; 6.5]	0.630

* two sided
^^The treatment difference between mean insulin doses at the 24 month visit was analyzed using a mixed model for repeated measures (MMRM) within subjects using an unstructured residual covariance matrix among visits at 3, 6, 9, 12, 15, 18, 21 and 24 months of the study. Interactions between visit and treatment and with baseline dose were included as fixed effects. Baseline dose was the first basal insulin dose reported by investigator for analyses of basal dose, whereas it was the dose at visit 3 for analyses of total insulin dose and bolus insulin dose
Source: table 6 in information request //cdsesub1/evsprod/NDA203314/0147/m1/us/re-fda-ir-20171024.pdf

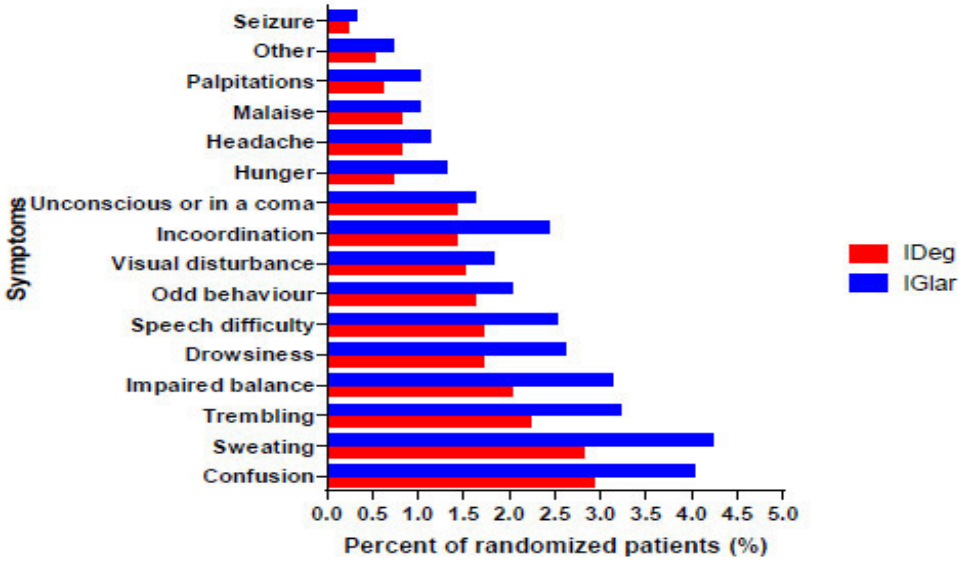
Source: DMEP clinical review

Relevant observations from her review include the following:

- While inspection of the narratives for some events led Dr Condarco to disagree with categorization of a handful of CV death events, overall she agreed with the adjudication of events in DEVOTE
- Most of the symptoms associated with the EAC confirmed severe hypoglycemic events were non-specific; only 21% of events were reported clear neuroglycopenic symptoms such as unconsciousness, coma, or seizure.
- Most of the EAC confirmed severe hypoglycemic events had available self-measured plasma glucose levels available, with more than 80% of events reporting a value less than 54 mg/dL.
- Glycemic control was similar (for hemoglobin A1C) or better (for fasting plasma glucose) among patients randomized to insulin degludec compared to insulin glargine.
- Numeric differences in basal insulin dosage and post baseline use of various antidiabetic medicines across treatment arms were documented, but were small and unlikely to explain the differences observed in the incidence of severe hypoglycemic events across treatment arms.

Dr. Condarco reviewed at length the characteristics of the events of EAC confirmed severe hypoglycemia. As noted above, she observed that the majority of these events lacked neurologic symptoms that would clearly classify as “severe”, as opposed to “symptomatic” or “documented symptomatic”.

Figure 6: Characteristics of EAC confirmed severe hypoglycemia events by treatment arm - FAS



Source: DMEP clinical review

Dr. Condarco noted that the EAC relied on a broad interpretation of the definition of severe hypoglycemia (an episode requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions and during which plasma glucose concentration may not have been available, but where neurological recovery following the return of plasma glucose to normal was considered sufficient evidence that the event was induced by a low plasma glucose concentration) to rely on reversal of such symptoms as evidence of neurological recovery. Similarly, Dr. Condarco noted that few details were available for most events to distinguish between instances where the patient "required assistance" as opposed to instances where the patient simply received some assistance. However, Dr. Condarco also noted that the she agreed that the events constituted, at a minimum, clinically significant events of hypoglycemia and that the design of the trial (including blinding of patients, investigator, sponsor, and EAC) minimized the potential for bias in the identification and classification of events.

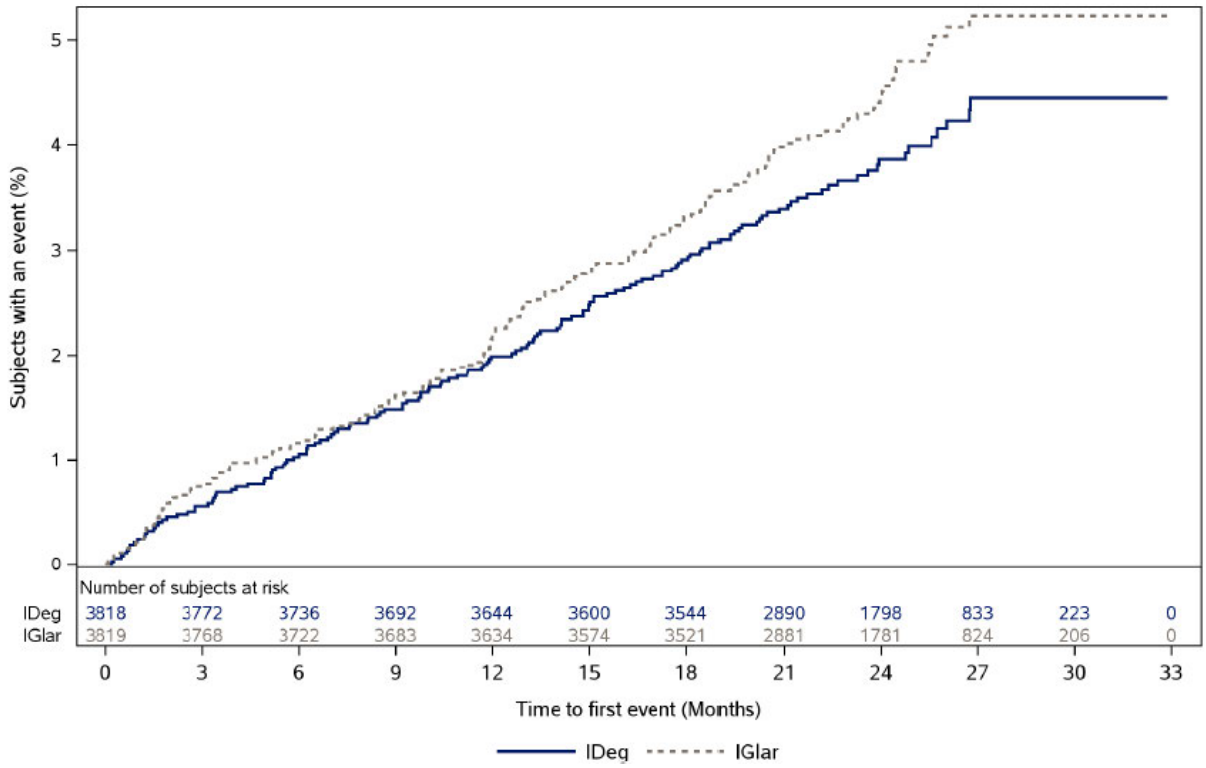
CDTL comment: I concur with the conclusion of Dr. Condarco that, while some ambiguity exists regarding whether all of the EAC confirmed events meet the definition of "severe hypoglycemia", the data demonstrate that a difference in the incidence of clinically significant events of hypoglycemia. Further, I believe it is not unreasonable to characterize these observed events as "severe hypoglycemia", despite acknowledging some limitations with the assessments.

7. Safety

As described above, Dr. Condarco concluded, and I concur, that the data from DEVOTE establishes that 1) insulin degludec as equivalent cardiovascular safety compared to insulin glargine in a population with high rates of cardiovascular disease and 2) insulin degludec has a lower event rate and patient incidence of severe hypoglycemia than insulin glargine. In addition to her review of the primary MACE and severe hypoglycemia endpoints, Dr. Condarco also reviewed all of the clinical data from DEVOTE from the point-of-view of safety. While the overall safety of insulin degludec had already been established at the time approval, the DEVOTE trial afforded the opportunity to evaluate further the safety profile over a mean patient observation period of 2 years.

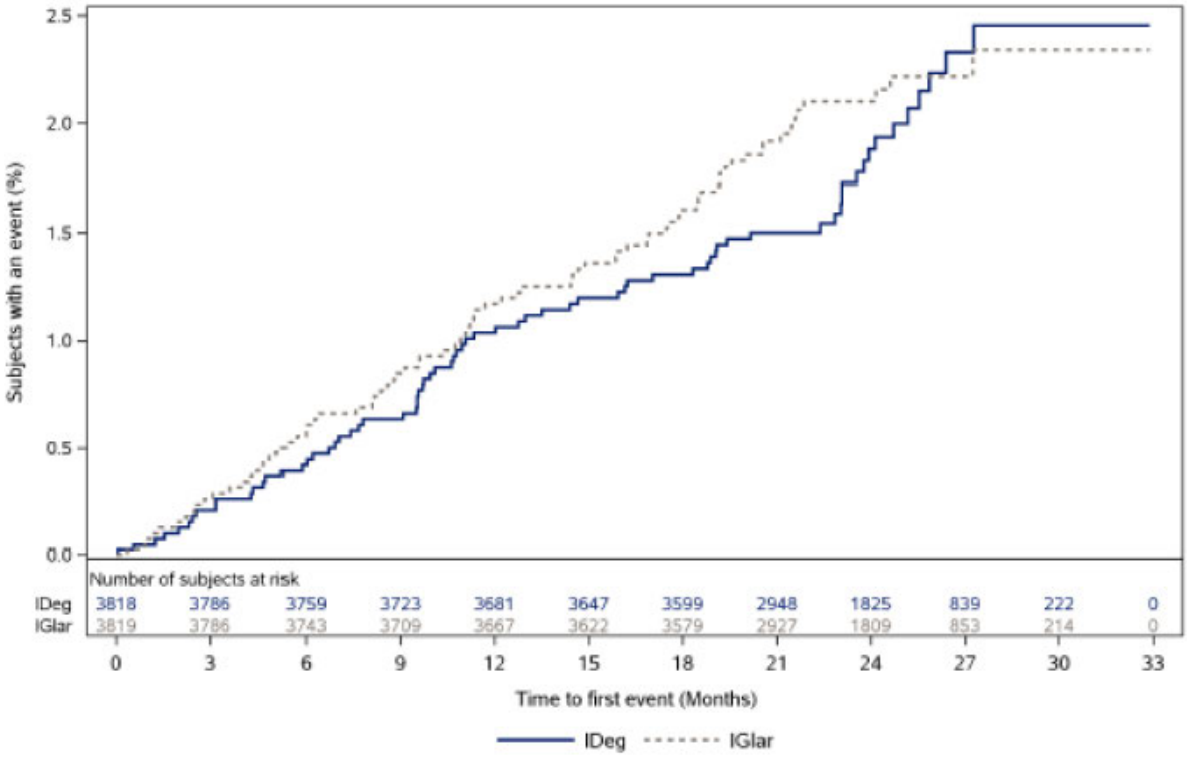
Beyond the evaluation of the primary MACE endpoint, Dr. Condarco's clinical review of the cardiovascular safety data considered the individual components of the MACE endpoint and the expanded 4-point MACE (CV death, non-fatal stroke, non-fatal MI, and unstable angina pectoris requiring hospitalization). In general, these exploratory analyses were consistent with the finding of the primary MACE outcome. For each component of the 4-point MACE safety endpoint, the point estimate hazard ratio favored insulin degludec over insulin glargine. Figure 7, Figure 8, and Figure 9 show Kaplan-Meier plots of time to first non-fatal MI, time to first non-fatal stroke, and time to cardiovascular death. These analyses are also consistent with the conclusion that insulin degludec is not associated with an unacceptable increase in cardiovascular risk compared to insulin glargine.

Figure 7: Time to first non-fatal MI - FAS



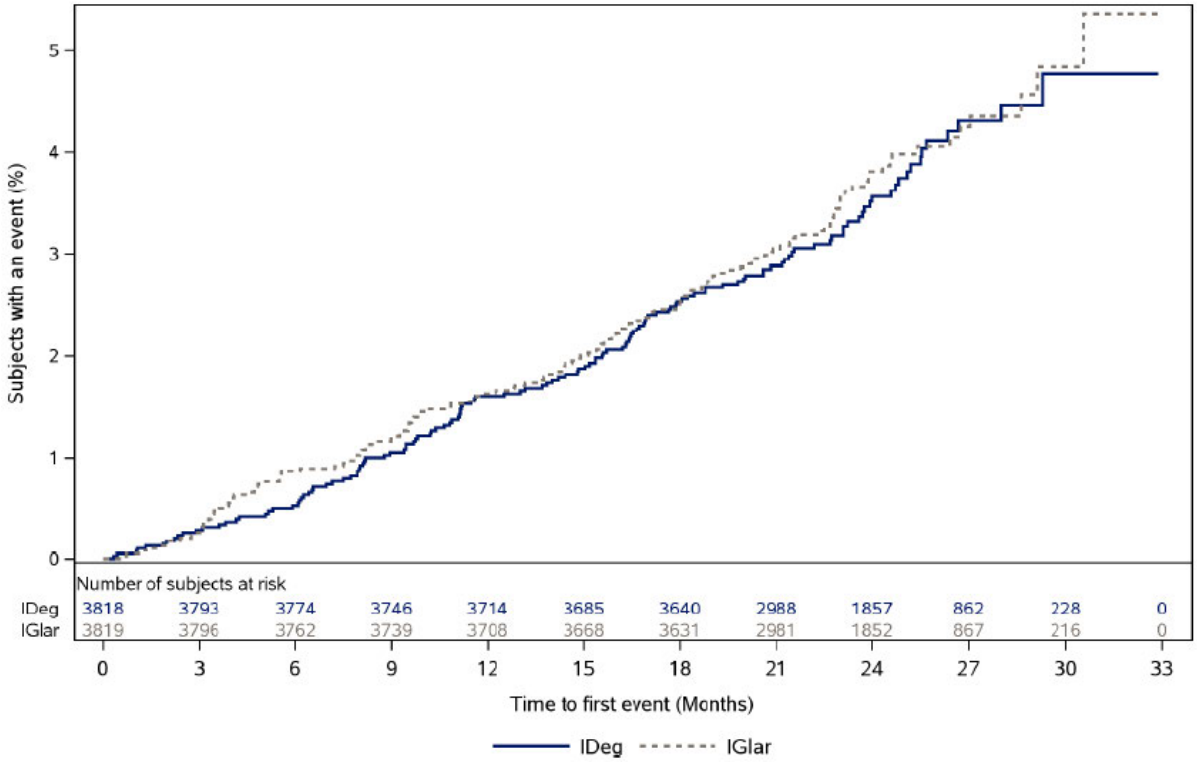
Source: DMEP clinical review

Figure 8: Time to first non-fatal stroke - FAS



Source: DMEP clinical review

Figure 9: Time to cardiovascular death - FAS



Source: DMEP clinical review

Other than the primary outcomes and additional exploratory endpoints related to cardiovascular safety and hypoglycemia, DEVOTE systematically collected safety data including serious adverse events (SAEs), adverse events (AEs) leading to discontinuation of the investigational product, and medication errors leading to an SAE.

Dr. Condarco's review also considered all cause death and non-cardiovascular death. Numerically, there were numerically fewer all cause deaths and non-cardiovascular deaths (as well as cardiovascular deaths) observed in the patients randomized to insulin degludec relative to those randomized to insulin glargine.

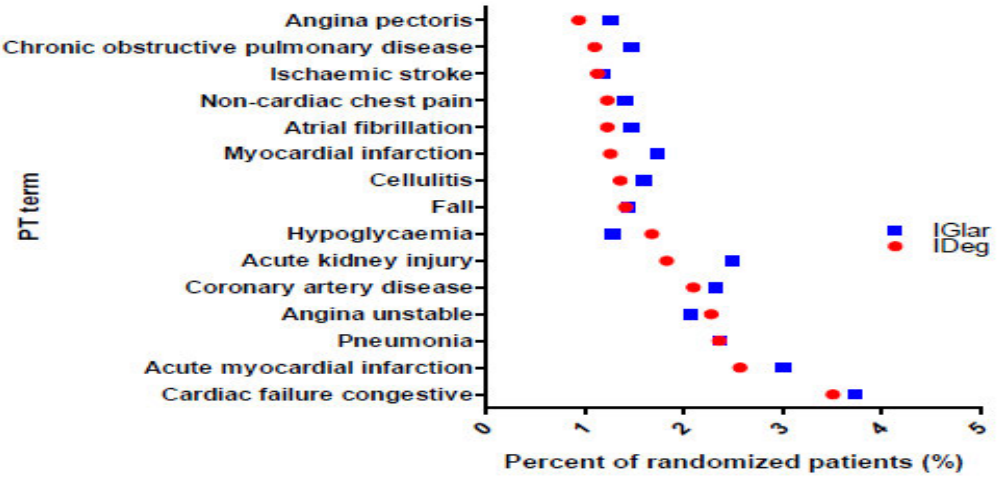
Table 7: Characteristics of EAC-adjudicated deaths - FAS

	IDeg			IGlar		
	N (%)	E	R	N (%)	E	R
FAS	3818			3819		
PYO	7568			7558		
Total deaths (all cause)	202 (5.3)	202	2.67	221 (5.8)	221	2.92
Cardiovascular deaths	97 (2.5)	97	1.28	106 (2.8)	106	1.40
Sudden cardiac death	57 (1.5)	57	0.75	55 (1.4)	55	0.73
Acute MI	14 (0.4)	14	0.19	22 (0.6)	22	0.29
Heart failure	13 (0.3)	13	0.17	11 (0.3)	11	0.15
Cerebrovascular event	6 (0.2)	6	0.08	13 (0.3)	13	0.17
Cardiovascular procedure	0	0	0	2 (0.1)	2	0.03
Cardiovascular hemorrhage	0	0	0	1 (0)	1	0.01
Other cardiovascular causes^*	7 (0.2)	7	0.09	2 (0.1)	2	0.03
Non-cardiovascular deaths	66 (1.7)	66	0.87	79 (2.1)	79	1.05
Pulmonary causes	9 (0.2)	9	0.12	12 (0.3)	12	0.16
Renal causes	4 (0.1)	4	0.05	3 (0.1)	3	0.04
Gastrointestinal causes	2 (0.1)	2	0.03	1 (0)	1	0.01
Hepatobiliary causes	0	0	0	4 (0.1)	4	0.05
Pancreatic causes	0	0	0	0	0	0
Infection (including sepsis)	20 (0.5)	20	0.26	21 (0.5)	21	0.28
Non-infectious (systemic inflammatory response, SIRS)	0	0	0	0	0	0
Hemorrhage that is neither CV bleeding or stroke	0	0	0	0	0	0
Non-CV procedure or surgery	0	0	0	0	0	0
Trauma	3 (0.1)	3	0.04	6 (0.2)	6	0.08
Suicide	0	0	0	2 (0.1)	2	0.03
Non-prescription drug reaction or overdose	0	0	0	0	0	0
Prescription drug reaction or overdose	0	0	0	0	0	0
Neurological (non – cardiovascular)	0	0	0	3 (0.1)	3	0.04
Malignancy	25 (0.7)	25	0.33	25 (0.7)	25	0.33
Other non-cardiovascular ¤Ω	3 (0.1)	3	0.04	2 (0.1)	2	0.03
Undetermined cause	39 (1.0)	39	0.52	36 (0.9)	36	0.48

Source: DMEP clinical review

Approximately 38.6% of patients randomized to insulin degludec experienced an SAE, compared to 39.7% of patients randomized to insulin glargine. Inspection at various MedDRA levels did not reveal notable differences in rates of SAEs across treatment arms for any category of event. At the level of Preferred Terms, incident rates of SAEs were generally slightly numerically smaller among patients randomized to insulin degludec; notable exception included the Preferred Terms of “acute myocardial infarction” and “hypoglycemia” (where event rates adjudicated by a dedicated endpoint committee revealed the opposite).

Figure 10: Preferred terms of SAEs occuring in at least 1% of patients



Source: DMEP clinical review

Similarly, no significant differences were observed in assessments of lipid laboratories, weight gain, vital signs, or renal function.

CDTL comment: I concur with Dr. Condarco, who concluded that the overall clinical safety outcomes were similar between treatment groups, with the exception of rates of severe hypoglycemic events.

8. Clinical Inspection Summary

The review from the Office of Scientific Investigations concluded that the inspectional findings support the validity of data as reported by the sponsor under the sNDA. The inspection comprised four domestic clinical sites and also the sponsor. No regulatory violations were found at three of the clinical sites and no regulatory violations were found at the sponsor; the classification for these sites and for the sponsor is No Action Indicated. The classification for the fourth clinical site (Dr. Woods) is Voluntary Action Indicated.

Dr. Kleppinger concluded, and I concur, that the regulatory violations identified are unlikely to significantly impact the primary safety and efficacy analyses of the application and that the data from the site is acceptable for use.

9. Advisory Committee Meeting

No new efficacy or safety issue rose to the level of requiring the input from an advisory panel. Therefore, an advisory committee meeting was *not* convened for this NDA.

10. Pediatrics

The Division determined that this application does not trigger the Pediatric Research Equity Act. Therefore, no pediatric studies under PREA are recommended.

11. Labeling

The data from DEVOTE provides compelling evidence that use of insulin degludec does not lead to an unacceptable increase in the incidence of MACE compared to the use of insulin glargine. In addition, the data from DEVOTE provides compelling evidence that the use of insulin degludec caused fewer hypoglycemic events than the use of insulin glargine in the patient population studied. Accordingly, the data in the sNDA submission supported minor changes to the Tresiba PI to Section 6.1 (ADVERSE REACTIONS) and to Sections 8.5 and 8.6 (SPECIAL POPULATIONS): these edits largely serve ensure that the overall PI is internally consistent, given the additional information introduced by more significant edits made to Section 14 (CLINICAL STUDIES), in which Section 14.4 (Safety Outcomes Trial) was added to present the data from DEVOTE.

The new Section 14.4 contains a description of DEVOTE (including trial design, patient population, MACE outcomes, and hypoglycemia outcomes), as reproduced below.

1 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

Drs. Condarco, Hamilton, Wang, and Andraca-Carrerra all reviewed and agreed with this new labeling. I concur with their conclusions.

CDTL comment: The new labeling, particularly the data as presented in Table 15 and Table 16 of the revised Tresiba PI, reflects the conclusions of the overall review that 1) the data from DEVOTE suffices to exclude a 30% increase in the incidence of MACE attributable to exposure to insulin degludec relative to exposure to insulin glargine and 2) insulin degludec was superior to insulin glargine in the context of DEVOTE for two measures of the incidence of severe hypoglycemia.

12. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

Approval

- Risk Benefit Assessment

The Applicant has submitted a prior approval supplement (PAS) containing clinical data from EX1250-4080 (DEVOTE). The Applicant designed and conducted the DEVOTE trial to

address a deficiency that resulted from the MACE signal observed in the original NDA submission for Tresiba (insulin degludec). Specifically, the CR letter stated "you will need to submit additional clinical trial data from a dedicated, double-blind, cardiovascular outcomes trial using glargine as the comparator. The trial should be powered to exclude an excess cardiovascular risk based on a composite of cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke (MACE)…" DEVOTE also incorporated incorporated secondary endpoints into the design of DEVOTE to show that the use of insulin degludec resulted in fewer hypoglycemia events compared to the use of insulin glargine in patients with T2D.

I agree with the conclusions of the statistical and clinical reviewers that the results from DEVOTE establish that insulin degludec is not associated with an unacceptable increase in MACE relative to insulin glargine. I also nconclude that PMR 2954-2 [To conduct a randomized, double-blind, active-controlled trial evaluating the effect of Tresiba (insulin degludec injection) on the incidence of major adverse cardiovascular events (MACE) in subjects with type 2 diabetes mellitus. The primary objective of the trial should be to demonstrate that the upper bound of the 2-sided 95% confidence interval for the estimated risk ratio comparing the incidence of adjusted MACE (non-fatal myocardial infarction, non-fatal stroke, cardiovascular death) observed with Tresiba to that observed in the comparator group in less than 1.3] has been fulfilled.

I also agree with the conclusions of the statistical and clinical reviewers that that insulin degludec was superior to insulin glargine with regards to the incidence of severe hypoglycemia in the context of the DEVOTE patient population. This finding was statistically significant, robust, and could not be explained by overall differences in glycemic control or insulin titration. However, I have not concluded that this finding from DEVOTE can be broadly extrapolated. (b) (4)

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

No new safety findings from this clinical development program prompt the need for a postmarketing risk evaluation and management strategies.

- Recommendation for other Postmarketing Requirements and Commitments

No new safety findings from this clinical development program prompt the need for a postmarketing requirements and commitments. PREA is not triggered by this NDA.

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/s/

PATRICK ARCHDEACON
03/23/2018

MARY T THANH HAI
03/24/2018

Division Summary Memo for Regulatory Action and CDTL review

Date	March 23, 2018
From	Patrick Archdeacon, MD
Subject	Division of Metabolism and Endocrinology Products (DMEP) Summary Memo for Regulatory Action
NDA # / Sequence #:	203314 / S0135
Applicant	Novo Nordisk
Date of Submission Receipt	May 26, 2017
PDUFA Goal Date	March 26, 2018
Proprietary Name / Established (USAN) names	Tresiba Insulin degludec injection
Dosage forms / Strength	Tresiba U-100 Individualized dose for sc injection once daily 100 units/mL
Proposed Indication	(b) (4)
Recommended Action	Approval

1. Introduction

This document contains the 'Summary Basis for Regulatory Action' memo for sNDA 2033314/S0135 [prior approval supplement (PAS) containing clinical data from EX1250-4080 (DEVOTE); Supplement 8] for Tresiba (insulin degludec injection; NDA 203-314). DEVOTE was a randomized, double-blind, active-controlled trial evaluating the effect of insulin degludec on the incidence of major adverse cardiovascular events (MACE) in subjects with type 2 diabetes mellitus (T2DM) relative to the effect of insulin glargine. Tresiba was approved on September 2015 based on an interim analysis of DEVOTE with a postmarketing requirement (PMR; 2954-2) to complete DEVOTE and exclude a 30% increase in the incidence of MACE attributable to exposure to insulin degludec relative to exposure to insulin glargine. In addition to the primary outcome of MACE, DEVOTE evaluated two additional pre-specified secondary endpoints: 1) the total number of adjudicated severe hypoglycemic events, 2) the number of patients experiencing at least one episode of severe hypoglycemia.

The clinical data contained in the PAS has been determined to satisfy PMR 2954-2 and also to support the addition of new labeling for Tresiba to describe the superiority of insulin degludec relative to insulin glargine observed with regards to the incidence of severe hypoglycemia in patients with type 2 diabetes (T2D), as demonstrated in DEVOTE. No new labeling regarding hypoglycemia in patients with type 1 diabetes (T1D) is supported by the data in the PAS. (b) (4) [redacted] The reader is referred to Section 11 and Section 12 of this Summary Memo for details about the new labeling, including the determination to report the pattern of hypoglycemic events observed in the DEVOTE trial but not to extrapolate broadly the findings to populations not studied in DEVOTE.

Simultaneously with the addition of new labeling on the basis of the PAS, new language to address a safety risk associated with visual impairment is also being added to the Tresiba labeling. (b) (4) [redacted]

The reader is referred to the multiple discipline reviews for a more comprehensive review and detailed discussion of this prior approval supplement for Tresiba. For the sake of completeness, the reader is also referred to the DMEPA review addressing the safety signal related to visual impairment. This memo references the following documents/sources:

Subject	Author	Date
Clinical Efficacy and Safety Review (DMEP)	Dr. Tania Condarco	February 20, 2018
Statistical review (DBII)	Dr. Kiya Hamilton	February 16, 2018
Statistical review (DBVII)	Dr. Eugenio Andraca-Carrera	February 9, 2018
Office of Scientific Investigation (OSI)	Dr. Cynthia Kleppinger	February 9, 2018
Office of Prescription Drug Promotion (OPDP)	Ankur Kalola	March 5, 2018
Division of Medication Error Prevention and Analysis (DMEPA)	Ariane Conrad and Hina Mehta	November 17, 2017

2. Background

Tresiba (insulin degludec or IDeg) has been approved for marketing in the US since September of 2015. It is indicated to improve glycemic control in patients 1 year of age and older with diabetes mellitus. Insulin degludec is a recombinant, long-acting, once-daily insulin analog; it differs from human insulin by the deletion of the threonine amino acid at position B30 and the conjugation of hexadecanedioic acid via a glutamic acid spacer to the amino acid lysine at position B29. The addition of the hexadecanedioic acid results in the formation of multi-hexamers after subcutaneous injection, thereby forming a depot of insulin in the subcutaneous tissue. Insulin degludec monomers gradually separate, leave the depot, and enter into the circulation. The result is a slow delivery of insulin degludec to the patient such that a consistent concentration of drug is maintained.

Regulatory History

The Applicant originally submitted the insulin degludec New Drug Application (NDA) on September 29, 2011. During the review of the NDA, the Division of Metabolism and Endocrinology Products (DMEP) identified a safety signal generated by a pre-specified meta-analysis of cardiovascular risk associated with insulin degludec. While insulin products are not typically subject to the formal cardiovascular risk assessment that the Agency has required of non-insulin antihyperglycemic agents since 2008, a meta-analysis of sixteen trials from the degludec and degludec/aspart programs suggested the possibility that degludec products could increase the risk of cardiovascular event – including cardiovascular death, myocardial infarction, stroke, and unstable angina – by 10% relative to active comparators. These data were presented at an Advisory Committee meeting held on November 8, 2012; the committee unanimously voted that the signal merited evaluation by a dedicated cardiovascular outcome trial (CVOT). On February 8, 2013, DMEP issued a Complete Response (CR) Letter that included a request for a CVOT to assess the cardiovascular safety of insulin degludec, based on the composite endpoint of major adverse cardiovascular events (MACE) including

cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke. Specifically, the CR letter stated "you will need to submit additional clinical trial data from a dedicated, double-blind, cardiovascular outcomes trial using glargine as the comparator. The trial should be powered to exclude an excess cardiovascular risk based on a composite of cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke (MACE), not MACE+. The risk margin to exclude that is necessary for approval should be discussed with the Agency at an End-of-Review meeting. At a minimum, the resubmission must include enough MACE events to definitively exclude a hazard of 80% with a reassuring point estimate." At an April 4, 2013 meeting between the Agency and the Applicant, the design of the CVOT was discussed. The requirements for the trial were summarized in the meeting minutes as follows: "While we will accept for resubmission and potentially approve your product based on an interim analysis excluding a CV risk margin of 1.8, assuming a reassuring point estimate and no other countervailing safety signals identified in the resubmission, you will be required to exclude an excess hazard of 30% postmarketing."

The Applicant designed and conducted the DEVOTE trial to address the deficiency that resulted from the MACE signal observed in the original submission accordingly. On the basis of an interim analysis of data from DEVOTE that met the standard of excluding a hazard ratio (HR) greater than 1.8, insulin degludec (under the trade name of Tresiba) and insulin degludec/aspart were approved for marketing on September 25, 2015. While the Agency approved insulin degludec based on the results of the interim analysis, it also issued Post-Marketing Requirement (PMR) #2954-2, requiring the Applicant to "conduct a randomized, double-blind, active-controlled trial evaluating the effect of Tresiba (insulin degludec injection) on the incidence of major cardiovascular events (MACE) in subjects with type 2 diabetes mellitus. The primary objective of the trial should be to demonstrate that the upper bound of the 2-sided 95% confidence interval for the estimated risk ratio comparing the incidence of adjudicated MACE (non-fatal myocardial infarction, non-fatal stroke, cardiovascular death) observed with Tresiba to that observed in the comparator group is less than 1.3." In order to ensure sufficient power to exclude the required hazard ratio, the DEVOTE trial was designed to continue until 633 MACE events were collected and confirmed. The May 26, 2017 PAS submission includes the final results of DEVOTE, including the data related to MACE events in 681 subjects.

Hypoglycemia was also a topic at the initial November 8, 2012 Advisory Committee meeting and of the original NDA review. While the Applicant had argued that the unique PK/PD characteristics of insulin degludec (avoiding the peaks and troughs typically associated with insulin products) should mitigate events of hypoglycemia, the Applicant was informed that a hypoglycemia risk reduction claim would require additional demonstration of a meaningful risk reduction over other available once-daily basal insulins. Though the original NDA submission included some clinical data addressing hypoglycemia, those data were deemed insufficient to establish a benefit due to several deficiencies [including the reliance on open-label trials, lack of consistent trends across different definitions of hypoglycemia (i.e., "Novo confirmed hypoglycemia", "nocturnal confirmed hypoglycemia", "severe hypoglycemia", and "documented hypoglycemia") and different patient populations (i.e., T1D and T2D)].

In response to the deficiencies related to the claim of a benefit related to hypoglycemia cited in the February 8, 2013 CR letter, the Applicant incorporated secondary endpoints into the design of DEVOTE to show that the use of insulin degludec resulted in fewer hypoglycemia events compared to the use of insulin glargine in patients with T2D. The secondary endpoints related to hypoglycemia were statistically powered and relied on the America Diabetes Association definition of severe hypoglycemia: an episode requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions and during which plasma glucose concentration may not have been available, but where neurological recovery following the return of plasma glucose to normal was considered sufficient evidence that the event was induced by a low plasma glucose concentration. (b) (4)

(b) (4)

The current action, therefore, addresses hypoglycemia only in the context of T2D.

3. CMC/Device

The PAS did not include any new data related to CMC or device issues.

4. Nonclinical Pharmacology/Toxicology

The PAS did not include any new nonclinical data.

5. Clinical Pharmacology/Biopharmaceutics

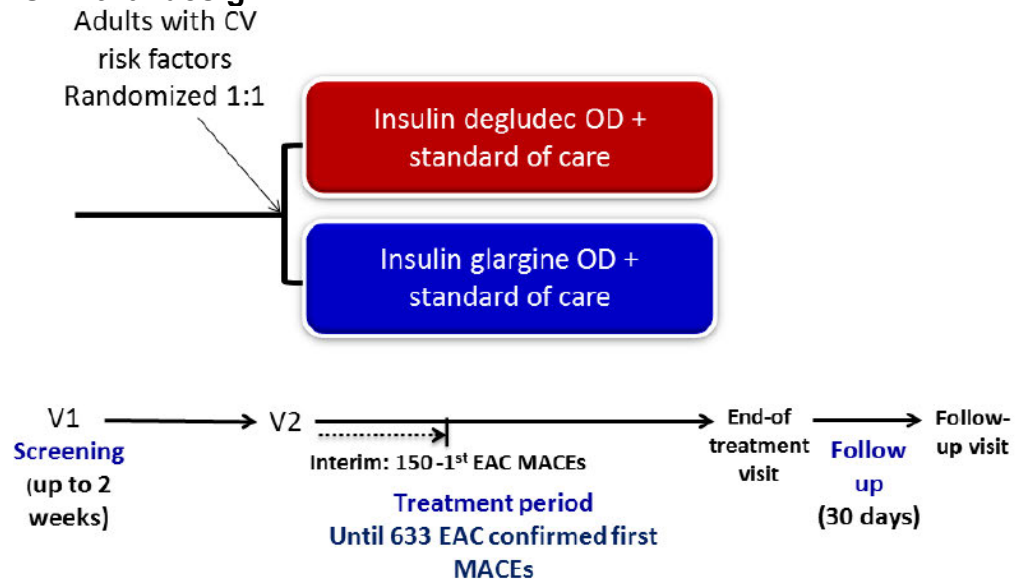
The PAS did not raise any new clinical pharmacology issues.

6. Clinical/Statistical- Efficacy

The clinical [Dr Condarco from the Division of Metabolism and Endocrinology Products (DMEP)] and both statistical review teams [Dr Andraca-Carrera and Dr Mark Levenson from Division from the Division of Biometrics VII (DBVII), who evaluated the MACE data; Dr Kiya Hamilton and Dr Yun Wang from the Division of Biometrics II (DBII), who evaluated the hypoglycemia data] did not identify any issues from their analyses of the primary and secondary endpoints of the DEVOTE trial that would preclude approval of the PAS. All of the teams recommended approval of the supplement, pending agreement on new labeling language.

As previously described, DEVOTE compared the cardiovascular safety of insulin degludec to insulin glargine; its secondary objectives included assessments of the effect of insulin degludec relative to insulin glargine on markers of glycemic control (including comparisons of outcomes related to hypoglycemia that were allocated statistical power). It was an event driven, multi-center, double-blinded, randomized control trial comparing insulin degludec (U100) to insulin glargine (U100) added to standard of care in patients with type 2 diabetes at high risk of cardiovascular events.

Figure 1: DEVOTE trial design



Abbreviations: CV: cardiovascular; EAC: event adjudication committee; MACE: Major adverse cardiovascular event; OD: daily; V1: screening visit; V2: randomization and start of treatment

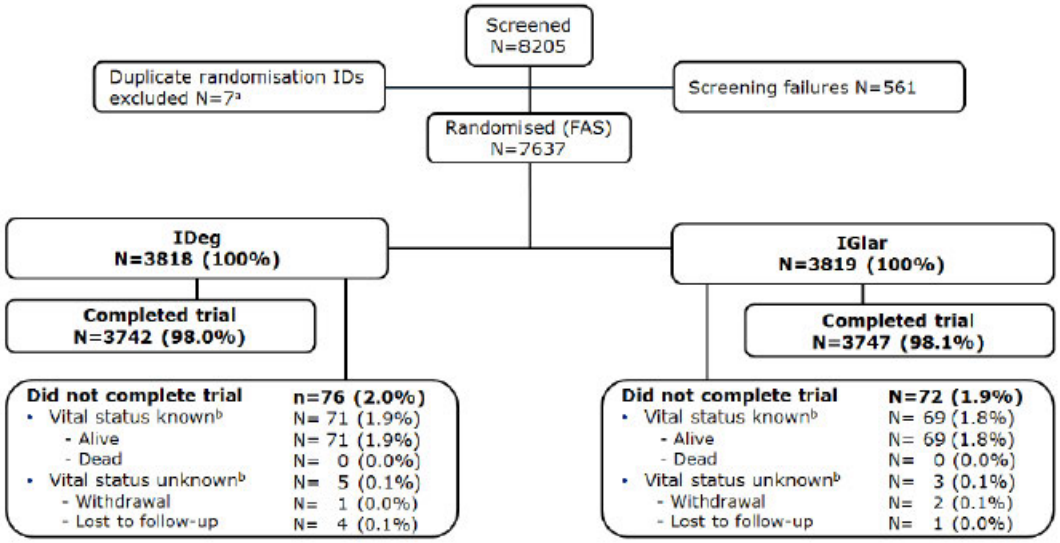
Source: Figure 9-1, DEVOTE Clinical Study Report

The trial recruited patients with poorly controlled blood glucose or who needed basal insulin at enrollment and who had either a previously established history of cardiovascular disease or risk factors for cardiovascular disease. After enrolling 1500 patients who met the criteria of "age ≥ 60 with cardiovascular risk factors", further enrollment of such patients were stopped, to ensure that a substantial fraction of the total trial population of 7500 patients would have more advanced cardiovascular disease. Enrolled subjects required a minimum of 20 units of insulin a day, to ensure adequate exposure to the investigational products. The trial used a "treat-to-target" strategy targeting an HbA1c<7%.

The trial period included a screening period, a randomization visit, an estimated treatment period of up to 59 months, and a 30-day post-treatment follow-up period. Subjects were scheduled to visit the site every month for the first six months, then every three months for the rest of the trial, in addition to monthly phone contacts. These contacts were used to assess the occurrence of outcomes, adherence to study medication, and changes in concomitant therapies.

DEVOTE initiated in October 2013 and completed its last study visit in October 2016. A total of 8205 subjects were screened; 7637 were randomized to a study treatment (3818 were randomized to insulin degludec and 3819 were randomized to insulin glargine) and comprised the Full Analysis Set (FAS) population. Among the FAS population, 98.1% of subjects completed the trial. Among those subjects who did not complete the trial, 10 out of 76 subjects randomized to insulin degludec and 4 out of 72 subjects randomized to insulin glargine experienced a non-fatal MACE prior to trial discontinuation. That is, 66 subjects randomized to insulin degludec and 68 subjects randomized to insulin glargine (total 132 randomized subjects) withdrew or were lost to follow up prior to experience a MACE. The Applicant was able to determine final vital status for all but 8 of these 132 subjects (5 randomized to insulin degludec and 3 randomized to insulin glargine).

Figure 2: Disposition of Subjects in DEVOTE



Source: DBVII statistical review

Table 1: Demographics and Baseline Characteristics of FAS

	IDeg N = 3818	IGlar N = 3819	Total N = 7637
Age (years) *			
Mean (SD)	64.9 (7.3)	65.0 (7.5)	65.0 (7.4)
Sex			
Female	1422 (37.2)	1437 (37.6)	2859 (37.4)
Male	2396 (62.8)	2382 (62.4)	4778 (62.6)
Region			
Europe	438 (11.5)	437 (11.4)	875 (11.5)
North America	2625 (68.8)	2646 (69.3)	5271 (69.0)
South America	304 (8.0)	281 (7.4)	585 (7.7)
Asia excluding India	151 (4.0)	141 (3.7)	292 (3.8)
India	168 (4.4)	189 (4.9)	357 (4.7)
Africa	132 (3.5)	125 (3.3)	257 (3.4)
Ethnicity			
Hispanic or Latino	582 (15.2)	555 (14.5)	1137 (14.9)
Not Hispanic or Latino	3235(84.7)	3263 (85.4)	6498 (85.1)
Unknown	1 (0.0)	1 (0.0)	2 (0.0)
Race			
White	2903 (76.0)	2872 (75.2)	5755 (75.6)
Black or African American	401 (10.5)	431 (11.3)	832 (10.9)
Asian	391 (10.2)	385 (10.1)	776 (10.2)
America Indian or Alaska Native	17 (0.4)	13 (0.3)	30 (0.4)
Native Hawaiian or Other Pacific Islander	11 (0.3)	13 (0.3)	24 (0.3)
Other	94 (2.5)	104 (2.7)	198 (206)
Unknown	1 (0)	1 (0)	2(0)
BMI (kg/m^2)			
Mean (SD)	33.6 (6.8)	33.6 (6.8)	33.6 (6.8)
HbA$_{1c}$ (%)			
Mean (SD)	8.4 (1.6)	8.4 (1.7)	8.4 (1.7)
Diabetes Duration (years)			
Mean (SD)	16.6 (8.8)	16.2 (8.9)	16.4 (8.9)

N: Number of subjects; * Including 3 subjects with age < 50 years
Source: DBII review

The median on-treatment follow-up time was similar in both treatment arms (678 days on insulin degludec and 677 days in insulin glargine). The distribution of exposure time was also similar across treatment arms.

The primary and secondary endpoints were tested in a pre-defined hierarchical sequence: in the hierarchy, it was necessary to fulfill each test criteria of an endpoint to proceed to the next step.

- Step 1: Non-inferiority of insulin degludec relative to insulin glargine for the primary endpoint of 3-point MACE
- Step 2: Superiority of insulin degludec vs insulin glargine for the number of EAC-confirmed hypoglycemic episodes
- Step 3: Superiority of insulin degludec vs insulin glargine for the occurrence of at least one EAC-confirmed severe hypoglycemic episode within a patient

The alpha level for the statistical tests was not adjusted because the statistical results of the interim analysis did not affect the continuation of the trial or the statistical tests and the results of the full trial.

MACE

Dr. Andraca-Carrera of DBVII conducted the statistical evaluation of the data for the primary objective of DEVOTE (to show that the hazard ratio of MACE associated with insulin degludec relative to insulin glargine does not exceed the pre-specified risk margin of 1.3). Dr. Andraca-Carrerra concluded that the DEVOTE trial met this primary objective and that insulin degludec is not associated with an unacceptable increase risk of MACE compared to insulin glargine.

Conduct of the trial was to continue until at least 633 first event adjudication committee (EAC)-confirmed MACE events accrued; at study close, a total of 681 subjects had experienced at least one adjudicated primary MACE events. The primary analysis of MACE was conducted in the FAS population, following the intention-to-treat (ITT) principle. Sensitivity analyses were conducted in the FAS population censoring subjects at time of treatment discontinuation and also in the FAS population censoring subjects at time of treatment discontinuation + 30 days.

The pre-specified primary analysis of time to first MACE used a Cox proportional hazards regression model with study treatment as the only covariate. Non-inferiority of insulin degludec relative to insulin glargine was considered confirmed if the upper bound of the two-side 95% CI for the HR was smaller than 1.3.

Subjects randomized to insulin degludec experienced numerically fewer MACE, including numerically fewer events in each MACE category (CV deaths, non-fatal MIs, and non-fatal strokes), than subjects randomized to insulin glargine. The estimated HR based on the pre-specified Cox proportional hazards model was 0.91 with corresponding 95% CI (0.78, 1.06).

Table 2: Primary Analysis of MACE in DEVOTE trial

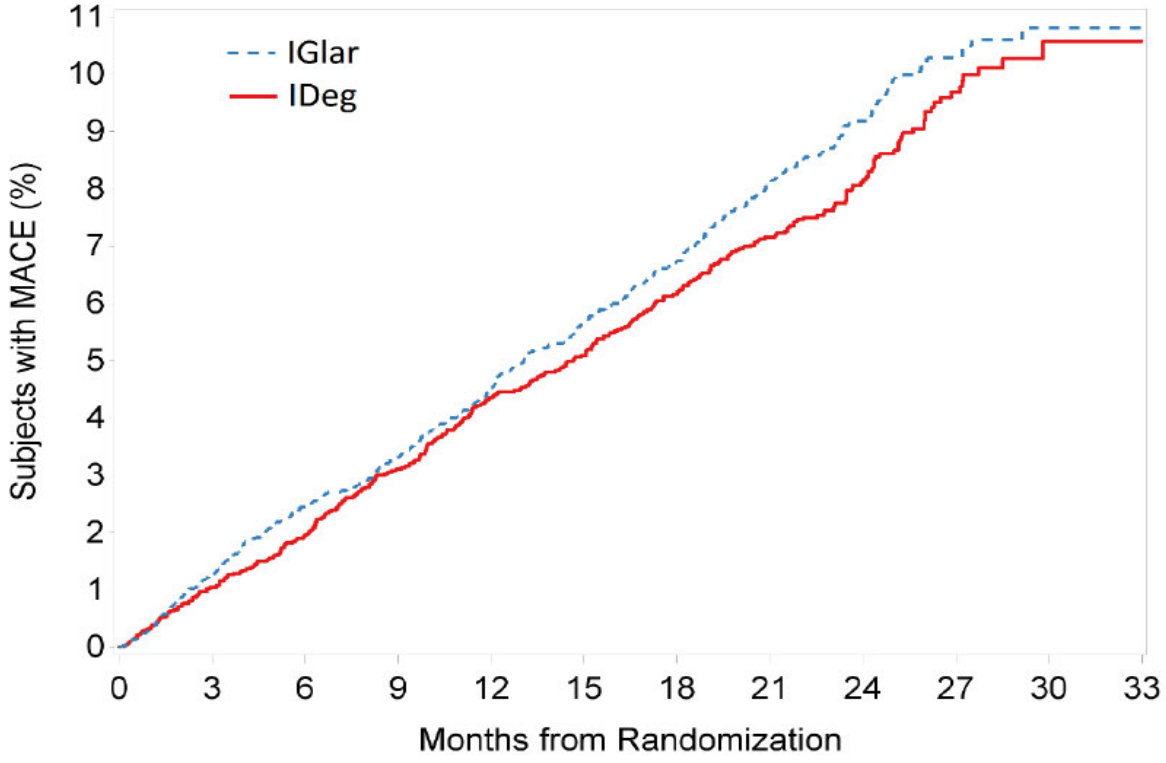
	IDeg N=3818 PY[1]=7366	**IGlar** N=3819 PY[1]=7326	**Hazard Ratio (95% CI)**
MACE	325 [4.4]	356 [4.9]	0.91 (0.78, 1.06)
Cardiovascular death	136	142	
Non-fatal MI	144	169	
Non-fatal Stroke	71	79	

[1]Patient-Years based on time to first MACE in the FAS population censored at the time of MACE, death, or trial discontinuation
[ ] incidence rate per 100 person-years based on first observed MACE event

Source: DBVII statistical review

The cumulative probability of experiencing MACE numerically favored insulin degludec compared to insulin glargine at all time points after randomization, though the differences between the two curves was not statistically significant.

Figure 3: Cumulative Probability of MACE by Treatment Arm - FAS Population



Source: DBVII statistical review

The sensitivity analyses, censoring events that were observed after discontinuation of the study treatments, returned results consistent with the primary MACE analysis.

Table 3: Analyses of MACE - FAS Population, On-Treatment Censoring

Censoring Scheme	IDeg N=3818 PY[1]=6725	IGlar N=3819 PY[1]=6643	Hazard Ratio (95% CI)
On-treatment	241 [3.6]	273 [4.1]	0.87 (0.73, 1.04)
On-treatment + 30 days	294 [4.2]	319 [4.6]	0.91 (0.78, 1.07)

[1]Patient-Years based on time to first MACE in the FAS population censored at the time of treatment discontinuation

Source: DBVII statistical review

A tipping point analysis was also conducted to evaluate the potential impact of missing data from the 66 subjects randomize to insulin degludec and 68 subjects randomize to insulin glargine who withdrew from the trial or were lost to follow-up prior to experiencing a MACE. The analysis showed that even if all 66 subjects randomized to insulin degludec and no subjects randomized to insulin glargine were imputed to have experienced a MACE, the estimated hazard ratio would be 1.09 and the corresponding 95% CI would be (0.95, 1.26) – still meeting the pre-specified risk margin of 1.3.

Similarly, Dr. Andraca-Carrera conducted subgroup analyses according to sex (male or female), race (white, Asian, or black), age (≤ 65 years or > 65 years), country (USA or non-USA), HbA1c (< 8% or ≥ 8%), renal function (normal/mild impairment or moderate/sever impairment), previous insulin use (yes or no), diabetes duration (≤ 15 years or > 15 years), and statin use (yes or no). The point estimate of the hazard ratio favored insulin degludec over insulin glargine for every subgroup analyzed with the single exception of the non-statin user subgroup. The non-statin user subgroup was a relatively small (798 patients randomized to insulin degludec and 836 patients randomized to insulin glargine) with a wide CI that overlapped 1: the point estimate was 1.12 with corresponding CI (0.81, 1.57).

CDTL comment: The sensitivity analyses, the tipping point analysis, and the subgroup analyses demonstrate the robustness of the primary analysis of MACE.

Hypoglycemia

Dr. Hamilton of DBII conducted the statistical evaluation of the data for the secondary objective of DEVOTE related to assessing the effect of insulin degludec relative to insulin glargine on markers of glycemic control, including the two statistically powered secondary endpoints based on observations of severe hypoglycemic events previously described. Specifically, these secondary endpoints were the number of EAC-confirmed severe hypoglycemic events and the number of patients who experienced at least one EAC-confirmed hypoglycemic event. Dr. Hamilton concluded that superiority was achieved for insulin degludec with regards to both of these endpoints and that no statistical issues were identified that would preclude approval of the PAS.

The evaluation of the hypoglycemia endpoints was conducted using the data from the FAS. The number of EAC-confirmed severe hypoglycemic episodes was analyzed using a negative binomial regression model with log-link function and logarithm of the observation times as offset. The occurrence of at least one EAC-confirmed severe hypoglycemic episode within a patient was analyzed using a logistic regression model with log-link function. The pre-specified analyses established that statistically fewer overall EAC-confirmed severe hypoglycemic events were observed in patients randomized to insulin degludec compared to insulin glargine (280 vs 472) and that statistically fewer patients randomized to insulin degludec compared to insulin glargine experienced at least one EAC-confirmed severe hypoglycemic event (187 vs 252); these conclusions were further supported by the additional analyses. For the first of these two endpoints, the estimated relative risk is 0.6 with 95% CI (0.48, 0.76); for the second of these two endpoints, the estimated relative risk is 0.73 with 95% CI (0.60, 0.89).

Table 4: EAC-Confirmed Severe Hypoglycemic Events FAS

	IDeg				IGlar			
	N	(%)	E	R	N	(%)	E	R
Number of Subjects	3818				3819			
PYO	7568				7558			
EAC confirmed events	187	(4.9)	280	3.70	252	(6.6)	472	6.25

Source: DBII statistical review

To evaluate the robustness of these analyses, the FDA statistical review also included additional statistical models and on-treatment analyses to evaluate the collected data and also considered tipping point analyses to examine the potential impact of missing data. All of these approaches providing support to the conclusions arrived at with the pre-specified analyses. Similarly, subgroup analyses according to age, sex, region, and race were conducted – the findings of these evaluations were also consistent. In all subgroups, the point estimate favored insulin degludec over insulin glargine, with the sole exception of the "Asian race" subgroup (for which the point estimate was 1.21 favoring insulin glargine with wide confidence intervals due to the relatively small size of this subgroup).

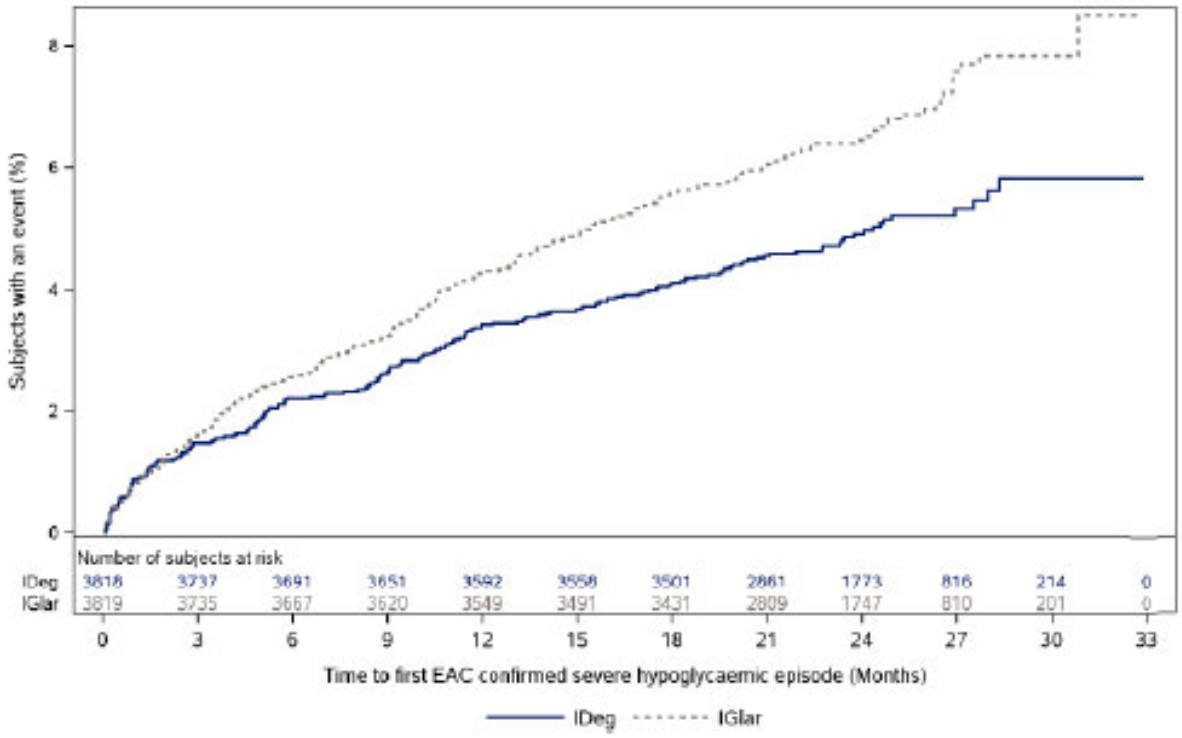
CDTL comment: [redacted] (b) (4) *. I concur with this recommendation.*

Clinical review of MACE and severe hypoglycemia events

Dr. Condarco from DMEP also reviewed the outcome data related to MACE and severe hypoglycemia events. Her findings were consistent with those of the statistical reviewers. In addition, her review discussed the clinical context of these outcomes and provided important insights into the nature of the clinical events, particularly the events of severe hypoglycemia.

Dr. Condarco conducted a Kaplan-Meier analysis of time to first EAC-confirmed severe hypoglycemic event. The exploratory analysis suggested that a difference with regards to incidence of severe hypoglycemia was detectable starting around month 3 and increased thereafter.

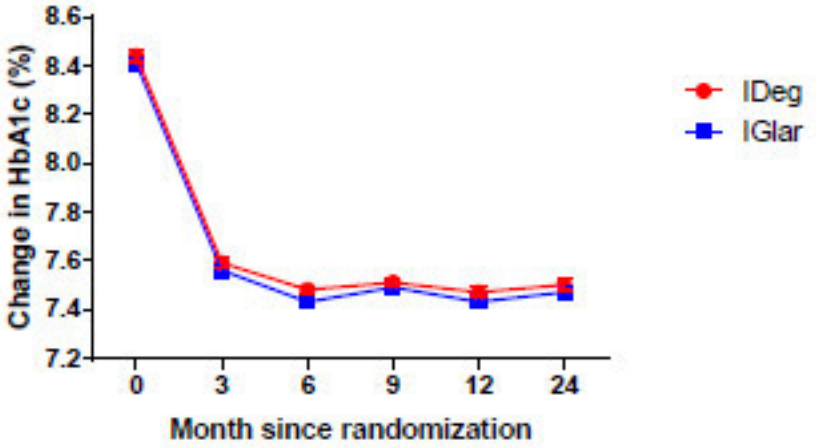
Figure 4: Time to first EAC-confirmed severe hypoglycemic event - FAS



Source: DMEP clinical review

Dr. Condarco also considered clinical data related to glycemic control to understand whether difference in incidence of hypoglycemia was explained by differences in efficacy and/or dose of the investigational products. The longitudinal HbA1c, fasting plasma glucose, and self-monitored plasma glucose data all indicated that the two treatment arms exhibited similar glycemic control. In addition, the data on insulin titration and insulin dose supports that both treatment arms used the investigational products in a similar fashion.

Figure 5: HbA1c over time - FAS



Time	0	3	6	9	12	24
IDeg (N)	3774	3656	3608	3535	3525	2458
IGlar (N)	3776	3640	3562	3516	3500	2424

Source: DMEP clinical review

Table 5: Titration targets at baseline for randomized patients

	Standard titration goal 71-90 mg/dL		Titration goal of 126 mg/dL		Other titration goal	
	IDeg	IGlar	IDeg	IGlar	IDeg	IGlar
N (%)	3153 (82.5)	3154 (82.5)	133 (3.5)	132 (3.5)	532 (13.9)	533 (13.9)

Source: DMEP clinical review

Table 6: Insulin doses at baseline and 24 months

Insulin dose analysis	Tx	N FAS	n	Baseline Mean insulin dose (SD)	N	24 month LS Mean dose (SD)	Change from baseline LS Mean insulin dose (SE)	LS Mean difference in insulin dose ^	Treatment difference (95% CI)	p-value*
BASAL INSULIN DOSE (Units)										
All randomized patients	IDeg IGlar	3818 3819	3717 3694	41.3 (30.4) 40.4 (30.3)	3717 3695	65.1(0.74) 61.9 (0.74)	24.4 (0.74) 21.1 (0.74)	3.2	[1.2; 5.3]	0.002
Patients also using bolus	IDeg IGlar	3818 3819	2308 2348	48.4 (31.6) 47.2 (31.7)	2311 2338	72.3 (1.00) 67.5 (0.99)	24.8 (1.00) 20.0 (0.99)	4.8	[2.0; 7.6]	<0.001
Patients NOT using bolus	IDeg IGlar	3818 3819	1416 1375	29.9 (24.3) 28.9 (23.7)	1406 1357	53.0 (1.06) 52.5 (1.08)	23.7 (1.06) 23.2 (1.08)	0.5	[-2.5; 3.5]	0.739
BOLUS INSULIN DOSE (Units)										
Patients using bolus	IDeg IGlar	3818 3819	1709 1719	42.5 (38.1) 39.9 (33.9)	2265 2292	61.6 (1.25) 65.0 (1.25)	28.7 (1.25) 32.1 (1.25)	-3.4	[-6.9; 0.0]	0.052
TOTAL INSULIN DOSE (Units)										
All randomized patients (with or without bolus)	IDeg IGlar	3818 3819	3734 3731	60.7 (54.1) 58.7 (50.7)	3717 3695	100.6 (1.27) 100.1 (1.27)	41.5 (1.27) 41.1 (1.27)	0.5	[-3.1; 4.0]	0.801
Patients also using bolus	IDeg IGlar	3818 3819	2317 2356	79.5 (58.4) 76.1 (54.1)	2311 2338	129.1 (1.88) 127.8 (1.87)	52.5 (1.88) 51.2 (1.87)	1.3	[-3.9; 6.5]	0.630

* two sided
^^The treatment difference between mean insulin doses at the 24 month visit was analyzed using a mixed model for repeated measures (MMRM) within subjects using an unstructured residual covariance matrix among visits at 3, 6, 9, 12, 15, 18, 21 and 24 months of the study. Interactions between visit and treatment and with baseline dose were included as fixed effects. Baseline dose was the first basal insulin dose reported by investigator for analyses of basal dose, whereas it was the dose at visit 3 for analyses of total insulin dose and bolus insulin dose
Source: table 6 in information request //cdsesub1/evsprod/NDA203314/0147/m1/us/re-fda-ir-20171024.pdf

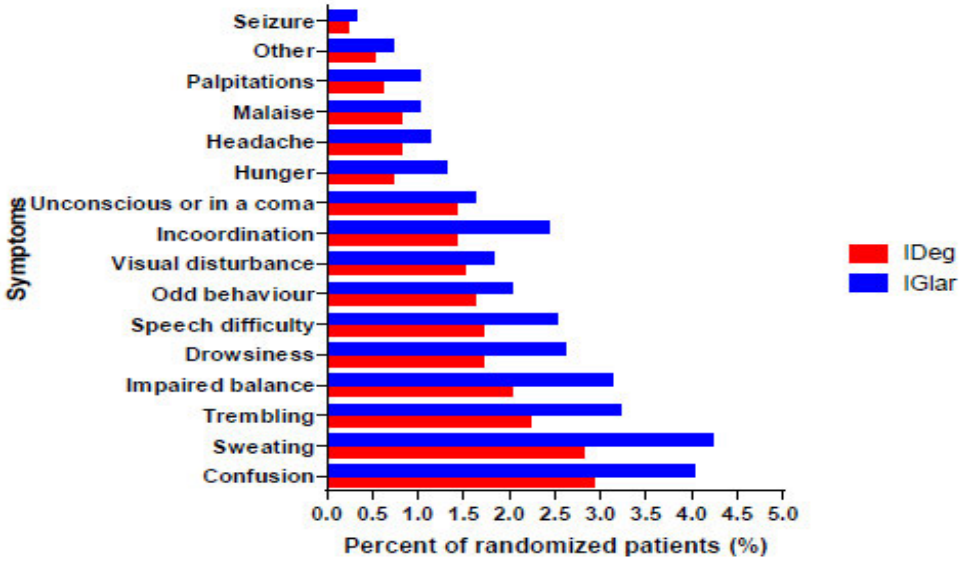
Source: DMEP clinical review

Relevant observations from her review include the following:

- While inspection of the narratives for some events led Dr Condarco to disagree with categorization of a handful of CV death events, overall she agreed with the adjudication of events in DEVOTE
- Most of the symptoms associated with the EAC confirmed severe hypoglycemic events were non-specific; only 21% of events were reported clear neuroglycopenic symptoms such as unconsciousness, coma, or seizure.
- Most of the EAC confirmed severe hypoglycemic events had available self-measured plasma glucose levels available, with more than 80% of events reporting a value less than 54 mg/dL.
- Glycemic control was similar (for hemoglobin A1C) or better (for fasting plasma glucose) among patients randomized to insulin degludec compared to insulin glargine.
- Numeric differences in basal insulin dosage and post baseline use of various antidiabetic medicines across treatment arms were documented, but were small and unlikely to explain the differences observed in the incidence of severe hypoglycemic events across treatment arms.

Dr. Condarco reviewed at length the characteristics of the events of EAC confirmed severe hypoglycemia. As noted above, she observed that the majority of these events lacked neurologic symptoms that would clearly classify as “severe”, as opposed to “symptomatic” or “documented symptomatic”.

Figure 6: Characteristics of EAC confirmed severe hypoglycemia events by treatment arm - FAS



Source: DMEP clinical review

Dr. Condarco noted that the EAC relied on a broad interpretation of the definition of severe hypoglycemia (an episode requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions and during which plasma glucose concentration may not have been available, but where neurological recovery following the return of plasma glucose to normal was considered sufficient evidence that the event was induced by a low plasma glucose concentration) to rely on reversal of such symptoms as evidence of neurological recovery. Similarly, Dr. Condarco noted that few details were available for most events to distinguish between instances where the patient "required assistance" as opposed to instances where the patient simply received some assistance. However, Dr. Condarco also noted that the she agreed that the events constituted, at a minimum, clinically significant events of hypoglycemia and that the design of the trial (including blinding of patients, investigator, sponsor, and EAC) minimized the potential for bias in the identification and classification of events.

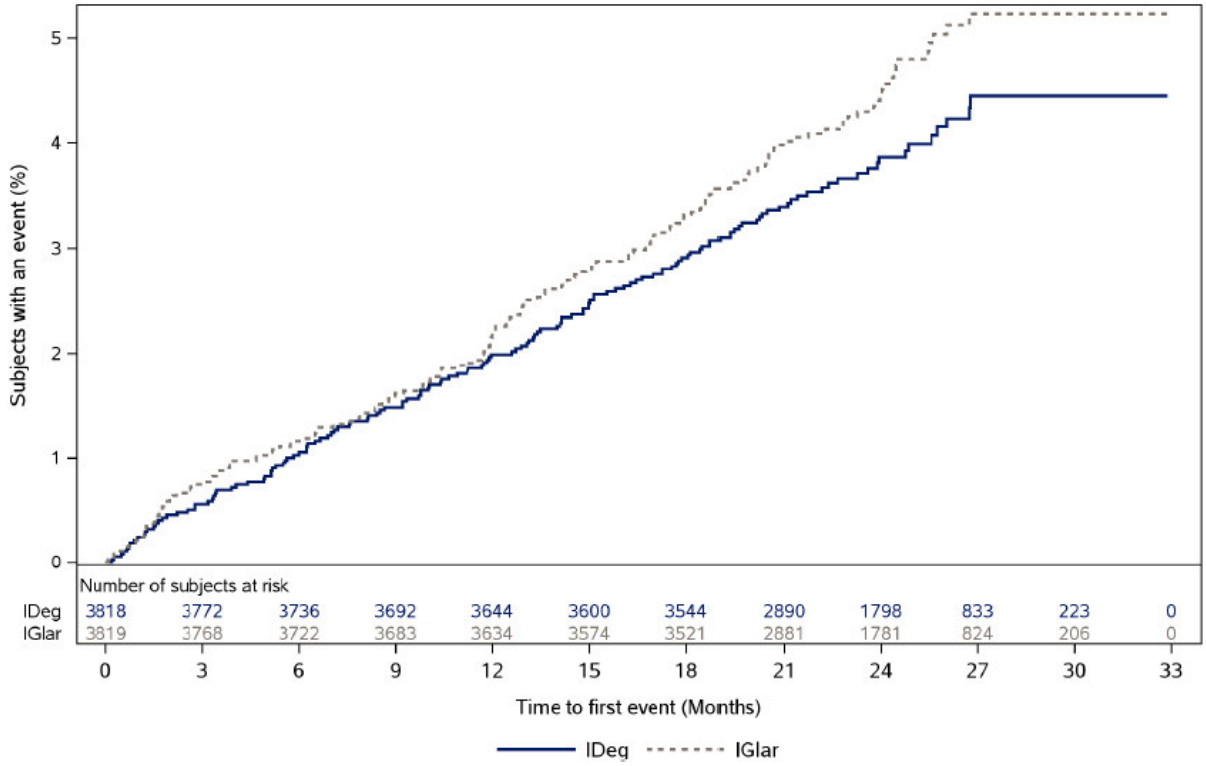
CDTL comment: I concur with the conclusion of Dr. Condarco that, while some ambiguity exists regarding whether all of the EAC confirmed events meet the definition of "severe hypoglycemia", the data demonstrate that a difference in the incidence of clinically significant events of hypoglycemia. Further, I believe it is not unreasonable to characterize these observed events as "severe hypoglycemia", despite acknowledging some limitations with the assessments.

7. Safety

As described above, Dr. Condarco concluded, and I concur, that the data from DEVOTE establishes that 1) insulin degludec as equivalent cardiovascular safety compared to insulin glargine in a population with high rates of cardiovascular disease and 2) insulin degludec has a lower event rate and patient incidence of severe hypoglycemia than insulin glargine. In addition to her review of the primary MACE and severe hypoglycemia endpoints, Dr. Condarco also reviewed all of the clinical data from DEVOTE from the point-of-view of safety. While the overall safety of insulin degludec had already been established at the time approval, the DEVOTE trial afforded the opportunity to evaluate further the safety profile over a mean patient observation period of 2 years.

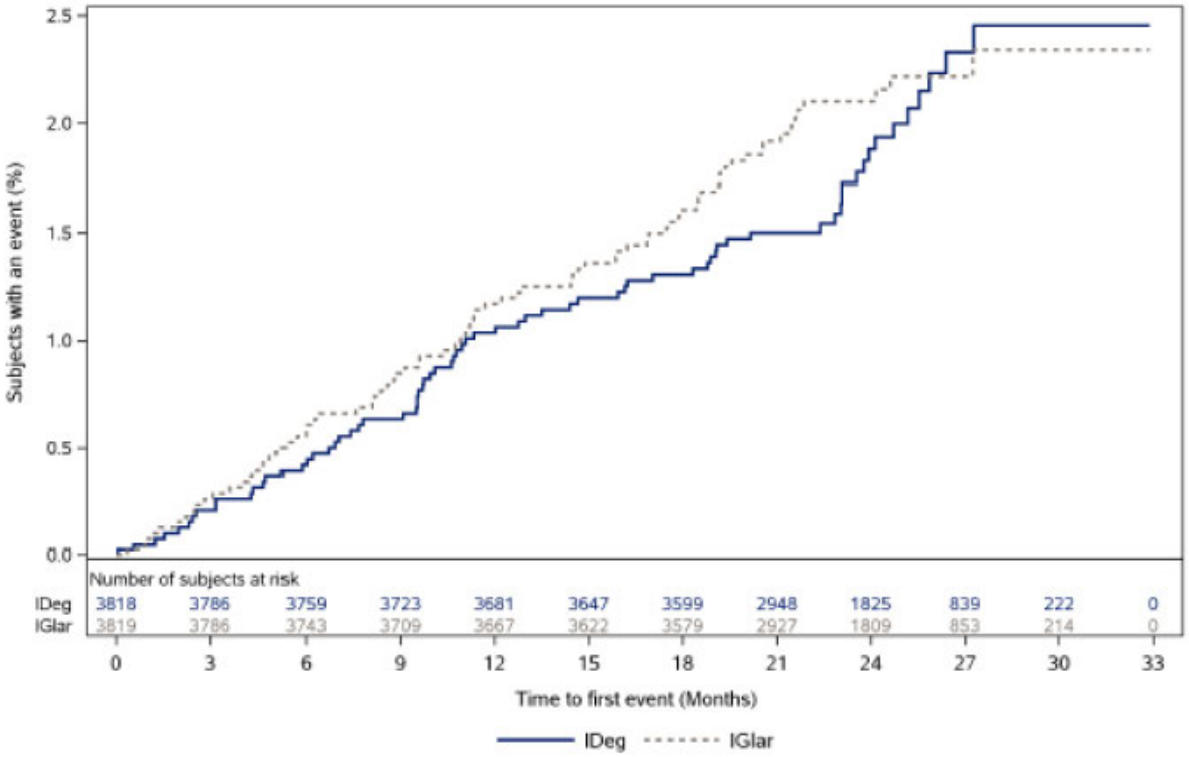
Beyond the evaluation of the primary MACE endpoint, Dr. Condarco's clinical review of the cardiovascular safety data considered the individual components of the MACE endpoint and the expanded 4-point MACE (CV death, non-fatal stroke, non-fatal MI, and unstable angina pectoris requiring hospitalization). In general, these exploratory analyses were consistent with the finding of the primary MACE outcome. For each component of the 4-point MACE safety endpoint, the point estimate hazard ratio favored insulin degludec over insulin glargine. Figure 7, Figure 8, and Figure 9 show Kaplan-Meier plots of time to first non-fatal MI, time to first non-fatal stroke, and time to cardiovascular death. These analyses are also consistent with the conclusion that insulin degludec is not associated with an unacceptable increase in cardiovascular risk compared to insulin glargine.

Figure 7: Time to first non-fatal MI - FAS



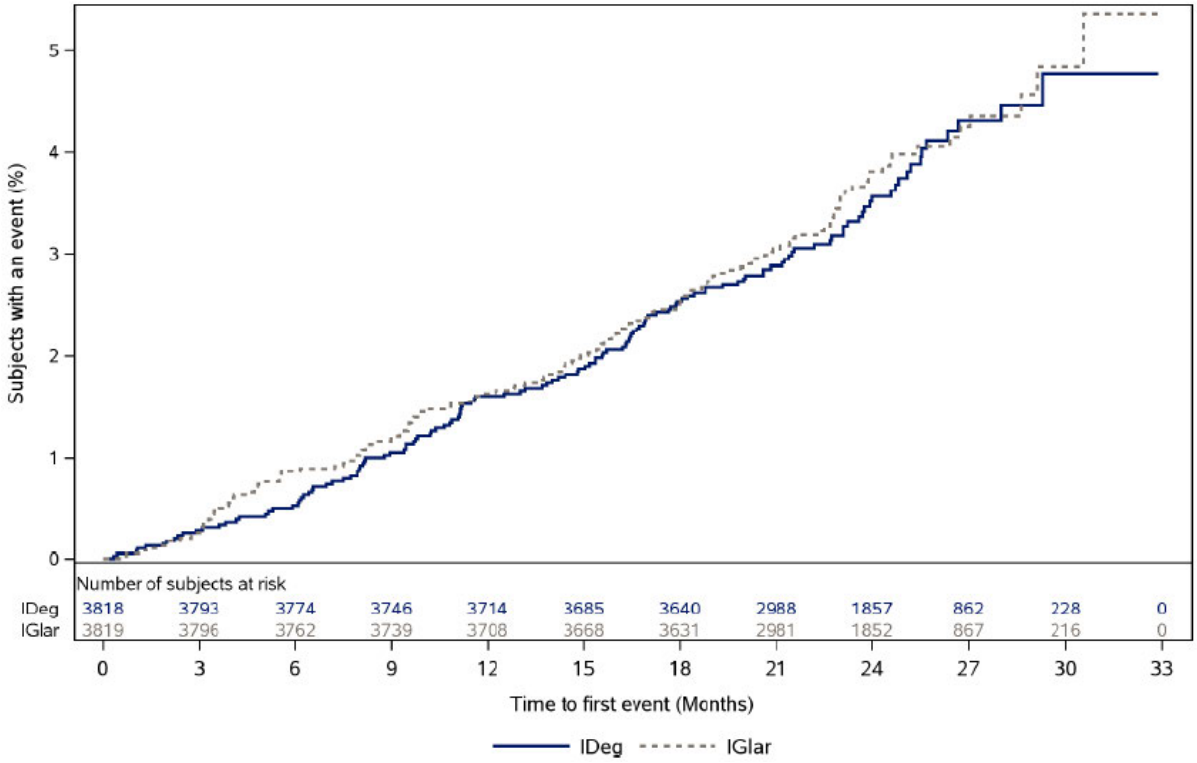
Source: DMEP clinical review

Figure 8: Time to first non-fatal stroke - FAS



Source: DMEP clinical review

Figure 9: Time to cardiovascular death - FAS



Source: DMEP clinical review

Other than the primary outcomes and additional exploratory endpoints related to cardiovascular safety and hypoglycemia, DEVOTE systematically collected safety data including serious adverse events (SAEs), adverse events (AEs) leading to discontinuation of the investigational product, and medication errors leading to an SAE.

Dr. Condarco's review also considered all cause death and non-cardiovascular death. Numerically, there were numerically fewer all cause deaths and non-cardiovascular deaths (as well as cardiovascular deaths) observed in the patients randomized to insulin degludec relative to those randomized to insulin glargine.

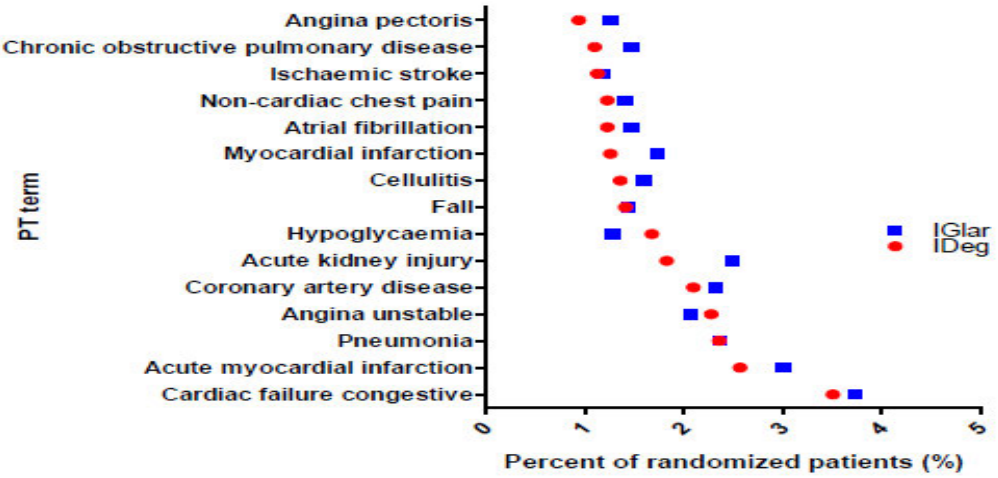
Table 7: Characteristics of EAC-adjudicated deaths - FAS

	IDeg			IGlar		
	N (%)	E	R	N (%)	E	R
FAS	3818			3819		
PYO	7568			7558		
Total deaths (all cause)	202 (5.3)	202	2.67	221 (5.8)	221	2.92
Cardiovascular deaths	97 (2.5)	97	1.28	106 (2.8)	106	1.40
Sudden cardiac death	57 (1.5)	57	0.75	55 (1.4)	55	0.73
Acute MI	14 (0.4)	14	0.19	22 (0.6)	22	0.29
Heart failure	13 (0.3)	13	0.17	11 (0.3)	11	0.15
Cerebrovascular event	6 (0.2)	6	0.08	13 (0.3)	13	0.17
Cardiovascular procedure	0	0	0	2 (0.1)	2	0.03
Cardiovascular hemorrhage	0	0	0	1 (0)	1	0.01
Other cardiovascular causes^*	7 (0.2)	7	0.09	2 (0.1)	2	0.03
Non-cardiovascular deaths	66 (1.7)	66	0.87	79 (2.1)	79	1.05
Pulmonary causes	9 (0.2)	9	0.12	12 (0.3)	12	0.16
Renal causes	4 (0.1)	4	0.05	3 (0.1)	3	0.04
Gastrointestinal causes	2 (0.1)	2	0.03	1 (0)	1	0.01
Hepatobiliary causes	0	0	0	4 (0.1)	4	0.05
Pancreatic causes	0	0	0	0	0	0
Infection (including sepsis)	20 (0.5)	20	0.26	21 (0.5)	21	0.28
Non-infectious (systemic inflammatory response, SIRS)	0	0	0	0	0	0
Hemorrhage that is neither CV bleeding or stroke	0	0	0	0	0	0
Non-CV procedure or surgery	0	0	0	0	0	0
Trauma	3 (0.1)	3	0.04	6 (0.2)	6	0.08
Suicide	0	0	0	2 (0.1)	2	0.03
Non-prescription drug reaction or overdose	0	0	0	0	0	0
Prescription drug reaction or overdose	0	0	0	0	0	0
Neurological (non – cardiovascular)	0	0	0	3 (0.1)	3	0.04
Malignancy	25 (0.7)	25	0.33	25 (0.7)	25	0.33
Other non-cardiovascular ¤Ω	3 (0.1)	3	0.04	2 (0.1)	2	0.03
Undetermined cause	39 (1.0)	39	0.52	36 (0.9)	36	0.48

Source: DMEP clinical review

Approximately 38.6% of patients randomized to insulin degludec experienced an SAE, compared to 39.7% of patients randomized to insulin glargine. Inspection at various MedDRA levels did not reveal notable differences in rates of SAEs across treatment arms for any category of event. At the level of Preferred Terms, incident rates of SAEs were generally slightly numerically smaller among patients randomized to insulin degludec; notable exception included the Preferred Terms of “acute myocardial infarction” and “hypoglycemia” (where event rates adjudicated by a dedicated endpoint committee revealed the opposite).

Figure 10: Preferred terms of SAEs occuring in at least 1% of patients



Source: DMEP clinical review

Similarly, no significant differences were observed in assessments of lipid laboratories, weight gain, vital signs, or renal function.

CDTL comment: I concur with Dr. Condarco, who concluded that the overall clinical safety outcomes were similar between treatment groups, with the exception of rates of severe hypoglycemic events.

8. Clinical Inspection Summary

The review from the Office of Scientific Investigations concluded that the inspectional findings support the validity of data as reported by the sponsor under the sNDA. The inspection comprised four domestic clinical sites and also the sponsor. No regulatory violations were found at three of the clinical sites and no regulatory violations were found at the sponsor; the classification for these sites and for the sponsor is No Action Indicated. The classification for the fourth clinical site (Dr. Woods) is Voluntary Action Indicated.

Dr. Kleppinger concluded, and I concur, that the regulatory violations identified are unlikely to significantly impact the primary safety and efficacy analyses of the application and that the data from the site is acceptable for use.

9. Advisory Committee Meeting

No new efficacy or safety issue rose to the level of requiring the input from an advisory panel. Therefore, an advisory committee meeting was *not* convened for this NDA.

10. Pediatrics

The Division determined that this application does not trigger the Pediatric Research Equity Act. Therefore, no pediatric studies under PREA are recommended.

11. Labeling

The data from DEVOTE provides compelling evidence that use of insulin degludec does not lead to an unacceptable increase in the incidence of MACE compared to the use of insulin glargine. In addition, the data from DEVOTE provides compelling evidence that the use of insulin degludec caused fewer hypoglycemic events than the use of insulin glargine in the patient population studied. Accordingly, the data in the sNDA submission supported minor changes to the Tresiba PI to Section 6.1 (ADVERSE REACTIONS) and to Sections 8.5 and 8.6 (SPECIAL POPULATIONS): these edits largely serve ensure that the overall PI is internally consistent, given the additional information introduced by more significant edits made to Section 14 (CLINICAL STUDIES), in which Section 14.4 (Safety Outcomes Trial) was added to present the data from DEVOTE.

The new Section 14.4 contains a description of DEVOTE (including trial design, patient population, MACE outcomes, and hypoglycemia outcomes), as reproduced below.

1 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

Drs. Condarco, Hamilton, Wang, and Andraca-Carrerra all reviewed and agreed with this new labeling. I concur with their conclusions.

CDTL comment: The new labeling, particularly the data as presented in Table 15 and Table 16 of the revised Tresiba PI, reflects the conclusions of the overall review that 1) the data from DEVOTE suffices to exclude a 30% increase in the incidence of MACE attributable to exposure to insulin degludec relative to exposure to insulin glargine and 2) insulin degludec was superior to insulin glargine in the context of DEVOTE for two measures of the incidence of severe hypoglycemia.

12. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

Approval

- Risk Benefit Assessment

The Applicant has submitted a prior approval supplement (PAS) containing clinical data from EX1250-4080 (DEVOTE). The Applicant designed and conducted the DEVOTE trial to

address a deficiency that resulted from the MACE signal observed in the original NDA submission for Tresiba (insulin degludec). Specifically, the CR letter stated "you will need to submit additional clinical trial data from a dedicated, double-blind, cardiovascular outcomes trial using glargine as the comparator. The trial should be powered to exclude an excess cardiovascular risk based on a composite of cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke (MACE)…" DEVOTE also incorporated incorporated secondary endpoints into the design of DEVOTE to show that the use of insulin degludec resulted in fewer hypoglycemia events compared to the use of insulin glargine in patients with T2D.

I agree with the conclusions of the statistical and clinical reviewers that the results from DEVOTE establish that insulin degludec is not associated with an unacceptable increase in MACE relative to insulin glargine. I also nconclude that PMR 2954-2 [To conduct a randomized, double-blind, active-controlled trial evaluating the effect of Tresiba (insulin degludec injection) on the incidence of major adverse cardiovascular events (MACE) in subjects with type 2 diabetes mellitus. The primary objective of the trial should be to demonstrate that the upper bound of the 2-sided 95% confidence interval for the estimated risk ratio comparing the incidence of adjusted MACE (non-fatal myocardial infarction, non-fatal stroke, cardiovascular death) observed with Tresiba to that observed in the comparator group in less than 1.3] has been fulfilled.

I also agree with the conclusions of the statistical and clinical reviewers that that insulin degludec was superior to insulin glargine with regards to the incidence of severe hypoglycemia in the context of the DEVOTE patient population. This finding was statistically significant, robust, and could not be explained by overall differences in glycemic control or insulin titration. However, I have not concluded that this finding from DEVOTE can be broadly extrapolated. (b) (4)

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

No new safety findings from this clinical development program prompt the need for a postmarketing risk evaluation and management strategies.

- Recommendation for other Postmarketing Requirements and Commitments

No new safety findings from this clinical development program prompt the need for a postmarketing requirements and commitments. PREA is not triggered by this NDA.

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/s/

PATRICK ARCHDEACON
03/23/2018

MARY T THANH HAI
03/24/2018
I concur with Dr. Archdeacon's assessment and overall recommendation.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203314Orig1s008

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	sNDA
Application Number(s)	203314
Priority or Standard	Standard
Submit Date(s)	May 26, 2017
Received Date(s)	May 26, 2017
PDUFA Goal Date	
Division / Office	DMEP/ODE II
Reviewer Name(s)	Tania A. Condarco, M.D.
Review Completion Date	February 16, 2018
Established Name	Insulin degludec
(Proposed) Trade Name	Tresiba
Therapeutic Class	Long-acting insulin analog.
Applicant	Novo Nordisk
Formulation(s)	Tresiba U-100
Dosing Regimen	Individualized dose administered subcutaneously once daily
Indication(s)	To improve glycemic control
Intended Population(s)	In adults with diabetes mellitus

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

During the first submission of the insulin degludec New Drug Application (NDA), on September 29, 2011, a cardiovascular signal was identified in a pre-specified meta-analysis aimed at assessing the cardiovascular risk [1]of insulin degludec. On February 8, 2013, the Division issued a Complete Response Letter to the Sponsor with a request for the Sponsor to conduct a dedicated cardiovascular outcomes trial to further assess the cardiovascular safety of insulin degludec.

DEVOTE was the cardiovascular outcomes trial which was agreed upon to assess insulin degludec's cardiovascular risk. On September 2015, insulin degludec, under the trade name Tresiba, was approved for marketing in the United States, after successfully meeting the 2008 Guidance's recommendation for a pre-marketing risk margin less than 1.8.[2]

The current submission includes the final results of DEVOTE. In this submission, insulin degludec ruled out cardiovascular harm with an upper bound of the two-sided 95% confidence interval below 1.3 as compared to insulin glargine. In addition, the trial met both of its secondary endpoints, showing a lower event rate and patient incidence of severe hypoglycemia for insulin degludec than insulin glargine, a pre-specified and blindly adjudicated endpoint. The efficacy findings were in the setting of the already established safety of both drug products. No additional safety concerns were identified in this review. Overall, the benefit-risk ratio favors the approval of this supplement for patients with type 2 diabetes mellitus; this recommendation is contingent on agreement on labeling. This supplement also fulfills PMR #2954-2.

1.2 Risk Benefit Assessment

The Benefit Risk Assessment of this review is based on the results of DEVOTE.

On May 26, 2017, Novo Nordisk submitted the prior approval efficacy supplement (PAS) which contained the results of the DEVOTE trial to NDA 203314 (for insulin degludec) to both fulfill the post-marketing requirement (PMR # 2954-2) and to include a hypoglycemia comparative safety claim in the labeling of insulin degludec as compared to insulin glargine.

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[1] Cardiovascular risk was based on MACE+, defined as a composite of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke and unstable angina pectoris and also based on a strict MACE definition, which included: cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke.
[2] 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

In my opinion, DEVOTE has shown that insulin degludec has equivalent cardiovascular safety when compared to insulin glargine in a population of mostly established cardiovascular disease. In addition, DEVOTE has shown that insulin degludec has a lower event rate and patient incidence of severe hypoglycemia as compared to insulin glargine, over a 2-year observation period.

Novo Nordisk was required to conduct a cardiovascular outcomes trial because there was an increased cardiovascular risk detected in the original insulin degludec application (submitted on September 2011) which resulted in a Complete Response of the application.[3] DEVOTE reflects the agreed upon cardiovascular outcomes trial designed to assess the cardiovascular risk of insulin degludec.

DEVOTE was a prospective, double-blind, randomized, active-controlled trial evaluating the effect of insulin degludec 100 U/mL compared to insulin glargine 100 U/mL, administered between dinner and bedtime, in conjunction to standard of care. The primary objective was to rule out the incidence of adjudicated major adverse cardiovascular events (MACE – defined in this study as a composite of cardiovascular death, non-fatal myocardial infarction or non-fatal stroke), in patients with largely established cardiovascular disease and type 2 diabetes mellitus (T2DM). In accordance with the 2008 Guidance for Industry,[2] DEVOTE was designed to rule out a pre-specified non-inferiority margin of 1.3, thereby ruling out a 30% relative increase in cardiovascular risk when compared to insulin glargine.

In addition, DEVOTE had two pre-specified and stratified efficacy secondary endpoints; the first was to show the superiority of insulin degludec as compared to insulin glargine for the number of adjudicated severe hypoglycemic events, the second was to show the superiority of insulin degludec as compared to insulin glargine for the patient incidence of adjudicated severe hypoglycemic episodes.

I discuss the benefits, limitations and risks in the DEVOTE trial by separating the discussion in the headings “Cardiovascular discussion” and “Hypoglycemia discussion” below.

Cardiovascular discussion
A total of 7637 patients with type 2 diabetes mellitus and largely established cardiovascular disease were randomized to insulin degludec or insulin glargine. After a median patient exposure of 1.8 years, 325 patients (8.5%) randomized to insulin degludec and 356 patients (9.3%) randomized to insulin glargine experienced a first adjudicated major adverse cardiovascular events. There were 4.29 and 4.71 MACE events per 100 years observed for insulin degludec and insulin glargine respectively, resulting in a hazard ratio of 0.91 (95% confidence interval 0.78; 1.06; p=0.209). This

[3] Refer to the DARRTs review of the original submission by Dr. Guettier and Dr. Bo Li. Of note, the CV data for the original submission was based on a meta-analysis of all available cardiovascular events accrued in 17 glycemic efficacy trials, and not from a dedicated study.

analysis excludes the possibility that insulin degludec is associated with an excess in cardiovascular risk of 30% over insulin glargine, a comparator basal insulin with no known cardiovascular risk.

The MACE findings are supported by the fact that 98% of patients completed the study (defined as patients who completed a follow-up visit or died during the trial) and by the low rate of unaccountable vital status (0.1%, or 8 patients). In addition, although not pre-specified as efficacy endpoints, the components of MACE and the composite 4-point MACE findings were consistent with the overall primary endpoint. These safety endpoints had hazard ratios comparing insulin degludec to insulin glargine below one with the 95% confidence interval crossing 1, thereby supporting the notion that there was no statistical difference in the cardiovascular risk comparing insulin degludec to insulin glargine.

It is notable that despite the hypoglycemia findings favoring insulin degludec as compared to insulin glargine (discussed below), there was only a slight numerical difference, favoring insulin degludec, in all-cause mortality between treatment arms. The all-cause death event rate was 2.67 and 2.91 per 100 years of observation for insulin degludec and insulin glargine respectively; in all, there were 19 more deaths in the insulin glargine arm than in the insulin degludec arm. The lack of a mortality difference between treatment arms may not be altogether surprising since the trial was not powered to detect this difference. For comparison, the ACCORD trial had an average of 3.5 years before a difference in death between treatment groups was detected between treatment arms.[4]

Hypoglycemia discussion
Hypoglycemia affects the quality of life of individual patients and has a significant public health impact. Data from the Centers for Disease Control and Prevention (CDC), show that in 2009 there were 298,000 emergency department visits for hypoglycemia for adults age 18 years or older in the United States.[5] Limiting the morbidity and mortality associated with hypoglycemia is an important aim in clinical practice.

DEVOTE captured192 fewer events that were confirmed as meeting the severe hypoglycemia definition for insulin degludec as compared to insulin glargine, resulting in an event rate of 3.70 and 6.25 per 100 years observed for insulin degludec and insulin glargine, respectively. The relative risk comparing insulin degludec to insulin glargine resulted in a rate ratio of 0.60 (95% confidence interval 0.48,0.76; p <0.001). This analysis corresponds to a 40% decreased in the rate of severe hypoglycemia when comparing insulin degludec to insulin glargine and has an absolute risk reduction of 2.55 events per 100 years of observation. This analysis suggests that 39 patients[6]

[4]Group TAtCCRiDS. Effects of Intensive Glucose Lowering in Type 2 Diabetes. New England Journal of Medicine 2008;358:2545-59
[5] https://www.cdc.gov/diabetes/statistics/hypoglycemia/fig1.htm
[6] NNT corresponds to the inverse of the absolute risk reductions per year of observation: 1/ 0.0255

needed to be treated for one year to prevent one episode of severe hypoglycemia. Or in other words, insulin degludec resulted in a ~40% reduction in severe hypoglycemia events and a ~26% reduction in proportion of patients affected as compared to insulin glargine.[7] For context, the American Diabetes Association Working Group on Hypoglycemia[8] regards a 10-20% reduction in severe (i.e. requiring assistance of another individual) hypoglycemia (in the proportion of patients and/or event rates) as a meaningful reduction.

The patient incidence rate for insulin degludec was also lower than insulin glargine. Sixty-five fewer patients experienced at least one adjudicated severe hypoglycemia events for insulin degludec as compared to insulin glargine. The estimated odds ratio was 0.73 (95% confidence interval 0.60; 0.89; p-value 0.001). The estimated odds ratio reflects a 27% reduced risk of experiencing at least one adjudicated event of severe hypoglycemia when treated with insulin degludec as compared to insulin glargine.

The glycemic data in DEVOTE suggest that the hypoglycemia findings were not explained by glycemic differences between the two arms. Throughout the duration of DEVOTE, the glycemic control was either equivalent (in HbA1c) or better (in fasting plasma glucose) when comparing insulin degludec to insulin glargine.

Furthermore, across multiple exploratory analyses (MedDRA queries, database analyses, time to event analysis), and across most subpopulation analyses the severe hypoglycemia results showed a lower patient incidence and event rate with insulin degludec when compared to insulin glargine. Findings were primarily driven by sites in the United States, the country with the largest number of randomized patients. These analyses were not explained by baseline differences or antidiabetic use. For instance, although bolus insulin use was associated with increased risk of severe hypoglycemia, accounting for the use of bolus insulin in the time to severe hypoglycemia did not explain the differences in treatment arms. Other differences, including slightly higher use of GLP-1 use post-baseline for IDeg as compared to IGlar was seen in a small proportion of the population but did not likely fully explain the hypoglycemia differences observed in DEVOTE.

Importantly, unlike previous trials (b) (4) (including the phase 3 trials in the original submission, (b) (4) DEVOTE's hypoglycemia findings were based on a clinically significant and specific definition of severe hypoglycemia: an episode requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions and during which plasma glucose concentration may not have been available, but where neurological recovery following the return of plasma glucose to normal was considered sufficient evidence that the event was induced by a low plasma glucose concentration.

[7] Event percent reduction: [(280-472)/472]*100, proportion of patients reduction: [(187-252)/252]*100
[8] Defining and Reporting Hypoglycemia in Diabetes. A report from the American Diabetes Association Workgroup on Hypoglycemia 2005;28:1245-9

Despite the hypoglycemia benefits noted above, there are some limitations to the findings. These limitations are included in the benefit risk assessment for transparency. I don't believe that these findings overwhelmingly undermine the overall hypoglycemia findings because these concerns do not change the overall trends in hypoglycemia, as discussed above. However, these limitations create some uncertainty in the overall findings due to a broader interpretation of the definition of severe hypoglycemia by the Event Adjudication Committee.

Among the limitations is that the patient incidence and event rates may have been somewhat inflated due to capture of hypoglycemia events that did not *strictly* meet the severe hypoglycemia definition. Despite choosing a specific definition of hypoglycemia, and blinded adjudication, only 21% of confirmed events had severe neuroglycopenic symptoms (i.e. seizure or unconsciousness or coma), with numerical imbalances still favoring insulin degludec. In fact, most of the reported symptoms were non-specific for severe hypoglycemia and included symptoms which do not strictly-speaking, characterize symptoms consistent with neuroglycopenia (i.e. the most common symptoms were confusion, sweating, and trembling).

Another concern with the hypoglycemia data is that some events had few details regarding whether patients '*required* assistance' or were assisted by a bystander for other reasons (i.e. it is not unusual for family members to aid a chronically ill family member who is having hypoglycemia symptoms). Evaluation of the severity of the symptoms and the '*requirement'* for assistance is not possible to ascertain for most of the cases that were confirmed as severe hypoglycemia.

Despite these limitations, I believe that for the most part, clinically significant events of hypoglycemia were captured. Elements that bolster the robustness of the results include the trial design, which minimized bias by ensuring blinding of patients, sponsor, investigators and the independent blinded Event Adjudication Committee. In addition, the relatively large size of the trial, the consistent hypoglycemia effect seen across trial sites, and subgroups and the persuasive statistical evidence of a beneficial effect support the findings. The hypoglycemia findings are in the setting of the already established risk profile of insulin degludec. There are no new safety findings identified.

The results from DEVOTE should not be used to infer a benefit in patients with type 1 diabetes. There is *insufficient* evidence to support these hypoglycemia findings in patients with type 1 diabetes mellitus. The meta-analysis of previously submitted phase 3 trials[9] suggested a hypoglycemia benefit only in patients with type 2 diabetes and no benefit in patients with type 1 diabetes (in fact, in the phase 3 trials, the hazard ratio crossed 1, thereby favoring insulin glargine). (b) (4)

[9] See discussion in section 2.6 Other Relevant Background Information

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None identified.

1.4 Recommendations for Postmarket Requirements and Commitments

None identified.

2 Introduction and Regulatory Background

2.1 Product Information

Insulin degludec (IDeg) is once-daily basal insulin approved for marketing on September 2015. IDeg is a basal insulin that after subcutaneous injection forms multi-hexamers creating a depot of insulin in the subcutaneous tissue. The IDeg monomers gradually separate resulting in a slow delivery of IDeg into the circulation.

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 pharmacological classes for the treatment of type 2 diabetes includes the following classes of therapies:

- Insulin and insulin analogs
- Sulfonylureas (SU)
- Biguanides
- Meglitinides
- Thiazolidinediones (TZDs)
- Inhibitors of alpha-glucosidase
- Analogues of Glucagon-like Peptide 1 (GLP-1)
- Synthetic analogues of human amylin
- Inhibitors of the enzyme dipeptidyl peptidase 4 (DPP4)
- Bile acid sequestrants
- Dopamine agonists
- Sodium-glucose co-transporter 2 (SGLT-2) inhibitors

2.3 Availability of Proposed Active Ingredient in the United States

Insulin degludec has been available in the United States since its approval in September 2015.

2.4 Important Safety Issues With Consideration to Related Drugs

There are three main adverse events associated with use of all insulin products: hypoglycemia, hyperglycemia and immunogenicity. Insulin degludec is labeled for all of these adverse events.

The sequela from hypoglycemia includes death, from untreated severe hypoglycemia. At the other extreme, under-dosing of insulin can result in life-threatening hyperglycemia typically characterized as diabetic ketoacidosis or hyperglycemic hyperosmolar state. Overtime chronic under-dosing can result in microvascular and macrovascular complications.

Use of insulin products can also result in immunogenic reactions.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

During the first review cycle (submitted on 9/11/11), the Sponsor submitted 2 NDAs for review: NDA 203314 (IDeg) and NDA 203313 (IDegAsp, 70%:30% fixed-ratio combination). Please refer to Dr. Guettier's primary review for pre-submission regulatory activity related to this first submission.

During the first review cycle, an increased cardiovascular (CV) safety signal was identified by the FDA reviewers. This risk was identified in a meta-analysis of sixteen phase 3 trials in the degludec and degludec/aspart programs.[10] This risk "estimated that use of degludec products could increase the composite risk of cardiovascular death, non-fatal MI, non-fatal stroke and unstable angina by 10% relative to active comparators."[11] An updated analysis with 17 trials, including the original trials, revealed a 30% increase in the composite risk of cardiovascular death, non-fatal MI, non-fatal stroke and unstable angina relative to active comparators.[12]
Figure 1**.**

[10] Per EMDAC briefing packet, page 210 "included 11 trials for IDeg (Studies 3579, 3580, 3582, 3583, 3585, 3586, 3668, 3672, 3718, 3724, and 3770) and 5 trials for IDegAsp (Studies 3590, 3592, 3593, 3594/3645, and 3597)."
[11] This estimate was based on 80 cases and approximately 5444 patient years of exposure. The uncertainty (i.e., 95% confidence interval) around the estimate of hazard was large and demonstrated that the true risk could be as high as 77% or alternatively that degludec products could lower cardiovascular risk by 32%. Information obtained from the EMDAC briefing packet.
[12] Hazard ratio1.30 (95% confidence interval:0.88, 1.93)

Figure 1 – MACE+analysis from the original submission

Table 3: Summary results of MACE+ in Updated Database (FAS, 7 and 30 Day Censoring)

	Censoring: 7 Days		Censoring: 30 Days	
	IDeg/IDegAsp (N = 5794) [PYE = 5153.6]	Comparator (N = 3461) [PYE = 2562.7]	IDeg/IDegAsp (N = 5794) [PYE = 5153.6]	Comparator (N = 3461) [PYE = 2562.7]
MACE+	95 (1.6) [18.4]	37 (1.1) [14.4]	99 (1.7) [19.2]	39 (1.1) [15.2]
Acute Coronary Syndrome	59 (1.0) [11.4]	25 (0.7) [9.8]	61 (1.1) [11.8]	25 (0.7) [9.8]
UAP *	25 (0.4) [4.9]	16 (0.5) [6.2]	25 (0.4) [4.9]	16 (0.5) [6.2]
MI	34 (0.6) [6.6]	9 (0.3) [3.5]	36 (0.6) [7.0]	9 (0.3) [3.5]
MI-STEMI	15 (0.3) [2.9]	3 (0.1) [1.2]	15 (0.3) [2.9]	3 (0.1) [1.2]
MI-NSTEMI	19 (0.3) [3.7]	6 (0.2) [2.3]	21 (0.4) [4.1]	6 (0.2) [2.3]
Stroke	24 (0.4) [4.7]	6 (0.2) [2.3]	25 (0.4) [4.9]	7 (0.2) [2.7]
CV Death	12 (0.2) [2.3]	6 (0.2) [2.3]	13 (0.2) [2.5]	7 (0.2) [2.7]

Results are reported as counts, (%), and [incident rate per 1,000 PYE]
* UAP is excluded from strict MACE.

Table 4: CPH Analysis Results for MACE+ based on Original and Updated Databases (FAS, 7 and 30 Day Censoring)

	Original Analysis		Updated Analysis	
	IDeg/IDegAsp (*N* = 5647)	Comparator (*N* = 3312)	IDeg/IDegAsp (*N* = 5794)	Comparator (*N* = 3461)
Censoring: 7 Days				
MACE+	53	27	95	37
HR (95% CI)	-	1.10 (0.68, 1.77)	-	1.30 (0.88, 1.93)
Censoring: 30 Days				
MACE+	56	27	99	39
HR (95% CI)	-	1.17 (0.73, 1.87)	-	1.29 (0.88, 1.89)

Table 5: CPH Analysis Results for MACE based on Original and Updated Databases (FAS, 7 and 30 Day Censoring)

	Original Analysis		Updated Analysis	
	IDeg/IDegAsp (*N* = 5647)	Comparator (*N* = 3312)	IDeg/IDegAsp (*N* = 5794)	Comparator (*N* = 3461)
Censoring: 7 Days				
MACE	39	15	70	21
HR (95% CI)	-	1.39 (0.76, 2.57)	-	1.67 (1.01, 2.75)
Censoring: 30 Days				
MACE	42	15	74	23
HR (95% CI)	-	1.50 (0.82, 2.75)	-	1.61 (1.00, 2.61)

Source: EMDAC background document, page 211-212

As part of the first cycle review, an advisory committee meeting was held on November 8, 2012, to discuss the safety and efficacy of both products. The Advisory Committee agreed that there was an increase in CV risk observed in most of the clinical trials, and although some of the results were not statistically significant, they were potentially concerning. The committee unanimously voted (12-yes, 0-No) that the Sponsor should conduct a cardiovascular outcomes trial.

A Complete Response letter (CRL) was issued by the FDA on February 8, 2013. The main reason for the CRL was due to the 'consistent and persistent signal of excess cardiovascular (CV) risk associated with insulin degludec and insulin degludec/aspart relative to comparators observed across multiple analyses'.

The path forward presented was for the Sponsor to conduct a dedicated, double-blind, cardiovascular outcomes trial using glargine as the comparator. The trial was to be powered to exclude an excess cardiovascular risk based on a composite of cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke (MACE).

A second issue addressed during the first review cycle and advisory committee was the Sponsor's hypoglycemia risk reduction claim. During the first review cycle, the Agency was unable to identify a unique benefit of insulin degludec and insulin degludec/aspart over existing insulin therapies to offset a potential adverse CV effect. The Sponsor was informed that to establish a hypoglycemia risk reduction claim, they would need to show a meaningful reduction of this risk over other available once-daily basal insulins that could be attributed to the unique PK/PD characteristics of insulin degludec.

On March 26, 2015 the Sponsor submitted the interim results of DEVOTE; refer to Dr. Li's statistical review for details. The interim database contained a total of 150 EAC-confirmed first MACEs. Per the FDA statistical review: "72 MACEs were observed among 3818 patients randomized to IDeg (3.9 MACEs per 100 patient years) and 78 events were observed among 3820 patients randomized to IGlar (4.2 MACEs per 100 patient year)." The cox proportional hazards model of MACE associated with IDeg compared to IGlar was 0.92 with a 95% confidence interval of 0.67 to 1.27. The interim results excluded the possibility that insulin degludec was associated with an excess in CV-risk of 80% over a comparator and resulted in the approval of insulin degludec and insulin degludec/aspart on September 25, 2015. As part of the approval, the following Post-Marketing Requirement (PMR) was issued:

PMR number 2954-2:
"Conduct a randomized, double-blind, active-controlled trial evaluating the effect of Tresiba (insulin degludec injection) on the incidence of major adverse cardiovascular events (MACE) in subjects with type 2 diabetes mellitus. The primary objective of the trial should be to demonstrate that the upper bound of the 2-sided 95% confidence interval for the estimated risk ratio comparing the incidence of adjudicated MACE (non-fatal myocardial infarction, non-fatal stroke, cardiovascular death) observed with Tresiba to that observed in the comparator group is less than 1.3."

2.6 Other Relevant Background Information

This section discusses the background information pertaining to the topic of hypoglycemia for insulin degludec in its development program. Trials comparing insulin

degludec to insulin glargine are highlighted in this section since these are the same drugs which are evaluated in the DEVOTE study.

On September 7, 2017 at the request of the Division, the Sponsor sent an overview of development program for hypoglycemia findings in trials that compared insulin degludec vs. insulin glargine for patients with type 1 and type 2 diabetes mellitus; see **Table 1** for T2DM and **Table 2** for T1DM programs. The highlighted trial names in the table refer to post marketing trials which systematically evaluated hypoglycemia.

Table 1 – Trials in Type 2 diabetes mellitus comparing IDeg to IGlar

Trial/ Region	Antidiabetic therapy at screening	R	Trial duration (weeks)	Randomized (N), or incl. in extension (N [%])		Completers[a] (%)		Non-completers[a] (%)		Exposed (%)		PYE/planned PYE (%)	
				IDeg	IGlar	IDeg	IGlar	IDeg	IGlar	IDeg	IGlar	IDeg	IGlar
Long-term, multi-center, double-blind, , parallel-group cardiovascular outcomes trial comparing IDeg (OD) and IGlar (OD) – DEVOTE													
4080 Global	Insulin-naïve or insulin-experienced incl. OADs	1:1	Event-driven Median-1.8 years	3818	3819	98.0	98.1	2.0	1.9	99.8	99.7	93.6[b]	92.7[b]
Multi-center, double-blind, two-period, crossover trial comparing IDeg (OD) and IGlar (OD) – SWITCH 2													
3998 US	Basal insulin ± BG-lowering agents	1:1	64 (32 IDeg; 32 IGlar)	671[c]	665[c]	90.2	89.9	10.4	10.5	100.0	100.0	88.8	87.2
Multi-center, open-label, parallel-group or crossover Phase 3 trials comparing IDeg (OD) and IGlar (OD)													
3579-main	Insulin-naive + met ± DPP4/SU/glinide	3:1	52	773	257	78.5	76.7	21.5	23.3	99.1	100.0	86.4	84.9
3643- ext.[d] Global			52	551 (71.3)	174 (67.7)	65.3	59.9	6.0	7.8	-	-	77.7	74.5
3582-main	Basal, BB or premix insulin ± OAD	3:1	52	755	251	81.9	84.1	18.1	15.9	99.7	100.0	89.2	91.7
3667- ext.[d] Global			26	566 (75.0)	191 (76.1)	71.4	72.9	3.6	3.2	-	-	84.4	86.3
3586 Pan-Asia	Insulin naive + OAD (–DPP4 or TZD)	2:1	26	289	146	89.3	93.2	10.7	6.8	98.3	100.0	92.5	96.4
3587 China	Insulin naïve + met	2:1	26	555	278	94.2	91.4	5.8	8.6	99.6	100.0	96.6	96.3
3668 Global	Basal insulin + met ±SU ± pioglitazone ± glinide	1:1:1	26	FF:229 OD:228	230	FF:88.6 OD:89.5	88.3	FF:11.4 OD:10.5	11.7	FF:230 OD:226 (N)	229 (N)	FF:92.6 OD:92.1	92.0
3672 Global	Insulin-naive + met ± DPP4	1:1	26	230	230	87.0	87.4	13.0	12.6	99.1	99.1	92.8	93.3
3943 US	Insulin-naive + OAD	1:1	16 each in 2 periods	140	142	97.1	95.8	2.9	4.2	100.0	100.0	95.1	95.6

[a] In the extension trials, the proportion of completers/non-completers is out of the randomized number of patients
[b] PYO/planned PYO for DEVOTE
[c] Represents the number of patients exposed. The full analysis set constituted 720 patients and 7 patients withdrew before exposure. Due to the cross-over design and drop-outs in treatment period 1, all patients in the full analysis set could not initiate treatment.
[d] All subjects who completed the main trial and were found eligible for the extension trial were encouraged to participate.
Abbreviations: BB, basal-bolus; BG, blood glucose; DPP4, dipeptidyl peptidase 4 inhibitor; FF, fixed flexible; IDeg; insulin degludec; IGlar, insulin glargine; met, metformin; N, number of patients; OAD, oral anti-diabetic drug; OD; once-daily; PYE, patient years of exposure; PYO, patient years of observation; R, randomization ratio: SU, sulfonylurea; T2DM, type 2 diabetes mellitus; TZD, thiazolidinedione.

Source: NDA 203314 "follow-up to discussion with the FDA on July 5, 2017" document dated September 7, 2017, table 2

Table 2 – Trials in Type 1 diabetes mellitus comparing IDeg to IGlar

Trial/ Region	Antidiabetic therapy at screening	R	Trial duration (weeks)	Randomized (N), or incl. in extension (N [%])		Completers[a] (%)		Non-completers[a] (%)		Exposed (%)		PYE/planned PYE (%)	
				IDeg	IGlar	IDeg	IGlar	IDeg	IGlar	IDeg	IGlar	IDeg	IGlar
Double-blind, two-period, crossover trial comparing IDeg (OD) and IGlar (OD) – SWITCH 1													
3995 Global	Basal-bolus or CSII	1:1	64 (32 IDeg; 32 IGlar)	454[b]	460[b]	89.0	88.0	11.0	12.2	100.0	100.0	84.5	84.8
Multi-center, multinational, parallel, open-label Phase 3 trials comparing IDeg (OD) and IGlar (OD)													
3583-main	Basal-bolus	3:1	52	472	157	85.6	87.3	14.4	12.7	100.0	98.1	88.7	89.6
3644- ext. Global			52	351 (74.4)	118 (75.2)	69.9	72.0	4.4	3.2	-	-	82.2	82.7
3770-main Global	Basal-bolus or premix insulin	1:1:1	26	FF:164 OD:165	164	FF: 84.1 OD: 84.2	92.7	FF: 15.9 OD: 15.8	7.3	FF: 100.0 OD: 100.0	98.2	FF: 88.6 OD: 92.1	95.5
3770-main- ext.[c] Global	Basal-bolus or premix insulin	2:1	52	329[d]	164	67.8	74.4	4.9	6.7	100.0	98.2	80.4	86.4

[a] In the extension trials, the proportion of completers/non-completers is out of the randomized number of patients.
[b] Represents the number of patients exposed to treatment. The full analysis set constituted 501 patients and 1 patient (listed as a non-completer) was withdrawn before exposure to any treatment. Due to the cross-over design and drop-outs in treatment period 1, all patients in the full analysis set could not initiate treatment.
[c] All patients completing the main trial period were invited to participate in the trial. Number of patients (%) entering the extension phase: IDeg, 239 (72.6); IGlar, 133 (81.1%).
[d] Represents the combined number of patients in the IDeg FF and IDeg OD arms.
Abbreviations: CSII, continuous subcutaneous insulin infusion; ext, extension phase; FF, fixed flexible; IDeg, insulin degludec; IGlar, insulin glargine; OD, once-daily; PYE, patient years of exposure; R, randomization ratio; T1DM, type 1 diabetes mellitus.

Source: NDA 203314 "follow-up to discussion with the FDA on July 5, 2017" document dated September 7, 2017, table 3

The hypoglycemia findings of the phase 3 efficacy and safety trials, submitted in the original submission, were discussed in the November 2012 EMDAC meeting. The following issues regarding the hypoglycemia findings were discussed at that time:

- Open label trials which were susceptible to bias
- Reliance on a point of care device
- Exclusion of population of patients at increased risk of having hypoglycemia
- Did not show that hypoglycemia risk reduction led to better glycemic control based on HbA1c reduction from baseline or proportion of patients achieving HbA1c target
    - Lack of consistent trends of hypoglycemia across hypoglycemia definitions, as shown in **Table 3.**
    - There was a lack of clear benefit in the most susceptible population: type 1 diabetes mellitus, with higher withdrawal rates due to hypoglycemia in the T1DM trials when randomized to IDeg than comparators
    - Numerically, T1DM patients were more likely to have at least one event of hypoglycemia and more numerous events of hypoglycemia per exposure time when randomized to IDeg than comparator

Table 3 – Hypoglycemia findings in Phase 3 trials metanalysis

	Rate Ratio (95% CI)	
	T1DM	**T2DM**
Novo confirmed hypoglycemia	1.11 (0.94, 1.31)	0.84 (0.76, 0.93)
Nocturnal confirmed hypoglycemia	0.85 (0.68, 1.05)	0.69 (0.59, 0.81)

Severe hypoglycemia	1.06 (0.65, 1.73)	0.74 (0.40, 1.36)
Documented hypoglycemia	1.12 (0.98, 1.29)	1.01 (0.94, 1.10)
*Rate ratios were estimated with a negative binomial model within each subgroup adjusting for: trial, age, gender, insulin at baseline, treatment and treatment by type of diabetes interaction. Source: Dr. Andraca-Carrera slide, EMDAC meeting Novmeber 8, 2012.		

Following the November 2012 EMDAC meeting and February 2013 Complete Response Letter, (b) (4)

(b) (4)

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

This section addresses the evaluation of the trial's integrity as evaluated by the Sponsor, and by the FDA. At the end of this section, the reviewer also presents an assessment of unblinded patients in the trial to evaluate for any differential unblinding by treatment groups.

Internally, the Sponsor had additional safeguards to preserve the integrity of the trial including:

- Monitors performing site visits to ensure protocol adherence, documentation and data verification. In total 12 external inspections and 119 internal audits were performed by the Sponsor.
- An external independent DMC performed ongoing and independent evaluation of accumulated data from the trial.

The FDA evaluated the submission's integrity by review of the changes in trial conduct, site inspections and evaluation of protocol deviations.
The following sites were selected for inspection by the Office of Scientific Investigations (OSI):

- Robert Wood/ Site 761/Kentucky Ranked #13. Enrolled 28. Higher than average efficacy. Has never been inspected. Old complaint (closed).
- James Thrasher/ Site 928/ Arkansas. Ranked #14. Enrolled 44. Very low number of protocol violations (may signal poor monitoring). Has never been inspected.
- John Agaiby/Site 763/ Wisconsin. Ranked #31. Enrolled 18. Fairly large safety numbers. Previous complaint stated that sub-PI was signing name to documents. Has never been inspected.
- Ronald Harris /Site 942. Ranked #54. He had a large number of both positively adjudicated severe hypo events/patients. He has never been inspected.

In addition to these site inspections, the Sponsor was inspected to further evaluate the unauthorized access of unblinded data of the DEVOTE interim analysis by a Novo Nordisk employee.[13] The FDA was informed of this unauthorized access on October 17, 2016, via an e-mail communication. This communication stated that because of a manual publishing error, 49 un-authorized Novo Nordisk employees within the Regulatory Affairs Department had access to the restricted sequences from October 3, 2016 (when the manual error occurred) to October 11, 2016, when the error was identified. The Sponsor queried all 49 employees with potential access to the restricted sequences and determined that one employee saw unblinded data. The employee was reassigned to other responsibilities (not related to the degludec project) and was physically separated from the degludec project colleagues until the DEVOTE database was locked. The employee was added to the DAMP and signed confidentially documents to ensure that she did not disclose any unblinded information.

In response to the Sponsor's e-mail, OSI sent an information request to the Sponsor for further details. The Sponsor responded to the information request on October 21, 2016.[14] This response addressed the following:

- The access to unblinded interim results of DEVOTE occurred due to a publisher (i.e., Publishers linked, compiled and published documents containing unblinded

[13] Report was communicated to the Division via e-mail on October 17, 2016, and formally submitted on October 18, 2016 \\CDSESUB1\evsprod\IND076496\0557
[14] Response is located in \\CDSESUB1\evsprod\NDA203314\0105\m1\us\response-ir-20161017.pdf

data in the eCTD structure and submitted these to the FDA) inadvertently selecting the application folder instead of the sequence to the appropriate user group—this step made the unblinded sequence available to the unauthorized Regulatory Affairs user group. The error was made by a new hire when uploading new sequences in the Novo viewing tool on October 3, 2016. The Sponsor conducted employee interviews and determined that one employee (working in Denmark as a Regulatory Affairs Global Regulatory Lead in the Long Acting Insulin Projects area) viewed unblinded information from the interim analysis and viewed the MACE hazard ratio.

- The sponsor determined that 49 employees had access to the restricted NDA sequences based on the access to the system. The employees were queried (via email) regarding their access to the restricted sequence (the system does not provide an audit trail of access of the documents), and only one admitted to having accessed the unblinded data.

Because of this event, the Sponsor retrained publishers responsible for US submissions and added an additional cross-check by a second publisher until the data base lock of DEVOTE.

Reviewer's comment: The February 9 Clinical Inspection Summary in DARRTS states that "based on the inspection of the four clinical sites and the sponsor, the inspectional findings support validity of data as reported by the sponsor under this sNDA." With regards to this possible unblinding, the inspection revealed that "interviews with sponsor staff and review of documents did not indicate that there were any other staff who inappropriately reviewed the interim analysis data. Sponsor took appropriate corrective actions and put into place preventive actions to avoid a similar event in the future."

An assessment of differential unblinding by treatment groups was also evaluated. The Sponsor was asked to submit a dataset containing the subjects that were unblinded to treatment. Review of this dataset revealed that 43 (1.1%) vs. 39 (1.0%) patients using IDeg vs. IGlar respectively were unblinded during the trial. Of these patients, 3 patients had the blind broken by the investigator during the trial.[15] The remaining patients had the blind broken by the Sponsor for SUSAR submission. Review of PT terms of the adverse event which resulted in unblinding is shown in the appendix, **Table 65**; PT categories were varied with few patients in each PT term (i.e. each PT term had less than 10 patients).

Reviewer's comments: There was no evidence of differential unblinding between treatment arms which could be expected to significantly impact the overall trial findings.

[15] Subject ID (b) (6) due to hospitalization for sepsis (on IDeg); subject ID (b) (6) due to reporting acute coronary syndrome (on IGlar); subject ID (b) (6) reported due to pulmonary embolism (on IGlar).

3.2 Compliance with Good Clinical Practices

The trial was conducted in accordance with the protocol, Declaration of Helsinki, International Conference on Harmonization (ICH) Good Clinical Practice (GCP) and to FDA 21 Code of Federal Regulations (CFR) 312.120 in the United States (US). Prior to trial start, the protocol and patient information were reviewed and approved according to local regulations by appropriate health authorities and by an Independent Ethics Committee/Institutional Review Board.

3.3 Financial Disclosures

Refer to **Table 63** in the appendix for specific details regarding the disclosure of investigators.

Seventy-four of the 2469 total investigators (~3%) had disclosable information. 1209 (15.8%) patients were randomized in sites where investigators had disclosable financial information. Of the identified investigators with disclosable information, 25 investigators had disclosable payments of $100,000 or more. These investigators and the sum of money received in addition to the number of patients randomized are show in **Table 64**.

Despite the potential for bias from financial contribution, the trial design (i.e. double blinded trial design), and the use of a blinded event adjudication committee, decreases the potential bias.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

There was no new information included in this supplement pertaining to this section of the review.[16]

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

The data for this review were derived from a single trial, listed below:

DEVOTE: A trial comparing cardiovascular safety of insulin degludec versus insulin glargine in subjects with type 2 diabetes at high risk of cardiovascular events.

[16] The following sections have been omitted from this review, since there is no information pertinent to each section: 4.1 Chemistry Manufacturing and Controls, 4.2 Clinical Microbiology, 4.3 Preclinical Pharmacology/Toxicology, 4.4 Clinical Pharmacology, 4.4.1 Mechanism of Action, 4.4.2 Pharmacodynamics, 4.4.2 Pharmacodynamics, 4.4.3 Pharmacokinetics.

5.2 Review Strategy

The review of the DEVOTE results was performed by reviewing the clinical trial report, study protocols, Statistical Analysis Plan, Data Monitoring Committee charter and minutes (open and closed), Steering Committee Charter and minutes, Event Adjudication Committee charter and minutes. In addition to the documents reviewed, the reviewer also used the datasets submitted with the application to further characterize pertinent safety concerns (as discussed through the review). For questions pertaining to the data or Sponsor's results, the reviewer queried the Sponsor for additional information.

5.3 Discussion of Individual Studies/Clinical Trials

The Sponsor submitted DEVOTE, also referred to as Trial EX1250-4080, to meet the postmarketing requirement 2954-2. This postmarketing requirement asked that the Sponsor perform a trial to exclude a 30% excess cardiovascular risk, as delineated in the 2008 CVOT Guidance.[2]

Protocol amendments: Protocol amendments occurred locally (i.e. affecting sites specific countries) and globally (affecting all sites). There were two local amendments (Japan- described the transcribing of all AEs in the eCRF; and Mexico –included the number of patients to be recruited). There was one global protocol amendment (i.e. affecting all trial sites) which included the following changes:

- Clarification on how to document and evaluate eligibility and treatment continuation
    - The protocol addendum accepted inclusion criteria to be based on medical history, rather than from medical records.
- Additional secondary endpoints and statistical considerations
    - The following endpoints were added: adverse events leading to discontinuation of investigational product, and analyses of change from baseline for biochemistry and hematology assessments.
- The process for external evaluation of hypoglycemia was clarified.
    - Severe hypoglycemia was added an event to be adjudicated
        - Initially, the protocol stated that all reported events of severe hypoglycemia were to be sent to an expert classification – this language was changed to state that episodes of hypoglycemia were sent to be adjudicated by the Event Adjudication Committee.

Study Title: DEVOTE: A trial comparing cardiovascular safety of insulin degludec versus insulin glargine in subjects with type 2 diabetes at high risk of cardiovascular events

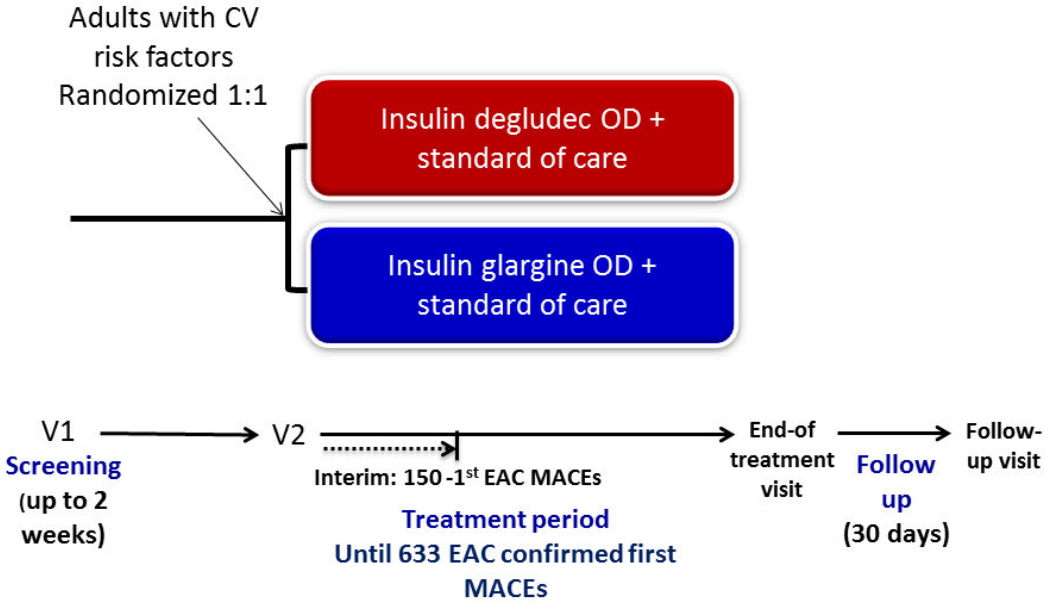
Primary objective: to confirm the cardiovascular safety of insulin degludec compared to that of insulin glargine.

Secondary objectives: to assess efficacy of insulin degludec on markers of glycemic control and to assess safety on other parameters in subjects with type 2 diabetes at high risk of cardiovascular events.

Trial sites: The trial was conducted at 438 sites in 20 countries: Algeria: 6 sites; Argentina: 4 sites; Brazil: 10 sites; Canada: 6 sites; Croatia: 5 sites; Greece: 6 sites; India: 26 sites; Italy: 10 sites; Japan: 8 sites; Republic of Korea: 4 sites; Malaysia: 8 sites; Mexico: 7 sites; Poland: 8 sites; Romania: 4 sites; Russian Federation: 20 sites; South Africa: 15 sites; Spain: 6 sites; Thailand: 6 sites; United Kingdom: 8 sites; United States: 271 sites.

Study design: Event driven, multi-center, multi-national, randomized 1:1, double blinded, parallel group, controlled trial comparing insulin degludec (U100) to insulin glargine (U100), when added to standard of care in patients with type 2 diabetes, at high risk of cardiovascular events; see **Figure 2**.

Figure 2 – DEVOTE trial design



Abbreviations: CV: cardiovascular; EAC: event adjudication committee; MACE: Major adverse cardiovascular event; OD: daily; V1: screening visit; V2: randomization and start of treatment

Source: Figure 9-1, CSR, page 47

Trial duration:
The trial was event-driven and was to continue until at least 633 first EAC confirmed 3-component major adverse cardiovascular events (comprising cardiovascular death, non-fatal myocardial infarction or nonfatal stroke) accrued.

After 150 positively adjudicated events were collected, an interim analysis was performed to assess for non-inferiority of IDeg to IGlar for the primary endpoint. Refer to the clinical review, dated August 31, 2015 (in DAARTS), for the review of the interim analysis for DEVOTE.

For each patient, the trial duration was estimated to be a *maximum* of 60.5 months.[17] The first day of trial closure was referred to as the trial stop date (May 30, 2016). From this date, all subsequent site visits were to be carried out as end-treatment visits. For patients who prematurely discontinued treatment with investigational product (IMP), a combined end-treatment and follow-up visit could be performed (starting on 29 June 2016, when the follow-up visits could be scheduled for all patients).

The trial closure was initiated on May 30, 2016 when the 633 MACE events were met. This date was the earliest possible end of treatment and follow up visit dates for any randomized patient.

Reviewer's comments: DEVOTE is an entirely event driven trial, which is somewhat different from other CVOTs, which also have a minimum trial duration component.

Inclusion/Exclusion criteria[18]:

The inclusion and exclusion criteria are shown in **Table 4**. Overall, the inclusion criteria aimed at including patients with poorly controlled blood glucose, or in need of basal insulin and with either previous cardiovascular disease or risk factors for cardiovascular disease. Exclusion criteria focused on excluding patients with advanced medical conditions, previous malignancy, or patients with recent cardiovascular events.

In order to enroll a population with sufficient cardiovascular risk, the Sponsor stopped the randomization of "patients with Age ≥ 60 years at screening and at least one risk factor (in criteria 5b)" when 1500 of these patients were enrolled.

Reviewer's comment: the limited enrollment of patients age≥ 60 with risk factors, ensured that this population made up a maximum of 20% of the total randomized patients (i.e. 1500 of the expected 7500 randomized patients), and thus would result in the enrollment of patients with more advanced cardiovascular disease. This approach likely shortened the trial duration as patients with more advanced disease are likely to have more cardiovascular events than patients with less

[17] With a screening period of up to 2 weeks, treatment period of up to 59 months and a post treatment follow up of 30 days.
[18] The investigator determined if there was sufficient evidence to ensure eligibility of a patient based on the patient's medical history or decided if additional medical records were needed.

advanced disease. For context, a similar approach was performed by Novo Nordisk in the LEADER trial.

Table 4 – Inclusion and exclusion criteria

Inclusion criteria	
Informed consent in men or women with type 2 diabetes and	
HbA1c*	≥7% or <7% and insulin treatment corresponding to ≥20 units/day of basal insulin
Antidiabetic Tx.	Treatment with ≥1 oral or injectable anti-diabetic agent(s)
CV risk "criteria 5"	**a) Age ≥ 50 years at screening and at least one of the below conditions:** 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 pectoris 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 kidney disease corresponding to glomerular filtration rate 30 – 59 mL/min/1.73m2 per CKD-Epi *OR* **b) Age ≥ 60 years at screening and at least one of the below risk factors:** i. microalbuminuria or proteinuria^ j. hypertension and left ventricular hypertrophy by ECG or imaging k. left ventricular systolic and diastolic dysfunction by imaging l. ankle/brachial index < 0.9
Exclusion criteria	
Recent CV event	An acute coronary or cerebrovascular event in the previous 60 days
Planned procedure	Planned coronary, carotid or peripheral artery revascularization
Advanced heart/renal disease	- Chronic heart failure NYHA class IV - Current hemodialysis or peritoneal dialysis or eGFR < 30 mL/min/1.73 m2 per CKD-Epi
Other advanced disease	-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
Other	- Known or suspected hypersensitivity to trial products or related products - Female of child-bearing potential who is pregnant, breast-feeding or intends to become pregnant or is not using adequate contraceptive methods - Simultaneous participation in any other clinical trial of an investigational medicinal product. Participation in a clinical trial with stent(s) is allowed. -Receipt of any investigational medicinal product within 30 days before randomization. **Brazil:** Receipt of any investigational medicinal product within one year before randomization unless there is a direct benefit to the subject at the investigator´s discretion - Current or past (within the last 5 years) malignant neoplasms (except basal cell and squamous cell skin carcinoma) - Any condition that in the investigator's opinion would make the subject unable to adhere to the initial trial visit schedule and procedures

*The most recent available HbA1c, measured within the last three months was to be used. HbA1c measured at a laboratory or by a health care professional could be used. If HbA1c was not measured recently a new test was needed. Documentation of HbA1c is not needed for subjects on pre-trial insulin treatment corresponding to ≥ 20 U/day of basal insulin.
^refer to appendix, **Figure 47** for the provided guidance regarding microalbuminuria /macroalbuminuria

Reviewer's comments: the inclusion/exclusion criteria are consistent with the criteria used by other, previously reviewed cardiovascular outcomes trials in the Division and were in line with the FDA's previous recommendations. In general, high cardiovascular risk patients were enrolled (in accordance with the Diabetes Guidance, [2] while excluding potentially vulnerable patients.

The criteria were also consistent with the FDA advice in the Type A, End of Review Meeting.[19] In this communication, the Division expressed that adequate exposure to insulin should be ensured. the trial should enroll patients who require at a minimum 20 units of insulin per day. In addition, the Division recommended that titration of insulin should be done according to the same glycemic target as were used in the phase 3 programs.

Withdrawal from trial vs. discontinuation of investigational product:

Similar to other CVOTs, DEVOTE made a distinction between patient withdrawal and the discontinuation of investigational product. Patients could withdraw from the trial at any time by withdrawing consent. Patients who withdrew would still be followed for MACE-related outcomes until the conclusion of the trial (if the patient accepted being contacted).

Discontinuation (permanent or temporary) of treatment with investigational product did not lead to withdrawal from the trial.

Study procedures:
Refer to **Table 71,** in the appendix, for a comprehensive trial flow chart. Patients attended visit 1 (screening visit) to assess their eligibility, based on the inclusion/exclusion criteria (discussed above) and informed consent was signed. At visit 2, eligible patients were randomized 1:1 to IDeg or IGlar.

Patients were to attend the site at one and two weeks after randomization and every month during the first 6 months. Thereafter, patients were to attend the site every third month and have monthly phone contacts with the investigator between site visits. To facilitate phone contact, in five out of 20 countries (outside the U.S.), some patients were provided with a mobile phones and prepaid phone cards. Of note, these phones were not used to record SMPG results or to capture adverse events.

[19] Reference: meeting minutes for type A meeting on April 4, 2013

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 and ensuring vital status was accounted. For patients who stopped treatment with investigational product, the end of treatment visit could occur on the same date as the follow up visit.

Patients were asked about adverse events (AE) at every site contact. AEs that were serious (SAEs) or that led to discontinuation of investigational drug were recorded. See below for further discussion on the capture of AEs.

Treatments:
Treatments included investigational and non-investigational products.

- **Investigational products:**
  - **Basal insulin:**
    - Insulin degludec (IDeg), 100 U/mL, 10 mL vial or
    - Insulin glargine (IGlar), 100 U/mL, 10 mL vial
  - Was to be administered subcutaneously. Rotation of the injection site within a region (thigh, upper arm, abdominal wall) was recommended
  - The time of administration was between dinner and bedtime
- **Non-investigational products:**
  - **Bolus insulin:** could be replaced with insulin aspart; 100U/mL, 3mL prefilled injector pen, FlexPen (free of charge and provided with the investigational product) for patients on bolus insulin prior to trial; or was started if patient was on premix/biphasic insulin (at investigator's discretion). Of note, bolus insulin was to be injected according to the local label.
  - **Other current antidiabetic therapy:** (other than basal insulin) was continued as per pre-trial

The following auxiliary supplies were provided by the sponsor: syringes, needles, FlexPen needles (if FlexPen dispensed), blood glucose meters, including lancets, plasma calibrated test strips and control solution.

Concomitant medications were defined as medications other than investigational medications, taken during the trial. Cardiovascular diseases and risk factors were to be treated according to local standard of care, at the investigator's discretion.

Concomitant medications taken to treat SAEs, diabetes and cardiovascular related disease were transcribed to the CRF.

Adjustments to insulin dose at randomization

To optimize glycemic control the investigators were provided with the guidelines in **Table 5** to adjust insulin doses. Insulin naïve patients started basal insulin at 10 units, while patients on previous daily basal insulin or bolus insulin were switched unit-to-unit

to the basal investigational product or aspart insulin respectively. For patients on premix insulin/biphasic insulin administered at least twice a day, it was recommended to decrease the investigational basal insulin dose by 20-30% and change regimen to daily administration.

Table 5 – Recommended adjustments to insulin regimen at randomization

Population	Recommendations
Insulin naïve	10 Units OD between dinner and bedtime
Switch from previous basal insulin	• If on OD basal insulin→ switch unit to unit dose • If on BID (or more) basal insulin → lower total basal dose by 20-30% and change regimen to OD
Switch from previous bolus insulin	Unit to unit switch to insulin aspart
Switch from previous premix/biphasic insulin regimen	• If on OD premix/biphasic insulin→ calculate basal and bolus component and switch unit-to-unit for basal and bolus insulin* • If on BID (or more) premix/biphasic insulin→ reduce the total basal component by 20-30% when switch to investigational product. Bolus component should be switched to insulin aspart*
*bolus insulin is given at the most appropriate meal the investigator's discretion BID: twice a day; OD: daily Source: Reviewer derived from information in CSR	

Titration of insulin dose during the trial
Adjustments to the insulin dose was ultimately based on the investigators' clinical judgement, which considered previous episodes of hypoglycemia and/or hyperglycemia.

Figure 3 provides an overview of recommended insulin adjustments during DEVOTE. Adjustments to basal insulin and bolus insulin were done weekly. The adjustments of the basal insulin dose was based on the lowest of the of three pre-breakfast SMPG values measured preferably 2 days prior to titration and on the day of titration. There were two titration algorithms for basal insulin. The original titration algorithm had a pre-breakfast SMPG goal between 71-90 mg/dL; while the alternative titration algorithm had a SMPG goal of 91-126 mg/dL.

The alternative titration algorithm for basal insulin was developed by the Steering Committee to provide investigators an option for less-stringent pre-breakfast SMPG targets for individual patients (as per the American Diabetes Association Standards of Medical care in diabetes).

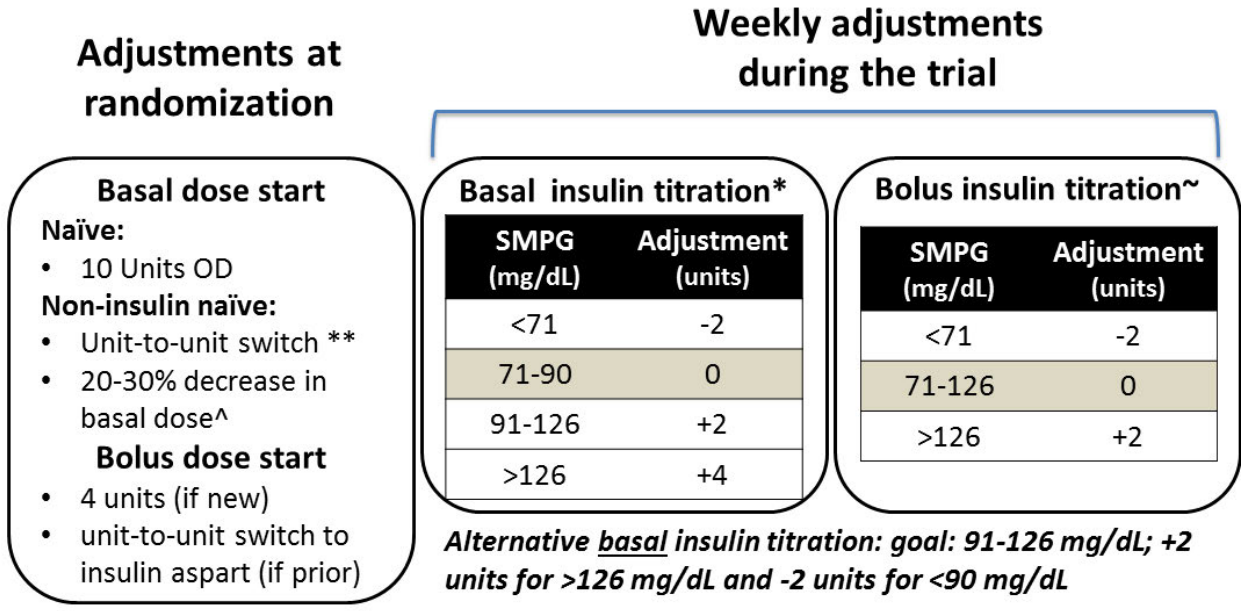
To capture the titration scheme used by the investigators, the screening case report form included a section to document whether the patient qualified for the recommended glycemic titration target of 71 - 90 mg/dL (yes/no). If no, the investigator could specify the target and reason for alternative target.

Investigators were recommended to follow the basal algorithm; if not followed, the investigator was to record a reason for deviation from algorithm.

Bolus insulin was recommended to be started at 4 Units per relevant meal, if needed (as per investigator). Bolus insulin was to be adjusted weekly based on pre-meal or bedtime SMPG values measured on three days prior to titration with a target goal of 71-126 mg/dL.[20] Additional bolus insulin dose could be administered at the investigator's discretion.

Titration of bolus insulin could also be done based on carbohydrate counting (based on the investigator's discretion; no specific guidelines were provided for carbohydrate counting).

Figure 3- Adjustments of insulin in DEVOTE



*Basal insulin titration was based on the lowest of three pre-breakfast SMPG values
**patients previously on OD basal insulin or OD premix/biphasic insulin
^Premix/biphasic insulin BID (or more)
~bolus insulin titration was based on the lowest of 3 pre-prandial or bedtime SMPG values or on carbohydrate counting (as per investigator)

Source: reviewer derived figure from information in protocol

The Novo Nordisk Insulin Titration Group was to centrally monitor titration. If significant deviations were detected, these deviations were to be discussed with the investigators (including at visit sites). The aim of the visits was to reduce the time periods in which patients were receiving an incorrect dose.

Reviewer's comments: the titration goals are in line with the type 2 diabetes phase 3 programs for insulin degludec. However, the titration scheme for DEVOTE is more conservative than in the T2DM trials, as shown in Table 6. In the

[20] Adjustment of a pre-breakfast dose was based on pre-lunch SMPG; lunch dose was based on pre-dinner SMPG; dinner dose was adjusted based on bedtime SMPG value.

phase 3 trials, titration could occur more quickly for patients with poor glycemic control with increases of insulin of up to 8 units, whereas the maximum dose increase in DEVOTE was of 4 units. As compared to the Phase 3 trials, the DEVOTE titration scheme would likely result in a longer titration period but would not affect the overall interpretation of the trial results.

In addition, both targets used in DEVOTE (i.e. the original titration scheme and the steering committee titration scheme) would allow the capture of sufficient number of hypoglycemic events, as recommended by the Division in prior communications.[21]

Table 6 – Original submission- basal insulin dose adjustment type 2 diabetes IDeg trials

Mean Pre-Breakfast Self-Monitored Glucose		Dose Adjustment
mg/dL	mmol/L	
<56	<3.1	Decrease by 4 U
<70	<3.9	Decrease by 2 U
<90	<5.0	No adjustment
<126	<7.0	Increase by 2 U
<144	<8.0	Increase by 4 U
<162	<9.0	Increase by 6 U
≥162	≥9.0	Increase by 8 U

Source: Adapted from NDA 203314; Table 1-10; IDeg Summary of Clinical Efficacy (SCE)
Source: Dr. Guettier's clinical review, page 52

Treatment compliance:
Throughout the trial the investigator would remind patients to follow the trial procedures and requirements. Adherence to IMP treatment was assessed on an ongoing basis.

At each site visit/phone contact, the most recent data from the prior week was to be transcribed into the eCRF, including:

- 3 pre-breakfast SMPG values and 1 basal insulin dose before and after adjustment
- For patients on bolus insulin: up to 3 pre-meal or bedtime SMPG values (the lowest of 3 measurements) and the corresponding bolus insulin dose(s) before and after adjustment
- Reason for deviation from algorithm

Event adjudication
Refer to **Table 67,** in the appendix, for the special committees in DEVOTE. This section will focus on the structure, responsibilities and proceedings of the EAC. In addition, this section will cover how events triggered review by the EAC.

The structure, responsibilities and proceedings of the EAC

[21] Type A end of review meeting Agency minutes 5/1/2013

The adjudication process was performed by an external independent event adjudication committee (EAC). The EAC performed adjudication in a blinded manner for the following events: acute coronary syndrome, cerebrovascular events, fatal events and severe hypoglycemia events (see Table 68). The EAC adjudication results were used as the main source of information for all statistical outputs.

The adjudication process was managed by an external vendor (Quintiles CEVA) who compiled source documents and anonymized information creating adjudication packages for the EAC.
The EAC was composed of 11 members:

- 4 cardiologists (adjudicated fatal events and acute coronary syndrome events)
- 3 neurologists (adjudicated cerebrovascular events and fatal events if death related to neurological event) and
- 4 endocrinologists (adjudicated severe hypoglycemia events).

Each event sent for adjudication was evaluated independently by two primary adjudicators of the appropriate specialty using the predefined definitions and guidelines (shown in the appendix, **Table 68**). The adjudicators also adjudicated the onset date of the event. Events were adjudicated as either

- 'confirmed' (positively adjudicated) with the following levels of information
    - Complete information – source documentation was sufficient to confirm the event met criteria
    - Incomplete information – it was not possible to document that the event met the predefined criteria, but using clinical judgement the adjudicator deemed that the event did or did not fall under the event category
- 'non-confirmed' – event did not meet pre-specified adjudication criteria.

If the two adjudicators agreed in the categorization of the event (as either "confirmed" or "not confirmed"), then the categorization was considered final. If the adjudicators did not agree, a 'consensus process' was followed:

1. **1st consensus communication:** The adjudicators were allowed to discuss the case based on a review of each other's adjudication eCRF with the possibility to update their own evaluation
2. **2nd consensus communication:** if there was no agreement with the 1st consensus communication, two reviewers of the appropriate specialty (reviewers could be the same or different from the ones participating in the 1st consensus communication) and the EAC chair discussed the case. The chair completed a single adjudication form with the final decision.

The EAC had predefined methods[22] to exclude duplicate events sent for adjudication more than once for the same event at the patient level. Duplicate events did not

[22] The EAC was to ensure that the same adjudicated event was not confirmed more than once by reviewing other confirmed events for the same patient within the same adjudication queue in the event adjudication database. The same event could be entered in the adjudication database twice if for

contribute to the statistical analyses of EAC-confirmed events. An example of how duplicate events were only counted once includes the handling of ACS and cerebrovascular events with fatal outcome. These events were sent for adjudication in both the fatal queue and the relevant event queue. If the adjudicators confirmed the events as ACS or stroke with fatal outcome, they marked these events as related by stating the fatal event was related to another confirmed event- therefore fatal EAC confirmed MI and stroke events were only counted once (as CV death).

Events triggering adjudication:
As noted earlier, four event types were adjudicated: acute coronary syndrome events, cerebrovascular events, fatal events and severe hypoglycemia events. These events are discussed further below.

CV events and deaths:

The specific definitions of the adjudicated events are found in **Table 68** (in the appendix). The pre-specified definitions used for adjudication of CV events were established to conform to the 2012 version of the FDA Standardized Definitions for Cardiovascular Outcomes Trials[23] and the 2012 Third universal Definition of Myocardial Infarction.[24] Silent MIs were part of the MACE endpoint and 'undetermined causes' of deaths were considered cardiovascular in the statistical analysis, and hence were part of the MACE endpoint.

As shown in **Table 7**, cardiovascular and death events were identified by investigators, central ECG readers, Sponsor-pre-defined PT searches, and by EAC identification.

Hypoglycemia:
As previously noted, severe hypoglycemia events were designated to be adjudicated in version 3 of the trial protocol. In previous versions, severe hypoglycemia events were part of the testing hierarchy as secondary confirmatory endpoints, but were not adjudicated. Refer to **Table 69** for a graphical view of the version changes to the protocol vs. other documents.

Only events considered to meet either severe hypoglycemia or serious (as per regulatory definition) hypoglycemia were systematically captured and considered for

example, and MI was reported by the investigator and the event was also identified by the central ECG review.
[23] Standardized Definitions for Endpoint Events in Cardiovascular Trials. FDA Center for Drug Evaluation and Research (CDER). Draft Version 09 November 2012.
[24] Thygesen, Kristian, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, and White HD on 1019 behalf of the Joint ESC/ACCF/AHA/WHF Task Force for the Universal Definition of Myocardial Infarction, Third Universal Definition of Myocardial Infarction. Circulation, 2012, 126:2020-2035 (published online August 24, 2012).

adjudication.[25] Therefore, non-serious and non-severe hypoglycemia events were not systematically collected (with the exception of events reported in the Japanese sites)[26]

The 2013 American Diabetes Association (ADA) definition of severe hypoglycemia was used to identify severe hypoglycemia events.[27] This definition specified these episodes required assistance of another person to actively administer carbohydrate, glucagon or to take other corrective action. Plasma glucose concentration was not necessary to be recorded for an event, but neurological recovery after the return of plasma glucose to normal was considered sufficient evidence that the event was a result of low plasma glucose concentration.

Reviewer's comment: The ADA's 2017 description of severe hypoglycemia is as follows "hypoglycemia associated with severe cognitive impairment requiring external assistance for recovery."[28] The 2013 definition does not clearly state that severe hypoglycemia events are associated with "severe cognitive impairment" instead; it notes that "neurological recovery following the return of plasma glucose to normal" should occur after corrective therapy. In my opinion, the phrasing in the 2013 definition used in DEVOTE may potentially capture events which fit into the category of symptomatic or documented symptomatic hypoglycemia.

As shown in **Table 7**, the episodes of severe hypoglycemia were identified by the investigator,[29] by a MedDRA search[30], by the adjudication of selected fatal events for

[25] The following information was to be captured in reporting these events: date of episode: time of episode; whether the patient was able to treat him/herself (if no: who assisted in treatment and where, was transportation in an ambulance involved?); how was the patient treated, and were symptoms alleviated? (i.e. oral carbohydrates, intravenous carbohydrates, glucagon, other); symptoms associated with the hypoglycemic episode; whether the patient was unconscious/comatose; plasma glucose level before treating the episode (if available); time and type (basal or bolus) of last insulin administration prior to episode; time of last main meal prior to episode; whether the episode occurred in relation to increased physical activity; if asleep, whether the symptoms of the hypoglycemic episode woke up the patient.
[26] It was pre-defined in a Japanese protocol, that all events of hypoglycemia were to be reported for Japanese patients
[27] Hypoglycemia and Diabetes: A Report of a Workgroup of the American Diabetes Association and The Endocrine Society" by Seaquist et al, Diabetes care 2013, DOI: 10.2337/dc12-2480
[28] American Diabetes Association. Glycemic targets. Sec. 6. In Standards of Medical Care in Diabetesd2017. Diabetes Care 2017;40(Suppl. 1):S48–S56.
[29] Patients were instructed to inform the investigator if they experienced an episode of hypoglycemia where they were not able to treat themselves. The patient was to document available information in the paper diaries provided; See sample hypoglycemia diary **Figure 48**.Patients were encouraged to record AEs, diabetic medications, cardiovascular disease, certain fasting SMPG values and doses of investigational drug taken. For hypoglycemic episodes where a patient was unable to treat him/herself, patients were to note the date, time and plasma glucose. The investigator was to fill out a hypoglycemic episode form if the patient stated he/she was unable to self-treat or that the episode fulfilled the definition of an SAE. Some of these hypoglycemia events were also reported in the AE form.
[30] Based on relevant terms from SMQs, SOCs, high level group terms (HLGTs), and relevant PTs of 'accidents and injuries' (SMQ - narrow scope), 'convulsions' (SMQ - broad scope) and 'hypoglycemia' (NNMQ - NN maintained search string - narrow scope).

hypoglycemia[31] and by the identification of hypoglycemia events by the EAC during the review of source data for other events.

Table 7 – Pathways for identification of events relevant for adjudication

Source name	Applicable queues				Methodology for identification
	Death	ACS	Cerebrov. event	Severe hypo.	
Investigator	X	X	X	X^	Investigators identified the event relevant for adjudication (in the eCRF system). The event was sent to for EAC along with relevant source information.
ECG		X			Central ECG readers (cardiologists/internists) evaluated all ECGs from scheduled and unscheduled visits for evidence of abnormal 12-lead ECG findings representative of new MI (compared to the previous ECG). If the central reader identified a new abnormality consistent with MI, the investigator was asked to complete an ECG adjudication form, and to perform a confirmatory ECG to be sent for EAC adjudication.
Sponsor MedDRA search		X	X	X	Sponsor applied pre-defined PT searches for cardiovascular events [a] (on all reported AEs) and for hypoglycemic events [b] (on all reported **S**AEs) to identify potential events for adjudication.
EAC		X	X	X	EAC adjudicators identified, during review of source data, events relevant for adjudication that had not been reported as an AE by the investigator/site
Selected fatal events				X	Selected fatal events were sent for adjudication if regarded as potential severe hypoglycemic episodes. The fatal events for severe hypoglycemic adjudication were selected based on classification [c] by the EAC of cause of death

Abbreviations : ACS: acute coronary syndrome; AE: adverse event; cerebrov. : cerebrovascular; EAC: Event Adjudication Committee; ECG: electrocardiogram; eCRF: electronic case report form; hypo: hypoglycemia; MedDRA: Medical Dictionary for Regulatory Activities; MI: myocardial infarction; PT: preferred term; SAE: serious adverse event
[a] based on the standard MedDRA queries (SMQ): 'ischemic heart disease' and 'central nervous system hemorrhages and cerebrovascular conditions.'
[b] based on relevant terms from SMQs, SOCs, high level group terms (HLGTs), and relevant PTs on 'accidents and injuries' (SMQ-narrow scope), 'convulsions' (SMQ broad scope) and 'hypoglycemia' (NNMQ- NN maintained search string- narrow scope).
[c] Based on the following EAC causes of deaths: 'sudden cardiac death' (cardiovascular death), non-cardiovascular deaths caused by 'trauma', 'non-prescription drug reaction or overdose' , 'prescription drug reaction or overdose', 'neurological (non-cardiovascular)', 'other non-cardiovascular' and deaths with an 'undetermined cause'
^ Investigator obtained pertinent information from patient paper diaries, phone contacts/site visits, hospital discharge summaries, emergency records or other available information.
source: Modified adjudication Appendix 16.1.13, table 1

[31] CV deaths (sudden cardiac death); Non-CV-deaths (trauma, non-prescription drug reaction or overdose, prescription drug reaction or overdose; neurological , other non-cardiovascular); and undetermined cause of death

Reviewer's comments: Overall, the Sponsor had a broad approach at capturing possible events of interest to be sent for adjudication. This approach has high sensitivity but low specificity (especially when specific PT terms in the MedDRA searches are reviewed). This approach, however, is acceptable because review by the EAC would likely identify and reject unqualified events.

Since the majority of hypoglycemia events were identified by investigators, the methodology of the investigator capture of these events is highlighted in **Figure 4**, which describes the Hypoglycemic Episode Form.

Figure 4 - Hypoglycemic Episode Form

Investigators were to complete a specific "hypoglycemia Episodes Form" for only hypoglycemia episodes that the patient *was not able to treat him/herself.* If the event met this criterion, the form collected further information regarding:

- Who assisted the treatment of the patient (check boxes: family/friend/co-worker, doctor, paramedic or other [with free text])
- How was the episode treated (check boxes: oral, IV, glucagon, other [free text])
- Whether symptoms were alleviated by the treatment (check box: Yes, no)
- What were the symptoms associated with episode (check boxes with categories of hypoglycemia diary; see **Figure 48**)
- Whether patient was unconscious or in a coma (check box: yes, no)
- If asleep- the patient was awoken by symptoms (check box: Yes, no, not applicable)
- Location where symptoms were treated (check boxes: at home/at a friend's/at work or similar, in an ambulance, in the ED or hospital, other [free text box])
- Did the treatment involve transportation in an ambulance (check box: yes, no)
- Plasma glucose level before treatment (free text box)
- Type and time of last administration of insulin (check boxy for bolus and basal insulin with free text boxes for each to specify time and date)
- Time of last meal (free text box for time)
- Association to physical activity (check box yes, no)
- Whether the hypoglycemic episode was also an SAE (check box yes, no)
- Free text form space to describe the episode.

Reviewer's comment: the capture of severe hypoglycemia events were performed in a systematic method. The basic elements of the definition of severe hypoglycemia were captured in the Hypoglycemic episode form.

For specific details regarding the algorithms used by EAC adjudicators please refer to the Appendix (algorithms are shown in **Figure 43** for acute coronary syndrome, **Figure** 44 for cerebrovascular event, **Figure 45** for death, and **Figure 46** for hypoglycemia).

Reviewer's comment: Throughout the development program of IDeg, hypoglycemia was assessed, with varying degrees of rigor, as shown in Table 8. The common element throughout the trials is that across the development program, hypoglycemia was specified as an endpoint. Unlike the other studies in

the IDeg program, DEVOTE focused only on the definition of severe hypoglycemia as an endpoint.

Table 8 – hypoglycemia assessments in the development program of IDeg

	Severe hypo requiring assistance to treat- ADA criteria			Documentation of BG		Symptoms collected		Hypo endpoint
	Inv. report	EAC adjudicated (pre-DBL)	EAC blinded classify (post-hoc)	Paper diary	e-diary	Yes	No	
DEVOTE	X	X		X		X		Severe hypo (ADA 2013)
SWITCH 1	X	X			X	X		Severe (ADA 2013) or BG-confirmed hypo (<56 mg/dL) with symptoms
SWITCH 2	X	X		X		X		
Phase 3	X		X	X		X		Severe (ADA 2005) or BG confirmed (<56 mg/dL) regardless of symptoms

DEVOTE, SWITCH 1 and SWITCH 2 used the ADA 2013 definition of severe hypoglycemia: An episode requiring assistance of another person to actively administer carbohydrate, glucagon, or take other corrective actions. Plasma glucose values may not be available during an event, but neurological recovery following the return of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration. Phase 3 trials employed the ADA 2005 definition of severe hypoglycemia: An episode requiring assistance of another individual.
Abbreviations: ADA, American Diabetes Association; BG, blood glucose; EAC, External Adjudication Committee
Source: NDA 203314 "follow-up to discussion with the FDA on July 5, 2017" document dated September 7, 2017, table 4

Statistical Considerations:
Refer to the clinical review, dated August 31, 2015 (in DAARTS), for the review of the interim analysis for DEVOTE. This review will focus on the overall trial results and mention the interim results where relevant.

Refer to **Changes** to trial-related documents
Table 69 (in the appendix) for an overview of changes to trial-related documents. The SAP was finalized on October 9, 2014 prior to the interim analysis. At the time there were 6,318 randomized patients (83% of randomized patients). Because of the interim analysis, the Sponsor did not amend the SAP. Instead, the Sponsor published the following statistical memos, while the Sponsor remained blinded to the interim results and prior to database lock:

- Memo 1: was prepared to clarify data handling rules and to update selected statistical analysis
- Memo 2: pre-defined additional statistical analyses not specified in the protocol or SAP. These analyses were sensitivity analyses of the primary and secondary

confirmatory analyses. All the statistical analyses described in Memo 2 are presented in the CTR submitted to the FDA.
- Two additional memos were produced which pre-defined sensitivity analyses taking into account duplicate patients[32]

The following analyses were made after database lock:
- *Post hoc* analyses (mixed model for repeated measurements) for change from baseline in HbA1c after 24 months
- *Post hoc* change from baseline in FPG after 24 months and 'time from randomization to first occurrence of heart failure requiring hospitalization' for events captured using an alternative MedDRA search (SMQ 'heart failure').

As previously discussed, DEVOTE was a double blinded trial. The preservation of blinding was safeguarded by the Sponsor, particularly because DEVOTE had a pre-planned interim analysis based on unblinded safety data

Reviewer's comment: The review of the interim results of DEVOTE showed that the trial was well conducted and in accordance with Agency recommendations. At that time, there were no trial performance issues identified which could have influenced the primary objective. Refer to section titled 3.1 Submission Quality and Integrity **for comments regarding the overall integrity of the trial.**

Sample size calculation:
The sample size calculation was based on the number of first EAC confirmed MACEs in the FAS. Calculations based on a log-rank test showed that a total of 633 first MACEs would provide 91% power to rule out the upper bound of the 95% confidence interval of the hazard ratio (IDeg vs. IGlar) exceeding 1.3, assuming a true hazard ratio of 1.0.

To accrue a total of 633 first MACEs, a trial duration of five years was expected with 3,750 patients randomized 1:1 to IDeg and IGlar, for a total of 7,500 randomized patients. The following assumptions were followed for the sample size calculation:
- The rate of first MACEs was 2.1 per 100 patient year (PYE) in both treatment groups throughout the trial
- Recruitment into the trial is uniform in 18 months
- The lost-to-follow-up rate is 1% per year throughout the trial
- Last patient last visit (LPLV) occurs 60 months (5 years) after first patient randomized

The trial duration was based on: a recruitment period of 18 months, a lost to follow up rate of 1% per year and 7,500 patients randomized.

[32] The first memo was finalized prior to DBL for the interim analysis and detailed the handling of 6 duplicate patients. The second memo was finalized prior to DBL for the full trial and described an additional 7 duplicate patients in sensitivity analyses.

Analysis sets:
The analyses sets in **Table 9** were used in DEVOTE.

Table 9 – Analyses sets used in DEVOTE

Analysis set	Definition	Exposure period
Full analysis set (FAS)	All randomized patients. Follow the intention-to-treat (ITT) principle and patients contributed to the evaluation "as randomized."	- Period from randomization to last contact with investigator (scheduled at 30 days after last dose with the IMP). - For patients lost to follow-up: from randomization to last contact with the patient
Per-protocol (PP) analysis set	All patients who have been either: - Continuously on IMP the first 3 months after randomization - Patients having a MACE event within the first 3 months and who took at least one dose of IMP before the event	- Time from randomization until subjects have an accumulated off-treatment period* exceeding 120 days (i.e. where only continuous treatment pauses of at least 30 days were counted in the calculation of accumulated treatment pause time), provided this date occurred before the patient's end of trial date as used in the primary analysis.
IMP: investigational medicinal product *Off treatment period is defined as the period where a subject has not administered IMP		

See **Table 10** for definitions of pre-defined time periods in the trial.

Table 10 – Description of time periods in DEVOTE

Time period	Description
End of trial date	Date of the follow-up visit, - If patient did not attend follow-up visit, then the individual end of trial date is based on: o Death date (occurring prior to global LPLV) o Date of EAC confirmed MACE (prior to actual global LPLV) o Last direct contact for patients
Observation time	**Per statistical Memo 1:** Observation time was time from randomization until the individual end of trial date. Incidence rates of all event types were based on the patient's individual observation time
Exposure time	**Per statistical Memo 1:** Time from date of the first dose of IMP to the date of the last dose of IMP+1, excluding drug holidays
On treatment time	Time period when the patients were taking IMP. It included the first day after the last dose of IMP (i.e. the day on which the patient ceased to take IMP and began an 'off-treatment' period).

Censoring
All first EAC-confirmed MACEs which occurred from randomization until the individual end of trial date (i.e. observation time) were included. Patients not having an EAC-confirmed MACE were censored at their individual end of trial date. Patients who were randomized but never exposed to IMP were censored at the date of randomization. Time to event and time to censoring were calculated from the randomization date.

The term "complete", with regards to patients, was used to evaluate patient disposition. Completers were defined as fulfilling at least one of the following criteria:

- death during the trial

- follow-up visit completed (defined as direct contact between patient and site)

Otherwise, patients were defined as non-completers.

If health status could not be obtained, patients were categorized as 'lost to follow-up.'[33]

Time points referring to "baseline"
In an information request the Sponsor was asked to define what was meant by "baseline" in the efficacy and safety endpoints. **Table 11** captures the Sponsor's response

Table 11 – Time point used for baseline measuremetn for efficacy and safety analyses

Time point baseline refers to	Endpoint/parameter
Randomization	HbA1c, FPG, lipids, biochemistry, hematology, renal function, antidiabetic medications, cardiovascular medications
Week 1	IMP dose, bolus insulin dose, total insulin dose
Screening	Blood pressure, pulse rate, body weight, BMI, age, duration of diabetes, smoking, cardiovascular risk factors
Source: IR dated October 31, 2017, question 2: file://cdsesub1/evsprod/NDA203314/0147/m1/us/re-fda-ir-20171024.pdf	

Events included in the statistical analyses

All potential MACEs, fatal events and severe hypoglycemic events reported from randomization up to DBL were to be adjudicated and included in the statistical analyses (if positively adjudicated). Therefore events adjudicated by the EAC and occurring prior to randomization or after the patient's end-of-trial date were not included in the statistical analyses.

The onset date of EAC adjudicated events was the date determined by the EAC. If no date was given by the EAC, a date was imputed. For EAC-confirmed severe hypoglycemic episodes with a missing onset date, the midpoint of the patient's observation time was used as the onset date (this applied to only one episode in the study). No EAC confirmed MACE had a missing onset date.

Primary endpoint:
The primary endpoint was the time from randomization to the first occurrence of an EAC confirmed 3-component major adverse cardiovascular event, MACE (defined as cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke).

The primary endpoint was to be presented descriptively in a Kaplan-Meier plot and analyzed using a Cox proportional hazard approach with treatment (IDeg and IGlar) as factor. The hazard ratio and one-sided 95% confidence interval was to be estimated using the FAS population.

[33] A patient was not considered lost to follow-up until a number of contact attempts had been made and documented

Non-inferiority of IDeg to IGlar was confirmed if the upper limit of the two-sided 95% confidence interval for the hazard ratio was below 1.3.

Of note, because the interim analysis had no impact on the continuation of the trial, no adjustment of the alpha level for the statistical test, in the final evaluation was necessary. No changes to the trial design and conduct were made based on the results of the interim analysis.

See **Table 12** for the pre-specified sensitivity analyses of the primary endpoint.

Table 12 – Sensitivity analyses of the primary endpoint

Model	Population	Observation period
Cox regression	FAS	On treatment (strict censoring)*
		On treatment+30 days (strict censoring)**
		On treatment, ignoring any prior EAC-confirmed MACE that occurred off treatment^
		On treatment +30 days, ignoring any prior EAC-confirmed MACE that occurred off treatment~
		Full observation period, but censored at the date of last contact prior to follow-up visit in case of no contact with the patient for >6 months prior to the follow-up visit
	FAS, but where all patients who were randomized twice were assumed to have been randomized to IDeg$^{\Omega}$	Full observation period
	PP	Full observation period, but censored when accumulated treatment pause time exceeds 120 days where only continuous treatment pauses of at least 30 days are counted
Cox regression + adjustment for additional covariates$^{£}$	FAS	Full observation period
Cox regression	FAS with imputation of missing data (tipping point analyses)$^{¥}$	Full observation period (extended for non-completers on IDeg not having an EAC-confirmed MACE)
*the first EAC confirmed MACE was included in the analysis if it occurred during an on-treatment period. Otherwise the patients observation time was censored at the time of the first EAC confirmed MACE (i.e. during off treatment) or at the time the patient discontinued treatment –if the patient did not have a MACE event. Of note, this analysis excluded off-treatment periods with the exception of EAC confirmed MACE events occurring during an off treatment period. ** rules were the same as the on treatment (strict censoring), with the additional extension of 30 days after taking the last dose of IMP ^The first EAC confirmed MACE occurred during an on-treatment period was included irrespective of whether an EAC confirmed MACE occurred in a prior off-treatment period. This analysis excluded any off-treatment periods. ~The first EAC confirmed MACE occurring during an on-treatment period (extended up to 30 days after taking the last dose of IMP) was included in the analysis irrespective of whether the MACE had occurred		

more than 30 days into a prior off treatment period. Time to first EAC confirmed MACE and time to censoring excluded any off-treatment periods except the first 30 days of any off-treatment period.
[Ω]applied to 14 subject numbers (7 patients) in the US randomized in error at 2 sites (i.e. randomized twice) Patients continued at the site where they were initially randomized and were withdrawn from the site where they were subsequently randomized.
[£]adjustments for the following covariates (in addition to treatment which was included in the primary analysis): sex, region (Africa, Asia, Europe, North America, south America), baseline age , (regression), smoking status at baseline (never, previous, current smoker), diabetes duration at baseline (regression), cardiovascular risk at baseline (high, medium), insulin naïve at baseline (yes, no) and renal function eGFR at baseline (regression)
[¥]this analysis addressed the impact of missing information for patients not completing the trial. Events were added for patients randomized to IDeg not having an EAC confirmed MACE in the primary analysis who were non-completers and patients lost to follow up.

Source: CSR, table 9-12

Additional analyses of the primary endpoint included: the exclusion of deaths due to undetermined causes, competing risks[34] and subgroup analyses.

The pre-specified subgroup analyses were performed using the same model as the primary analyses for the baseline variables as shown in **Table 13**.

Table 13 – Pre-specified subgroup analyses for primary endpoint and for multiplicity adjusted secondary endpoints

	Subgroup
Age group	<65 years or ≥65 years; <75 years or ≥75 years
BMI group	<30 kg/m^2 or ≥30 kg/m^2
Ethnicity	Hispanic or Latino or not Hispanic or Latino
Race	White or not White
Renal impairment severity	Normal renal function (eGFR ≥ 90 mL/min/1.73m2 per CKD-EPI), Mild renal impairment (60 ≤ eGFR < 90 mL/min/1.73m2 per CKD-EPI), Moderate renal impairment (30 ≤ eGFR < 60 mL/min/1.73m2 per CKD-EPI), or Severe renal impairment (eGFR < 30 mL/min/1.73m2 per CKD-EPI)
Sex	Female or male
Cardiovascular medication	With statins or without statins
Cardiovascular risk group	Established cardiovascular disease/chronic kidney disease or risk factors for cardiovascular disease
Duration of diabetes	≤15 years or >15 years
HbA1c at baseline	<8% or ≥8%
Previous insulin treatment	Basal only; basal/bolus including premix; insulin naïve
Qualify for titration target of 4-5 mmol/L	Yes or no
Region	Africa, Asia, Europe, North America, or South America, Region US or Rest of world
Note: Not White includes the following races: Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander and Other. Abbreviations: BMI: body mass index; CKD-EPI: chronic kidney disease epidemiology collaboration;	

[34] Cumulative incidence functions were made for the primary endpoint that accounted for the competing risks of non-cardiovascular death, lost to follow-up and withdrawal.

eGFR: estimated glomerular filtration rate; HbA1c: glycated hemoglobin
Source: CSR, Table 9-13, page 105

Multiplicity
The primary and secondary endpoints were tested in a pre-defined hierarchical sequence to control type I error. In this hierarchy, it was necessary to fulfil each preceding the test criteria to go to the next step. If the corresponding null hypothesis was not rejected, the testing stopped.

- Step 1: Non-inferiority of IDeg vs. IGlar for the primary endpoint of 3-point MACE
- Step 2: Superiority of IDeg vs. IGlar for the number of EAC confirmed severe hypoglycemic episodes
- Step 3: Superiority of IDeg vs. IGlar for the occurrence of at least one EAC-confirmed severe hypoglycemic episode within a patient

The alpha level for the statistical tests was not adjusted since the statistical results of the interim analysis did not affect the continuation of the trial or the statistical tests and results of the full trial.

Secondary endpoints adjusted for multiplicity

- *Number of EAC-confirmed severe hypoglycemic episodes*

The number of EAC-confirmed severe hypoglycemia episodes was analyzed using a negative binomial regression model with log-link function and the logarithm of the observation time as offset. The model included treatment (IDeg vs. IGlar) as a fixed factor and was fitted using the FAS.

Superiority was considered confirmed if the upper limit of the two-sided 95% confidence interval for the rate ratio (RR) was below 1. It was considered equivalent if the one sided test of null hypothesis: RR≥1.0 against the alternative hypothesis: RR<1.0, was less than 2.5%.

- *Occurrence of at least one EAC-confirmed severe hypoglycemic episode within a patient (yes/no)*

This was analyzed using a logistic regression model with log-link function. The model included treatment (IDeg vs. IGlar) as a fixed factor and was fitted using the FAS. Superiority was considered confirmed if the upper limit of the two-sided 95% confidence interval for the odds ratio (OR) was below 1 or equivalent if the p-value for the one-sided test of H0: RR≥1.0 against Ha: OR<1.0 was less than 2.5%.

Reviewer's comment: of note, the analysis of the EAC confirmed severe hypoglycemic episodes were changed in the Statistical memo 1, from the SAP. The SAP stated that these episodes would be analyzed using a negative binomial regression model with a log-link function and the logarithm of the duration of the exposure time as offset. Memo 1 stated that this analysis would be done with offset equal to the logarithm of the observation time, as the time where severe hypoglycemic events are counted is then the same as the off-set which is also

consistent with the ITT principle and the FAS definition. I defer interpretation of the statistical implication of this change to the FDA statistician.

In addition, the Sponsor pre-specified the primary and secondary endpoints to meet a one-sided p-value. The FDA has precedence in labeling the 2-sided p-value (most recently, this topic was noted in the EMDAC meeting for LEADER).[35] A one sided p-value may appear to be "smaller" than a two-sided p-value and thus may be misleading, therefore if labeling of these endpoints is pursued, I recommend the labeling of the two-sided p-value.

Sensitivity analyses of the multiplicity adjusted secondary endpoints

Table 14 shows the sensitivity analyses used for the multiplicity adjusted secondary endpoints.

Table 14 – Sensitivity analyses of multiplicity adjusted secondary endpoints

Model	Population	Observation period
Number of EC-confirmed severe hypoglycemic episodes		
Negative binomial regression	FAS	On treatment
		On treatment +7 days
Negative binomial regression + adjustment for additional covariates ^	FAS	Full observation period
Negative binomial regression (but where endpoint is truncated at a maximum of 3 episodes per patient)*	FAS	Full observation period
Negative binomial regression	FAS with multiple imputation of missing data (tipping point analyses)	Full observation period (extended to LPLV for patients on IDeg who were non-completers)
Occurrence of at least one EAC-confirmed severe hypoglycemic episode within a patient (yes/no)		
Logistic regression	FAS	On treatment
		On treatment +7 days
Logistic regression	FAS with imputation of missing data (tipping point analyses)	Full observation period
*analysis was done to evaluate the extent of the results influenced by patients with high rates of severe hypoglycemia, by truncating the episodes by patient to 3 episodes. ^ adjustments for baseline insulin treatment (basal-bolus, basal only, insulin naïve) Source: CSR, table 9-14, page 107		

The sponsor pre-specified an analysis of subgroups for the multiplicity adjusted endpoints. These subgroup analyses were the same as for the primary endpoint (as shown in **Table 13**).

[35] Refer to the June 20, 2017 EMDAC meeting
https://www.fda.gov/AdvisoryCommittees/Calendar/ucm560479.htm

Other Secondary endpoints (not adjusted for multiplicity)

Other secondary endpoints (not adjusted for multiplicity) are shown in **Table 15**. These endpoints included additional efficacy glycemic endpoints, safety endpoints, and change from baseline endpoints. These endpoints were summarized using the FAS.

Table 15 – Other secondary endpoints

Efficacy endpoints (Change from baseline to the last assessment in): • **HbA1c, (central laboratory)~** • **FPG (central laboratory)^** • Pre-breakfast SMPG • 8-point profiles (including one day and across visits and mean of 8-point SMPG profile)* • Investigational product dose¥ • Bolus insulin dose (only end of treatment) • Total insulin dose¥ • Treatment ratio between mean insulin dose at 24 visitΩ

Safety endpoints:
• Time from randomization to first occurrence of an EAC-confirmed 4 point MACE (cardiovascular death, non-fatal MI, non-fatal stroke and UAP requiring hospitalization)- cox regression analysis
• Time from randomization to the following EAC confirmed events (cox regression analysis):
  • CV death
  • CV death excluding undetermined cause of death
  • All cause death
  • Nonfatal MI
  • Non-fatal stroke
  • UAP requiring hospitalization
• Time from randomization to first occurrence of heart failure requiring hospitalization£
• Time to first EAC confirmed severe hypoglycemia (cox proportional hazard regression with treatment)Dg and IGlar as factor)
• Number of nocturnal EAC-confirmed severe hypoglycemic episodes (time 00:01- 05:59 per investigator)
• Number of SAEs
• AEs leading to discontinuation of investigational product
• Number of medication errors leading to SAEs
• Number of AEs related to technical complaints

Change from baseline to the last assessment: • Blood pressure • Pulse rate • **Lipids (total cholesterol, HDL cholesterol, LDL cholesterol [was calculated], triglycerides)** • **Biochemistry (eGFR [was calculated], alanine aminotransferase, sodium, potassium, albumin, bilirubin)** • Hematology (hemoglobin, hematocrit, erythrocytes, thrombocytes, leucocytes) • Body weight (screening and yearly collection) • Body mass index • Renal function (eGFR by CKD-Epi) (collected at visit 2 and yearly)

Central laboratory analyses are **bolded**
~was obtained pre-treatment (visit 2) and at 3, 6, 9, 12 and 24 months after treatment initiation and at the end of treatment visit.
^ fasting is defined as no food or drink except water for the last 8 hours. FPG were obtained at visit 2, 12, 24 months and end treatment visit
*performed yearly. SMPG profile is to be recorded in diary and can be used for optimizing insulin treatment. SMPG sample is to be done before breakfast, 90minutes after start of breakfast, before lunch, 90 minutes after start of lunch, before main evening meal, 90 minutes after the start of main evening meal, at bedtime and before breakfast the next day
Ω Analysis was done using a mixed model for repeated measures within patients using an unstructured residual covariate matrix among visit 3, 6,9,12,15,18,21 and 24 months of study. Interactions between visit and treatment and with log (baseline dose) were included as fixed effects. Baseline dose was the first basal insulin dose reported by investigator for analyses of basal dose, where it was the total dose at visit 3 for the analysis of total insulin dose
¥analysis with MMRM model with adjustment for baseline covariates (i.e. visit interactions with previous insulin regimen, age, BMI, alternative titration target [yes/no] as fixed effects).
£refer to **Table 72** for a table of MedDRA searches for heart failure requiring hospitalization. This endpoint was not adjudicated by the EAC

Reviewer's comments: the identification of heart failure events in DEVOTE by inspection of the results ofMedDRA searches, and not by adjudication, is considered less reliable than the identification of the adjudicated MACE events in the trial. The methodology employed also did not consider criteria that are usually recommended, such as: a hospitalization period (i.e. the hospitalization period is typically recommended to be at least 24 hours), clinical symptoms of heart failure (i.e. orthopnea) and signs (i.e. edema) of worsening heart failure, and need for additional increase in therapy (i.e. initiation of IV diuretic) and no other cardiac etiology. In addition, time from randomization to first occurrence of heart failure requiring hospitalization was part of a post hoc analyses. Therefore, the findings from the heart failure analysis are considered exploratory.

Refer to the section titled **7.1.2 Categorization of Adverse Events** for general definitions of adverse events**.**

Neoplasms
Patient with a malignant neoplasm within the past 5 years before screening (except for basal and squamous cell skin cancers) were excluded from the trial (see inclusion/exclusion criteria in **Table 4**.

Neoplasms were not adjudicated, instead, two medical oncologists independently "classified" neoplasms. All SAEs detected in the SOC 'Neoplasms benign, malignant and unspecified (including cysts and polyps)' were sent for blinded classification. Unlike the EAC, the evaluation and classification of neoplasm events was based on information in case narratives; no source data was collected and there was no possibility for classifiers to raise queries. For discrepancies, the two classifiers could discuss and resolve discrepancy. If consensus could not be reached a third classifier (chairperson) made the final decision.

Events were classified as malignant or not malignant. Malignant events were further classified into primary organ site category.[36] When there was insufficient data to determine if the type of neoplasm, then the event was categorized as 'unclassifiable'.

Other safety assessments

Pregnancy tests were performed for female patients considered to be of child-bearing potential. Clinical laboratory assessments including hematology, lipids and biochemistry laboratory tests (shown in **Table 15**) in addition to physical examinations were performed.

A 12-lead ECG was performed at baseline, yearly and at the end-treatment. Centralized analysis of scheduled visit-ECGs was performed by external cardiologists. In addition, unscheduled ECGs received from the investigator were also reviewed by the central ECG reader. ECGs were forwarded to central reader to capture silent infarctions.[37] If baseline ECG suggested a prior MI, the investigator was notified and the event was reported as a concomitant illness.

Vital signs were assessed at screening, at 6 month intervals during treatment and at end-treatment.

6 Review of Efficacy

Efficacy Summary

The glycemic-lowering effect of insulin degludec was established in the pre-marketing phase 3 trials in the original NDA submission. DEVOTE was a post-marketing study assessing the cardiovascular and severe hypoglycemia safety of insulin degludec as compared to insulin glargine, in patients with type 2 diabetes mellitus, with largely established cardiovascular disease, treated with standard of care therapies. This section contains a summary of the pre-specified primary and multiplicity-adjusted secondary endpoints in DEVOTE.

DEVOTE was a double-blinded, 1:1 randomized, multi-national, cardiovascular outcomes trial enrolling 7637 patients with established cardiovascular disease/chronic kidney disease or patients at risk for cardiovascular disease, treated with insulin

[36] If malignant, the level of evidence of each neoplasm was determined categorized as "definite" if histo-pathological evidence of malignancy was available, "probable" if imaging reports, evidence of treatment for malignant neoplasm, laboratory test or tumor marker were available and suggestive of malignant neoplasm. "possible" refers if only a physician's note is available mentioning treatment of a malignant neoplasm

[37] As defined by the third universal definition of myocardial infarction: Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, et al. Third universal definition of myocardial infarction. Circulation. 2012;126(16):2020-35.

degludec (n=3818) or insulin glargine (n=3819) each administered once daily between dinner and bedtime, as add-on to standard of care therapies. DEVOTE was designed to accrue a minimum of 633 first EAC confirmed major adverse cardiovascular events.

The patient demographics were consistent with an enriched population for cardiovascular events. Most patients had high cardiovascular risk or established cardiovascular or chronic kidney disease. There were no pre-specified criteria for hypoglycemia risk. In addition, more than two-thirds of enrolled patients were from the United States.

The patient retention was relatively high. Approximately 98% of patients were classified as "completers," meaning these patients completed a follow up visit or died during the trial. The vital status was available for 99% of randomized patients (vital status was unavailable for only 8 patients in the trial).

For all efficacy endpoints, events considered spanned the time from randomization to an individual end of trial date.

The primary endpoint was time to the first Event Adjudication Committee's confirmed *first* occurrence of any component of the Major Adverse Cardiovascular Event (MACE) composite endpoint (MACE comprised cardiovascular death, non-fatal MI, or non-fatal stroke). Events considered for the primary endpoint spanned the time from randomization to an individual end of trial date.[38]

A total of 325 and 356 first EAC-confirmed MACEs were captured in patients randomized to insulin degludec and insulin glargine, respectively. Based on a Cox proportional hazard regression model with treatment as the only factor, the hazard ratio for time to first EAC-confirmed MACE for IDeg vs. IGlar was 0.91 with a 95% confidence interval of 0.78 to 1.06. The upper bound of the 95% confidence interval ruled out the risk margin of 1.3, as per the 2008 Guidance for Industry[2], thereby excluding a 30% relative increase in MACE with use of insulin degludec as compared to insulin glargine (2-sided p-value of time to first EAC confirmed MACE event: 0.209; one sided p-value for non –non-inferiority <0.001).

The results of other secondary *safety* cardiovascular endpoints, including time-to-event analyses of the components of major adverse cardiovascular events, and 4-point MACE are shown in **Table 16.** Across analyses, hazard ratios were slightly below 1 with the 95% upper confidence interval crossing 1. These exploratory cardiovascular results were consistent with the results of the primary endpoint.

There was no demonstrated mortality benefit with use of insulin degludec as compared to insulin glargine despite the lower rate of severe hypoglycemia in the trial.

[38] For events with the same date of onset the selection priority for the first event was: cardiovascular death (including undetermined cause of death) > non-fatal myocardial infarction > non-fatal stroke

There were two pre-specified hierarchically tested secondary endpoints. The first endpoint tested the superiority of insulin degludec vs. insulin glargine with respect to number of EAC-confirmed severe hypoglycemic episodes.

- A total of 752 EAC confirmed episodes of severe hypoglycemia were captured in the trial: 280 and 472 episodes for insulin degludec and insulin glargine respectively.
- The rate ratio (RR) based on negative binomial regression with log-link function and log (duration of observation time) as offset showed a HR 0.601 with a 95% confidence interval of 0.476 to 0.759; p-value for one-sided test <0.001. Superiority of insulin degludec vs. insulin glargine with respect to the number of EAC confirmed severe hypoglycemic episodes was confirmed since the upper limit of the two sided 95% confidence interval for the rate ratio was below 1. The findings were reproduced across sub-populations and sensitivity analyses.

The second endpoint tested the superiority of insulin degludec vs. insulin glargine with respect to occurrence of at least one EAC confirmed severe hypoglycemia episodes within a patient (yes/no).

- A total of 439 patients experienced at least one EAC-confirmed severe hypoglycemic episode: 187 or 4.9% of patients randomized to insulin degludec and 252 or 6.6% of patients randomized to insulin glargine.
- The odds ratio of insulin degludec vs. insulin glargine based on logistic binomial regression was 0.729 with a 95% confidence interval of 0.600 to 0.886; p-value for one-sided test p<0.001. Superiority of insulin degludec vs. insulin glargine with respect to the number of EAC confirmed severe hypoglycemic episodes was confirmed since the upper limit of the two sided 95% confidence interval for the odds ratio was below 1. The findings were reproduced across sub-populations and sensitivity analyses.

The following exploratory observations pertain to the severe hypoglycemia findings:

- Redundant methods (i.e. investigator capture, MedDRA search, EAC capture) for the systematic capture of severe hypoglycemia events ensured that most events were not missed.
- Events which were excluded from hypoglycemia adjudication were appropriately screened by the EAC chair/delegate as events which did not needing adjudication.
- 94% of events confirmed for severe hypoglycemia had complete source information to confirm that the event met severe hypoglycemia criteria.[39]
- The hypoglycemia findings were mostly driven by single events, rather than multiple events in a few individuals (3.7% vs. 4.4% of patients randomized to IDeg and IGlar experienced single events respectively)

[39] 705 events of a total of 752 events

- The time to first EAC confirmed severe hypoglycemia episodes showed a difference between treatment arms occurring after 3 months in the trial.
- Exploratory analyses of the adverse events (ADAE dataset)[40] and hypoglycemia events (ADHYPO dataset) were consistent with the adjudication results.
- 76.9%[41] of EAC confirmed severe hypoglycemia events were from sites in the United States
- Most of the symptoms associated with the confirmed severe hypoglycemia were non-specific, and did not have clear neuroglycopenic symptoms, (only 21% of events were reported as having unconsciousness or coma or seizure).[42] Therefore it is likely that some cases represent symptomatic hypoglycemia or documented symptomatic hypoglycemia.
- Most of the EAC confirmed severe hypoglycemia events had an available self-measured plasma glucose value available, with over 80% of events having a self-measured plasma glucose value less than 54 mg/dL.
- Most of the hypoglycemic findings, regardless of treatment arm, were driven by patients also using bolus insulin.
- Accounting for use of bolus insulin in the time to severe hypoglycemia analysis did not fully explain the differences in treatment arms; therefore, implying some effect of basal insulin
- Glycemic control was similar (for hemoglobin A1C) or better (with regards to fasting plasma glucose) when comparing insulin degludec to insulin glargine from randomization to 24-months.
- Higher basal insulin dosage was noted for insulin degludec (~3 units more) as compared to insulin glargine for the randomized population. The use of higher insulin degludec was more prominent in the subset of patients also using bolus insulin (~4.8 units more of basal insulin). In this subgroup of patients, the bolus insulin dose was lower (by ~3.4 units) for insulin degludec than insulin glargine.
- Differences in antidiabetic medications started post baseline revealed slightly higher proportion of patients randomized to insulin degludec (4%) as compared to insulin glargine (3.1%) starting a GLP-1 receptor agonist, and a lower proportion of patients starting bolus insulin for insulin degludec (18.7%) versus insulin glargine (19.8%).

[40] Analyses of Accidents and injuries SMQ, convulsions SMQ and hypoglycemia SMQ
[41] 578 events out of 752 events
[42] Events for IDeg: seizures- 11 unconsciousness/coma- 60; IGlar: seizures- 11 unconsciousness/coma- 75. 157/752=21%

Table 16- Time to first EAC confirmed event –FAS- Sponsor's analyses

	IDeg			IGlar			Total		Hazard ratio	95% CI	P-value
	N (%)	E	R	N (%)	E	R	N (%)	R			
FAS	3818			3819							
Interim analysis (150 MACEs identified) +	72 (1.9)	72	3.9	78 (2.0)	78	4.2	150 (2.0)	4.0	0.92	0.67; 1.27	
Primary endpoint: MACE£	325 (8.5)	325	4.29	356 (9.3)	356	4.71	681 (8.9)	4.5	0.91	0.78; 1.06	0.209 –time to 1st EAC MACE-(2 sided; HZ=1) <0.001- Non-inferiority test (1-sided)
4-point MACE											
4-point MACEΩ	386 (10.1)	386	5.10	419(11.0)	419	5.54	805(10.5)	5.32	0.917	0.799; 1.053	0.220 (2 sided of HZ=1)
All-cause mortality											
All cause death ^	202 (5.3)	202	2.67	221 (5.8)	221	2.91	423 (5.5)	2.79	0.913	0.755; 1.105	0.352 (2 sided of HZ=1)
Not EAC adjudicated (*post hoc analysis)*											
Hospitalization for heart failure	296 (7.8)	296	3.91	322(8.4)	322	4.26	618 (8.1)	4.09	0.912	0.779; 1.068	0.251 (2 sided of HZ=1)
Components of MACE and 4-point MACE											
Cardiovascular death	136 (3.6)	136	1.80	142 (3.7)	142	1.88	278 (3.6)	1.84	0.957	0.756; 1.211	0.714 (2 sided of HZ=1)
Non-fatal stroke	71 (1.9)	71	0.94	79 (2.1)	79	1.05	150 (2.0)	0.99	0.896	0.650; 1.234	0.502 (2 sided of HZ=1)
Non-fatal MI	144 (3.8)	144	1.90	169 (4.4)	169	2.24	313 (4.1)	2.07	0.849	0.680;1.061	0.150 (2 sided of HZ=1)
Unstable angina requiring hospitalization	71 (1.9)	71	0.94	75 (1.96)	75	0.98	146 (1.9)	0.96	0.946	0.684; 1.309	0.737 (2 sided of HZ=1)
Multiplicity adjusted secondary endpoints											
Number of EAC-confirmed severe hypoglycemic episodes*	187 (4.9)	280	3.70	252 (6.6)	472	6.25	752 (9.9)	4.98	0.601	0.476; 0.759	<0.001 (1-sided)
EAC-confirmed severe hypoglycemic episode (yes/no)~	187 (4.9)	280	3.70	252 (6.6)	472	6.25	752 (9.9)	4.98	0.729	0.600; 0.886	<0.001 (1-sided)

Shaded boxes are the pre-specified, hierarchical tested efficacy hypothesis in DEVOTE
+pre-specified analysis of primary MACE when 150 MACEs identified; refer to table 1 from the FDA statistical review of the interim results, dated August 28, 2015.
^ Hazard ratio (HR) (IDeg vs IGlar) based on Cox regression with investigational medicinal product as Factor; p-value refers to one-sided test of HR >= 1.3 (against Ha: HR<1.3)
£ Includes cardiovascular death, non-fatal stroke, and non-fatal MI
^Times were right censored at time of last direct contact (phone or visit) incl. unscheduled contacts for subjects without a first EAC confirmed MACE
Ω Includes cardiovascular death, non-fatal stroke, non-fatal MI and unstable angina requiring hospitalization
* rate ratio (RR) (IDeg vs IGlar) based on negative binomial regression with log-link function and log(duration of observation time) as offset; p-value refers to one-sided test of RR >= 1.0 (against Ha: RR<1.0)
~odds ratio (OR) (IDeg vs IGlar) based on logistic (binomial) regression; p-value refers to one-sided test of OR >= 1.0 (against Ha: OR<1.0)
Source: CSR, table 11-2, page 145; table 11-2, page 145, table 14.2.59, page359; table 14.2.62, page 362; table 14.2.68, page 368; table 14.2.54, page 354; Table 14.2.104, page 409

6.1 Indication

Insulin degludec is "indicated to improve glycemic control in patients 1 year of age and older with diabetes mellitus." The Sponsor does not aim to expand the indication of insulin degludec as a result of the current submission.

6.1.1 Methods

My general review strategy was to focus on the pre-specified primary cardiovascular and secondary hypoglycemia endpoints, since the Sponsor purports labeling these data. For the evaluation of efficacy, I mainly used the Sponsor's analyses; please refer to the reviews authored by Dr. Eugenio Andraca-Carrera for the cardiovascular analyses) and Dr. Kiya Hamilton (for the hypoglycemia analyses) for the FDA statistical analyses. As part of the clinical review, I performed exploratory analyses for areas of interest by using the Sponsor provided datasets. These exploratory analyses are delineated in the review.

Although there is no pooling of data from previously submitted trials, because of the Sponsor's interest in labeling comparative hypoglycemia data, comments regarding previous Novo Nordisk and other relevant studies evaluating hypoglycemia will be noted in the review. The purpose of discussing other trials is to provide context for the DEVOTE results.

In addition, I performed an audit of a random sample of the adjudication packets and patient narratives for endpoints of interest. I did not re-adjudicate any of the cardiovascular or hypoglycemic events.

6.1.2 Demographics

Overall, patients randomized to IDeg and IGlar were well balanced with regards to baseline characteristics. As shown in **Table 17** the mean age of patients was approximately 65 years of age. Close to 48% of patients were less than 65 years of age and over 10% were greater than 75 years of age. Over 60% of patients were male. The racial breakdown of the population was more than three quarters White and over 10% of patients categorized as either Black or Asian. Approximately 15% of patients were Hispanic or Latino. By region, the largest contributor was North America with 68% of patients.

Table 17- Demographics – FAS

Demographic Variable	IDeg N=3818	IGlar N=3819
Age, mean ± SD – yr.	64.9 (7.3)	65.0 (7.5)
50-59 years n (%)*	855 (22.4)	884 (23.1)

60-64 years n (%)	980 (25.7)	963 (25.2)
65-74 years n (%)	1602 (42.0)	1534 (40.2)
≥75 years n (%)	381 (10.0)	438 (11.5)
Female sex, n (%)	1422 (37.2)	1437 (37.6)
Race no (%)		
White	2903 (76.0)	2872 (75.2)
Black/African American	401 (10.5)	431 (11.3)
Asian	391 (10.2)	385 (10.1)
American Indian or Alaskan Native	17 (0.4)	13 (0.3)
Native Hawaiian or other Pacific Islander	11 (0.3)	13 (0.3)
Other	94 (2.5)	104 (2.7)
Unknown	1 (0.0)	1 (0.0)
Ethnic group (Hispanic), no. (%)	582 (15.2)	555 (14.5)
Region, no (%)		
Europe	438 (11.5)	437 (11.4)
North America	2625 (68.8)	2646 (69.3)
South America	304 (8.0)	281 (7.4)
Asia excluding India	151 (4.0)	141 (3.7)
India	168 (4.4)	189 (4.9)
Africa	132 (3.5)	125 3.3)
*Includes 3 patients with age <50 years Source, CSR, table 10-2 page 119		

As shown in **Table 18** within the North American region, the United States made up close to 68% of the patients randomized.

Table 18- Proportion of patients randomized by country of origin

COUNTRY	IDeg OD N=3818		IGlar OD N=3819	
	N	(%)	N	(%)
Algeria	26	0.68	37	0.97
Argentina	56	1.47	64	1.68
Brazil	165	4.32	138	3.61
Canada	30	0.79	40	1.05
Croatia	29	0.76	17	0.45
Greece	40	1.05	50	1.31
India	168	4.4	189	4.95
Italy	67	1.75	73	1.91
Japan	35	0.92	26	0.68
Korea, Republic of	33	0.86	28	0.73
Malaysia	47	1.23	55	1.44
Mexico	83	2.17	79	2.07
Poland	71	1.86	64	1.68
Romania	47	1.23	37	0.97
Russian Federation	113	2.96	127	3.33
South Africa	106	2.78	88	2.30
Spain	33	0.86	27	0.71
Thailand	36	0.94	32	0.84
United Kingdom	38	1.00	42	1.10
United States	2595	67.97	2606	68.24
Source: ADSL.xpt				

Overall, patients randomized to IDeg and IGlar were well balanced with regard to baseline disease characteristics. **Table 19** shows the baseline concomitant illness and medical history of patients. On average, patients were obese (BMI 33.6 kg/m^2), and had an average duration of diabetes of approximately 16 years. Only 11% of patients were current smokers with the remainder being prior or never smokers. The average eGFR was 68 ml/min/1.73m^2 (CKD-EPI). 35.4% and 2.8% of patients had moderate and severe renal impairment respectively. The distribution of patient across renal impairment classes by treatment group was similar.

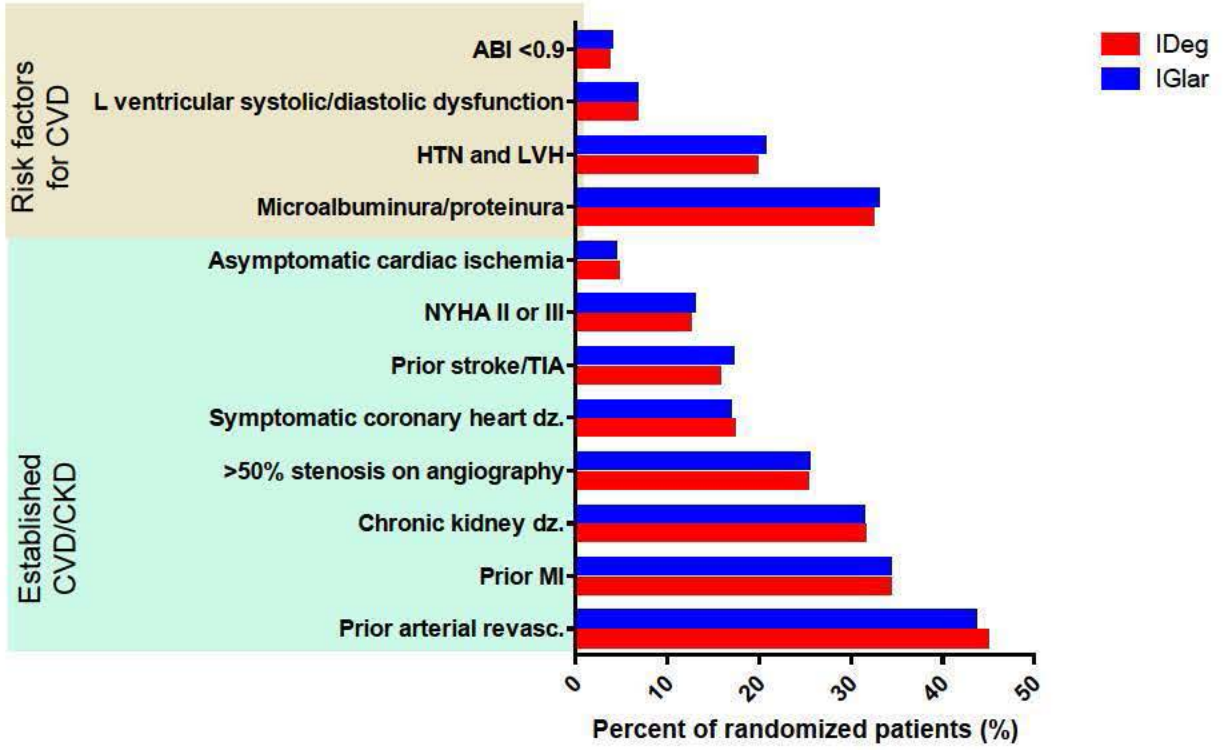
On average, blood glucose was poorly controlled. Patients had an average HbA1c of 8.4% with a mean fasting plasma glucose level close to 170 mg/dL (169.7 mg/dL for IDeg and 173.3 mg/dL for IGlar).

As previously discussed, the Sponsor used specific enrichment criteria to enroll T2DM at high risk of cardiovascular events (see **Table 4**). Of the 7637 subjects randomized, 85.2% met criteria 5a: were aged ≥50 years with established cardiovascular disease or chronic kidney disease; 14.5 % met criteria 5b: were aged ≥60 years with risk factors for cardiovascular disease at baseline. The remaining 23 subjects (0.3%) had unknown cardiovascular disease risk at baseline.

When evaluating by patients with established CV/CKD, *regardless of the age* specified in the inclusion criteria 5a (see **Figure 5**), prior arterial revascularization was seen in over 40% of patients (with slightly more patients in the IDeg than IGlar group- 44.8% and 43.5%, respectively). Prior myocardial infarction and chronic kidney failure were seen in 31-34% of patients, while stenosis on angiography was seen in a quarter of patients. Other categories were seen in less than 17% of patients.

When evaluating by patients with risk factors for CV disease, *regardless of the age* specified in the inclusion criteria 5b (see **Figure 5**), microalbuminuria or proteinuria was most commonly seen in close to a third of patients. Hypertension and left ventricular hypertrophy were seen in close to 20% of patients.

Figure 5 – Inclusion criteria according to cardiovascualr risk regardless of age



Source: CSR, table 10-5, page 124

Reviewer's comment: The extent of cardiovascular disease in the population enrolled is consistent with other CVOTs reviewed (i.e. LEADER trial).

Other diabetic complications including diabetic nephropathy, neuropathy and retinopathy were seen in approximately 10%, 23% and 14% of randomized patients and were similarly distributed. History of hypoglycemia was documented in 9 patients (0.2%) and 17 patients (0.4%) randomized to IDeg and IGlar respectively.

Reviewer's comments: the low percentage of patients with documented history of hypoglycemia is likely affected by the fact that this information was not systematically collected.

Table 19- Baseline characteristics – FAS

Baseline characteristics	**IDeg N= 3818**	**IGlar N=3819**
BMI, kg/m^2 mean ± SD	33.6 (6.8)	33.6 (6.8)
Body weight, kg mean ± SD	96.1 (22.9)	96.1 (22.9)
Systolic blood pressure, mmHg, mean ± SD	135.4 (18.0)	135.7 (18.1)
Diastolic blood pressure, mmHg, mean ± SD	76.1 (10.3)	76.2 (10.4)
Heart rate (beats/minute), mean ± SD	72.9 (11.4)	73.3 (11.3)
Duration of diabetes, year(s), mean ± SD	16.6 (8.8)	16.2 (8.9)

eGFR, ml/min/1.73m^2 (CKD-EPI), mean ± SD	68.11 (21.50)	67.81 (21.57)
Severe n (%)	108 (2.8)	106 (2.8)
Moderate n (%)	1321 (34.6)	1383 (36.2)
Mild n (%)	1596 (41.8)	1522 (39.9)
Normal n (%)	740 (19.4)	746 (19.5)
Unknown n (%)	53 (1.4)	62 (1.6)
HbA1c (%), mean ± SD	8.44 (1.63)	8.41 (1.67)
Fasting plasma glucose (mg/dL)	169.7 (70.2)	173.3 (70.7)
LDL (mg/dL), mean ± SD	84.82 (36.48)	86.08 (36.52)
HDL (mg/dL), mean ± SD	44.21 (12.88)	44.61 (12.80)
Total Cholesterol (mg/dL), mean ± SD	163.95 (47.17)	166.23 (47.02)
Triglycerides (mg/dL), mean ± SD	182.96 (150.56)	187.17 (169.28)
Cardiovascular history		
Subjects with established CV/CKD		
prior arterial revascularization	1709 (44.8)	1662 (43.5)
prior myocardial infarction	1303 (34.1)	1303 (34.1)
chronic kidney failure	1197 (31.4)	1193 (31.2)
>50% stenosis on angiography	960 (25.1)	965 (25.3)
documented history of symptomatic coronary heart disease	653 (17.1)	637 (16.7)
prior stroke or prior transient ischemic attack	593 (15.5)	649 (17.0)
chronic heart failure NYHA II or III	468 (12.3)	487 (12.8)
documented asymptomatic cardiac ischemia	170 (4.5)	160 (4.2)
Subjects with risk factors for CV disease		
microalbuminuria or proteinuria	1233 (32.3)	1256 (32.9)
hypertension and left ventricular hypertrophy	750 (19.6)	784 (20.5)
left ventricular systolic or diastolic dysfunction	253 (6.6)	251 (6.6)
ankle/brachial index <0.9	134 (3.5)	145 (3.8)
Unknown CVD risk	15 (0.4)	8 (0.2)
Other diabetic complications n (%)		
Diabetic nephropathy	393 (10.3)	369 (9.7)
Diabetic neuropathy	910 (23.8)	912 (23.9)
Diabetic retinopathy	558 (14.6)	542 (14.2)
Hypoglycemia	9 (0.2)	17 (0.4)

Note: Measurements were obtained at baseline visit (visit 2-randomization visit) except age, height, body weight, blood pressure, pulse and duration of diabetes which were obtained at screening (visit 1). HbA1c and fasting plasma glucose measured at central laboratory. * Including 3 subjects with age <50 years.
The classification for renal impairment is based on eGFR calculated using the CKD-EPI equation: normal renal function: eGFR ≥90 mL/min/1.73m^2; mild renal impairment: 60 ≤ eGFR <90 mL/min/1.73m^2; moderate renal impairment: 30 ≤ eGFR < 60 mL/min/1.73m^2; severe renal impairment: eGFR <30 mL/min/1.73m^2
Abbreviations: %: percentage of subjects relative to the number of randomized subjects; CKD-EPI: chronic kidney disease epidemiology collaboration; eGFR: estimated glomerular filtration rate; HbA1c: glycated hemoglobin; N:number of subjects; SD: standard deviation
Source: CSR table 10-3, page 121; table 14,1.22, page 262, table 10-5, page 124

The baseline and post-baseline diabetic and cardiovascular medications are shown in **Table 20**.

At baseline, the use of these medications was well balanced between treatment groups.

81% of patients were on an insulin regimen at trial start (with ~16% insulin naïve patients). Metformin was the most common oral antidiabetic drug used (~60%), followed by sulfonylureas (29%) and DPP4 inhibitors (~12%) with smaller percentages of other drugs.

As would be expected, in patients with established or at risk of cardiovascular disease, at baseline, most patients were taking antihypertensive treatments (93.1%), lipid lowering drugs (82.2%), and platelet aggregation inhibitors (71.9%).

When comparing the post-baseline changes by diabetic and cardiovascular medications, for the most part, medicines appeared to be well balanced between treatments groups, with exceptions noted. The most frequent anti-diabetic therapy started post-baseline was bolus insulin. Bolus insulin was started in slightly fewer patients on IDeg than IGlar (~19% vs 20%). Other commonly antidiabetic therapies started post baseline, included SGLT-2 inhibitors and GLP-1 receptor agonists. Of note, there was slightly higher proportion of patients starting a GLP-1 receptor agonist, post baseline, in patients randomized to IDeg (4%) vs. IGlar (3.1%). Please refer to section titled: **Severe hypoglycemia in relation to anti-diabetic medications**, for further discussion on the relationship between anti-diabetic medications and hypoglycemia findings.

Cardiovascular medications most commonly started post-baseline included beta blockers, calcium channel blockers, loop diuretics, and statins. Overall, post-baseline, there was no clear difference between treatment arms for cardiovascular medications.

Table 20- Baseline and post-baseline diabetic and cardiovascular medications – FAS

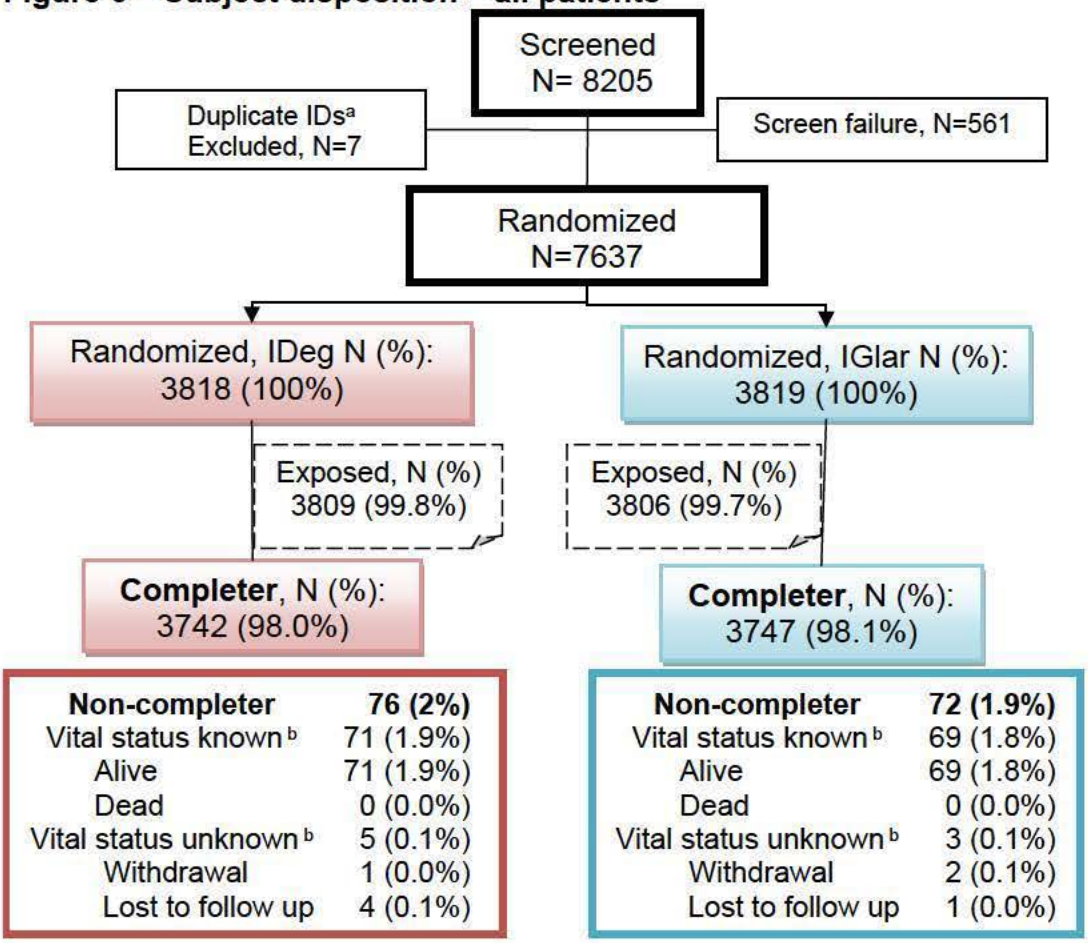
	BASELINE		POST-BASELINE	
Baseline characteristics	**IDeg N= 3818**	**IGlar N=3819**	**IDeg N= 3818**	**IGlar N=3819**
Insulin naive	604 (15.8)	624 (16.3)		
Insulin long acting	2298 (60.2)	2299 (60.2)		
Insulin intermediate acting*	537 (14.1)	537 (14.1)		
Insulin short acting	1407 (36.9)	1424 (37.3)	715 (18.7)	756 (19.8)
Insulin Premix	408 (10.7)	374 (9.8)		
OADs				
Metformin	2294 (60.1)	2270 (59.4)	117 (3.1)	115 (3.0)
SU	1118 (29.3)	1111 (29.1)	84 (2.2)	82 (2.1)
Alpha glucosidase inhibitors	63 (1.7)	70 (1.8)	25 (0.7)	22 (0.6)
TZD	145 (3.8)	123 (3.2)	50 (1.3)	40 (1.0)
DPP4 inhibitors	463 (12.1)	480 (12.6)	122 (3.2)	136 (3.6)
GLP1 receptor agonist	300 (7.9)	304 (8.0)	151 (4.0)	118 (3.1)
SGLT2 inhibitors	82 (2.1)	86 (2.3)	163 (4.3)	153 (4.0)
Others	50 (1.3)	68 (1.8)	28 (0.7)	19 (0.5)
CVD medications, n (%)	3761 (98.5)	3747 (98.1)	1383 (36.2)	1393 (36.5)
Antihypertensive therapy	3559 (93.2)	3550 (93.0)	731 (19.1)	734 (19.2)
Beta blockers	2210 (57.9)	2190 (57.3)	205 (5.4)	205 (5.4)
Calcium channel blockers	1214 (31.8)	1244 (32.6)	266 (7.0)	273 (7.1)
ACE inhibitors	1831 (48.0)	1796 (47.0)	135 (3.5)	151 (4.0)
Angiotensin receptor blockers	1289 (33.8)	1266 (33.2)	159 (4.2)	168 (4.4)
Renin inhibitors	3 (0.1)	7 (0.2)	2 (0.1)	1 (0.0)
Others	399 (10.5)	368 (9.6)	179 (4.7)	160 (4.2)
Diuretics	1902 (49.8)	1914 (50.1)	560 (14.7)	505 (13.2)
Loop diuretics	856 (22.4)	882 (23.1)	292 (7.6)	287 (7.5)
Thiazides	887 (23.2)	855 (22.4)	155 (4.1)	131 (3.4)
Thiazide-like diuretics	240 (6.3)	239 (6.3)	117 (3.1)	82 (2.1)
Aldosterone antagonists	232 (6.1)	238 (6.2)	95 (2.5)	93 (2.4)
Others	65 (1.7)	57 (1.5)	30 (0.8)	16 (0.4)
Lipid lowering drugs	3147 (82.4)	3127 (81.9)	284 (7.4)	289 (7.6)
Statins	3020 (79.1)	2982 (78.1)	181 (4.7)	181 (4.7)
Ezetimibe	175 (4.6)	171 (4.5)	33 (0.9)	34 (0.9)
Fibrates	425 (11.1)	426 (11.2)	56 (1.5)	57 (1.5)
Niacin	104 (2.7)	103 (2.7)	10 (0.3)	17 (0.4)
Others	27 (0.7)	34 (0.9)	20 (0.5)	19 (0.5)
Platelet aggregation inhibitors	2749 (72.0)	2741 (71.8)	351 (9.2)	334 (8.7)
Acetylsalicylic acid (ASA)	2501 (65.5)	2491 (65.2)	163 (4.3)	149 (3.9)
Clopidogrel, Tioclopidine, pasugrel, Tigagrelor	841 (22.0)	812 (21.3)	200 (5.2)	199 (5.2)
Others	69 (1.8)	75 (2.0)	38 (1.0)	28 (0.7)
Anti-thrombotic medication	308 (8.1)	289 (7.6)	330 (8.6)	355 (9.3)
Vitamin K antagonists	229 (6.0)	207 (5.4)	60 (1.6)	60 (1.6)
Direct thrombin inhibitors	19 (0.5)	22 (0.6)	15 (0.4)	27 (0.7)
Direct factor Xa inhibitors	51 (1.3)	49 (1.3)	84 (2.2)	96 (2.5)
Heparin group	11 (0.3)	11 (0.3)	228 (6.0)	237 (6.2)
Others	2 (0.1)	3 (0.1)	11 (0.3)	10 (0.3)
Source: CSR table 10-7, page 126; table 10-8, page 127				

6.1.3 Subject Disposition

A total of 8,205 patients were screened for DEVOTE. Approximately 6.8% of screened patients were screen failures[43]. A total of 7,637 patients were randomized (1:1) to IDeg and IGlar, as shown in **Figure 6**. Over 99% of patients in either treatment arm were exposed to either IDeg or IGlar. Over 98% in either treatment arm had a follow-up visit or died during the trial and were considered as having "completed the trial." The remaining 2% of patients did not complete the trial in either treatment arm. Of the patients that did not complete the trial, there were only eight patients (5 for IDeg and 3 for IGlar) with unknown vital status; therefore vital status was available for 99.9% of patients randomized in the trial.

[43] Most of screen failures did not meet one or more selection criteria (5%); with the remainder (2.3%) being screen failures due to other reasons

Figure 6 – Subject disposition – all patients



Note: Completer defined as: follow-up visit completed or died during trial.
[a] 7644 subjects randomized in total; 7 patients were randomized at 2 different sites;
[b] status during trial closure: from the first subject's follow-up visit (29 June 2016) to the actual last patient last visit (16 October 2016). Source: CSR, figure 10-1, page 116

Reviewer's comments: The overall screen failure rate is relatively low (making up 2.3% of all patients screened). This rate may indicate that the trial's inclusion/exclusion criteria were not too stringent and perhaps allowed a broader range of patients with type 2 diabetes mellitus to participate.

Also, the high known vital status in this trial is also notable, especially when considering the length of the trial.

6.1.4 Analysis of Primary Endpoint(s)

The analyses discussed below reflect the Sponsor's results. Please refer to the statistical review by Dr. Eugenio Andraca-Carrera or the FDA analyses of the primary endpoint.

As noted previously, insulin degludec was approved under the trade name Tresiba, after a second resubmission which included the interim analysis of DEVOTE. These interim results reflected the accrual of 24% of the overall trial MACE events. The interim results excluded a pre-marketing 80% excess in CV risk.

The primary endpoint of DEVOTE was time from randomization to the first occurrence of EAC-confirmed MACE; defined as cardiovascular death, non-fatal MI, non-fatal stroke which occurred during the individual observation period (from randomization to the patient's end of trial visit).[44] The analysis of the primary endpoint was based on the full analysis set: all randomized patients regardless of drug exposure.

Table 21 shows the first EAC confirmed events by treatment arms. In total 681 (8.9%) patients experienced a first MACE event; 8.5% (325 patients) randomized to IDeg and 9.3% (356 patients) randomized to IGlar. Slight numerical differences were seen for the components of MACE which tended to be slightly higher for IGlar than IDeg.

Table 21 – First EAC- confirmed MACE- FAS

	IDeg			IGlar		
	N	**%**	**R**	**N**	**%**	**R**
FAS	3818			3819		
PYO	7568			7558		
EAC confirmed 3-point MACE	325	8.5	4.29	356	9.3	4.71
Cardiovascular death*	114	3	1.51	119	3.1	1.57
Non-fatal MI	143	3.7	1.89	163	4.3	2.16
Non-fatal stroke	68	1.8	0.90	74	1.9	0.98

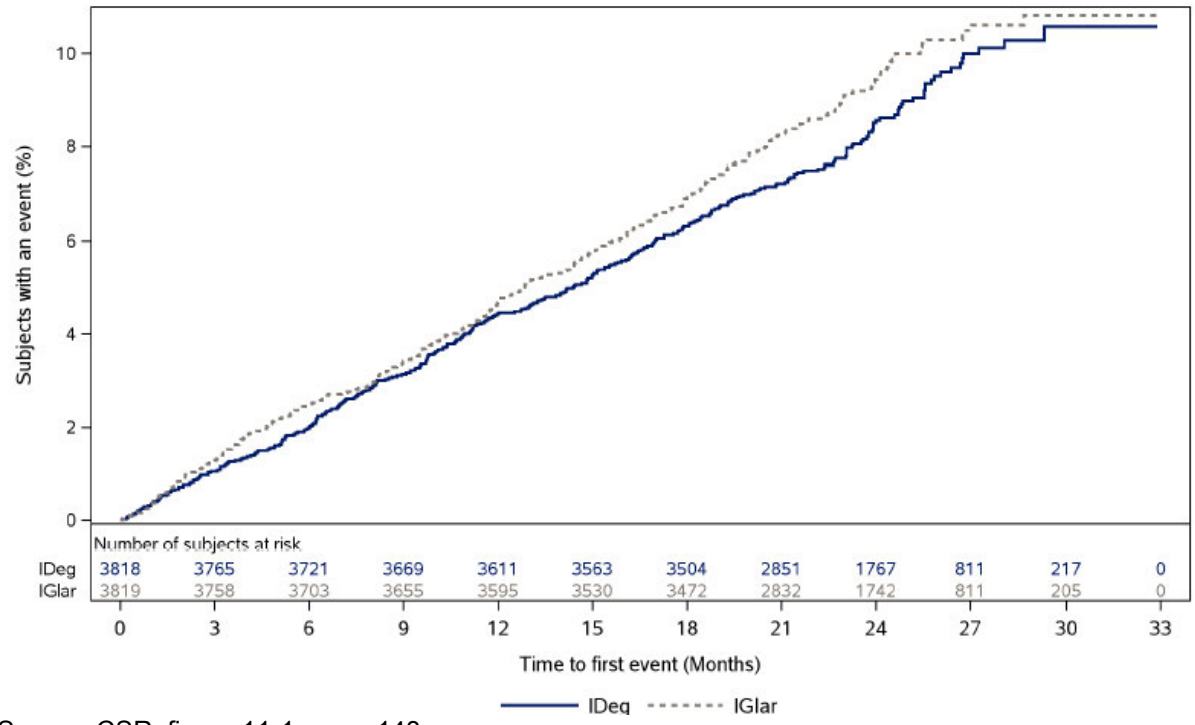
* Cardiovascular death includes 66 patients with undetermined cause of death. No patient experienced more than one EAC-confirmed MACE on the day of the first occurrence of an MACE
Abbreviations: EAC: event adjudication committee; MACE: major adverse cardiovascular event, N: number of subjects; PYO: patient-years of observation; R: event rate per 100 PYO; %: percentage of subjects
Source: CSR table 11-1, page 142

Figure 7 shows the Kaplan-Meier plot of EAC-confirmed first MACE over time for IDeg and IGlar.

The hazard ratio for time to first EAC-confirmed MACE of IDeg vs. IGlar was 0.91 with a 95% confidence interval of [0.78; 1.06]. The results exclude a 30% excess increased cardiovascular risk since the upper 95% CI (1.06) is below 1.3, and confirming the pre-specified hypothesis of noninferiority of IDeg relative to IGlar.

[44] In case events had the same date of onset the priority for selecting the first event was: cardiovascular death (including undetermined cause of death) > non-fatal MI > nonfatal stroke

Figure 7 – Time to first EAC-confirmed MACE- Kaplan-Meier plot-FAS



Source: CSR, figure 11-1, page 143

Reviewer's comment: The Kaplan-Meier curves for the two treatments seem to come together at two points (between month 6-9 and near month 12), with some divergence of the curves after month 12. Overall, the primary efficacy results meet the FDA Guidance for postmarketing study by excluding a 30% excess increased cardiovascular risk.

Notably, the trial was originally expected to have a duration of 5 years to accrue the expected 633 first EAC confirmed MACEs (which would provide the trial 91% power to rule out the upper bound of the 95% confidence interval of the hazard ratio (IDeg vs. IGlar) exceeding 1.3, assuming a true HR of 1.0). The original expected event rate was 2.1 events per 100 patient years of observation; this estimate is much lower than the actual observed event rate (4.5 events per 100 patient years) and the trial duration was much shorter. This discrepancy between what was expected at the trial planning stage and what was observed with the trial, is likely the result of the trial's greater recruitment of more ill-patients (i.e. patients meeting inclusion criteria 5a: age ≥50 years and established cardiovascular disease or chronic kidney disease made up 85.2% of patients randomized).

The findings of non-inferiority for the primary MACE endpoint in in DEVOTE is consistent with the findings in the ORIGIN study,[45] where insulin glargine (i.e. Lantus) was compared with standard of care and found to have no significant differences in regards to a MACE endpoint.

Sensitivity analyses

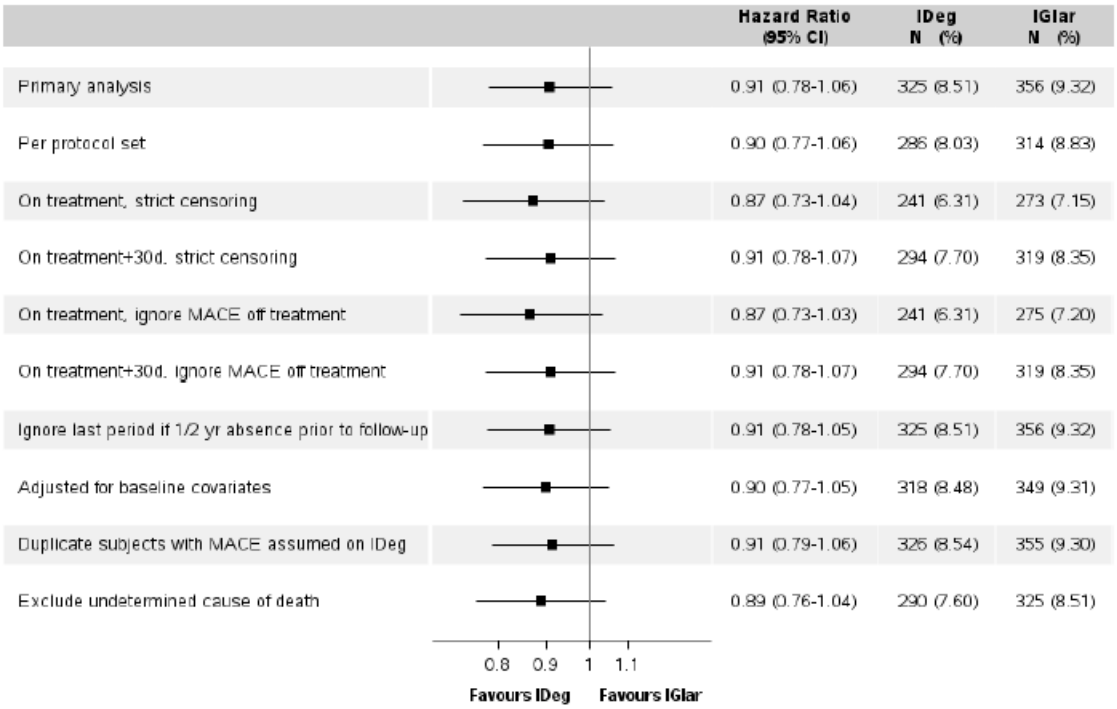
The sensitivity analyses of the primary endpoint are shown in **Figure 8**. Across multiple sensitivity analyses, (including the exclusion of undetermined causes of death) the results were consistent with the primary analysis: the upper bound of the 95% CI remained below 1.3 (with a maximum value of 1.07). The hazard ratio from multiple sensitivity analyses ranged from 0.87 to 0.91.

Tipping point analyses showed that the tipping point was not reached until 80 MACEs were added to the IDeg group; thus exceeding by 14 the number of IDeg-randomized patients who did not have an EAC-confirmed MACE and who did not complete the trial.

Please refer to Dr. Eugenio Andraca-Carrera review for the FDA's sensitivity analyses.

[45] Refer to Clinical review, in DAARTS dated 10/11/13, by Dr. Lisa Yanoff NDA 021081 supplement 057. ORIGIN was a randomized, open-label, cardiovascular outcomes trial which evaluated insulin glargine compared to standard of care in patients with impaired fasting glucose, impaired glucose tolerance or early type 2 diabetes mellitus with a prior cardiovascular event or existing cardiovascular risk factors. The exposure adjusted rate per 100 patient years for time to first occurrence of CV death, non-fatal MI or non-fatal stroke in ORIGIN was 2.94 for insulin glargine and 2.85 for standard of care. The hazard ratio for the 3 point MACE outcome was 1.02 with the 95% confidence interval of 0.93 to 1.11.

Figure 8 – Forest plot of sensitivivity analyses of time to first EAC-confirmed MACE



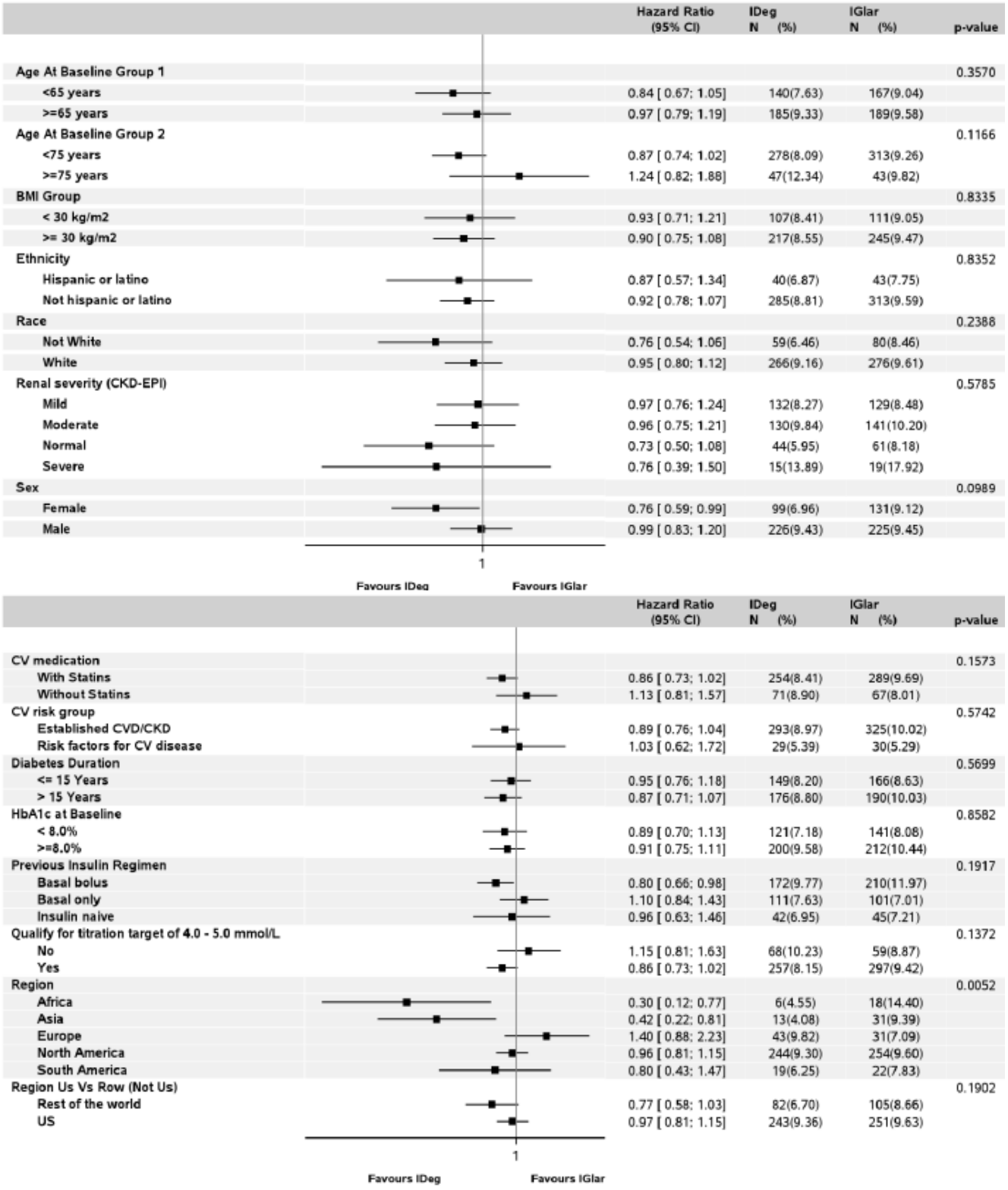
Source: CSR, figure 11-2, page 144

Subgroup analyses

The subgroup analyses for the primary endpoint are shown in **Figure 9.** Across subgroup examined, there was no clear difference in MACE between treatment groups; with the exception of the regions of Africa and Asia. For these two regions, the MACE findings favored IDeg. However the number of patients affected in these two regions was very small. For Africa there were only 6 and 18 patients with MACE events for IDeg and IGlar, respectively. While for Asia there were 13 and 31 MACE events for IDeg and IGlar, respectively. Therefore the findings in these regions may be due to chance.

Refer to Dr. Eugenio Andraca-Carrera review for further discussion on subgroup analyses.

Figure 9 –Time to first EAC-confirmed EAC confirmed MACE -Subgroup analyses



Note: %: percentage of subjects with first EAC-confirmed MACE, relative to the number of randomised subjects; p-value refers to interaction effect; N: number of subjects with a first EAC-confirmed MACE during trial
Note: Not White includes the following races: Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander and Other; %: percentage of subjects with first EAC-confirmed MACE, relative to the number of randomised subjects; p-value refers to interaction effect; N: number of subjects with a first EAC-confirmed MACE during trial
Abbreviations: CI: Confidence interval; EAC: event adjudication committee; MACE: major adverse cardiovascular event
Source: CSR, figure 12-8, page 186 and figure 12-9, page 187

Identification of cardiovascular events

As noted in **Table 7**, events were identified for adjudication by multiple methods.[46] To evaluate the trends in cardiovascular safety, I reviewed the adverse events which were sent for adjudication.[47] And in general, I agree with these events being sent for adjudication.

I also reviewed the adverse event dataset for adverse events that were reported by investigators but were not sent for adjudication.[48] The purpose of evaluating these events was to determine events that were possible missed in the evaluation of MACE.

All the events which were in the adverse event dataset but were not sent for adjudication are shown in **Table 81**, in the appendix. I reviewed the list of PT terms for a sample of possible events which I considered, could indicate ACS or CVS event but were not sent for adjudication; these are shown in **Table 22**. In an information request the Sponsor was asked to clarify why the following events were not sent for adjudication.

Table 22- Exploratory analysis- events which were not sent for adudication but that in the reviewer's opinion could meet criteria for adjudication

SOC	PT term	IDeg OD		IGlar OD	
		N	%	N	%
Cardiac disorders	Angina pectoris	20	0.52	28	0.73
	Angina unstable	6	0.16	3	0.08
	Cardiac arrest	3	0.08	5	0.13
	Cardiac discomfort	0	0	1	0.03
	Cardiogenic shock	1	0.03	1	0.03
	Cardio-respiratory arrest	1	0.03	2	0.05
	Coronary artery embolism	0	0	1	0.03
	Coronary artery insufficiency	2	0.05	1	0.03
	Coronary artery occlusion	9	0.24	2	0.05

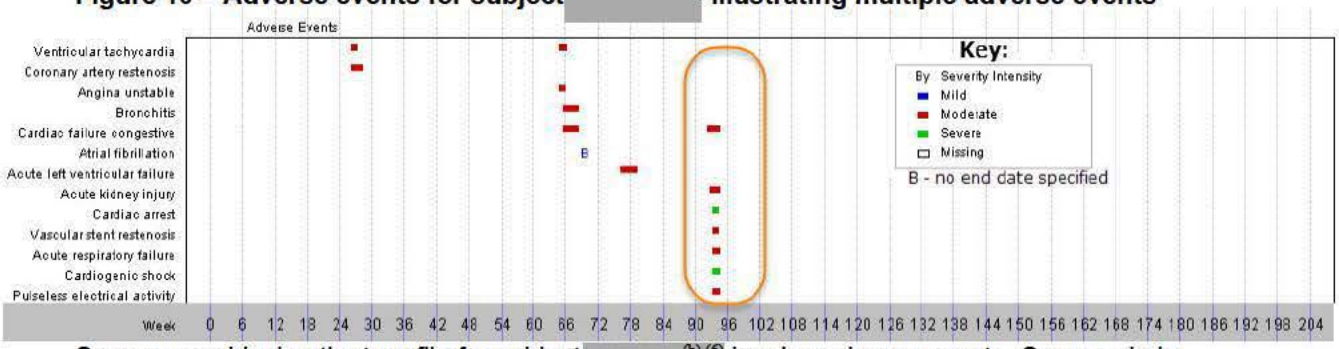
[46] Serious adverse events were to be documented in the eCRF AE form. These events are captured in the ADAE dataset. Some of these events were sent for adjudication. These events are captured in the adjudication dataset (ADADJ).
[47] I reviewed the ADAE dataset for events with the flags ACSQID, CVQID, DTHQID, HYPOQID, which identified events that were sent for adjudication
[48] Events were identified by the reviewer by selecting for events that were not sent for adjudication (i.e. these flags were left blank: ACSQID, CVQID, DTHQID, HYPOQID and restricting the events for the trial period (ANL01FL=Y) in the full analysis set (FASFL=Y).

	Coronary artery stenosis	11	0.29	4	0.1
	Coronary ostial stenosis	1	0.03	0	0
	Myocardial infarction	0	0	1	0.03
	Myocardial ischaemia	6	0.16	15	0.39
	Prinzmetal angina	0	0	1	0.03
General disorders and administration site conditions	Chest discomfort	7	0.18	11	0.29
	Chest pain	22	0.58	25	0.65
Investigations	Troponin increased	1	0.03	4	0.1
Nervous system disorders	Cerebral ischaemia	0	0	1	0.03
	Hemiparesis	2	0.05	2	0.05
	Transient ischaemic attack	10	0.26	8	0.21
Source: reviewer derived table from ADAE dataset. PT terms highlighted reflect PT terms which were not part of the pre-specified SMQ search					

On October 31, 2017, the Sponsor provided an information request with the EAC chair or delegate's rationale for not sending the event (in **Table 22)** for adjudication. I reviewed the rationale provided for each event.

For PT terms under SOC "nervous system disorder," (as shown in **Table 22**), events did not undergo stroke adjudication because the EAC chair documented negative imaging for most cases. The remaining events did not undergo adjudication for ACS because the EAC chair documented that the patient underwent a non-emergent, scheduled cardiac catherization or scheduled coronary artery bypass graft. In other cases, the patient was not hospitalized, or if the patient was hospitalized, then during hospitalization, either clinical information was unrevealing, or there was no medical intervention provided, or available documentation pointed to alternate etiology, i.e. "stable angina." In some cases, the event was categorized as a duplicate event, which was adjudicated under another PT term. To illustrate the latter point, refer to the **Figure 10,** which shows the adverse event for subject ID (b) (6) Although the term 'cardiogenic shock' was not sent for adjudication, the events of 'vascular stent restenosis, PEA and acute respiratory failure, which occurred on the same day, were sent for ACS adjudication.

Figure 10 – Adverse events for subject (b) (6) illustrating multiple adverse events



Source: graphical patient profile for subject (b) (6) showing adverse events. Orange circle emphasizes that the events occurred on the same day.

The Sponsor noted that the following PT terms were not part of the pre-specified SMQ search for Ischemic heart disease' and 'central nervous system hemorrhages and cerebrovascular conditions': 'Cardiac arrest', 'Cardiac discomfort', 'Cardiogenic shock', 'Cardio-respiratory arrest', 'Chest discomfort' and 'Chest pain,' 'chest discomfort', 'chest pain,' and 'troponin increased' (as highlighted in **Table 22**). When evaluating the proportion of patients affected by individual PT terms, there does not appear to be clear difference between treatment arms in the proportion of patients affected.

Reviewer's comments: Overall, an exploratory search for events which were not sent for adjudication did not reveal differences between treatment arms which would drastically change the overall MACE findings.

Discussion of the components of MACE
This section will discuss the safety for the overall cardiovascular findings (i.e. total events) of MACE, expanded MACE, deaths and hospitalization for heart failure. The discussion of these endpoints is carried out in this section, rather than in the safety section, to provide context for the primary endpoint findings.

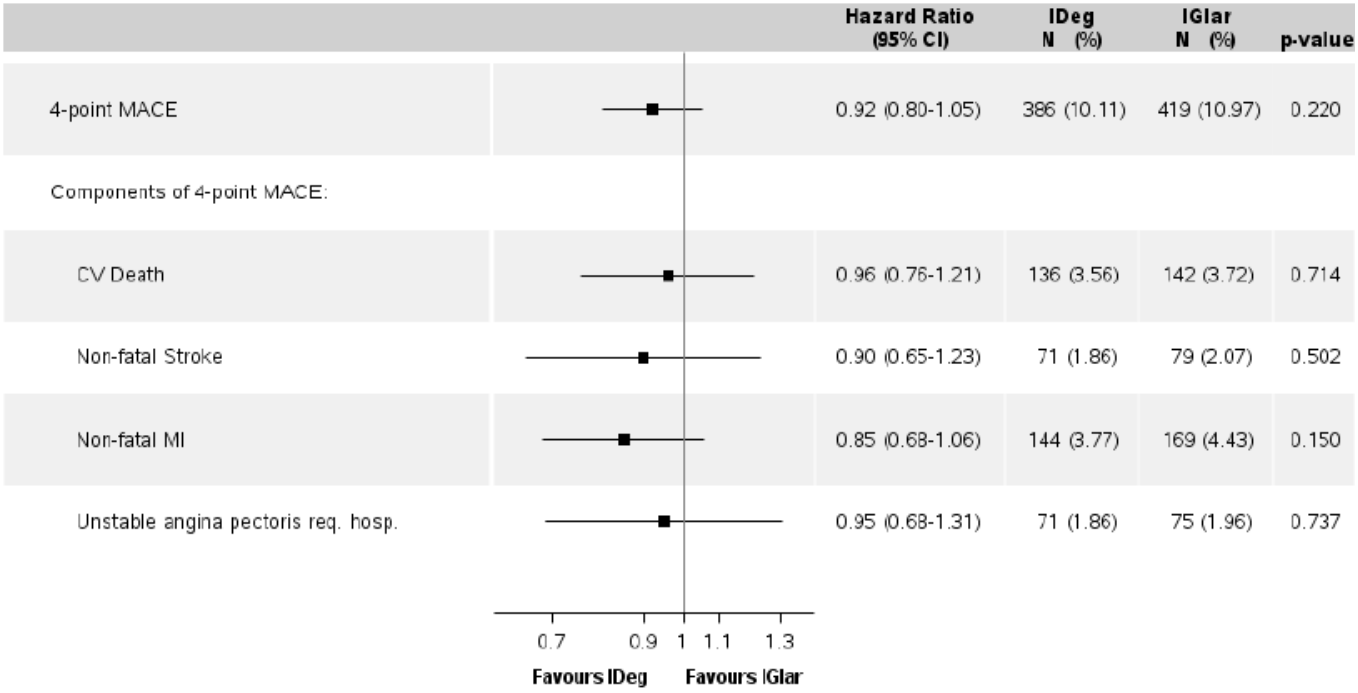
EAC confirmed MACE
In total, 799 MACE events (first and recurrent) were confirmed by the EAC. Slightly lower number of MACE events occurred for IDeg 5.05 PYO per 100 years vs. IGlar 5.52 PYO per 100 years. There were slight numerical differences in the components of MACE between treatment groups, as shown in **Table 23**. For each MACE component there were slightly lower number of patients and events for IDeg vs. IGlar.

Table 23 – EAC confirmed MACE (all events) - FAS

	IDeg			IGlar		
	N (%)	E	R	N (%)	E	R
FAS	3818			3819		
PYO	7568			7558		
MACEs	325 (8.5)	382	5.05	356 (9.3)	417	5.52
Non-fata MI	144 (3.8)	172	2.27	169 (4.4)	187	2.47
Non-fatal stroke	71 (1.9)	74	0.98	79 (2.1)	88	1.16
Cardiovascular death	136 (3.6)	136	1.8	142 (3.7)	142	1.88
Source CSR table 12-7, page 185, * Cardiovascular death includes 75 subjects with undetermined cause of death. Events with EAC onset date during trial are included.						

The 4-point MACE endpoint was pre-specified as a safety endpoint, and not an efficacy endpoint. The 4-point MACE endpoint included the following components: CV death, non-fatal stroke, non-fatal MI and unstable angina pectoris requiring hospitalization; see results in **Figure 11.** There were numerical differences favoring IDeg for 4-point MACE (i.e.10.11% vs. 10.97% patients with 4-point MACE).

Figure 11 – 4-point MACE and components



Source: CSR, figure 12-10, page 188

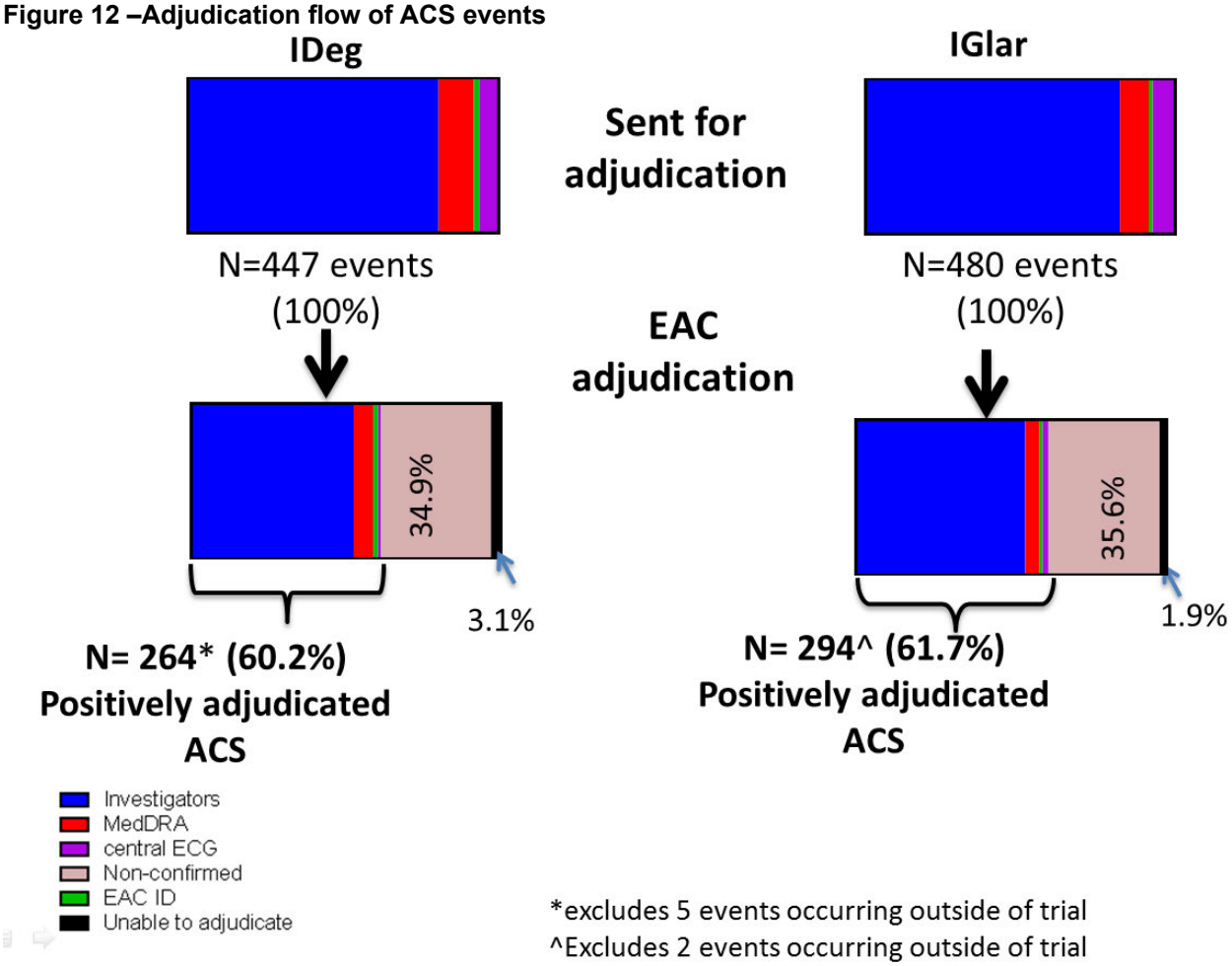
Reviewer's comment: Overall, the findings for 4-point MACE were similar to the primary endpoint findings. In both analyses, the hazard ratio was slightly less than 1 with the 95% confidence interval crossing 1 but remaining below 1.3 (i.e. ruling out a 30% increased cardiovascular risk).

ACS discussion

As noted in **Table 7**, ACS events, included myocardial infarctions and unstable angina pectoris requiring hospitalization. These events were captured via the investigator, sponsor MedDRA search and via ECG readers of both scheduled and unscheduled ECGs.[49] Of 927 events sent for adjudication, 558 or 60% of events sent for adjudication were "confirmed" by the EAC as meeting ACS criteria; see **Figure 12.**

[49] In all 24,376 ECGs were reviewed by central readers, of these 23,630 were scheduled ECGs (97 %), while 746 were unscheduled ECGs.

Figure 12 –Adjudication flow of ACS events



Source: reviewer graphed CSR, Table 14.2.102, page 404
Note: The trial period is defined as the time from randomization to last direct contact or EAC-confirmed MACE/death prior to LPLV (whichever occurred last). Percentages are based on number of subjects with the event of interest

The characteristics of the ACS events that were confirmed by the EAC are shown in **Table 24**. Overall, there were numerically less patients and EAC confirmed ACS events for IDeg than for IGlar. Approximately 70% of all ACS events were confirmed as MIs with the ~30% remaining events confirmed as UAP requiring hospitalization.[50] Most MIs were non-fatal MIs with slightly less proportion of patients (3.8% vs. 4.4%) and event rate (2.27 vs. 2.47 events per 100 PYE) seen for IDeg vs IGlar, respectively. Only 13 and 23 MIs were fatal for IDeg and IGlar respectively.

[50]"hospitalization" was defined as admission to an inpatient unit or visit to an emergency department that results in at least 24 hours stay (or change in calendar date if the hospital admission or discharge times are not available). In addition, hospitalization had to be unscheduled, occurring within 24 hours of the event.

Silent MIs made up a minority of the MI events in either treatment arm (5 and 9 events for IDeg and IGlar, respectively).

Reviewer's comment: the small percentage of the silent MI's (~3% of all MIs) in this trial is somewhat surprising since all ECGs were considered (i.e., including ECGs during pre-specified visits and outside of the trial visits). The shorter duration of the trial as compared to other CVOTs may explain why the number of these events is relatively small.

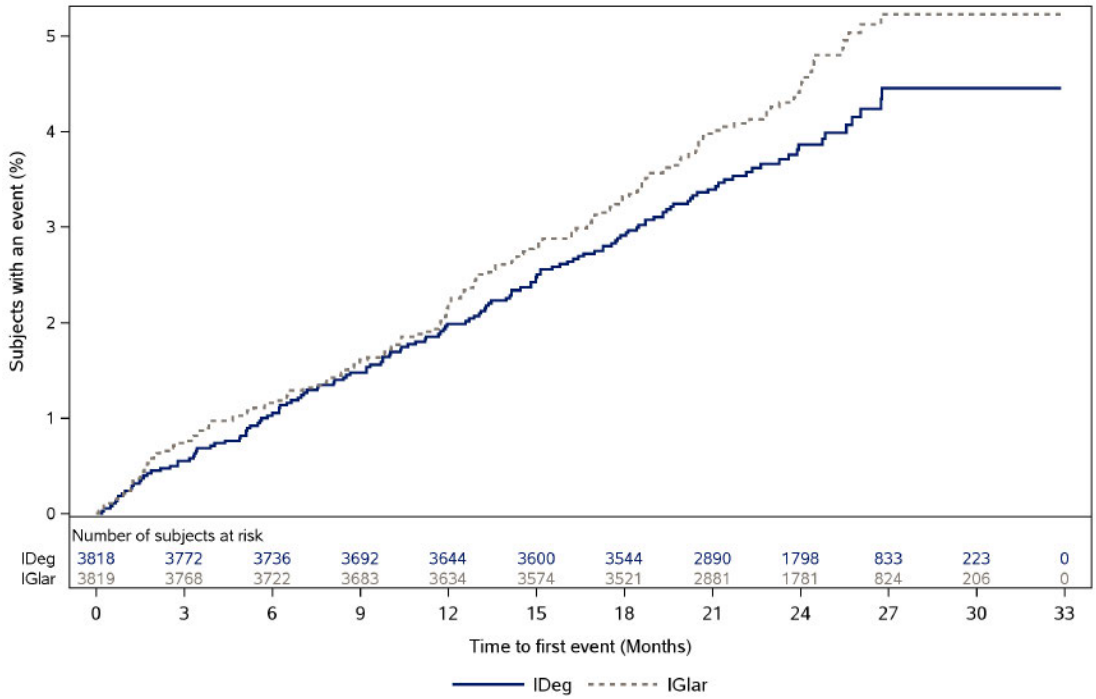
Table 24 – Characteristics of EAC confirmed acute coronary syndrome – summary -FAS

	IDeg			IGlar		
	N (%)	**E**	**R**	**N (%)**	**E**	**R**
FAS	3818			3819		
PYO	7568			7558		
All EAC confirmed ACS	216 (5.7)	264	3.49	252 (6.6)	294	3.89
EAC confirmed UAP req. hosp.	71 (1.9)	79	1.04	75 (2.0)	84	1.11
EAC confirmed MI	154 (4.0)	185	2.44	187 (4.9)	210	2.78
All Non-fatal MI	144 (3.8)	172	2.27	169 (4.4)	187	2.47
Symptomatic MI	140 (3.7)	167	2.21	162 (4.2)	178	2.36
Silent MI	5 (0.1)	5	0.07	9 (0.2)	9	0.12
Types of Acute MI						
STEMI	21 (0.6)	24	0.32	30 (0.8)	30	0.40
NSTEMI	109 (2.9)	128	1.69	124 (3.2)	138	1.83
Cannot be determined	13 (0.3)	15	0.20	10 (0.3)	10	0.13
Recurrent MI	18 (0.5)	27	0.36	12 (0.3)	16	0.21
Fatal MI	13 (0.3)	13	0.17	23 (0.6)	23	0.30
Symptomatic MI	13 (0.3)	13	0.17	23 (0.6)	23	0.30
Silent MI	0	0	0	0	0	0
Types of acute MI						
STEMI	4 (0.1)	4	0.05	4 (0.1)	4	0.05
NSTEMI	5 (0.1)	5	0.07	9 (0.2)	9	0.12
Cannot be determined	4 (0.1)	4	0.05	10 (0.3)	10	0.13

ACS: acute coronary syndrome; MI: myocardial infarction UAP: unstable angina pectoris, req. hosp: requiring hospitalization.
Source: modified CSR, table 14.2.103, page 405

Figure 13 shows the time to the first non-fatal MI. Events occurred similarly throughout the trial for IDeg and IGlar. The Sponsor's statistical analysis for time to first non-fatal MI showed a HR 0.85 with a 95% confidence interval of [0.68; 1.06].

Figure 13 – Time to first non-fatal MI – Kaplan- Meier plot- FAS

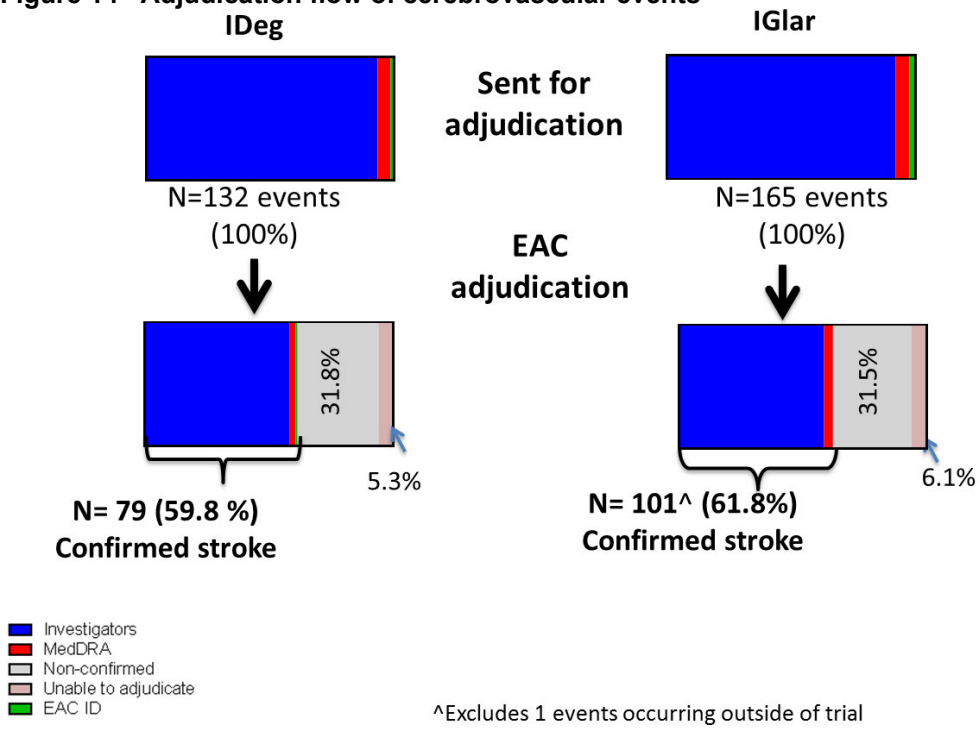


Source: CSR, figure 12-14, page 193

Stroke

As noted in **Table 7**, stroke events were captured via the investigator, sponsor MedDRA search and by the EAC. Of 297 events sent for adjudication, 180 or ~60% of events sent for adjudication were confirmed by the EAC as meeting stroke definition; see **Figure 14.**

Figure 14 –Adjudication flow of cerebrovascular events



Source: reviewer graphed CSR, Table 14.2.100, page 402
Note: The trial period is defined as the time from randomization to last direct contact or EAC-confirmed MACE/death prior to LPLV (whichever occurred last). Percentages are based on number of subjects with the event of interest

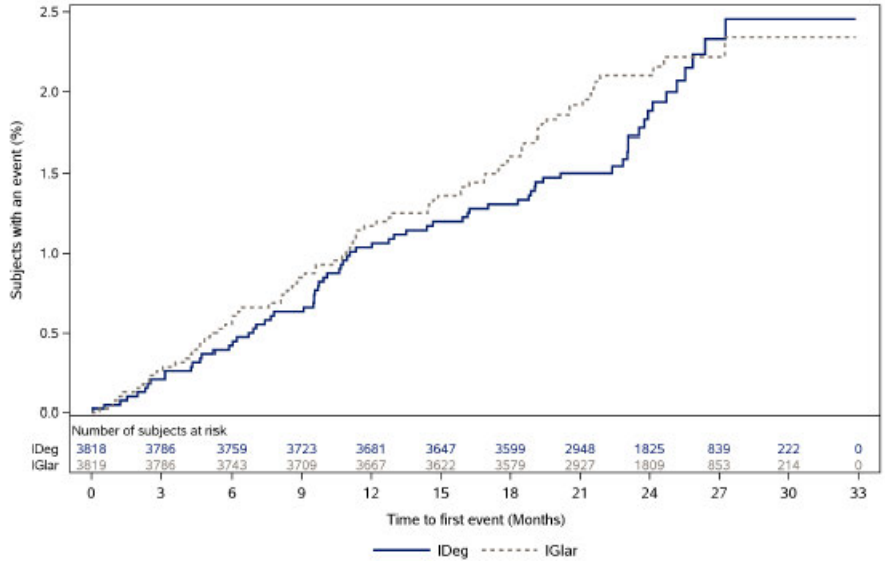
As shown in **Table 25**, although there were small numerical differences between treatment groups, strokes were similarly distributed between treatment arms. Most stroke events were classified as non-fatal strokes, with more than 80% classified as non-fatal ischemic strokes. Fatal strokes were seen in 5 and 8 patients in the IDeg and IGlar groups respectively.

Table 25 – Characteristics of EAC confirmed stroke events– summary –FAS

	IDeg			IGlar		
	N (%)	**E**	**R**	**N (%)**	**E**	**R**
FAS	3818			3819		
PYO	7568			7558		
All strokes	74 (1.9)	79	1.04	88 (2.3)	101	1.34
Non-fatal stroke	71 (1.9)	74	0.98	79 (2.1)	88	1.16
Ischemic stroke	64 (1.7)	67	0.89	76 (2.0)	85	1.12
Hemorrhagic stroke	7 (0.2)	7	0.09	3 (0.1)	3	0.04
Undetermined stroke	0	0	0	0	0	0
Recurrent stroke	3 (0.1)	3	0.04	8 (0.2)	9	0.12
Fatal stroke	5 (0.1)	5	0.07	13 (0.3)	13	0.17
Ischemic stroke	4 (0.1)	4	0.05	5 (0.1)	5	0.07
Hemorrhagic stroke	1 (0.0)	1	0.01	7 (0.2)	7	0.09
Undetermined stroke	0	0	0	1 (0.0)	1	0.01
Source: modified CSR, table 14.2.101, page 403						

Figure 15 shows the time to the first non-fatal stroke. Events occurred similarly throughout the trial for IDeg and IGlar. The Sponsor's statistical analysis for time to first non-fatal stroke had a HR 0.90 with a 95% confidence interval of [0.65; 1.23].

Figure 15 – Time to first non-fatal stroke – Kaplan- Meier plot- FAS



Source: CSR, figure 12-16, page 195

CV-death

In the MACE analysis, the component of CV-death was made up by events which the EAC classified as "CV-death" and by events which the EAC classified as death from "undetermined cause." As shown in **Table 26,** 2.5% and 2.8% deaths were classified by the EAC as "CV-death" for IDeg and IGlar respectively. Undetermined causes of death were confirmed by the EAC in 1.0% and 0.9% of patients for IDeg and IGlar respectively.

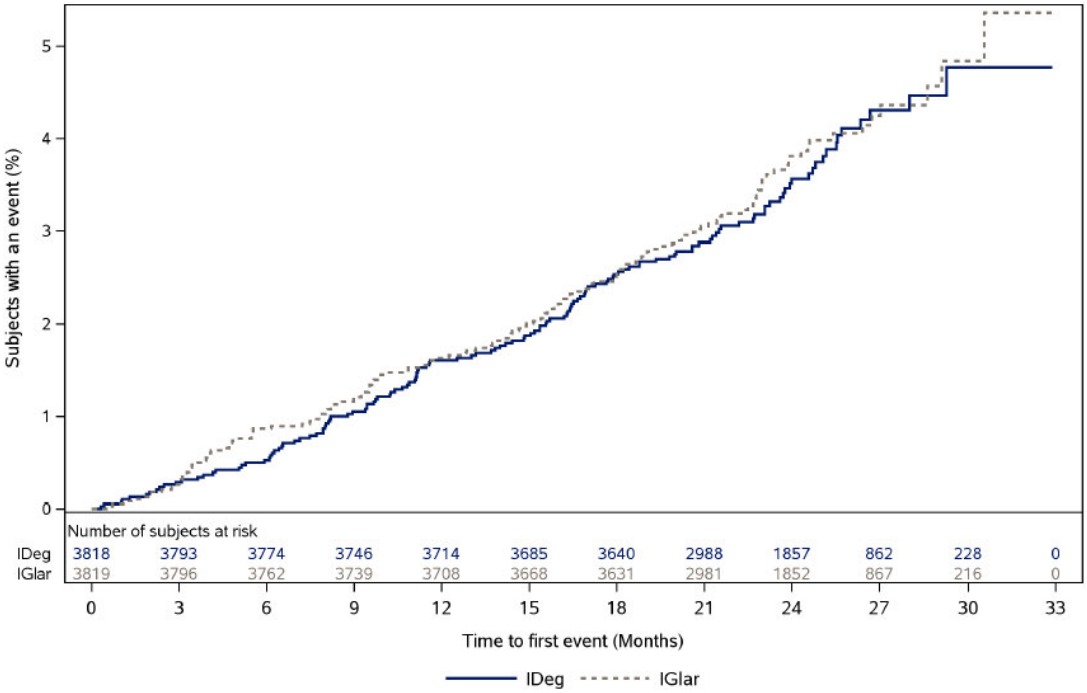
The most common cause of EAC categorized “CV-death” for both treatment group was sudden cardiac death; affecting 1.5% vs 1.4% of patients randomized to IDeg and IGlar, respectively. Acute MI was seen slightly less frequently in IDeg (0.4%) as compared to IGlar (0.6%). Other CV-death categories had small numerical imbalances between treatment groups. Review of a sample of death narratives was overall consistent with the EAC adjudication.

Approximately ~18% (75 total undetermined deaths from 423 total deaths) of all deaths were classified as undetermined. Review of a sample of deaths classified as having an “undetermined cause” by the EAC, revealed cases in which there were due to multiple possible contributing factors or very few details available surrounding the death to clearly ascertain the cause of death.

Reviewer’s comments: Overall, I agree with the EAC adjudication of CV-deaths and undetermined causes of deaths. The occurrence of CV-deaths appears to be balanced between treatment groups.

As shown in **Figure 16,** CV-deaths occurred throughout trial for IDeg and IGlar. The Sponsor’s analysis of time to CV-death had a hazard ratio of 0.96 with a 95% confidence interval of [0.76; 1.21].

Figure 16 – Time to cardiovascular death- Kaplan-Meier plot-FAS



Source: CSR, figure 12-12, page 190

All cause death and non-CV death

Table 26 shows all the deaths that occurred in DEVOTE as categorized by the EAC; see **Table 68.** There were a total of 423 deaths which occurred during the trial. Deaths occurred in 5.3% of patients randomized to IDeg and 5.8% of patients randomized to IGlar. The classification of deaths included 203 confirmed as cardiovascular deaths, 145 confirmed non-cardiovascular deaths and 75 undetermined deaths.[51] For both treatment groups cardiovascular deaths made up 48% of all deaths. There were slight differences in the proportion of non-CV deaths (33% vs. 36% for IDeg vs. IGlar) and undetermined deaths (19% vs. 16% for IDeg vs. IGlar). Please refer to section titled **CV-death** for an in-depth discussion on CV deaths and undetermined deaths (which were classified as CV-death for analyses of MACE).

Of note, there were 10 additional deaths which occurred between the end of trial and database lock and were considered outside of the trial period.[52]

The Preferred Terms (PT) "Other cardiovascular" and "other non-cardiovascular" events are included at the bottom of **Table 26.** I reviewed PT terms that were not consistent with the overall adjudication by the EAC and discuss these narratives after **Table 26**.

[51] In the primary endpoint analysis, the undetermined deaths were counted as cardiovascular deaths, as per the 2012 version of the FDA Standardized Definitions for Cardiovascular Outcomes Trials

[52] These deaths included 6 patients who had fatal AEs with onset after end of trial as determined by both investigator and EAC (subject ID (b) (6) randomized to IDeg and subject IDs (b) (6) (b) (6) (b) (6) (b) (6) and (b) (6) randomized to IGlar) and 4 patients who had fatal AEs with onset during the trial period but for whom death was determined by the EAC to occur after the end of trial (subject IDs (b) (6) (b) (6) and (b) (6) randomized to IDeg and subject ID (b) (6) randomized to IGlar).

Table 26 – Characteristics of EAC adjudicated deaths- summary- FAS

	IDeg			IGlar		
	N (%)	E	R	N (%)	E	R
FAS	3818			3819		
PYO	7568			7558		
Total deaths (all cause)	202 (5.3)	202	2.67	221 (5.8)	221	2.92
Cardiovascular deaths	97 (2.5)	97	1.28	106 (2.8)	106	1.40
Sudden cardiac death	57 (1.5)	57	0.75	55 (1.4)	55	0.73
Acute MI	14 (0.4)	14	0.19	22 (0.6)	22	0.29
Heart failure	13 (0.3)	13	0.17	11 (0.3)	11	0.15
Cerebrovascular event	6 (0.2)	6	0.08	13 (0.3)	13	0.17
Cardiovascular procedure	0	0	0	2 (0.1)	2	0.03
Cardiovascular hemorrhage	0	0	0	1 (0)	1	0.01
Other cardiovascular causes^*	7 (0.2)	7	0.09	2 (0.1)	2	0.03
Non-cardiovascular deaths	66 (1.7)	66	0.87	79 (2.1)	79	1.05
Pulmonary causes	9 (0.2)	9	0.12	12 (0.3)	12	0.16
Renal causes	4 (0.1)	4	0.05	3 (0.1)	3	0.04
Gastrointestinal causes	2 (0.1)	2	0.03	1 (0)	1	0.01
Hepatobiliary causes	0	0	0	4 (0.1)	4	0.05
Pancreatic causes	0	0	0	0	0	0
Infection (including sepsis)	20 (0.5)	20	0.26	21 (0.5)	21	0.28
Non-infectious (systemic inflammatory response, SIRS)	0	0	0	0	0	0
Hemorrhage that is neither CV bleeding or stroke	0	0	0	0	0	0
Non-CV procedure or surgery	0	0	0	0	0	0
Trauma	3 (0.1)	3	0.04	6 (0.2)	6	0.08
Suicide	0	0	0	2 (0.1)	2	0.03
Non-prescription drug reaction or overdose	0	0	0	0	0	0
Prescription drug reaction or overdose	0	0	0	0	0	0
Neurological (non – cardiovascular)	0	0	0	3 (0.1)	3	0.04
Malignancy	25 (0.7)	25	0.33	25 (0.7)	25	0.33
Other non-cardiovascular σΩ	3 (0.1)	3	0.04	2 (0.1)	2	0.03
Undetermined cause	39 (1.0)	39	0.52	36 (0.9)	36	0.48

Source CSR table 14.2.99, page 400-401
^IDeg PT terms: Pulmonary embolus (subject ID (b) (6)); acute respiratory failure (subject ID (b) (6) ventricular fibrillation (subject ID (b) (6) intestinal ischemia (subject ID (b) (6) hypertensive heart disease (ID (b) (6)
*IGlar PT terms: skin necrosis (subject ID (b) (6) vascular dementia (subject ID (b) (6)
σ IDeg PT terms: Fall (Subject ID (b) (6) cardiac failure congestive (subject ID (b) (6) multiple organ dysfunction syndrome (subject ID (b) (6)
Ω IGlar PT terms: hyponatremia (subject ID (b) (6) Multiple organ dysfunction syndrome (subject ID (b) (6)

The following death cases were reviewed further due to inconsistent classification of the death by the investigator and EAC:

- Subject ID (b) (6) (IDeg) was reported by the investigator with PT term of acute respiratory failure, and was adjudicated as cause of death by "other cardiovascular cause"
    - Patient was admitted with abdominal pain and was intubated because of respiratory failure. He was found to have a bilateral massive pulmonary embolus and developed anoxic brain injury. He also developed acute kidney injury. Family proceeded with comfort measures.
    - Review of the adjudication packet revealed that the adjudicators were initially in disagreement (adjudicator 1 adjudicated the event as "other CV cause" due to pulmonary embolus resulting in anoxic encephalopathy, while adjudicator 2 adjudicated the event as "other CV cause"). Eventually the adjudicators came to agreement and adjudicated the event as CV death.

      Reviewer's comment: the clinical presentation is consistent with a cause of death due to pulmonary embolus, a CV-cause of death.
- Subject ID (b) (6) (IDeg) was reported by the investigator with PT term of intestinal ischemia, and was adjudicated as cause of death by "other cardiovascular cause"
    - Patient presented to the emergency department with severe abdominal pain and was admitted. The medical records state that the patient had ischemic bowel and underwent emergent exploratory laparotomy. Post operatively the patient was intubated and admitted to the intensive care unit. The patient was thought to have sepsis, and acute renal failure. Patient's family withdrew life support and admitted patient to hospice.
    - Review of the adjudication packet revealed that the adjudicators were initially in disagreement (adjudicator 1 adjudicated event at Other CV death, while adjudicator 2 adjudicated event as non-CV death due to GI cause). Eventually, the adjudicators came to agreement and adjudicated the event as CV-death.

      Reviewer's comment: I disagree with the adjudication of this event as CV-death. It appears as though the patient experienced multi-organ failure as a result of bowel ischemia.
- Subject ID (b) (6) (IGlar) was reported by the investigator with PT term of skin necrosis, and was adjudicated as cause of death by "other cardiovascular cause"
    - Report states that patient attended routine appointment for necrotic heel at vascular clinic and was admitted for surgical debridement. Patient underwent a below the knee amputation and treatment with antibiotics. After amputation the patient decompensated, developed oliguria, hyperkalemia, fluid overload and hypotension. Patient did not receive dialysis. The cause of death is listed as "1a: acute kidney disease, 1b sepsis, 1c end stage vascular disease, 2 diabetes, IHD, CKD"
    - Review of the adjudication packet revealed that the adjudicators were initially in disagreement (adjudicator 1 adjudicated event at CV death,

while adjudicator 2 adjudicated event as non-CV death). Eventually, the adjudicators came to agreement and adjudicated the event as CV-death.

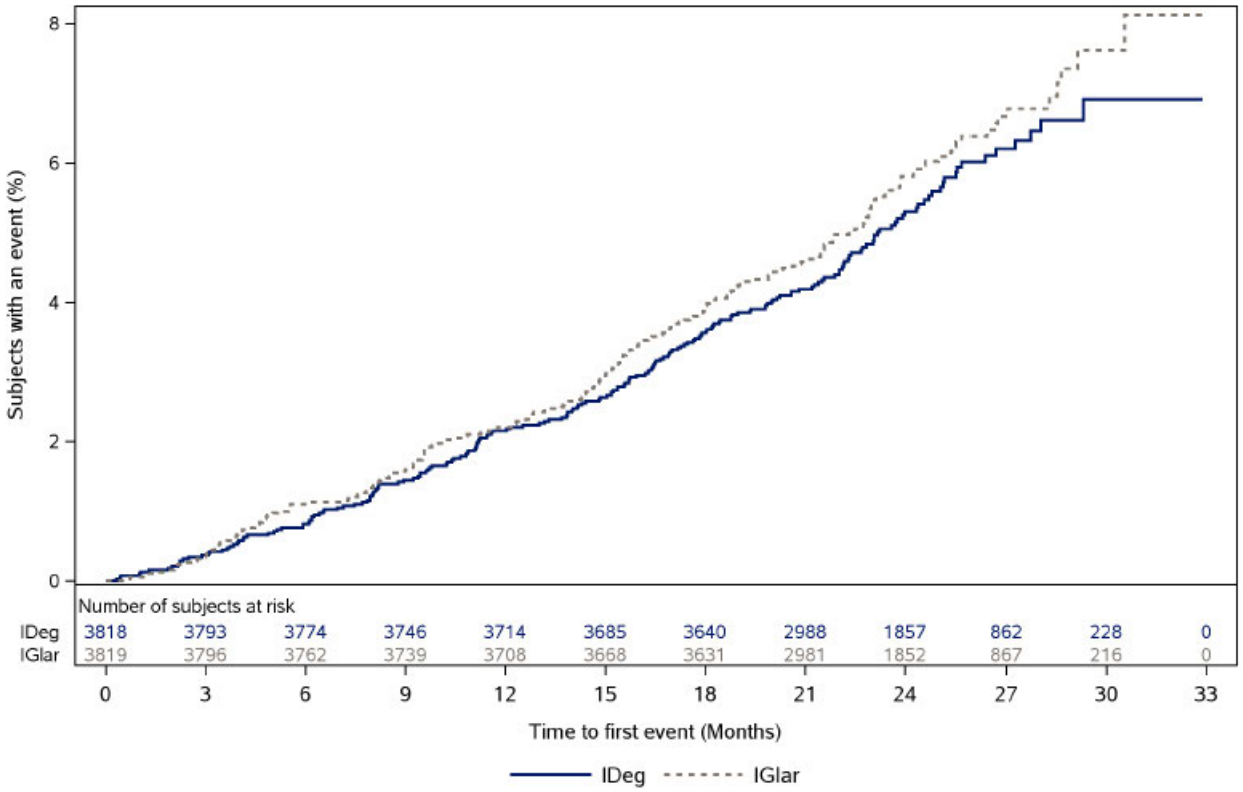
Reviewer's comment: I disagree with the adjudication of this event as CV death. The clinical picture is consistent with development of acute renal failure.

- Subject ID (b) (6) (IGlar) was reported by the investigator with PT term of vascular dementia, and was adjudicated as cause of death by "other cardiovascular cause"
    - Patient had a history of dementia and previous hospitalizations for falls, seizures and failure to thrive. The patient's family placed him on hospice. While at hospice, the patient was found dead. The cause of death in the death certificate states vascular dementia.
    - Review of the adjudication packet revealed that the adjudicators were initially in disagreement (adjudicator 1 adjudicated event at CV death, while adjudicator 2 adjudicated event as non-CV death- due to vascular dementia). Eventually, the adjudicators came to agreement and adjudicated the event as CV-death.
      Reviewer's comment: I disagree with the adjudication of this event as CV death. The clinical picture is consistent with vascular dementia and/or failure to thrive.

Reviewer's comments: Despite the handful of narratives discussed above, I overall agree with the adjudication of deaths in DEVOTE.

As shown in **Figure 17,** all-cause deaths occurred evenly in the trial for IDeg and IGlar. The Sponsor's analysis of time to all-cause death showed a hazard ratio of 0.91 with a 95% confidence interval of [0.75; 1.11].

Figure 17 – Time to all-cause death- Kaplan-Meier plot-FAS



Source: CSR, figure 12-2, page 169

The reviewer also evaluated all-cause mortality by reviewing the MedDRA classification of the adverse event. The percentage of patients who died is shown in **Table 76;** in the appendix. Across System organ class (SOC) and preferred term (PT) categories, there are no clear treatment-specific trends noted.

Reviewer's comment: The all-cause mortality findings for DEVOTE do not provide any evidence that the difference in severe hypoglycemia (discussed below) affected the mortality findings in the trial. However, it is important to keep in mind that the trial was not powered to detect a mortality difference.

In order to explore the safety of the low glycemic targets used in DEVOTE, the Sponsor was asked to provide the proportion of deaths between different titration target groups; see **Table 27.**

Across titration schemes, the number of patients per treatment arm was well balanced. As could be expected, there were differences in glycemic control based on the titration algorithm chosen. The lowest HbA1c was seen in the standard titration goal. DEVOTE did not seem to indicate a relationship between low glycemic goals and increased mortality rates, although it is important to keep in mind that the number of patients using

alternative titration goals were small and the titration regimen may have changed throughout the trial (which was not systematically captured in the trial).

Table 27 – HbA1c (%) and all-cause death by titration target at baseline - FAS

	Standard titration goal [a]		Steering committee alternative titration goal [b]		Other type of titration goal [c]	
Treatment	IDeg	IGlar	IDeg	IGlar	IDeg	IGlar
Randomization N (%)	3153 (82.5)	3154 (82.5)	133 (3.5)	132 (3.5)	532 (13.9)	533 (13.9)
HbA1c (%) end of trial visit), mean SD	7.55 (1.29)	7.52 (1.27)	7.72 (1.20)	7.57 (1.10)	7.67 (1.18)	7.68 (1.27)
Death (all cause) N (%)	155 (4.9)	180 (5.7)	11 (8.3)	2 (1.5)	36 (6.8)	39 (7.3)
Mortality rate (per 100 PYE)	2.46	2.86	4.47	0.78	3.50	3.86

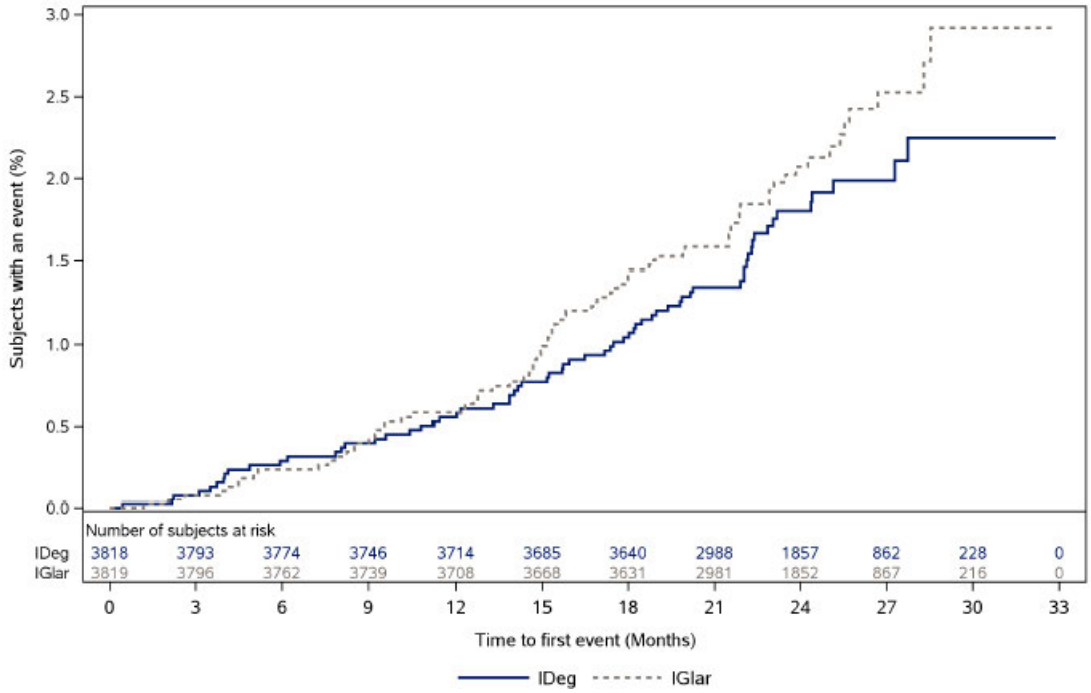
[a] Data based on patients that qualified for glycemic targets of 71-90 mg/dL
[b] Data based on patients for a glycemic titration target of 126 mg/dL
[c] Data based on patients for other glycemic titration targets (above or below 126 mg/dL) as determined by investigator
source: information request \\CDSESUB1\evsprod\NDA203314\0138\m1\us\re-fda-ir-20170731.pdf (question 8 and 9)

Reviewer's comments: based on the exploratory analysis, there were no clear trends in glycemic control and relationship to deaths.

Non-CV deaths

As shown in **Table 26,** non-CV deaths were numerically lower for IDeg when compared to IGlar (1.7% vs. 2.1% respectively). When evaluating by EAC categories, malignancy and infection (including sepsis) were the most common causes of non-CV deaths which occurred in the same proportion of patients for IDeg and IGlar (0.7% for malignancy and 0.5% for infection). Other categories of non-CV deaths were seen in smaller numbers. The Sponsor's analysis of time to non-CV death showed a hazard ratio of 0.84 with a 95% confidence interval of [0.6; 1.16]. **Figure 18** shows a Kaplan-Meier plot of time to non-CV death.

Figure 18 – Time to non-cardiovascular death-Kaplan Meier plot- FAS



Source: CSR, table 14.2.88, page 388

Reviewer's comment: Across MedDRA classification, there was no clear treatment difference in non-CV deaths.

Hospitalization for heart failure
As noted previously, heart failure events were not systematically captured nor adjudicated in DEVOTE. Instead, the Sponsor performed a pre-specified MedDRA search of all the investigator-reported SAEs for heart failure related events. The Sponsor also selected events in which patients were concomitantly hospitalized, not necessarily due to heart failure.

Using this MedDRA search, heart failure requiring hospitalization occurred in 296 (7.8%) of patients in the IDeg group and 322 (8.4%) in the IGlar group. A *post hoc* analysis of time to first heart failure requiring hospitalization event comparing IDeg to IGlar had an estimated hazard ratio of 0.88 with a 95% confidence interval of 0.72 to 1.08.

Reviewer's comments: as noted previously, this analysis is considered exploratory. Typically, heart failure events are adjudicated with the other cardiovascular endpoints. The lack of adjudication for this endpoint may have permitted the capture of less specific events. In addition, the capture of events in which patients were also hospitalized but not necessarily due to heart failure, adds to the noise and lack of specificity for this endpoint making it less reliable

than the other endpoints discussed. Despite the shortcomings of this endpoint, this analysis does not raise a safety signal.

6.1.5 Analysis of Secondary Endpoints(s)

The analyses discussed below reflect the Sponsor's results and my exploratory analyses. Please refer to the statistical review by Dr. Kiya Hamilton for the FDA analyses of the secondary, pre-specified, multiplicity-adjusted, hypoglycemia endpoints.

After the confirmation of the non-inferiority of IDeg vs. IGlar with regards to the first occurrence of EAC-confirmed MACE (the primary endpoint), the Sponsor then proceeded to test the following endpoints:

- Testing for superiority of IDeg vs. IGlar with respect to number of EAC-confirmed severe hypoglycemic episodes and then
- Testing for superiority of IDeg vs. IGlar with respect to occurrence of at least one EAC-confirmed severe hypoglycemic episodes within a patient (yes/no)

As part of the exploratory analyses of hypoglycemia, I evaluated the following datasets submitted in the NDA: ADADJ (adjudication dataset), ADAE dataset (adverse event dataset) and the ADHYPO dataset (hypoglycemia dataset). Although the Sponsor's efficacy analyses come from the 'confirmed' adjudicated events in the ADADJ dataset, the reviewer also evaluated the ADHYPO and ADAE datasets (which included events which were not necessarily sent for adjudication) to evaluate for internal consistency with the adjudicated findings. I discuss my exploratory findings after discussing the Sponsor's results.

Reviewer's comment: Adjudication of severe hypoglycemia was established in Version 3 of the protocol. In the 9 months between version 3 and version 2 of the protocol, there were a total of 23 patients experiencing 34 events of severe hypoglycemia which were not initially adjudicated (For IDeg: 11 patients with 12 episodes vs. for IGlar: 12 patients with 22 episodes). These events were retrospectively adjudicated after the approval of the new protocol. Therefore, although adjudication was established after the trial start, all relevant events were adjudicated.

<u>Secondary endpoint (1): Testing for superiority of IDeg vs. IGlar with respect to number of EAC-confirmed severe hypoglycemic episodes</u>

Severe hypoglycemic episodes were evaluated from randomization to individual end of trial date.[53]

Table 28 shows the EAC confirmed severe hypoglycemic episodes in DEVOTE.

There were a total of 752 episodes of severe hypoglycemia experienced by 439 patients. 280 and 472 episodes of severe hypoglycemia were experienced for IDeg and IGlar respectively, corresponding to an event rate per 100 patient years observation (PYO) of 3.70 and 6.25, respectively. The rate ratio (RR) of IDeg vs. IGlar, based on negative binomial regression with log-link function and log (duration of observation time) as offset, was 0.601 with a 95% confidence interval of 0.476 to 0.759; p-value for the pre-specified, one-sided test <0.001. The superiority of IDeg vs. IGlar with respect to the number of EAC confirmed severe hypoglycemic episodes (first secondary endpoint) was confirmed, since the upper limit of the two sided 95% confidence interval for the rate ratio was below 1.

Table 28- EAC-confirmed severe hypoglycemic episodes- summary-FAS

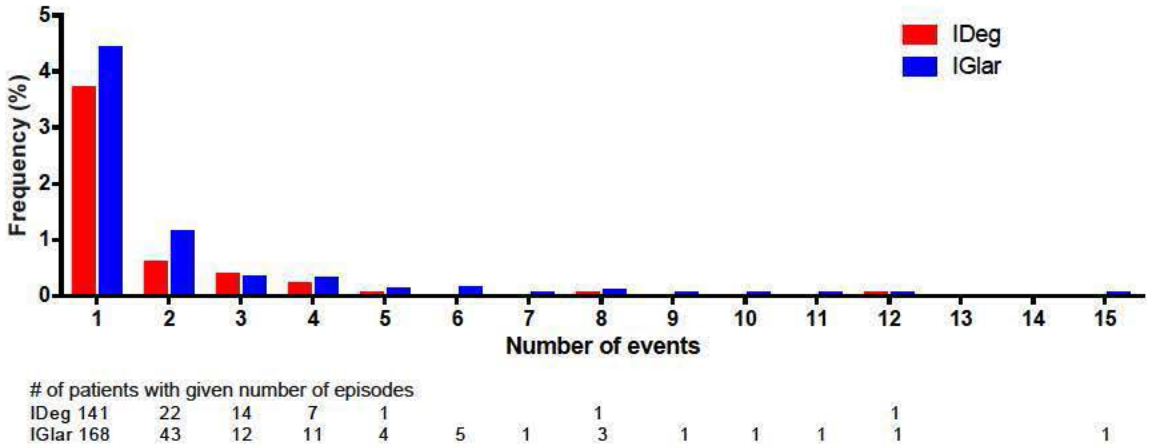
	IDeg			IGlar		
	N (%)	**E**	**R**	**N (%)**	**E**	**R**
Number of patients	3818			3819		
PYO	7568			7558		
EAC confirmed events*	187 (4.9%)	280	3.70	252 (6.6%)	472	6.25

* EAC-confirmed severe hypoglycemic episodes defined per ADA. Episodes with EAC onset date during trial are included.
ADA: American diabetes association; E: Number of events; EAC: Event adjudication committee; N:Number of subjects; PYO: Patient years of observation; R: Event rate per 100 PYO; %: percentage of subjects relative to the number of randomized subjects
Source: CSR, table 11-2, page 145

Figure 19 shows the distribution of the number of severe hypoglycemia events for the patients with EAC confirmed severe hypoglycemia. Most randomized patients, 3.7% vs. 4.4% for IDeg and IGlar respectively, experienced 1 event with smaller proportions of patients experienced more than one event.

[53] In circumstances where a subject did not complete the follow-up visit, the individual end of trial date was the date of last direct contact, last EAC-confirmed MACE before LPLV or death before LPLV (whichever occurred last)

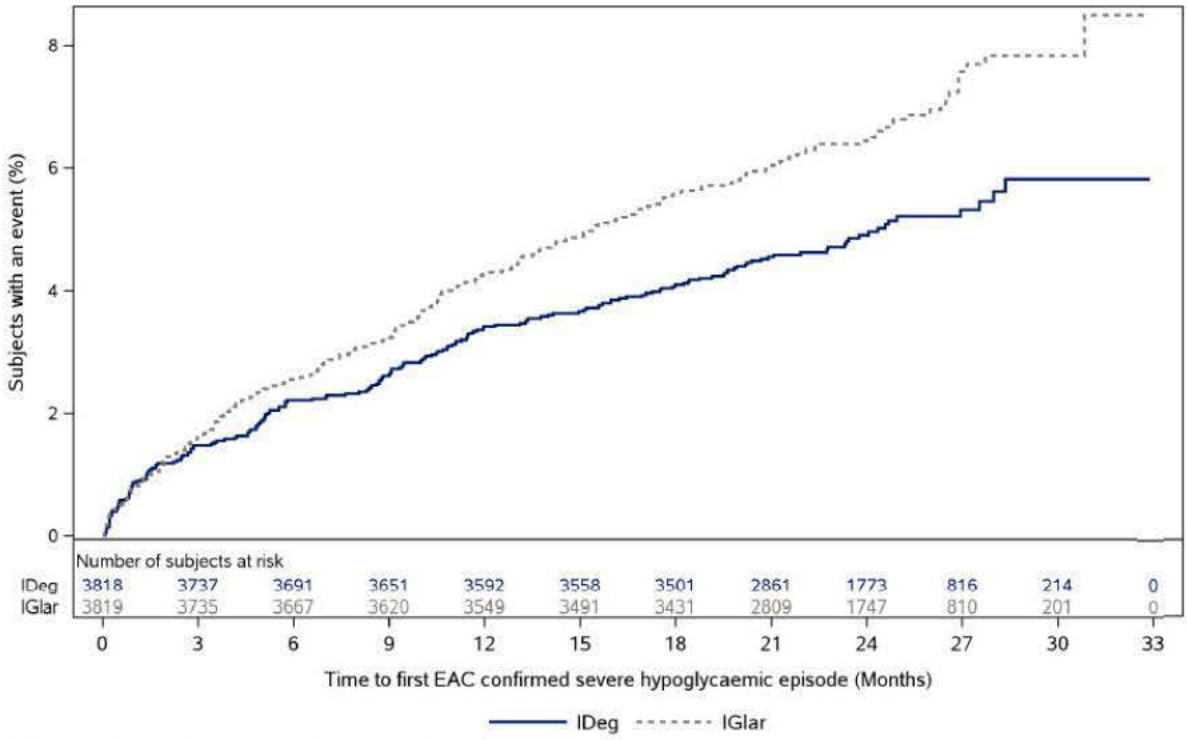
Figure 19 – EAC-confirmed severe hypoglycemic events- patients with at least one episode



Source: reviewer created graph from ADADJ dataset and CSR Figure 12-21, page 205

Figure 20 shows the exploratory analysis of time to first EAC-confirmed severe hypoglycemic episodes. Based on this graph, it appears that the incidence of hypoglycemia was similar between the two treatment groups until around month 3, after which the curves separate; see **Table 29** for an exploratory statistical assessment.

Figure 20 – Time to first EAC-confirmed severe hypoglycemic episodes- Kaplan-Meier plot -FAS



Source: CSR, figure 14.2.109, page 414

Table 29 – Time to first EAC confirmed severe hypoglycemic episode- FAS

	FAS	N	Hazard ratio	95% CI	P-value
Estimated means					
IDeg	3818	187			
IGlar	3819	252			
IDeg/IGlar			0.736	0.609; 0.889	0.0015

Model is a Cox Regression including treatment as only factor.
%: Percentage of subjects with EAC confirmed severe hypoglycemic episode, relative to the number of randomized subjects.
Episodes which occur before randomization date are not used for defining first event (i.e. times were left censored at the randomization date). p-value: Refers to two-sided test of hazard ratio = 1.0

Source: CSR, table 11-4, page 152

To further explore the early hypoglycemia trends, the reviewer presents the hypoglycemia findings from the interim analysis adjudication dataset below. **Table 30** shows that at the time of the submission of the interim results, there were a total of 179 patients with 262 severe hypoglycemia events submitted for EAC adjudication. Of note, unlike the current submission where the 'confirmed' severe hypoglycemia events were marked with the "ANL01FL=y," the interim dataset (submitted in March 26, 2015) did not include this flag.

Table 30 – Severe hypoglycemia events sent for adjudication at the time of the interim analysis

	IDeg OD		IGlar OD		Total	
	N (%)	E	N (%)	E	N (%)	E
	3818		3819		7637	
SEVERE HYPOGLYCAEMIC EVENT submitted for EAC review	83 (2.2)	103	96 (2.5)	159	179 (2.3)	262

Source: 2nd NDA submission ADADJ.xpt FASFL=Y ADJEVCDE=Severe hypoglycemic event

Reviewer's comments: Based on the datasets submitted at the time of the interim analysis, the trends in severe hypoglycemia numerically favored IDeg.

Secondary endpoint (2): Testing for superiority of IDeg vs. IGlar with respect to occurrence of at least one EAC-confirmed severe hypoglycemic episodes within a patient (yes/no)

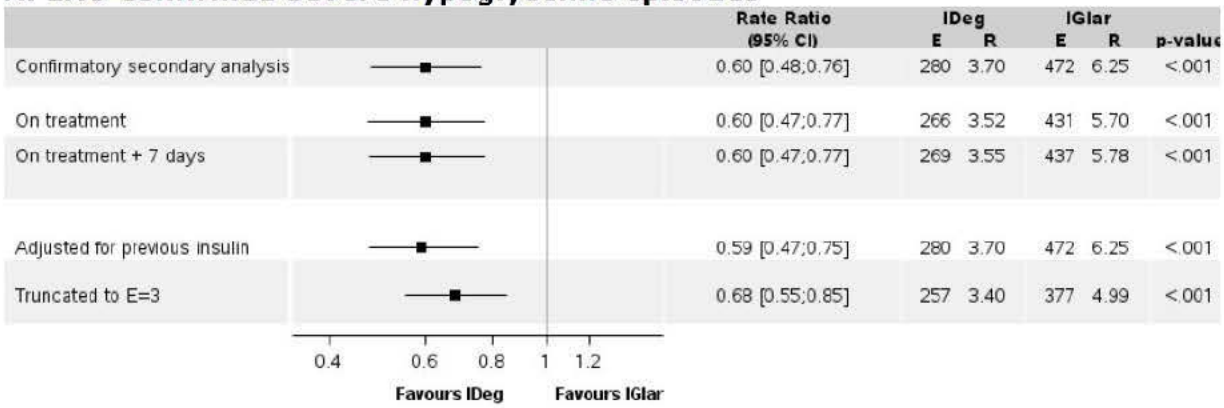
The second, secondary endpoint was the occurrence of at least one EAC-confirmed severe hypoglycemic episode within a patient. 187 (4.9%) and 252 (6.6%) patients for IDeg and IGlar experienced at least one EAC-confirmed severe hypoglycemic episode. The Odds ratio (OR) of IDeg vs. IGlar based on logistic (binomial) regression was 0.729 with a 95% confidence interval of 0.600 to 0.886; p-value for the pre-specified one-sided test p<0.001. The superiority of IDeg vs. IGlar with respect to severe hypoglycemic episodes within a patient was confirmed since the upper limit of the two sided 95% confidence interval for the odds ratio was below 1.

The Sponsor conducted sensitivity analyses for both multiplicity-adjusted secondary endpoints; shown in **Figure 21**.

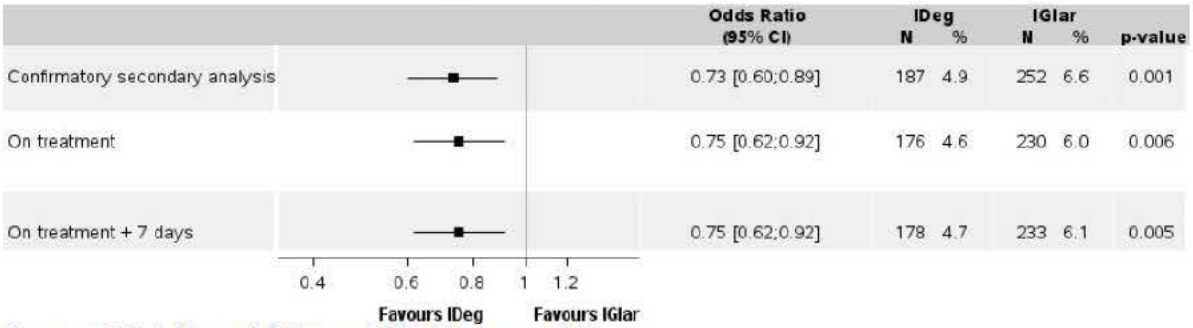
For both secondary endpoints, across multiple sensitivity analyses, the upper bound of the 95% CI remained below 1. Tipping point analyses for the first secondary endpoint required 133 additional of severe hypoglycemia added to the IDeg group for the results to tip. While for the second secondary endpoint, tipping point analyses required additional 25 non-completers experiencing severe hypoglycemic episodes for the results to tip. Please refer to Dr. Kiya Hamilton's review for the FDA's sensitivity analyses.

Figure 21 – Sensitivity analyses for multiplicity adjusted secondary endpoints

A. EAC-confirmed severe hypoglycemic episodes



B. EAC-confirmed severe hypoglycemic episodes within a patient



Source: CSR, figure 11-3 page147, 11-4 page 149

Reviewer's comment: Here I discuss hypoglycemia event rates/patient incidence for (b) (4) trials ((b) (4) , ORIGIN and ACCORD) to provide some context to the findings of DEVOTE. (b) (4)

-

(b) (4)

- (b) (4)

- **ORIGIN: was a cardiovascular outcomes trial comparing insulin glargine to standard of care**
  - **The number of patients with severe hypoglycemia[56] events per 100 years was 1.05[57] for insulin glargine and 0.30 for standard care group.**
  - **A similar factor between ORIGIN and DEVOTE was the glycemic target (≤95 mg/dL[58]).**

---

54 (b) (4)

55 (b) (4)

a) ≥1 severe hypo in the last year, per ADA definition, April 2013*.
b) Moderate CRF, defined as glomerular filtration rate 30 - 59 mL/min/1.73 m^2 per CKD-Epi
c) Hypo symptom unawareness^
d) DM duration: for trial 3995 >15 years; for trial 3998: >5 years
e) Recent hypo (defined by symptoms of hypo and/or episode with low glucose measurement (≤70 mg/dL)) within the last 12 weeks prior to visit 1 (screening)

The goal was to include 20% of patients meeting criteria a to d. Remaining subjects should meet criteria e.

[56] defined as an event with clinical symptoms consistent with hypoglycemia in which the participant required the assistance of another person, and one of the following: a) the event was associated with a documented self-measured or laboratory plasma glucose level ≤36 mg/dL; or b) the event was associated with prompt recovery after oral carbohydrate, intravenous (IV) glucose, or glucagon administration

[57] See 10/11/13 clinical review NDA 021081, S057, by Dr. Yanoff, page 63

[58] See 10/11/13 clinical review NDA 021081, S057, by Dr. Yanoff, page 21

- **ACCORD: was a cardiovascular outcomes trial comparing whether an HbA1c <6% would decrease cardiovascular events compared to an HbA1c of 7%-7.9%.[59]**
    - **The proportion of patients requiring medical assistance for hypoglycemia was 3.1% for the intensive therapy arm vs. 1.0% in the standard therapy arm.**

The overall differences in event rates and patient incidence (for ACCORD) among trials is likely due to trial design differences. The rates of hypoglycemia appear to be higher for the Novo Nordisk sponsored trials (i.e. DEVOTE (b) (4)) than other trials, (i.e. ORIGIN and ACCORD). However, the event rates in DEVOTE seem to be generally lower than what has been reported in the literature, as high as 35 to 70 per 100 patient years in patients with type 2 diabetes mellitus.[27]

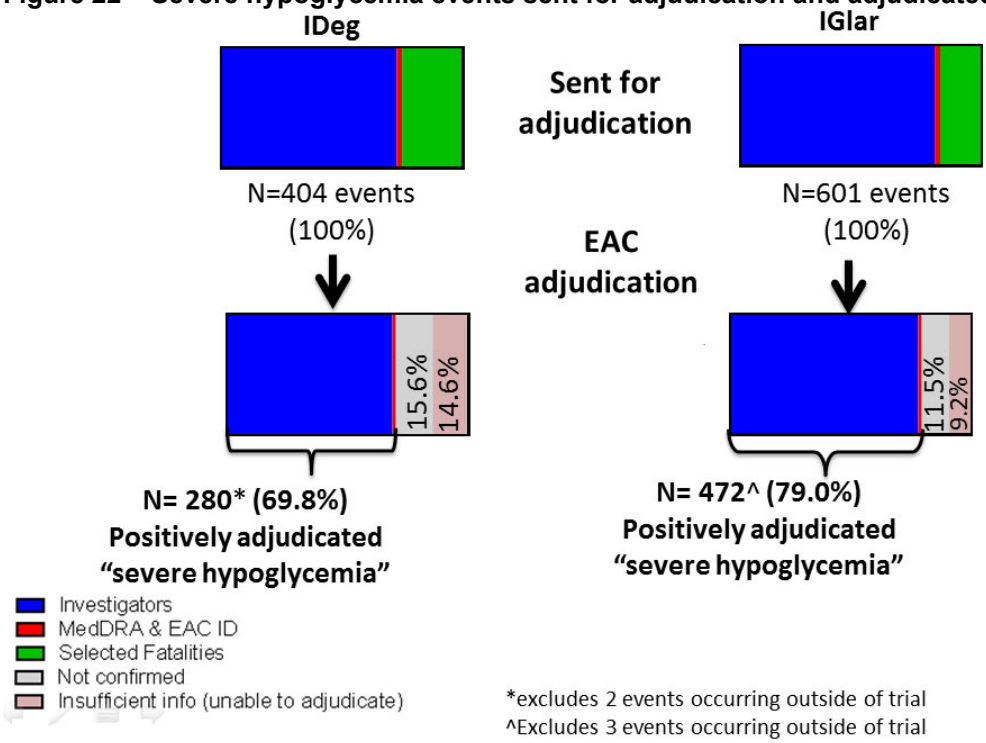
Identification of Severe hypoglycemia events

Figure 22 shows the flow of events that were sent for adjudication and were either confirmed or not confirmed as "severe hypoglycemia" for IDeg and IGlar. The total events sent for adjudication were lower for IDeg than IGlar (404 events vs. 601 events respectively). For both treatment groups, the largest proportion of events originated from investigators (72.5% vs. 80.5% for IDeg and IGlar respectively) followed by selected fatal events (25.2% vs 17.1 for IDeg and IGlar respectively) with smaller percentages from MedDRA searches or identification from the EAC.

Of the 1005 severe hypoglycemia events captured in DEVOTE, approximately 280 events (69.8% of all submitted events) and 472 events (79% of submitted events) for IDeg and IGlar, respectively were adjudicated as meeting criteria for severe hypoglycemia. In total, 752 were adjudicated as severe hypoglycemia, corresponding to a rate of 4.97 events per 100 PYO (3.70 episodes per 100 PYO for IDeg and 6.25 episodes per 100 PYO for IGlar).

[59] Group TAtCCRiDS. Effects of Intensive Lowering in type 2 diabetes. New England Journal of Medicine 2008;358:2545-59.

Figure 22 – Severe hypoglycemia events sent for adjudication and adjudicated by the EAC



Source: reviewer graphed information from CSR, table 14.2.140, page 444

Reviewer's comment: The trends of higher hypoglycemia events for IGlar are seen at the level of events "sent for adjudication" (i.e. 192 extra events [472-280]) and events that were "positively adjudicated," (i.e. 124 extra events [404-280]). These differences between treatment arms, however, are not likely due to differences in reporting bias by investigators, since DEVOTE was a double blinded trial. Also, a review of a sample of adjudication packets for both treatment groups did not reveal any differences in the documents used by investigators, which would suggest un-blinding.

It is also notable that the proportion of events which could not be adjudicated, because the source documentation was insufficient, was not large.

As noted previously, the EAC could confirm events with either complete or incomplete information; the latter necessitating clinical inference. To determine the level of certainty with which the confirmed severe hypoglycemia events were adjudicated, I reviewed the level of information that was available for adjudicators to base their decision (i.e. complete information or incomplete information). As shown on **Table 31**, most of the cases were adjudicated with complete information. Only 47 events were adjudicated with incomplete information, meaning that it was not possible to document that the event met the predefined criteria, but based on clinical judgement, the adjudicator felt that the event met the criteria for severe hypoglycemia.

Table 31 – Level of information for adjudicated severe hypoglycemia events

	IDeg OD N=3818			IGlar OD N=3819		
	N	%	E		%	E
ADJUDICATED WITH COMPLETE INFORMATION	169	4.4	258	238	6.2	447
ADJUDICATED WITH INCOMPLETE INFORMATION	21	0.6	22	21	0.5	25
Reviewer conducted analysis: ADADJ dataset, ANAL01=y, by ADJSTS and TRTP						

Reviewer's comments: Even if one discounts the cases of adjudicated events with incomplete information for both treatment groups, there is still an imbalance between treatment arms that favors IDeg.

I reviewed the Sponsor submitted datasets to evaluate if the hypoglycemia findings (discussed above) persisted when evaluating events more broadly.

As noted in **Table 7**, the Sponsor employed multiple methods for capturing events of severe hypoglycemia. In one method, the Sponsor applied pre-defined SMQ searches for hypoglycemic events on all reported SAEs (and not on all AEs). I conducted an exploratory Standardized MedDRA Query analysis using the adverse event dataset (as compared to the adjudication dataset from which the Sponsor's efficacy analyses are derived) therefore evaluating events that were not necessarily sent for adjudication. For this analysis, I considered all adverse events, and not just SAEs. The results of the analysis are shown in **Table 32.** The SMQ used for this analysis is similar to the SMQ analyses indicated by the Sponsor; see **Table 7**. Across SMQs, both the proportion of patients and number of events are smaller for IDeg when compared to IGlar except for the SMQ for convulsions broad and narrow.

Table 32 – Exploratory Standardized MedDRA Query analysis of hypoglycemia

	IDeg (N = 3818)			*IGlar (N = 3819)*		
	Number of subjects	*(%)*	*Events*	*Number of subjects*	*(%)*	*Events*
Custom query of the following broad SMQs combined into 1 search: Hypoglycemia Convulsions Accidents and injuries	316	8.3	469	336	8.8	505
Hypoglycemia broad	190	4.98	265	207	5.42	291
Hypoglycemia narrow	131	3.43	188	136	3.56	191
Convulsions broad	9	0.24	14	10	0.26	12
Convulsions narrow	9	0.24	14	10	0.26	12
Accidents and injuries broad	147	3.85	190	151	3.95	202
Accidents and injuries narrow	139	3.64	174	141	3.69	186

As consistent with the analyses of all the data in the dataset the following were specified in the analysis: Demography, where statement FASFL=Y and adverse events where ANL01FL=Y. MAED was used for this analysis. Analysis was verified by an IR request source: question 1: \\CDSESUB1\evsprod\NDA203314\0144\m1\us\re-fda-ir-20171011.pdf

The PT terms within each SMQ are shown in **Table 33.** Highlighted in yellow are events with more than 10 patients per arm. These events are highlighted to identify events that may be driving the findings within the SMQ. In general, the PT terms for 'fall,' 'hypoglycemia unconsciousness' and 'syncope' were similar between treatment groups. While the PT terms 'road traffic accident' and 'hypoglycemia' were slightly higher for IDeg vs. IGlar.

Table 33 – Preferred terms in the exploratory Standardized MedDRA Query analysis of hypoglycemia

		IDeg N=3818		IGlar N=3819	
SMQ name	**PT term**	**N**	**%**	**N**	**%**
Accidents and injuries (SMQ)	Accident at work	0	0	2	0.05
	Adrenal gland injury	1	0.03	0	0
	Animal bite	0	0	2	0.05
	Ankle fracture	2	0.05	5	0.13
	Back injury	1	0.03	1	0.03
	Brachial plexus injury	0	0	1	0.03
	Burns third degree	1	0.03	1	0.03
	Cervical vertebral fracture	0	0	1	0.03
	Chest injury	1	0.03	2	0.05
	Clavicle fracture	1	0.03	0	0
	Concussion	1	0.03	0	0
	Contusion	5	0.13	8	0.21
	Corneal abrasion	1	0.03	0	0
	Craniocerebral injury	1	0.03	1	0.03
	Excoriation	1	0.03	1	0.03
	Eye injury	0	0	1	0.03
	Face injury	1	0.03	0	0
	Facial bones fracture	1	0.03	2	0.05
	Fall	62	1.62	63	1.65
	Femoral neck fracture	0	0	2	0.05
	Femur fracture	3	0.08	5	0.13
	Fibula fracture	0	0	1	0.03
	Foot fracture	3	0.08	6	0.16
	Fracture	1	0.03	0	0
	Gastrointestinal injury	1	0.03	0	0
	Haemothorax	1	0.03	0	0
	Hand fracture	3	0.08	1	0.03
	Head injury	0	0	1	0.03
	Heat stroke	1	0.03	0	0
	Hip fracture	1	0.03	3	0.08
	Humerus fracture	1	0.03	3	0.08
	Hypothermia	1	0.03	0	0
	Ilium fracture	1	0.03	0	0
	Injury	1	0.03	2	0.05
	Joint dislocation	3	0.08	2	0.05
	Joint injury	0	0	3	0.08
	Laceration	7	0.18	7	0.18

	Ligament rupture	2	0.05	0	0
	Ligament sprain	1	0.03	3	0.08
	Limb injury	1	0.03	3	0.08
	Lower limb fracture	2	0.05	0	0
	Meniscus injury	1	0.03	3	0.08
	Multiple fractures	1	0.03	0	0
	Multiple injuries	1	0.03	1	0.03
	Muscle rupture	1	0.03	0	0
	Muscle strain	5	0.13	5	0.13
	Musculoskeletal injury	0	0	1	0.03
	Nerve compression	1	0.03	0	0
	Oesophageal rupture	0	0	1	0.03
	Pelvic fracture	0	0	3	0.08
	Pneumothorax traumatic	1	0.03	0	0
	Post concussion syndrome	1	0.03	0	0
	Pubis fracture	1	0.03	0	0
	Pulmonary contusion	0	0	1	0.03
	Radius fracture	2	0.05	1	0.03
	Retinal detachment	1	0.03	1	0.03
	Retinal tear	1	0.03	0	0
	Rib fracture	8	0.21	3	0.08
	Road traffic accident	23	0.6	18	0.47
	Skin abrasion	0	0	1	0.03
	Spinal compression fracture	1	0.03	1	0.03
	Spinal fracture	0	0	1	0.03
	Stab wound	1	0.03	0	0
	Stress fracture	1	0.03	0	0
	Subdural haematoma	5	0.13	4	0.1
	Subdural haemorrhage	0	0	1	0.03
	Tendon rupture	3	0.08	2	0.05
	Thermal burn	3	0.08	0	0
	Thoracic vertebral fracture	1	0.03	0	0
	Tibia fracture	0	0	2	0.05
	Traumatic haematoma	0	0	1	0.03
	Upper limb fracture	0	0	2	0.05
	Ureteric injury	1	0.03	0	0
	Vitreous detachment	1	0.03	0	0
	Wound	2	0.05	6	0.16
	Wrist fracture	4	0.1	3	0.08
Convulsions (SMQ)	Generalised tonic-clonic seizure	0	0	3	0.08
	Hyperglycaemic seizure	0	0	1	0.03
	Hypoglycaemic seizure	3	0.08	0	0
	Migraine-triggered seizure	0	0	1	0.03
	Post stroke seizure	0	0	1	0.03
	Seizure	6	0.16	6	0.16
	Status epilepticus	1	0.03	0	0
Hypoglycaemia (SMQ)	Agitation	1	0.03	0	0
	Altered state of consciousness	2	0.05	0	0
	Anxiety	6	0.16	4	0.1
	Blood glucose decreased	1	0.03	2	0.05
	Confusional state	5	0.13	8	0.21
	Diplopia	1	0.03	3	0.08
	Dysarthria	1	0.03	3	0.08
	Gait disturbance	1	0.03	1	0.03
	Generalised tonic-clonic seizure	0	0	3	0.08
	Hyperhidrosis	2	0.05	1	0.03
	Hypoglycaemia	108	2.83	106	2.78

	Hypoglycaemia unawareness	1	0.03	0	0
	Hypoglycaemic coma	1	0.03	1	0.03
	Hypoglycaemic seizure	3	0.08	0	0
	Hypoglycaemic unconsciousness	29	0.76	29	0.76
	Lethargy	1	0.03	1	0.03
	Loss of consciousness	4	0.1	5	0.13
	Metabolic encephalopathy	7	0.18	10	0.26
	Presyncope	3	0.08	13	0.34
	Seizure	6	0.16	6	0.16
	Somnolence	2	0.05	1	0.03
	Status epilepticus	1	0.03	0	0
	Syncope	27	0.71	29	0.76
	Tremor	1	0.03	3	0.08
	Vision blurred	1	0.03	1	0.03
	Visual impairment	1	0.03	1	0.03

Reviewer's comments: Despite small numerical imbalances when looking at specific PT terms, exploratory analyses using SMQs are generally consistent with the Sponsor's hypoglycemia analysis, although the overall numbers are smaller.

Another exploratory analysis I conducted was to examine the ADHYPO dataset. This dataset reflects data reported on hypoglycemic episode forms.

When considering all the events (not just events sent for adjudication) that occurred in the intention to treat population during the trial, 1047 patients were identified (496 for IDeg and 551 for IGlar) as reported as having a hypoglycemia event.

Table 34 – Exploratory analysis of hypoglycemia analysis of all reported hypoglycemia events occurring during the trial period -FAS

	IDeg N=3818		IGlar N=3819	
	N	**%**	**N**	**%**
Patients with episodes of hypoglycemia	496	12.99	551	14.43
Source: ADHYPO dataset, FASFL=y, ANL01FL=Y				

Reviewer's comments: an analysis of all hypoglycemia events in the trial period revealed a numerical imbalance favoring IDeg, which is consistent with the overall hypoglycemia findings discussed previously.

Another analysis performed by the reviewer was an evaluation of adverse events which were NOT sent for adjudication by review of the ADAE (adverse event) dataset. The Sponsor set up the HYPOQID variable in the adverse event dataset to flag events that were sent for adjudication. I evaluated events that were not sent for adjudication (HYPOQID variable was blank) to search for events whose PT terms suggested hypoglycemia. The purpose of this analysis was to possibly detect missed events.

For this exploratory analysis, I evaluated the PT terms which included the terms "fall" and "hypoglycemia" as serious (Y or N); see **Table 35.** Across PT terms there were small numerical differences in the proportion of patients between treatment arms.

The Sponsor was asked to clarify why these events were not sent for adjudication, since the event would have been identified by SMQ search, if not initially identified by the investigator.

Table 35 – Selected hypoglycemia events in the ADAE dataset not sent for adjudication

Serious Event	PT	IDeg		IGlar		Total	
		N (%)	Events	N (%)	Events	N	Events
N							
	Fall	8 (0.21%)	8	8 (0.21%)	8	16 (0.21%)	16
	Hypoglycaemia	51 (1.34%)	72	58 (1.51%)	88	109 (1.43%)	160
	Hypoglycaemia unawareness	1 (0.02%)	1	0 (0.00%)	0	1 (0.01%)	1
	Hypoglycaemic unconsciousness	2 (0.05%)	2	0 (0.00%)	0	2 (0.03%)	2
	Total	60 (1.57)	83	66 (1.73)	96	126 (1.65)	179
Y							
	Fall	52 (1.36%)	55	53 (1.39%)	57	105 (1.37%)	112
	Hypoglycaemia	2 (0.05%)	2	0 (0.00%)	0	2 (0.03%)	2
	Total	54 (1.41)	57	53 (1.39)	57	107 (1.40)	114
Source: reviewer created table from ADAE dataset, selecting for PT terms: fall, hypoglycemia, hypoglycemia unawareness, hypoglycemic unconsciousness excluding events with a HYPOQID flag							

In an information request on October 18, 2017, the Sponsor clarified that of the 179 non-SAE events identified in the AE dataset, 140 were reported in the hypoglycemia form of which 131 were sent for adjudication (although they were not marked in the AE dataset with the HYPOQID flag) the remaining 9 events were not sent for adjudication because the patient was able to treat himself. Thirty-nine non-SAEs were not reported in the hypoglycemia form and were not sent for adjudication. Furthermore, all 114 SAEs identified were captured in the MedDRA search and were sent for pre-evaluation to the EAC chair/delegate and were deemed not relevant for adjudication; see **Figure 23** .

The Sponsor provided the EAC chair or delegates' rationale for not sending the 114 SAEs for adjudication.[60] For most of the "fall" events, it was noted that "no reports of hypoglycemia" accompanied the event or that "hypoglycemia was not a factor in the fall" per the study site. Review of the EAC documentation revealed that most the falls were due to mechanical falls. The one of the SAEs with the PT 'hypoglycemia' was a duplicate event (which was sent for hypoglycemia adjudication) while the second 'hypoglycemia' event did not require assistance with treatment since the blood glucose value was 105 mg/dL (per documentation in eCRF).

Figure 23 – Explanation of events sent or not sent for adjudication for selected events in the ADAE dataset

Serious hypo: 114

-All terms were captured by MedDRA SMQ screening and sent for pre-evaluation by EAC chair or delegate. Events were deemed not relevant for adjudication.

Non-serious hypo: 179

- **140 Non-SAEs reported in hypo form**

Serious Event	Preferred term	IDeg OD N	(%)	E	IGlar OD N	(%)	E	Total N	(%)	E
N	Hypoglycaemia	41	(1.07)	60	52	(1.36)	77	93	(1.22)	137
	Hypoglycaemia unawareness	1	(0.03)	1				1	(0.01)	1
	Hypoglycaemic unconsciousness	2	(0.05)	2				2	(0.03)	2
	Total	**43**	**(1.13)**	**63**	**52**	**(1.36)**	**77**	**95**	**(1.24)**	**140**

Data is based on the trial EX1250-4080.
N: Number of subjects, %: Percentage of subjects, E: Number of events

  - 131 Non-SAEs reported on a hypo form and sent for adjudication (but were not marked in the AE dataset with the HYPOQID flag)

Serious Event	Preferred term	IDeg OD N	(%)	E	IGlar OD N	(%)	E	Total N	(%)	E
N	Hypoglycaemia	40	(1.05)	59	50	(1.31)	70	90	(1.18)	129
	Hypoglycaemic unconsciousness	2	(0.05)	2				2	(0.03)	2
	Total	**41**	**(1.07)**	**61**	**50**	**(1.31)**	**70**	**91**	**(1.19)**	**131**

Data is based on the trial EX1250-4080.
N: Number of subjects, %: Percentage of subjects, E: Number of events

  - 9 Non-SAEs were not sent for adjudication because the subject was able to treat himself

- **39 Non-SAEs not reported on hypo form**

Serious Event	Preferred term	IDeg OD N	(%)	E	IGlar OD N	(%)	E	Total N	(%)	E
N	Fall	8	(0.21)	8	8	(0.21)	8	16	(0.21)	16
	Hypoglycaemia	10	(0.26)	12	8	(0.21)	11	18	(0.24)	23
	Total	**18**	**(0.47)**	**20**	**16**	**(0.42)**	**19**	**34**	**(0.45)**	**39**

Data is based on the trial EX1250-4080.
N: Number of subjects, %: Percentage of subjects, E: Number of events

[60] See IR file://cdsesub1/evsprod/NDA203314/0147/m1/us/re-fda-ir-20171024.pdf Question 8

Source: information request, question 4 \\CDSESUB1\evsprod\NDA203314\0144\m1\us\re-fda-ir-20171011.pdf

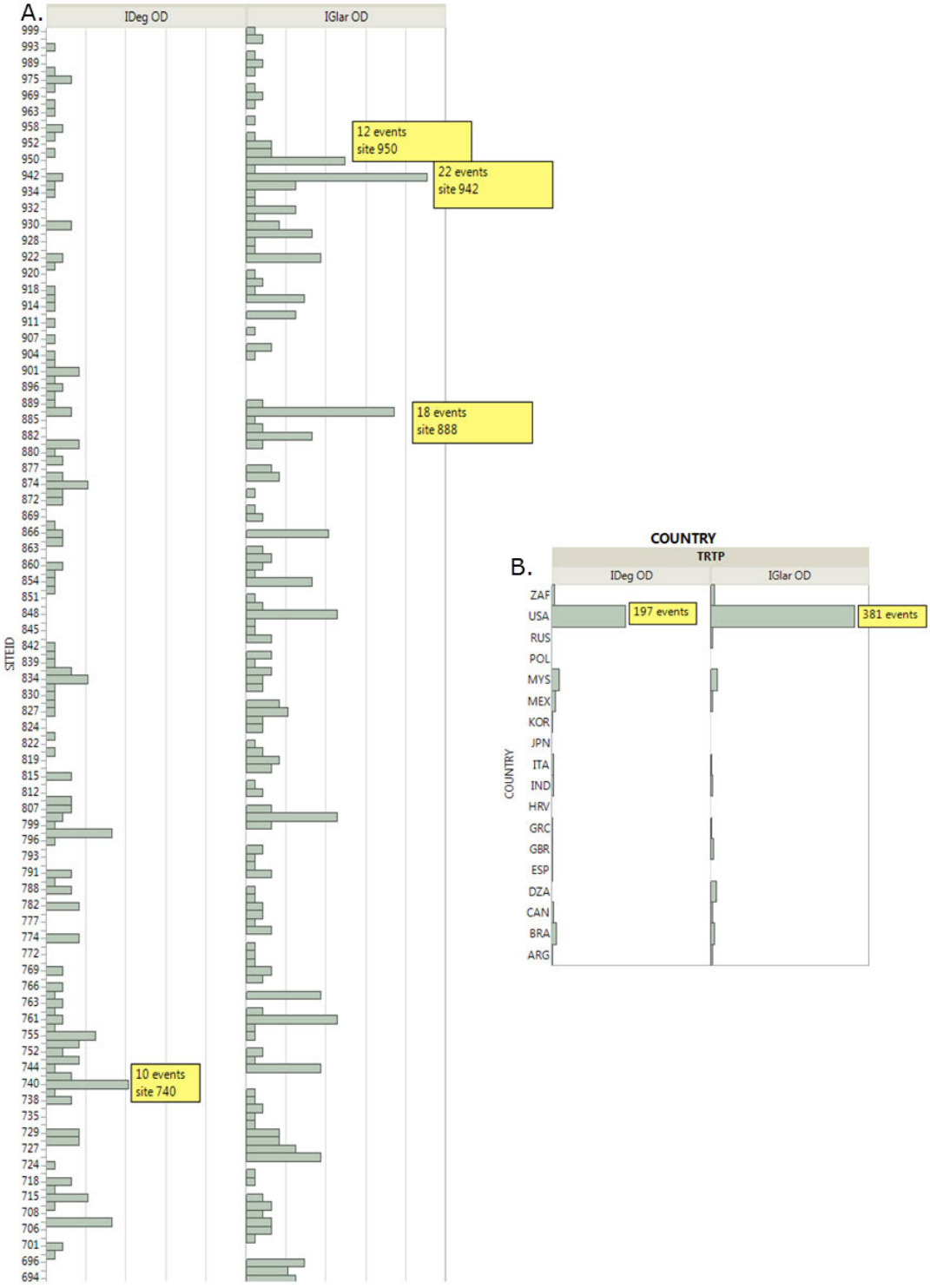
Reviewer's comments: Review of the EAC chair/delegate's documentation for events excluded from adjudication suggests appropriate screening of these events.

In addition, the number of events and patients who had a hypoglycemia event but were not sent for adjudication were similar between treatment arms (for non-SAEs reported on hypo form: 20 events in 18 patients for IDeg and 19 events in 16 patients for IGlar. For SAEs not sent for adjudication: 57 events in 54 patients for IDeg and 57 events for 53 patients for IDeg). Therefore, even if these events were to be considered in the hypoglycemia analysis (which I don't suggest would be appropriate), they are unlikely to alter the overall treatment difference between arms.

Another analysis looked at whether the results were driven by a specific site. **Figure 24** shows the EAC confirmed severe hypoglycemia events by sites in the USA and by country. Most of the hypoglycemic events (70.4% of the confirmed events for IDeg and 80.7% of the confirmed events for IGlar)[61] came from the United States. When evaluating by trial site within the U.S., it was noted that for IDeg, most sites had less than 10 events confirmed by the EAC; while there were more sites with more than 10 confirmed events for IGlar. The three sites with the most EAC confirmed events for IGlar were sites: 942 (22 events), 888 (18 events), and 950 (12 events).

[61] For IDeg 197 of 280 events; for IGlar 381 of 472 events

Figure 24 – Hypoglycemia events by A) site in the USA and B) by country



Reviewer's comment: Across U.S. sites the confirmed severe hypoglycemia events tended to be higher in the U.S. sites. Although there were 3 sites in the

U.S. with a high number of events confirmed by the EAC (a total of 52 events were confirmed in these 3 sites), these events make up only 11%[62] of the total confirmed events for IGlar. Even when one excludes these events from these sites, an imbalance in EAC confirmed severe hypoglycemia events persists.

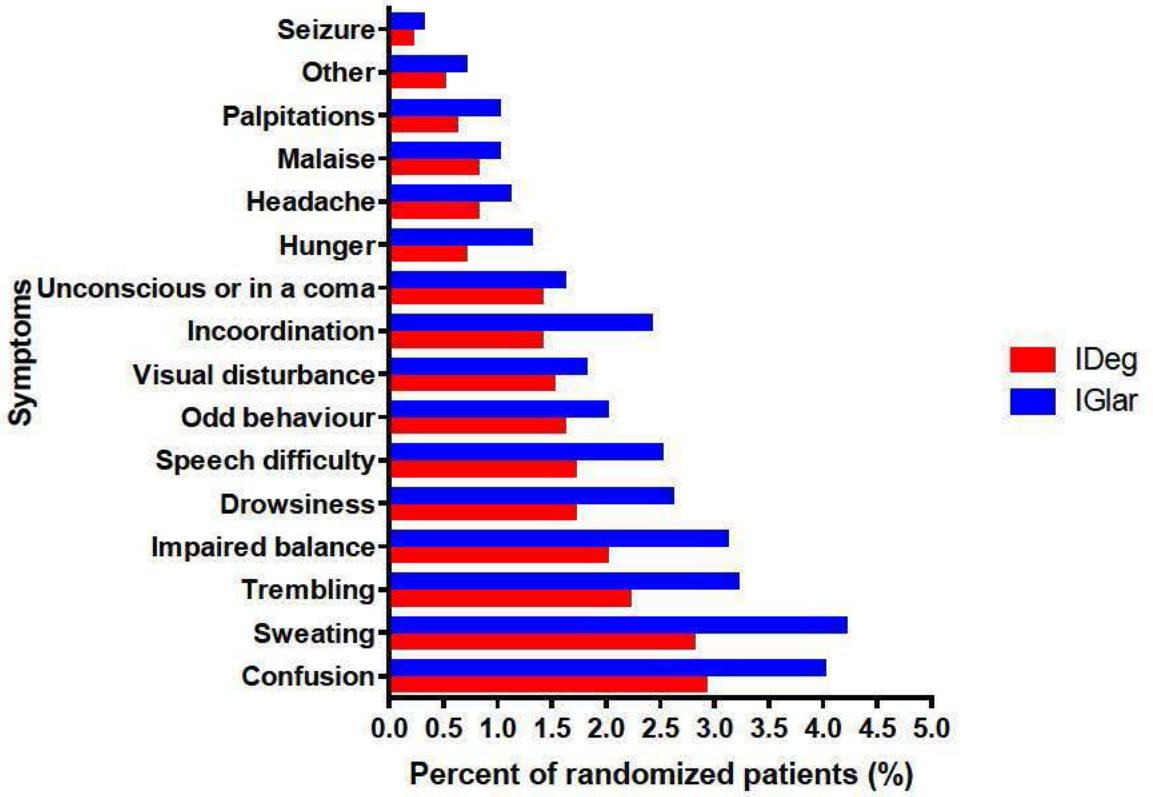
Symptoms of confirmed cases of severe hypoglycemia

Figure 25 shows the symptoms associated with EAC confirmed severe hypoglycemic episodes. These symptoms were systematically collected in the patient's diaries (see **Figure 48** in appendix) and were to be reported by investigators in dedicated hypoglycemia forms (see **Figure 4**). Overall, there were a greater proportion of patients experiencing any of the identified hypoglycemia symptoms for IGlar than IDeg. For both treatment groups, the most common symptoms identified included confusion (3.5%), sweating (3.5%) and trembling (2.7%).

Notably, seizures were identified in 0.2% (9 patients experiencing 11 events) vs. 0.3% (10 patients experiencing 11 events) patients for IDeg and IGlar respectively. Unconsciousness or coma was identified in 1.4% (54 patients experiencing 60 events) and 1.6% (63 patients experiencing 75 events) patients for IDeg and IGlar respectively. The category 'Other,' was experienced by 19 patients (0.5%) in the IDeg group and 28 (0.7%) patients in the IGlar group.

[62] 52 events out of 472 confirmed events in the three sites with the highest number of confirmed severe hypoglycemia events.

Figure 25 – Characteristics of EAC confirmed hypoglycemia episodes by patients-summary- FAS



Source: table 14.2.141, page 445

Reviewer's comment: Many of the symptoms reported for patients experiencing severe hypoglycemia, are non-specific (i.e. hunger, malaise), and may not necessarily indicate a state of severe cognitive impairment; i.e., neuroglycopenia. The two categories which have a greater specificity for neuroglycopenia are "seizures" and "unconsciousness and coma." The small numerical imbalance in these categories favors IDeg over IGlar, however it is noted that the difference is made up by a small number of cases.

To further characterize the confirmed severe hypoglycemia cases, I reviewed a random sample of adjudication packets which were confirmed as meeting the severe hypoglycemia definition. In this review, I found some cases where it was sometimes difficult to ascertain if the hypoglycemic episode was reflective of symptomatic hypoglycemia or documented symptomatic hypoglycemia, rather than severe hypoglycemia. To better illustrate this point, some examples are provided below.

Subject ID (b) (6) (IGlar, hypo event 2) - Investigator reported that patient felt symptoms of hypoglycemia, including: sweating, incoordination, malaise, headache, trembling, palpitations, confusion, drowsiness, and seizures (seizures were noted in the diary, however both adjudicators felt that patient did not seize

because symptoms abated with “sweet tea”). Also, there was no intervention documented even though event took place in a hospital. The note states that the patient’s daughter gave her sweet tea and the patient felt better.

Subject ID (b) (6) (IGlar, hypo event 2) – The investigator’s phone contact note states that the patient felt disoriented and did not feel safe to drive. A friend drove her to fast food place and bought a sugary drink. Symptoms resolved within 20 minutes.

Subject ID (b) (6) (IGlar, hypo event 1) - Patient was awaiting an appointment with another provider and was found to have lightheadedness and sweating in the lobby. Patient was given potato chips and juice. Blood glucose was not checked prior to intake of food. After eating blood glucose was 115 mg/dL.

Subject ID (b) (6) (IGlar hypo event 1) - Patient had sweating and trembling while shopping. Patient’s wife gave him a candy bar and he was “OK.” Per diary entry (but not dataset) blood glucose was 143 mg/dL. Both adjudicators felt that this blood glucose was not specified as occurring at the time of the hypoglycemia event but rather was reflective of a morning reading.

Subject ID (b) (6) (IDeg hypo event 1) – While patient was seen for site visit, she complained her blood glucose being low. Patient was given a piece of candy. Blood glucose after 10 minutes was 73 mg/dL. Her symptoms continued; she was given 2 glucose tablets and symptoms resolved within 10 minutes. Other symptoms included hunger and malaise.

Subject ID (b) (6) (IGlar hypo event 2) – The adjudication packet does not contain any written description of the hypoglycemic event. The packet just contains the blood glucose logs and a copy of the diary as shown below.

(b) (4)

Reviewer's comment: A key component of the definition of the severe hypoglycemia definition is the "neurological recovery" component. This component implies that there was some neurological symptom associated with a severe hypoglycemia event that will recover after another person actively administrates corrective treatment. However, some events that were adjudicated as severe hypoglycemia do not clearly have evident neuroglycopenic symptoms.

These cases may instead represent cases of symptomatic hypoglycemia or in the cases where a blood glucose was obtained, documented symptomatic hypoglycemia. Based on the symptoms collected by the Sponsor (in Figure 25**), it is likely that most the cases are not, strictly speaking, severe hypoglycemia.**

Since the symptoms of "seizures" and "unconscious or in a coma" are among the most extreme clinical presentations of severe hypoglycemia, I reviewed adjudication packets for cases that were confirmed by the EAC as meeting criteria for severe hypoglycemia, to evaluate whether these cases were associated with concomitant illnesses that would affect the interpretation of these events. I reviewed 139 adjudication packages and identified 7 cases which were EAC confirmed for severe hypoglycemia and had additional medical issues identified at or near the time of the hypoglycemia event; see **Table 28**. Of the events identified, there was 1 case for patient (b) (6) *(in italics)* which

I did not feel provided sufficient information regarding the hypoglycemia event to clearly adjudicate as severe hypoglycemia. The other 2 cases in italics (subject ID (b) (6) and (b) (6) also had some missing components to definitively identify the cases as severe hypoglycemia; however, based on the clinical history and subsequent events adjudicated for patient ((b) (6) these events likely represent cases of severe hypoglycemia. For the remaining cases, there was sufficient information to determine that the event was consistent with severe hypoglycemia.

Figure 26- Events of confirmed events of severe hypoglycemia with symptoms of "unconscious or in a coma" or "seizure" with concomitant medical illnesses

Subject ID	Treatment	Blood glucose	Clinical description
(b) (6) Hypo event 1	IDeg	24 mg/dL	Patient was found unresponsive by family. EMS checked blood glucose (24 mg/dL), treated with D10. Blood glucose improved to 128. Patient did not gain consciousness. Patient was intubated for airway protection. While in the emergency department he was febrile 101 and was treated for Staph aureus pneumonia from respiratory cultures. Patient did not regain consciousness during hospitalization and was discharged to a rehab facility. Per the discharge summary the patient had had blood glucose readings of 42 and 39 in the 2 mornings prior to this episode with resolution after eating.
(b) (6) Hypo event 1	IGlar	None (ED report says<40 mg/dL)	Patient had a respiratory infection with subjective fever which led to decreased appetite. Patient woke up disoriented and diaphoretic. Per ED note, patient passed out. Family called 911. EMS blood glucose was "low" treated with D50W, blood glucose increased to 113 mg/dL with improved mental status.
(b) (6) *Hypo event 1*	*IGlar*	*None*	*Patient was admitted to the hospital with "severe hypoglycemia" per clinician letter. There are no further details regarding the hypoglycemia episode. The note further describes the patient's hospital course which includes being hypoxic and development of acute renal failure, atrial fibrillation, pulmonary hypertension and eventual death. Event was adjudicated with "incomplete information" by the EAC.*
(b) (6) *Hypo event 1*	*IGlar*	*32 mg/dL*	*Patient was hospitalized for a right foot subtalar fusion. During the hospitalization, a general medicine consult was requested for management of diabetes. Medicine consult states that the patient had an episode of hypoglycemia associated with fasting. Point of care glucose reading was 32 mg/dL, followed by 192 mg/dL 5 minutes later. There is no documentation from the hospitalization describing the patient as unconscious. The investigator addendum reports that the patient reports being unconscious. There is no documentation of improvement of symptoms, just a blood glucose of 192 mg/dL in the POC log. There are also no records of what was administered for treatment of hypoglycemia. Event was adjudicated with "incomplete information" by the EAC.*

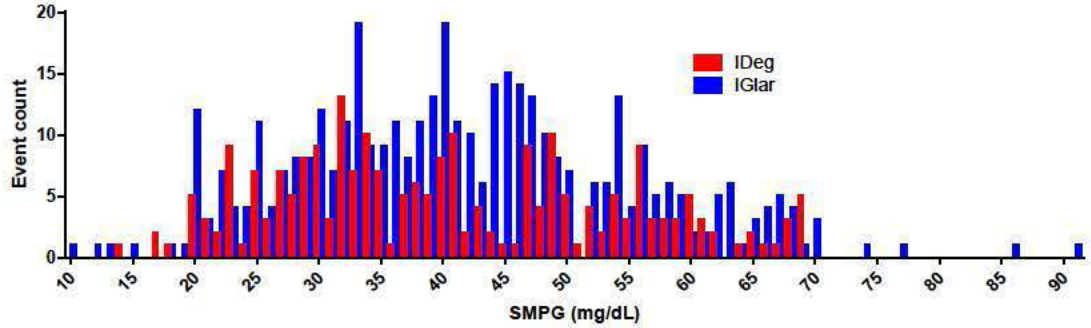
(b) (6) *Hypo event 12*	*IGlar*	*37 mg/dL*	*Patient was hospitalized for treatment for a left renal abscess. She had an episode of hypoglycemia; blood glucose value 37 mg/dL. The investigator notes that the patient experienced confusion and lack of coordination. The diary entry indicates that the patient was also was unconscious. She was administered "15% serum glucose," but there are no details regarding the improvement of symptoms post this intervention. There is also no subsequent glucose value provided. Event was adjudicated with "complete information" by the EAC.*
(b) (6) Hypo event 1	IGlar	41 mg/dL	Patient was found by neighbor. Neighbor could not arouse patient and called EMS. Neighbor administered glucose tablets. EMS checked blood glucose value: 40 mg/dL. Patient regained consciousness and was not taken to the hospital. He was being treated for diarrhea with ciprofloxacin.
(b) (6) Hypo event 3	IGlar	44 mg/dL	Patient presented with a blood glucose value of 65 mg/dL and called the investigator to ask if he should receive insulin prior to his meal. He was advised to inject 3 units of insulin after breakfast. The patient ate a small meal blood glucose was 44 mg/dL. The patient was administered honey and juice at home and woke up. He was still somnolent. He was advised to go to the hospital where he was diagnosed with sepsis, with a possible pulmonary or urinary source. Blood glucose in the hospital was 21 mg/dL. IV glucose was given. Other complications included worsened renal failure and need of vent support. Patient died.

Reviewer's comment: Concomitant medical events did not seem to drastically affect the severe hypoglycemia findings in patients with symptoms of unconsciousness or in a coma or seizure. Overall, I agree with the adjudication of the EAC for events with symptoms of seizure or unconsciousness or in a coma.

Because review of adjudication packets (discussed above) revealed that some of the EAC confirming hypoglycemia events did not have neuroglycopenia, I wanted to further characterize the EAC confirmed events. Since the International Hypoglycemia Study Group considers an SMPG <54 mg/dL as a glucose level that is sufficiently low to indicate serious, clinically important hypoglycemia, I explored to what extent confirmed EAC events met this threshold.

Of the 280 EAC confirmed severe hypoglycemia events for IDeg, 232 had an available SMPG at the time of the event and of the 472 EAC confirmed severe hypoglycemia events for IGlar, 405 had an available SMPG at the time of the event. The SMPG value at the time of the hypoglycemia event is shown in **Figure 27**. Over 80% of events with an available SMPG value were less than 54 mg/dL.

Figure 27- SMPG values for EAC confirmed severe hypoglycemia events.



Source: ADAJ dataset, QRT3

Reviewer's comments: Because most EAC confirmed severe hypoglycemia events met a glycemic threshold (<54 mg/dL), these events would be considered clinically important by the health care community.[63] In addition, these events were accompanied by symptoms of hypoglycemia (which is not a requirement proposed for glucose levels reporting by the International Hypoglycemia Study Group).

Therefore, in my opinion, although there is some ambiguity in the events confirmed by the EAC as severe hypoglycemia, most of the events remain clinically meaningful.

Since treatment of severe hypoglycemia may vary (i.e. in cases where the patient is unconscious, parenteral therapy may be preferred), I also reviewed the types of treatments administered to patients as an indirect analysis of the severity of the events confirmed by the EAC. Investigators reported how hypoglycemic episodes were treated in the hypoglycemic episodes form. Episodes could have been treated with more than one method.

As shown in **Table 36**, most EAC confirmed severe hypoglycemia events were treated using oral therapy followed by IV or IM therapy. Across treatment categories, there was an imbalance favoring IDeg over IGlar. However, the difference between treatment arms was smaller when considering IV or IM therapy, with 1.8% of patients randomized to IDeg and 2.1% of patients randomized to IGlar receiving parenteral administration.

Table 36 – Treatment of all EAC confirmed severe hypoglycemia episodes-FAS

	IDeg	IGlar

[63] In 2016, the International hypoglycemia study group published a Joint position statement for the American Diabetes Association and the European Association recommending that the "frequency of detection of a glucose concentration <3 mmol/L (<54 mg/dL), which it considers to be clinically significant biochemical hypoglycemia, be included in reports of clinical trials of glucose lowering drugs evaluated for the treatment of diabetes mellitus. Publication: Glucose Concentrations of Less Than 3.0 mmol/L (54 mg/dL) Should Be Reported in Clinical Trials: A Joint Position Statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 2016.

Treatment	N	%	E	N	%	E
Number of patients	3818			3819		
Oral therapy	104	2.7	152	183	4.8	327
IV or IM therapy	68	1.8	81	80	2.1	99
Unknown method of treatment*	5	0.1	5	0	0	0
Other therapy specified^	37	1	47	42	1.1	66
Other therapy, not specified	3	0.1	3	3	0.1	3
*no response was provided in the hypoglycemic episode form ^Free text responses entered by investigators. Most of these responses indicate intake of oral carbohydrates Source: Information request dated October 6, 2017, question 3: \\CDSESUB1\evsprod\NDA203314\0143\m1\us\re-fda-ir-20170929.pdf						

Reviewer's comment: the use of parenteral therapies for EAC confirmed cases of severe hypoglycemia shows a slight imbalance favoring IDeg over IGlar.

Glycemic control

Since differences in glycemic control can affect hypoglycemia findings, the reviewer evaluated glycemic trends with the purpose of determining if there was equivalent glycemic control between treatment arms.

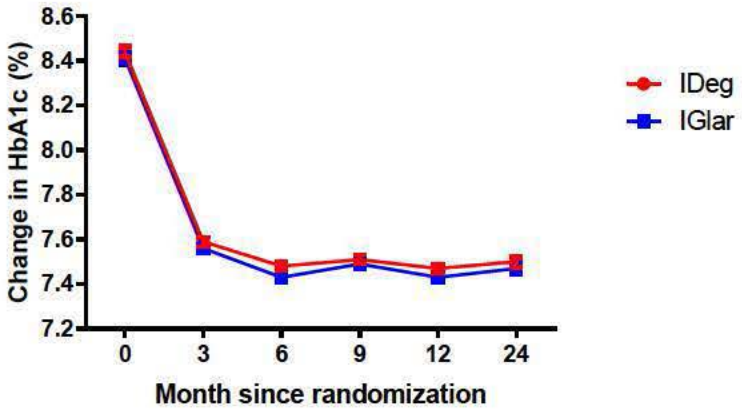
DEVOTE assessed glycemic control based on HbA1c (centrally measured), FPG (centrally measured) and SMPG measurements. Each glycemic measure will be discussed in this section.

HbA1c

Because of the event-driven nature of the trial design, the month 24 visit was the last scheduled visit, apart from the end-of treatment visit during which efficacy parameters were assessed for most patients (64%). The Sponsor did not select the end of treatment visit for analysis since the observation time was different among individual patients.

Figure 28 shows the HbA1c over time for both treatment groups. At baseline, the mean HbA1c was 8.44% for IDeg vs. 8.41 for IGlar. The largest drop in HbA1c was seen after three months of treatment for both treatment arms (mean HbA1c 7.59% vs. 7.56% for IDeg vs. IGlar respectively); with small variations following the initial three months of treatment. At 24 months, the mean HbA1c was 7.50% for IDeg and 7.47% for IGlar in both treatment groups.

Figure 28 – HbA1c- mean ± standard errror of the mean curves over time-FAS



Time	0	3	6	9	12	24
IDeg (N)	3774	3656	3608	3535	3525	2458
IGlar (N)	3776	3640	3562	3516	3500	2424

Source: CSR, table 14.2.154, page 458.

Reviewer's comment: Glycemic control based on HbA1c was similar between IDeg and IGlar from randomization to month 24. It is notable that the glycemic control with IDeg did not appear to be better than IGlar.

Table 37 shows the reported HbA1c values by visit. When looking at the mean HbA1c values between treatment groups it appears that IDeg was slightly higher than IGlar at every visit. The difference between the mean HbA1c at each visit, however was small, ranging from 0.02 to 0.05 higher for IDeg.

Table 37- Mean HbA1c by visit

Month	IDeg			IGlar			
	Mean HbA1c	SD	N	Mean HbA1c	SD	N	Mean Diff IDeg-IGlar
0	8.44	1.63	3774	8.41	1.67	3776	0.03
3	7.59	1.23	3656	7.56	1.23	3640	0.03
6	7.48	1.18	3608	7.43	1.16	3562	0.05
9	7.51	1.21	3535	7.49	1.24	3516	0.02
12	7.47	1.23	3525	7.43	1.21	3500	0.04
24	7.50	1.20	2458	7.47	1.20	2424	0.03
Data points obtained from CSR table 14.2.154, page 458 SD: standard deviation, N: number of patients							

To explore the trends in HbA1c, the Sponsor performed a *post hoc* analysis to evaluate the mean change from baseline to month 24. As shown in **Table 38,** the treatment difference of IDeg versus IGlar for the change from baseline to 24 months remained slightly above zero (0.008).

Table 38 –HbA1c change from baseline to 24 month visit- *post hoc* analysis -FAS

	FAS	N	Estimate	95% CI	P-value
Change from baseline at 24 months					
Estimated means IDeg IGlar	 3818 3819	 3707 3695	 -0.864 -0.872		
Treatment difference			+0.008	[-0.050;0.066]	0.779
Change from baseline to 24 months visit analyzed using a mixed model for repeated measures (MMRM) within subjects using an unstructured residual covariance matrix among visits at 6, 12 and 24 months of study. Interaction between visit and treatment and visit and baseline are included as fixed effects. **Abbreviations:** CI: confidence interval; FAS: full analysis set; HbA1c: glycated hemoglobin; N: number of patients contributing to analysis					

For context, I provide the HbA1c findings for T2DM patients in prior reviewed/under-review studies in the IDeg program for trials comparing IDeg to IGlar (administered once daily and U100 formulation). As shown in **Table 39**, across trials, the point estimates of treatment difference (IDeg- IGlar) favors IGlar (i.e., is slightly higher for IDeg).

Table 39 –HbA1c (%) results for previously submitted Phase 3 trials

Study	Duration	Treatment group	Primary hypothesis	Treatment difference (IDeg- control)	
				LS mean	95% CI
PHASE 3 trials submitted on the original submission					
3582	52 weeks	IDeg+ IAsp ±OAD(s) IGlar+ IAsp ±OAD(s)	Non-inferiority	+0.07	-0.06,0.20
3579	52 weeks	IDeg +OAD(s) IGlar+ OAD(s)	Non-inferiority	+0.08	-0.05,0.21
3586	26 weeks	IDeg+ OAD(s) IGlar+ OAD(s)	Non-inferiority	+0.08	-0.05, 0.22
Post approval trials (under review)					
3998^	64 weeks	IDeg ± OAD(s) IGlar ± OAD(s)	Non-inferiority	*Period 1:* +0.09 *Period 2:* +0.06	 -0.04,0.23 -0.07, 0.18
^ trial was a double-blind crossover trial with 2 treatment period. Source: Statistical review, table 48, Dr. Liu DAARTS dated Novemeber 14, 2012, SWITCH primary clinical review					

Reviewer's comment: HbA1c control between treatment arms from randomization to 24 months was very similar. Slight differences between treatment arms noted in crude calculations likely reflect the baseline differences between treatment arms. The glycemic findings in DEVOTE contrasts with the findings from previous Phase 3 trials, where glycemic control was slightly worse for IDeg than IGlar.

Since the pre-specified analysis of severe hypoglycemia was based on severe hypoglycemia events from randomization to the individual end of trial date, while the glycemic findings (as shown above), included 24 months, the Sponsor was asked to provide an analysis of severe hypoglycemia only including events occurring from randomization to 24 months – since this is the period for which there were central laboratory-glycemic findings available. **Table 40** shows the confirmed severe hypoglycemic episodes from randomization to 24 months. Overall there were a lower

proportion of patients and a lower number of events confirmed as severe hypoglycemia for IDeg than IGlar. The Sponsor was also asked to evaluate the hierarchical tested secondary endpoints for this period. Overall, the statistical analyses for EAC confirmed severe hypoglycemia episodes from randomization to 24 months were consistent with the pre-specified secondary analyses; EAC confirmed severe hypoglycemic episodes relative ratio of 0.61 with a 95% confidence interval of 0.48 to 0.78; for EAC confirmed severe hypoglycemic episodes within a patient, odds ratio 0.75 with a 95% confidence interval of 0.61 to 0.91.

Table 40 – EAC confirmed severe hypoglycemic episodes- from randomization to 24 months- summary –full analysis set

	IDeg				IGlar				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects	3818				3819				7637			
PYO	7083				7071				14153			
EAC confirmed events*	178	(4.7)	269	3.80	235	(6.2)	450	6.36	413	(5.4)	719	5.08

EAC: Event adjudication committee, N: Number of subjects,
%: Percentage of subjects relative to the number of randomised subjects,
E: Number of events, PYO: Patient years of observation, R: Event rate per 100 PYO,
* EAC confirmed severe hypoglycaemic episodes defined according to ADA
Episodes with EAC onset date during trial are included,
ADA: American diabetes association

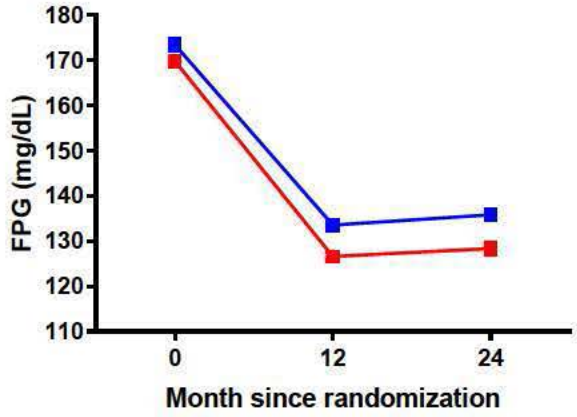
Source: information request received August 29, 2017, question 7, \\CDSESUB1\evsprod\NDA203314\0140

Reviewer's comment: the hypoglycemia findings persist even when evaluating only from the periods of randomization to 24 months.

FPG (Fasting plasma glucose)

Figure 29 shows the FPG over time for both treatment groups. At baseline, the mean FPG was lower for IDeg vs. IGlar (169.8 mg/dL vs. 173.5 mg/dL). The largest drop from baseline in FPG occurred at 12 months with a mean decrease of -43.7 mg/dL for IDeg and -39.0 for IGlar. At 24 months, FPG decreased from baseline by -39.9 mg/dL for IDeg and -34.9 mg/dL for IGlar.

Figure 29 – Fasting plasma glucose (mg/dL) mean ± standard errror of the mean by visit summary- FAS



Time (months)	0	12	24
IDeg (N)	3757	3521	2457
IGlar (N)	3760	3498	2425

Source: CSR table 14.2.165, page 471.

The Sponsor performed a *post hoc* analysis evaluating the mean change of FPG for IDeg-IGlar from baseline to 24 months. Although the analysis was not pre-specified, the results are overall consistent with the visual findings in the trends in FPG: namely that FPG was lower for IDeg and IGlar from randomization to month 24.

Table 41 – P*ost hoc analysis* – FPG change from baseline to 24 months visit- FAS

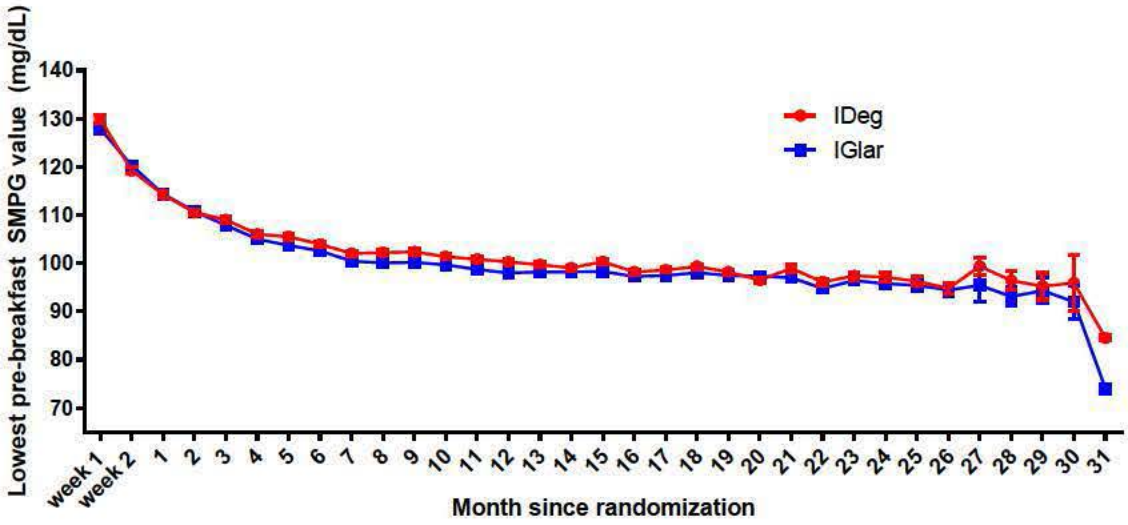
	FAS	N	Estimate	95% CI	P-value
Estimated means					
IDeg	3818	3505	-41.13		
IGlar	3819	3496	-33.92		
Treatment difference					
IDeg-IGlar			-7.203	[-10.29; -4.118]	<0.001
Change from baseline to 24 months visit analyzed using a mixed model for repeated measures (MMRM) within subjects using an unstructured residual covariance matrix among visits at 6, 12 and 24 months of study. Interaction between visit and treatment and visit and baseline are included as fixed effects.					

Source: CSR, table 11-4, page 152

Self-measured plasma glucose measurements

Figure 30 shows the SMPG trends over time for both treatment groups. Throughout the duration of the study the curves have similar values. Overall, the decline in plasma glucose is gradual and reaches a nadir at around 7 months.

Figure 30 – Pre-breakfast SMPG (mg/dL) - mean ± standard errror of the mean- by visit- summary- FAS



Source: CSR, table 14.2.178, page 486.

Analyses of 8-point SMPG profiles over 1 day (month 12, month 24 and end of treatment visit) are shown in the appendix (see **Figure 49)**. Overall, the trends in 8-point SMPGs across time points were either similar or slightly lower for IDeg as compared to IGlar.

Reviewer's comments: Across glycemic measures, glycemic control appears to have been overall similar, (HbA1c and SMPG), to slightly better (for FPG) for IDeg over IGlar.

Titration/ Insulin doses

The discussion on titration and insulin dose is carried out to provide context for the glycemia and hypoglycemia findings.

As noted in **Figure 3**, in addition to the protocol-recommended titration target of 71-90 mg/dL there was a second titration target of 91-126 mg/dL, which was recommended by the Steering Committee. The use of this additional target was solely a decision of the investigator. Investigators could also use other titration targets, if clinically appropriate.

After randomization, the capture of titration targets was not systemically captured, even though investigators could decide to change titration algorithm at any point in the trial. Investigators could document use of a different titration algorithm as a reason for deviation from the protocol recommended titration guidelines (in the SMPG and titration form eCRFs).

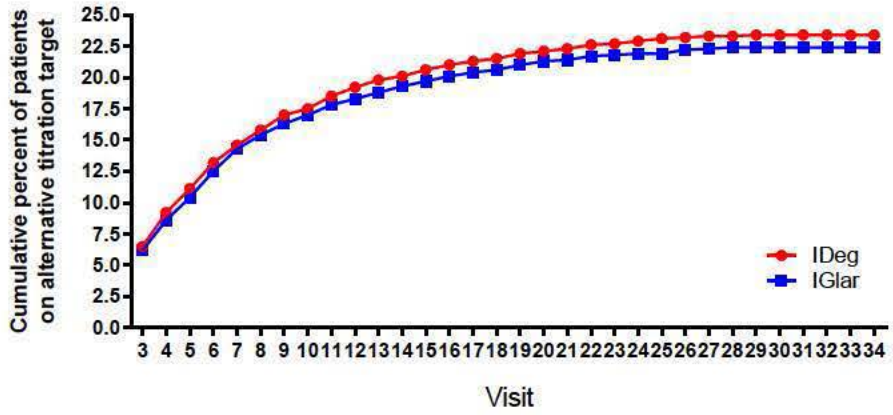
The titration targets used by patients at baseline are shown in **Table 42**. More than 82% of patients used the standard titration goal with the remaining patients using other titration targets.

Table 42 – Titration targets at baseline for randomized patients

	Standard titration goal 71-90 mg/dL		Titration goal of 126 mg/dL		Other titration goal	
	IDeg	IGlar	IDeg	IGlar	IDeg	IGlar
N (%)	3153 (82.5)	3154 (82.5)	133 (3.5)	132 (3.5)	532 (13.9)	533 (13.9)
Source: Information request, 07 August 2017, Table 8-1 \\CDSESUB1\evsprod\NDA203314\0138\m1\us\re-fda-ir-20170731.pdf						

Evaluation of documented titration violations revealed that there were a slightly larger proportion of patients on IDeg as compared to IGlar using an alternative titration target; see **Figure 31**.

Figure 31 – Cumulative percentage of patients on alternative titration documented as a reason for titration deviation by visit



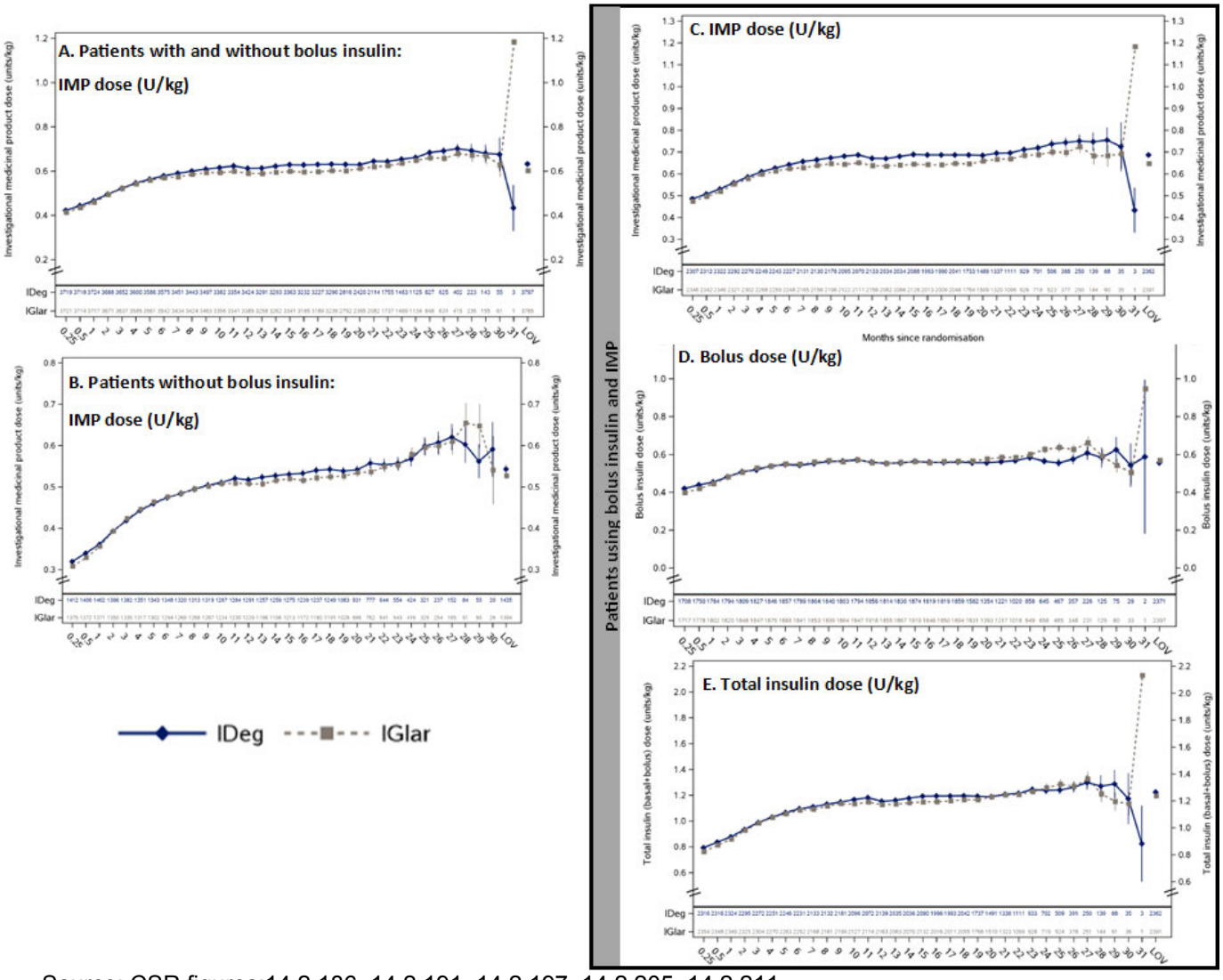
Source: Information request 27 July 2017, Table 2 \\CDSESUB1\evsprod\NDA203314\0137\m1\us\re-fda-ir-20170720.pdf

Reviewer's comment: Treatment differences in titration goals may elucidate differences in insulin use between treatment groups. Although it appears that a larger proportion of patients randomized to IDeg used alternative titration targets than IGlar, the limitations with these analyses should be considered, particularly the fact that use of other titration targets was not systematically collected. In addition, the specific target goals were not collected in the CRFs and thus are not available.

This section discusses the doses of insulin in DEVOTE by evaluating data for the following groups: all randomized patients, patients using bolus and basal insulin ± OADs and patients using basal insulin ± OADs. Patients using bolus insulin are considered separately from patients not using bolus insulin because these two groups are clinically different and because they have a different risk of hypoglycemia.

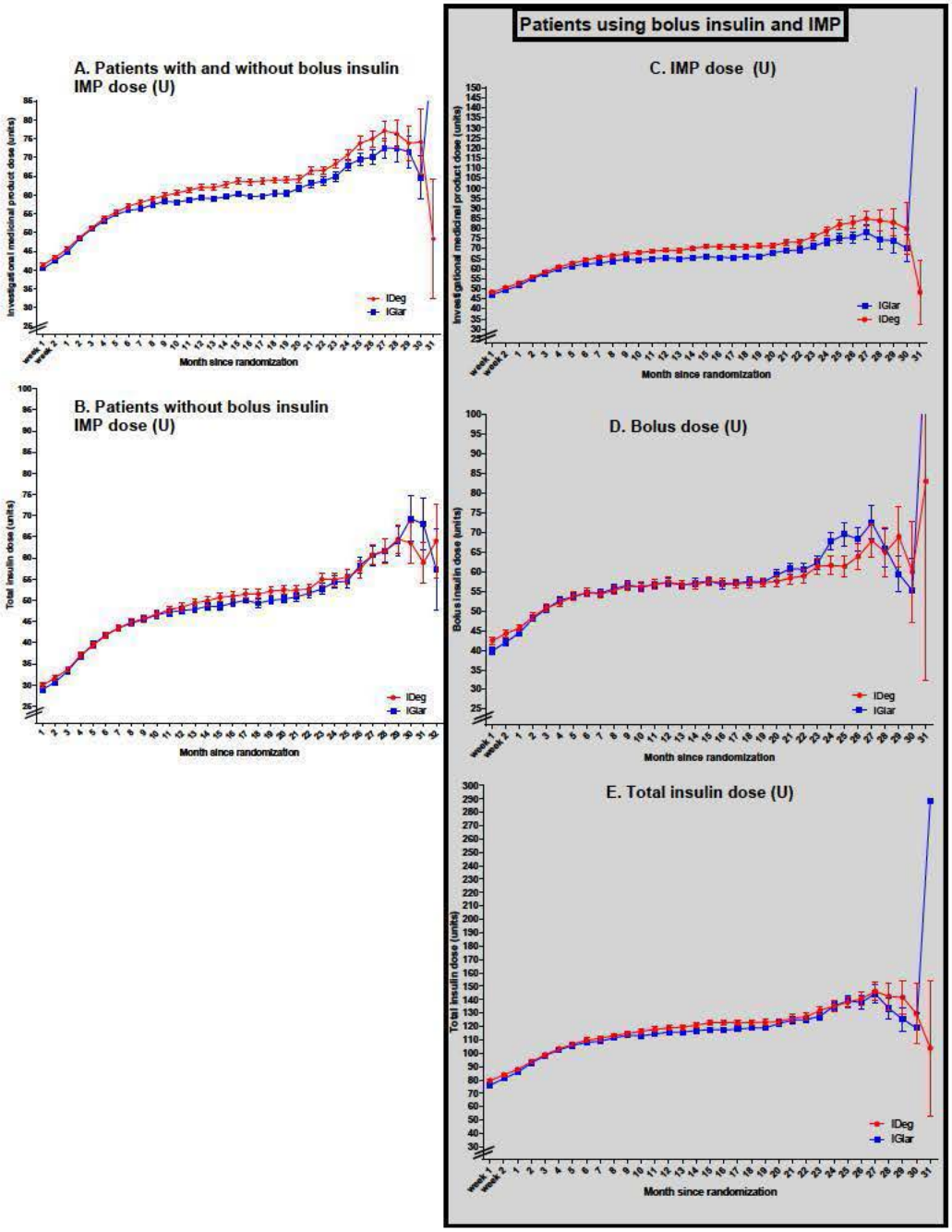
The insulin dose data is summarized in **Figure 32** for units/kg and **Figure 33** for units. **Table 43** shows the insulin doses used at randomization and month 24. Of note, the Sponsor considers baseline as week 1 (i.e. not the randomization visit, i.e. week 0).

Figure 32 – Insulin doses (U/kg): A. patients with and without bolus insulin: IMP dose; B: Patients without bolus insulin: IMP dose; C. Patients using bolus insulin and IMP: IMP dose; D: Patients using bolus insulin and IMP: bolus dose; E. Patients using bolus insulin and IMP: total insulin dose



Source: CSR figures:14.2.186, 14.2.191, 14.2.197, 14.2.205, 14.2.211

Figure 33 – Insulin doses (Units): A. Patients with and without bolus insulin: IMP dose; B: Patients without bolus insulin: IMP dose; C. Patients using bolus insulin and IMP: IMP dose; D: Patients using bolus insulin and IMP: bolus dose; E. Patients using bolus insulin and IMP: total insulin dose



Source: CSR tables: 14.2.182, 14.2.188, 14.2.194, 14.2.202, 14.2.208

Table 43 – Insulin doses at baseline and 24 months (Units)

Insulin dose analysis	Tx	N FAS	n	Baseline Mean insulin dose (SD)	N	24 month LS Mean dose (SD)	Change from baseline LS Mean insulin dose (SE)	LS Mean difference in insulin dose ^	Treatment difference (95% CI)	p-value*
BASAL INSULIN DOSE (Units)										
All randomized patients	IDeg IGlar	3818 3819	3717 3694	41.3 (30.4) 40.4 (30.3)	3717 3695	65.1(0.74) 61.9 (0.74)	24.4 (0.74) 21.1 (0.74)	3.2	[1.2; 5.3]	0.002
Patients also using bolus	IDeg IGlar	3818 3819	2308 2348	48.4 (31.6) 47.2 (31.7)	2311 2338	72.3 (1.00) 67.5 (0.99)	24.8 (1.00) 20.0 (0.99)	4.8	[2.0; 7.6]	<0.001
Patients NOT using bolus	IDeg IGlar	3818 3819	1416 1375	29.9 (24.3) 28.9 (23.7)	1406 1357	53.0 (1.06) 52.5 (1.08)	23.7 (1.06) 23.2 (1.08)	0.5	[-2.5; 3.5]	0.739
BOLUS INSULIN DOSE (Units)										
Patients using bolus	IDeg IGlar	3818 3819	1709 1719	42.5 (38.1) 39.9 (33.9)	2265 2292	61.6 (1.25) 65.0 (1.25)	28.7 (1.25) 32.1 (1.25)	-3.4	[-6.9; 0.0]	0.052
TOTAL INSULIN DOSE (Units)										
All randomized patients (with or without bolus)	IDeg IGlar	3818 3819	3734 3731	60.7 (54.1) 58.7 (50.7)	3717 3695	100.6 (1.27) 100.1 (1.27)	41.5 (1.27) 41.1 (1.27)	0.5	[-3.1; 4.0]	0.801
Patients also using bolus	IDeg IGlar	3818 3819	2317 2356	79.5 (58.4) 76.1 (54.1)	2311 2338	129.1 (1.88) 127.8 (1.87)	52.5 (1.88) 51.2 (1.87)	1.3	[-3.9; 6.5]	0.630

* two sided
^^The treatment difference between mean insulin doses at the 24 month visit was analyzed using a mixed model for repeated measures (MMRM) within subjects using an unstructured residual covariance matrix among visits at 3, 6, 9, 12, 15, 18, 21 and 24 months of the study. Interactions between visit and treatment and with baseline dose were included as fixed effects. Baseline dose was the first basal insulin dose reported by investigator for analyses of basal dose, whereas it was the dose at visit 3 for analyses of total insulin dose and bolus insulin dose
Source: table 6 in information request //cdsesub1/evsprod/NDA203314/0147/m1/us/re-fda-ir-20171024.pdf

Basal insulin use (IMP)
For all randomized patients (i.e. patients with and without bolus insulin), there was a rapid increase in basal insulin dose for the first ~6 months of treatment followed by a period of dose stabilization for both treatment arms. The unit dose analysis reveals a second increase in doses for both treatment arms after month 21, however this second increase in dose is not seen when evaluating dose by Units/kg (see **Figure 32** A and **Figure 33** A). When looking at between treatment trends, after month 6, the basal insulin dose for IDeg appears to be higher than IGlar, a difference that is more notable when looking at Units rather than Units/kg.

The basal insulin dose remains slightly higher for IDeg when compared to IGlar when looking at patients using bolus insulin and IMP (see **Figure 32** C and **Figure 33**C) and when looking at patients without bolus insulin (see **Figure 32** B and **Figure 33** B).

The basal insulin dose trends were confirmed when evaluating basal insulin dose changes from baseline to 24 months. Patients using IDeg used an additional 3.2 units, for all randomized patients and an additional 4.8, units for patients also using bolus insulin as compared to patients using IGlar. This difference in insulin dose was statistically different between treatment groups; see **Table 43**.

Reviewer's comment: the mean doses achieved of trial product show adequate exposure during the trial, and is in line with previous recommendations from the Division.

Bolus insulin dose
For patients using bolus insulin in addition to basal insulin, the bolus insulin dose increased over the first 3 months in the trial after which it remained steady for the duration of the trial (see **Figure 32** D and **Figure 33** D).There were no apparent differences between treatment arms as the curves appeared superimposed on each other until ~month 24, after which the curves suggest that the bolus dose for IDeg was lower than IGlar. However, the number of observations after this period was small.[64] An analysis of dose changes from baseline to 24 months in bolus dose revealed that patients randomized to IDeg had approximately 3.4 units less of bolus insulin than patients randomized to IGlar; see **Table 43.**

Total insulin dose

In patients using bolus insulin and IMP, the total insulin dose was similar to maybe slightly higher for IDeg when compared to IGlar when looking at months 10-19 with similar doses for other months (see **Figure 32** E and **Figure 33** E).

[64] 645 and 658 patients randomized to IDeg and IGlar respectively

The total insulin dose analysis analyses from baseline to 24 months showed a slightly higher total insulin dose of IDeg compared to IGlar for all randomized patients (0.5 Units) and patients also using bolus insulin (1.3 units higher); see **Table 43**.

Reviewer's comments: the basal insulin dose analyses across population groups (i.e. randomized population, patients on basal and bolus insulin, and patients on basal insulin without bolus insulin) suggests that basal insulin doses were higher for IDeg as compared to IGlar. This difference in insulin doses is also reflected (although more attenuated) in the total insulin dose for the entire population and the subset population of patients using basal and bolus insulin. Although the average bolus insulin dosing was not statistically different for IDeg than IGlar when evaluating baseline to 24 months, there is a hint that the dosing may have been slightly lower for IDeg than IGlar. It is unclear how differences in bolus dosing may have affected the hypoglycemia findings in DEVOTE. I discuss differences in the proportions of patients using bolus insulin in the following section.

Severe hypoglycemia in relation to anti-diabetic medications

To evaluate possible differences in anti-diabetic medications between treatment arms, the reviewer performed multiple exploratory analyses which are discussed in this section.

Differences in antidiabetic medications at baseline for the total randomized population is discussed in section **6.1.2 Demographics**.

An analysis evaluating the difference in the number of anti-diabetic medications at baseline and post-baseline was performed. The Sponsor provided information regarding the number of anti-diabetic medications per patient at baseline and post baseline in an information request dated August 29, 2017; see **Table 44**. Overall, there was no difference in the number of medications at baseline or post-baseline for IDeg and IGlar.

Table 44 – Antidiabetic medication-summary full analysis set

	Baseline		Post Baseline	
	IDeg OD	IGlar OD	IDeg OD	IGlar OD
Average number of antidiabetic medications per patient	2.40	2.39	2.98	2.97
Median number of antidiabetic medications per patient	2	2	3	3
Range of antidiabetic medications per patient	0 - 6	0 - 7	0 - 8	0 - 8

Source: information request, question #4, \\CDSESUB1\evsprod\NDA203314\0140

A second analysis evaluated what were the differences in post-baseline anti-diabetic medications between treatment arms. Table 45 shows the proportion of patients starting antidiabetic

medications post baseline (table was reproduced from Table 20 in the section 6.1.2 Demographics for reader's ease).

Table 45 – Proportion of patients starting any antidiabetic medication after baseline- FAS

	POST-BASELINE	
	IDeg N (%)	**IGlar N (%)**
Number of patients	3818	3819
Any antidiabetic medication	1155 (30.3)	1182 (31.0)
Bolus insulin	715 (18.7)	756 (19.8)
OADs		
Metformin	117 (3.1)	115 (3.0)
SU	84 (2.2)	82 (2.1)
Alpha glucosidase inhibitors	25 (0.7)	22 (0.6)
TZD	50 (1.3)	40 (1.0)
DPP4 inhibitors	122 (3.2)	136 (3.6)
GLP1 receptor agonist	151 (4.0)	118 (3.1)
SGLT2 inhibitors	163 (4.3)	153 (4.0)
Others	28 (0.7)	19 (0.5)

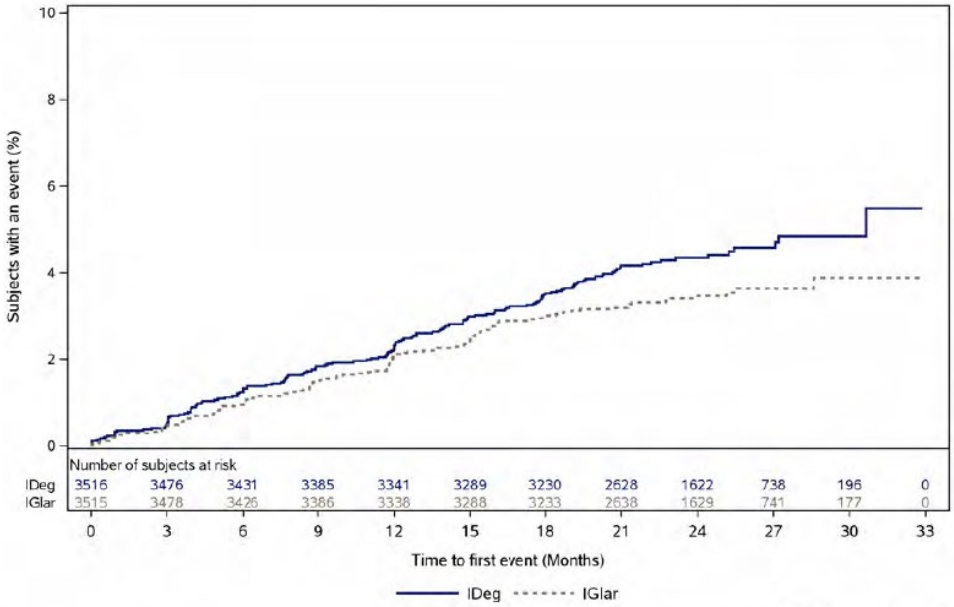
The following observations are noted from Table 45:

- There was a similar proportion of patients who started any anti-diabetic medication for IDeg (30.3%) vs. IGlar (31%).
- GLP-1 receptor agonists were started in a higher proportion of patients randomized to IDeg (4%) as compared to IGlar (3.1%)
- Bolus insulin was started in a similar proportion of patients randomized to IDeg (18.7%) vs. IGlar (19.8%)

To evaluate these post-baseline differences, additional analyses were requested by the FDA.

In order to explore the GLP-1 RA differences, the Sponsor was asked to perform a time to GLP-1 RA start analysis; see **Figure 34**. This analysis does not include patients using GLP-1 RA at baseline.

Figure 34 – Time to GLP-1 RA start- Kaplan Meier plot FAS



Source: Information request, 06 October 2017, Figure 2
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As shown in **Figure 34**, the number of patients starting a GLP1-RA was similar between the treatment groups until month 3, at which point the curves split, with a larger proportion of patients starting a GLP-1 RA in the IDeg group than the IGlar group. The Sponsor also provided an analysis using a Cox proportional hazard regression with treatment (IDeg and IGlar) as factor; this analysis is shown in **Table 46**.

Table 46 – Time to GLP-1 RA start- statistical analysis- FAS

		First events				
Treatment	FAS	N	Prop.(%)	Hazard ratio	95% CI	p-value
IDeg	3516	151	(4.29)			
IGlar	3515	118	(3.36)			
IDeg/IGlar				1.280	[1.006 ; 1.629]	0.044

FAS: Number of subjects randomised to given treatment excluding subjects on bolus at baseline
N: Number of subjects with a first bolus dose
%: Percentage of subjects with first bolus dose, relative to the number of randomised subjects
CI: 95% confidence interval
p-value: Refers to two-sided test of hazard ratio = 1.0

Source: Information request, 06 October 2017, Table 7
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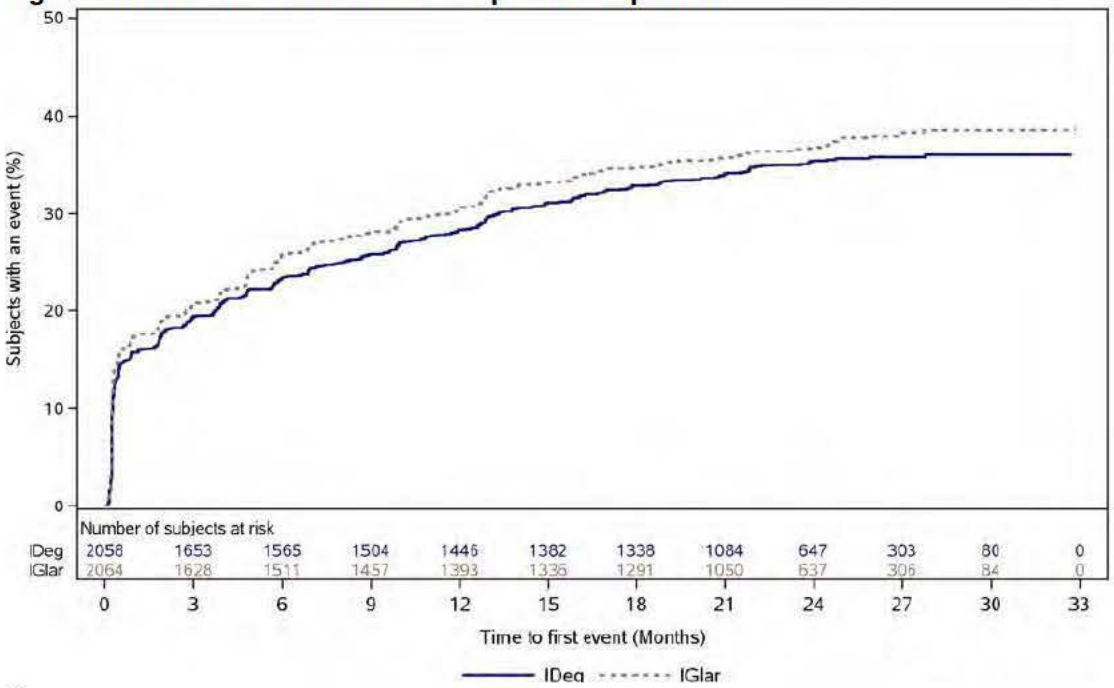
Per the Sponsor's analysis, there appears to be a marginal (p=0.044) difference with a higher proportion of patients starting a GLP-1 RA post-baseline in patients randomized to IDeg when compared to patients randomized to IGlar.

A second exploratory analysis evaluated the post-baseline difference in bolus insulin. For this analysis, the Sponsor was asked to provide an analysis of time to first bolus

dose; see **Figure 35**. This analysis did not include patients using bolus insulin at baseline.

Figure 35- Time to first bolus dose- Kaplan Meier plot- FAS



Source: Source: Information request, 06 October 2017, Figure 1
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As shown in **Figure 35**, the number of patients starting bolus insulin was not statistically different between treatment arms (with the curves converging at multiple points). The Sponsor also provided an analysis using a Cox proportional hazard regression with treatment (IDeg and IGlar) as factor; this analysis is shown in **Table 47**.

Table 47 – Time to bolus insulin start- statistical analysis- FAS

		First events				
Treatment	FAS	N	Prop.(%)	Hazard ratio	95% CI	p-value
IDeg	2058	715	(34.74)			
IGlar	2064	756	(36.63)			
IDeg/IGlar				0.930	[0.839 ; 1.030]	0.163

FAS: Number of subjects randomised to given treatment excluding subjects on bolus at baseline
N: Number of subjects with a first bolus dose
%: Percentage of subjects with first bolus dose, relative to the number of randomised subjects
CI: 95% confidence interval
p-value: Refers to two-sided test of hazard ratio = 1.0

Source: Information request, 06 October 2017, Table 4
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An analysis evaluating a time to event analysis adjusting for bolus insulin, is shown in **Table 48.** This analysis, is consistent with the previously shown in **Table 29,** therefore implying that the difference between treatment arms is not fully explained using bolus insulin. However, use of bolus insulin was associated with hypoglycemia (Y/N; see below).

Table 48 – Time to first EAC confirmed severe hypoglycemic episode adjusted for bolus insulin use during trial prior to the episode- FAS

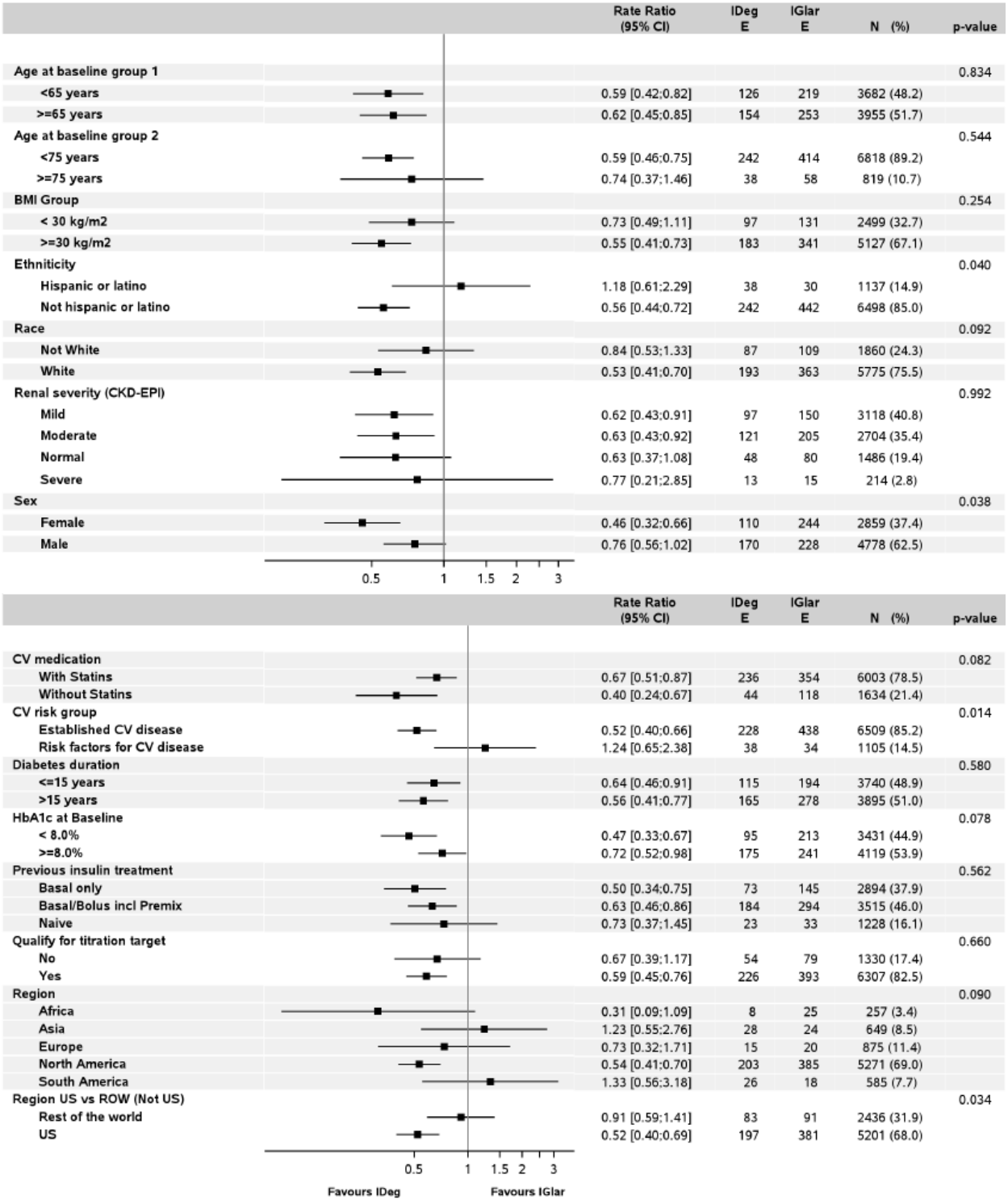
	Hazard ratio	95% CI	P-value
Time to first severe hypoglycemic episodes (days)			
Planned treatment IDeg/IGlar	0.74	0.61;0.89	0.0017
Previous bolus insulin group Y/N	2.38	1.91;2.96	<0.0001
2-sided p-value Hazard ratio based on cox regression with treatment and bolus use as time-varying covariate. Previous bolus insulin group (N): no previous bolus dose taken; Previous bolus insulin group (Y): previous bolus dose taken For events occurring on the same day as bolus dose, 0.5 day was added to the day of the event. All patients start with no previous bolus dose and change at time of first bolus dose>0 Source: CSR table 14.2.128, page 432			

Subgroup evaluation of hypoglycemia

Figure 36 shows the subgroup findings for patients experiencing EAC confirmed severe hypoglycemia. Overall, the findings favored IDeg across subgroups, except for the following demographics: Hispanic or Latino, Risk factors for CV disease category, and Asia and South America regions. However, the number of patients in these categories was very small and the findings may be reflective of chance.

Please refer to Dr. Hamilton's review for the FDA's subgroup analyses pertaining to hypoglycemia.

Figure 36 – EAC confirmed severe hypoglycemia episodes by subgroups



Reviewer's comment: Across subgroup categories, the findings of severe hypoglycemia were generally consistent with the pre-specified secondary endpoints. Interpretation of the hypoglycemia subgroup findigns should be

cautious given that this was a secondary endpoint and the overall numbers are small in many categories.

Nocturnal severe hypoglycemia

Nocturnal EAC-confirmed severe hypoglycemia was not a hierarchical tested secondary endpoint in DEVOTE. The analysis of this endpoint was pre-specified as a safety endpoint; refer to **Table 15**. Nocturnal severe hypoglycemia events were defined as occurring with onset between 00:01 and 05:59 am (as reported by investigator), both time points inclusively. As noted previously, basal insulin was to be administered between dinner and bedtime.

Reviewer's comment: (b) (4) **EVOTE the administration insulin only occurred in the evening.**

Table 49 shows the number of nocturnal EAC confirmed severe hypoglycemia events. Of the 752 confirmed severe hypoglycemia events, approximately 24 (8.57%) and 33 (6.99%) EAC-confirmed events for IDeg and IGlar respectively did not have a time point reported. These events were not included in the statistical analysis discussed below.

Approximately 1% vs. 1.9% of patients in the IDeg vs. IGlar group experienced a confirmed nocturnal severe hypoglycemia event.

Table 49 – Nocturanl EAC-confirmed severe hypoglycemic epsides- summary- FAS

	IDeg			IGlar		
	N (%)	E	R	N (%)	E	R
Number of patients	3818			3819		
PYO	7568			7558		
EAC confirmed nocturnal events *	38 (1)	49	0.65	73 (1.9)	106	1.4

* EAC-confirmed severe hypoglycemic episodes defined according to ADA. Episodes with EAC onset date during trial are included. Nocturnal severe hypoglycemic episodes are those that occur between 00:01 and 05:59, both time points included. 24 (8.57%) of the EAC-confirmed hypoglycemic episodes did not have a time point reported in IDeg group. 33(6.99%) of the EAC-confirmed hypoglycemic episodes did not have a time point reported in IGlar group.
Source: CSR, table 12-9, page 203

The rate of nocturnal severe hypoglycemia was lower with IDeg than with IGlar with a risk ratio of 0.47 [0.31; 0.73]95% CI.

Reviewer's comment: the nocturnal severe hypoglycemia findings are considered exploratory. Although the findings are consistent with the overall hypoglycemia findings of the trial, it is important to keep in mind that the overall numbers are small. In addition, other limitations include the amount of missing (i.e. missing administration time), and the evening administration time of the basal insulins. Therefore, I do not support the labeling of nocturnal hypoglycemia, as proposed by the Sponsor.

6.1.6 Other Endpoints

Safety endpoints are discussed in the section titled, **Discussion of the components of MACE,**

6.1.7 Subpopulations

Subpopulations are discussed for the primary endpoint and the multiplicity adjusted endpoints in section **Subgroup analyses** and section **Subgroup evaluation of hypoglycemia** respectively.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Insulin dose is individualized. Refer to the Prescribing Information for Tresiba for dosing recommendations.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Section is not applicable to this supplement.

6.1.10 Additional Efficacy Issues/Analyses

Additional efficacy analyses are discussed above, as pertinent.

7 Review of Safety

Safety Summary

Since the overall safety of insulin degludec was established at the time of approval, DEVOTE contained an abbreviated assessment of safety. Serious adverse events, adverse events resulting in discontinuation of investigational products, selected laboratory values, and neoplasms were evaluated in the trial.

Both insulin degludec and insulin glargine had a similar mean patient observation period which was close to 2 years and a mean patient exposure time of 1.8 years.

The patient incidence and event rate of serious adverse events were similar between insulin degludec and insulin glargine, with most events clustering in the system organ classes of Cardiac disorders and Nervous system disorders. There were no clear preferred terms driving the numerical differences in specific serious adverse events between treatment arms.

The adverse events resulting in discontinuation of insulin degludec or insulin glargine were overall similar and most events were part of the system organ class of cardiac disorders, infections and infestations or nervous system disorders. In addition, there was no clear evidence that the investigational drug was discontinuation due to hypoglycemia. Trends in laboratory parameters for central tendencies and outliers were similar between treatment arms. Finally, few neoplasms were captured in DEVOTE, with no clear treatment differences.

7.1 Methods

The safety review was focused on the adverse events that were systematic collected. The safety analyses used the full analysis set population, which followed the intention-to-treat principle, evaluating patients as randomized. There was no pooling of data from other studies (i.e. previous submissions). Because hypoglycemia is a pre-specified secondary efficacy endpoint, this safety issue is only addressed in the efficacy section and not in the safety section of this review.

Similarly, to the analyses of efficacy, the reviewer performed exploratory analyses using the Sponsor's databases to evaluate safety areas of interest.

Because the safety of insulin degludec has been thoroughly evaluated in the original submission, specific topics,[65] which were previously evaluated in the original submission, are not included in the review of current supplement. These topics have been omitted from this review since the Sponsor did not collect information pertaining to these topics in the DEVOTE program. The selective data collection in this program is consistent with post approval clinical studies.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The evaluation of safety was based on DEVOTE: A trial comparing cardiovascular safety of insulin degludec versus insulin glargine in subjects with type 2 diabetes at high risk of cardiovascular events

[65] 7.2.2 Explorations for dose response, 7.2.3 Special animal and/or in vitro testing; 7.2.4 routine clinical testing, 7.2.5 Metabolic, clearance and interaction workup, 7.2.6 Evaluation for potential adverse events for similar drugs in drug class, 7.4.1 common adverse events, 7.45 Special safety studies/Clinical trials, 7.4.6 immunogenicity, 7.5.1 dose dependency for adverse events, 7.5.2 time dependency for adverse events, 7.5.3 Drug-demographic interactions, 7.5.4 Drug-disease interactions, 7.5.5 Drug-drug interactions, 7.6.3 Pediatrics and assessment of effects on growth, 7.6.4 Overdose, drug abuse potential, withdrawal and rebound, 7.7 additional submission/ Safety issues.

7.1.2 Categorization of Adverse Events

Adverse events were defined as any untoward medical occurrence in a patient administered a medicinal product which does not necessarily have a causal relationship with treatment. Neither pre-existing conditions nor pre-planned procedures, unless the condition for which the procedure as planned has worsened, were to be reported as AEs. All AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 19.0.

The following AEs were systematically collected and recorded by the investigator in DEVOTE:[66]

- Serious Adverse Events (SAEs)
- AEs leading to discontinuation of investigational product
- Medication errors leading to an SAE[67] and
- Technical complaints[68]
- Episodes of severe hypoglycemia

The investigator was to complete the relevant ACS form or cerebrovascular form and the ACS adjudication or cerebrovascular adjudication form if an AE was reported whether an event was in his/her opinion was an ACS or a cerebrovascular event or none of the above.

During each contact, the investigator asked patients about AEs. By asking “have you experienced any problem since the last contact?”

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 “hospitalized” when any of the following were met:

[66] Of note, only in Japanese subjects, as per the Japanese authorities, non-serious AEs and non-severe hypoglycemia episodes were systematically reported.
[67] These include the administration of wrong drug or use of wrong device, wrong route of administration (IM vs. subcutaneous), administration of a high dose with the intention to cause harm (i.e. suicide), administration of accidental overdose (irrespective of whether it meets SAE criteria).
[68] A technical complaint is any written, electronic or oral communication that alleges product defects. The technical complaint could be (or not be) associated with an AE. Technical complains were recorded for the following products: insulin degludec, insulin glargine vials; insulin aspart pen injector and needles used for FlexPen. The investigator was to assess whether the technical complaint was related to an AE. Novo Nordisk Customer Complaint Centre could perform local unblinding in case of a technical complaint on the IMP. This was to be done via a controlled and documented process, where unblinded data were not to be shared with Novo Nordisk staff outside of Customer Complaint Centre or production.

- Patient was admitted to the hospital/inpatient irrespective of the duration of physical stay or a stay in the hospital for treatment or observation for >24 hours
- Patient was not admitted but stays in the hospital for treatment/observation for >24 hours

Administrative, trial-related, social purposes and planned surgical procedures hospitalizations were not considered AEs or SAEs.

For SAEs that could have resulted from hypoglycemia (i.e. sudden death, seizure, trauma, fractures, fall, motor vehicle accident etc.), narratives included information whether hypoglycemia could have contributed to the event.

All SAEs were to be followed up until the outcome of the event was "recovered/ resolved," or resolved with sequela or was fatal.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

There was no pooling of data for the analyses of safety in this review.

7.2 Adequacy of Safety Assessments

The size of the safety database is overall appropriate when considering the duration of treatment, demographics and disease characteristics for patients with established or at risk for cardiovascular disease.

As part of the safety review, I reviewed whether the investigator term was adequately coded to the preferred term in the adverse event dataset. In general, most events were adequately coded. I detected possible missed events in the coding of the PT's "fall" and "motor vehicle accident." In side-by-side comparison of PT term to investigator reported terms for PTs "fall" and "motor vehicle accident," I noted that some of the investigator terms included additional events (mostly fractures), which were not captured in the adverse event dataset. Review of the terms did not suggest a difference in coding by treatment group; refer to **Table 82** for a sample of the investigator terms I believe were under-coded.

Reviewer's comment: In general, the overall safety assessments, including overall coding of adverse events seems appropriate.

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

As shown in **Table 10,** the observation time was defined as the time form randomization until either last direct contact with site, last EAC-confirmed MACE or death before LPLV

(whichever came last). Exposure time was defined as the time from the date of the first dose of IMP to the last dose of IMP+1 excluding drug holidays.

The mean and median observation time was the same for IDeg and IGlar (~2 years). The median exposure time was slightly less than the observation time with again similar mean and median values for IDeg and IGlar (~1.8 years).

Table 50 – Exposure and observation time- summary- FAS

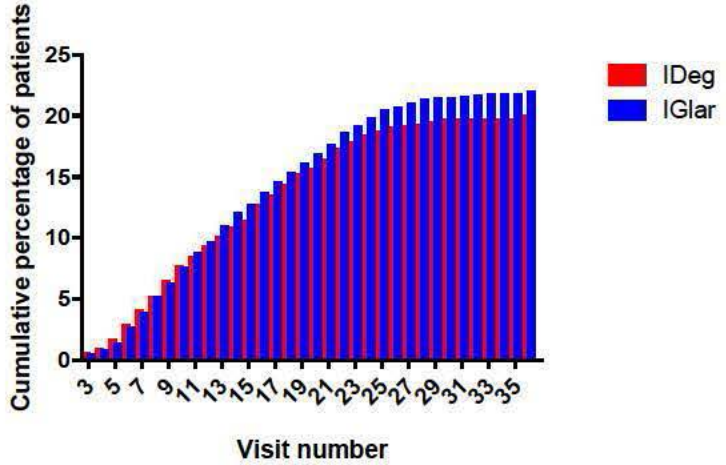
	IDeg	IGlar
Number of patients	3818	3819
Patient years observation (years)		
Total	7568	7558
Mean (SD)	1.98 (0.38)	1.98 (0.39)
Median	1.99	1.99
Patient year exposure (years)		
Total	6792	6730
Mean (SD)	1.78 (0.49)	1.76 (0.52)
Median	1.84	1.83
Source: CSR, table 14.2.1, page 297		

Reviewer's comments: the study duration was adequate for most safety concerns, with the exception of malignancies. Given that malignancies can take many years (maybe even decades) to develop, the exposure in DEVOTE would not be sufficient to fully characterize malignancies detected during the trial.

Treatment pauses

The Reviewer asked the Sponsor to conduct additional analyses to evaluate the proportion of patients with treatment pause from investigational product (**Figure 37**). There were slightly more patients in the IGlar group who cumulatively had a treatment pause than IDeg (21.9% vs. 19.9%).

Figure 37 – Patients with treatment pause by visit-summary FAS



Source: \\CDSESUB1\evsprod\NDA203314\0138\m1\us\re-fda-ir-20170731.pdf

Question 10, this includes patients with treatment pauses at any time up to the current visit, including patients who ended treatment before this visit but had a previous treatment pause.

For the patients with a treatment pause, the Sponsor was asked to provide proportion of patients who during the treatment pause were taking the other study drug (i.e. if randomized to IDeg, during the treatment pause patient received IGlar and vice versa).

The proportion of patients who were randomized to IDeg but during a treatment pause received IGlar was 4% (151 patients), while only 0.1% (3 patients) randomized to IGlar received IDeg during a treatment pause.

Reviewer's comment: the number of patients with treatment pauses was slightly higher for IGlar compared to IDeg. The higher number of patients who were originally randomized to IDeg but received IGlar during a treatment pause was small. It is unclear how exposure to IDeg (when randomized to IGlar) or IGlar, when randomized to IDeg during a treatment pause would affect the efficacy or safety findings.

7.3 Major Safety Results

7.3.1 Deaths

Deaths are discussed in sections titled: **CV-death** and **All cause death and non-CV death.**

7.3.2 Nonfatal Serious Adverse Events

As discussed previously, the Sponsor did not systematically collect all adverse events. Only SAEs, AEs resulting in permanent to discontinuation of IMP, SAEs resulting in medication errors and AEs resulting in technical complaints were collected. This section discusses the fatal and non-fatal SAEs captured in DEVOTE.

Table 51 shows SAEs by SOC. Approximately 38.6% of patients randomized to IDeg and 39.7% of patients randomized to IGlar experienced an SAE. The most common SOC for both treatment groups was Cardiac disorders (15.6% of SAEs) followed by Nervous system disorders (6.6% of SAEs). There were small differences in the proportion of patients by SOC categories with less than 1% difference in proportion of patients between treatment arms across SOCs. The SOCs with the largest difference between difference groups were seen for the SOCs Cardiac disorders (15.2% vs. 16.1%

for IDeg vs. IGlar respectively) and Nervous system disorders (6.1% vs. 7.04% for IDeg vs. IGlar respectively).

Table 51- SAEs by system organ class categories- FAS

	IDeg OD (N = 3818)			*IGlar OD (N = 3819)*		
SOC	*Number of subjects*	*Proportion (%)*	*Events*	*Number of subjects*	*Proportion (%)*	*Events*
Total number of SAEs	1473	38.6	3341	1517	39.7	3745
Blood and lymphatic system disorders	29	0.76	31	57	1.49	68
Cardiac disorders	579	15.17	873	616	16.13	972
Congenital, familial and genetic disorders	1	0.03	1	8	0.21	8
Ear and labyrinth disorders	9	0.24	9	8	0.21	8
Endocrine disorders	6	0.16	6	3	0.08	3
Eye disorders	20	0.52	25	15	0.39	17
Gastrointestinal disorders	150	3.93	178	148	3.88	186
General disorders and administration site conditions	122	3.2	130	142	3.72	158
Hepatobiliary disorders	38	1	39	32	0.84	38
Immune system disorders	3	0.08	3	3	0.08	3
Infections and infestations	367	9.61	501	394	10.32	549
Injury, poisoning and procedural complications	130	3.4	165	132	3.46	170
Investigations	16	0.42	16	17	0.45	17
Metabolism and nutrition disorders	149	3.9	183	137	3.59	183
Musculoskeletal and connective tissue disorders	118	3.09	134	118	3.09	134
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	109	2.85	116	109	2.85	119
Nervous system disorders	233	6.1	282	269	7.04	345
Product issues	5	0.13	6	8	0.21	9
Psychiatric disorders	34	0.89	42	38	1	46
Renal and urinary disorders	144	3.77	171	172	4.5	210
Reproductive system and breast disorders	20	0.52	22	13	0.34	14
Respiratory, thoracic and mediastinal disorders	148	3.88	194	172	4.5	241
Skin and subcutaneous tissue disorders	36	0.94	40	31	0.81	33
Social circumstances	1	0.03	1	0	0	0
Surgical and medical procedures	37	0.97	40	41	1.07	43
Vascular disorders	122	3.2	133	143	3.74	171
Source: ADSL, ADAE datasets, ANAL01FL=y, FASFL=y						

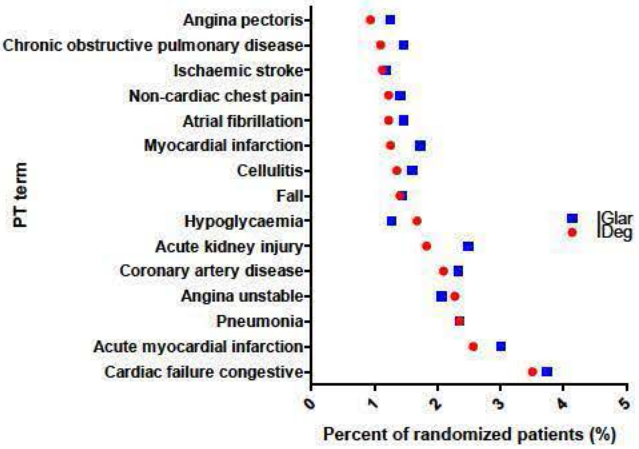
Review of the PT terms in the Cardiac disorders SOC revealed (see **Table 79** in appendix), that there was no clear preferred term driving these differences. The most frequent PT terms under this SOC were: ‘Angina unstable’ (2.28% vs. 2.07% for IDeg vs. IGlar respectively), ‘Cardiac failure congestive’ (3.51% vs. 3.74% for IDeg vs. IGlar respectively) ‘Coronary artery disease’ (2.1% vs. 2.33% for IDeg and IGlar respectively)

and acute myocardial infarction (2.57% vs. 3.01% IDeg vs. IGlar respectively). Other PT terms in this SOC were seen in smaller proportions of patients with small variations between treatment arms. Refer to section titled: **ACS discussion**, for a discussion on EAC adjudicated cardiac events.

Similar findings as that of the Cardiac disorders SOC were seen for the Nervous system disorders SOC. There was no clear clustering of PT terms. The most common PT term observed was Ischemic stroke seen in 1.13% of patients randomized to IDeg and 1.18% of patients randomized to IGlar.

The preferred terms containing a minimum of 1% patients in either treatment group experiencing an SAE is shown in **Figure 38**.

Figure 38 –Preferred terms of SAEs occuring in at least 1% of patients (%)



Source: ADSL, ADAE datasets, ANAL01FL=y, FASFL=y by TRTP

The PT terms in this figure, belonged to a variety of SOCs including: Cardiac disorders, Infections and infestations, Respiratory thoracic and mediastinal disorders, Nervous system disorders, Injury, poisoning and procedural complications, Metabolism and nutrition disorders, and Renal and urinary disorders. The pattern of affected patients by these common PT terms was overall similar between treatment groups. The following PT terms had notable differences between treatment groups.

- The proportion of patients with the PT term 'hypoglycemia' is slightly higher for IDeg as compared to IGlar (1.68% vs. 1.28%, respectively); findings which contrast with the secondary endpoints in DEVOTE. These findings however capture only a fraction of the overall hypoglycemia events sent for adjudication (i.e. this PT term captures 77 and 66 events for IDeg and IGlar respectively, while there were 404 and 601 events sent for adjudication for IDeg and IGlar respectively; refer to **Figure 22**).
- The proportion of patients with acute kidney injury is slightly lower for IDeg than for IGlar (1.83% vs. 2.19% respectively). The PT terms in the Renal and urinary disorders are shown in **Table 52.** Most of the difference between treatment arms

was made up by a slightly larger proportion of patients and events for the following PT terms: 'acute kidney injury,' 'chronic kidney disease,' and 'renal failure.' Refer to **Table 59** and **Figure 40** for an analysis of renal laboratories.

Table 52 – SOC Renal and urinary disorders

		IDeg			IGlar		
SOC	PT	N	%	E	N	%	E
		3818			3819		
Renal and urinary disorders	All	160	4.19	171	191	5	210
	Acute kidney injury	70	1.83	79	95	2.49	110
	Chronic kidney disease	16	0.42	18	26	0.68	30
	Renal failure	14	0.37	14	17	0.45	17
	End stage renal disease	12	0.31	12	9	0.24	9
	Nephrolithiasis	11	0.29	11	9	0.24	9
	Urinary retention	9	0.24	9	2	0.05	2
	Renal impairment	3	0.08	3	4	0.1	4
	Ureterolithiasis	3	0.08	3	5	0.13	5
	Acute prerenal failure	2	0.05	2	2	0.05	2
	Azotaemia	2	0.05	2	1	0.03	1
	Haematuria	2	0.05	2	3	0.08	3
	Hydronephrosis	2	0.05	2	3	0.08	3
	Stag horn calculus	2	0.05	2	0	0	0
	Stress urinary incontinence	2	0.05	2	0	0	0
	Bladder outlet obstruction	1	0.03	1	0	0	0
	Calculus bladder	1	0.03	1	0	0	0
	Cystitis noninfective	1	0.03	1	0	0	0
	Diabetic nephropathy	1	0.03	1	3	0.08	3
	Glomerulonephritis rapidly progressive	1	0.03	1	0	0	0
	Nephrosclerosis	1	0.03	1	0	0	0
	Nephrotic syndrome	1	0.03	1	2	0.05	2
	Renal mass	1	0.03	1	0	0	0
	Urethral stenosis	1	0.03	1	0	0	0
	Urinary hesitation	1	0.03	1	0	0	0
	Anuria	0	0	0	2	0.05	2
	Bladder neck obstruction	0	0	0	1	0.03	1
	Calculus urinary	0	0	0	1	0.03	1
	Nephropathy	0	0	0	1	0.03	1
	Nephropathy toxic	0	0	0	1	0.03	1
	Renal artery stenosis	0	0	0	1	0.03	1
	Renal colic	0	0	0	1	0.03	1
	Renal tubular necrosis	0	0	0	1	0.03	1
	Tubulointerstitial nephritis	0	0	0	1	0.03	1

Source: datasets ADAE and ADSL dataset, ANL01FL=y, AESER=y by TRTP

Reviewer's comment: overall the SAE findings were similar between treatment groups.

7.3.3 Dropouts and/or Discontinuations

Table 53 shows the proportion of patients who permanently discontinued IMP due to adverse events by SOC. In total 422 patients or 5.5% of all randomized patients permanently discontinued treatment due to adverse events (5.2% vs. 5.8% for IDeg and IGlar respectively). Across SOC adverse events resulting in permanent discontinuation of IMP were well distributed by treatment arm. The top 3 SOCs resulting in permanent discontinuation were Cardiac disorders, Infections and infestations and Nervous system disorders. Refer to **Table 80**, in the appendix, for adverse events resulting in permanent discontinuation by SOC and PT. Review of individual PT terms did not reveal a clustering of events only specific to a treatment group.

Table 53 – Patients with adverse events leading to discontinuetion of investigational medicinal product excluding patients resuming treatmetn by SOC-FAS

Primary System Organ Class	IDeg OD N=3818	IGlar OD N=3819	Total N=7637
Total	200 (5.24%)	222 (5.81%)	422 (5.5%)
Cardiac disorders	51 (1.34%)	52 (1.36%)	103 (1.26%)
Infections and infestations	36 (0.94%)	25 (0.65%)	61 (0.74%)
Nervous system disorders	31 (0.81%)	37 (0.97%)	68 (0.83%)
Respiratory, thoracic and mediastinal disorders	18 (0.47%)	19 (0.50%)	37 (0.45%)
Respiratory, thoracic and mediastinal disorders	18 (0.47%)	19 (0.50%)	37 (0.45%)
Gastrointestinal disorders	16 (0.42%)	15 (0.39%)	31 (0.38%)
Renal and urinary disorders	13 (0.34%)	14 (0.37%)	27 (0.33%)
Metabolism and nutrition disorders	13 (0.34%)	17 (0.45%)	30 (0.37%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	13 (0.34%)	9 (0.24%)	22 (0.27%)
Injury, poisoning and procedural complications	12 (0.31%)	12 (0.31%)	24 (0.29%)
General disorders and administration site conditions	11 (0.29%)	19 (0.50%)	30 (0.37%)
Vascular disorders	10 (0.26%)	15 (0.39%)	25 (0.30%)
Musculoskeletal and connective tissue disorders	9 (0.24%)	6 (0.16%)	15 (0.18%)
Surgical and medical procedures	6 (0.16%)	2 (0.05%)	8 (0.10%)
Psychiatric disorders	4 (0.10%)	7 (0.18%)	11 (0.13%)
Skin and subcutaneous tissue disorders	4 (0.10%)	5 (0.13%)	9 (0.11%)
Endocrine disorders	2 (0.05%)	1 (0.03%)	3 (0.04%)
Hepatobiliary disorders	2 (0.05%)	7 (0.18%)	9 (0.11%)
Blood and lymphatic system disorders	2 (0.05%)	4 (0.10%)	6 (0.07%)

Investigations	2 (0.05%)	5 (0.13%)	7 (0.09%)
Eye disorders	1 (0.03%)	2 (0.05%)	3 (0.04%)
Ear and labyrinth disorders	0 (0.00%)	1 (0.03%)	1 (0.01%)
Product issues	0 (0.00%)	2 (0.05%)	2 (0.02%)
Reproductive system and breast disorders	0 (0.00%)	1 (0.03%)	1 (0.01%)
Source: ADSL, ADAE datasets ANAL01FL=Y and FASFL=Y and TRTDISCFL=Y and ENDTRTFL=N			

Among these SOC, Infections and infestations had the largest difference between treatment arms (0.94% vs. 0.65% for IDeg and IGlar respectively). As shown in **Table 54**, there were small numerical differences between treatment groups within the preferred terms under this SOC. Most of the differences between PT terms were made up by 1-3 patients. Therefore, the slight differences in treatment arms do not appear to be driven by a specific type of event.

Table 54 – Preferred terms of Infections and infestations resulting in permanent discontinuation of IMP

Preferred terms	IDeg OD N=3818	IGlar OD N=3819	Total N=7637
Bacteraemia	0 (0.00%)	1 (0.03%)	1 (0.01%)
Bronchitis	1 (0.03%)	2 (0.05%)	3 (0.04%)
Bronchitis viral	1 (0.03%)	0 (0.00%)	1 (0.01%)
Cellulitis	1 (0.03%)	3 (0.08%)	4 (0.05%)
Cellulitis staphylococcal	1 (0.03%)	0 (0.00%)	1 (0.01%)
Clostridium difficile colitis	0 (0.00%)	1 (0.03%)	1 (0.01%)
Cystitis	1 (0.03%)	0 (0.00%)	1 (0.01%)
Dengue fever	2 (0.05%)	0 (0.00%)	2 (0.02%)
Empyema	1 (0.03%)	0 (0.00%)	1 (0.01%)
Endocarditis	0 (0.00%)	1 (0.03%)	1 (0.01%)
Gangrene	0 (0.00%)	1 (0.03%)	1 (0.01%)
H1N1 influenza	0 (0.00%)	1 (0.03%)	1 (0.01%)
Incision site infection	1 (0.03%)	0 (0.00%)	1 (0.01%)
Infected dermal cyst	1 (0.03%)	0 (0.00%)	1 (0.01%)
Localized infection	0 (0.00%)	1 (0.03%)	1 (0.01%)
Lower respiratory tract infection	1 (0.03%)	0 (0.00%)	1 (0.01%)
Mucormycosis	1 (0.03%)	0 (0.00%)	1 (0.01%)
Esophageal candidiasis	0 (0.00%)	1 (0.03%)	1 (0.01%)
Osteomyelitis	2 (0.05%)	0 (0.00%)	2 (0.02%)
Pneumonia	7 (0.18%)	4 (0.10%)	11 (0.13%)
Postoperative abscess	1 (0.03%)	0 (0.00%)	1 (0.01%)
Postoperative wound infection	1 (0.03%)	0 (0.00%)	1 (0.01%)
Pulmonary sepsis	0 (0.00%)	1 (0.03%)	1 (0.01%)
Sepsis	5 (0.13%)	1 (0.03%)	6 (0.07%)
Sepsis syndrome	1 (0.03%)	0 (0.00%)	1 (0.01%)
Septic shock	3 (0.08%)	2 (0.05%)	5 (0.06%)
Sinusitis	0 (0.00%)	1 (0.03%)	1 (0.01%)
Staphylococcal sepsis	0 (0.00%)	1 (0.03%)	1 (0.01%)

Upper respiratory tract infection	1 (0.03%)	0 (0.00%)	1 (0.01%)
Urinary tract infection	3 (0.08%)	2 (0.05%)	5 (0.06%)
Urinary tract infection bacterial	0 (0.00%)	1 (0.03%)	1 (0.01%)
Urosepsis	2 (0.05%)	1 (0.03%)	3 (0.04%)
Viremia	1 (0.03%)	0 (0.00%)	1 (0.01%)
Source: ADSL, ADAE datasets ANAL01FL=Y and FASFL=Y and TRTDISCFL=Y and ENDTRTFL=N			

The reviewer performed an exploratory evaluation of events resulting in discontinuation of IMP because of hypoglycemia by evaluating terms with PT terms including 'fall,' and 'hypoglycemia,' see **Table 55.**

Table 55 – Permanent discontinution for PT terms suggesting hypoglycemia

Preferred term	IDeg	IGlar
	N=3818	N=3819
Fall	7 (0.18%)	5 (0.13%)
Hypoglycaemia	5 (0.13%)	4 (0.10%)
Hypoglycaemic seizure	1 (0.03%)	0
Hypoglycaemic unconsciousness	5 (0.13%)	4 (0.10%)
Total	17 (0.45%)	13 (0.34%)
Source: ADSL, ADAE datasets ANAL01FL=Y and FASFL=Y and TRTDISCFL=Y and ENDTRTFL=N		

Reviewer's comment: The overall number of events captured by this exploratory analysis was small (0.45% vs. 0.34% of patients randomized to IDeg and IGlar respectively). What is notable, however, is that there is no overwhelming evidence that patients permanently discontinued the investigational drug as a result of hypoglycemia, at least as captured by investigators.

7.3.4 Significant Adverse Events

Hypoglycemia is addressed in sections **6.1.5 Analysis of Secondary Endpoints(s).**

7.3.5 Submission Specific Primary Safety Concerns

The Sponsor systematically collected adverse events pertaining to technical complaints and serious adverse events resulting from medication errors.

Technical complaints were defined as any communication that alleges product defects (i.e. noted changes in the physical or chemical appearance of IMPs, packaging materials, or for patients receiving sponsor provided insulin aspart, problems related to devices).

In total, there were three adverse events related to technical complaints: 2 and 1 events in the IDeg and IGlar group respectively. Adverse events associated with the technical

complaints included the following PT terms: for IDeg injection site reaction and injection site pruritus, for IGlar general system disorders NEC.

Medication errors resulting in SAEs were identified by standard MedDRA queries and included the administration of wrong drug or use of wrong device, wrong route of administration (IM vs. subcutaneous), administration of a high dose with the intention to cause harm (i.e. suicide), and administration of accidental overdose.

There was a total of 8 medication errors resulting in SAEs identified: 4 events each for IDeg and IGlar; as shown in **Table 56**.

Table 56 – Medication errors resulting in SAEs

Preferred Term	**IDeg** N=3818		**IGlar** N=3819	
	N	%	N	%
Accidental overdose	2	0.05	3	0.08
Drug administration error	1	0.03	0	0
Extra dose administered	0	0	1	0.03
Wrong drug administered	1	0.03	0	0
Source: ADAE dataset, CQ10FL=Y and AESER=Y				

Reviewer's comments: there were few events, with no differences noted between treatment arms for the pre-specified categories of technical complaints and serious adverse events resulting from medication errors.

7.4 Supportive Safety Results

7.4.2 Laboratory Findings

Analyses of lipid laboratories and renal function are discussed at the end of this section. Further discussion of these laboratory parameters was performed in order to evaluate parameters that could potentially affect the overall primary efficacy findings (i.e. changes in lipid parameters in relationship to cardiovascular safety) and due to enrichment of a population with renal impairment in DEVOTE.

Laboratories were drawn at randomization and yearly thereafter, (refer to **Table 71**) in the appendix for laboratory schedule). The Sponsor performed analyses of central tendencies and outliers. Across laboratory parameters, central tendency analyses (i.e. mean laboratory value over time) were similar between IDeg and IGlar and are not explicitly discussed below. Evaluation of categorical outliers is shown in **Table 57**.

Table 57 – Outlier analyses of laboratory values

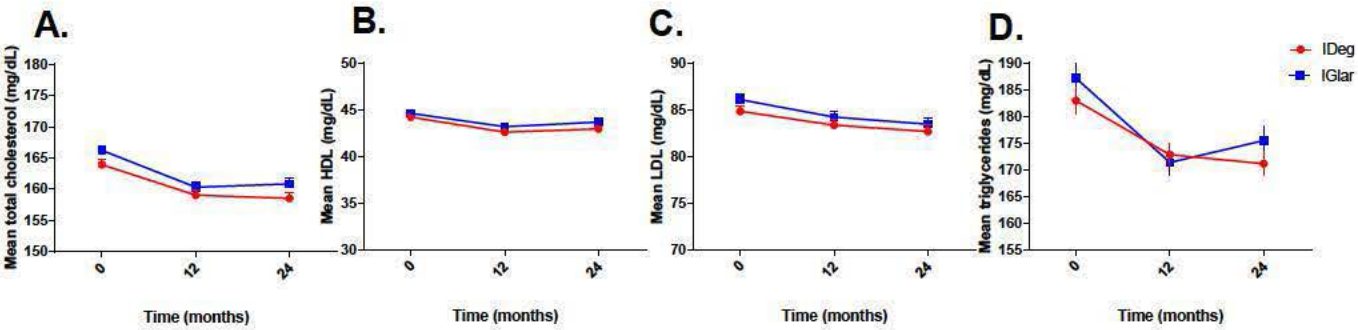
	IDeg	IGlar
Hemoglobin (g/dL)		
Highest post baseline value (N) Mean (SD) g/dL	3611 13.69 (1.56)	3589 13.57 (1.57)
Lowest post baseline value (N) Mean (SD) g/dL	3611 12.93 (1.60)	3589 12.82 (1.64)
Change from normal baseline To: N(%)		
Low @ end treatment	328 (8.6%)	337 (9.9%)
Normal @ end treatment	2269 (59.4%)	2118 (55.5%)
High @ end treatment	7 (0.2%)	10 (0.3%)
Missing	343 (9%)	381 (10%)
Hematocrit		
Highest post baseline value (N) Mean (SD)	3608 42.83 (4.74)	3582 42.43 (4.76)
Lowest post baseline value (N) Mean (SD)	3608 40.39 (4.79)	3582 40.05 (4.90)
Change from normal baseline To: N(%)		
Low @ end treatment	225 (5.9%)	245 (6.4%)
Normal @ end treatment	2361 (61.8%)	2262 (59.2%)
High @ end treatment	88 (2.3%)	64 (1.7%)
Missing	369 (9.7%)	392 (10.3%)
Thrombocytes (10^9/L)		
Highest post baseline value (N) Mean (SD) 10^9/L	3591 246.84 (70.40)	3573 244.19 (67.71)
Lowest post baseline value (N) Mean (SD) 10^9/L	3591 218.66 (61.56)	3573 215.97 (59.26)
Change from normal baseline To: N(%)		
Low @ end treatment	70 (1.8%)	70 (1.8%)
Normal @ end treatment	2929 (76.7%)	2862 (74.9%)
High @ end treatment	14 (0.4%)	8 (0.2%)
Missing	463 (12.1%)	545 (14.3%)
Leucocytes (10^9/L)		
Highest post baseline value (N) Mean (SD) 10^9/L	3611 8.54 (2.28)	3589 8.53 (2.88)
Lowest post baseline value (N) Mean (SD) 10^9/L	3611 7.28 (1.91)	3589 7.23 (1.88)
Change from normal baseline To: N(%)		
Low @ end treatment	23 (0.6%)	26 (0.7%)
Normal @ end treatment	3036 (79.5%)	2985 (78.2%)
High @ end treatment	68 (1.8%)	65 (1.7%)
Missing	449 (11.8%)	503 (13.2)
Alanine aminotransferase (U/L)		
Highest post baseline value (N) Mean (SD) U/L	3606 26.32 (16.51)	3591 27.63 (21.33)
Lowest post baseline value (N) Mean (SD) U/L	3606 19.16 (9.65)	3591 19.89 (11.83)
Change from normal baseline To: N(%)		
Low @ end treatment	0 (0%)	0 (0%)
Normal @ end treatment	2782 (72.9%)	2692 (70.5%)
High @ end treatment	119 (3.1%)	146 (4.2%)
Missing	411(10.8%)	475(12.4%)
Sodium (mmol/L)		
Highest post baseline value (N) Mean (SD) mmo/L	3606 142.75 (2.70)	3592 142.60 (2.63)
Lowest post baseline value (N) Mean (SD) mmol/L	3606 140.21 (2.87)	3592 140.05 (2.76)

Change from normal baseline To: N(%)		
Low @ end treatment	52 (1.4%)	49 (1.3%)
Normal @ end treatment	3120 (81.7%)	3024 (79.2%)
High @ end treatment	28 (0.7%)	27 (0.7%)
Missing	432 (11.3%)	499 (13.1%)
Potassium (mmol/L)		
Highest post baseline value (N) Mean (SD) mmol/L	3605 4.82 (0.55)	3589 4.83 (0.55)
Lowest post baseline value (N) Mean (SD) mmol/L	3605 4.40 (0.44)	3589 4.41 (0.44)
Change from normal baseline To: N(%)		
Low @ end treatment	13 (0.3%)	10 (0.3%)
Normal @ end treatment	2511 (65.8%)	2400 (62.8%)
High @ end treatment	286 (7.5%)	278 (7.3%)
Missing	392 (10.3%)	450(11.8%)
Albumin (g/dL)		
Highest post baseline value (N) Mean (SD) mEq/L	3596 4.13 (0.33)	3579 4.13 (0.33)
Lowest post baseline value (N) Mean (SD) mEq/L	3606 4.24 (0.31)	3592 4.25 (0.32)
Change from normal baseline To: N(%)		
Low @ end treatment	57 (1.5%)	54 (1.4%)
Normal @ end treatment	3203 (83.9%)	3139 (82.2%)
High @ end treatment	0 (0%)	0 (0%)
Missing	444 (11.6%)	503 (13.2%)
Bilirubin (mg/dL)		
Highest post baseline value (N) Mean (SD) mg/dL	3606 0.49 (0.25)	3591 0.50 (0.28)
Lowest post baseline value (N) Mean (SD) mg/dL	3606 0.37 (0.19)	3591 0.37 (0.20)
Change from normal baseline To: N(%)		
Low @ end treatment	55 (1.4%)	49 (1.3%)
Normal @ end treatment	3138 (82.2%)	3082 (80.7%)
High @ end treatment	17 (0.4%)	21 (0.5%)
Missing	499(11.8%)	511 (13.4%)

Source: CSR tables:14.3.5.2,6,9,12,21,24,27,30,34,38,41,44,50,52,56,60,64,66,72,74, 78,82,86,90, 94,98,102,106
Baseline: Visit 2 (Week 0), End treatment: Visit 63 (Month 59)
Hemoglobin: Normal ranges for females (mmol/L): age 12-65 [7.19-10.05], age 66-101 [6.82-9.98]; Normal ranges for males (mmol/L): age 18-65 [8.06-10.85], age 66-101 [8.06-10.98]; **Hematocrit:** Normal ranges for females (%): age 12-65 [35-47], age 66-101 [33-46]; Normal ranges for males (%): age 18-65 [40-52], age 66-101 [37-50]; **Thrombocytes**: Normal range (10^9/L): [140-450]. Leucocytes: Normal range (10^9/L): [4.1-12.3]; **Creatinine:** Normal range for females (umol/L): [44-80]; Normal range for males (umol/L): [62-106]; ALAT**:** Normal range for females (U/L): [0-33]; Normal range for males (U/L): [0-41]
Sodium: Normal range (mmol/L): [135-147]; **Potassium**: Normal range (mmol/L): [3.3-5.1]; **Albumin:** Normal range (g/dL): [3.5-5.2]
Bilirubin: Normal ranges for females (umol/L): age 1-90 [3-21], age 91-110 [3-15]; Normal ranges for males (umol/L): age 1-90 [3-21], age 91-110 [3-15]

Central tendency trends of lipid laboratories are shown in **Figure 39.** Overall, IDeg and IGlar had similar trends in total cholesterol, HDL, LDL and triglycerides throughout the trial.

Figure 39 – A. Mean total cholesterol (mg/dL); B. Mean HDL (mg/dL); C. Mean LDL (mg/dL); D. triglycerides (mg/dL) over time



Source: CSR 14.3.5.78, 86, 94, and 102

Outlier analyses of lipid values are show in **Table 58**. Trends in outliers were similar between treatment arms.

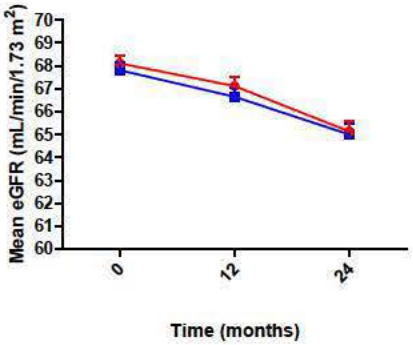
Table 58 – Outlier analyses of lipid values

	IDeg	IGlar
Total cholesterol (mg/dL)		
Highest post baseline value (N) Mean (SD) mg/dL	3603 172.96 (48.53)	3590 174.10 (47.55)
Lowest post baseline value (N) Mean (SD) mg/dL	3603 146.87 (40.17)	3590 148.50 (38.83)
Change from normal baseline To: N(%)		
Low @ end treatment	0 (0%)	0 (0%)
Normal @ end treatment	2422 (63.4%)	2387 (62.5%)
High @ end treatment	281 (7.4%)	251 (6.6%)
Missing	368 (9.6%)	382 (10%)
LDL (mg/dL)		
Highest post baseline value (N) Mean (SD) mg/dL	3602 94.19 (39.05)	3588 94.93 (38.58)
Lowest post baseline value (N) Mean (SD) mg/dL	3602 72.56 (31.82)	3588 73.59 (31.32)
Change from normal baseline To: N(%)		
Low @ end treatment	0 (0%)	0 (0%)
Normal @ end treatment	2723 (71.3%)	2685 (70.6%)
High @ end treatment	215 (5.6%)	181(4.7%)
Missing	403 (10.6%)	431(11.3%)
HDL (mg/dL)		
Highest post baseline value (N) Mean (SD) mg/dL	3603 45.62 (13.33)	3590 46.42 (13.42)
Lowest post baseline value (N) Mean (SD) mg/dL	3603 40.06 (11.69)	3590 40.62 (11.61)
Change from normal baseline To: N(%)		
Low @ end treatment	155 (4.1%)	131 (3.4%)
Normal @ end treatment	168 (4.4%)	198 (5.2%)
High @ end treatment	0(0%)	0 (0%)
Missing	53 (1.4%)	59 (1.5%)
Triglycerides (mg/dL)		
Highest post baseline value (N) Mean (SD) mg/dL	3603 208.36 (170.52)	3590 205.44 (167.16)
Lowest post baseline value (N)	3603	3590

Mean (SD) mg/dL	145.94 (98.46)	145.52 (105.13)
Change from normal baseline To: N(%)		
Low @ end treatment	0 (0%)	0 (0%)
Normal @ end treatment	1283 (33.6%)	1242 (32.5%)
High @ end treatment	424 (11.1%)	385 (10.1%)
Missing	237 (6.2%)	245 (6.4%)
Total cholesterol: Normal range (mmol/L): [0-5.17]; **HDL**: Normal range (mmol/L): [1.56-999]; **LDL:** Normal range (mmol/L): [0-3.36]; **Triglycerides:** Normal range (mmol/L): [0-1.69]		

Mean estimated eGFR (by CKD-EPI) over time is shown in **Figure 40.** Over the course of the trial, mean eGFR tended to decrease similarly for both treatment groups. Trends in outlier values for creatinine and eGFR also seemed to trend similarly between treatment groups; see **Table 59**.

Figure 40 –Mean eGFR CKD-EPI over time



Source: CSR, table 14.3.6.33

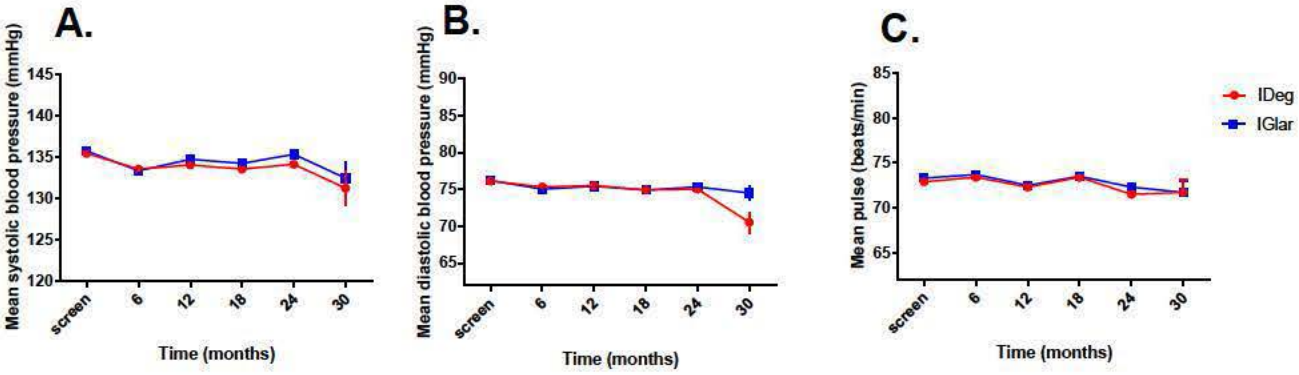
Table 59 – Outlier analyses of renal function

	IDeg	IGlar
Creatinine (mg/dL)		
Highest post baseline value (N) Mean (SD) mg/dL	3606 1.29 (0.62)	3592 1.30 (0.69)
Lowest post baseline value (N) Mean (SD) mg/dL	3606 1.11 (0.44)	3592 1.13 (0.50)
Change from normal baseline To: N(%)		
Low @ end treatment	33 (0.9%)	21 (0.5%)
Normal @ end treatment	1456 (38.1%)	1351 (35.4%)
High @ end treatment	352 (9.2%)	335 (8.8%)
Missing	198 (5.2%)	241(6.3%)
eGFR by CKD-EPI (mL/min/1.73 m²)		
Highest post baseline value (N) Mean (SD) mL/min/1.73 m²	3606 70.42 (33.08)	3592 69.73 (22.30)
Lowest post baseline value (N) Mean (SD) mL/min/1.73 m²	3606 61.91	3592 61.42 (22.19)
Source: CSR, table 14.3.6.33		

7.4.3 Vital Signs

Evaluation of blood pressure and pulse were performed every 6 months, while evaluation of weight was performed yearly. Overall, after baseline, there were small variations in vital sign values across time points; but the mean values between treatment groups were similar; refer to **Figure 41**.

Figure 41 – A. Mean systolic blood pressure (mmHg); B. Mean diasolic blood pressure (mmHg); C. Mean pulse (beats/min) over time



Source: CSR 14.3.6.1.,7 and 13.

Evaluations of outliers for vital signs were also similar between treatment arms; see **Table 60.**

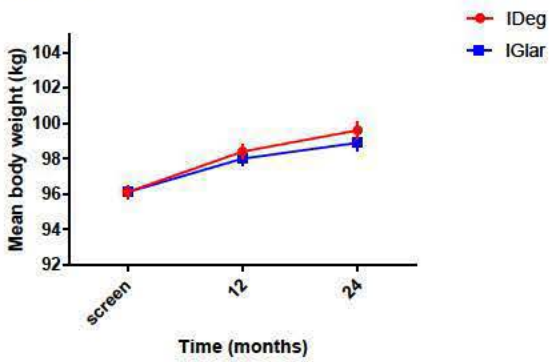
Table 60 - Outlier analyses of vital signs

	IDeg	IGlar
Diastolic blood pressure		
Highest post baseline value (N) Mean (SD) mmHg	3710 82.3 (9.4)	3686 82.3 (9.1)
Lowest post baseline value (N) Mean (SD) mmHg	3710 68.2 (9.2)	3686 68.1 (9.0)
Systolic blood pressure		
Highest post baseline value (N) Mean (SD) mmHg	3710 146.1 (17.3)	3686 146.9 (17.2)
Lowest post baseline value (N) Mean (SD) mmHg	3710 121.7 (14.4)	3686 121.9 (14.3)
Pulse		
Highest post baseline value (N) Mean (SD) beats/min	3710 80.2 (11.3)	3686 80.2 (10.9)
Lowest post baseline value (N) Mean (SD) beats/min	3710 66.0 (9.5)	3686 66.4 (9.4)
Source: CSR, table 14.3.6.1, 7 and 13		

Reviewer's comments: vital sign measurements for central tendencies and outlier analyses were similar between treatment arms. Trends in these values did not appear to have influenced any of the two treatment groups in regards to cardiovascular safety.

Weight tended to increase in a similar fashion, for both treatment groups, over the course of the trial; see **Figure 42.** From a screening weight of 96.1 kg for each treatment, at month 24, the mean weight was 99.6 kg vs. 98.9 kg for IDeg and IGlar respectively.

Figure 42- Mean weight (kg) over time



Source: CSR, table 14.3.6.19

Table 61 - Outlier analyses of body weight (kg)

	IDeg	IGlar
Body weight		
Highest post baseline value (N) Mean (SD) Kg	3596 100.0 (24.2)	3573 97.9 (23.5)
Lowest post baseline value (N) Mean (SD) Kg	3596 96.5 (23.3)	3573 96.1 (22.9)
Source: CSR, table 14.3.6.19		

Reviewer's comment: the increase in body weight over the course of the trial is consistent with the known anabolic functions of all insulins.

7.4.4 Electrocardiograms (ECGs)

ECGs were evaluated by central ECG readers for evidence of abnormal 12-lead ECG findings suggesting of a new MI; as discussed in section **5.3 Discussion of Individual Studies/Clinical Trials.** There was no general assessment of safety for ECGs in the DEVOTE trial.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

As discussed in section **5.3 Discussion of Individual Studies/Clinical Trials**, neoplasms were not adjudicated, instead, two medical oncologists independently classified neoplasms based on information in case narratives. All SAEs detected in the SOC 'Neoplasms benign, malignant and unspecified (including cysts and polyps) were sent for blinded classification. Therefore, these events were not systematically captured.

There were 255 events sent for external classification of which 253 were classified as benign or malignant with 2 events classified as "unclassifiable."[69] The neoplasm event

[69] The two events that could not be classified included 1 event of colon cancer and 1 event of hepatic neoplasm.

rate was similar between treatment groups 1.69 vs. 1.68 events per 100 PYE for IDeg vs. IGlar. Malignant neoplasms made up the majority of neoplasm events (1.32 per 100 PYE vs. 1.42 per 100PYE for IDeg and IGlar respectively). Across malignant classification categories there were small differences between treatment groups, as shown in **Table 62**. There were also small differences between treatment groups in the sub-classification of benign neoplasms by SOC (see appendix, **Table 77**).

Table 62 – Classified neoplasms by primary organ site category- serious adverse events - summary- FAS

	IDeg			IGlar		
	N (%)	E	R	N (%)	E	R
FAS	3818			3819		
PYO	7568			7558		
Overall events	121 (3.2)	128	1.69	115 (3.0)	127	1.68
Malignant	93 (2.4)	100	1.32	99 (2.6)	107	1.42
Breast	9 (0.2)	9	0.12	10 (0.3)	11	0.15
Colorectal	7 (0.2)	7	0.09	12 (0.3)	14	0.19
Gastrointestinal other than colorectal	16 (0.4)	17	0.22	16 (0.4)	17	0.22
Gallbladder and bile ducts	1 (0.0)	1	0.01	3 (0.1)	3	0.04
Liver	3 (0.1)	3	0.04	6 (0.2)	7	0.09
Esophagus	2 (0.1)	2	0.03	2 (0.1)	2	0.03
Other GI malignancy	1 (0.0)	1	0.01	1 (0.0)	1	0.01
Pancreas	7 (0.2)	8	0.11	3 (0.1)	3	0.04
Stomach	2 (0.1)	2	0.03	1 (0.0)	1	0.01
Genitourinary other than prostate	13 (0.3)	16	0.21	13 (0.3)	13	0.17
Bladder	6 (0.2)	8	0.11	5 (0.1)	5	0.07
Kidney	7 (0.2)	8	0.11	4 (0.1)	4	0.05
Other GU malignancy	0	0	0	2 (0.1)	2	0.03
Testis	0	0	0	2 (0.1)	2	0.03
Gynecologic	8 (0.2)	8	0.11	5 (0.1)	5	0.07
Ovary	3 (0.1)	3	0.04	0	0	0
Uterus	5 (0.1)	5	0.07	5 (0.1)	5	0.07
Hematological malignancies	9 (0.2)	9	0.12	7 (0.2)	7	0.09
Leukemia	3 (0.1)	3	0.04	3 (0.1)	3	0.04
Lymphoid	6 (0.2)	6	0.08	3 (0.1)	3	0.04
Other hematological malignancy	0	0	0	1 (0.0)	1	0.01
Head and neck	4 (0.1)	4	0.05	3 (0.1)	3	0.04
Other head/neck malignancy	1 (0.0)	1	0.01	1 (0.0)	1	0.01
Pharynx or mouth	1 (0.0)	1	0.01	1 (0.0)	1	0.01
Thyroid	2 (0.1)	2	0.03	1 (0.0)	1	0.01
Lung and pleura	13 (0.3)	14	0.19	11 (0.3)	12	0.16
Lung	13 (0.3)	14	0.19	11 (0.3)	12	0.16
Musculoskeletal	0	0	0	2 (0.1)	2	0.03
Prostate	11 (0.3)	11	0.15	10 (0.3)	10	0.13
Skin	5 (0.1)	5	0.07	6 (0.2)	6	0.08
Malignant melanoma	2 (0.1)	2	0.03	0	0	0
Skin other than melanoma	3 (0.1)	3	0.04	6 (0.2)	6	0.08
Unknown	0	0	0	4 (0.1)	7	0.09
Benign	26 (0.7)	26	0.34	19 (0.5)	20	0.26
Unclassifiable	2 (0.1)	2	0.03	0	0	0
Source: CSR, table 12-10, 12-11 pages 208 and 210; table 14.3.74, page 1073						

In order to gain a global perspective on the neoplasms captured in the trial, the reviewer analyzed the system organ class 'Neoplasms benign, malignant and unspecified (incl cysts and polyps)' for both serious and non-serious events; refer to **Table 78** in the

appendix. Overall, few events for each preferred term were identified and the proportion of patients and neoplastic events were similar between treatment arms. Slight differences of 1 or 2 patients per PT term, were seen between treatment groups. An exception was noted for the PT 'prostate cancer.' There were 14 patients with 14 events identified for IDeg while 5 patients had 5 events for IGlar. However, when considering other preferred terms (i.e. 'prostate cancer,' 'prostate cancer metastatic', 'prostate cancer stage I,' 'prostate cancer stage II') the difference between treatment groups decreases (i.e. 15 patients vs. 10 patients for IDeg vs. IGlar respectively).

Reviewer's comment: It is important to remember that the trial was not designed to capture neoplasm events. Inadequate collection of events was likely to result from the self-reported methods. From the events captured, it can be concluded that across multiple classification of neoplasms (evaluating the serious malignant and serious benign neoplasms and overall neoplasms), there were slight numerical differences between treatment groups. For the numerical differences identified, there was insufficient follow up in the trial to clearly determine any causality.

7.6.2 Human Reproduction and Pregnancy Data

There were no pregnancies in DEVOTE.

8 Postmarket Experience

9 Appendices

9.1 Literature Review/References

References are listed where pertinent in the document.

9.2 Labeling Recommendations

Labeling recommendations are included throughout the review. Labeling recommendations for the hypoglycemia findings are discussed below.

I propose that the hypoglycemia findings be labeled in section 14. As with all insulin products, insulin degludec continues to carry a risk of hypoglycemia, which should continue to be labeled in sections 5 and 6. In addition, labeling should capture that the hypoglycemia differences were mainly driven by patients using basal and bolus insulin. Providers may also benefit in knowing that differences in hypoglycemia may be detected as early as 3 months after start of therapy and that only ~21% of the positively adjudicated events of severe hypoglycemia had unconsciousness or in a coma or seizures documented.

9.3 Advisory Committee Meeting

There was no advisory committee for this supplement.

Appendices

Financial disclosures

Table 63 – Financial disclosure

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 2469 (1840 were investigators in the USA~73% of all investigators)		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 2 (spouse of clinical investigator was an employee of Novo Nordisk)		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 74		
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: 74 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) 14		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from applicant)

Table 64 – Investigators with disclosable interests of >$100,000

Site no.	Investigator	Disclosable financial Interests			Total Amount received	Number of patients randomized to site
		Explanation	Amount	Date		
(b) (6)		Honorarium/Fees Advisory Board	$211,140 $128,650	10/15/2013 - 09/24/2016	$339,790	(b) (6)
		Honorarium/Fees	$187,050	12/12/2013 - 10/06/2016	$187,050	
		Honorarium/Fees Advisory Board	$202,080 $16,360	09/19/2013 - 09/23/2016	$218,440	
		Honorarium/Fees	$263,700	10/09/2013 - 11/16/2016	$263,700	
		Honorarium/Fees	$209,000	10/14/2013 - 09/22/2016	$209,000	
		Honorarium/Fees	$275,260	09/21/2013 - 10/29/2016	$275,260	
		Honorarium/Fees Advisory Board	$160,436 $18,887	09/24/2013 - 10/21/2016	$179,323	
		Honorarium/Fees	$165,120	09/19/2013 - 09/15/2016	$165,120	
		Honorarium/Fees	$128,380	09/19/2013 - 06/10/2016	$128,380	

(b) (6)	Honorarium/Fees	$194,900	09/27/2013 - 09/22/2016	$194,900	(b) (6)
	Honorarium/Fees	$133,950	09/25/2013 - 08/25/2016	$133,950	
	Honorarium/Fees	$136,145	09/25/2013 - 06/22/2016	$136,145	
	Honorarium/Fees	$103,120	09/19/2013 - 09/12/2016	$103,120	
	Honorarium/Fees	$203,020	09/20/2013 - 10/27/2016	$203,020	
	Honorarium/Fees	$177,220	10/11/2013 - 08/18/2016	$177,220	
	Honorarium/Fees	$151,070	09/24/2013 - 08/18/2016	$151,070	
	Honorarium/Fees	$138,060	10/03/2013 - 10/25/2016	$138,060	
	Honorarium/Fees	$133,230	10/11/2013 - 10/06/2016	$133,230	
	Honorarium/Fees Advisory Board	$241,908 $84,277	09/19/2013 - 10/31/2016	$326,185	
	Honorarium/Fees	$133,320	10/11/2013 - 09/06/2016	$133,320	
	Honorarium/Fees	$179,290	10/11/2013 - 09/14/2016	$179,290	
	Honorarium/Fees Advisory Board	$247,710 $9,900	10/11/2013 - 10/21/2016	$257,610	
	Honorarium/Fees Advisory Board	$110,700 $114,512	09/21/2013 - 10/14/2016	$225,212	
	Honorarium/Fees Advisory Board	$62,400 $43,849	11/09/2013 - 09/16/2016	$106,249	
	Honorarium/Fees	$114,460	09/19/2013 - 09/28/2016	$114,460	

Table 65 – Patients unblinded during the trial

Reason for breaking blind	PT	IDeg		IGlar	
		N	%	N	%
Patients unblinded		43	1.1	39	1.0
Investigator	Acute myocardial infarction	0	0	1	0.03
	Pulmonary embolism	0	0	1	0.03
	Sepsis	1	0.03	0	0
	All	1	0.03	2	0.05
Sponsor for SUSAR submission	Acute coronary syndrome	1	0.03	1	0.03
	Acute kidney injury	0	0	2	0.05
	Angina pectoris	0	0	2	0.05
	Angina unstable	8	0.21	3	0.08
	Atrial fibrillation	1	0.03	1	0.03
	Bile duct obstruction	0	0	1	0.03
	Breast cancer metastatic	0	0	1	0.03
	Bundle branch block left	1	0.03	0	0
	Cardiac failure	1	0.03	0	0
	Cardiac failure acute	0	0	1	0.03
	Cardiac failure chronic	0	0	1	0.03
	Cardiac failure congestive	3	0.08	5	0.13
	Cataract	1	0.03	0	0

	Cellulitis	1	0.03	1	0.03
	Cholangiocarcinoma	0	0	1	0.03
	Cholecystitis	0	0	1	0.03
	Cholecystitis acute	0	0	1	0.03
	Chronic kidney disease	2	0.05	0	0
	Chronic obstructive pulmonary disease	0	0	1	0.03
	Colon cancer	0	0	1	0.03
	Coronary arterial stent insertion	0	0	1	0.03
	Coronary artery bypass	1	0.03	0	0
	Coronary artery disease	4	0.1	1	0.03
	Coronary artery insufficiency	0	0	1	0.03
	Deafness neurosensory	1	0.03	0	0
	Diabetes mellitus	1	0.03	0	0
	Diabetes mellitus inadequate control	2	0.05	0	0
	Diabetic foot	0	0	2	0.05
	Dilatation intrahepatic duct acquired	0	0	1	0.03
	Diverticulitis	1	0.03	0	0
	Dizziness	1	0.03	0	0
	End stage renal disease	1	0.03	0	0
	Enteritis	1	0.03	0	0
	Fall	3	0.08	0	0
	Fibula fracture	0	0	1	0.03
	Gastroenteritis Escherichia coli	0	0	1	0.03
	Gastrooesophageal reflux disease	1	0.03	0	0
	Gout	0	0	1	0.03
	Hepatocellular carcinoma	0	0	1	0.03
	Hyperhidrosis	1	0.03	0	0
	Hyperkalaemia	1	0.03	0	0
	Hypoglycaemia	0	0	1	0.03
	Hypokalaemia	1	0.03	0	0
	Hypothyroidism	1	0.03	0	0
	Infected dermal cyst	1	0.03	0	0
	Joint dislocation	1	0.03	0	0
	Labyrinthitis	1	0.03	0	0
	Left ventricular dysfunction	0	0	1	0.03
	Loss of consciousness	1	0.03	1	0.03
	Lower respiratory tract infection	0	0	1	0.03
	Metabolic encephalopathy	0	0	1	0.03
	Mucormycosis	1	0.03	0	0
	Non-cardiac chest pain	1	0.03	0	0
	Orthostatic hypotension	0	0	1	0.03
	Pain in extremity	1	0.03	0	0
	Pancreatic carcinoma metastatic	1	0.03	0	0
	Pneumonia	2	0.05	1	0.03
	Post concussion syndrome	1	0.03	0	0
	Presyncope	0	0	1	0.03
	Pulmonary embolism	0	0	1	0.03
	Renal failure	0	0	1	0.03
	Respiratory failure	2	0.05	0	0

	Retinal artery occlusion	1	0.03	0	0
	Rib fracture	1	0.03	0	0
	Salivary gland cancer	0	0	1	0.03
	Sepsis	0	0	1	0.03
	Septic shock	1	0.03	0	0
	Sinus node dysfunction	1	0.03	0	0
	Subarachnoid haemorrhage	1	0.03	0	0
	Syncope	2	0.05	0	0
	Tibia fracture	0	0	1	0.03
	Toxic goitre	0	0	1	0.03
	Transient ischaemic attack	1	0.03	2	0.05
	Trifascicular block	0	0	1	0.03
	Urinary tract infection	0	0	1	0.03
	Vomiting	1	0.03	1	0.03
	All	62	1.62	53	1.39
All	All	63	1.65	55	1.44
Source: dataset unblind.xpt					

EAC Charter

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

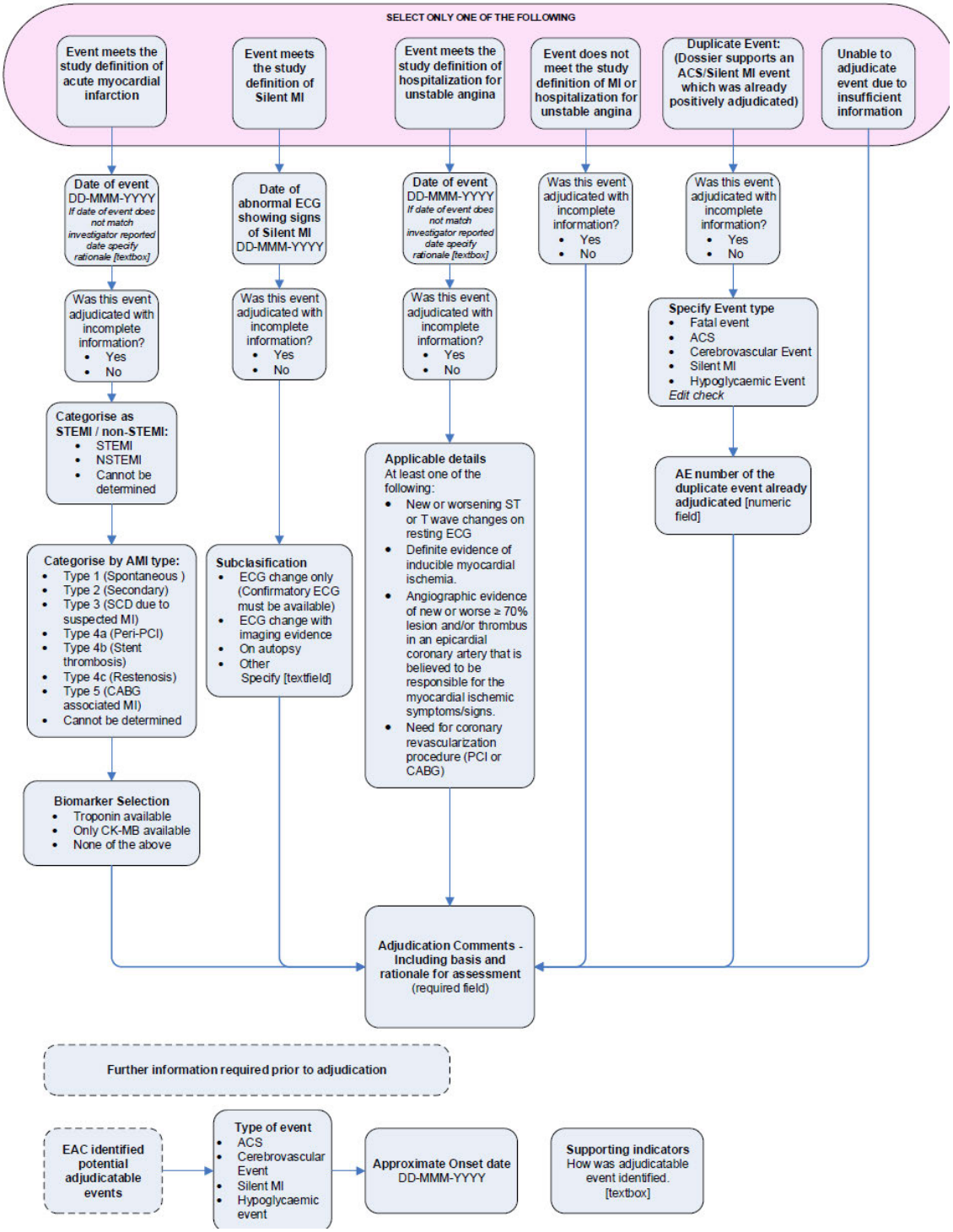
Table 66 – Changes to the EAC charter

Date of version EAC version #	Relevant changes to the EAC charter
Version 1 4 September 2013	
Version 2 28 February 2014	-"severe hypoglycemia" added to the list of endpoints for adjudication - included endocrinologists as EAC members -included MedDRA SMQ list for severe hypoglycemia -documents for EAC dossier specified Process for selecting events for severe hypoglycemia adjudication based on adjudication outcome of fatal events identified
Version 3 9 January 2015	-process for identification of ECG events from central ECG read further specified -all reported ACS and CVS with fatal outcome were sent for adjudication I both the fatal queue and the relevant event queue
Version 4 08 December 2015	Process for identification of ECG events clarified.

Table 67 – Special committees in DEVOTE

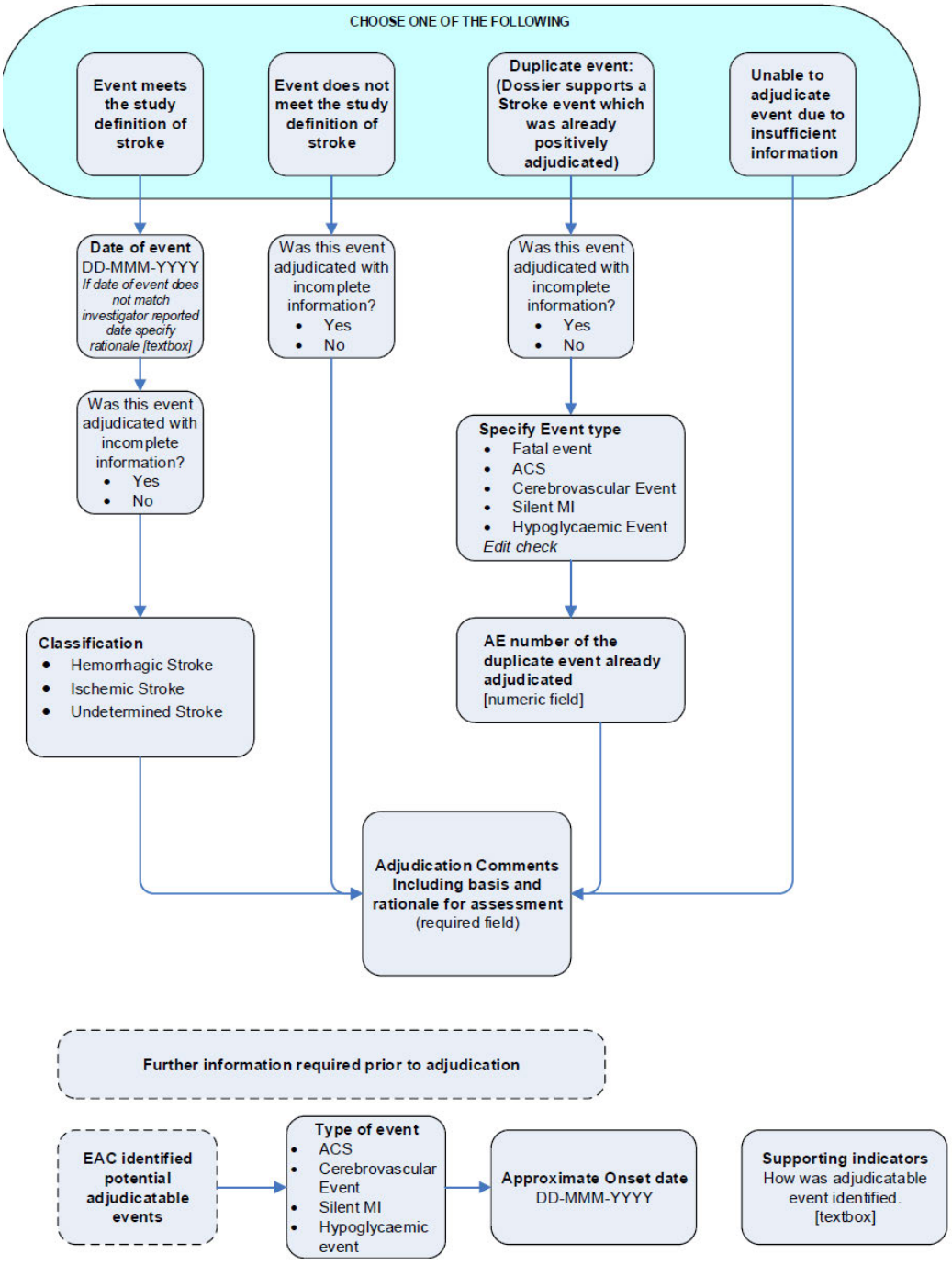
	Description
Data monitoring committee (DMC)	-composed of 5 permanent members (cardiologist, endocrinology, neurology and statistics) -reviewed semi-unblinded or unblinded data to evaluate safety profile -received unblinded statistical output from the external statistician after database lock for interim analysis -provided recommendations to the internal Novo Nordisk safety committee on trial termination, modification or continuation
Steering committee	Provided scientific and operational leadership for the trial. Expertise in cardiology, diabetes, endocrinology and statistics from outside Novo Nordisk.
Global expert panel	Global expert panel of investigators from participating countries.
Event adjudication committee (EAC)	-adjudicated fatal events, predefined cardiovascular events and episodes of severe hypoglycemia in a blinded manner.
Event adjudication CRO	Managed the adjudication process. The CRO oversaw the site personnel uploaded source documents needed for adjudication
Neoplasm classification CRO classification management	Provided technical support relating to the web-based application used by the external independent consultants to classify neoplasms in a blinded fashion
Neoplasm classification group	3 experts in medical oncology acted as external independent consultants and performed ongoing classification of neoplasms reported as SAEs
Novo Nordisk titration surveillance	Surveillance of insulin titration was performed centrally by Novo Nordisk Insulin Titration Group. Data was reviewed in a blinded fashion. Deviations from algorithm were discussed with the investigator, if applicable.
Novo Nordisk safety committee	Internal safety committee for IDeg to review blinded data and recommend appropriate actions based on ongoing safety surveillance of blinded data from clinical trials including DEVOTE, non-clinical findings, postmarketing surveillance and other sources in relation to other products containing IDeg
Novo Nordisk event adjudication group (NN-EAG)	-Team assured that automated notification of newly reported events for adjudication were sent to the event adjudication CRO. -identified events qualifying for adjudication via predefined screening of adverse event database for specific preferred terms.

Figure 43- ACS adjudication algorithm



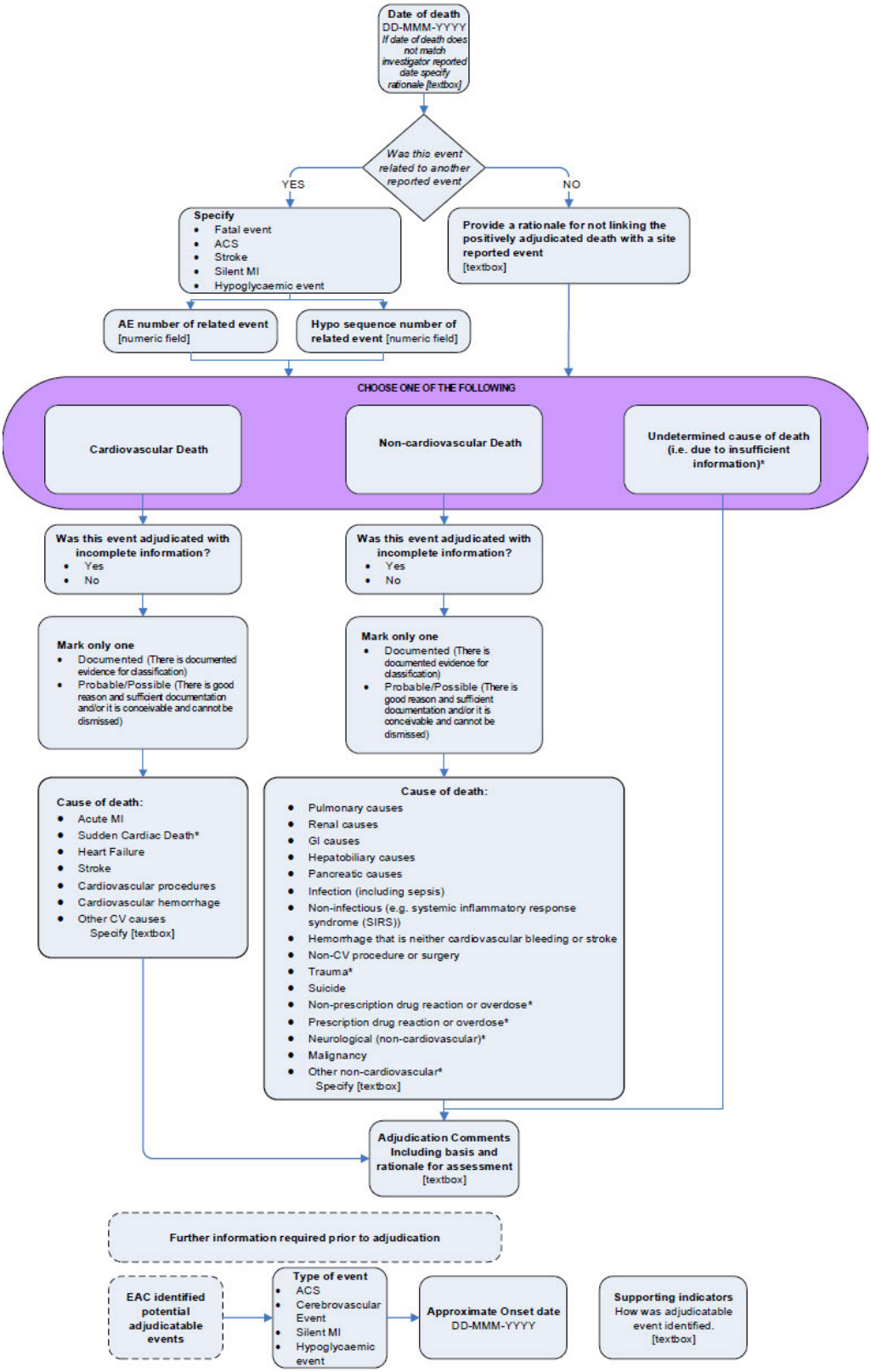
Source: Special committee documents, SRS version 6- page 94

Figure 44- Cerebrovascular adjudication algorithm



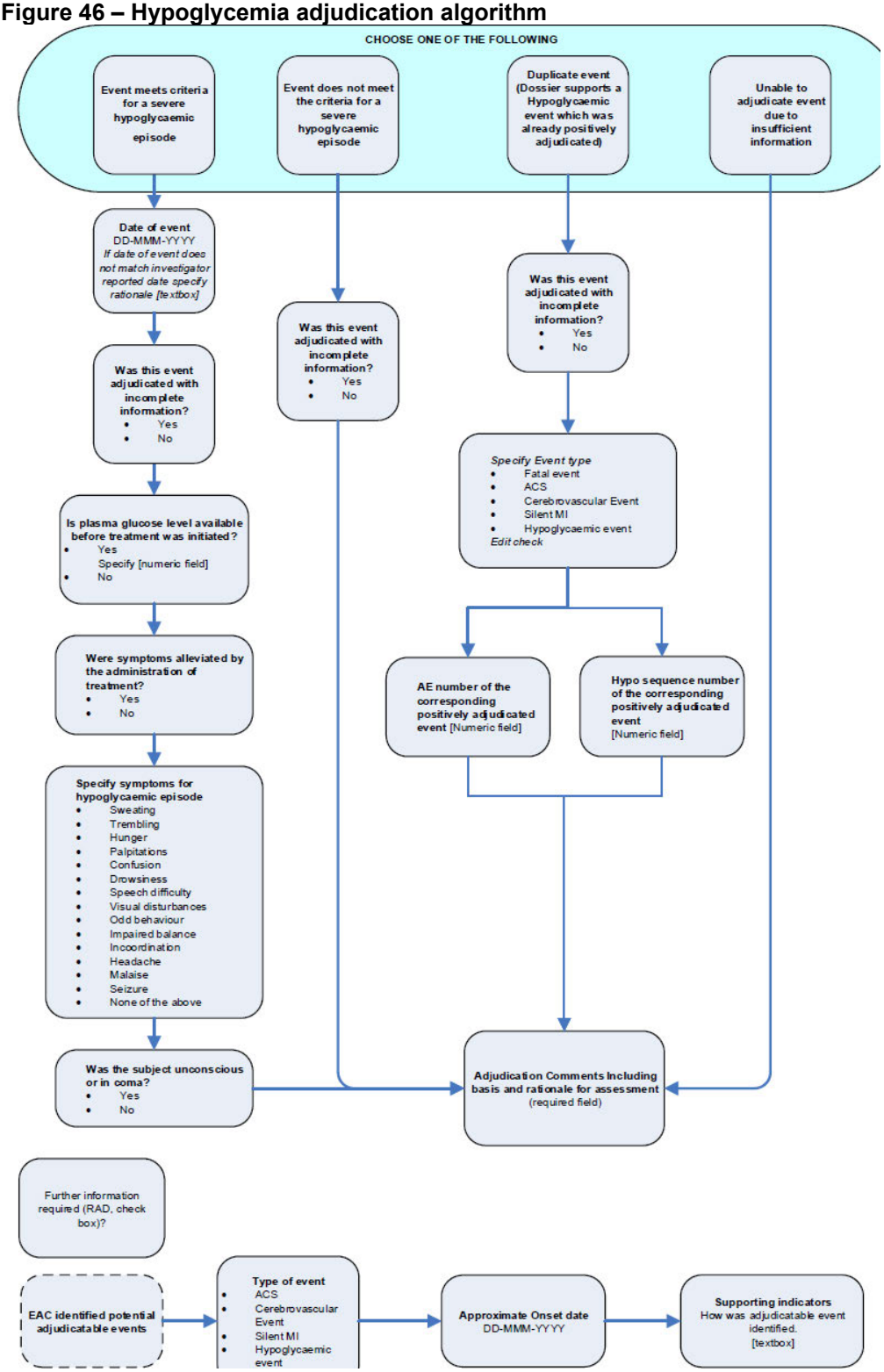
Source: Special committee documents, SRS version 6- page 95

Figure 45- Death adjudication algorithm



Source: Special committee documents, SRS version 6- page 96

Figure 46 – Hypoglycemia adjudication algorithm



Source: Special committee documents, SRS version 6- page 98

Table 68 – Event definitons used for the EAC adjudication of events

Event	Definition
Death	**Definition of Cardiovascular Death** Causes of death events will initially be identified as either "Known" or "Unknown." If classified as Unknown, the event will be considered a CV death and 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-related 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 and the adjudicator will be asked to indicate the cause of cardiovascular death from the list below: • Sudden Cardiac Death • Acute MI • Heart Failure • Cerebrovascular Event • Cardiovascular procedures • Cardiovascular hemorrhage • Other CV causes If "Unlikely" is selected the adjudicator will be asked to indicate the cause of death from the list below: • Pulmonary causes • Renal causes • GI causes • Hepatobiliary causes • Pancreatic causes • Infection (including sepsis) • Non-infectious (e.g. systemic inflammatory response syndrome (SIRS)) • Hemorrhage that is neither cardiovascular bleeding or stroke • Non-CV procedure or surgery • Trauma • Suicide • Non-prescription drug reaction or overdose • Prescription drug reaction or overdose • Neurological (non-cardiovascular) • Malignancy • Other non-cardiovascular The definitions of classifications are as follows: 1. Documented — There is documented evidence for classification 2. Probable/Possible — There is good reason and sufficient documentation and/or it is conceivable and cannot be dismissed 3. Unlikely — The event is most likely related to an alternative cause other than a cardiovascular cause (e.g., medical history relevant for cancer)
Acute Coronary Syndrome	Acute Coronary Syndrome (ACS) conditions include ST-elevation acute myocardial infarction (STEMI), non-ST elevation acute myocardial infarction (NSTEMI), and unstable angina pectoris (UAP) requiring hospitalization.

Event	Definition
Myocardial infarction	**Criteria for acute myocardial infarction** The term acute myocardial infarction (AMI) should be used when there is evidence of myocardial necrosis in a clinical setting consistent with myocardial ischemia. Under these conditions any one of the following criteria meets the diagnosis for AMI: • Detection of a rise and/or fall of cardiac biomarker values [preferably cardiac troponin (cTn)] with at least one value above the 99th percentile upper reference limit (URL) and with at least one of the following: - Symptoms of ischaemia. - New or presumed new significant ST-segment–T wave (ST–T) changes or new left bundle branch block (LBBB). - Development of pathological Q waves in the ECG. - Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality. - Identification of an intracoronary thrombus by angiography or autopsy. • Cardiac death with symptoms suggestive of myocardial ischaemia and presumed new ischaemic ECG changes or new LBBB but death occurred before cardiac biomarkers were obtained, or before cardiac biomarker values would be increased. • Percutaneous coronary intervention (PCI) related MI is arbitrarily defined by elevation of cTn values (>5 x 99th percentile URL) in patients with normal baseline values (≤99th percentile URL) or a rise of cTn values >20% if the baseline values are elevated and are stable or falling. In addition, either (i) symptoms suggestive of myocardial ischaemia or (ii) new ischaemic ECG changes or (iii) angiographic findings consistent with a procedural complication or (iv) imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality are required. • Stent thrombosis associated with MI when detected by coronary angiography or autopsy in the setting of myocardial ischaemia and with a rise and/or fall of cardiac biomarker values with at least one value above the 99th percentile URL. • Coronary artery bypass grafting (CABG) related MI is arbitrarily defined by elevation of cardiac biomarker values (>10 x 99th percentile URL) in patients with normal baseline cTn values (≤99th percentile URL). In addition, either (i) new pathological Q waves or new LBBB, or (ii) angiographic documented new graft or new native coronary artery occlusion, or (iii) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality The totality of the clinical, electrocardiographic, and cardiac biomarker information should be considered to determine whether or not an AMI has occurred. Specifically, timing and trends in cardiac biomarkers and electrocardiographic information require careful analysis. The adjudication of AMI should also take into account the clinical setting in which the event occurs. AMI may be adjudicated for an event that has characteristics of an AMI but which does not meet the strict definition because biomarker or electrocardiographic results are not available. **Biomarker Elevations** For cardiac biomarkers, laboratories should report an upper reference limit (URL). If the 99th percentile of the upper reference limit (URL) from the respective laboratory performing the assay is not available, then the URL the laboratory uses to diagnose myocardial infarction (decision limit) should be used. In general, troponins are preferred and take precedence over CKMB when both biomarkers are available. CK-MB should be used if troponins are not available, and total CK may be used in the absence of CK-MB and troponin. **Acute Myocardial Infarction categorization** Since the prognostic significance of different types of myocardial infarctions (e.g., periprocedural myocardial infarction versus spontaneous myocardial infarction) may be different, all AMI events will be categorized by subtype as outlined below and further described in the third Universal Definition for Myocardial Infarction referenced below. • *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; • *Type 4b:* stent thrombosis documented by angiography or autopsy. • *Type 4c:* thrombosis not documented but restenosis is found by angiography or autopsy with no other obvious cause. • *Type 5:* MI associated with CABG. *ESC/ACCF/AHA/WHF Expert Consensus Document:* *Third Universal Definition of Myocardial Infarction.* *K Thygesen, J S. Alpert, A S. Jaffe, M L. Simoons, B R. Chaitman, H D. White* *Circulation. 2012;August 24 2012.*

Silent myocardial infarction
Asymptomatic patients who develop new pathologic Q wave
criteria for MI detected during routine ECG follow-up, or reveal
evidence of MI by cardiac imaging, that cannot be directly attributed to a coronary revascularization procedure, should be termed 'silent MI'. The diagnosis of a new silent Q wave MI should be confirmed by a repeat ECG or by an imaging study and by focused questioning about potential interim ischemic symptoms.

General considerations:

Electrocardiogram (ECG) Changes associated with myocardial infarction

Electrocardiographic changes can be used to support or confirm a myocardial infarction (MI). Supporting evidence may be ischemic changes and confirmatory information may be new Q waves.

ECG manifestations of acute myocardial ischemia (in absence of left ventricular hypertrophy (LVH) and left bundle branch block (LBBB)):

ST elevation

New ST elevation at the J point in two contiguous leads with the cut-points: > 0.1 mV in all leads other than leads V2-V3 where the following cut-points apply: ≥ 0.2 mV in men ≥ 40 years (≥ 0.25 mV in men < 40 years) or ≥ 0.15 mV in women.

ST depression and T-wave changes.

New horizontal or down-sloping ST depression ≥ 0.05 mV in two contiguous leads and/or new T inversion ≥ 0.1 mV in two contiguous leads with prominent R wave or R/S ratio > 1.

The above ECG criteria illustrate patterns consistent with myocardial ischemia. 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.

Pathological Q-wave

- Any Q-wave in leads V2-V3 ≥ 0.02 seconds or QS complex in leads V2 and V3.
- Q-wave ≥ 0.03 seconds and ≥ 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; V1-V6; II, III, and aVF)[a].

[a]The same criteria are used for supplemental leads V7-V9, and for the Cabrera frontal plane lead grouping.

Criteria for STEMI in the setting of AMI:

- New ST elevation as defined above

Criteria for Non-STEMI in the setting of AMI:

- Absence of ECG criteria for STEMI.

Criteria for ECG changes associated with silent myocardial infarction

- Pathological Q-waves, as defined above.

R-wave ≥ 0.04 seconds in V1-V2 and R/S ≥ 1 with a concordant positive T-wave in the absence of a conduction defect.

Event	Definition
Unstable Angina Pectoris requiring hospitalization	**Unstable angina pectoris requiring hospitalization** is defined as 1. Ischemic discomfort (angina, or symptoms thought to be equivalent) ≥ 10 minutes in duration occurring • at rest, or • in an accelerating pattern with frequent episodes associated with progressively decreased exercise capacity. **AND** 2. Prompting an unscheduled hospitalization **within 24 hours** of the most recent symptoms. Hospitalization is defined as an admission to an inpatient unit or a visit to an emergency department that results in at least a 24 hour stay (or a change in calendar date if the hospital admission or discharge times are not available). **AND** 3. At least one of the following: a. New or worsening ST or T wave changes on resting ECG (in the absence of confounders, such as LBBB or LVH) Transient ST elevation (duration < 20 minutes). New ST elevation at the J point in two contiguous leads with the cut-points: ≥ 0.1 mV in all leads other than leads V2-V3 where the following cut-points apply: ≥ 0.2 mV in men ≥ 40 years (≥ 0.25 mV in men < 40 years) or ≥ 0.15 mV in women. *ST depression and T-wave changes:* New horizontal or down-sloping ST depression ≥ 0.05 mV in two contiguous leads and/or new T inversion ≥ 0.3 mV in two contiguous leads with prominent R wave or R/S ratio > 1. b. Definite evidence of inducible myocardial ischemia as demonstrated by: an early positive exercise stress test, defined as ST elevation or ≥ 2 mm ST depression prior to 5 mets **OR** stress echocardiography (reversible wall motion abnormality) **OR** myocardial scintigraphy (reversible perfusion defect), **OR** MRI (myocardial perfusion deficit under pharmacologic stress). and believed to be responsible for the myocardial ischemic symptoms/signs. c. Angiographic evidence of new or worse ≥ 70% lesion and/or thrombus in an epicardial coronary artery that is believed to be responsible for the myocardial ischemic symptoms/signs. d. Need for coronary revascularization procedure (PCI or CABG) for the presumed culprit lesion(s). This criterion would be fulfilled if revascularization was undertaken during the unscheduled hospitalization, or subsequent to transfer to another institution without interceding home discharge. **AND** 4. Negative cardiac biomarkers and no evidence of acute MI **General Considerations** 1. Escalation of pharmacotherapy for ischemia, such as intravenous nitrates or increasing dosages of β-blockers, should be considered supportive but not diagnostic of UAP. However, a typical presentation and admission to the hospital with escalation of pharmacotherapy, without any of the additional findings listed under category 3, would be insufficient to support classification as hospitalization for UAP. 2. If subjects are admitted with suspected UAP, and subsequent testing reveals a non-cardiac or non-ischemic etiology, this event should not be recorded as hospitalization for UAP. Potential ischemic events meeting the criteria for myocardial infarction should not be adjudicated as UAP. 3. Planned hospitalization or rehospitalisation for performance of an elective revascularization in patients who do not fulfil the criteria for UAP should not be considered a hospitalization for UAP. For example, • Hospitalization of a patient with stable exertional angina for coronary angiography and PCI that is prompted by a positive outpatient stress test should not be considered hospitalization for UAP. • Rehospitalisation of a patient meeting the criteria for UAP who was stabilized, discharged, and subsequently readmitted for revascularization, does not constitute a second hospitalization for UAP. A patient who undergoes an elective catheterization where incidental coronary artery disease is found and who subsequently undergoes coronary revascularization will not be considered as meeting the hospitalization for UAP end point.

Event	Definition
Stroke	Stroke is defined as an acute episode of focal or global neurological dysfunction caused by brain, spinal cord, or retinal vascular injury as a result of hemorrhage or infarction. An event will only meet the criteria for a stroke if: • Symptoms are present for more than 24 hours **OR** • Imaging evidence consistent with stroke is identified in a patient with neurological symptoms present for less than 24 hours, Classification: **A.** Ischemic Stroke Ischemic stroke is defined as an acute episode of focal cerebral, spinal, or retinal dysfunction caused by infarction of central nervous system tissue. Hemorrhage may be a consequence of ischemic stroke. In this situation, the stroke is an ischemic stroke with hemorrhagic transformation and not a hemorrhagic stroke. **B.** Hemorrhagic Stroke Hemorrhagic stroke is defined as an acute episode of focal or global cerebral or spinal dysfunction caused by intraparenchymal, intraventricular, or subarachnoid hemorrhage. Subdural hematomas are intracranial hemorrhagic events and not strokes. **C.** Undetermined Stroke Undetermined stroke is defined as an acute episode of focal or global neurological dysfunction caused by presumed brain, spinal cord, or retinal vascular injury as a result of hemorrhage or infarction but with insufficient information to allow categorization as A or B. 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.
Severe Hypoglycaemia	Severe hypoglycaemia will be adjudicated based on the definition published by the American Diabetes Association.[3] **ADA definition** An episode requiring assistance of another person to actively administer carbohydrate, glucagon, or take other corrective actions. Plasma glucose values may not be available during an event, but neurological recovery following the return of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration.

Source: 16-1-13 Special committee documents, EAC charter final version 4, Appendix 2, pages 24-29

Changes to trial-related documents

Table 69 – Time course of changes to patient flow, protocol, SAP and data handling

	2013						2014												2015												2016									
Month in a year	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 10/3-10/11 un-blinding#
Pt. flow: R: 1st pt. randomized **FPE:** 1st pt. enrolled **LPR**: last pt randomized				FPE	R												LPR																		Ω	Ω	Ω	Ω	Ω 10/16- Trial completed (LPLV)
Protocol changes **V:** version	V2*									V3																													
SAP changes **V:** version																V1			Memo for duplicate pts.[a]																Memo [b]				-10/19 – SAP memo1 -10/31- SAP memo 2
Data handling **CB:** Code break **DL:** Database lock																	DAMP		-Cut off- date –DL interim analysis		Submit FDA -DAMP (Add1)																-10/13 DAMP add2 -10/31-Data unblinding 10/31- final DL
EAC charter changes			V1					V2											V3										V4										

*V1 of the protocol was used for internal purposes only
Ω- Trial closure period- spanned the first subjects' follow up visit (29 June 2016) to DBL (31 October 2016)
#- from 10/3 to 10/11, 49 Sponsor employees were unblinded due to a manual publishing error, see section :**3.1** **Submission Quality and Integrity**
[a] memo about duplicate patients (6 patients -12 subject numbers in the US) in 2 sites
[b] memo about one additional duplicate patient (1 patient randomized at 2 sires in the)

Source: reviewer generated table based on IR \\cdsesub1\evsprod\NDA203314\0135\m1\us\resp-fda-ir-20170508.pdf

Table 70 – Statistical documents (SAP, statistical memos)

October 9, 2014 Original SAP (version 1)

October 19, 2016 (MEMO 1)

Clarification of CV events

DATES

- onset date of an EAC adjudicated event =date determined by EAC
- End of trial = last patient last visit (LPLV)
- follow up visit must take place at least 30 days after last dose of IMP and not earlier than 29 June 2016

CV EVENTS

-Time to event analyses of MACE and 4-point MACE where a CV death is linked to an earlier fatal MI or stroke, the patient will contribute to the analysis with time to the CV death and will be included as CV death

-Priority of selecting events occurring on the same day: Death>non-fatal myocardial infarction>non-fatal stroke>unstable angina pectoris requiring hospitalization

OBSERVATION TIME

-each patient has an individual trial period considered as the time from randomization to the end of trial date for each specific patient (i.e. date of the follow up visit), if did not complete follow up visit, then date is based on: death date (if occurs prior to global LPLV), date of EAC confirmed MACE (that occurs prior to global LPLV), last direct contact for patients

-an exception to the date of complete follow up visit is in the case a CV-death occurs after follow-up visit but the CV death is linked to a fatal MACE that occurs prior to date of follow up visit (in this case the date of CV death is the end of trial date)

-All potential MACEs, fatal events and severe hypoglycemic episodes reported up to code break must be adjudicated

-observation time is form randomization until individual end-of trial date; exposure time is time from date for first dose of IMP to date of last dose +1 excluding drug holidays

CLASSIFICATION OF PATIENTS

-1. Patients with complete information for the primary endpoint or censored at follow up visit (i.e. EAC confirmed MACE during the trial, non-CV death during the trial, follow-up visit completed).

-2. Patients with in-complete information to the primary analysis (i.e. vital status known, unknown (withdrawal of consent or lost to follow up)

Unknown MACE date

If not date is given for a MACE event by the EAC then the date was imputed (the day after last contact)

Rev comment: Per an information request, the Sponsor clarified that no dates for MACE events were imputed

OFFSET IN analysis of severe hypoglycemia

The confirmatory analysis was done with the offset equal to the logarithm of the observation time as the time where severe hypoglycemic events were counted is then

the same as the off-set consistent with the ITT principle and the FAS definition

October 19, 2016 (MEMO 2)

This memo described additional analyses. As shown below. These analyses are not considered pre-specified.

Output & rationale	Comments
Deaths after individual end of trial date (see MEMO#1 for definition) and before DBL **Rationale:** Anticipated that this will be requested by FDA	Late reported EAC confirmed events, that is events that occur after individual end-of-trial date will be summarised separately.
Baseline characteristics will be summarised by MACE status at end of trial **Rationale:** Requested for LEADER	All baseline characteristics, cardiovascular risk factors, cardiovascular medications and antidiabetic medications summarised for the CTR for the overall trial population will also be summarized by MACE status.
Concomitant medication **Rationale:** Requested for primary manuscript for and used in submission of LEADER	CV-medication intensified during trial will be summarised. Intensified means when an additional medication in same or different ATC group is added, e.g. beta blockers at baseline, intensified with ACE-inhibitors.
Summaries of baseline information, exposure, MACE and severe hypoglycaemia **Rationale:** Will be requested by FDA for most of the subgroups, was done for LEADER and other CVOTs and needed for EU risk management plan	Summaries will be made by subgroups defined by • Sex • Age group • Renal impairment • HbA1c at baseline • Diabetes duration • Region • US vs rest of the world, • Race • Ethnicity • CV-risk group • Previous anti-diabetic treatment • CV-medication • BMI For cut-offs, see SPS

Output & rationale	Comments
Expanded MACE **Rationale:** Standard for CVOTs	Analyses and outputs similar to those for the primary endpoint (MACE) will be done for expanded MACE. In addition to components included in primary endpoint, expanded MACE includes EAC confirmed unstable angina pectoris requiring hospitalisation
Non CV-death **Rationale:** Standard for recent CVOTs (EMPA-REG and LEADER)	In line with the primary endpoint the two components of all-cause death will be analysed. CV-death is specified in the SAP, but non-CV-death will also be analysed with a Cox regression model accounting only for treatment.

Deaths due to unknown cause **Rationale:** Discussion point at ADCOM for EMPA-REG	The primary endpoint and CV-death will be re-analysed where deaths due to unknown causes are not considered a CV-death.
Heart failure requiring hospitalisation **Rationale:** A discussion point at recent ADCOMs for other CVOT's. A publication is planned by the StC.	Use the pre-specified MedDRA search from LEADER to search for these events. Repeat primary analysis on this endpoint and selected summaries.
CV-endpoints adjusted baseline information **Rationale:** used in the LEADER submission and for the primary manuscript	MACE, expanded MACE and the individual components will if necessary be analysed with sensitivity analysis such as on-treatment and correction for baseline information: sex, region, age, diabetes duration, CV-risk, anti-diabetic and CV medication at baseline and renal function eGFR
On-treatment analysis **Rationale:** Discussion point at FDA-ADCOMs for CVOTs with DPP4i (SAVOR-TIMI and EXAMINE) in spring 2015	In addition to the "on treatment" and "on treatment + 30 days" analyses specified in SAP, on-treatment analyses will be added using continuous expansion of the ascertainment window, by allowing an added "safety follow-up" window from 1 to 30 days. The estimated hazards ratios and 95% CI will be plotted against the number of days added to the window. The same model as used for analysis of primary endpoint will be applied. The analysis will be repeated for the expanded MACE definition.
Competing Risks **Rationale:** Standard for recent CVOTs (EMPA-REG and LEADER)	Competing risks for MACE and the individual components will be evaluated by examining cumulative incidence functions (CIFs) rather than by Kaplan-Meier curves (will be included in CTR). Competing risks include lost-to-follow-up, withdrawal and death from other causes.
Multiple imputation **Rationale:** Standard missing data analysis	Multiple imputation methods will be considered for the primary outcome for all non-completers and for the subset of non-completers that are lost to follow-up
Tipping point analysis for MACE **Rationale:** Standard missing data analysis, FDA did similar for CVOT: IMPROVE-IT	Tipping point analyses will be conducted for MACE if non-inferiority for IDeg vs IGlar has been established in the primary analysis. This involves stepwise imputation of first MACEs for subjects randomised to IDeg for non-completers until the upper bound of the CI is not below 1.3. Two tipping-point analysis will be performed, one where only lost-to-follow-up subjects are imputed and one where non-completers are imputed
Subgroup analysis **Rationale:** Done for LEADER, FDA will likely request parts of the subgroup analysis to be posted on the their snapshot-page	The primary analysis will be repeated for the subgroups defined by: • Sex • Age group • Renal impairment • HbA1c at baseline • Diabetes duration • Region • US vs rest of the world, • Race • Ethnicity • CV-risk group • Previous anti-diabetic treatment • CV-medication • BMI For cut-offs, see SPS Treatment effects will be reported from a model that includes an interaction effect, and the p-value for testing the relevant interaction is reported with the subgroup specific treatment effects

Output & rationale	Comments
On treatment analyses **Rationale:** Relevant to address treatment emergent severe hypoglycaemia	Sensitivity analysis of EAC confirmed severe hypoglycaemic episodes will be done using the different "on-treatment" definitions defined in the SAP and SPS. Sensitivity analysis for on-treatment will also apply to proportion of subjects that experience an EAC confirmed severe hypoglycaemic episode
Analysis using truncation of number of events **Rationale:** FDA concern during the special protocol assessment process for the SWITCH studies	In order to estimate differences in rates without subjects that experience a large number of severe hypoglycaemic episodes driving the difference, the main analysis is repeated where the number of episodes is truncated at 3
Time to first severe hypoglycaemic event analysis **Rationale:** Analysis done for LEADER and suggested by external advisors for SWITCH, and will give the possibility to account for added bolus treatment which will impact the rate of severe hypoglycaemia.	As an alternative approach to the two analyses conducted according to protocol and SAP a Cox-regression model will be used for analysis of time to first severe hypoglycaemic episode, accounting for treatment group only. The analysis will be repeated accounting for insulin treatment regimen as time-dependent variable
Number of severe hypoglycaemic episodes adjusted for antidiabetic treatment at baseline. **Rationale:** Significant predictor for hypoglycaemia.	Number of severe hypoglycaemic episodes will be analysed using the negative binomial model where baseline antidiabetic treatment group is accounted for.
Subgroup analyses **Rationale:** FDA will likely request subgroup analysis for snapshot web-page	Similarly to primary endpoint but also according to whether the subject is on an alternative titration target or not(yes/no)
Nocturnal severe hypoglycaemic episodes **Rationale:** Nocturnal severe hypoglycaemia is less impacted by bolus treatment	Similar analyses as done for all EAC confirmed severe hypoglycaemic episodes will be done for nocturnal severe hypoglycaemic episodes, defined as occurring between (00:01 and 05:59), both time points included
Multiple Imputation Analysis of Severe Hypoglycaemic Episodes **Rationale:** standard missing data analysis	Subjects with incomplete information with respect to hypoglycaemia will be imputed using multiple imputations.
Tipping point analyses **Rationale:** standard missing data analysis	If superiority of IDeg vs IGlar is confirmed a tipping point analysis will be performed. The analysis will be based on the multiple imputation methods where subjects in the IDeg arm with incomplete information are imputed with increasing rate of severe hypoglycaemia until the upper bound of the 95% confidence interval is no longer below 1

Output & rationale	Comments
Dose **Rationale:** A difference in dose is important for market access.	If HbA1c appears similar in maintenance period, that is difference in observed means between treatment arms <0.3% at 6, 9, 12 and 24 months follow-up then an analysis will be conducted comparing insulin doses between treatment groups. This will both be done for the basal insulin dose and the total insulin dose. A MMRM model with treatment and visit as factors and interactions between visit and treatment will be used. The dosing data will be log-transformed before analysis. An unstructured covariance structure for the repeated measurements will be assumed. From this model the treatment effect by visit will be estimated. Ratios and corresponding 95% CIs will be estimated. Baseline information will be accounted for, i.e. titration target, BMI. The difference in dose will be reported at 24 months follow-up. If the model does not converge a simpler covariance matrix will be used.
Sensitivity analysis of efficacy endpoints will be carried out as appropriate.	
Neoplasms	Occurrence of serious adverse events reported as neoplasms and confirmed by external classification will be summarised separately by treatment. Neoplasms output will be summarized as benign, unclassifiable and malignant neoplasms.

Other tables and figures

Table 71- Flow chart –site visits

EX1250-4080 Site visits	Screening	Randomisation	Trial treatment																										End treatment (ET)	Follow-up
Visit number (V)	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V13	V16	V19	V22	V25	V28	V31	V34	V37	V40	V43	V46	V49	V52	V55	V58	V61			
Time of phone contact (P) – monthly contacts (For assessments see separate flow chart)										P11 P12	P14 P15	P17 P18	P20 P21	P23 P24	P26 P27	P29 P30	P32 P33	P35 P36	P38 P39	P41 P42	P44 P45	P47 P48	P50 P51	P53 P54	P56 P57	P59 P60	P62			
Time of visit (months, unless otherwise specified) Time of visits are calculated in relation to V2 date, except follow-up visit	Up to -2 wks	0	1 wks	2 wks	1	2	3	4	5	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54	57	59	ET +30 days
Visit window (days)			±3	±3	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	+7
Informed consent	x																												
In/Exclusion criteria	x																												
Demography, smoking	x																												
Diabetes, concomitant illness, medical history	x																												
Concomitant medication	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Height	x																											x	
Body weight	x											x				x				x				x				x	
Blood pressure and pulse	x									x		x		x		x		x		x		x		x		x		x	
Physical examination	x																											x	
Electrocardiogram		x										x				x				x				x				x	
Pregnancy urine test females child-bearing potential	x																											x	
Blood sampling		x					x			x	x	x				x				x				x				x	
Glycosylated haemoglobin (HbA_{1c})		x					x			x	x	x				x				x				x				x	
Fasting plasma glucose (FPG)		x										x				x				x				x				x	
Lipids		x										x				x				x				x				x	
Haematology		x										x				x				x				x				x	
Biochemistry		x										x				x				x				x				x	
Randomisation		x																											
Instruction in use of trial products		x																											
Instruction in use/hand-out of blood glucose meter		x																											
Adverse events, severe hypoglycaemic episodes		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Technical complaints			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Subject compliance			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Insulin dose adjustments			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
HbA_{1c} site measurement			x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
SMPG pre-breakfast			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
8-point SMPG profile												x				x				x				x				x	
Provide diary (and if applicable, mobile phone and pre-paid phone cards) instruction		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Collect diaries, (mobile phones, if applicable), review data			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Remind to bring all trial products to next site visit					x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
Record first and last date and dose of investigational product in the eCRF			x																									x	
End of trial																													x

Source: Figure 2-1 protocol, page 90

Figure 47- Measurements of albuminuria

	Normal	Microalbuminuria	Macroalbuminuria
Urine dipstick for protein	–	–	+
Urine 24-hour protein (mg)	< 150	< 500	≥ 500
Urine 24-hour albumin (mg)	< 30	30-300	> 300
Timed urine collection (µg/min)	< 20	20-200	> 200
Spot urine collection (µg albumin/mg creatinine)	< 30	30-300	> 300

Source: Protocol, figure 6-1 page 23,

Table 72- MedDra search used to identify heart failure requiring hospitalization

SMQ[a]	HLGT
Arrhythmia related investigations, signs and symptoms Bradyarrhythmia terms, nonspecific Bradyarrhythmias (incl conduction defects and disorders of sinus node function) Cardiac arrhythmia terms (incl bradyarrhythmias and tachyarrhythmias) Cardiac arrhythmia terms, nonspecific Cardiac failure Conduction defects Disorders of sinus node function Supraventricular tachyarrhythmias Tachyarrhythmia terms, nonspecific Tachyarrhythmias (incl supraventricular and ventricular tachyarrhythmias Torsade de pointes/QT prolongation Ventricular tachyarrhythmias	Heart failures **PT** Dyspnoea Dyspnoea at rest Dyspnoea exertional Generalised oedema Reexpansion pulmonary oedema

Note: [a]All SMQs are broad scope

Abbreviations: HLGT: high level group term; PT: preferred term; SMQ: Standard MedDRA Query

Source: CSR, table 9-15, page 111

Table 73 – patients with no direct match between outcome from adjudication in the death queue and adjudication in the cerebrovascular events queue - FAS

Subject ID	Treatment group	AE no.	Preferred term	EAC cause of death	EAC classification of stroke
(b) (6)	IDeg	1	Intracranial aneurysm	**Stroke**	(not sent for adjudication in cerebrovascular queue)
	IGlar	1	Ischaemic stroke	**Stroke**	(Ischaemic stroke[b])
	IGlar	3	Ischaemic stroke		**Stroke** Ischaemic stroke
		4	Respiratory failure[a]	Pulmonary causes	

Note: This table presents data from the ADaM.ADADJ dataset and the ADaM.ADAE dataset (preferred terms only), both based on FAS.
A comparison of subject IDs has been done between events where ADJEVCDE = 'DEATH' and QR3T = 'DEATH DUE TO STROKE' and events where ADJEVCDE = 'CEREBROVASCULAR EVENTS' and DETHREYN ='Y'. The table displays subject IDs not matching between the two searches.
a: The ischaemic stroke occurred 2 months prior to his death. Comment from adjudicator 1 (death queue): "*Died of complications after stroke May 29 2015. Final terminal event ARF and pneumonia*"
b: The adjudicators did not marked this event as 'death-related' in the adjudication eCRF
Abbreviations: EAC: event adjudication committee; FAS: full analysis set

Source: Appendix 16.1.13, table 3

Table 74 – Patients with no direct match between outcome from adjudication in the death queue and adjudication in the ACS queue- FAS

Subject ID	Treatment group	AE no.	Preferred term	EAC cause of death	EAC classification of ACS
(b) (6)	IDeg	1	Cardiac arrest	**Acute myocardial infarction**	(not sent for adjudication in ACS queue)
	IGlar	5	Arrhythmia	**Acute myocardial infarction**	(not sent for adjudication in ACS queue)
	IDeg	1	Cardiac failure congestive	**Acute myocardial infarction**	(not sent for adjudication in ACS queue)
	IDeg	2	Myocardial infarction	Sudden cardiac death	**Myocardial infarction** (subtype cannot be determined)
	IGlar	6	Acute myocardial infarction		**Myocardial infarction** NSTEMI, Type 1
		8	Right ventricular failure	Sudden cardiac death	
	IGlar	2	Acute myocardial infarction	Sudden cardiac death	**Myocardial infarction** NSTEMI, Type 1

Note: This table presents data from the ADaM.ADADJ dataset and preferred terms from the ADaM.ADAE dataset, both based on FAS.
A comparison of subject IDs has been done between events where ADJEVCDE = 'DEATH' and QR3T = 'DEATH DUE TO ACUTE MYOCARDIAL INFARCTION' and events where ADJEVCDE = 'ACS' and DETHREYN ='Y'. The table displays subject IDs not matching between the two searches.
Abbreviations: ACS: acute coronary syndrome; EAC: event adjudication committee; FAS: full analysis set

Source: Appendix 16.1.13, table 2

Table 75 -Adjudication documents included in the EAC dossier

Adjudication event	Source of documents for adjudication
Fatal event	• Clinical description of event/admission history (including ER records) and physical exam • Autopsy report (if performed) • Code/resuscitation attempt summary (if applicable) • Death certificate
ACS (MI, UAP)	• Admission history (including ER records and physical exam) • ECG tracings (prior to event, during event and following event resolution) • Cardiac biomarkers (troponin, CK-MB, normal ranges and myocardial necrosis and myocardial infarction reference limits) and biochemistry labs • Imaging reports (MRI, CTA, cardiac cauterization and angiography, etc.) • Cardiology consult report • Discharge summary • If revascularization was performed: (revascularization procedure report, and discharge summary) • If patient died from the event: all documents in relation to the fatal outcome
ECG found to have changes suggestive of new prior MI during central ECG review	• Admission history (ER records) and physical exam • ECG tracings • Cardiac biomarkers and biochemistry labs • Imaging reports (MRI, CTA angiography, echo, nuclear medicine, etc.) • Procedure reports • Cardiology consult • Discharge summary • If revascularization was performed (revascularization report and discharge summary), all ECG tracings.
Cerebrovascular events	• Admission history (including ER records) • Discharge summary • Reports of CT scan, MRI ultrasound or other imaging • Cerebral/carotid angiography reports • Neurological consult report • Physical exam findings (times of symptom onset and resolution) • If revascularization procedure performed: revascularization report and discharge summary • If patient died from the event: all documents related to the death
Severe hypoglycemia	• Patient diary • Investigator notes • Admission history (ER records included) and physical exam • Lab data • Discharge summary
Source: 16-1-13 Special protocol document, EAC charter version 4- page 16.	

Table 76 – Deaths occuring during the trial period classified by PT and SOC terms-FAS

		IDeg		IGlar		All	
		N	%	N	%	N	%
	N	3818		3819		7637	
SOC	**PT terms**						
Cardiac disorders	Cardiac arrest	21	0.6	15	0.4	36	0.5
	Myocardial infarction	15	0.4	16	0.4	31	0.4

	Cardiac failure congestive	10	0.3	10	0.3	20	0.3
	Cardio-respiratory arrest	11	0.3	6	0.2	17	0.2
	Acute myocardial infarction	6	0.2	9	0.2	15	0.2
	Arteriosclerosis coronary artery	1	0	5	0.1	6	0.1
	Cardiac failure	3	0.1	3	0.1	6	0.1
	Coronary artery disease	4	0.1	2	0.1	6	0.1
	Ventricular fibrillation	4	0.1	1	0	5	0.1
	Cardiomyopathy	1	0	3	0.1	4	0.1
	Arrhythmia	1	0	2	0.1	3	0
	Cardiopulmonary failure	1	0	2	0.1	3	0
	Hypertensive heart disease	1	0	2	0.1	3	0
	Acute coronary syndrome	1	0	1	0	2	0
	Atrial fibrillation	1	0	1	0	2	0
	Acute left ventricular failure	0	0	1	0	1	0
	Angina pectoris	0	0	1	0	1	0
	Angina unstable	0	0	1	0	1	0
	Cardiac disorder	0	0	1	0	1	0
	Cardiac failure acute	0	0	1	0	1	0
	Cardiac failure chronic	1	0	0	0	1	0
	Cardiogenic shock	0	0	1	0	1	0
	Cardiovascular disorder	0	0	1	0	1	0
	Cor pulmonale	1	0	0	0	1	0
	Ischaemic cardiomyopathy	0	0	1	0	1	0
	Myocardial ischaemia	1	0	0	0	1	0
	Right ventricular failure	0	0	1	0	1	0
	All	84	2.2	87	2.3	171	2.2
General disorders and administration site conditions	Death	27	0.7	21	0.5	48	0.6
	Sudden death	1	0	8	0.2	9	0.1
	Sudden cardiac death	1	0	3	0.1	4	0.1
	Cardiac death	1	0	2	0.1	3	0
	Multiple organ dysfunction syndrome	1	0	1	0	2	0
	All	31	0.8	35	0.9	66	0.9
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Hepatocellular carcinoma	1	0	3	0.1	4	0.1
	Lung adenocarcinoma metastatic	1	0	1	0	2	0
	Metastases to liver	1	0	1	0	2	0
	Metastatic renal cell carcinoma	2	0.1	0	0	2	0
	Pancreatic carcinoma	1	0	1	0	2	0
	Pancreatic carcinoma metastatic	2	0.1	0	0	2	0
	Small cell lung cancer	1	0	1	0	2	0
	Small cell lung cancer metastatic	2	0.1	0	0	2	0
	Acute lymphocytic leukaemia	1	0	0	0	1	0
	Adenocarcinoma gastric	1	0	0	0	1	0
	Adult T-cell lymphoma/leukaemia	1	0	0	0	1	0
	Brain neoplasm	1	0	0	0	1	0
	Breast cancer metastatic	0	0	1	0	1	0
	Cholangiocarcinoma	0	0	1	0	1	0
	Diffuse large B-cell lymphoma recurrent	0	0	1	0	1	0
	Gallbladder cancer metastatic	0	0	1	0	1	0
	Gastrointestinal cancer metastatic	0	0	1	0	1	0
	Hepatic cancer	0	0	1	0	1	0
	Hepatic cancer metastatic	0	0	1	0	1	0

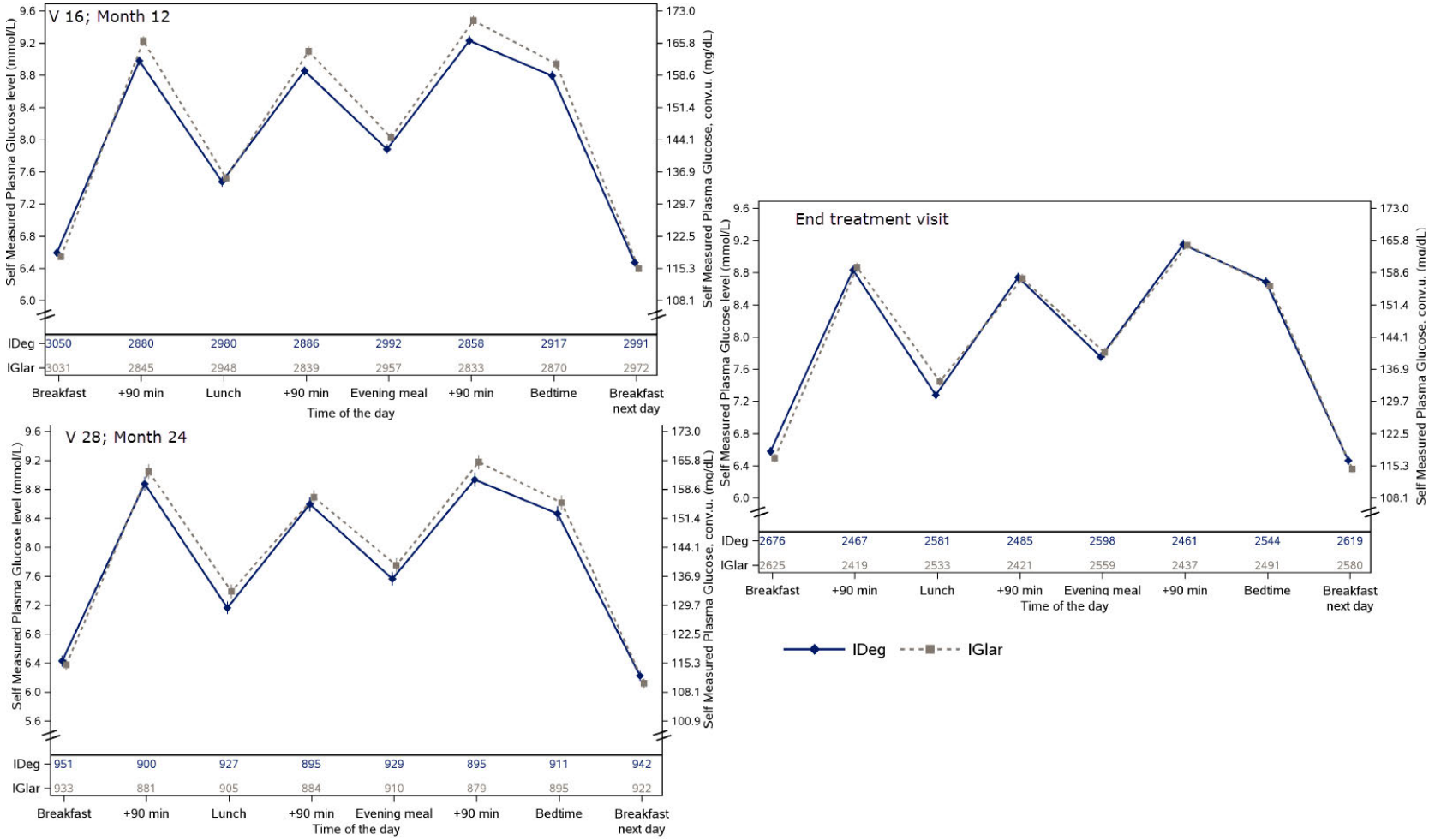
	Lung adenocarcinoma	0	0	1	0	1	0
	Lung adenocarcinoma stage II	0	0	1	0	1	0
	Lung adenocarcinoma stage IV	0	0	1	0	1	0
	Lung cancer metastatic	0	0	1	0	1	0
	Lymphoma	1	0	0	0	1	0
	Malignant peritoneal neoplasm	1	0	0	0	1	0
	Mesothelioma malignant	1	0	0	0	1	0
	Metastases to central nervous system	0	0	1	0	1	0
	Metastatic neoplasm	0	0	1	0	1	0
	Neuroendocrine carcinoma metastatic	1	0	0	0	1	0
	Non-small cell lung cancer metastatic	0	0	1	0	1	0
	Oesophageal carcinoma	1	0	0	0	1	0
	Ovarian cancer stage IV	1	0	0	0	1	0
	Pancreatic carcinoma stage IV	1	0	0	0	1	0
	Papillary thyroid cancer	1	0	0	0	1	0
	Rectal adenocarcinoma	1	0	0	0	1	0
	Soft tissue sarcoma	0	0	1	0	1	0
	All	24	0.6	22	0.6	46	0.6
Nervous system disorders	Cerebrovascular accident	5	0.1	6	0.2	11	0.1
	Haemorrhage intracranial	0	0	3	0.1	3	0
	Ischaemic stroke	1	0	2	0.1	3	0
	Brain stem haemorrhage	0	0	2	0.1	2	0
	Cerebral haemorrhage	0	0	2	0.1	2	0
	Parkinson's disease	1	0	1	0	2	0
	Brain injury	1	0	0	0	1	0
	Cerebral arteriosclerosis	1	0	0	0	1	0
	Cerebral infarction	0	0	1	0	1	0
	Dementia Alzheimer's type	0	0	1	0	1	0
	Dizziness	1	0	0	0	1	0
	Embolic stroke	1	0	0	0	1	0
	Haemorrhagic cerebral infarction	1	0	0	0	1	0
	Haemorrhagic stroke	0	0	1	0	1	0
	Intracranial aneurysm	1	0	0	0	1	0
	Metabolic encephalopathy	0	0	1	0	1	0
	Subarachnoid haemorrhage	0	0	1	0	1	0
	Thalamus haemorrhage	1	0	0	0	1	0
	Vascular dementia	0	0	1	0	1	0
	All	14	0.4	22	0.6	36	0.5
Infections and infestations	Septic shock	5	0.1	4	0.1	9	0.1
	Pneumonia	6	0.2	2	0.1	8	0.1
	Sepsis	3	0.1	3	0.1	6	0.1
	Urosepsis	2	0.1	1	0	3	0
	Pulmonary sepsis	1	0	1	0	2	0
	Extradural abscess	0	0	1	0	1	0
	Liver abscess	0	0	1	0	1	0
	Lower respiratory tract infection	1	0	0	0	1	0
	Sepsis pasteurella	1	0	0	0	1	0
	Staphylococcal infection	0	0	1	0	1	0
	Staphylococcal sepsis	1	0	0	0	1	0
	All	20	0.5	14	0.4	34	0.4
Respiratory, thoracic and mediastinal disorders	Acute respiratory failure	3	0.1	4	0.1	7	0.1
	Chronic obstructive pulmonary	2	0.1	5	0.1	7	0.1

	disease						
	Respiratory failure	1	0	5	0.1	6	0.1
	Pulmonary embolism	4	0.1	1	0	5	0.1
	Pulmonary hypertension	2	0.1	0	0	2	0
	Acute pulmonary oedema	1	0	0	0	1	0
	Hypoxia	1	0	0	0	1	0
	Pulmonary fibrosis	0	0	1	0	1	0
	Pulmonary oedema	0	0	1	0	1	0
	Pulmonary veno-occlusive disease	0	0	1	0	1	0
	All	14	0.4	18	0.5	32	0.4
Injury, poisoning and procedural complications	Road traffic accident	4	0.1	2	0.1	6	0.1
	Fall	1	0	1	0	2	0
	Craniocerebral injury	0	0	1	0	1	0
	Hip fracture	0	0	1	0	1	0
	Post procedural haemorrhage	1	0	0	0	1	0
	Subdural haematoma	0	0	1	0	1	0
	All	6	0.2	6	0.2	12	0.2
Renal and urinary disorders	End stage renal disease	2	0.1	2	0.1	4	0.1
	Acute kidney injury	2	0.1	1	0	3	0
	Azotaemia	1	0	0	0	1	0
	Chronic kidney disease	1	0	0	0	1	0
	Renal failure	0	0	1	0	1	0
	All	6	0.2	4	0.1	10	0.1
Hepatobiliary disorders	Acute hepatic failure	0	0	1	0	1	0
	Hepatic cirrhosis	0	0	1	0	1	0
	Hepatorenal syndrome	0	0	1	0	1	0
	Liver disorder	0	0	1	0	1	0
	All	0	0	4	0.1	4	0.1
Vascular disorders	Accelerated hypertension	0	0	1	0	1	0
	Aortic stenosis	0	0	1	0	1	0
	Arteriosclerosis	0	0	1	0	1	0
	Hypotension	1	0	0	0	1	0
	All	1	0	3	0.1	4	0.1
Gastrointestinal disorders	Acute abdomen	0	0	1	0	1	0
	Diarrhea	0	0	1	0	1	0
	Intestinal ischemia	1	0	0	0	1	0
	All	1	0	2	0.1	3	0
Metabolism and nutrition disorders	Diabetes mellitus inadequate control	1	0	0	0	1	0
	Hyponatraemia	0	0	1	0	1	0
	All	1	0	1	0	2	0
Psychiatric disorders	Completed suicide	0	0	2	0.1	2	0
	All	0	0	2	0.1	2	0
Skin and subcutaneous tissue disorders	Skin necrosis	0	0	1	0	1	0
	All	0	0	1	0	1	0
All	All	202	5.3	221	5.8	423	5.5

Source: reviewer generated from ADAE dataset, DTHQID (death queue, not blank). Omited patients whose death did not occur during the trial period.

Figure 48 –Hypoglycemia Patient diary form

Figure 49 – 8 point SMPG profile over one day at month 12, 24 and end of treatment visits



Source: CSR figure 14.2174-176, pages 482-484

Table 77 – classified benign neoplasms by SOC, high level group term and preferred term- serious adverse events- summary- FAS

	IDeg				IGlar			
	N	e	E	R	N	e	E	R
Number of subjects	3818				3819			
PYO	7568				7558			
Number of events	26	(0.7)	26	0.34	19	(0.5)	20	0.26
Gastrointestinal disorders	5	(0.1)	5	0.07	4	(0.1)	4	0.05
Benign neoplasms gastrointestinal	5	(0.1)	5	0.07	4	(0.1)	4	0.05
Gastrointestinal polyp haemorrhage	1	(0.0)	1	0.01	1	(0.0)	1	0.01
Large intestine polyp	4	(0.1)	4	0.05	3	(0.1)	3	0.04
General disorders and administration site conditions	2	(0.1)	2	0.03	1	(0.0)	1	0.01
General system disorders NEC	1	(0.0)	1	0.01	0			
Polyp	1	(0.0)	1	0.01	0			
Tissue disorders NEC	1	(0.0)	1	0.01	1	(0.0)	1	0.01
Cyst	1	(0.0)	1	0.01	1	(0.0)	1	0.01
Infections and infestations	1	(0.0)	1	0.01	0			
Infections - pathogen unspecified	1	(0.0)	1	0.01	0			
Infected dermal cyst	1	(0.0)	1	0.01	0			
Musculoskeletal and connective tissue disorders	0				1	(0.0)	1	0.01
Synovial and bursal disorders	0				1	(0.0)	1	0.01
Synovial cyst	0				1	(0.0)	1	0.01
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	14	(0.4)	14	0.19	12	(0.3)	12	0.16
Endocrine neoplasms benign	3	(0.1)	3	0.04	2	(0.1)	2	0.03
Adrenal adenoma	0				1	(0.0)	1	0.01
Benign neoplasm of thyroid gland	1	(0.0)	1	0.01	0			
Parathyroid tumour benign	1	(0.0)	1	0.01	1	(0.0)	1	0.01
Pituitary tumour benign	1	(0.0)	1	0.01	0			
Endocrine neoplasms malignant and unspecified	1	(0.0)	1	0.01	0			
Phaeochromocytoma	1	(0.0)	1	0.01	0			
Gastrointestinal neoplasms benign	6	(0.2)	6	0.08	3	(0.1)	3	0.04
Colon adenoma	3	(0.1)	3	0.04	2	(0.1)	2	0.03
Gastrointestinal tract adenoma	1	(0.0)	1	0.01	0			
Papillary cystadenoma lymphomatosum	1	(0.0)	1	0.01	1	(0.0)	1	0.01
Rectal adenoma	1	(0.0)	1	0.01	0			
Hepatobiliary neoplasms malignant and unspecified	0				1	(0.0)	1	0.01
Tumour of ampulla of Vater	0				1	(0.0)	1	0.01
Miscellaneous and site unspecified neoplasms benign	0				2	(0.1)	2	0.03
Cardiac valve fibroelastoma	0				1	(0.0)	1	0.01
Fibroma	0				1	(0.0)	1	0.01
Nervous system neoplasms benign	3	(0.1)	3	0.04	0			
Meningioma benign	3	(0.1)	3	0.04	0			
Renal and urinary tract neoplasms benign	0				1	(0.0)	1	0.01
Benign neoplasm of bladder	0				1	(0.0)	1	0.01
Reproductive neoplasms female benign	0				1	(0.0)	1	0.01
Benign ovarian tumour	0				1	(0.0)	1	0.01
Soft tissue neoplasms benign	1	(0.0)	1	0.01	2	(0.1)	2	0.03
Leiomyoma	0				1	(0.0)	1	0.01
Lipoma	1	(0.0)	1	0.01	1	(0.0)	1	0.01
Reproductive system and breast disorders	2	(0.1)	2	0.03	0			
Cervix disorders (excl infections and inflammations)	1	(0.0)	1	0.01	0			
Cervical cyst	1	(0.0)	1	0.01	0			
Ovarian and fallopian tube disorders	1	(0.0)	1	0.01	0			
Ovarian cyst	1	(0.0)	1	0.01	0			
Respiratory, thoracic and mediastinal disorders	1	(0.0)	1	0.01	1	(0.0)	1	0.01
Upper respiratory tract disorders (excl infections)	1	(0.0)	1	0.01	1	(0.0)	1	0.01
Nasal polyps	1	(0.0)	1	0.01	1	(0.0)	1	0.01
Skin and subcutaneous tissue disorders	1	(0.0)	1	0.01	0			
Cutaneous neoplasms benign	1	(0.0)	1	0.01	0			
Dermal cyst	1	(0.0)	1	0.01	0			
Vascular disorders	0				1	(0.0)	1	0.01
Lymphatic vessel disorders	0				1	(0.0)	1	0.01
Lymphocele	0				1	(0.0)	1	0.01

Table 78 – Neoplasms identified form the Neoplasms benign, malignant and unspecified (incl cysts and polyps) SOC - FAS

	IDeg OD (N = 3818)			*IGlar OD (N = 3819)*		
PT	*Events*	*Number of subjects*	*Proportion (%)*	*Events*	*Number of subjects*	*Proportion (%)*
Acute leukaemia	1	1	0.03	0	0	0
Acute lymphocytic leukaemia	1	1	0.03	0	0	0
Acute myeloid leukaemia	0	0	0	1	1	0.03
Adenocarcinoma	0	0	0	1	1	0.03
Adenocarcinoma gastric	2	2	0.05	1	1	0.03
Adenocarcinoma of colon	2	2	0.05	5	5	0.13
Adenocarcinoma pancreas	0	0	0	1	1	0.03
Adenoma benign	0	0	0	1	1	0.03
Adrenal adenoma	0	0	0	1	1	0.03
Adrenal neoplasm	0	0	0	1	1	0.03
Adult T-cell lymphoma/leukaemia	1	1	0.03	0	0	0
B-cell lymphoma	2	2	0.05	0	0	0
B-cell lymphoma stage III	0	0	0	1	1	0.03
Basal cell carcinoma	8	8	0.21	5	5	0.13
Benign neoplasm of bladder	0	0	0	1	1	0.03
Benign neoplasm of thyroid gland	1	1	0.03	0	0	0
Benign ovarian tumour	0	0	0	1	1	0.03
Benign salivary gland neoplasm	2	1	0.03	0	0	0
Bile duct adenocarcinoma	1	1	0.03	0	0	0
Bladder cancer	1	1	0.03	3	3	0.08
Bladder cancer recurrent	1	1	0.03	0	0	0
Bladder cancer stage 0, with cancer in situ	1	1	0.03	0	0	0
Bladder transitional cell carcinoma	1	1	0.03	1	1	0.03
Bladder transitional cell carcinoma recurrent	2	2	0.05	0	0	0
Bladder transitional cell carcinoma stage I	1	1	0.03	0	0	0
Bone cancer	0	0	0	1	1	0.03
Bowen's disease	0	0	0	1	1	0.03
Brain neoplasm	1	1	0.03	0	0	0
Breast cancer	1	1	0.03	2	2	0.05
Breast cancer metastatic	1	1	0.03	1	1	0.03
Breast cancer stage I	0	0	0	2	2	0.05
Breast cancer stage II	1	1	0.03	0	0	0
Breast cancer stage IV	1	1	0.03	0	0	0
Cardiac valve fibroelastoma	0	0	0	1	1	0.03
Cholangiocarcinoma	0	0	0	1	1	0.03
Choroid melanoma	1	1	0.03	0	0	0
Chronic lymphocytic leukaemia	0	0	0	1	1	0.03
Chronic myeloid leukaemia	0	0	0	1	1	0.03
Colon adenoma	3	3	0.08	2	2	0.05
Colon cancer	2	2	0.05	1	1	0.03
Colon cancer metastatic	2	2	0.05	1	1	0.03
Colon cancer stage III	0	0	0	1	1	0.03
Colorectal cancer metastatic	0	0	0	1	1	0.03
Diffuse large B-cell lymphoma recurrent	0	0	0	1	1	0.03
Endometrial adenocarcinoma	3	3	0.08	3	3	0.08
Fibroma	0	0	0	1	1	0.03
Gallbladder adenocarcinoma	0	0	0	1	1	0.03
Gallbladder cancer metastatic	0	0	0	1	1	0.03

Gastrointestinal cancer metastatic	0	0	0	1	1	0.03
Gastrointestinal tract adenoma	1	1	0.03	0	0	0
Haemangioma of liver	0	0	0	1	1	0.03
Hepatic cancer	0	0	0	2	2	0.05
Hepatic cancer metastatic	0	0	0	2	2	0.05
Hepatic neoplasm	1	1	0.03	0	0	0
Hepatocellular carcinoma	3	3	0.08	4	4	0.1
Intraductal proliferative breast lesion	3	3	0.08	2	2	0.05
Invasive ductal breast carcinoma	2	2	0.05	5	5	0.13
Leiomyoma	0	0	0	1	1	0.03
Leukaemia	0	0	0	1	1	0.03
Lipoma	1	1	0.03	3	3	0.08
Lung adenocarcinoma	0	0	0	1	1	0.03
Lung adenocarcinoma metastatic	1	1	0.03	2	2	0.05
Lung adenocarcinoma stage II	1	1	0.03	1	1	0.03
Lung adenocarcinoma stage IV	0	0	0	1	1	0.03
Lung cancer metastatic	0	0	0	1	1	0.03
Lung neoplasm malignant	2	2	0.05	0	0	0
Lymphoma	2	1	0.03	1	1	0.03
Malignant melanoma	1	1	0.03	3	2	0.05
Malignant melanoma in situ	1	1	0.03	0	0	0
Malignant peritoneal neoplasm	1	1	0.03	0	0	0
Meningioma benign	3	3	0.08	0	0	0
Mesothelioma malignant	1	1	0.03	0	0	0
Metastases to bone	0	0	0	1	1	0.03
Metastases to central nervous system	0	0	0	1	1	0.03
Metastases to liver	1	1	0.03	2	2	0.05
Metastases to lung	0	0	0	1	1	0.03
Metastases to lymph nodes	0	0	0	1	1	0.03
Metastatic neoplasm	0	0	0	1	1	0.03
Metastatic renal cell carcinoma	3	3	0.08	0	0	0
Metastatic squamous cell carcinoma	0	0	0	1	1	0.03
Mucinous endometrial carcinoma	0	0	0	1	1	0.03
Myelodysplastic syndrome	0	0	0	1	1	0.03
Neuroendocrine carcinoma metastatic	1	1	0.03	0	0	0
Non-small cell lung cancer	1	1	0.03	1	1	0.03
Non-small cell lung cancer metastatic	0	0	0	1	1	0.03
Non-small cell lung cancer stage I	0	0	0	1	1	0.03
Oesophageal adenocarcinoma	0	0	0	2	2	0.05
Oesophageal carcinoma	2	2	0.05	0	0	0
Ovarian cancer recurrent	1	1	0.03	0	0	0
Ovarian cancer stage IV	1	1	0.03	0	0	0
Pancreatic carcinoma	3	3	0.08	1	1	0.03
Pancreatic carcinoma metastatic	3	3	0.08	0	0	0
Pancreatic carcinoma stage IV	1	1	0.03	0	0	0
Papillary cystadenoma lymphomatosum	1	1	0.03	1	1	0.03
Papillary thyroid cancer	1	1	0.03	1	1	0.03
Parathyroid tumour benign	1	1	0.03	2	2	0.05
Penile squamous cell carcinoma	0	0	0	1	1	0.03
Phaeochromocytoma	1	1	0.03	0	0	0
Pituitary tumour benign	1	1	0.03	0	0	0
Plasma cell myeloma	3	3	0.08	0	0	0
Prostate cancer	**14**	**14**	**0.37**	**5**	**5**	**0.13**
Prostate cancer metastatic	0	0	0	2	2	0.05
Prostate cancer stage I	0	0	0	3	3	0.08
Prostate cancer stage II	1	1	0.03	0	0	0
Rectal adenocarcinoma	2	2	0.05	0	0	0

Rectal adenoma	1	1	0.03	0	0	0
Rectal cancer	1	1	0.03	2	2	0.05
Rectal cancer metastatic	1	1	0.03	0	0	0
Renal cancer	2	2	0.05	0	0	0
Renal cancer metastatic	1	1	0.03	1	1	0.03
Renal cell carcinoma	1	1	0.03	3	3	0.08
Salivary gland cancer	0	0	0	1	1	0.03
Seborrhoeic keratosis	1	1	0.03	2	2	0.05
Small cell lung cancer	2	2	0.05	1	1	0.03
Small cell lung cancer extensive stage	0	0	0	1	1	0.03
Small cell lung cancer metastatic	3	3	0.08	0	0	0
Soft tissue sarcoma	0	0	0	1	1	0.03
Squamous cell carcinoma	3	3	0.08	2	2	0.05
Squamous cell carcinoma of lung	2	2	0.05	1	1	0.03
Squamous cell carcinoma of skin	0	0	0	1	1	0.03
Squamous cell carcinoma of the tongue	0	0	0	2	2	0.05
Testicular seminoma (pure) stage I	0	0	0	1	1	0.03
Testis cancer	0	0	0	1	1	0.03
Thyroid cancer	1	1	0.03	0	0	0
Tonsil cancer	1	1	0.03	0	0	0
Transitional cell carcinoma	0	0	0	1	1	0.03
Tumour of ampulla of Vater	0	0	0	1	1	0.03
Ureteric cancer	0	0	0	1	1	0.03
Uterine cancer	2	2	0.05	1	1	0.03
Uterine leiomyoma	1	1	0.03	0	0	0

Table 79 – SAEs by system organ class and preferred terms-summary-FAS

		IDeg OD			IGlar OD		
SOC	PT	N	%	E	N	%	E
		3818			3819		
Blood and lymphatic system disorders	Anaemia	11	0.29	12	34	0.89	40
	Autoimmune haemolytic anaemia	0	0	0	1	0.03	1
	Coagulopathy	1	0.03	1	1	0.03	1
	Coombs negative haemolytic anaemia	0	0	0	1	0.03	1
	Evans syndrome	0	0	0	1	0.03	1
	Haemolytic anaemia	0	0	0	1	0.03	2
	Haemorrhagic anaemia	7	0.18	7	9	0.24	9
	Hypochromic anaemia	0	0	0	1	0.03	1
	Iron deficiency anaemia	3	0.08	3	4	0.1	4
	Leukocytosis	3	0.08	4	2	0.05	2
	Nephrogenic anaemia	1	0.03	1	0	0	0
	Neutropenia	1	0.03	1	3	0.08	3
	Normochromic normocytic anaemia	1	0.03	1	2	0.05	2
	Pancytopenia	0	0	0	1	0.03	1
	Thrombocytopenia	1	0.03	1	0	0	0
	All	29	0.76	31	61	1.6	68
Cardiac disorders	Acute coronary syndrome	11	0.29	12	8	0.21	8
	Acute left ventricular failure	7	0.18	7	6	0.16	6
	Acute myocardial infarction	98	2.57	111	115	3.01	123
	Angina pectoris	36	0.94	37	48	1.26	53
	Angina unstable	87	2.28	94	79	2.07	93
	Aortic valve disease	3	0.08	3	0	0	0
	Aortic valve stenosis	7	0.18	8	5	0.13	5
	Arrhythmia	1	0.03	1	5	0.13	5
	Arteriosclerosis coronary artery	4	0.1	4	7	0.18	7
	Arteriospasm coronary	1	0.03	1	0	0	0
	Atrial fibrillation	47	1.23	55	56	1.47	75
	Atrial flutter	11	0.29	11	6	0.16	6
	Atrial tachycardia	1	0.03	1	3	0.08	3
	Atrioventricular block	0	0	0	3	0.08	3
	Atrioventricular block complete	6	0.16	6	3	0.08	3
	Atrioventricular block first degree	2	0.05	2	0	0	0
	Atrioventricular block second degree	2	0.05	2	1	0.03	1
	Atrioventricular dissociation	0	0	0	2	0.05	2
	Bradycardia	8	0.21	9	9	0.24	9
	Bundle branch block left	2	0.05	2	0	0	0
	Bundle branch block right	0	0	0	1	0.03	1
	Cardiac arrest	26	0.68	26	20	0.52	21
	Cardiac discomfort	0	0	0	1	0.03	1
	Cardiac disorder	0	0	0	1	0.03	1
	Cardiac failure	24	0.63	26	30	0.79	33
	Cardiac failure acute	7	0.18	7	8	0.21	8
	Cardiac failure chronic	8	0.21	12	10	0.26	11
	Cardiac failure congestive	134	3.51	177	143	3.74	206
	Cardiac hypertrophy	0	0	0	1	0.03	1

	Cardiac ventricular thrombosis	1	0.03	1	1	0.03	1
	Cardiogenic shock	1	0.03	1	1	0.03	1
	Cardiomegaly	2	0.05	2	2	0.05	2
	Cardiomyopathy	4	0.1	4	7	0.18	7
	Cardiopulmonary failure	1	0.03	1	2	0.05	2
	Cardiorenal syndrome	1	0.03	1	0	0	0
	Cardio-respiratory arrest	12	0.31	12	9	0.24	9
	Cardiovascular disorder	0	0	0	1	0.03	1
	Chordae tendinae rupture	0	0	0	1	0.03	1
	Chronic left ventricular failure	0	0	0	1	0.03	1
	Congestive cardiomyopathy	3	0.08	3	0	0	0
	Cor pulmonale	1	0.03	1	2	0.05	2
	Cor pulmonale acute	1	0.03	1	0	0	0
	Coronary artery disease	80	2.1	85	89	2.33	91
	Coronary artery dissection	1	0.03	1	0	0	0
	Coronary artery embolism	0	0	0	1	0.03	1
	Coronary artery insufficiency	1	0.03	1	1	0.03	1
	Coronary artery occlusion	12	0.31	12	5	0.13	6
	Coronary artery stenosis	12	0.31	12	5	0.13	5
	Coronary ostial stenosis	1	0.03	1	0	0	0
	Diastolic dysfunction	1	0.03	1	0	0	0
	Heart valve incompetence	0	0	0	1	0.03	1
	Hypertensive cardiomyopathy	0	0	0	1	0.03	1
	Hypertensive heart disease	1	0.03	1	4	0.1	4
	Intracardiac thrombus	1	0.03	1	0	0	0
	Ischaemic cardiomyopathy	3	0.08	3	7	0.18	7
	Left ventricular dysfunction	1	0.03	1	3	0.08	3
	Left ventricular failure	6	0.16	7	3	0.08	3
	Left ventricular hypertrophy	1	0.03	1	0	0	0
	Long QT syndrome	0	0	0	1	0.03	1
	Mitral valve incompetence	2	0.05	2	2	0.05	2
	Myocardial infarction	48	1.26	51	66	1.73	68
	Myocardial ischaemia	7	0.18	7	9	0.24	9
	Nodal arrhythmia	1	0.03	1	1	0.03	1
	Palpitations	1	0.03	1	1	0.03	1
	Pericardial effusion	1	0.03	1	2	0.05	2
	Pericarditis	1	0.03	1	1	0.03	1
	Prinzmetal angina	0	0	0	1	0.03	1
	Pulseless electrical activity	1	0.03	1	0	0	0
	Restrictive cardiomyopathy	0	0	0	1	0.03	1
	Right ventricular failure	2	0.05	2	2	0.05	2
	Silent myocardial infarction	4	0.1	4	2	0.05	2
	Sinus arrest	0	0	0	1	0.03	1
	Sinus bradycardia	1	0.03	1	3	0.08	3
	Sinus node dysfunction	6	0.16	6	5	0.13	5
	Sinus tachycardia	1	0.03	1	0	0	0
	Stress cardiomyopathy	1	0.03	1	0	0	0
	Supraventricular tachycardia	4	0.1	4	4	0.1	4
	Systolic dysfunction	1	0.03	1	0	0	0
	Tachyarrhythmia	0	0	0	1	0.03	1
	Tachycardia	1	0.03	1	5	0.13	5
	Tricuspid valve incompetence	1	0.03	1	1	0.03	1
	Trifascicular block	0	0	0	2	0.05	2
	Ventricular arrhythmia	1	0.03	1	0	0	0
	Ventricular extrasystoles	0	0	0	2	0.05	2
	Ventricular fibrillation	6	0.16	7	5	0.13	5
	Ventricular hypokinesia	1	0.03	1	1	0.03	1

	Ventricular tachycardia	8	0.21	9	12	0.31	16
	All	781	20.46	873	849	22.23	972
Congenital, familial and genetic disorders	Congenital ureterocele	1	0.03	1	0	0	0
	Factor V deficiency	0	0	0	1	0.03	1
	Gastrointestinal arteriovenous malformation	0	0	0	1	0.03	1
	Haemorrhagic arteriovenous malformation	0	0	0	2	0.05	2
	Hypertrophic cardiomyopathy	0	0	0	1	0.03	1
	Osteogenesis imperfecta	0	0	0	1	0.03	1
	Phimosis	0	0	0	2	0.05	2
	All	1	0.03	1	8	0.21	8
Ear and labyrinth disorders	Deafness neurosensory	1	0.03	1	0	0	0
	Inner ear disorder	0	0	0	1	0.03	1
	Meniere's disease	1	0.03	1	0	0	0
	Sudden hearing loss	1	0.03	1	0	0	0
	Vertigo	5	0.13	5	3	0.08	3
	Vertigo positional	1	0.03	1	3	0.08	3
	Vestibular disorder	0	0	0	1	0.03	1
	All	9	0.24	9	8	0.21	8
Endocrine disorders	Adrenal insufficiency	1	0.03	1	0	0	0
	Goitre	1	0.03	1	1	0.03	1
	Hypothyroidism	2	0.05	2	0	0	0
	Thyroid mass	2	0.05	2	0	0	0
	Toxic goitre	0	0	0	1	0.03	1
	Toxic nodular goitre	0	0	0	1	0.03	1
	All	6	0.16	6	3	0.08	3
Eye disorders	Blindness	0	0	0	2	0.05	2
	Cataract	9	0.24	13	3	0.08	4
	Cataract diabetic	1	0.03	1	0	0	0
	Diabetic retinopathy	4	0.1	4	1	0.03	1
	Glaucoma	1	0.03	1	1	0.03	1
	Macular fibrosis	1	0.03	1	2	0.05	2
	Neurotrophic keratopathy	0	0	0	1	0.03	1
	Optic ischaemic neuropathy	1	0.03	1	0	0	0
	Pterygium	0	0	0	1	0.03	1
	Retinal artery occlusion	1	0.03	1	0	0	0
	Retinal detachment	1	0.03	1	1	0.03	1
	Retinal vein occlusion	1	0.03	1	0	0	0
	Retinopathy	0	0	0	1	0.03	1
	Retinopathy proliferative	1	0.03	1	0	0	0
	Visual impairment	0	0	0	1	0.03	1
	Vitreous haemorrhage	0	0	0	2	0.05	2
	All	21	0.55	25	16	0.42	17
Gastrointestinal disorders	Abdominal discomfort	0	0	0	1	0.03	1
	Abdominal hernia	1	0.03	1	1	0.03	1
	Abdominal hernia obstructive	0	0	0	2	0.05	2
	Abdominal mass	1	0.03	1	0	0	0
	Abdominal pain	10	0.26	10	10	0.26	10
	Abdominal pain upper	3	0.08	3	1	0.03	1
	Abdominal wall haematoma	1	0.03	1	0	0	0
	Acid peptic disease	0	0	0	1	0.03	1
	Acute abdomen	0	0	0	1	0.03	1
	Alcoholic pancreatitis	1	0.03	1	0	0	0

	Appendix disorder	0	0	0	1	0.03	1
	Ascites	0	0	0	1	0.03	1
	Barrett's oesophagus	1	0.03	1	1	0.03	1
	Chronic gastritis	1	0.03	1	2	0.05	2
	Colitis	6	0.16	6	6	0.16	6
	Colitis ischaemic	3	0.08	6	2	0.05	2
	Constipation	4	0.1	4	0	0	0
	Crohn's disease	1	0.03	1	2	0.05	2
	Diabetic gastroparesis	1	0.03	1	2	0.05	2
	Diarrhoea	11	0.29	14	3	0.08	3
	Diverticular perforation	1	0.03	1	0	0	0
	Diverticulum	5	0.13	5	0	0	0
	Diverticulum intestinal	2	0.05	2	0	0	0
	Diverticulum intestinal haemorrhagic	0	0	0	1	0.03	1
	Duodenal stenosis	0	0	0	1	0.03	1
	Duodenal ulcer	1	0.03	1	1	0.03	1
	Duodenal ulcer haemorrhage	0	0	0	1	0.03	1
	Duodenal vascular ectasia	1	0.03	1	0	0	0
	Duodenitis	1	0.03	1	0	0	0
	Dysphagia	0	0	0	3	0.08	3
	Enteritis	1	0.03	1	0	0	0
	Enterocele	1	0.03	1	0	0	0
	Epigastric discomfort	1	0.03	1	0	0	0
	Erosive duodenitis	0	0	0	1	0.03	1
	Gastric antral vascular ectasia	0	0	0	1	0.03	1
	Gastric perforation	1	0.03	1	1	0.03	1
	Gastric ulcer	2	0.05	2	3	0.08	3
	Gastric ulcer haemorrhage	1	0.03	2	0	0	0
	Gastric ulcer perforation	0	0	0	1	0.03	2
	Gastritis	8	0.21	8	6	0.16	7
	Gastritis erosive	2	0.05	2	0	0	0
	Gastroduodenitis haemorrhagic	1	0.03	1	0	0	0
	Gastrointestinal angiodysplasia	1	0.03	1	0	0	0
	Gastrointestinal haemorrhage	10	0.26	10	15	0.39	16
	Gastrointestinal polyp haemorrhage	1	0.03	1	1	0.03	1
	Gastrointestinal ulcer haemorrhage	0	0	0	2	0.05	2
	Gastrooesophageal reflux disease	6	0.16	7	9	0.24	10
	Haematochezia	1	0.03	2	4	0.1	4
	Haemorrhoidal haemorrhage	0	0	0	1	0.03	1
	Haemorrhoids	4	0.1	4	1	0.03	1
	Hiatus hernia	0	0	0	2	0.05	2
	Ileus	2	0.05	2	0	0	0
	Ileus paralytic	0	0	0	1	0.03	1
	Impaired gastric emptying	4	0.1	5	7	0.18	9
	Inguinal hernia	3	0.08	3	4	0.1	4
	Intestinal ischaemia	2	0.05	2	1	0.03	1
	Intestinal obstruction	4	0.1	4	2	0.05	2
	Intestinal perforation	0	0	0	2	0.05	2
	Intra-abdominal haematoma	1	0.03	1	0	0	0
	Irritable bowel syndrome	0	0	0	1	0.03	1
	Large intestinal haemorrhage	0	0	0	1	0.03	1

	Large intestinal ulcer haemorrhage	0	0	0	1	0.03	1
	Large intestine polyp	4	0.1	4	3	0.08	3
	Lower gastrointestinal haemorrhage	3	0.08	3	3	0.08	3
	Mallory-Weiss syndrome	0	0	0	1	0.03	1
	Mesenteric haematoma	1	0.03	1	0	0	0
	Nausea	2	0.05	2	2	0.05	2
	Neutropenic colitis	0	0	0	1	0.03	1
	Oesophageal rupture	0	0	0	1	0.03	1
	Oesophageal ulcer haemorrhage	1	0.03	1	1	0.03	1
	Oesophageal varices haemorrhage	0	0	0	1	0.03	1
	Oesophagitis	2	0.05	2	2	0.05	2
	Pancreatic mass	1	0.03	1	0	0	0
	Pancreatitis	7	0.18	8	5	0.13	5
	Pancreatitis acute	6	0.16	7	11	0.29	16
	Pancreatitis chronic	1	0.03	1	2	0.05	2
	Peptic ulcer	2	0.05	2	1	0.03	2
	Peptic ulcer perforation	1	0.03	1	0	0	0
	Periodontal disease	1	0.03	1	0	0	0
	Pneumatosis intestinalis	0	0	0	1	0.03	1
	Rectal haemorrhage	1	0.03	1	3	0.08	3
	Rectal ulcer haemorrhage	1	0.03	1	0	0	0
	Salivary gland calculus	1	0.03	1	0	0	0
	Salivary gland mass	1	0.03	1	0	0	0
	Small intestinal obstruction	9	0.24	10	6	0.16	6
	Spigelian hernia	1	0.03	1	0	0	0
	Umbilical hernia	1	0.03	1	2	0.05	2
	Upper gastrointestinal haemorrhage	0	0	0	8	0.21	8
	Varices oesophageal	0	0	0	1	0.03	1
	Vomiting	5	0.13	5	7	0.18	7
	All	165	4.32	178	174	4.56	186
General disorders and administration site conditions	Asthenia	3	0.08	3	5	0.13	5
	Cardiac complication associated with device	1	0.03	1	0	0	0
	Cardiac death	1	0.03	1	2	0.05	2
	Catheter site haematoma	0	0	0	1	0.03	1
	Chest discomfort	2	0.05	2	5	0.13	5
	Chest pain	16	0.42	16	21	0.55	22
	Complication associated with device	1	0.03	1	0	0	0
	Cyst	1	0.03	1	1	0.03	1
	Death	27	0.71	27	21	0.55	21
	Fatigue	1	0.03	1	1	0.03	1
	Foreign body reaction	1	0.03	1	0	0	0
	Gait disturbance	1	0.03	1	1	0.03	1
	Generalised oedema	4	0.1	4	3	0.08	3
	Impaired healing	1	0.03	1	2	0.05	2
	Local swelling	1	0.03	1	0	0	0
	Medical device site haemorrhage	0	0	0	1	0.03	1
	Multiple organ dysfunction	1	0.03	1	2	0.05	2

	syndrome						
	Non-cardiac chest pain	47	1.23	48	54	1.41	63
	Oedema	0	0	0	3	0.08	4
	Oedema due to cardiac disease	1	0.03	1	0	0	0
	Oedema peripheral	4	0.1	4	4	0.1	4
	Pain	2	0.05	2	0	0	0
	Peripheral swelling	1	0.03	1	2	0.05	2
	Polyp	1	0.03	1	0	0	0
	Pyrexia	1	0.03	1	1	0.03	1
	Sudden cardiac death	1	0.03	1	3	0.08	3
	Sudden death	1	0.03	1	8	0.21	8
	Surgical failure	1	0.03	1	0	0	0
	Systemic inflammatory response syndrome	2	0.05	2	3	0.08	3
	Vascular stent restenosis	3	0.08	3	2	0.05	3
	Vascular stent stenosis	1	0.03	1	0	0	0
	Vascular stent thrombosis	1	0.03	1	0	0	0
	All	129	3.38	130	146	3.82	158
Hepatobiliary disorders	Acute hepatic failure	1	0.03	1	1	0.03	1
	Alcoholic liver disease	1	0.03	1	0	0	0
	Bile duct obstruction	0	0	0	2	0.05	2
	Bile duct stone	1	0.03	1	1	0.03	1
	Biliary dyskinesia	0	0	0	1	0.03	1
	Cholangitis	1	0.03	1	2	0.05	2
	Cholecystitis	8	0.21	8	4	0.1	4
	Cholecystitis acute	6	0.16	6	4	0.1	4
	Cholecystitis chronic	3	0.08	3	5	0.13	5
	Cholelithiasis	8	0.21	8	8	0.21	8
	Chronic hepatic failure	0	0	0	1	0.03	1
	Dilatation intrahepatic duct acquired	0	0	0	1	0.03	1
	Hepatic cirrhosis	3	0.08	3	1	0.03	1
	Hepatic failure	1	0.03	1	0	0	0
	Hepatic lesion	0	0	0	1	0.03	1
	Hepatitis chronic active	1	0.03	1	0	0	0
	Hepatorenal failure	0	0	0	1	0.03	1
	Hepatorenal syndrome	0	0	0	1	0.03	1
	Ischaemic hepatitis	0	0	0	1	0.03	1
	Jaundice	0	0	0	1	0.03	1
	Jaundice cholestatic	1	0.03	1	0	0	0
	Liver disorder	1	0.03	1	1	0.03	1
	Non-alcoholic steatohepatitis	0	0	0	1	0.03	1
	Portal vein thrombosis	1	0.03	1	0	0	0
	Sphincter of Oddi dysfunction	1	0.03	1	0	0	0
	Steatohepatitis	1	0.03	1	0	0	0
	All	39	1.02	39	38	1	38
Immune system disorders	Anaphylactic reaction	0	0	0	1	0.03	1
	Anaphylactic shock	1	0.03	1	0	0	0
	Drug hypersensitivity	1	0.03	1	2	0.05	2
	Renal transplant failure	1	0.03	1	0	0	0
	All	3	0.08	3	3	0.08	3
Infections and infestations	Abdominal abscess	0	0	0	1	0.03	1
	Abdominal sepsis	1	0.03	1	0	0	0

	Abdominal wall abscess	2	0.05	2	1	0.03	1
	Abdominal wall infection	1	0.03	1	0	0	0
	Abscess limb	0	0	0	5	0.13	5
	Abscess rupture	0	0	0	1	0.03	1
	Abscess soft tissue	0	0	0	1	0.03	1
	Acute endocarditis	1	0.03	1	0	0	0
	Appendicitis	4	0.1	4	6	0.16	6
	Arteriosclerotic gangrene	0	0	0	1	0.03	1
	Arthritis bacterial	4	0.1	4	3	0.08	3
	Bacteraemia	0	0	0	1	0.03	1
	Bacterial infection	1	0.03	1	0	0	0
	Bacterial pyelonephritis	1	0.03	1	0	0	0
	Bacterial sepsis	0	0	0	1	0.03	1
	Beta haemolytic streptococcal infection	1	0.03	1	2	0.05	2
	Bronchitis	16	0.42	17	21	0.55	21
	Bronchitis bacterial	1	0.03	1	1	0.03	1
	Bronchitis viral	2	0.05	2	2	0.05	2
	Catheter site infection	1	0.03	1	0	0	0
	Cellulitis	52	1.36	64	61	1.6	72
	Cellulitis orbital	0	0	0	1	0.03	1
	Cellulitis staphylococcal	1	0.03	1	2	0.05	2
	Cellulitis streptococcal	1	0.03	1	0	0	0
	Chest wall abscess	1	0.03	1	0	0	0
	Cholecystitis infective	1	0.03	1	1	0.03	1
	Clostridium difficile colitis	8	0.21	8	4	0.1	4
	Clostridium difficile infection	0	0	0	1	0.03	1
	Colonic abscess	0	0	0	1	0.03	1
	Conjunctivitis	1	0.03	1	0	0	0
	Cystitis	1	0.03	1	3	0.08	3
	Dengue fever	3	0.08	3	0	0	0
	Dermatitis infected	1	0.03	1	0	0	0
	Device related infection	3	0.08	3	1	0.03	1
	Diabetic foot infection	4	0.1	4	8	0.21	8
	Diabetic gangrene	0	0	0	2	0.05	2
	Disseminated cryptococcosis	1	0.03	1	0	0	0
	Diverticulitis	11	0.29	13	14	0.37	14
	Dysentery	1	0.03	1	0	0	0
	Eczema infected	0	0	0	2	0.05	2
	Empyema	1	0.03	1	0	0	0
	Endocarditis	0	0	0	1	0.03	1
	Epiglottitis	1	0.03	1	0	0	0
	Erysipelas	0	0	0	1	0.03	1
	Escherichia sepsis	2	0.05	2	2	0.05	2
	Escherichia urinary tract infection	1	0.03	1	0	0	0
	External ear cellulitis	1	0.03	1	0	0	0
	Extradural abscess	0	0	0	2	0.05	2
	Gangrene	5	0.13	5	13	0.34	16
	Gas gangrene	1	0.03	2	0	0	0
	Gastroenteritis	13	0.34	13	12	0.31	12
	Gastroenteritis Escherichia coli	0	0	0	1	0.03	1
	Gastroenteritis viral	2	0.05	2	7	0.18	7
	Graft infection	0	0	0	1	0.03	1
	Groin abscess	1	0.03	1	0	0	0
	H1N1 influenza	0	0	0	1	0.03	1
	Helicobacter gastritis	1	0.03	1	0	0	0

	Herpes zoster	3	0.08	3	0	0	0
	Incision site infection	1	0.03	1	1	0.03	1
	Infected bite	0	0	0	1	0.03	1
	Infected dermal cyst	1	0.03	1	0	0	0
	Infected seroma	0	0	0	1	0.03	1
	Infected skin ulcer	3	0.08	3	2	0.05	2
	Infectious colitis	0	0	0	2	0.05	2
	Influenza	5	0.13	5	3	0.08	3
	Infusion site infection	0	0	0	1	0.03	2
	Intervertebral discitis	0	0	0	1	0.03	1
	Joint abscess	1	0.03	1	0	0	0
	Klebsiella sepsis	0	0	0	1	0.03	1
	Labyrinthitis	2	0.05	2	0	0	0
	Liver abscess	0	0	0	1	0.03	1
	Localised infection	4	0.1	4	3	0.08	3
	Lower respiratory tract infection	2	0.05	2	3	0.08	3
	Lyme disease	0	0	0	1	0.03	1
	Meningitis aseptic	1	0.03	1	0	0	0
	Meningitis viral	1	0.03	1	0	0	0
	Mucormycosis	1	0.03	1	0	0	0
	Necrotising fasciitis	1	0.03	1	0	0	0
	Oesophageal candidiasis	0	0	0	3	0.08	3
	Oral candidiasis	0	0	0	1	0.03	1
	Orchitis	0	0	0	2	0.05	2
	Osteomyelitis	20	0.52	26	22	0.58	23
	Osteomyelitis acute	1	0.03	1	1	0.03	1
	Osteomyelitis chronic	3	0.08	3	4	0.1	4
	Otitis externa	1	0.03	1	1	0.03	2
	Otitis media chronic	1	0.03	1	0	0	0
	Paraspinal abscess	1	0.03	1	0	0	0
	Paronychia	1	0.03	1	1	0.03	1
	Perineal abscess	1	0.03	1	0	0	0
	Perirectal abscess	0	0	0	2	0.05	2
	Peritoneal abscess	0	0	0	1	0.03	1
	Peritonitis	2	0.05	2	0	0	0
	Peritonitis bacterial	0	0	0	1	0.03	1
	Pharyngitis	0	0	0	1	0.03	1
	Pilonidal cyst	0	0	0	1	0.03	1
	Pneumonia	90	2.36	99	90	2.36	102
	Pneumonia bacterial	2	0.05	2	4	0.1	4
	Pneumonia influenzal	0	0	0	2	0.05	2
	Pneumonia klebsiella	0	0	0	2	0.05	2
	Pneumonia mycoplasmal	1	0.03	1	0	0	0
	Pneumonia pneumococcal	0	0	0	1	0.03	1
	Pneumonia pseudomonal	1	0.03	1	2	0.05	2
	Pneumonia staphylococcal	1	0.03	1	2	0.05	2
	Pneumonia streptococcal	2	0.05	2	0	0	0
	Pneumonia viral	0	0	0	1	0.03	1
	Post procedural cellulitis	1	0.03	1	0	0	0
	Post procedural infection	8	0.21	8	2	0.05	2
	Post procedural sepsis	0	0	0	1	0.03	1
	Postoperative abscess	3	0.08	3	0	0	0
	Postoperative wound infection	11	0.29	12	2	0.05	2
	Prostate infection	0	0	0	1	0.03	1
	Prostatitis Escherichia coli	0	0	0	1	0.03	1
	Pseudomonal bacteraemia	0	0	0	1	0.03	1

	Pulmonary sepsis	2	0.05	2	4	0.1	4
	Pyelonephritis	2	0.05	2	11	0.29	11
	Pyelonephritis acute	4	0.1	4	1	0.03	1
	Pyuria	0	0	0	1	0.03	1
	Rectal abscess	1	0.03	1	1	0.03	1
	Renal abscess	0	0	0	1	0.03	1
	Respiratory syncytial virus bronchitis	0	0	0	1	0.03	1
	Respiratory tract infection	2	0.05	2	1	0.03	1
	Respiratory tract infection viral	0	0	0	1	0.03	1
	Salpingitis	1	0.03	1	0	0	0
	Sepsis	36	0.94	37	31	0.81	31
	Sepsis pasteurella	1	0.03	1	0	0	0
	Sepsis syndrome	1	0.03	1	0	0	0
	Septic arthritis staphylococcal	1	0.03	1	1	0.03	1
	Septic embolus	0	0	0	1	0.03	1
	Septic shock	11	0.29	11	12	0.31	13
	Sialoadenitis	1	0.03	1	0	0	0
	Sinusitis	2	0.05	2	2	0.05	2
	Soft tissue infection	2	0.05	2	0	0	0
	Staphylococcal abscess	0	0	0	2	0.05	2
	Staphylococcal bacteraemia	0	0	0	2	0.05	2
	Staphylococcal infection	3	0.08	3	5	0.13	6
	Staphylococcal sepsis	2	0.05	2	5	0.13	5
	Streptococcal bacteraemia	0	0	0	3	0.08	3
	Streptococcal sepsis	3	0.08	3	0	0	0
	Subcutaneous abscess	1	0.03	1	3	0.08	3
	Subdiaphragmatic abscess	1	0.03	1	0	0	0
	Tooth abscess	0	0	0	1	0.03	1
	Tracheobronchitis	0	0	0	2	0.05	2
	Tuberculosis	0	0	0	1	0.03	1
	Upper respiratory tract infection	5	0.13	5	5	0.13	5
	Urinary tract infection	34	0.89	37	30	0.79	37
	Urinary tract infection bacterial	0	0	0	2	0.05	3
	Urosepsis	10	0.26	11	9	0.24	9
	Viraemia	1	0.03	1	0	0	0
	Viral infection	1	0.03	1	3	0.08	3
	Viral pericarditis	1	0.03	1	0	0	0
	Vulval abscess	1	0.03	1	1	0.03	1
	Wound infection	2	0.05	2	4	0.1	4
	All	464	12.15	501	510	13.35	549
Injury, poisoning and procedural complications	Accident at work	0	0	0	2	0.05	2
	Accidental overdose	2	0.05	2	3	0.08	3
	Alcohol poisoning	2	0.05	2	0	0	0
	Anaemia postoperative	1	0.03	1	0	0	0
	Anaesthetic complication	1	0.03	1	0	0	0
	Anaesthetic complication pulmonary	0	0	0	1	0.03	1
	Anastomotic ulcer	0	0	0	1	0.03	1
	Animal bite	0	0	0	1	0.03	1
	Ankle fracture	2	0.05	2	5	0.13	5
	Brachial plexus injury	0	0	0	1	0.03	1
	Burns third degree	0	0	0	1	0.03	1
	Cardiac valve replacement	1	0.03	1	0	0	0

	complication						
	Cervical vertebral fracture	0	0	0	1	0.03	1
	Clavicle fracture	1	0.03	1	0	0	0
	Concussion	1	0.03	1	0	0	0
	Contusion	1	0.03	2	0	0	0
	Coronary artery restenosis	2	0.05	2	1	0.03	1
	Coronary vascular graft occlusion	2	0.05	2	1	0.03	1
	Craniocerebral injury	1	0.03	1	1	0.03	1
	Drug administration error	1	0.03	1	0	0	0
	Extra dose administered	0	0	0	1	0.03	1
	Eye injury	0	0	0	1	0.03	1
	Facial bones fracture	0	0	0	2	0.05	2
	Fall	54	1.41	57	55	1.44	59
	Femoral neck fracture	0	0	0	2	0.05	2
	Femur fracture	3	0.08	3	5	0.13	5
	Fibula fracture	0	0	0	1	0.03	1
	Foot fracture	2	0.05	2	4	0.1	4
	Fracture	1	0.03	1	0	0	0
	Gastrointestinal anastomotic leak	0	0	0	1	0.03	1
	Gastrointestinal injury	1	0.03	1	0	0	0
	Gastrointestinal stoma complication	1	0.03	1	0	0	0
	Gastrostomy tube site complication	1	0.03	1	0	0	0
	Hand fracture	1	0.03	1	0	0	0
	Hip fracture	1	0.03	1	3	0.08	3
	Humerus fracture	1	0.03	1	2	0.05	2
	Ilium fracture	1	0.03	1	0	0	0
	Incarcerated incisional hernia	0	0	0	1	0.03	1
	Incision site haemorrhage	1	0.03	1	0	0	0
	Incisional hernia	1	0.03	1	0	0	0
	Injury	0	0	0	1	0.03	1
	Intentional overdose	0	0	0	1	0.03	1
	Joint dislocation	2	0.05	2	2	0.05	2
	Laceration	3	0.08	3	4	0.1	4
	Ligament rupture	1	0.03	1	0	0	0
	Limb injury	0	0	0	1	0.03	1
	Lower limb fracture	2	0.05	2	0	0	0
	Meniscus injury	1	0.03	1	2	0.05	2
	Multiple fractures	1	0.03	1	0	0	0
	Multiple injuries	0	0	0	1	0.03	1
	Muscle strain	1	0.03	1	1	0.03	1
	Overdose	1	0.03	1	2	0.05	2
	Pelvic fracture	0	0	0	3	0.08	3
	Pneumothorax traumatic	1	0.03	1	0	0	0
	Post concussion syndrome	1	0.03	1	0	0	0
	Post procedural complication	1	0.03	1	2	0.05	2
	Post procedural haematoma	2	0.05	2	0	0	0
	Post procedural haemorrhage	5	0.13	5	2	0.05	2
	Post procedural myocardial infarction	2	0.05	2	0	0	0
	Postoperative fever	1	0.03	1	0	0	0
	Postoperative ileus	1	0.03	1	0	0	0
	Postoperative respiratory failure	2	0.05	2	1	0.03	1

	Postoperative thoracic procedure complication	0	0	0	1	0.03	1
	Postoperative wound complication	0	0	0	1	0.03	1
	Procedural complication	0	0	0	1	0.03	1
	Procedural haemorrhage	0	0	0	1	0.03	1
	Procedural hypotension	1	0.03	1	0	0	0
	Procedural intestinal perforation	1	0.03	1	0	0	0
	Pulmonary contusion	0	0	0	1	0.03	1
	Radius fracture	2	0.05	2	0	0	0
	Rib fracture	4	0.1	4	2	0.05	2
	Road traffic accident	20	0.52	21	18	0.47	18
	Seroma	0	0	0	1	0.03	1
	Spinal compression fracture	1	0.03	1	1	0.03	1
	Spinal fracture	0	0	0	1	0.03	1
	Stab wound	1	0.03	1	0	0	0
	Stoma site reaction	1	0.03	1	0	0	0
	Stress fracture	1	0.03	1	0	0	0
	Subdural haematoma	5	0.13	5	4	0.1	4
	Subdural haemorrhage	0	0	0	1	0.03	1
	Tendon rupture	1	0.03	1	1	0.03	1
	Thermal burn	2	0.05	2	0	0	0
	Thoracic vertebral fracture	1	0.03	1	0	0	0
	Tibia fracture	0	0	0	2	0.05	2
	Toxicity to various agents	1	0.03	1	1	0.03	1
	Transfusion-related acute lung injury	0	0	0	1	0.03	1
	Traumatic haematoma	0	0	0	1	0.03	1
	Upper limb fracture	0	0	0	2	0.05	2
	Ureteric injury	1	0.03	1	0	0	0
	Vascular procedure complication	0	0	0	1	0.03	1
	Vascular pseudoaneurysm	1	0.03	1	0	0	0
	Wound	0	0	0	2	0.05	2
	Wrist fracture	0	0	0	2	0.05	2
	Wrong drug administered	1	0.03	1	0	0	0
	All	160	4.19	165	166	4.35	170
Investigations	Arteriogram coronary	2	0.05	2	2	0.05	2
	Biopsy lung	0	0	0	1	0.03	1
	Blood creatine phosphokinase increased	1	0.03	1	1	0.03	1
	Blood creatinine increased	1	0.03	1	0	0	0
	Blood glucose decreased	0	0	0	1	0.03	1
	Blood glucose increased	1	0.03	1	2	0.05	2
	Blood magnesium decreased	1	0.03	1	0	0	0
	Blood potassium decreased	2	0.05	2	1	0.03	1
	Blood potassium increased	0	0	0	1	0.03	1
	Blood pressure increased	1	0.03	1	0	0	0
	Cardiac monitoring	0	0	0	1	0.03	1
	Catheterisation cardiac	1	0.03	1	0	0	0
	Coagulation time prolonged	1	0.03	1	0	0	0
	Ejection fraction decreased	1	0.03	1	0	0	0
	Electrocardiogram ST segment abnormal	0	0	0	1	0.03	1
	Electrocardiogram ST segment elevation	1	0.03	1	0	0	0

	Electrocardiogram ST-T change	0	0	0	1	0.03	1
	Hepatic enzyme increased	0	0	0	1	0.03	1
	International normalised ratio increased	0	0	0	2	0.05	2
	Medical observation	1	0.03	1	0	0	0
	Troponin increased	1	0.03	1	2	0.05	2
	Weight decreased	1	0.03	1	0	0	0
	All	16	0.42	16	17	0.45	17
Metabolism and nutrition disorders	Decreased appetite	1	0.03	1	1	0.03	1
	Dehydration	23	0.6	23	16	0.42	16
	Diabetes mellitus	1	0.03	1	4	0.1	4
	Diabetes mellitus inadequate control	5	0.13	5	4	0.1	4
	Diabetic complication	0	0	0	1	0.03	1
	Diabetic ketoacidosis	5	0.13	5	14	0.37	14
	Diabetic metabolic decompensation	2	0.05	2	2	0.05	2
	Electrolyte imbalance	2	0.05	2	1	0.03	1
	Failure to thrive	1	0.03	1	0	0	0
	Fluid overload	4	0.1	5	2	0.05	5
	Gout	4	0.1	4	7	0.18	7
	Hyperammonaemia	1	0.03	2	0	0	0
	Hyperglycaemia	11	0.29	12	16	0.42	16
	Hyperkalaemia	18	0.47	21	22	0.58	24
	Hypernatraemia	0	0	0	1	0.03	1
	Hypoglycaemia	64	1.68	77	49	1.28	66
	Hypokalaemia	3	0.08	3	5	0.13	5
	Hypomagnesaemia	1	0.03	1	0	0	0
	Hyponatraemia	8	0.21	8	7	0.18	7
	Hypovolaemia	2	0.05	2	2	0.05	3
	Lactic acidosis	1	0.03	1	2	0.05	2
	Metabolic acidosis	3	0.08	3	1	0.03	1
	Obesity	3	0.08	3	1	0.03	1
	Pseudohyponatraemia	0	0	0	1	0.03	1
	Type 2 diabetes mellitus	1	0.03	1	1	0.03	1
	All	164	4.3	183	160	4.19	183
Musculoskeletal and connective tissue disorders	Ankle deformity	0	0	0	1	0.03	1
	Arthralgia	5	0.13	6	8	0.21	9
	Arthritis	3	0.08	3	7	0.18	8
	Arthropathy	2	0.05	2	0	0	0
	Back disorder	0	0	0	1	0.03	1
	Back pain	7	0.18	7	12	0.31	12
	Bursitis	0	0	0	3	0.08	3
	Cervical spinal stenosis	5	0.13	5	3	0.08	3
	Chondrocalcinosis pyrophosphate	0	0	0	2	0.05	2
	Costochondritis	2	0.05	2	0	0	0
	Dactylitis	1	0.03	1	0	0	0
	Enthesopathy	1	0.03	1	0	0	0
	Exostosis	1	0.03	1	0	0	0
	Flank pain	1	0.03	1	2	0.05	2
	Foot deformity	1	0.03	1	0	0	0
	Gouty arthritis	2	0.05	2	2	0.05	2

	Haemarthrosis	0	0	0	1	0.03	1
	Intervertebral disc degeneration	4	0.1	4	4	0.1	4
	Intervertebral disc disorder	1	0.03	1	1	0.03	1
	Intervertebral disc protrusion	9	0.24	9	3	0.08	3
	Joint effusion	0	0	0	1	0.03	1
	Lumbar spinal stenosis	12	0.31	13	7	0.18	7
	Muscle spasms	1	0.03	1	2	0.05	2
	Muscular weakness	4	0.1	4	4	0.1	4
	Musculoskeletal chest pain	3	0.08	3	6	0.16	6
	Musculoskeletal pain	3	0.08	3	3	0.08	3
	Myopathy	0	0	0	1	0.03	1
	Neck pain	2	0.05	2	1	0.03	1
	Osteitis	1	0.03	1	0	0	0
	Osteoarthritis	32	0.84	35	30	0.79	31
	Osteonecrosis	0	0	0	1	0.03	1
	Osteopenia	1	0.03	1	0	0	0
	Osteoporosis	1	0.03	2	0	0	0
	Pain in extremity	3	0.08	3	3	0.08	3
	Polyarthritis	2	0.05	2	0	0	0
	Polymyalgia rheumatica	0	0	0	1	0.03	1
	Pseudarthrosis	0	0	0	1	0.03	1
	Rhabdomyolysis	4	0.1	4	4	0.1	4
	Rotator cuff syndrome	2	0.05	2	2	0.05	3
	Soft tissue necrosis	0	0	0	1	0.03	1
	Spinal column stenosis	4	0.1	4	4	0.1	4
	Spinal osteoarthritis	3	0.08	3	2	0.05	2
	Spondylitis	0	0	0	1	0.03	1
	Spondylolisthesis	2	0.05	2	2	0.05	2
	Synovial cyst	0	0	0	1	0.03	1
	Tendon disorder	1	0.03	1	0	0	0
	Tendonitis	1	0.03	1	1	0.03	1
	Vertebral foraminal stenosis	1	0.03	1	1	0.03	1
	All	128	3.35	134	130	3.4	134
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Acute leukaemia	1	0.03	1	0	0	0
	Acute lymphocytic leukaemia	1	0.03	1	0	0	0
	Acute myeloid leukaemia	0	0	0	1	0.03	1
	Adenocarcinoma	0	0	0	1	0.03	1
	Adenocarcinoma gastric	2	0.05	2	1	0.03	1
	Adenocarcinoma of colon	2	0.05	2	5	0.13	5
	Adenocarcinoma pancreas	0	0	0	1	0.03	1
	Adrenal adenoma	0	0	0	1	0.03	1
	Adrenal neoplasm	0	0	0	1	0.03	1
	Adult T-cell lymphoma/leukaemia	1	0.03	1	0	0	0
	Basal cell carcinoma	2	0.05	2	2	0.05	2
	B-cell lymphoma	2	0.05	2	0	0	0
	B-cell lymphoma stage III	0	0	0	1	0.03	1
	Benign neoplasm of bladder	0	0	0	1	0.03	1
	Benign neoplasm of thyroid gland	1	0.03	1	0	0	0
	Benign ovarian tumour	0	0	0	1	0.03	1
	Bile duct adenocarcinoma	1	0.03	1	0	0	0
	Bladder cancer	1	0.03	1	3	0.08	3

	Bladder cancer recurrent	1	0.03	1	0	0	0
	Bladder cancer stage 0, with cancer in situ	1	0.03	1	0	0	0
	Bladder transitional cell carcinoma	1	0.03	1	1	0.03	1
	Bladder transitional cell carcinoma recurrent	2	0.05	2	0	0	0
	Bladder transitional cell carcinoma stage I	1	0.03	1	0	0	0
	Bone cancer	0	0	0	1	0.03	1
	Bowen's disease	0	0	0	1	0.03	1
	Brain neoplasm	1	0.03	1	0	0	0
	Breast cancer	1	0.03	1	1	0.03	1
	Breast cancer metastatic	1	0.03	1	1	0.03	1
	Breast cancer stage I	0	0	0	2	0.05	2
	Breast cancer stage II	1	0.03	1	0	0	0
	Breast cancer stage IV	1	0.03	1	0	0	0
	Cardiac valve fibroelastoma	0	0	0	1	0.03	1
	Cholangiocarcinoma	0	0	0	1	0.03	1
	Choroid melanoma	1	0.03	1	0	0	0
	Chronic myeloid leukaemia	0	0	0	1	0.03	1
	Colon adenoma	3	0.08	3	2	0.05	2
	Colon cancer	2	0.05	2	1	0.03	1
	Colon cancer metastatic	2	0.05	2	1	0.03	1
	Colon cancer stage III	0	0	0	1	0.03	1
	Colorectal cancer metastatic	0	0	0	1	0.03	1
	Diffuse large B-cell lymphoma recurrent	0	0	0	1	0.03	1
	Endometrial adenocarcinoma	3	0.08	3	3	0.08	3
	Fibroma	0	0	0	1	0.03	1
	Gallbladder adenocarcinoma	0	0	0	1	0.03	1
	Gallbladder cancer metastatic	0	0	0	1	0.03	1
	Gastrointestinal cancer metastatic	0	0	0	1	0.03	1
	Gastrointestinal tract adenoma	1	0.03	1	0	0	0
	Hepatic cancer	0	0	0	2	0.05	2
	Hepatic cancer metastatic	0	0	0	2	0.05	2
	Hepatic neoplasm	1	0.03	1	0	0	0
	Hepatocellular carcinoma	3	0.08	3	4	0.1	4
	Intraductal proliferative breast lesion	3	0.08	3	2	0.05	2
	Invasive ductal breast carcinoma	2	0.05	2	5	0.13	5
	Leiomyoma	0	0	0	1	0.03	1
	Leukaemia	0	0	0	1	0.03	1
	Lipoma	1	0.03	1	1	0.03	1
	Lung adenocarcinoma	0	0	0	1	0.03	1
	Lung adenocarcinoma metastatic	1	0.03	1	2	0.05	2
	Lung adenocarcinoma stage II	1	0.03	1	1	0.03	1
	Lung adenocarcinoma stage IV	0	0	0	1	0.03	1
	Lung cancer metastatic	0	0	0	1	0.03	1
	Lung neoplasm malignant	2	0.05	2	0	0	0
	Lymphoma	1	0.03	1	1	0.03	1
	Malignant melanoma	1	0.03	1	0	0	0
	Malignant melanoma in situ	1	0.03	1	0	0	0

	Malignant peritoneal neoplasm	1	0.03	1	0	0	0
	Meningioma benign	3	0.08	3	0	0	0
	Mesothelioma malignant	1	0.03	1	0	0	0
	Metastases to bone	0	0	0	1	0.03	1
	Metastases to central nervous system	0	0	0	1	0.03	1
	Metastases to liver	1	0.03	1	2	0.05	2
	Metastases to lung	0	0	0	1	0.03	1
	Metastases to lymph nodes	0	0	0	1	0.03	1
	Metastatic neoplasm	0	0	0	1	0.03	1
	Metastatic renal cell carcinoma	3	0.08	3	0	0	0
	Metastatic squamous cell carcinoma	0	0	0	1	0.03	1
	Mucinous endometrial carcinoma	0	0	0	1	0.03	1
	Myelodysplastic syndrome	0	0	0	1	0.03	1
	Neuroendocrine carcinoma metastatic	1	0.03	1	0	0	0
	Non-small cell lung cancer	1	0.03	1	1	0.03	1
	Non-small cell lung cancer metastatic	0	0	0	1	0.03	1
	Non-small cell lung cancer stage I	0	0	0	1	0.03	1
	Oesophageal adenocarcinoma	0	0	0	2	0.05	2
	Oesophageal carcinoma	2	0.05	2	0	0	0
	Ovarian cancer recurrent	1	0.03	1	0	0	0
	Ovarian cancer stage IV	1	0.03	1	0	0	0
	Pancreatic carcinoma	3	0.08	3	1	0.03	1
	Pancreatic carcinoma metastatic	3	0.08	3	0	0	0
	Pancreatic carcinoma stage IV	1	0.03	1	0	0	0
	Papillary cystadenoma lymphomatosum	1	0.03	1	1	0.03	1
	Papillary thyroid cancer	1	0.03	1	1	0.03	1
	Parathyroid tumour benign	1	0.03	1	1	0.03	1
	Penile squamous cell carcinoma	0	0	0	1	0.03	1
	Phaeochromocytoma	1	0.03	1	0	0	0
	Pituitary tumour benign	1	0.03	1	0	0	0
	Plasma cell myeloma	3	0.08	3	0	0	0
	Prostate cancer	11	0.29	11	5	0.13	5
	Prostate cancer metastatic	0	0	0	2	0.05	2
	Prostate cancer stage I	0	0	0	3	0.08	3
	Prostate cancer stage II	1	0.03	1	0	0	0
	Rectal adenocarcinoma	2	0.05	2	0	0	0
	Rectal adenoma	1	0.03	1	0	0	0
	Rectal cancer	0	0	0	2	0.05	2
	Rectal cancer metastatic	1	0.03	1	0	0	0
	Renal cancer	2	0.05	2	0	0	0
	Renal cancer metastatic	1	0.03	1	1	0.03	1
	Renal cell carcinoma	1	0.03	1	3	0.08	3
	Salivary gland cancer	0	0	0	1	0.03	1
	Small cell lung cancer	2	0.05	2	1	0.03	1
	Small cell lung cancer extensive stage	0	0	0	1	0.03	1
	Small cell lung cancer metastatic	3	0.08	3	0	0	0

	Soft tissue sarcoma	0	0	0	1	0.03	1
	Squamous cell carcinoma	1	0.03	1	2	0.05	2
	Squamous cell carcinoma of lung	2	0.05	2	1	0.03	1
	Squamous cell carcinoma of skin	0	0	0	1	0.03	1
	Squamous cell carcinoma of the tongue	0	0	0	1	0.03	1
	Testicular seminoma (pure) stage I	0	0	0	1	0.03	1
	Testis cancer	0	0	0	1	0.03	1
	Thyroid cancer	1	0.03	1	0	0	0
	Tonsil cancer	1	0.03	1	0	0	0
	Transitional cell carcinoma	0	0	0	1	0.03	1
	Tumour of ampulla of Vater	0	0	0	1	0.03	1
	Ureteric cancer	0	0	0	1	0.03	1
	Uterine cancer	2	0.05	2	1	0.03	1
	All	116	3.04	116	119	3.12	119
Nervous system disorders	Altered state of consciousness	1	0.03	1	0	0	0
	Aphasia	1	0.03	1	1	0.03	1
	Ataxia	1	0.03	1	0	0	0
	Balance disorder	0	0	0	1	0.03	1
	Brain injury	3	0.08	3	0	0	0
	Brain stem haemorrhage	0	0	0	2	0.05	2
	Brain stem infarction	2	0.05	2	4	0.1	4
	Brain stem stroke	0	0	0	1	0.03	1
	Carotid artery disease	2	0.05	2	2	0.05	2
	Carotid artery occlusion	0	0	0	3	0.08	3
	Carotid artery stenosis	15	0.39	15	14	0.37	15
	Cerebellar infarction	1	0.03	1	3	0.08	3
	Cerebral arteriosclerosis	1	0.03	1	0	0	0
	Cerebral haemorrhage	3	0.08	3	4	0.1	4
	Cerebral infarction	5	0.13	5	4	0.1	5
	Cerebral ischaemia	1	0.03	1	0	0	0
	Cerebral small vessel ischaemic disease	1	0.03	1	0	0	0
	Cerebrovascular accident	11	0.29	11	22	0.58	23
	Cervical myelopathy	2	0.05	2	1	0.03	1
	Cranial nerve paralysis	0	0	0	1	0.03	1
	Dementia	2	0.05	2	1	0.03	1
	Dementia Alzheimer's type	0	0	0	2	0.05	2
	Diabetic mononeuropathy	0	0	0	1	0.03	1
	Diabetic neuropathy	2	0.05	2	0	0	0
	Dizziness	7	0.18	7	4	0.1	4
	Dysarthria	1	0.03	1	1	0.03	1
	Embolic cerebral infarction	0	0	0	1	0.03	1
	Embolic stroke	4	0.1	4	2	0.05	2
	Encephalopathy	6	0.16	6	4	0.1	4
	Epidural lipomatosis	0	0	0	1	0.03	1
	Essential tremor	0	0	0	1	0.03	1
	Facial paralysis	1	0.03	1	1	0.03	1
	Generalised tonic-clonic seizure	0	0	0	2	0.05	2
	Guillain-Barre syndrome	1	0.03	1	1	0.03	1
	Haemorrhage intracranial	1	0.03	1	3	0.08	3
	Haemorrhagic cerebral	1	0.03	1	0	0	0

	infarction						
	Haemorrhagic stroke	3	0.08	3	4	0.1	4
	Haemorrhagic transformation stroke	0	0	0	1	0.03	1
	Headache	4	0.1	4	6	0.16	6
	Hemiparesis	3	0.08	3	2	0.05	2
	Hemiplegic migraine	1	0.03	1	0	0	0
	Hepatic encephalopathy	2	0.05	2	3	0.08	3
	Hydrocephalus	1	0.03	2	1	0.03	1
	Hyperglycaemic seizure	0	0	0	1	0.03	1
	Hypertensive encephalopathy	0	0	0	1	0.03	1
	Hypoaesthesia	0	0	0	1	0.03	1
	Hypoglycaemic coma	1	0.03	1	1	0.03	2
	Hypoglycaemic seizure	3	0.08	5	0	0	0
	Hypoglycaemic unconsciousness	27	0.71	29	29	0.76	33
	Hypoxic-ischaemic encephalopathy	1	0.03	1	1	0.03	1
	IIIrd nerve paralysis	0	0	0	1	0.03	1
	Intensive care unit acquired weakness	0	0	0	1	0.03	1
	Intracranial aneurysm	1	0.03	1	0	0	0
	Intracranial pressure increased	0	0	0	1	0.03	1
	Ischaemic cerebral infarction	1	0.03	1	1	0.03	1
	Ischaemic stroke	43	1.13	44	45	1.18	50
	Lacunar infarction	5	0.13	5	2	0.05	2
	Lacunar stroke	1	0.03	1	0	0	0
	Lethargy	0	0	0	1	0.03	1
	Loss of consciousness	4	0.1	4	4	0.1	4
	Lumbar radiculopathy	2	0.05	2	2	0.05	2
	Memory impairment	1	0.03	1	0	0	0
	Metabolic encephalopathy	7	0.18	7	9	0.24	10
	Migraine	3	0.08	3	0	0	0
	Migraine-triggered seizure	0	0	0	1	0.03	1
	Mononeuropathy multiplex	0	0	0	1	0.03	1
	Motor neurone disease	1	0.03	1	0	0	0
	Multiple sclerosis relapse	0	0	0	1	0.03	2
	Myasthenia gravis	0	0	0	1	0.03	1
	Nerve root compression	1	0.03	1	0	0	0
	Neuropathy peripheral	1	0.03	1	0	0	0
	Normal pressure hydrocephalus	2	0.05	2	0	0	0
	Paraesthesia	0	0	0	1	0.03	1
	Parkinson's disease	1	0.03	1	4	0.1	4
	Peripheral sensory neuropathy	1	0.03	1	0	0	0
	Post-injection delirium sedation syndrome	1	0.03	1	0	0	0
	Presyncope	3	0.08	3	12	0.31	12
	Radicular pain	0	0	0	1	0.03	1
	Radiculopathy	0	0	0	2	0.05	2
	Reversible ischaemic neurological deficit	1	0.03	1	0	0	0
	Sciatica	0	0	0	2	0.05	2
	Seizure	6	0.16	8	6	0.16	6
	Senile dementia	0	0	0	1	0.03	1
	Spinal cord compression	0	0	0	2	0.05	2
	Spondylitic myelopathy	0	0	0	1	0.03	1

	Status epilepticus	1	0.03	1	0	0	0
	Subarachnoid haemorrhage	2	0.05	2	2	0.05	2
	Syncope	25	0.65	27	24	0.63	29
	Thalamic infarction	1	0.03	1	3	0.08	3
	Thalamus haemorrhage	1	0.03	1	1	0.03	1
	Thrombotic stroke	1	0.03	1	0	0	0
	Toxic encephalopathy	1	0.03	1	2	0.05	2
	Transient global amnesia	0	0	0	1	0.03	1
	Transient ischaemic attack	28	0.73	29	42	1.1	44
	Tremor	0	0	0	1	0.03	1
	Ulnar nerve palsy	1	0.03	1	0	0	0
	Vascular dementia	1	0.03	1	2	0.05	2
	Vascular headache	0	0	0	1	0.03	1
	Vertebrobasilar insufficiency	0	0	0	1	0.03	1
	Visual field defect	0	0	0	1	0.03	1
	VIth nerve paralysis	1	0.03	1	0	0	0
	All	271	7.1	282	323	8.46	345
Product issues	Device dislocation	1	0.03	1	2	0.05	2
	Device failure	1	0.03	1	0	0	0
	Device fastener issue	1	0.03	1	0	0	0
	Device inappropriate shock delivery	0	0	0	1	0.03	1
	Device lead damage	0	0	0	1	0.03	1
	Device loosening	0	0	0	1	0.03	1
	Device malfunction	1	0.03	1	2	0.05	3
	Lead dislodgement	1	0.03	2	1	0.03	1
	All	5	0.13	6	8	0.21	9
Psychiatric disorders	Acute stress disorder	1	0.03	1	0	0	0
	Affective disorder	1	0.03	1	1	0.03	1
	Aggression	1	0.03	1	0	0	0
	Agitation	1	0.03	1	0	0	0
	Alcohol withdrawal syndrome	1	0.03	1	2	0.05	2
	Anxiety	1	0.03	1	2	0.05	2
	Bipolar disorder	3	0.08	3	3	0.08	3
	Completed suicide	0	0	0	2	0.05	2
	Confusional state	3	0.08	3	4	0.1	4
	Delirium	2	0.05	2	5	0.13	5
	Depression	5	0.13	5	4	0.1	4
	Depression suicidal	1	0.03	1	1	0.03	1
	Hallucination, visual	1	0.03	1	0	0	0
	Intentional self-injury	1	0.03	1	0	0	0
	Major depression	2	0.05	2	2	0.05	2
	Mental status changes	7	0.18	7	8	0.21	8
	Paranoia	1	0.03	1	0	0	0
	Personality change due to a general medical condition	1	0.03	1	0	0	0
	Post stroke depression	0	0	0	1	0.03	1
	Post-traumatic stress disorder	0	0	0	1	0.03	1
	Psychotic disorder	0	0	0	1	0.03	1
	Schizoaffective disorder	0	0	0	1	0.03	1
	Schizoaffective disorder bipolar type	0	0	0	1	0.03	2
	Schizophrenia	3	0.08	3	0	0	0
	Suicidal ideation	5	0.13	6	3	0.08	3
	Suicide attempt	0	0	0	3	0.08	3
	All	41	1.07	42	45	1.18	46
Renal and urinary	Acute kidney injury	70	1.83	79	95	2.49	110

disorders							
	Acute prerenal failure	2	0.05	2	2	0.05	2
	Anuria	0	0	0	2	0.05	2
	Azotaemia	2	0.05	2	1	0.03	1
	Bladder neck obstruction	0	0	0	1	0.03	1
	Bladder outlet obstruction	1	0.03	1	0	0	0
	Calculus bladder	1	0.03	1	0	0	0
	Calculus urinary	0	0	0	1	0.03	1
	Chronic kidney disease	16	0.42	18	26	0.68	30
	Cystitis noninfective	1	0.03	1	0	0	0
	Diabetic nephropathy	1	0.03	1	3	0.08	3
	End stage renal disease	12	0.31	12	9	0.24	9
	Glomerulonephritis rapidly progressive	1	0.03	1	0	0	0
	Haematuria	2	0.05	2	3	0.08	3
	Hydronephrosis	2	0.05	2	3	0.08	3
	Nephrolithiasis	11	0.29	11	9	0.24	9
	Nephropathy	0	0	0	1	0.03	1
	Nephropathy toxic	0	0	0	1	0.03	1
	Nephrosclerosis	1	0.03	1	0	0	0
	Nephrotic syndrome	1	0.03	1	2	0.05	2
	Renal artery stenosis	0	0	0	1	0.03	1
	Renal colic	0	0	0	1	0.03	1
	Renal failure	14	0.37	14	17	0.45	17
	Renal impairment	3	0.08	3	4	0.1	4
	Renal mass	1	0.03	1	0	0	0
	Renal tubular necrosis	0	0	0	1	0.03	1
	Stag horn calculus	2	0.05	2	0	0	0
	Stress urinary incontinence	2	0.05	2	0	0	0
	Tubulointerstitial nephritis	0	0	0	1	0.03	1
	Ureterolithiasis	3	0.08	3	5	0.13	5
	Urethral stenosis	1	0.03	1	0	0	0
	Urinary hesitation	1	0.03	1	0	0	0
	Urinary retention	9	0.24	9	2	0.05	2
	All	160	4.19	171	191	5	210
Reproductive system and breast disorders	Balanoposthitis	1	0.03	1	1	0.03	1
	Benign prostatic hyperplasia	9	0.24	9	7	0.18	7
	Breast enlargement	1	0.03	1	0	0	0
	Cervical cyst	1	0.03	1	0	0	0
	Cervical dysplasia	0	0	0	2	0.05	2
	Cervix haemorrhage uterine	1	0.03	1	0	0	0
	Cystocele	2	0.05	2	0	0	0
	Endometrial hyperplasia	3	0.08	3	0	0	0
	Ovarian cyst	1	0.03	1	0	0	0
	Prostatitis	1	0.03	1	1	0.03	1
	Prostatomegaly	0	0	0	1	0.03	1
	Rectocele	1	0.03	1	0	0	0
	Uterine mass	1	0.03	1	0	0	0
	Uterine prolapse	0	0	0	1	0.03	1
	Vaginal haemorrhage	0	0	0	1	0.03	1
	All	22	0.58	22	14	0.37	14
Respiratory, thoracic and mediastinal disorders	Acquired diaphragmatic eventration	0	0	0	1	0.03	1
	Acute pulmonary oedema	6	0.16	9	6	0.16	6
	Acute respiratory distress	3	0.08	3	0	0	0

	syndrome						
	Acute respiratory failure	24	0.63	26	31	0.81	35
	Asthma	6	0.16	7	8	0.21	8
	Asthma-chronic obstructive pulmonary disease overlap syndrome	1	0.03	1	0	0	0
	Atelectasis	1	0.03	1	4	0.1	4
	Bronchial hyperreactivity	0	0	0	1	0.03	1
	Chronic obstructive pulmonary disease	42	1.1	54	56	1.47	70
	Chronic respiratory failure	2	0.05	2	0	0	0
	Cough	2	0.05	2	1	0.03	1
	Dyspnoea	11	0.29	11	17	0.45	19
	Dyspnoea exertional	4	0.1	4	1	0.03	1
	Dyspnoea paroxysmal nocturnal	0	0	0	1	0.03	1
	Epistaxis	1	0.03	1	3	0.08	4
	Haemothorax	1	0.03	1	0	0	0
	Hypoxia	3	0.08	3	8	0.21	8
	Idiopathic pulmonary fibrosis	1	0.03	1	0	0	0
	Interstitial lung disease	1	0.03	1	3	0.08	3
	Laryngeal stenosis	1	0.03	1	0	0	0
	Nasal polyps	1	0.03	1	1	0.03	1
	Nasal septum deviation	1	0.03	1	1	0.03	1
	Non-cardiogenic pulmonary oedema	1	0.03	1	0	0	0
	Obstructive airways disorder	1	0.03	1	0	0	0
	Pharyngeal oedema	2	0.05	2	0	0	0
	Pickwickian syndrome	0	0	0	1	0.03	1
	Pleural effusion	1	0.03	1	6	0.16	6
	Pleurisy	0	0	0	3	0.08	3
	Pleuritic pain	0	0	0	1	0.03	1
	Pneumonia aspiration	1	0.03	1	3	0.08	3
	Pneumonitis	0	0	0	1	0.03	1
	Pneumothorax	3	0.08	3	1	0.03	1
	Pneumothorax spontaneous	0	0	0	1	0.03	1
	Pulmonary congestion	1	0.03	1	1	0.03	1
	Pulmonary embolism	15	0.39	15	10	0.26	10
	Pulmonary fibrosis	1	0.03	1	1	0.03	1
	Pulmonary hypertension	6	0.16	6	5	0.13	5
	Pulmonary mass	1	0.03	1	2	0.05	2
	Pulmonary oedema	6	0.16	6	9	0.24	9
	Pulmonary sarcoidosis	0	0	0	1	0.03	1
	Pulmonary veno-occlusive disease	0	0	0	1	0.03	1
	Respiratory distress	2	0.05	2	2	0.05	2
	Respiratory failure	22	0.58	23	18	0.47	19
	Respiratory tract inflammation	0	0	0	1	0.03	1
	Sleep apnoea syndrome	0	0	0	7	0.18	7
	Upper respiratory tract inflammation	0	0	0	1	0.03	1
	All	175	4.58	194	219	5.73	241
Skin and subcutaneous tissue disorders	Angioedema	3	0.08	4	8	0.21	9
	Decubitus ulcer	1	0.03	1	2	0.05	2
	Dermal cyst	1	0.03	1	0	0	0

	Dermatitis	1	0.03	1	0	0	0
	Diabetic foot	10	0.26	10	11	0.29	11
	Diabetic neuropathic ulcer	0	0	0	1	0.03	1
	Eczema	1	0.03	1	0	0	0
	Hidradenitis	1	0.03	1	0	0	0
	Hyperhidrosis	1	0.03	1	0	0	0
	Hypersensitivity vasculitis	1	0.03	1	0	0	0
	Neuropathic ulcer	2	0.05	2	1	0.03	1
	Pemphigoid	0	0	0	1	0.03	1
	Rash	1	0.03	1	0	0	0
	Skin necrosis	0	0	0	1	0.03	1
	Skin ulcer	13	0.34	13	6	0.16	6
	Skin ulcer haemorrhage	0	0	0	1	0.03	1
	Stasis dermatitis	2	0.05	2	0	0	0
	Urticaria	1	0.03	1	0	0	0
	All	39	1.02	40	32	0.84	33
Social circumstances	Social stay hospitalisation	1	0.03	1	0	0	0
	All	1	0.03	1	0	0	0
Surgical and medical procedures	Abdominal hernia repair	0	0	0	1	0.03	1
	Abdominal panniculectomy	1	0.03	1	0	0	0
	Amputation	0	0	0	1	0.03	1
	Angioplasty	2	0.05	2	0	0	0
	Aortic aneurysm repair	0	0	0	1	0.03	1
	Aortic stent insertion	1	0.03	1	0	0	0
	Aortic valve replacement	1	0.03	1	0	0	0
	Arteriovenous fistula operation	0	0	0	1	0.03	1
	Cardiac ablation	1	0.03	1	2	0.05	2
	Cardiac pacemaker battery replacement	0	0	0	1	0.03	1
	Cardiac pacemaker insertion	1	0.03	1	1	0.03	1
	Cardiac pacemaker replacement	0	0	0	4	0.1	4
	Cataract operation	1	0.03	1	1	0.03	1
	Colectomy	1	0.03	1	0	0	0
	Colostomy closure	1	0.03	1	0	0	0
	Coronary arterial stent insertion	0	0	0	1	0.03	1
	Coronary artery bypass	1	0.03	1	2	0.05	2
	Duodenal switch	1	0.03	1	0	0	0
	Gastrectomy	4	0.1	4	3	0.08	3
	Gastric bypass	3	0.08	3	4	0.1	4
	Hernia repair	1	0.03	1	0	0	0
	Hip arthroplasty	2	0.05	2	0	0	0
	Hysterectomy	1	0.03	1	0	0	0
	Implantable defibrillator insertion	2	0.05	2	1	0.03	1
	Implantable defibrillator replacement	0	0	0	1	0.03	1
	Inguinal hernia repair	2	0.05	2	1	0.03	1
	Intervertebral disc operation	1	0.03	1	0	0	0
	Intra-ocular injection	1	0.03	1	0	0	0
	Jejunostomy	0	0	0	1	0.03	1
	Joint arthroplasty	1	0.03	1	0	0	0
	Knee arthroplasty	4	0.1	5	7	0.18	8
	Knee operation	1	0.03	1	0	0	0
	Leg amputation	0	0	0	1	0.03	1

	Metabolic surgery	0	0	0	1	0.03	1
	Oesophagectomy	0	0	0	1	0.03	1
	Rotator cuff repair	0	0	0	1	0.03	1
	Roux loop conversion	0	0	0	1	0.03	1
	Spinal decompression	0	0	0	1	0.03	1
	Spinal fusion surgery	1	0.03	1	0	0	0
	Spinal laminectomy	2	0.05	2	0	0	0
	Thyroidectomy	0	0	0	1	0.03	1
	Transurethral prostatectomy	0	0	0	1	0.03	1
	Umbilical hernia repair	1	0.03	1	0	0	0
	All	39	1.02	40	42	1.1	43
Vascular disorders	Accelerated hypertension	4	0.1	4	7	0.18	7
	Aneurysm	0	0	0	1	0.03	1
	Angiopathy	0	0	0	1	0.03	1
	Aortic aneurysm	3	0.08	3	3	0.08	3
	Aortic stenosis	3	0.08	3	3	0.08	3
	Arterial haemorrhage	0	0	0	2	0.05	2
	Arteriosclerosis	3	0.08	3	2	0.05	2
	Blood pressure inadequately controlled	1	0.03	1	0	0	0
	Deep vein thrombosis	13	0.34	13	10	0.26	10
	Dry gangrene	2	0.05	2	1	0.03	1
	Embolism	1	0.03	1	0	0	0
	Embolism arterial	0	0	0	2	0.05	2
	Embolism venous	1	0.03	1	1	0.03	1
	Essential hypertension	1	0.03	1	0	0	0
	Extremity necrosis	1	0.03	1	3	0.08	3
	Hypertension	17	0.45	19	23	0.6	24
	Hypertensive crisis	8	0.21	8	8	0.21	8
	Hypertensive emergency	3	0.08	3	3	0.08	3
	Hypotension	14	0.37	14	14	0.37	15
	Hypovolaemic shock	0	0	0	2	0.05	2
	Intermittent claudication	2	0.05	2	6	0.16	6
	Ischaemic limb pain	0	0	0	1	0.03	1
	Leriche syndrome	0	0	0	1	0.03	1
	Lymphocele	0	0	0	1	0.03	1
	Malignant hypertension	3	0.08	3	5	0.13	5
	Microangiopathy	1	0.03	1	0	0	0
	Obstructive shock	1	0.03	1	0	0	0
	Orthostatic hypotension	6	0.16	6	8	0.21	8
	Peripheral arterial occlusive disease	13	0.34	13	12	0.31	12
	Peripheral artery aneurysm	1	0.03	1	1	0.03	1
	Peripheral artery occlusion	4	0.1	4	4	0.1	5
	Peripheral artery stenosis	2	0.05	3	4	0.1	4
	Peripheral artery thrombosis	1	0.03	1	0	0	0
	Peripheral embolism	0	0	0	1	0.03	1
	Peripheral ischaemia	3	0.08	3	7	0.18	7
	Peripheral vascular disorder	11	0.29	12	14	0.37	17
	Peripheral venous disease	0	0	0	2	0.05	2
	Phlebitis	0	0	0	1	0.03	1
	Reperfusion injury	0	0	0	1	0.03	1
	Shock haemorrhagic	0	0	0	2	0.05	2
	Subclavian steal syndrome	1	0.03	1	0	0	0
	Superior vena cava stenosis	0	0	0	1	0.03	1
	Temporal arteritis	1	0.03	1	0	0	0
	Thrombosis	4	0.1	4	2	0.05	4

	Vascular insufficiency	0	0	0	1	0.03	3
	All	129	3.38	133	161	4.22	171
All	All	3113	81.53	3341	3443	90.15	3745
Source: datasets ADAE and ADSL dataset, ANL01FL=y, AESER=y by TRTP							

Table 80 – Adverse events resulting in permanent discontinuation of IMP by SOC and PT-FAS

Primary System Organ Class	Dictionary Derived Term	IDeg OD	IGlar OD	Subjects(filtered)
Blood and lymphatic system disorders	Anaemia	1 (0.03%)	2 (0.05%)	3 (0.04%)
	Iron deficiency anaemia	0 (0.00%)	1 (0.03%)	1 (0.01%)
	Leukocytosis	1 (0.03%)	0 (0.00%)	1 (0.01%)
	Neutropenia	0 (0.00%)	1 (0.03%)	1 (0.01%)
Cardiac disorders	Acute coronary syndrome	0 (0.00%)	1 (0.03%)	1 (0.01%)
	Acute myocardial infarction	9 (0.24%)	8 (0.21%)	17 (0.21%)
	Angina pectoris	4 (0.10%)	2 (0.05%)	6 (0.07%)
	Angina unstable	7 (0.18%)	4 (0.10%)	11 (0.13%)
	Arrhythmia	1 (0.03%)	0 (0.00%)	1 (0.01%)
	Atrial fibrillation	3 (0.08%)	5 (0.13%)	8 (0.10%)
	Cardiac arrest	1 (0.03%)	2 (0.05%)	3 (0.04%)
	Cardiac failure	3 (0.08%)	1 (0.03%)	4 (0.05%)
	Cardiac failure chronic	2 (0.05%)	1 (0.03%)	3 (0.04%)
	Cardiac failure congestive	9 (0.24%)	14 (0.37%)	23 (0.28%)
	Cardiomyopathy	1 (0.03%)	1 (0.03%)	2 (0.02%)
	Cardio-respiratory arrest	0 (0.00%)	1 (0.03%)	1 (0.01%)
	Coronary artery disease	6 (0.16%)	5 (0.13%)	11 (0.13%)
	Coronary artery occlusion	2 (0.05%)	0 (0.00%)	2 (0.02%)
	Coronary artery stenosis	1 (0.03%)	0 (0.00%)	1 (0.01%)
	Hypertensive heart disease	0 (0.00%)	1 (0.03%)	1 (0.01%)
	Mitral valve incompetence	1 (0.03%)	1 (0.03%)	2 (0.02%)
	Myocardial infarction	3 (0.08%)	5 (0.13%)	8 (0.10%)
	Myocardial ischaemia	0 (0.00%)	1 (0.03%)	1 (0.01%)
	Palpitations	0 (0.00%)	1 (0.03%)	1 (0.01%)
	Right ventricular failure	1 (0.03%)	0 (0.00%)	1 (0.01%)
	Sinus bradycardia	0 (0.00%)	1 (0.03%)	1 (0.01%)
	Sinus node dysfunction	0 (0.00%)	1 (0.03%)	1 (0.01%)
	Sinus tachycardia	1 (0.03%)	0 (0.00%)	1 (0.01%)
	Supraventricular tachycardia	0 (0.00%)	1 (0.03%)	1 (0.01%)
	Tachyarrhythmia	0 (0.00%)	1 (0.03%)	1 (0.01%)
	Tachycardia	0 (0.00%)	1 (0.03%)	1 (0.01%)
	Ventricular fibrillation	2 (0.05%)	0 (0.00%)	2 (0.02%)
	Ventricular tachycardia	0 (0.00%)	1 (0.03%)	1 (0.01%)
Ear and labyrinth disorders	Vertigo positional	0 (0.00%)	1 (0.03%)	1 (0.01%)
Endocrine disorders	Goitre	0 (0.00%)	1 (0.03%)	1 (0.01%)
	Thyroid mass	2 (0.05%)	0 (0.00%)	2 (0.02%)
Eye disorders	Angle closure glaucoma	0 (0.00%)	1 (0.03%)	1 (0.01%)
	Diplopia	0 (0.00%)	1 (0.03%)	1 (0.01%)
	Vision blurred	1 (0.03%)	0 (0.00%)	1 (0.01%)
Gastrointestinal disorders	Abdominal hernia obstructive	0 (0.00%)	1 (0.03%)	1 (0.01%)
	Abdominal pain	3 (0.08%)	0 (0.00%)	3 (0.04%)
	Abdominal pain upper	1 (0.03%)	0 (0.00%)	1 (0.01%)
	Acute abdomen	0 (0.00%)	1 (0.03%)	1 (0.01%)
	Anal incontinence	0 (0.00%)	1 (0.03%)	1 (0.01%)
	Appendix disorder	0 (0.00%)	1 (0.03%)	1 (0.01%)
	Colitis	1 (0.03%)	0 (0.00%)	1 (0.01%)
	Diabetic gastroparesis	1 (0.03%)	0 (0.00%)	1 (0.01%)

	Diarrhoea	1 (0.03%)	2 (0.05%)	3 (0.04%)
	Diverticulum intestinal	1 (0.03%)	0 (0.00%)	1 (0.01%)
	Duodenal vascular ectasia	1 (0.03%)	0 (0.00%)	1 (0.01%)
	Enteritis	1 (0.03%)	0 (0.00%)	1 (0.01%)
	Gastric ulcer	0 (0.00%)	1 (0.03%)	1 (0.01%)
	Gastrointestinal haemorrhage	0 (0.00%)	1 (0.03%)	1 (0.01%)
	Gastrointestinal polyp haemorrhage	0 (0.00%)	1 (0.03%)	1 (0.01%)
	Gastrooesophageal reflux disease	1 (0.03%)	1 (0.03%)	2 (0.02%)
	Ileus	1 (0.03%)	0 (0.00%)	1 (0.01%)
	Intestinal ischaemia	1 (0.03%)	0 (0.00%)	1 (0.01%)
	Nausea	0 (0.00%)	1 (0.03%)	1 (0.01%)
	Oesophageal varices haemorrhage	0 (0.00%)	1 (0.03%)	1 (0.01%)
	Oesophagitis	1 (0.03%)	0 (0.00%)	1 (0.01%)
	Pancreatitis	1 (0.03%)	1 (0.03%)	2 (0.02%)
	Peptic ulcer perforation	1 (0.03%)	0 (0.00%)	1 (0.01%)
	Small intestinal obstruction	0 (0.00%)	1 (0.03%)	1 (0.01%)
	Upper gastrointestinal haemorrhage	0 (0.00%)	1 (0.03%)	1 (0.01%)
	Vomiting	0 (0.00%)	2 (0.05%)	2 (0.02%)
General disorders and administration site conditions	Asthenia	1 (0.03%)	4 (0.10%)	5 (0.06%)
	Chest discomfort	0 (0.00%)	2 (0.05%)	2 (0.02%)
	Chest pain	2 (0.05%)	4 (0.10%)	6 (0.07%)
	Death	1 (0.03%)	0 (0.00%)	1 (0.01%)
	Fatigue	1 (0.03%)	0 (0.00%)	1 (0.01%)
	Generalised oedema	0 (0.00%)	1 (0.03%)	1 (0.01%)
	Injection site pain	0 (0.00%)	1 (0.03%)	1 (0.01%)
	Malaise	0 (0.00%)	1 (0.03%)	1 (0.01%)
	Multiple organ dysfunction syndrome	1 (0.03%)	1 (0.03%)	2 (0.02%)
	Non-cardiac chest pain	2 (0.05%)	2 (0.05%)	4 (0.05%)
	Oedema peripheral	2 (0.05%)	1 (0.03%)	3 (0.04%)
	Peripheral swelling	0 (0.00%)	1 (0.03%)	1 (0.01%)
	Sudden death	0 (0.00%)	1 (0.03%)	1 (0.01%)
	Surgical failure	1 (0.03%)	0 (0.00%)	1 (0.01%)
	Vascular stent restenosis	0 (0.00%)	1 (0.03%)	1 (0.01%)
Hepatobiliary disorders	Bile duct obstruction	0 (0.00%)	1 (0.03%)	1 (0.01%)
	Cholangitis	0 (0.00%)	1 (0.03%)	1 (0.01%)
	Cholecystitis	1 (0.03%)	0 (0.00%)	1 (0.01%)
	Cholecystitis acute	0 (0.00%)	1 (0.03%)	1 (0.01%)
	Cholecystitis chronic	0 (0.00%)	1 (0.03%)	1 (0.01%)
	Hepatic cirrhosis	0 (0.00%)	1 (0.03%)	1 (0.01%)
	Ischaemic hepatitis	0 (0.00%)	1 (0.03%)	1 (0.01%)
	Liver disorder	0 (0.00%)	1 (0.03%)	1 (0.01%)
	Portal vein thrombosis	1 (0.03%)	0 (0.00%)	1 (0.01%)
Infections and infestations	Bacteraemia	0 (0.00%)	1 (0.03%)	1 (0.01%)
	Bronchitis	1 (0.03%)	2 (0.05%)	3 (0.04%)
	Bronchitis viral	1 (0.03%)	0 (0.00%)	1 (0.01%)
	Cellulitis	1 (0.03%)	3 (0.08%)	4 (0.05%)
	Cellulitis staphylococcal	1 (0.03%)	0 (0.00%)	1 (0.01%)
	Clostridium difficile colitis	0 (0.00%)	1 (0.03%)	1 (0.01%)
	Cystitis	1 (0.03%)	0 (0.00%)	1 (0.01%)
	Dengue fever	2 (0.05%)	0 (0.00%)	2 (0.02%)

	Empyema	1 (0.03%)	0 (0.00%)	1 (0.01%)
	Endocarditis	0 (0.00%)	1 (0.03%)	1 (0.01%)
	Gangrene	0 (0.00%)	1 (0.03%)	1 (0.01%)
	H1N1 influenza	0 (0.00%)	1 (0.03%)	1 (0.01%)
	Incision site infection	1 (0.03%)	0 (0.00%)	1 (0.01%)
	Infected dermal cyst	1 (0.03%)	0 (0.00%)	1 (0.01%)
	Localised infection	0 (0.00%)	1 (0.03%)	1 (0.01%)
	Lower respiratory tract infection	1 (0.03%)	0 (0.00%)	1 (0.01%)
	Mucormycosis	1 (0.03%)	0 (0.00%)	1 (0.01%)
	Oesophageal candidiasis	0 (0.00%)	1 (0.03%)	1 (0.01%)
	Osteomyelitis	2 (0.05%)	0 (0.00%)	2 (0.02%)
	Pneumonia	7 (0.18%)	4 (0.10%)	11 (0.13%)
	Postoperative abscess	1 (0.03%)	0 (0.00%)	1 (0.01%)
	Postoperative wound infection	1 (0.03%)	0 (0.00%)	1 (0.01%)
	Pulmonary sepsis	0 (0.00%)	1 (0.03%)	1 (0.01%)
	Sepsis	5 (0.13%)	1 (0.03%)	6 (0.07%)
	Sepsis syndrome	1 (0.03%)	0 (0.00%)	1 (0.01%)
	Septic shock	3 (0.08%)	2 (0.05%)	5 (0.06%)
	Sinusitis	0 (0.00%)	1 (0.03%)	1 (0.01%)
	Staphylococcal sepsis	0 (0.00%)	1 (0.03%)	1 (0.01%)
	Upper respiratory tract infection	1 (0.03%)	0 (0.00%)	1 (0.01%)
	Urinary tract infection	3 (0.08%)	2 (0.05%)	5 (0.06%)
	Urinary tract infection bacterial	0 (0.00%)	1 (0.03%)	1 (0.01%)
	Urosepsis	2 (0.05%)	1 (0.03%)	3 (0.04%)
	Viraemia	1 (0.03%)	0 (0.00%)	1 (0.01%)
Injury, poisoning and procedural complications	Accidental overdose	1 (0.03%)	0 (0.00%)	1 (0.01%)
	Alcohol poisoning	1 (0.03%)	0 (0.00%)	1 (0.01%)
	Anaesthetic complication pulmonary	0 (0.00%)	1 (0.03%)	1 (0.01%)
	Facial bones fracture	0 (0.00%)	1 (0.03%)	1 (0.01%)
	Fall	7 (0.18%)	5 (0.13%)	12 (0.15%)
	Femoral neck fracture	0 (0.00%)	1 (0.03%)	1 (0.01%)
	Femur fracture	0 (0.00%)	3 (0.08%)	3 (0.04%)
	Humerus fracture	1 (0.03%)	1 (0.03%)	2 (0.02%)
	Intentional overdose	0 (0.00%)	1 (0.03%)	1 (0.01%)
	Rib fracture	1 (0.03%)	0 (0.00%)	1 (0.01%)
	Subdural haematoma	1 (0.03%)	1 (0.03%)	2 (0.02%)
	Thoracic vertebral fracture	1 (0.03%)	0 (0.00%)	1 (0.01%)
	Wound	0 (0.00%)	1 (0.03%)	1 (0.01%)
Investigations	Alanine aminotransferase increased	0 (0.00%)	1 (0.03%)	1 (0.01%)
	Blood glucose decreased	0 (0.00%)	1 (0.03%)	1 (0.01%)
	Blood potassium increased	1 (0.03%)	0 (0.00%)	1 (0.01%)
	Electrocardiogram ST-T change	0 (0.00%)	1 (0.03%)	1 (0.01%)
	Hepatic enzyme increased	0 (0.00%)	1 (0.03%)	1 (0.01%)
	Weight increased	1 (0.03%)	1 (0.03%)	2 (0.02%)
Metabolism and nutrition disorders	Dehydration	0 (0.00%)	4 (0.10%)	4 (0.05%)
	Diabetes mellitus inadequate control	1 (0.03%)	3 (0.08%)	4 (0.05%)
	Diabetic ketoacidosis	1 (0.03%)	2 (0.05%)	3 (0.04%)

	Fluid retention	1 (0.03%)	0 (0.00%)	1 (0.01%)
	Hyperglycaemia	2 (0.05%)	2 (0.05%)	4 (0.05%)
	Hyperkalaemia	1 (0.03%)	2 (0.05%)	3 (0.04%)
	Hypoglycaemia	5 (0.13%)	4 (0.10%)	9 (0.11%)
	Hypokalaemia	0 (0.00%)	1 (0.03%)	1 (0.01%)
	Increased appetite	1 (0.03%)	0 (0.00%)	1 (0.01%)
	Metabolic acidosis	1 (0.03%)	0 (0.00%)	1 (0.01%)
Musculoskeletal and connective tissue disorders	Arthralgia	0 (0.00%)	1 (0.03%)	1 (0.01%)
	Arthritis	0 (0.00%)	1 (0.03%)	1 (0.01%)
	Back pain	1 (0.03%)	1 (0.03%)	2 (0.02%)
	Enthesopathy	1 (0.03%)	0 (0.00%)	1 (0.01%)
	Intervertebral disc degeneration	1 (0.03%)	0 (0.00%)	1 (0.01%)
	Intervertebral disc protrusion	1 (0.03%)	0 (0.00%)	1 (0.01%)
	Lumbar spinal stenosis	2 (0.05%)	0 (0.00%)	2 (0.02%)
	Muscle spasms	1 (0.03%)	0 (0.00%)	1 (0.01%)
	Muscular weakness	1 (0.03%)	0 (0.00%)	1 (0.01%)
	Musculoskeletal chest pain	0 (0.00%)	2 (0.05%)	2 (0.02%)
	Musculoskeletal pain	0 (0.00%)	1 (0.03%)	1 (0.01%)
	Osteoarthritis	2 (0.05%)	0 (0.00%)	2 (0.02%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Acute myeloid leukaemia	0 (0.00%)	1 (0.03%)	1 (0.01%)
	Adenocarcinoma gastric	1 (0.03%)	0 (0.00%)	1 (0.01%)
	Adrenal adenoma	0 (0.00%)	1 (0.03%)	1 (0.01%)
	Brain neoplasm	1 (0.03%)	0 (0.00%)	1 (0.01%)
	Gastrointestinal cancer metastatic	0 (0.00%)	1 (0.03%)	1 (0.01%)
	Hepatic cancer	0 (0.00%)	1 (0.03%)	1 (0.01%)
	Leukaemia	0 (0.00%)	1 (0.03%)	1 (0.01%)
	Lung cancer metastatic	0 (0.00%)	1 (0.03%)	1 (0.01%)
	Lung neoplasm malignant	1 (0.03%)	0 (0.00%)	1 (0.01%)
	Meningioma benign	2 (0.05%)	0 (0.00%)	2 (0.02%)
	Mesothelioma malignant	1 (0.03%)	0 (0.00%)	1 (0.01%)
	Metastatic neoplasm	0 (0.00%)	1 (0.03%)	1 (0.01%)
	Metastatic renal cell carcinoma	1 (0.03%)	0 (0.00%)	1 (0.01%)
	Oesophageal carcinoma	1 (0.03%)	0 (0.00%)	1 (0.01%)
	Pancreatic carcinoma metastatic	1 (0.03%)	0 (0.00%)	1 (0.01%)
	Papillary cystadenoma lymphomatosum	0 (0.00%)	1 (0.03%)	1 (0.01%)
	Prostate cancer	2 (0.05%)	0 (0.00%)	2 (0.02%)
	Rectal adenocarcinoma	1 (0.03%)	0 (0.00%)	1 (0.01%)
	Renal cell carcinoma	1 (0.03%)	0 (0.00%)	1 (0.01%)
	Small cell lung cancer metastatic	1 (0.03%)	0 (0.00%)	1 (0.01%)
	Uterine cancer	0 (0.00%)	1 (0.03%)	1 (0.01%)
Nervous system disorders	Ataxia	1 (0.03%)	0 (0.00%)	1 (0.01%)
	Balance disorder	0 (0.00%)	1 (0.03%)	1 (0.01%)
	Brain injury	1 (0.03%)	0 (0.00%)	1 (0.01%)
	Brain stem haemorrhage	0 (0.00%)	1 (0.03%)	1 (0.01%)
	Brain stem infarction	0 (0.00%)	2 (0.05%)	2 (0.02%)
	Carotid artery stenosis	1 (0.03%)	0 (0.00%)	1 (0.01%)
	Cerebral haemorrhage	0 (0.00%)	1 (0.03%)	1 (0.01%)
	Cerebral infarction	0 (0.00%)	1 (0.03%)	1 (0.01%)

	Cerebrovascular accident	1 (0.03%)	5 (0.13%)	6 (0.07%)
	Dementia	2 (0.05%)	0 (0.00%)	2 (0.02%)
	Dizziness	4 (0.10%)	0 (0.00%)	4 (0.05%)
	Dysarthria	1 (0.03%)	0 (0.00%)	1 (0.01%)
	Embolic stroke	1 (0.03%)	0 (0.00%)	1 (0.01%)
	Encephalopathy	1 (0.03%)	0 (0.00%)	1 (0.01%)
	Haemorrhage intracranial	0 (0.00%)	3 (0.08%)	3 (0.04%)
	Haemorrhagic stroke	1 (0.03%)	1 (0.03%)	2 (0.02%)
	Headache	2 (0.05%)	1 (0.03%)	3 (0.04%)
	Hemiparesis	1 (0.03%)	0 (0.00%)	1 (0.01%)
	Hyperglycaemic seizure	0 (0.00%)	1 (0.03%)	1 (0.01%)
	Hypoglycaemic seizure	1 (0.03%)	0 (0.00%)	1 (0.01%)
	Hypoglycaemic unconsciousness	5 (0.13%)	4 (0.10%)	9 (0.11%)
	Ischaemic stroke	4 (0.10%)	5 (0.13%)	9 (0.11%)
	Lacunar infarction	1 (0.03%)	0 (0.00%)	1 (0.01%)
	Loss of consciousness	0 (0.00%)	1 (0.03%)	1 (0.01%)
	Lumbar radiculopathy	1 (0.03%)	0 (0.00%)	1 (0.01%)
	Metabolic encephalopathy	2 (0.05%)	2 (0.05%)	4 (0.05%)
	Parkinson's disease	0 (0.00%)	1 (0.03%)	1 (0.01%)
	Syncope	0 (0.00%)	2 (0.05%)	2 (0.02%)
	Thalamic infarction	0 (0.00%)	1 (0.03%)	1 (0.01%)
	Thalamus haemorrhage	1 (0.03%)	0 (0.00%)	1 (0.01%)
	Transient ischaemic attack	2 (0.05%)	3 (0.08%)	5 (0.06%)
	Tremor	0 (0.00%)	1 (0.03%)	1 (0.01%)
	Vascular dementia	0 (0.00%)	1 (0.03%)	1 (0.01%)
Product issues	Device loosening	0 (0.00%)	1 (0.03%)	1 (0.01%)
	Device malfunction	0 (0.00%)	1 (0.03%)	1 (0.01%)
Psychiatric disorders	Alcohol withdrawal syndrome	1 (0.03%)	0 (0.00%)	1 (0.01%)
	Anger	0 (0.00%)	1 (0.03%)	1 (0.01%)
	Anxiety	1 (0.03%)	0 (0.00%)	1 (0.01%)
	Confusional state	1 (0.03%)	2 (0.05%)	3 (0.04%)
	Depression	0 (0.00%)	2 (0.05%)	2 (0.02%)
	Insomnia	1 (0.03%)	0 (0.00%)	1 (0.01%)
	Mental status changes	0 (0.00%)	2 (0.05%)	2 (0.02%)
	Suicidal ideation	0 (0.00%)	1 (0.03%)	1 (0.01%)
	Suicide attempt	0 (0.00%)	1 (0.03%)	1 (0.01%)
Renal and urinary disorders	Acute kidney injury	8 (0.21%)	8 (0.21%)	16 (0.20%)
	Chronic kidney disease	0 (0.00%)	2 (0.05%)	2 (0.02%)
	End stage renal disease	2 (0.05%)	0 (0.00%)	2 (0.02%)
	Nephrolithiasis	1 (0.03%)	0 (0.00%)	1 (0.01%)
	Nephrotic syndrome	0 (0.00%)	1 (0.03%)	1 (0.01%)
	Renal failure	1 (0.03%)	3 (0.08%)	4 (0.05%)
	Renal impairment	0 (0.00%)	1 (0.03%)	1 (0.01%)
	Urinary retention	3 (0.08%)	0 (0.00%)	3 (0.04%)
Reproductive system and breast disorders	Benign prostatic hyperplasia	0 (0.00%)	1 (0.03%)	1 (0.01%)
Respiratory, thoracic and mediastinal disorders	Acute pulmonary oedema	1 (0.03%)	0 (0.00%)	1 (0.01%)
	Acute respiratory failure	4 (0.10%)	5 (0.13%)	9 (0.11%)
	Asthma	0 (0.00%)	1 (0.03%)	1 (0.01%)
	Chronic obstructive pulmonary disease	5 (0.13%)	5 (0.13%)	10 (0.12%)
	Dyspnoea	2 (0.05%)	3 (0.08%)	5 (0.06%)
	Epistaxis	1 (0.03%)	1 (0.03%)	2 (0.02%)
	Hypoxia	0 (0.00%)	1 (0.03%)	1 (0.01%)

	Pharyngeal oedema	1 (0.03%)	0 (0.00%)	1 (0.01%)
	Pleurisy	0 (0.00%)	1 (0.03%)	1 (0.01%)
	Pneumonia aspiration	0 (0.00%)	1 (0.03%)	1 (0.01%)
	Pneumonitis	0 (0.00%)	1 (0.03%)	1 (0.01%)
	Pulmonary embolism	0 (0.00%)	2 (0.05%)	2 (0.02%)
	Pulmonary hypertension	1 (0.03%)	1 (0.03%)	2 (0.02%)
	Pulmonary veno-occlusive disease	0 (0.00%)	1 (0.03%)	1 (0.01%)
	Respiratory distress	0 (0.00%)	1 (0.03%)	1 (0.01%)
	Respiratory failure	3 (0.08%)	0 (0.00%)	3 (0.04%)
	Sleep apnoea syndrome	0 (0.00%)	1 (0.03%)	1 (0.01%)
Skin and subcutaneous tissue disorders	Angioedema	1 (0.03%)	1 (0.03%)	2 (0.02%)
	Dermatitis allergic	0 (0.00%)	1 (0.03%)	1 (0.01%)
	Diabetic foot	1 (0.03%)	0 (0.00%)	1 (0.01%)
	Hyperhidrosis	0 (0.00%)	1 (0.03%)	1 (0.01%)
	Pruritus generalised	0 (0.00%)	1 (0.03%)	1 (0.01%)
	Rash	1 (0.03%)	0 (0.00%)	1 (0.01%)
	Urticaria	1 (0.03%)	1 (0.03%)	2 (0.02%)
Surgical and medical procedures	Angioplasty	1 (0.03%)	0 (0.00%)	1 (0.01%)
	Aortic valve replacement	1 (0.03%)	0 (0.00%)	1 (0.01%)
	Arterial therapeutic procedure	1 (0.03%)	0 (0.00%)	1 (0.01%)
	Cardiac ablation	1 (0.03%)	1 (0.03%)	2 (0.02%)
	Cardiac pacemaker insertion	1 (0.03%)	0 (0.00%)	1 (0.01%)
	Inguinal hernia repair	1 (0.03%)	1 (0.03%)	2 (0.02%)
	Peripheral artery stent insertion	1 (0.03%)	0 (0.00%)	1 (0.01%)
Vascular disorders	Accelerated hypertension	0 (0.00%)	3 (0.08%)	3 (0.04%)
	Aortic aneurysm	0 (0.00%)	1 (0.03%)	1 (0.01%)
	Aortic stenosis	1 (0.03%)	0 (0.00%)	1 (0.01%)
	Embolism	1 (0.03%)	0 (0.00%)	1 (0.01%)
	Hypertension	1 (0.03%)	2 (0.05%)	3 (0.04%)
	Hypertensive crisis	2 (0.05%)	1 (0.03%)	3 (0.04%)
	Hypertensive emergency	0 (0.00%)	1 (0.03%)	1 (0.01%)
	Hypotension	1 (0.03%)	1 (0.03%)	2 (0.02%)
	Lymphocele	0 (0.00%)	1 (0.03%)	1 (0.01%)
	Malignant hypertension	0 (0.00%)	2 (0.05%)	2 (0.02%)
	Orthostatic hypotension	0 (0.00%)	1 (0.03%)	1 (0.01%)
	Peripheral arterial occlusive disease	1 (0.03%)	1 (0.03%)	2 (0.02%)
	Peripheral artery stenosis	1 (0.03%)	0 (0.00%)	1 (0.01%)
	Peripheral vascular disorder	1 (0.03%)	0 (0.00%)	1 (0.01%)
	Reperfusion injury	0 (0.00%)	1 (0.03%)	1 (0.01%)
	Thrombosis	1 (0.03%)	0 (0.00%)	1 (0.01%)
	Vascular insufficiency	0 (0.00%)	1 (0.03%)	1 (0.01%)
Total events	Subjects(filtered)	200 (5.24%)	222 (5.81%)	
	1stColItemSubjects	3818 (100.00%)	3819 (100.00%)	7637 (100%)

Table 81 – Exploratory analysis - Adverse events not sent for adjudication by SOC and PT-FAS

SOC	PT term	IDeg OD		IGlar OD	
		N	%	N	%
Blood and lymphatic system disorders	Anaemia	26	0.68	47	1.23

	Anaemia of chronic disease	1	0.03	0	0
	Anaemia vitamin B12 deficiency	0	0	1	0.03
	Autoimmune haemolytic anaemia	0	0	1	0.03
	Coagulopathy	1	0.03	1	0.03
	Coombs negative haemolytic anaemia	0	0	1	0.03
	Deficiency anaemia	0	0	1	0.03
	Evans syndrome	0	0	1	0.03
	Haemolytic anaemia	0	0	1	0.03
	Haemorrhagic anaemia	8	0.21	10	0.26
	Hilar lymphadenopathy	0	0	1	0.03
	Hypochromic anaemia	1	0.03	1	0.03
	Iron deficiency anaemia	3	0.08	4	0.1
	Leukocytosis	7	0.18	3	0.08
	Lymphadenitis	0	0	1	0.03
	Lymphadenopathy	1	0.03	1	0.03
	Microcytic anaemia	0	0	1	0.03
	Nephrogenic anaemia	2	0.05	1	0.03
	Neutropenia	1	0.03	3	0.08
	Normochromic normocytic anaemia	1	0.03	2	0.05
	Pancytopenia	0	0	1	0.03
	Polycythaemia	1	0.03	0	0
	Splenic calcification	0	0	1	0.03
	Thrombocytopenia	3	0.08	2	0.05
	Thrombocytosis	0	0	1	0.03
Cardiac disorders	Acute left ventricular failure	8	0.21	5	0.13
	Angina pectoris	20	0.52	28	0.73
	Angina unstable	6	0.16	3	0.08
	Aortic valve disease	3	0.08	0	0
	Aortic valve incompetence	2	0.05	1	0.03
	Aortic valve sclerosis	0	0	1	0.03
	Aortic valve stenosis	7	0.18	6	0.16
	Arrhythmia	0	0	4	0.1
	Arteriosclerosis coronary artery	4	0.1	4	0.1
	Atrial fibrillation	68	1.78	68	1.78
	Atrial flutter	14	0.37	11	0.29
	Atrial tachycardia	2	0.05	3	0.08
	Atrial thrombosis	0	0	1	0.03
	Atrioventricular block	0	0	3	0.08
	Atrioventricular block complete	6	0.16	4	0.1
	Atrioventricular block first degree	4	0.1	3	0.08
	Atrioventricular block second degree	2	0.05	2	0.05
	Atrioventricular dissociation	0	0	2	0.05
	Bradycardia	14	0.37	11	0.29
	Bundle branch block left	6	0.16	3	0.08
	Bundle branch block right	2	0.05	2	0.05
	Cardiac arrest	3	0.08	5	0.13
	Cardiac discomfort	0	0	1	0.03
	Cardiac failure	23	0.6	27	0.71
	Cardiac failure acute	7	0.18	7	0.18
	Cardiac failure chronic	10	0.26	10	0.26
	Cardiac failure congestive	133	3.48	149	3.9
	Cardiac flutter	0	0	1	0.03
	Cardiac hypertrophy	0	0	1	0.03
	Cardiac ventricular disorder	0	0	1	0.03

	Cardiac ventricular thrombosis	1	0.03	1	0.03
	Cardiogenic shock	1	0.03	1	0.03
	Cardiomegaly	7	0.18	2	0.05
	Cardiomyopathy	7	0.18	6	0.16
	Cardiorenal syndrome	1	0.03	0	0
	Cardio-respiratory arrest	1	0.03	2	0.05
	Chordae tendinae rupture	0	0	1	0.03
	Chronic left ventricular failure	0	0	1	0.03
	Congestive cardiomyopathy	4	0.1	0	0
	Cor pulmonale	0	0	2	0.05
	Cor pulmonale acute	1	0.03	0	0
	Cor pulmonale chronic	1	0.03	0	0
	Coronary artery disease	46	1.2	52	1.36
	Coronary artery dissection	1	0.03	0	0
	Coronary artery embolism	0	0	1	0.03
	Coronary artery insufficiency	2	0.05	1	0.03
	Coronary artery occlusion	9	0.24	2	0.05
	Coronary artery stenosis	11	0.29	4	0.1
	Coronary ostial stenosis	1	0.03	0	0
	Diastolic dysfunction	6	0.16	4	0.1
	Dilatation ventricular	1	0.03	1	0.03
	Extrasystoles	1	0.03	0	0
	Heart valve incompetence	1	0.03	1	0.03
	Hypertensive cardiomyopathy	1	0.03	1	0.03
	Hypertensive heart disease	0	0	2	0.05
	Intracardiac thrombus	1	0.03	0	0
	Ischaemic cardiomyopathy	6	0.16	6	0.16
	Left atrial dilatation	1	0.03	1	0.03
	Left ventricular dysfunction	3	0.08	3	0.08
	Left ventricular failure	6	0.16	3	0.08
	Left ventricular hypertrophy	5	0.13	6	0.16
	Long QT syndrome	0	0	1	0.03
	Mitral valve incompetence	7	0.18	4	0.1
	Mitral valve sclerosis	0	0	1	0.03
	Mitral valve stenosis	0	0	1	0.03
	Myocardial infarction	0	0	1	0.03
	Myocardial ischaemia	6	0.16	15	0.39
	Nodal arrhythmia	1	0.03	1	0.03
	Palpitations	5	0.13	7	0.18
	Pericardial cyst	1	0.03	0	0
	Pericardial effusion	1	0.03	2	0.05
	Pericarditis	2	0.05	1	0.03
	Prinzmetal angina	0	0	1	0.03
	Pulmonary valve incompetence	0	0	1	0.03
	Pulseless electrical activity	1	0.03	0	0
	Restrictive cardiomyopathy	0	0	1	0.03
	Right ventricular failure	2	0.05	1	0.03
	Sinus arrest	0	0	1	0.03
	Sinus arrhythmia	1	0.03	0	0
	Sinus bradycardia	6	0.16	3	0.08
	Sinus node dysfunction	6	0.16	6	0.16
	Sinus tachycardia	3	0.08	0	0
	Stress cardiomyopathy	1	0.03	0	0
	Supraventricular extrasystoles	4	0.1	1	0.03
	Supraventricular tachycardia	4	0.1	4	0.1
	Systolic dysfunction	1	0.03	0	0
	Tachyarrhythmia	0	0	1	0.03

	Tachycardia	1	0.03	10	0.26
	Torsade de pointes	1	0.03	0	0
	Tricuspid valve incompetence	3	0.08	2	0.05
	Trifascicular block	0	0	2	0.05
	Ventricular arrhythmia	1	0.03	0	0
	Ventricular extrasystoles	8	0.21	5	0.13
	Ventricular fibrillation	3	0.08	3	0.08
	Ventricular hypokinesia	2	0.05	2	0.05
	Ventricular tachycardia	10	0.26	11	0.29
Congenital, familial and genetic disorders	Atrial septal defect	0	0	1	0.03
	Congenital ureterocele	1	0.03	0	0
	Factor V deficiency	0	0	1	0.03
	Gastrointestinal arteriovenous malformation	0	0	1	0.03
	Haemorrhagic arteriovenous malformation	0	0	2	0.05
	Hydrocele	0	0	1	0.03
	Hypertrophic cardiomyopathy	0	0	1	0.03
	Osteogenesis imperfecta	0	0	1	0.03
	Phimosis	0	0	2	0.05
	Vertebral artery hypoplasia	0	0	1	0.03
Ear and labyrinth disorders	Deafness neurosensory	2	0.05	0	0
	Ear pain	2	0.05	1	0.03
	Excessive cerumen production	1	0.03	0	0
	Hypoacusis	1	0.03	0	0
	Inner ear disorder	0	0	1	0.03
	Meniere's disease	1	0.03	0	0
	Sudden hearing loss	1	0.03	0	0
	Tinnitus	2	0.05	1	0.03
	Vertigo	8	0.21	6	0.16
	Vertigo labyrinthine	1	0.03	0	0
	Vertigo positional	1	0.03	3	0.08
	Vestibular disorder	0	0	1	0.03
Endocrine disorders	Adrenal insufficiency	1	0.03	0	0
	Autoimmune thyroiditis	1	0.03	0	0
	Goitre	1	0.03	1	0.03
	Hypothyroidism	8	0.21	3	0.08
	Thyroid cyst	0	0	1	0.03
	Thyroid mass	3	0.08	1	0.03
	Toxic goitre	0	0	1	0.03
	Toxic nodular goitre	0	0	1	0.03
Eye disorders	Angle closure glaucoma	0	0	1	0.03
	Blepharitis	0	0	1	0.03
	Blindness	0	0	2	0.05
	Blindness unilateral	0	0	1	0.03
	Cataract	20	0.52	14	0.37
	Cataract diabetic	1	0.03	0	0
	Conjunctival haemorrhage	1	0.03	0	0
	Conjunctivitis allergic	1	0.03	0	0
	Diabetic retinal oedema	3	0.08	0	0
	Diabetic retinopathy	25	0.65	21	0.55
	Diplopia	1	0.03	3	0.08
	Dry eye	1	0.03	0	0
	Eye haemorrhage	3	0.08	0	0
	Eye irritation	1	0.03	1	0.03
	Eye pain	1	0.03	0	0

	Eyelid cyst	1	0.03	0	0
	Eyelid dermatochalasis	1	0.03	0	0
	Glaucoma	3	0.08	2	0.05
	Intraocular haematoma	0	0	1	0.03
	Macular degeneration	1	0.03	0	0
	Macular fibrosis	1	0.03	2	0.05
	Macular hole	1	0.03	0	0
	Macular oedema	0	0	1	0.03
	Neurotrophic keratopathy	0	0	1	0.03
	Normal tension glaucoma	1	0.03	0	0
	Ocular toxicity	1	0.03	0	0
	Pterygium	0	0	1	0.03
	Retinal artery occlusion	1	0.03	0	0
	Retinal detachment	1	0.03	1	0.03
	Retinal haemorrhage	0	0	1	0.03
	Retinal tear	1	0.03	0	0
	Retinal vein occlusion	1	0.03	0	0
	Retinopathy	2	0.05	2	0.05
	Retinopathy proliferative	1	0.03	0	0
	Vision blurred	1	0.03	1	0.03
	Visual impairment	1	0.03	1	0.03
	Vitreous detachment	1	0.03	0	0
	Vitreous floaters	2	0.05	1	0.03
	Vitreous haemorrhage	0	0	2	0.05
Gastrointestinal disorders	Abdominal discomfort	3	0.08	4	0.1
	Abdominal distension	2	0.05	2	0.05
	Abdominal hernia	2	0.05	1	0.03
	Abdominal hernia obstructive	0	0	2	0.05
	Abdominal mass	1	0.03	0	0
	Abdominal pain	18	0.47	14	0.37
	Abdominal pain lower	2	0.05	0	0
	Abdominal pain upper	4	0.1	3	0.08
	Abdominal wall haematoma	1	0.03	0	0
	Acid peptic disease	1	0.03	1	0.03
	Acquired oesophageal web	0	0	1	0.03
	Alcoholic pancreatitis	1	0.03	0	0
	Anal incontinence	0	0	2	0.05
	Anal pruritus	1	0.03	0	0
	Appendix disorder	0	0	1	0.03
	Ascites	0	0	1	0.03
	Barrett's oesophagus	3	0.08	2	0.05
	Chronic gastritis	3	0.08	3	0.08
	Colitis	6	0.16	8	0.21
	Colitis ischaemic	3	0.08	2	0.05
	Constipation	22	0.58	6	0.16
	Crohn's disease	1	0.03	2	0.05
	Dental caries	2	0.05	1	0.03
	Diabetic gastroparesis	1	0.03	3	0.08
	Diarrhoea	41	1.07	24	0.63
	Diverticular perforation	1	0.03	0	0
	Diverticulum	7	0.18	0	0
	Diverticulum intestinal	3	0.08	0	0
	Diverticulum intestinal haemorrhagic	0	0	1	0.03
	Dry mouth	0	0	2	0.05
	Duodenal stenosis	0	0	1	0.03
	Duodenal ulcer	1	0.03	3	0.08

	Duodenal ulcer haemorrhage	0	0	2	0.05
	Duodenal vascular ectasia	1	0.03	0	0
	Duodenitis	3	0.08	1	0.03
	Dyspepsia	2	0.05	3	0.08
	Dysphagia	1	0.03	5	0.13
	Enteritis	1	0.03	1	0.03
	Enterocele	1	0.03	0	0
	Epigastric discomfort	2	0.05	0	0
	Erosive duodenitis	0	0	1	0.03
	Eructation	1	0.03	0	0
	Faeces soft	0	0	2	0.05
	Flatulence	0	0	2	0.05
	Food poisoning	2	0.05	1	0.03
	Gastric antral vascular ectasia	0	0	1	0.03
	Gastric perforation	1	0.03	1	0.03
	Gastric polyps	4	0.1	2	0.05
	Gastric ulcer	4	0.1	5	0.13
	Gastric ulcer haemorrhage	1	0.03	0	0
	Gastric ulcer perforation	0	0	1	0.03
	Gastric varices	0	0	1	0.03
	Gastritis	13	0.34	10	0.26
	Gastritis erosive	2	0.05	1	0.03
	Gastroduodenitis	0	0	1	0.03
	Gastroduodenitis haemorrhagic	1	0.03	1	0.03
	Gastrointestinal angiodysplasia	1	0.03	0	0
	Gastrointestinal haemorrhage	11	0.29	15	0.39
	Gastrointestinal polyp haemorrhage	1	0.03	1	0.03
	Gastrointestinal ulcer haemorrhage	0	0	2	0.05
	Gastrooesophageal reflux disease	13	0.34	16	0.42
	Gingival pain	0	0	1	0.03
	Gingival recession	1	0.03	0	0
	Glossitis	0	0	1	0.03
	Haematemesis	0	0	1	0.03
	Haematochezia	2	0.05	4	0.1
	Haemorrhoidal haemorrhage	1	0.03	1	0.03
	Haemorrhoids	7	0.18	2	0.05
	Haemorrhoids thrombosed	1	0.03	0	0
	Hiatus hernia	7	0.18	4	0.1
	Hypoaesthesia oral	1	0.03	1	0.03
	Ileus	2	0.05	0	0
	Ileus paralytic	0	0	1	0.03
	Impaired gastric emptying	5	0.13	10	0.26
	Incarcerated umbilical hernia	1	0.03	0	0
	Inguinal hernia	4	0.1	4	0.1
	Intestinal ischaemia	1	0.03	1	0.03
	Intestinal obstruction	4	0.1	2	0.05
	Intestinal perforation	0	0	2	0.05
	Intra-abdominal haematoma	1	0.03	0	0
	Irritable bowel syndrome	0	0	2	0.05
	Large intestinal haemorrhage	0	0	1	0.03
	Large intestinal ulcer haemorrhage	0	0	1	0.03
	Large intestine polyp	10	0.26	8	0.21
	Lower gastrointestinal haemorrhage	5	0.13	3	0.08
	Mallory-Weiss syndrome	0	0	1	0.03
	Melaena	0	0	1	0.03

	Mesenteric haematoma	1	0.03	0	0
	Mouth ulceration	1	0.03	0	0
	Nausea	23	0.6	18	0.47
	Neutropenic colitis	0	0	1	0.03
	Oesophageal disorder	0	0	1	0.03
	Oesophageal polyp	1	0.03	0	0
	Oesophageal rupture	0	0	1	0.03
	Oesophageal ulcer haemorrhage	1	0.03	1	0.03
	Oesophageal varices haemorrhage	0	0	1	0.03
	Oesophagitis	3	0.08	6	0.16
	Pancreatic cyst	0	0	2	0.05
	Pancreatic disorder	0	0	1	0.03
	Pancreatic mass	1	0.03	0	0
	Pancreatitis	7	0.18	6	0.16
	Pancreatitis acute	6	0.16	11	0.29
	Pancreatitis chronic	1	0.03	4	0.1
	Pancreatitis relapsing	0	0	1	0.03
	Peptic ulcer	2	0.05	1	0.03
	Peptic ulcer perforation	1	0.03	0	0
	Perianal erythema	0	0	1	0.03
	Periodontal disease	2	0.05	0	0
	Pneumatosis intestinalis	0	0	1	0.03
	Rectal haemorrhage	1	0.03	4	0.1
	Rectal ulcer haemorrhage	1	0.03	0	0
	Salivary gland calculus	1	0.03	0	0
	Salivary gland mass	1	0.03	0	0
	Small intestinal obstruction	11	0.29	6	0.16
	Spigelian hernia	1	0.03	0	0
	Toothache	3	0.08	1	0.03
	Umbilical hernia	2	0.05	2	0.05
	Upper gastrointestinal haemorrhage	0	0	8	0.21
	Uvulitis	0	0	1	0.03
	Varices oesophageal	0	0	1	0.03
	Vomiting	16	0.42	15	0.39
General disorders and administration site conditions	Adverse drug reaction	0	0	1	0.03
	Adverse reaction	0	0	2	0.05
	Asthenia	5	0.13	9	0.24
	Cardiac complication associated with device	1	0.03	0	0
	Catheter site haematoma	0	0	1	0.03
	Chest discomfort	7	0.18	11	0.29
	Chest pain	22	0.58	25	0.65
	Complication associated with device	1	0.03	0	0
	Cyst	1	0.03	2	0.05
	Device intolerance	1	0.03	0	0
	Drug intolerance	0	0	1	0.03
	Exercise tolerance decreased	0	0	1	0.03
	Face oedema	1	0.03	0	0
	Fatigue	10	0.26	6	0.16
	Foreign body reaction	1	0.03	0	0
	Gait disturbance	1	0.03	1	0.03
	Generalised oedema	4	0.1	3	0.08
	Gravitational oedema	1	0.03	0	0
	Hypertrophy	0	0	1	0.03

	Hypothermia	1	0.03	0	0
	Impaired healing	1	0.03	2	0.05
	Inflammation	2	0.05	0	0
	Influenza like illness	3	0.08	4	0.1
	Infusion site extravasation	0	0	1	0.03
	Injection site erythema	0	0	1	0.03
	Injection site pain	0	0	4	0.1
	Injection site pruritus	1	0.03	0	0
	Injection site reaction	1	0.03	2	0.05
	Local swelling	1	0.03	0	0
	Malaise	0	0	1	0.03
	Mass	0	0	1	0.03
	Medical device site haemorrhage	0	0	1	0.03
	Multiple organ dysfunction syndrome	0	0	1	0.03
	Non-cardiac chest pain	49	1.28	48	1.26
	Oedema	1	0.03	8	0.21
	Oedema due to cardiac disease	1	0.03	0	0
	Oedema peripheral	38	1	17	0.45
	Pain	8	0.21	0	0
	Peripheral swelling	4	0.1	10	0.26
	Polyp	1	0.03	0	0
	Pyrexia	9	0.24	7	0.18
	Surgical failure	1	0.03	0	0
	Systemic inflammatory response syndrome	2	0.05	4	0.1
	Vascular stent restenosis	2	0.05	2	0.05
	Vascular stent stenosis	1	0.03	0	0
	Vascular stent thrombosis	1	0.03	1	0.03
Hepatobiliary disorders	Acute hepatic failure	1	0.03	0	0
	Alcoholic liver disease	1	0.03	0	0
	Bile duct obstruction	0	0	2	0.05
	Bile duct stone	3	0.08	1	0.03
	Biliary dilatation	0	0	1	0.03
	Biliary dyskinesia	0	0	1	0.03
	Biliary tract disorder	0	0	1	0.03
	Cholangitis	1	0.03	3	0.08
	Cholecystitis	8	0.21	4	0.1
	Cholecystitis acute	6	0.16	4	0.1
	Cholecystitis chronic	3	0.08	6	0.16
	Cholelithiasis	11	0.29	12	0.31
	Chronic hepatic failure	0	0	1	0.03
	Dilatation intrahepatic duct acquired	0	0	1	0.03
	Hepatic cirrhosis	3	0.08	0	0
	Hepatic cyst	0	0	1	0.03
	Hepatic failure	1	0.03	0	0
	Hepatic lesion	0	0	1	0.03
	Hepatic steatosis	3	0.08	4	0.1
	Hepatitis chronic active	1	0.03	0	0
	Hepatomegaly	1	0.03	0	0
	Hepatorenal failure	0	0	1	0.03
	Ischaemic hepatitis	0	0	1	0.03
	Jaundice	1	0.03	1	0.03
	Jaundice cholestatic	1	0.03	0	0
	Liver disorder	2	0.05	0	0
	Non-alcoholic steatohepatitis	0	0	1	0.03

	Portal vein thrombosis	1	0.03	0	0
	Sphincter of Oddi dysfunction	1	0.03	0	0
	Steatohepatitis	1	0.03	1	0.03
Immune system disorders	Allergy to arthropod sting	1	0.03	0	0
	Anaphylactic reaction	0	0	1	0.03
	Anaphylactic shock	1	0.03	0	0
	Drug hypersensitivity	4	0.1	4	0.1
	Hypersensitivity	2	0.05	2	0.05
	Reaction to preservatives	0	0	1	0.03
	Renal transplant failure	1	0.03	0	0
	Seasonal allergy	4	0.1	2	0.05
Infections and infestations	Abdominal abscess	0	0	1	0.03
	Abdominal sepsis	1	0.03	0	0
	Abdominal wall abscess	2	0.05	1	0.03
	Abdominal wall infection	1	0.03	0	0
	Abscess limb	0	0	7	0.18
	Abscess rupture	0	0	1	0.03
	Abscess soft tissue	0	0	1	0.03
	Acute endocarditis	1	0.03	0	0
	Acute sinusitis	5	0.13	3	0.08
	Angular cheilitis	1	0.03	0	0
	Appendicitis	4	0.1	6	0.16
	Arteriosclerotic gangrene	0	0	1	0.03
	Arthritis bacterial	4	0.1	3	0.08
	Atypical pneumonia	1	0.03	0	0
	Bacteraemia	0	0	1	0.03
	Bacterial infection	2	0.05	0	0
	Bacterial pyelonephritis	1	0.03	0	0
	Bacterial sepsis	0	0	1	0.03
	Beta haemolytic streptococcal infection	1	0.03	2	0.05
	Breast abscess	1	0.03	0	0
	Bronchitis	36	0.94	41	1.07
	Bronchitis bacterial	1	0.03	1	0.03
	Bronchitis viral	2	0.05	2	0.05
	Carbuncle	0	0	1	0.03
	Catheter site infection	1	0.03	0	0
	Cellulitis	57	1.49	76	1.99
	Cellulitis orbital	0	0	1	0.03
	Cellulitis staphylococcal	1	0.03	2	0.05
	Cellulitis streptococcal	1	0.03	0	0
	Chest wall abscess	1	0.03	0	0
	Cholecystitis infective	1	0.03	1	0.03
	Chronic sinusitis	1	0.03	1	0.03
	Clostridium difficile colitis	8	0.21	4	0.1
	Clostridium difficile infection	0	0	1	0.03
	Colonic abscess	0	0	1	0.03
	Conjunctivitis	1	0.03	1	0.03
	Conjunctivitis bacterial	1	0.03	0	0
	Cystitis	5	0.13	5	0.13
	Dengue fever	3	0.08	0	0
	Dermatitis infected	1	0.03	1	0.03
	Device related infection	3	0.08	1	0.03
	Diabetic foot infection	5	0.13	8	0.21
	Diabetic gangrene	0	0	2	0.05
	Disseminated cryptococcosis	1	0.03	0	0
	Diverticulitis	12	0.31	18	0.47

	Dysentery	1	0.03	0	0
	Ear infection	1	0.03	0	0
	Eczema infected	0	0	2	0.05
	Empyema	1	0.03	0	0
	Endocarditis	1	0.03	1	0.03
	Epiglottitis	1	0.03	0	0
	Erysipelas	0	0	1	0.03
	Escherichia infection	0	0	1	0.03
	Escherichia sepsis	2	0.05	2	0.05
	Escherichia urinary tract infection	1	0.03	0	0
	External ear cellulitis	1	0.03	0	0
	Extradural abscess	0	0	1	0.03
	Fungal infection	2	0.05	3	0.08
	Fungal skin infection	2	0.05	0	0
	Furuncle	0	0	1	0.03
	Gangrene	6	0.16	14	0.37
	Gas gangrene	1	0.03	0	0
	Gastritis viral	0	0	1	0.03
	Gastroenteritis	18	0.47	15	0.39
	Gastroenteritis Escherichia coli	0	0	1	0.03
	Gastroenteritis viral	14	0.37	13	0.34
	Gastrointestinal bacterial infection	0	0	1	0.03
	Gingivitis	1	0.03	0	0
	Graft infection	0	0	1	0.03
	Groin abscess	1	0.03	0	0
	H1N1 influenza	0	0	1	0.03
	Helicobacter gastritis	1	0.03	0	0
	Helicobacter infection	2	0.05	1	0.03
	Herpes virus infection	1	0.03	0	0
	Herpes zoster	9	0.24	6	0.16
	Incision site infection	1	0.03	1	0.03
	Infected bite	0	0	1	0.03
	Infected dermal cyst	1	0.03	0	0
	Infected seroma	0	0	1	0.03
	Infected skin ulcer	3	0.08	3	0.08
	Infectious colitis	0	0	2	0.05
	Influenza	21	0.55	19	0.5
	Infusion site infection	0	0	1	0.03
	Intervertebral discitis	0	0	1	0.03
	Joint abscess	1	0.03	0	0
	Keratitis viral	1	0.03	0	0
	Kidney infection	1	0.03	3	0.08
	Klebsiella sepsis	0	0	1	0.03
	Labyrinthitis	3	0.08	0	0
	Laryngitis	0	0	1	0.03
	Localised infection	6	0.16	8	0.21
	Lower respiratory tract infection	3	0.08	5	0.13
	Lung infection	1	0.03	0	0
	Lyme disease	0	0	1	0.03
	Meningitis aseptic	1	0.03	0	0
	Meningitis viral	1	0.03	0	0
	Mucormycosis	1	0.03	0	0
	Nail infection	0	0	1	0.03
	Nasopharyngitis	31	0.81	29	0.76
	Necrotising fasciitis	1	0.03	0	0
	Oesophageal candidiasis	2	0.05	3	0.08
	Oral candidiasis	2	0.05	1	0.03

	Oral herpes	1	0.03	0	0
	Orchitis	0	0	2	0.05
	Osteomyelitis	20	0.52	23	0.6
	Osteomyelitis acute	1	0.03	1	0.03
	Osteomyelitis chronic	3	0.08	4	0.1
	Otitis externa	1	0.03	3	0.08
	Otitis media	1	0.03	1	0.03
	Otitis media chronic	1	0.03	0	0
	Paraspinal abscess	1	0.03	0	0
	Paronychia	3	0.08	2	0.05
	Perineal abscess	1	0.03	0	0
	Periodontitis	1	0.03	0	0
	Perirectal abscess	0	0	2	0.05
	Peritoneal abscess	0	0	1	0.03
	Peritonitis	2	0.05	1	0.03
	Peritonitis bacterial	0	0	1	0.03
	Pharyngitis	3	0.08	2	0.05
	Pharyngitis streptococcal	0	0	1	0.03
	Pilonidal cyst	0	0	1	0.03
	Pneumonia	95	2.49	102	2.67
	Pneumonia bacterial	2	0.05	4	0.1
	Pneumonia influenzal	0	0	2	0.05
	Pneumonia klebsiella	0	0	2	0.05
	Pneumonia mycoplasmal	1	0.03	0	0
	Pneumonia pneumococcal	0	0	1	0.03
	Pneumonia pseudomonal	1	0.03	2	0.05
	Pneumonia staphylococcal	1	0.03	2	0.05
	Pneumonia streptococcal	2	0.05	0	0
	Pneumonia viral	0	0	3	0.08
	Post procedural cellulitis	1	0.03	0	0
	Post procedural infection	9	0.24	3	0.08
	Post procedural sepsis	0	0	1	0.03
	Postoperative abscess	3	0.08	1	0.03
	Postoperative wound infection	11	0.29	2	0.05
	Prostate infection	0	0	1	0.03
	Prostatitis Escherichia coli	0	0	1	0.03
	Pseudomonal bacteraemia	0	0	1	0.03
	Pulmonary sepsis	1	0.03	3	0.08
	Pyelonephritis	3	0.08	11	0.29
	Pyelonephritis acute	4	0.1	1	0.03
	Pyuria	0	0	1	0.03
	Rectal abscess	1	0.03	1	0.03
	Renal abscess	0	0	1	0.03
	Respiratory syncytial virus bronchitis	0	0	1	0.03
	Respiratory tract infection	2	0.05	4	0.1
	Respiratory tract infection viral	2	0.05	2	0.05
	Rhinitis	1	0.03	3	0.08
	Salpingitis	1	0.03	0	0
	Sepsis	32	0.84	31	0.81
	Sepsis syndrome	1	0.03	0	0
	Septic arthritis staphylococcal	1	0.03	1	0.03
	Septic embolus	0	0	1	0.03
	Septic shock	6	0.16	9	0.24
	Sialoadenitis	1	0.03	0	0
	Sinusitis	9	0.24	13	0.34
	Skin candida	1	0.03	0	0

	Skin infection	0	0	1	0.03
	Soft tissue infection	2	0.05	0	0
	Staphylococcal abscess	0	0	2	0.05
	Staphylococcal bacteraemia	0	0	2	0.05
	Staphylococcal infection	4	0.1	8	0.21
	Staphylococcal sepsis	2	0.05	5	0.13
	Streptococcal bacteraemia	0	0	3	0.08
	Streptococcal sepsis	3	0.08	0	0
	Subcutaneous abscess	1	0.03	7	0.18
	Subdiaphragmatic abscess	1	0.03	0	0
	Tinea pedis	1	0.03	2	0.05
	Tonsillitis	0	0	1	0.03
	Tooth abscess	4	0.1	1	0.03
	Tooth infection	1	0.03	2	0.05
	Tracheobronchitis	0	0	2	0.05
	Trichophytosis	0	0	1	0.03
	Tuberculosis	0	0	1	0.03
	Upper respiratory tract infection	43	1.13	34	0.89
	Urinary tract infection	52	1.36	60	1.57
	Urinary tract infection bacterial	0	0	4	0.1
	Urinary tract infection enterococcal	1	0.03	0	0
	Urosepsis	8	0.21	8	0.21
	Vaginitis bacterial	0	0	1	0.03
	Vestibular neuronitis	0	0	1	0.03
	Viraemia	1	0.03	0	0
	Viral infection	2	0.05	5	0.13
	Viral pericarditis	1	0.03	0	0
	Viral upper respiratory tract infection	3	0.08	3	0.08
	Vulval abscess	1	0.03	1	0.03
	Vulvovaginal mycotic infection	0	0	1	0.03
	Wound infection	2	0.05	5	0.13
Injury, poisoning and procedural complications	Accident at work	0	0	2	0.05
	Accidental overdose	3	0.08	2	0.05
	Adrenal gland injury	1	0.03	0	0
	Alcohol poisoning	2	0.05	0	0
	Anaemia postoperative	1	0.03	1	0.03
	Anaesthetic complication	1	0.03	0	0
	Anaesthetic complication pulmonary	0	0	1	0.03
	Anastomotic ulcer	0	0	1	0.03
	Animal bite	0	0	2	0.05
	Ankle fracture	2	0.05	5	0.13
	Arthropod bite	0	0	1	0.03
	Back injury	1	0.03	1	0.03
	Brachial plexus injury	0	0	1	0.03
	Burns third degree	1	0.03	1	0.03
	Cardiac valve replacement complication	1	0.03	0	0
	Cervical vertebral fracture	0	0	1	0.03
	Chest injury	1	0.03	2	0.05
	Clavicle fracture	1	0.03	0	0
	Concussion	1	0.03	0	0
	Contusion	5	0.13	8	0.21
	Corneal abrasion	1	0.03	0	0
	Coronary artery restenosis	1	0.03	1	0.03

	Coronary vascular graft occlusion	1	0.03	1	0.03
	Craniocerebral injury	1	0.03	0	0
	Deep vein thrombosis postoperative	0	0	1	0.03
	Drug administration error	1	0.03	0	0
	Drug dose omission	0	0	1	0.03
	Excoriation	1	0.03	1	0.03
	Extra dose administered	0	0	1	0.03
	Eye injury	0	0	1	0.03
	Face injury	1	0.03	0	0
	Facial bones fracture	1	0.03	2	0.05
	Fall	59	1.55	61	1.6
	Femoral neck fracture	0	0	2	0.05
	Femur fracture	3	0.08	5	0.13
	Fibula fracture	0	0	1	0.03
	Foot fracture	3	0.08	6	0.16
	Fracture	1	0.03	0	0
	Gastrointestinal anastomotic leak	0	0	1	0.03
	Gastrointestinal injury	1	0.03	0	0
	Gastrointestinal stoma complication	1	0.03	0	0
	Gastrostomy tube site complication	1	0.03	0	0
	Hand fracture	3	0.08	1	0.03
	Head injury	0	0	1	0.03
	Heat illness	0	0	1	0.03
	Heat stroke	1	0.03	0	0
	Hip fracture	1	0.03	2	0.05
	Humerus fracture	1	0.03	3	0.08
	Ilium fracture	1	0.03	0	0
	Inappropriate schedule of drug administration	2	0.05	0	0
	Incarcerated incisional hernia	0	0	1	0.03
	Incision site haemorrhage	1	0.03	0	0
	Incisional hernia	1	0.03	0	0
	Injury	1	0.03	2	0.05
	Intentional overdose	0	0	1	0.03
	Joint dislocation	3	0.08	2	0.05
	Joint injury	0	0	3	0.08
	Laceration	7	0.18	7	0.18
	Ligament rupture	2	0.05	0	0
	Ligament sprain	1	0.03	3	0.08
	Limb injury	1	0.03	3	0.08
	Lower limb fracture	2	0.05	0	0
	Medication error	1	0.03	0	0
	Meniscus injury	1	0.03	3	0.08
	Multiple fractures	1	0.03	0	0
	Multiple injuries	1	0.03	1	0.03
	Muscle rupture	1	0.03	0	0
	Muscle strain	5	0.13	5	0.13
	Musculoskeletal injury	0	0	1	0.03
	Overdose	1	0.03	2	0.05
	Pelvic fracture	0	0	3	0.08
	Pneumothorax traumatic	1	0.03	0	0
	Post concussion syndrome	1	0.03	0	0
	Post procedural complication	3	0.08	2	0.05
	Post procedural haematoma	2	0.05	0	0
	Post procedural haematuria	0	0	1	0.03

	Post procedural haemorrhage	4	0.1	2	0.05
	Postoperative fever	1	0.03	0	0
	Postoperative ileus	1	0.03	0	0
	Postoperative renal failure	0	0	1	0.03
	Postoperative respiratory failure	2	0.05	1	0.03
	Postoperative thoracic procedure complication	0	0	1	0.03
	Postoperative wound complication	0	0	1	0.03
	Postpericardiotomy syndrome	0	0	1	0.03
	Procedural complication	0	0	1	0.03
	Procedural haemorrhage	0	0	1	0.03
	Procedural hypotension	1	0.03	0	0
	Procedural intestinal perforation	1	0.03	0	0
	Procedural pain	0	0	1	0.03
	Pulmonary contusion	0	0	1	0.03
	Radius fracture	2	0.05	1	0.03
	Rib fracture	8	0.21	3	0.08
	Road traffic accident	19	0.5	16	0.42
	Seroma	0	0	1	0.03
	Skin abrasion	0	0	1	0.03
	Spinal compression fracture	1	0.03	1	0.03
	Spinal fracture	0	0	1	0.03
	Stab wound	1	0.03	0	0
	Stoma site reaction	1	0.03	0	0
	Stress fracture	1	0.03	0	0
	Subdural haematoma	4	0.1	3	0.08
	Subdural haemorrhage	0	0	1	0.03
	Tendon rupture	3	0.08	2	0.05
	Thermal burn	3	0.08	0	0
	Thoracic vertebral fracture	1	0.03	0	0
	Tibia fracture	0	0	2	0.05
	Toxicity to various agents	3	0.08	1	0.03
	Transfusion-related acute lung injury	0	0	1	0.03
	Traumatic haematoma	0	0	1	0.03
	Upper limb fracture	0	0	2	0.05
	Ureteric injury	1	0.03	0	0
	Vascular graft complication	0	0	1	0.03
	Vascular procedure complication	0	0	1	0.03
	Vascular pseudoaneurysm	1	0.03	0	0
	Wound	2	0.05	6	0.16
	Wound secretion	0	0	1	0.03
	Wrist fracture	4	0.1	3	0.08
	Wrong drug administered	1	0.03	0	0
Investigations	Alanine aminotransferase increased	4	0.1	1	0.03
	Anticoagulation drug level below therapeutic	0	0	1	0.03
	Arteriogram coronary	2	0.05	3	0.08
	Aspartate aminotransferase increased	2	0.05	0	0
	Biopsy kidney	0	0	1	0.03
	Biopsy lung	0	0	1	0.03
	Blood cholesterol increased	1	0.03	2	0.05
	Blood creatine increased	2	0.05	0	0
	Blood creatine phosphokinase increased	1	0.03	1	0.03

	Blood creatinine increased	7	0.18	9	0.24
	Blood glucose decreased	1	0.03	1	0.03
	Blood glucose increased	1	0.03	2	0.05
	Blood insulin decreased	0	0	1	0.03
	Blood lactic acid increased	0	0	1	0.03
	Blood magnesium decreased	1	0.03	0	0
	Blood potassium decreased	2	0.05	1	0.03
	Blood potassium increased	5	0.13	3	0.08
	Blood pressure increased	4	0.1	2	0.05
	Blood sodium decreased	0	0	1	0.03
	Blood testosterone decreased	0	0	1	0.03
	Blood triglycerides abnormal	0	0	1	0.03
	Blood uric acid increased	0	0	1	0.03
	Blood urine present	1	0.03	0	0
	Brain natriuretic peptide increased	1	0.03	0	0
	Cardiac monitoring	0	0	1	0.03
	Cardiac murmur	0	0	4	0.1
	Cardiac stress test	1	0.03	0	0
	Carotid bruit	1	0.03	1	0.03
	Catheterisation cardiac	2	0.05	2	0.05
	Coagulation time prolonged	1	0.03	0	0
	Colonoscopy	1	0.03	0	0
	Echocardiogram	1	0.03	0	0
	Ejection fraction	1	0.03	0	0
	Ejection fraction abnormal	0	0	1	0.03
	Ejection fraction decreased	2	0.05	1	0.03
	Electrocardiogram abnormal	2	0.05	4	0.1
	Electrocardiogram change	1	0.03	1	0.03
	Electrocardiogram Q wave abnormal	0	0	1	0.03
	Electrocardiogram QT prolonged	1	0.03	0	0
	Electrocardiogram ST segment abnormal	0	0	1	0.03
	Electrocardiogram ST segment depression	1	0.03	1	0.03
	Electrocardiogram ST-T change	1	0.03	1	0.03
	Electrocardiogram ST-T segment abnormal	2	0.05	0	0
	Electrocardiogram T wave abnormal	1	0.03	0	0
	Electrocardiogram T wave inversion	2	0.05	1	0.03
	Glycosylated haemoglobin increased	1	0.03	1	0.03
	Haematocrit decreased	1	0.03	0	0
	Haematocrit increased	1	0.03	0	0
	Haemoglobin decreased	1	0.03	0	0
	Heart rate decreased	1	0.03	1	0.03
	Heart rate irregular	1	0.03	1	0.03
	Helicobacter test positive	1	0.03	0	0
	Hepatic enzyme increased	2	0.05	1	0.03
	High density lipoprotein decreased	1	0.03	0	0
	International normalised ratio increased	1	0.03	3	0.08
	Intraocular pressure increased	1	0.03	0	0
	Laboratory test abnormal	0	0	1	0.03
	Low density lipoprotein increased	0	0	1	0.03

	Medical observation	1	0.03	0	0
	Occult blood positive	1	0.03	1	0.03
	Prostatic specific antigen increased	1	0.03	0	0
	QRS axis abnormal	0	0	1	0.03
	Scan myocardial perfusion abnormal	0	0	1	0.03
	Staphylococcus test positive	1	0.03	0	0
	Troponin increased	1	0.03	4	0.1
	Weight decreased	1	0.03	0	0
	Weight increased	5	0.13	6	0.16
Metabolism and nutrition disorders	Decreased appetite	1	0.03	2	0.05
	Dehydration	27	0.71	19	0.5
	Diabetes mellitus	1	0.03	4	0.1
	Diabetes mellitus inadequate control	4	0.1	7	0.18
	Diabetic complication	0	0	1	0.03
	Diabetic ketoacidosis	5	0.13	14	0.37
	Diabetic metabolic decompensation	2	0.05	2	0.05
	Dyslipidaemia	5	0.13	4	0.1
	Electrolyte imbalance	2	0.05	1	0.03
	Failure to thrive	1	0.03	0	0
	Fluid overload	3	0.08	3	0.08
	Fluid retention	3	0.08	0	0
	Gout	12	0.31	13	0.34
	Hyperammonaemia	1	0.03	0	0
	Hypercholesterolaemia	0	0	3	0.08
	Hyperglycaemia	17	0.45	28	0.73
	Hyperkalaemia	26	0.68	29	0.76
	Hyperlipidaemia	1	0.03	4	0.1
	Hypernatraemia	2	0.05	1	0.03
	Hypertriglyceridaemia	0	0	2	0.05
	Hyperuricaemia	6	0.16	2	0.05
	Hypocalcaemia	0	0	2	0.05
	Hypoglycaemia	53	1.39	58	1.52
	Hypoglycaemia unawareness	1	0.03	0	0
	Hypokalaemia	6	0.16	6	0.16
	Hypomagnesaemia	2	0.05	1	0.03
	Hyponatraemia	12	0.31	7	0.18
	Hypovolaemia	2	0.05	2	0.05
	Increased appetite	2	0.05	3	0.08
	Iron deficiency	0	0	1	0.03
	Lactic acidosis	1	0.03	2	0.05
	Metabolic acidosis	3	0.08	2	0.05
	Obesity	3	0.08	1	0.03
	Pseudohyponatraemia	0	0	1	0.03
	Type 1 diabetes mellitus	1	0.03	0	0
	Type 2 diabetes mellitus	2	0.05	2	0.05
	Vitamin B12 deficiency	1	0.03	0	0
	Vitamin D deficiency	3	0.08	1	0.03
Musculoskeletal and connective tissue disorders	Acquired claw toe	0	0	1	0.03
	Ankle deformity	0	0	1	0.03
	Arthralgia	20	0.52	17	0.45
	Arthritis	6	0.16	8	0.21

	Arthropathy	2	0.05	0	0
	Back disorder	0	0	1	0.03
	Back pain	24	0.63	29	0.76
	Bone loss	0	0	1	0.03
	Bursitis	1	0.03	4	0.1
	Cervical spinal stenosis	6	0.16	3	0.08
	Chondrocalcinosis pyrophosphate	0	0	2	0.05
	Connective tissue disorder	0	0	1	0.03
	Costochondritis	2	0.05	0	0
	Dactylitis	1	0.03	0	0
	Enthesopathy	1	0.03	0	0
	Exostosis	3	0.08	1	0.03
	Flank pain	1	0.03	2	0.05
	Foot deformity	1	0.03	1	0.03
	Gouty arthritis	2	0.05	2	0.05
	Haemarthrosis	0	0	1	0.03
	Intervertebral disc degeneration	4	0.1	4	0.1
	Intervertebral disc disorder	1	0.03	3	0.08
	Intervertebral disc protrusion	10	0.26	3	0.08
	Joint effusion	1	0.03	1	0.03
	Joint lock	1	0.03	0	0
	Joint swelling	2	0.05	1	0.03
	Lower extremity mass	0	0	1	0.03
	Lumbar spinal stenosis	13	0.34	7	0.18
	Muscle spasms	11	0.29	10	0.26
	Muscle swelling	1	0.03	0	0
	Muscular weakness	6	0.16	6	0.16
	Musculoskeletal chest pain	9	0.24	12	0.31
	Musculoskeletal pain	8	0.21	6	0.16
	Musculoskeletal stiffness	1	0.03	1	0.03
	Myalgia	7	0.18	3	0.08
	Myopathy	1	0.03	1	0.03
	Neck pain	3	0.08	6	0.16
	Neuropathic arthropathy	2	0.05	0	0
	Osteitis	1	0.03	0	0
	Osteoarthritis	41	1.07	34	0.89
	Osteonecrosis	0	0	1	0.03
	Osteopenia	2	0.05	0	0
	Osteoporosis	1	0.03	1	0.03
	Pain in extremity	12	0.31	13	0.34
	Pain in jaw	0	0	1	0.03
	Periarthritis	2	0.05	1	0.03
	Plantar fasciitis	0	0	1	0.03
	Polyarthritis	2	0.05	0	0
	Polymyalgia rheumatica	0	0	1	0.03
	Pseudarthrosis	0	0	1	0.03
	Rhabdomyolysis	4	0.1	5	0.13
	Rheumatoid arthritis	1	0.03	0	0
	Rotator cuff syndrome	3	0.08	4	0.1
	Scoliosis	0	0	1	0.03
	Soft tissue necrosis	0	0	1	0.03
	Spinal column stenosis	4	0.1	5	0.13
	Spinal disorder	0	0	1	0.03
	Spinal osteoarthritis	6	0.16	4	0.1
	Spondylitis	0	0	1	0.03
	Spondylolisthesis	2	0.05	2	0.05
	Synovial cyst	1	0.03	1	0.03

	Tendon disorder	1	0.03	0	0
	Tendonitis	2	0.05	5	0.13
	Tenosynovitis	0	0	1	0.03
	Tenosynovitis stenosans	0	0	1	0.03
	Trigger finger	0	0	2	0.05
	Upper extremity mass	0	0	1	0.03
	Vertebral foraminal stenosis	2	0.05	1	0.03
	Vertebral lesion	0	0	1	0.03
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Acute leukaemia	1	0.03	0	0
	Acute myeloid leukaemia	0	0	1	0.03
	Adenocarcinoma	0	0	1	0.03
	Adenocarcinoma gastric	1	0.03	1	0.03
	Adenocarcinoma of colon	2	0.05	5	0.13
	Adenocarcinoma pancreas	0	0	1	0.03
	Adenoma benign	0	0	1	0.03
	Adrenal adenoma	0	0	1	0.03
	Adrenal neoplasm	0	0	1	0.03
	Basal cell carcinoma	8	0.21	5	0.13
	B-cell lymphoma	2	0.05	0	0
	B-cell lymphoma stage III	0	0	1	0.03
	Benign neoplasm of bladder	0	0	1	0.03
	Benign neoplasm of thyroid gland	1	0.03	0	0
	Benign ovarian tumour	0	0	1	0.03
	Benign salivary gland neoplasm	1	0.03	0	0
	Bile duct adenocarcinoma	1	0.03	0	0
	Bladder cancer	1	0.03	3	0.08
	Bladder cancer recurrent	1	0.03	0	0
	Bladder cancer stage 0, with cancer in situ	1	0.03	0	0
	Bladder transitional cell carcinoma	1	0.03	1	0.03
	Bladder transitional cell carcinoma recurrent	2	0.05	0	0
	Bladder transitional cell carcinoma stage I	1	0.03	0	0
	Bone cancer	0	0	1	0.03
	Bowen's disease	0	0	1	0.03
	Breast cancer	1	0.03	2	0.05
	Breast cancer metastatic	1	0.03	0	0
	Breast cancer stage I	0	0	2	0.05
	Breast cancer stage II	1	0.03	0	0
	Breast cancer stage IV	1	0.03	0	0
	Cardiac valve fibroelastoma	0	0	1	0.03
	Choroid melanoma	1	0.03	0	0
	Chronic lymphocytic leukaemia	0	0	1	0.03
	Chronic myeloid leukaemia	0	0	1	0.03
	Colon adenoma	3	0.08	2	0.05
	Colon cancer	2	0.05	1	0.03
	Colon cancer metastatic	2	0.05	1	0.03
	Colon cancer stage III	0	0	1	0.03
	Colorectal cancer metastatic	0	0	1	0.03
	Endometrial adenocarcinoma	3	0.08	3	0.08
	Fibroma	0	0	1	0.03
	Gallbladder adenocarcinoma	0	0	1	0.03
	Gastrointestinal tract adenoma	1	0.03	0	0
	Haemangioma of liver	0	0	1	0.03

	Hepatic cancer	0	0	1	0.03
	Hepatic cancer metastatic	0	0	1	0.03
	Hepatic neoplasm	1	0.03	0	0
	Hepatocellular carcinoma	2	0.05	1	0.03
	Intraductal proliferative breast lesion	3	0.08	2	0.05
	Invasive ductal breast carcinoma	2	0.05	5	0.13
	Leiomyoma	0	0	1	0.03
	Leukaemia	0	0	1	0.03
	Lipoma	1	0.03	3	0.08
	Lung adenocarcinoma metastatic	0	0	1	0.03
	Lung adenocarcinoma stage II	1	0.03	0	0
	Lung neoplasm malignant	2	0.05	0	0
	Lymphoma	1	0.03	1	0.03
	Malignant melanoma	1	0.03	2	0.05
	Malignant melanoma in situ	1	0.03	0	0
	Meningioma benign	2	0.05	0	0
	Metastases to bone	0	0	1	0.03
	Metastases to liver	0	0	1	0.03
	Metastases to lung	0	0	1	0.03
	Metastases to lymph nodes	0	0	1	0.03
	Metastatic renal cell carcinoma	1	0.03	0	0
	Metastatic squamous cell carcinoma	0	0	1	0.03
	Mucinous endometrial carcinoma	0	0	1	0.03
	Myelodysplastic syndrome	0	0	1	0.03
	Non-small cell lung cancer	1	0.03	1	0.03
	Non-small cell lung cancer stage I	0	0	1	0.03
	Oesophageal adenocarcinoma	0	0	2	0.05
	Oesophageal carcinoma	1	0.03	0	0
	Ovarian cancer recurrent	1	0.03	0	0
	Pancreatic carcinoma	2	0.05	0	0
	Pancreatic carcinoma metastatic	1	0.03	0	0
	Papillary cystadenoma lymphomatosum	1	0.03	1	0.03
	Papillary thyroid cancer	0	0	1	0.03
	Parathyroid tumour benign	1	0.03	2	0.05
	Penile squamous cell carcinoma	0	0	1	0.03
	Phaeochromocytoma	1	0.03	0	0
	Pituitary tumour benign	1	0.03	0	0
	Plasma cell myeloma	3	0.08	0	0
	Prostate cancer	13	0.34	5	0.13
	Prostate cancer metastatic	0	0	2	0.05
	Prostate cancer stage I	0	0	3	0.08
	Prostate cancer stage II	1	0.03	0	0
	Rectal adenocarcinoma	1	0.03	0	0
	Rectal adenoma	1	0.03	0	0
	Rectal cancer	0	0	2	0.05
	Rectal cancer metastatic	1	0.03	0	0
	Renal cancer	2	0.05	0	0
	Renal cancer metastatic	1	0.03	1	0.03
	Renal cell carcinoma	1	0.03	3	0.08
	Salivary gland cancer	0	0	1	0.03
	Seborrhoeic keratosis	1	0.03	2	0.05
	Small cell lung cancer	1	0.03	0	0
	Small cell lung cancer extensive stage	0	0	1	0.03

	Small cell lung cancer metastatic	1	0.03	0	0
	Squamous cell carcinoma	3	0.08	2	0.05
	Squamous cell carcinoma of lung	2	0.05	1	0.03
	Squamous cell carcinoma of skin	0	0	1	0.03
	Squamous cell carcinoma of the tongue	0	0	2	0.05
	Testicular seminoma (pure) stage I	0	0	1	0.03
	Testis cancer	0	0	1	0.03
	Thyroid cancer	1	0.03	0	0
	Tonsil cancer	1	0.03	0	0
	Transitional cell carcinoma	0	0	1	0.03
	Tumour of ampulla of Vater	0	0	1	0.03
	Ureteric cancer	0	0	1	0.03
	Uterine cancer	2	0.05	1	0.03
	Uterine leiomyoma	1	0.03	0	0
Nervous system disorders	Altered state of consciousness	2	0.05	0	0
	Amnesia	0	0	1	0.03
	Aphasia	0	0	1	0.03
	Ataxia	1	0.03	0	0
	Autonomic nervous system imbalance	1	0.03	0	0
	Balance disorder	0	0	1	0.03
	Basilar migraine	1	0.03	0	0
	Brain injury	1	0.03	1	0.03
	Burning sensation	1	0.03	0	0
	Carotid artery disease	4	0.1	2	0.05
	Carotid artery occlusion	0	0	2	0.05
	Carotid artery stenosis	15	0.39	14	0.37
	Carpal tunnel syndrome	2	0.05	7	0.18
	Cerebellar atrophy	1	0.03	0	0
	Cerebral atrophy	1	0.03	0	0
	Cerebral ischaemia	0	0	1	0.03
	Cerebral small vessel ischaemic disease	1	0.03	0	0
	Cerebrovascular disorder	1	0.03	0	0
	Cervical myelopathy	2	0.05	1	0.03
	Chronic inflammatory demyelinating polyradiculoneuropathy	1	0.03	0	0
	Cranial nerve paralysis	0	0	1	0.03
	Dementia	4	0.1	1	0.03
	Dementia Alzheimer's type	0	0	1	0.03
	Dementia with Lewy bodies	1	0.03	0	0
	Diabetic mononeuropathy	0	0	1	0.03
	Diabetic neuropathy	14	0.37	10	0.26
	Dizziness	21	0.55	20	0.52
	Dizziness postural	1	0.03	0	0
	Dysarthria	1	0.03	3	0.08
	Dysgeusia	2	0.05	1	0.03
	Dystonia	1	0.03	0	0
	Encephalopathy	5	0.13	9	0.24
	Epidural lipomatosis	0	0	1	0.03
	Essential tremor	0	0	1	0.03
	Facial paralysis	3	0.08	2	0.05
	Generalised tonic-clonic seizure	0	0	3	0.08
	Guillain-Barre syndrome	1	0.03	1	0.03
	Headache	17	0.45	15	0.39

	Hemiparesis	2	0.05	2	0.05
	Hemiplegic migraine	1	0.03	0	0
	Hepatic encephalopathy	2	0.05	3	0.08
	Hydrocephalus	1	0.03	2	0.05
	Hyperaesthesia	1	0.03	0	0
	Hyperglycaemic seizure	0	0	1	0.03
	Hypertensive encephalopathy	0	0	2	0.05
	Hypoaesthesia	5	0.13	1	0.03
	Hypogeusia	0	0	1	0.03
	Hypoglycaemic unconsciousness	2	0.05	0	0
	Hyposmia	0	0	1	0.03
	Hypoxic-ischaemic encephalopathy	1	0.03	0	0
	IIIrd nerve paralysis	1	0.03	1	0.03
	Intensive care unit acquired weakness	0	0	1	0.03
	Intercostal neuralgia	0	0	1	0.03
	Intracranial pressure increased	0	0	1	0.03
	Lacunar infarction	0	0	1	0.03
	Lethargy	1	0.03	1	0.03
	Loss of consciousness	4	0.1	4	0.1
	Lumbar radiculopathy	3	0.08	4	0.1
	Memory impairment	1	0.03	1	0.03
	Meralgia paraesthetica	1	0.03	0	0
	Metabolic encephalopathy	7	0.18	9	0.24
	Migraine	5	0.13	0	0
	Migraine-triggered seizure	0	0	1	0.03
	Mononeuropathy multiplex	0	0	1	0.03
	Motor neurone disease	1	0.03	0	0
	Multiple sclerosis relapse	0	0	1	0.03
	Myasthenia gravis	0	0	1	0.03
	Myelopathy	0	0	1	0.03
	Nerve compression	1	0.03	0	0
	Nerve root compression	1	0.03	0	0
	Nervous system disorder	0	0	1	0.03
	Neuralgia	0	0	2	0.05
	Neuritis	0	0	2	0.05
	Neuromyopathy	0	0	1	0.03
	Neuropathy peripheral	9	0.24	7	0.18
	Normal pressure hydrocephalus	2	0.05	0	0
	Paraesthesia	2	0.05	3	0.08
	Parkinson's disease	1	0.03	4	0.1
	Peripheral sensorimotor neuropathy	1	0.03	0	0
	Peripheral sensory neuropathy	1	0.03	1	0.03
	Polyneuropathy	1	0.03	0	0
	Post stroke seizure	0	0	1	0.03
	Post-injection delirium sedation syndrome	1	0.03	0	0
	Presyncope	3	0.08	12	0.31
	Radicular pain	0	0	1	0.03
	Radiculopathy	0	0	2	0.05
	Sciatica	3	0.08	4	0.1
	Seizure	6	0.16	6	0.16
	Senile dementia	0	0	1	0.03
	Somnolence	2	0.05	1	0.03
	Spinal cord compression	0	0	2	0.05

	Spondylitic myelopathy	0	0	1	0.03
	Status epilepticus	1	0.03	0	0
	Subarachnoid haemorrhage	1	0.03	1	0.03
	Syncope	26	0.68	29	0.76
	Tension headache	0	0	1	0.03
	Toxic encephalopathy	1	0.03	2	0.05
	Transient global amnesia	0	0	1	0.03
	Transient ischaemic attack	10	0.26	8	0.21
	Tremor	1	0.03	3	0.08
	Ulnar nerve palsy	1	0.03	0	0
	Vascular dementia	1	0.03	0	0
	Vascular headache	0	0	1	0.03
	Vascular parkinsonism	1	0.03	0	0
	Vertebral artery occlusion	0	0	1	0.03
	Vertebrobasilar insufficiency	0	0	1	0.03
	Visual field defect	0	0	1	0.03
	VIth nerve paralysis	1	0.03	0	0
	VIth nerve paresis	1	0.03	0	0
Product issues	Device dislocation	1	0.03	2	0.05
	Device failure	1	0.03	0	0
	Device fastener issue	1	0.03	0	0
	Device inappropriate shock delivery	0	0	1	0.03
	Device lead damage	0	0	1	0.03
	Device loosening	0	0	1	0.03
	Device malfunction	0	0	2	0.05
	Lead dislodgement	1	0.03	1	0.03
Psychiatric disorders	Acute stress disorder	1	0.03	0	0
	Affective disorder	1	0.03	1	0.03
	Aggression	1	0.03	0	0
	Agitation	1	0.03	0	0
	Alcohol withdrawal syndrome	1	0.03	2	0.05
	Anger	0	0	1	0.03
	Anxiety	6	0.16	4	0.1
	Bipolar disorder	3	0.08	3	0.08
	Confusional state	5	0.13	8	0.21
	Delirium	4	0.1	6	0.16
	Depression	11	0.29	8	0.21
	Depression suicidal	1	0.03	1	0.03
	Hallucination, visual	1	0.03	0	0
	Head banging	0	0	1	0.03
	Insomnia	8	0.21	3	0.08
	Intentional self-injury	1	0.03	0	0
	Libido decreased	1	0.03	0	0
	Major depression	2	0.05	2	0.05
	Mental status changes	7	0.18	12	0.31
	Panic attack	1	0.03	0	0
	Paranoia	1	0.03	0	0
	Personality change due to a general medical condition	1	0.03	0	0
	Post stroke depression	0	0	1	0.03
	Post-traumatic stress disorder	0	0	1	0.03
	Psychotic disorder	0	0	1	0.03
	Schizoaffective disorder	0	0	1	0.03
	Schizoaffective disorder bipolar type	0	0	1	0.03
	Schizophrenia	3	0.08	0	0

	Suicidal ideation	5	0.13	3	0.08
	Suicide attempt	0	0	3	0.08
Renal and urinary disorders	Acute kidney injury	82	2.15	111	2.91
	Acute prerenal failure	2	0.05	2	0.05
	Anuria	0	0	2	0.05
	Azotaemia	1	0.03	0	0
	Bladder mass	0	0	1	0.03
	Bladder neck obstruction	0	0	1	0.03
	Bladder outlet obstruction	1	0.03	0	0
	Bladder spasm	1	0.03	0	0
	Calculus bladder	2	0.05	0	0
	Calculus urinary	0	0	1	0.03
	Chronic kidney disease	26	0.68	32	0.84
	Cystitis noninfective	1	0.03	0	0
	Diabetic nephropathy	3	0.08	8	0.21
	Dysuria	0	0	1	0.03
	End stage renal disease	10	0.26	7	0.18
	Glomerulonephritis rapidly progressive	1	0.03	0	0
	Glomerulosclerosis	0	0	1	0.03
	Haematuria	6	0.16	7	0.18
	Hydronephrosis	2	0.05	3	0.08
	Hypertonic bladder	1	0.03	0	0
	Incontinence	0	0	1	0.03
	Micturition urgency	2	0.05	0	0
	Nephritis	1	0.03	0	0
	Nephrolithiasis	15	0.39	15	0.39
	Nephropathy	2	0.05	1	0.03
	Nephropathy toxic	0	0	2	0.05
	Nephrosclerosis	1	0.03	0	0
	Nephrotic syndrome	1	0.03	3	0.08
	Nocturia	1	0.03	1	0.03
	Pollakiuria	3	0.08	2	0.05
	Polyuria	0	0	1	0.03
	Proteinuria	0	0	1	0.03
	Renal artery stenosis	0	0	1	0.03
	Renal colic	1	0.03	1	0.03
	Renal cyst	6	0.16	2	0.05
	Renal failure	17	0.45	19	0.5
	Renal impairment	11	0.29	9	0.24
	Renal mass	1	0.03	0	0
	Renal tubular necrosis	0	0	1	0.03
	Stag horn calculus	2	0.05	0	0
	Stress urinary incontinence	2	0.05	0	0
	Tubulointerstitial nephritis	0	0	1	0.03
	Ureterolithiasis	3	0.08	5	0.13
	Urethral stenosis	1	0.03	0	0
	Urinary hesitation	1	0.03	0	0
	Urinary incontinence	3	0.08	1	0.03
	Urinary retention	10	0.26	4	0.1
	Urinary tract obstruction	1	0.03	0	0
	Vesicoureteric reflux	0	0	1	0.03
Reproductive system and breast disorders	Acquired phimosis	1	0.03	0	0
	Balanoposthitis	1	0.03	1	0.03
	Benign prostatic hyperplasia	12	0.31	8	0.21
	Breast discomfort	1	0.03	0	0

	Breast enlargement	1	0.03	0	0
	Breast mass	1	0.03	0	0
	Cervical cyst	1	0.03	0	0
	Cervical dysplasia	0	0	2	0.05
	Cervix haemorrhage uterine	1	0.03	0	0
	Cystocele	2	0.05	0	0
	Endometrial hyperplasia	3	0.08	0	0
	Erectile dysfunction	2	0.05	0	0
	Ovarian cyst	2	0.05	0	0
	Postmenopausal haemorrhage	1	0.03	0	0
	Prostatism	1	0.03	0	0
	Prostatitis	2	0.05	4	0.1
	Prostatomegaly	3	0.08	2	0.05
	Rectocele	1	0.03	0	0
	Uterine mass	1	0.03	0	0
	Uterine prolapse	0	0	1	0.03
	Vaginal haemorrhage	0	0	2	0.05
	Vulvovaginal pruritus	1	0.03	0	0
Respiratory, thoracic and mediastinal disorders	Acquired diaphragmatic eventration	0	0	1	0.03
	Acute pulmonary oedema	6	0.16	6	0.16
	Acute respiratory distress syndrome	3	0.08	0	0
	Acute respiratory failure	21	0.55	28	0.73
	Allergic sinusitis	1	0.03	0	0
	Asthma	15	0.39	10	0.26
	Asthma-chronic obstructive pulmonary disease overlap syndrome	1	0.03	0	0
	Atelectasis	1	0.03	5	0.13
	Bronchial hyperreactivity	0	0	1	0.03
	Bronchitis chronic	0	0	1	0.03
	Catarrh	0	0	1	0.03
	Chronic obstructive pulmonary disease	45	1.18	60	1.57
	Chronic respiratory failure	2	0.05	0	0
	Cough	14	0.37	15	0.39
	Dyspnoea	31	0.81	37	0.97
	Dyspnoea exertional	13	0.34	4	0.1
	Dyspnoea paroxysmal nocturnal	1	0.03	2	0.05
	Epistaxis	4	0.1	8	0.21
	Haemothorax	1	0.03	0	0
	Hiccups	2	0.05	0	0
	Hydrothorax	0	0	1	0.03
	Hypoxia	4	0.1	8	0.21
	Idiopathic pulmonary fibrosis	1	0.03	0	0
	Interstitial lung disease	1	0.03	3	0.08
	Laryngeal stenosis	1	0.03	0	0
	Lung cyst	1	0.03	0	0
	Nasal polyps	2	0.05	1	0.03
	Nasal septum deviation	2	0.05	1	0.03
	Non-cardiogenic pulmonary oedema	1	0.03	0	0
	Obstructive airways disorder	1	0.03	0	0
	Oropharyngeal pain	2	0.05	1	0.03
	Orthopnoea	1	0.03	1	0.03
	Paranasal sinus hypersecretion	1	0.03	2	0.05

	Pharyngeal oedema	2	0.05	0	0
	Pickwickian syndrome	0	0	1	0.03
	Pleural effusion	2	0.05	6	0.16
	Pleurisy	1	0.03	3	0.08
	Pleuritic pain	0	0	1	0.03
	Pneumonia aspiration	1	0.03	4	0.1
	Pneumonitis	1	0.03	1	0.03
	Pneumothorax	3	0.08	1	0.03
	Pneumothorax spontaneous	0	0	1	0.03
	Productive cough	1	0.03	0	0
	Pulmonary congestion	1	0.03	1	0.03
	Pulmonary embolism	11	0.29	9	0.24
	Pulmonary fibrosis	1	0.03	0	0
	Pulmonary hypertension	6	0.16	6	0.16
	Pulmonary mass	6	0.16	3	0.08
	Pulmonary oedema	7	0.18	8	0.21
	Pulmonary sarcoidosis	0	0	1	0.03
	Reflux laryngitis	1	0.03	0	0
	Respiratory disorder	0	0	1	0.03
	Respiratory distress	2	0.05	2	0.05
	Respiratory failure	21	0.55	16	0.42
	Respiratory tract congestion	0	0	1	0.03
	Respiratory tract inflammation	0	0	1	0.03
	Rhinitis allergic	1	0.03	2	0.05
	Rhinorrhoea	1	0.03	1	0.03
	Sinus congestion	2	0.05	3	0.08
	Sleep apnoea syndrome	3	0.08	12	0.31
	Upper respiratory tract inflammation	2	0.05	2	0.05
	Wheezing	1	0.03	1	0.03
Skin and subcutaneous tissue disorders	Acne	1	0.03	0	0
	Actinic keratosis	3	0.08	0	0
	Angioedema	3	0.08	9	0.24
	Blister	2	0.05	1	0.03
	Chronic actinic dermatitis	1	0.03	0	0
	Cutis laxa	1	0.03	0	0
	Decubitus ulcer	1	0.03	2	0.05
	Dermal cyst	1	0.03	0	0
	Dermatitis	1	0.03	4	0.1
	Dermatitis allergic	1	0.03	2	0.05
	Dermatitis atopic	1	0.03	1	0.03
	Dermatitis contact	1	0.03	0	0
	Diabetic dermopathy	2	0.05	0	0
	Diabetic foot	11	0.29	17	0.45
	Diabetic neuropathic ulcer	0	0	1	0.03
	Diabetic ulcer	1	0.03	0	0
	Dry skin	2	0.05	1	0.03
	Ecchymosis	1	0.03	1	0.03
	Eczema	4	0.1	2	0.05
	Eczema nummular	0	0	1	0.03
	Erythema	0	0	1	0.03
	Granuloma annulare	0	0	1	0.03
	Hair disorder	1	0.03	0	0
	Hidradenitis	1	0.03	0	0
	Hyperhidrosis	2	0.05	1	0.03
	Hyperkeratosis	1	0.03	3	0.08

	Hypersensitivity vasculitis	1	0.03	0	0
	Hypotrichosis	1	0.03	0	0
	Ingrowing nail	1	0.03	0	0
	Miliaria	1	0.03	0	0
	Nail dystrophy	0	0	1	0.03
	Necrobiosis lipoidica diabeticorum	1	0.03	0	0
	Neuropathic ulcer	2	0.05	1	0.03
	Palmoplantar keratoderma	1	0.03	0	0
	Papule	0	0	1	0.03
	Pemphigoid	0	0	1	0.03
	Pruritus	4	0.1	5	0.13
	Pruritus generalised	2	0.05	2	0.05
	Rash	4	0.1	6	0.16
	Rash erythematous	0	0	1	0.03
	Rash pruritic	0	0	2	0.05
	Skin discolouration	1	0.03	0	0
	Skin fissures	1	0.03	0	0
	Skin induration	0	0	1	0.03
	Skin mass	1	0.03	0	0
	Skin odour abnormal	1	0.03	0	0
	Skin plaque	0	0	1	0.03
	Skin ulcer	20	0.52	19	0.5
	Skin ulcer haemorrhage	0	0	1	0.03
	Stasis dermatitis	2	0.05	2	0.05
	Swelling face	2	0.05	0	0
	Tuberculid	1	0.03	0	0
	Urticaria	3	0.08	3	0.08
Social circumstances	Social stay hospitalisation	1	0.03	0	0
Surgical and medical procedures	Abdominal hernia repair	0	0	1	0.03
	Abdominal panniculectomy	1	0.03	0	0
	Acrochordon excision	1	0.03	0	0
	Amputation	0	0	1	0.03
	Angioplasty	2	0.05	0	0
	Aortic aneurysm repair	0	0	1	0.03
	Aortic stent insertion	1	0.03	0	0
	Aortic valve replacement	1	0.03	0	0
	Arterial therapeutic procedure	1	0.03	0	0
	Arteriovenous fistula operation	1	0.03	1	0.03
	Cancer surgery	1	0.03	0	0
	Cardiac ablation	1	0.03	2	0.05
	Cardiac pacemaker battery replacement	0	0	2	0.05
	Cardiac pacemaker insertion	2	0.05	1	0.03
	Cardiac pacemaker replacement	0	0	5	0.13
	Carpal tunnel decompression	1	0.03	1	0.03
	Cataract operation	5	0.13	3	0.08
	Colectomy	1	0.03	0	0
	Colostomy closure	1	0.03	0	0
	Coronary arterial stent insertion	2	0.05	1	0.03
	Coronary artery bypass	1	0.03	2	0.05
	Cyst removal	1	0.03	0	0
	Dialysis device insertion	0	0	1	0.03
	Duodenal switch	1	0.03	0	0
	Eye operation	1	0.03	0	0
	Gastrectomy	4	0.1	3	0.08
	Gastric bypass	3	0.08	4	0.1
	Hernia repair	2	0.05	0	0

	Hip arthroplasty	3	0.08	0	0
	Hysterectomy	1	0.03	0	0
	Implantable defibrillator insertion	3	0.08	1	0.03
	Implantable defibrillator replacement	0	0	1	0.03
	Inguinal hernia repair	2	0.05	1	0.03
	Intervertebral disc operation	1	0.03	0	0
	Intra-ocular injection	2	0.05	0	0
	Jejunostomy	0	0	1	0.03
	Joint arthroplasty	1	0.03	0	0
	Knee arthroplasty	5	0.13	8	0.21
	Knee operation	1	0.03	0	0
	Laser therapy	0	0	1	0.03
	Leg amputation	0	0	1	0.03
	Metabolic surgery	0	0	1	0.03
	Mole excision	1	0.03	0	0
	Oesophagectomy	0	0	1	0.03
	Peripheral artery stent insertion	2	0.05	0	0
	Retinal laser coagulation	0	0	1	0.03
	Rotator cuff repair	0	0	1	0.03
	Roux loop conversion	0	0	1	0.03
	Spinal decompression	0	0	1	0.03
	Spinal fusion surgery	1	0.03	0	0
	Spinal laminectomy	3	0.08	0	0
	Spinal operation	0	0	1	0.03
	Stent placement	1	0.03	0	0
	Thyroidectomy	0	0	1	0.03
	Tooth extraction	3	0.08	1	0.03
	Transurethral prostatectomy	0	0	1	0.03
	Tympanoplasty	1	0.03	0	0
	Umbilical hernia repair	1	0.03	0	0
	Vitrectomy	2	0.05	0	0
Vascular disorders	Accelerated hypertension	4	0.1	5	0.13
	Aneurysm	0	0	1	0.03
	Angiopathy	0	0	1	0.03
	Aortic aneurysm	6	0.16	6	0.16
	Aortic arteriosclerosis	1	0.03	1	0.03
	Aortic calcification	0	0	1	0.03
	Aortic stenosis	3	0.08	3	0.08
	Arterial haemorrhage	0	0	2	0.05
	Arteriosclerosis	3	0.08	3	0.08
	Blood pressure inadequately controlled	1	0.03	0	0
	Deep vein thrombosis	16	0.42	10	0.26
	Diabetic vascular disorder	1	0.03	0	0
	Dry gangrene	2	0.05	1	0.03
	Embolism	1	0.03	1	0.03
	Embolism arterial	0	0	2	0.05
	Embolism venous	1	0.03	1	0.03
	Essential hypertension	1	0.03	0	0
	Extremity necrosis	2	0.05	4	0.1
	Flushing	0	0	1	0.03
	Haematoma	1	0.03	0	0
	Hot flush	1	0.03	0	0
	Hypertension	48	1.26	48	1.26
	Hypertensive angiopathy	3	0.08	2	0.05
	Hypertensive crisis	10	0.26	8	0.21

	Hypertensive emergency	3	0.08	2	0.05
	Hypotension	22	0.58	20	0.52
	Hypovolaemic shock	0	0	3	0.08
	Intermittent claudication	10	0.26	7	0.18
	Ischaemia	0	0	1	0.03
	Ischaemic limb pain	0	0	1	0.03
	Labile hypertension	0	0	1	0.03
	Leriche syndrome	0	0	1	0.03
	Lymphocele	0	0	1	0.03
	Malignant hypertension	2	0.05	5	0.13
	Microangiopathy	1	0.03	0	0
	Obstructive shock	1	0.03	0	0
	Orthostatic hypotension	10	0.26	10	0.26
	Peripheral arterial occlusive disease	17	0.45	14	0.37
	Peripheral artery aneurysm	1	0.03	1	0.03
	Peripheral artery occlusion	5	0.13	6	0.16
	Peripheral artery stenosis	4	0.1	7	0.18
	Peripheral artery thrombosis	1	0.03	0	0
	Peripheral embolism	0	0	1	0.03
	Peripheral ischaemia	4	0.1	7	0.18
	Peripheral vascular disorder	16	0.42	18	0.47
	Peripheral venous disease	1	0.03	2	0.05
	Phlebitis	0	0	2	0.05
	Reperfusion injury	0	0	1	0.03
	Shock haemorrhagic	0	0	2	0.05
	Subclavian steal syndrome	1	0.03	1	0.03
	Superior vena cava stenosis	0	0	1	0.03
	Systolic hypertension	1	0.03	0	0
	Temporal arteritis	1	0.03	0	0
	Thrombosis	4	0.1	2	0.05
	Vascular calcification	1	0.03	0	0
	Vascular insufficiency	0	0	1	0.03

Table 82 – Investigator reported adverse events which were coded as falls or motor vehicle accidents

Subject ID (b) (4)	Investigator reported term that was coded in PT term “fall”
	FALL - COMPRESSION FRACTURE OF L1 VERTEBRAE
	FALL LEADING TO CELLULITIS OF LEFT LEG
	FALL LEADING TO INTRACRANIAL BLEED
	FALL RESULTING IN FRACTURED RIGHT DISTAL FEMUR
	FALL WITH CONSEQUENT DETACHMENT OF THE STYLOID PROCESS OF THE ULNA AND FRACTURE AT THE LEVEL OF VII AND VIII COAST.
	FALL WITH SUBDURAL HEMATOMA AND 3 BROKEN RIBS
	FALL, CAUSING L1 VERTEBRA FRACUTURE
	FEMUR FRACTURE DUE TO FALL
	FIBULA FRACTURE FROM A FALL
	FRACTURE INTERTROCHANTERIC LEFT FEMUR DUE TO FALL
	FRACTURE LEFT LATERAL MALLEOLUS WITH DISPLACEMENT DUE TO FALL.
	FRACTURE OF RIGHT ACETABULAM DUE TO FALL
	FRACTURE OF THE RIGHT FEMUR DUE TO FALL
	FRACTURE OF THE RIGHT UPPER LIMB - THE PATIENT FELL IN HOME AND IT WAS THE COUSE OF THE FRACTURE.
	FRACTURE OF THE RIGHT WRIST + OPEN WOUND SCALP WITH 7 POINTS SUTURING. THE AE DIAGNOSIS IS "FALL".
	FRACTURED BACK BECAUSE OF FALL
	FRACTURED LEFT HIP DUE TO FALL
	FRACTURED PATELLA AND RADIAL HEAD DUE TO A FALL

(b) (4)	FRACTURED PELVIC BONE DUE TO FALL
	FRACTURED RIGHT ACETABULAR SECONDARY TO A MECHANICAL FALL
	GRADE III SEGMENTAL FRACTURE RIGHT TIBIA AND FIBULA(SLIP AND FALL)
	INJURED BACK TO DUE FALL ON ICE
	INJURY FROM FALL BROKEN RIBS AND BROKEN PELVIS
	INJURY OF RIGHT ANKLE DUE TO FALL
	INTEROTROCHANTERIC FRACTURE OF THE LEFT PROXIMAL FEMUR, SECONDARY TO FALL
	KNEE TRAUMA DUE TO FALL
	L HIP FRACTURE DUE TO TRIP/ FALL
	LEFT HUMERUS FRACTURE AND RIGHT RADIUS FRACTURE DUE TO FALL
	OPEN LEFT ANKLE FRACTURE/TRAUMA SUBJECT FELL
	PATIENT HAD A FALL (FRACTURED LEFT HIP)
	PELVIC FRACTURE DUE TO FALL
	POST-TRAUMATIC INTRACRANIAL HEMORRHAGE, WRIST FRACTURE, AND MULTIPLE CONTUSIONS AFTER SLIP AND FALL WITHOUT LOSS OF CONSCIOUSNESS
	RIGHT ANKLE DISLOCATION AND FRACTURE DUE TO FALL".
	RIGHT ANKLE FRACTURE DUE TO FALL
	RIGHT ANTERIOR SHOULDER DISCLOCATION DUE TO FALL
	RIGHT CHEST WALL CONTUSION 2ND TO BIKE FALL IN PARK
	RIGHT FRACTURE SURGICAL NECK HUMERUS DUE TO FALL
	RIGHT HIP AND RIGHT WRIST PAIN FOLLOWING A FALL EXPECTED TO BE CHRONIC
	RIGHT HIP PAIN SECONDARY TO FALL
	RIGHT HUMERAL FRACTURE DUE TO TRAUMATIC FALL
	RIGHT SHOULDER PAIN DUE TO BYCICLE FALL
	RIGHT TIBIA FRACTURE DUE TO FALL
	RIGHT ULNAR FRACTURE DUE TO FALL
	RIGHT WRIST FRACTURE DUE TO FALL
	S/P MECHANICAL FALL WITH CLOSED HEAD INJURY
	SWOLLEN LEFT KNEE SECONDARY TO FALL
	TENDON THIGH INJURY DUE TO FALL
	TORN RIGHT ROTATOR CUFF DUE TO FALL
	TRAUMATIC FALL WITH HEAD TRAUMA AND LOSS OF CONSCIOUSNESS
	WORSENING LEFT SHOULDER LIGAMENT TEAR SECONDARY TO FALL
Subject ID	Investigator reported term that was coded in PT term “motor vehicle accident”
(b) (4)	COMPRESSION FRACTURE OF THE LUMBAR VERTEBRA DUE TO CAR ACCIDENT
	FRACTURED RIBS DUE TO MOTOR VEHICLE ACCIDENT
	RIGHT ELBOW FRACTURE DUE TO MOTOR VEHICLE ACCIDENT.
	POSTTRAUMATIC SUBDURAL HEMATOMA (SECONDARY TO MVA)
	T9 VERTEBRAL BODY FRACTURE SECONDARY TO MVA.
	MULTIPLE TRAUMATIC FRACTURES DUE TO MVA
	MULTIPLE RIB FRACTURES SECONDAYR TO MOTOR VEHICLE ACCIDENT
	MULTIPLE TRAUMA FROM MOTOR VEHICLE ACCIDENT

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/s/

TANIA A CONDARCO
02/16/2018

PATRICK ARCHDEACON
02/20/2018

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203314Orig1s008

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

CLINICAL STUDIES

NDA #:	NDA 203314
Supplement #:	008
Drug Name:	Tresiba (insulin degludec injection) Strength: 100 units/mL, Dosage form: 10 mL vial
Indications:	Type 2 diabetes mellitus
Applicant:	Novo Nordisk Inc.
Dates:	Stamp date: 5/26/2017 PDUFA date: 3/26/2018 Review Completion Date: 2/16/2018
Review Priority:	Standard
Biometrics Division:	Division of Biometrics II
Statistical Reviewer:	Kiya Hamilton, Ph.D.
Concurring Reviewers:	Yun Wang, PhD, Team Leader Mark Rothmann, PhD, Acting Division Director
Medical Division:	Division of Metabolism and Endocrinology Product
Clinical Team:	Tania Condarco, M.D., Reviewer Lisa Yanoff, M.D., Team Leader
Project Manager:	Callie CappelLynch

Keywords: Cardiovascular Outcome, Severe Hypoglycemic Episode

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1 EXECUTIVE SUMMARY

Insulin degludec (IDeg) is a long-acting basal human insulin analogue, which is currently approved to improve glycemic control in patients 1 year of age and older with diabetes mellitus. Novo Nordisk submitted a supplemental new drug application (sNDA) to fulfill the FDA post marketing requirement for the already marketed Tresiba (insulin degludec injection). This post marketing requirement was for Novo Nordisk to conduct a randomized, double blind, active-controlled trial evaluating the effect of Tresiba on the incidence of major adverse cardiovascular events (MACE) in subjects with type 2 diabetes mellitus (T2DM). The sponsor refers to this study as DEVOTE. The secondary objective of this study was to assess the effect of IDeg on markers of glycemic control when compared to insulin glargine (IGlar).

The two confirmatory secondary endpoints were the number of EAC-confirmed severe hypoglycemic episode and occurrence of at least one EAC-confirmed severe hypoglycemic episodes within a subject (yes/no). Superiority was achieved for both confirmatory secondary endpoints, since the upper 95% confidence intervals were both below 1.0. In addition, there was an estimated 26% relative risk reduction in time from randomization to first occurrence of EAC confirmed severe hypoglycemic episodes in the IDeg group compared to the IGlar group.

There were no statistical issues identified during the course of this review that would preclude approval. The observed incidence rate was 3.7% in the IDeg group and 6.3% in the IGlar group. We concluded that the observed superiority in EAC-confirmed severe hypoglycemic episode for IDeg vs. IGlar is robust in the presence of missing values. Overall, the study demonstrated that Tresiba reduces the rate of EAC-confirmed hypoglycemia, compared to insulin glargine in subjects with T2DM.

2 INTRODUCTION

2.1 Overview

2.1.1 Class and Indication

Novo Nordisk has submitted their post marketing final report for Tresiba (insulin degludec injection). Tresiba (referred also as IDeg), a long-acting basal soluble insulin analogue, was approved on September 25, 2015 with an indication to improve glycemic control in adults with diabetes mellitus. This approval came with a post marketing requirement (2954-2) for Novo Nordisk to conduct a randomized, double-blind, active-controlled study evaluating the effect of Tresiba on the incidence of MACE in subjects with T2DM.

2.1.2 History of Drug Development

The majority of the history pertaining to the DEVOTE study focused on the primary endpoint, time from randomization to first EAC-confirmed MACE: cardiovascular death, non-fatal

myocardial infarction, or non-fatal stroke. See the review by Dr. Eugenio Andraca-Carrera for the results, interpretation, and conclusion on MACE.

2.1.3 Studies Reviewed

This review will focus on the secondary efficacy analyses results from study EX1250-4080 (hereafter referred to as 4080).

2.2 Data Sources

The submission of NDA 203314 was received on May 26, 2017. The study reports including protocols, statistical analysis plan, and all referenced literature were submitted electronically and archived under the network path location \\CDSESUB1\evsprod\NDA203314\0135. Information necessary for this review was contained in Module 1, Module 2, and Module 5.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

In general, the submitted data are acceptable in terms of quality and integrity. This statistical reviewer was able to reproduce the primary and secondary endpoint analyses for the clinical study submitted from the original data source.

3.2 Evaluation of Efficacy

This review evaluates the secondary efficacy endpoints.

3.2.1 Study Design and Endpoints

The Degludec Cardiovascular Outcomes Trial (DEVOTE) was a long term, multi-center, multi-national, randomized, double-blind, parallel-group, active-controlled study to confirm the cardiovascular safety of IDeg compared to insulin glargine (IGlar), when added to standard of care, in male and female subjects with T2DM at high risk of cardiovascular events. The primary objective of this study was to confirm the cardiovascular safety of IDeg compared to that of IGlar. The secondary objectives were to assess efficacy of IDeg on markers of glycemic control and to assess safety on other parameters in subjects with type 2 diabetes at high risk of cardiovascular events. This review will focus on the applicant's secondary objective on efficacy of IDeg.

A total of 7637 subjects with T2DM who were at a high risk of cardiovascular events were randomized 1:1 to receive either IDeg 100 units/mL or IGlar 100 units/mL in addition to standard of care therapy. The study consisted of 438 sites in 20 countries. The duration was

driven by the number of events and the study ended when a pre-specified number of at least 633 first event adjudication committee (EAC) confirmed MACE (cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke) were recorded.

There was a screening visit (up to 2 weeks), a treatment period (up to 59 months), and a follow-up period (30 days). A subject could be in the study up to a total of 60.5 months, however, subjects were under observation for no more than 36 months. Figure 1 below shows the schematic of the study design.

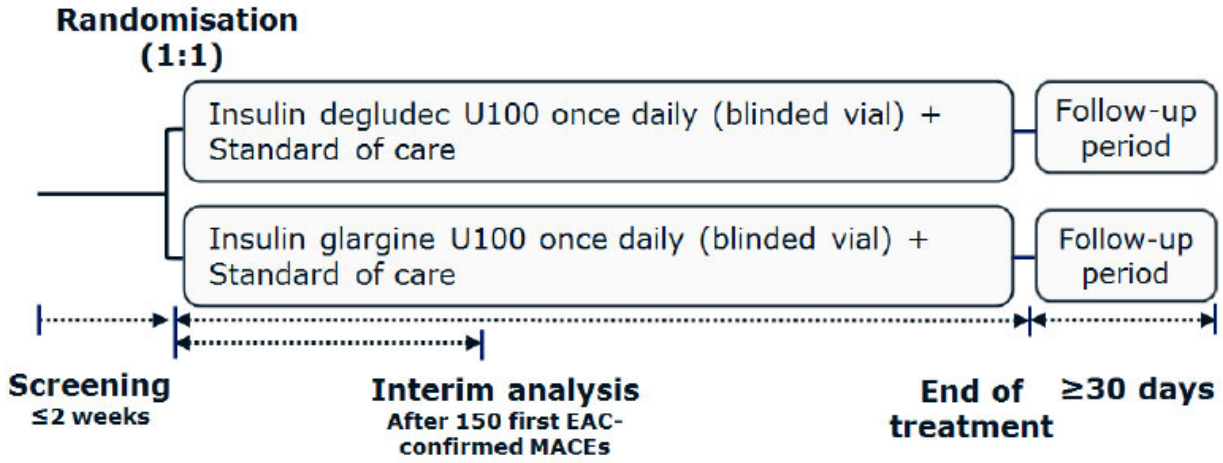
Even though the study was planned for 5 years, it was event driven. Once it was known that the pre-specified number of first EAC-confirmed MACEs (633 events) would be accrued by the end of the study, the trial closure was initiated. The applicant stated that the first day of trial closure was referred to as the trial stop date which occurred on May 30, 2016. From this date on, all subsequent site visits were to be carried out as end-treatment visits.

The applicant had all subjects continue treatment with the investigational medicinal product (IMP) until the end-treatment visit when subjects were to be switched to the marketed products. IV/WRS stopped dispensing trial products at the trial stop date. There was at least 30 days between the last dose of IMP and the follow-up visit. Subjects who prematurely discontinued treatment with IMP had a combined end-treatment and follow-up visit. This visit could be performed starting June 29, 2016 when the first follow-up visits could be scheduled for all subjects.

Each site was to make every effort to obtain the health status the follow-up visit with a focus on MACE-related events for each subject. At a minimum, the vital status was to be obtained. The end of trial was the last follow-up visit in the study. The applicant stated that this occurred on October 16, 2016. The trial closure was the period from the first subject's follow-up visit which occurred on June 29, 2016 to the database lock that occurred on October 31, 2016.

Subject median time in the study was 728 days for both treatment groups. The minimum time for subjects in the study was 1 day with a maximum time of 1,003 days for both treatment groups. The average time spent in the IDeg group was approximately 724 and approximately 723 days for the IGlar group. The first subject was randomized on November 4, 2013 and the last subject was randomized on November 28, 2014. The last subject last visit was on October 16, 2016.

Figure 1: Study Design



Abbreviations: EAC, external adjudication committee; MACE, major adverse cardiovascular event.
Source: Clinical Study Report Protocol EX1250-4080 Figure 9-1, page 47

The pre-specified secondary confirmatory endpoints (the focus of this review) were:

- Number of EAC-confirmed severe hypoglycemic episodes
- Occurrence of at least one EAC-confirmed severe hypoglycemic episode within a subject (yes/no).

A severe hypoglycemic episode was defined as an episode requiring assistance of another person to actively administer carbohydrate, glucagon, or take other corrective actions. Other secondary endpoints included in this review are glycated hemoglobin (HbA_{1c}), fasting plasma glucose (FPG), and insulin dose.

The applicant tested the primary and secondary confirmatory endpoints in a pre-defined hierarchical order to control the overall type I error. If the corresponding null hypothesis was not rejected, the testing was stopped and no further hypotheses were tested. The predefined order of hypotheses testing was as follows:

- Step 1: Non-inferiority of IDeg vs IGlar for the primary endpoint, MACE
- Step 2: Superiority of IDeg vs IGlar for the number of EAC-confirmed severe hypoglycemic episodes
- Step 3: Superiority of IDeg vs IGlar for the occurrence of at least one EAC-confirmed severe hypoglycemic episode within a subject

It was pre-specified in the protocol that an interim analysis was to be performed after a total of 150 first EAC-confirmed MACE had occurred. This was done to assess the preliminary non-inferiority of IDeg to IGlar for the primary endpoint. The interim analysis is not covered in this review.

3.2.2 Statistical Methodologies

All efficacy 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 IDeg vs. IGlar in the primary endpoint against a NI margin of 1.3 to rule out a 30% increase in cardiovascular risk.

The secondary confirmatory endpoint, number of EAC-confirmed severe hypoglycemic episodes, was analyzed using a negative binomial regression model with log-link function and logarithm of the observation times as offset. This model included treatment as a fixed factor. Superiority was achieved if the upper limit of the two-sided 95% confidence interval (CI) for the rate ratio (RR) was less than 1.0 or the p-value for the one-sided test of

$$H_0: RR >= 1.0 \text{ against } H_A: RR < 1.0,$$

was less than 2.5%.

If superiority of the number of EAC-confirmed severe hypoglycemic episodes is confirmed, then the second confirmatory secondary endpoint, occurrence of at least EAC-confirmed severe hypoglycemic episode within a subject (yes/no), was analyzed using a logistic regression model with log-link function. This model included treatment (IDeg/IGlar) as a fixed factor. Superiority of IDeg over IGlar was achieved if the upper limit of the two-sided 95% CI for the odds ratio (OR) was less than 1.0 or the p-value for the one-sided test of

$$H_0: OR >= 1.0 \text{ against } H_A: OR < 1.0,$$

was less than 2.5%.

The figure below shows the pre-specified additional analyses conducted by the applicant on the secondary confirmatory endpoints. Note, the additional covariate added to the model was adjustment for baseline insulin treatment (basal-bolus, basal only, insulin-naïve).

Figure 2. Additional Analyses of the Secondary Confirmatory Endpoints

	Number of EAC-confirmed severe hypoglycaemic episodes		
	Model	**Population**	**Observation period**
1	Negative binomial regression	FAS	On treatment
2			On treatment + 7 days
3	Negative binomial regression + adjustment for additional covariates	FAS	Full observation period
4	Negative binomial regression (but where endpoint is truncated at a maximum of 3 episodes per subject)	FAS	Full observation period
5	Negative binomial regression	FAS, with multiple imputation of missing data (Tipping point analyses)	Full observation period (extended to LPLV for subjects on IDeg who were non-completers)
	Occurrence of at least one EAC-confirmed severe hypoglycaemic episode within a subject (yes/no)		
	Model	**Population**	**Observation period**
1	Logistic regression	FAS	On treatment
2			On treatment + 7 days
3	Logistic regression	FAS, with imputation of missing data (Tipping point analyses)	Full observation period

Abbreviations: EAC: event adjudication committee; FAS: full analysis set

Source: Clinical Study Report Protocol EX1250-4080 Figure 9-14, page 107

Reviewer's comment:

The proposed negative binomial model is one of many possible statistical models for count data. The model can vary by the covariates it includes or by the statistical distribution chosen to fit the data. In this review, we estimate the goodness of fit of the proposed negative binomial model and compare it to a zero-inflated negative binomial (ZINB) model that may more adequately capture data with a high proportion of subjects with no events. The advantage of the ZINB model is that it accounts for a large proportion of subjects with zero events. The ZINB models the probability of zero hypoglycemic events and the probability of a positive number of hypoglycemic events separately as functions of the covariates. A zero-inflated negative binomial model was not proposed by the applicant but is included by this reviewer to assess the robustness of the study findings. The better model will be determined using the Akaike information criterion (AIC). The AIC is a measure of the goodness of fit of a statistical model to a given set of data. A smaller AIC implies a better model fit.

The time to first EAC-confirmed severe hypoglycemic episode was analyzed using a Cox proportional hazards regression model with treatment as a factor. Bolus insulin use could change over time during the study. And it is of interest to see if bolus insulin use prior to having a severe hypoglycemic event effects the outcome. Thus, this analysis was repeated to account for bolus insulin treatment prior to the episode of hypoglycemia as a time-dependent variable. The analysis of continuous endpoints was analyzed using a mixed model for repeated measures (MMRM). Summary of insulin dose are displayed.

Missing Data

Missing data were low for the primary (1.9%) and secondary endpoints. There were 148 subjects who did not complete the study. The applicant conducted tipping point analyses for both secondary endpoints to assess the possible impact of missing values on treatment effect. The following describes the sponsor's tipping point analysis for the secondary endpoints:

- *Number of EAC-confirmed severe hypoglycaemic episodes*
  Modifications to the confirmatory analysis were made by considering the non-completers randomized to IDeg and artificially extending their observation time to LPLV. Additional events for IDeg non-completers during their extended time were imputed via multiple random draws from a Poisson distribution with mean parameter calculated according to the expected number of events, given an assumed rate and the median extended observation time. For each scenario (i.e., assumed rate), 100 replications were done and mean results were presented.

  First, the following two scenarios were conducted where the event rate for IDeg non-completers during their extended observation period was assumed in the multiple imputation to be equal to:
  1) Actual observed event rate for IDeg non-completers during the trial
  2) Actual observed event rate for IGlar non-completers during the trial.

  Finally, the tipping point was established by successively increasing the assumed event rate for IDeg non-completers during their extended observation period until the tipping point (i.e., upper limit of the 95% CI for OR was >1.0) was reached.

  Data pertaining to other subjects (i.e., completers and IGlar non-completers) were not modified.

- *Occurrence of at least one EAC-confirmed severe hypoglycaemic episode within a subject (yes/no)*
  Modifications to the confirmatory analysis were made by considering the non-completers randomized to IDeg who did not already have an EAC-confirmed severe hypoglycaemic episode during the trial. The modifications that were conducted are shown below.

  1) Events imputed for all non-completers randomized to IDeg corresponding to incidence rate for subjects randomized to IGlar
  2) Events imputed for all non-completers randomized to IDeg until the tipping point (i.e., upper limit of the 95% CI for OR was >1.0) was reached.

  Data pertaining to other subjects (i.e., completers and IGlar non-completers) were not modified.

Rate ratios for the secondary confirmatory endpoint, number of EAC-confirmed severe hypoglycemic episodes will be calculated by subgroups of age, sex, region and race. A subgroup analysis for previous insulin will be shown as well.

3.2.3 Subject Disposition, Demographic and Baseline Characteristics

The summary of the subject disposition in the DEVOTE study is given in Table 1. The FAS population consisted of 7637 subjects: 3818 randomized to IDeg and 3819 randomized to IGlar. Approximately 2% of the subjects failed to complete the study, where completing the study was defined as completed follow-up visit or died during the study.

Table 1. Subject Disposition

	IDeg N = 3818 n (%)	IGlar N = 3819 n (%)	Total N = 7637 n (%)
FAS	3818 (100)	3819 (100)	7637 (100)
Exposed	3809 (99.8)	3806 (99.7)	7615 (99.7)
Withdrawals	19 (0.5)	25 (0.7)	44 (0.6)
Follow-up visit completed	3540 (92.7)	3526 (92.3)	7066 (92.5)
Deaths	202 (5.3)	221 (5.8)	423 (5.5)
Did not complete study	76 (2.0)	72 (1.9)	148 (1.9)
Vital status known**	71 (1.9)	69 (1.8)	140 (1.8)
Vital status unknown***	5 (0.1)	3 (0.1)	8 (0.1)
Withdrawals	1 (0.0)	2 (0.1)	3 (0.0)
Lost-to-follow up	4 (0.1)	1 (0.0)	5 (0.1)
Reason for Discontinuation			
Hypoglycemia	1 (0.03)	1 (0.03)	2 (0.03)
Lack of glycemic control	1 (0.03)	1 (0.03)	1 (0.03)
Adverse event (not hypoglycemia)	0	1 (0.03)	1 (0.03)
Other****	15 (0.4)	19 (0.5)	34 (0.4)
Not specified	55 (0.01)	49 (0.01)	101 (0.01)

Source: Full Clinical Study Report-Protocol Number EX1250-4080 Table 10-1, page 117
Note: Exposed: Subjects with a first drug dose date reported. Withdrawals: withdrew after randomization, but excluding those who later completed a visit. Only events (MACE, death, withdrawal) occurring during trial are included. During trial: time from randomization to last direct contact with site, MACE or death before LPLV (whichever occurs last).
* 7 subjects were randomized at two different sites; subject numbers from the 2nd site are excluded from 'Randomized'
** Regardless of whether or not MACE occurred during trial
*** Refers to the status during trial closure: from the first patient's follow-up visit (29 June 2016) to LPLV (16 October 2016)
****Other: Includes subject decision due to various reasons, but not due to adverse event

Baseline demographics for all randomized subjects in the study are shown in Table 2. Baseline characteristics were generally well-balanced across the treatment groups. The study population was mostly white (76%), and majority of the subjects were male, 62.6%. The average subject was 65 years old with an average BMI of 33.6 kg/m^2. About 69% of the subjects were from North America.

Table 2. Demographics and Baseline Characteristics - FAS

	IDeg N = 3818	IGlar N = 3819	Total N = 7637
Age (years) *			
Mean (SD)	64.9 (7.3)	65.0 (7.5)	65.0 (7.4)
Sex			
Female	1422 (37.2)	1437 (37.6)	2859 (37.4)
Male	2396 (62.8)	2382 (62.4)	4778 (62.6)
Region			
Europe	438 (11.5)	437 (11.4)	875 (11.5)
North America	2625 (68.8)	2646 (69.3)	5271 (69.0)
South America	304 (8.0)	281 (7.4)	585 (7.7)
Asia excluding India	151 (4.0)	141 (3.7)	292 (3.8)
India	168 (4.4)	189 (4.9)	357 (4.7)
Africa	132 (3.5)	125 (3.3)	257 (3.4)
Ethnicity			
Hispanic or Latino	582 (15.2)	555 (14.5)	1137 (14.9)
Not Hispanic or Latino	3235(84.7)	3263 (85.4)	6498 (85.1)
Unknown	1 (0.0)	1 (0.0)	2 (0.0)
Race			
White	2903 (76.0)	2872 (75.2)	5755 (75.6)
Black or African American	401 (10.5)	431 (11.3)	832 (10.9)
Asian	391 (10.2)	385 (10.1)	776 (10.2)
America Indian or Alaska Native	17 (0.4)	13 (0.3)	30 (0.4)
Native Hawaiian or Other Pacific Islander	11 (0.3)	13 (0.3)	24 (0.3)
Other	94 (2.5)	104 (2.7)	198 (206)
Unknown	1 (0)	1 (0)	2(0)
BMI (kg/m^2)			
Mean (SD)	33.6 (6.8)	33.6 (6.8)	33.6 (6.8)
HbA_{1c} (%)			
Mean (SD)	8.4 (1.6)	8.4 (1.7)	8.4 (1.7)
Diabetes Duration (years)			
Mean (SD)	16.6 (8.8)	16.2 (8.9)	16.4 (8.9)

Source: Full Clinical Study Report-Protocol Number EX1250-4080 Table 14.1.13, page 244 and Table 14.1.22, page 262

N: Number of subjects

* Including 3 subjects with age <50 years

3.2.4 Results and Conclusions

Number of EAC-confirmed severe hypoglycemic episode

Non-inferiority of the primary endpoint, MACE, was established. Thus, the secondary confirmatory endpoints can be tested. The number of EAC-confirmed severe hypoglycemic episodes along with the subjects' years of observation are displayed in Table 3. More EAC-confirmed severe hypoglycemic episodes were observed in the IGlar group with 472 episodes, compared to the IDeg group with 280.

Table 3. EAC-Confirmed Severe Hypoglycemic Episodes - Summary - FAS

	IDeg				IGlar			
	N	(%)	E	R	N	(%)	E	R
Number of Subjects	3818				3819			
PYO	7568				7558			
EAC confirmed events	187	(4.9)	280	3.70	252	(6.6)	472	6.25

Source: Full Clinical Study Report-Protocol Number EX1250-4080 Table 11-2, page 145
Note: * EAC-confirmed severe hypoglycaemic episodes defined according to ADA. Episodes with EAC onset date during trial are included
Abbreviations: ADA: American diabetes association; E: Number of events; EAC: Event adjudication committee; N: Number of subjects; PYO: Patient years of observation; R: Event rate per 100 PYO; %: Percentage of subjects relative to the number of randomized subjects

Table 4 displays the results from the analysis of the first secondary confirmatory endpoint, the number of EAC-confirmed severe hypoglycemic episodes. Note there were 187 subjects that had at least one severe hypoglycemic episode in the IDeg group compared to 252 subjects in the IGlar group (Table 3). The estimated rate ratio (RR) and corresponding 95% confidence interval (CI) for this endpoint comparing IDeg vs. IGlar are shown. The estimated RR from this model is 0.60 with 95% CI (0.48, 0.76). There is statistical evidence that IDeg reduces the rate of confirmed severe hypoglycemia compared to IGlar. Thus, superiority of IDeg over IGlar was achieved for the first confirmatory secondary endpoint, number of EAC-confirmed severe hypoglycemic episodes since the upper bound of the 95% confidence interval was below 1.0.

Table 4. Number of EAC-Confirmed Severe Hypoglycemic Episodes - Confirmatory Secondary Statistical Analysis – FAS

Treatment	FAS	Events	Rate ratio	95% CI P-value
IDeg	3818	280		
IGlar	3819	472		0.48, 0.76
IDeg/IGlar			0.60	<0.0001

Source: Full Clinical Study Report-Protocol Number EX1250-4080 Table 14.2.107, page 412
N: Number of subjects randomized to each treatment
Events: Number of EAC-confirmed severe hypoglycemic episodes

A post-hoc sensitivity analysis using a ZINB model was conducted by this reviewer due to the large number of subjects with zero events. The AIC fit statistic showed that the pre-specified negative binomial model fit the data slightly better in this case than the ZINB model, with just treatment as a factor in the model (Table 5).

Table 5. AIC Model Fit Statistic

	AIC
Confirmatory NB model	4320
ZINB model	4324

Source: Statistical Reviewer's Analysis

An additional analysis was conducted by this reviewer adding additional covariates to the model. The additional covariates included sex and bolus dose flag (yes or no), along with treatment. The fit statistic, AIC, suggested that this model fit the data slightly better. Table 6 displays the estimated RR and 95% CI for this model. This model which accounts for sex and insulin bolus produced a similar RR estimate and CI. This concurs with the superiority of IDeg over IGlar with respect to the number of EAC confirmed severe hypoglycemic episodes.

Table 6. Number of EAC-Confirmed Severe Hypoglycemic Episodes - Confirmatory Secondary Statistical Analysis – Additional Covariates - FAS

Treatment	FAS	Events	Rate ratio	95 % CI P-value
IDeg	3818	280		
IGlar	3819	472		0.49, 0.78
IDeg/IGlar			0.62	<0.0001

Source: Statistical Reviewer's Analysis
Negative binomial regression model with treatment, sex, and bolus dose flag included in the model
N: Number of subjects randomized to each treatment
Events: Number of EAC-confirmed severe hypoglycemic episodes

Tables 7-10 show the results of the pre-specified additional analysis for the first confirmatory endpoint. All these analyses results are consistent in demonstrating superiority of IDeg in reducing EAC-confirmed severe hypoglycemic episodes.

Table 7. Number of EAC-Confirmed Severe Hypoglycemic Episodes – On-Treatment

Treatment	FAS	Events	Rate ratio	95 % CI P-value
IDeg	3818	266		
IGlar	3819	431		0.47, 0.77
IDeg/IGlar			0.60	<0.0001

Source: Full Clinical Study Report-Protocol Number EX1250-4080 Table 14.2.117, page 421
N: Number of subjects randomized to each treatment
Events: Number of EAC-confirmed severe hypoglycemic episodes

Table 8. Number of EAC-Confirmed Severe Hypoglycemic Episodes – On-Treatment Plus 7 Days

Treatment	FAS	Events	Rate ratio	95 % CI P-value
IDeg	3818	269		
IGlar	3819	437		0.47, 0.77
IDeg/IGlar			0.60	<0.0001

Source: Full Clinical Study Report-Protocol Number EX1250-4080 Table 14.2.119, page 423
N: Number of subjects randomized to each treatment
Events: Number of EAC-confirmed severe hypoglycemic episodes

Table 9. Number of EAC-Confirmed Severe Hypoglycemic Episodes – Adjusted for Previous Insulin Treatment

Treatment	FAS	Events	Rate ratio	95 % CI P-value
IDeg	3818	280		
IGlar	3819	472		0.47, 0.75
IDeg/IGlar			0.59	<0.0001

Source: Full Clinical Study Report-Protocol Number EX1250-4080 Table 14.2.121, page 425
N: Number of subjects randomized to each treatment
Events: Number of EAC-confirmed severe hypoglycemic episodes

Table 10. Number of EAC-Confirmed Severe Hypoglycemic Episodes – Adjusted for Bolus Dose Flag (Y/N)

Treatment	FAS	Events	Rate ratio	95 % CI P-value
IDeg	3818	280		
IGlar	3819	472		0.48, 0.76
IDeg/IGlar			0.60	<0.0001

Source: Statistical Reviewer Analysis
N: Number of subjects randomized to each treatment
Events: Number of EAC-confirmed severe hypoglycemic episodes

Tipping point analysis

The sponsor conducted a tipping point analysis to address the impact of missing data for subjects not completing the study for the number of EAC-confirmed severe hypoglycemic episode. There were 148 subjects (1.9%) that did not complete the study (76 in the IDeg group and 72 in the IGlar group). The sponsor conducted three analyses. The first two were conducted assuming the rates of EAC-confirmed severe hypoglycemic episodes for IDeg during the extended observation period 1) Imputing events in IDeg non-completers during their extended observation time according to actual observed event rate in IDeg non-completers and 2) Imputing events in IDeg non-completers during their extended observation time according to actual observed event rate in IGlar non-completers. In the third analysis, the assumed event rate for IDeg non-completers during their extended observation period was increased until the topping point was reached.

As listed in section 3.2.2 under missing data, for the first two analyses the tipping point was not reached because the upper limit of the 95% confidence interval for RR was less than 1.0 for all

investigated possibilities. For the third analysis, the tipping point was not reached until 133 episodes of severe hypoglycemia per 100 patient years were added to the IDeg group. Note the median subject years of observation for the overall study was 1.99 years in both treatment groups. For the non-completers the subject years of observation was 1.43 years in the IDeg group and 1.24 years in the IGlar group. Please refer to Table 12.2.124 on Page 428 of DEVOTE clinical study report for further details on these tipping points analyses results.

Occurrence of at least one EAC-confirmed severe hypoglycemic episodes within a subject (Yes/No)

Since the first confirmatory secondary endpoint was statistically significant, the second confirmatory secondary endpoint, occurrence of at least one EAC confirmed severe hypoglycemic episodes (Yes/No) within a subject was tested. The results are displayed in Table 11. There were 187 subjects that experienced at least one episode in the IDeg group compared to 252 subjects in the IGlar group. The odds ratio was 0.73 with a 95% CI of (0.60, 0.89), confirming superiority of IDeg over IGlar with respect to the occurrence of at least one EAC-confirmed severe hypoglycemic episode within a subject.

Table 11. Occurrence of at Least One EAC confirmed Severe Hypoglycemic Episodes (Yes/No) – Confirmatory Secondary Statistical Analysis – FAS

Treatment	FAS	N	Odds ratio	95 % CI P-value
IDeg	3818	187		
IGlar	3819	252		0.60, 0.89
IDeg/IGlar			0.73	0.0015

Source: Full Clinical Study Report-Protocol Number EX1250-4080 Table 14.2.108, page 413
N: Number of subjects with at least one EAC confirmed severe hypoglycemic episode

Tables 12 and 13 display the results of the pre-specified additional analysis for the second confirmatory secondary endpoint. These analyses were also supportive of efficacy.

Table 12. Occurrence of at Least One EAC confirmed Severe Hypoglycemic Episodes (Yes/No) – Confirmatory Secondary Statistical Analysis - On-Treatment

Treatment	FAS	N	Odds ratio	95 % CI P-value
IDeg	3818	176		
IGlar	3819	230		0.62, 0.92
IDeg/IGlar			0.75	0.0059

Source: Full Clinical Study Report-Protocol Number EX1250-4080 Table 14.2.118, page 422
N: Number of subjects with at least one EAC confirmed severe hypoglycemic episode

Table 13. Occurrence of at Least One EAC confirmed Severe Hypoglycemic Episodes (Yes/No) – Confirmatory Secondary Statistical Analysis – On-Treatment Plus 7 Days

Treatment	FAS	N	Odds ratio	95 % CI P-value
IDeg	3818	178		
IGlar	3819	233		0.62, 0.92
IDeg/IGlar			0.75	0.0053

Source: Full Clinical Study Report-Protocol Number EX1250-4080 Table 14.2.120, page 424
N: Number of subjects with at least one EAC confirmed severe hypoglycemic episode

Tipping point analysis

The sponsor also conducted a tipping point analysis to address the impact of missing data for subjects not completing the study for the occurrence of at least one EAC-confirmed severe hypoglycemic episode within a subject. The sponsor conducted two analyses that considered non-completers randomized to IDeg who had not experienced a severe hypoglycemic episode prior to discontinuing the study. The first tipping point analysis imputed events for all non-completers randomized to IDeg corresponding to the incidence rate for subjects randomized to IGlar. Here the sponsor imputed episodes based on the incidence rate of 6.6% for the 5 non-completers that had unknown vital status. The second analysis imputed events for all non-completers randomized to IDeg until the tipping point was reached. The tipping point was reached once 25 non-completers randomized to IDeg were assumed to have had a severe hypoglycemic episode. Note the corresponding incidence rate was 34% (25 events/74 non-completers), which was much higher than the observed incidence rate of 4.9% in IDeg arm and 6.6% in IGlar arm.

Time from randomization to first occurrence of EAC confirmed severe hypoglycemic episode

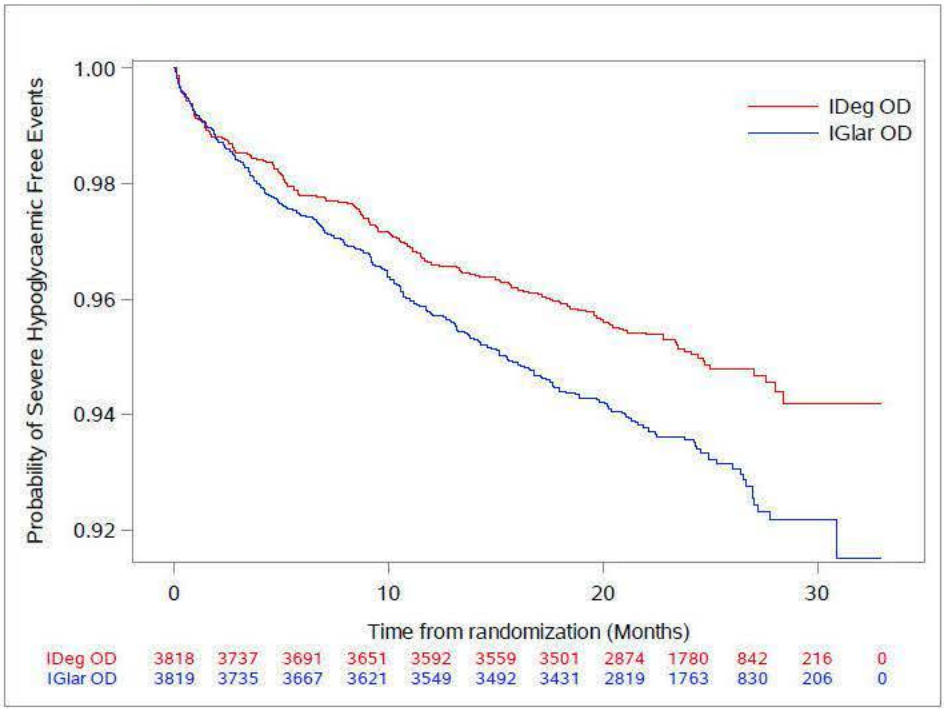
The results of the time from randomization to first occurrence of EAC-confirmed severe hypoglycaemic episode is shown in Table 14. The hazard ratio of 0.74 indicates a 26% relative risk reduction in occurrence of EAC confirmed severe hypoglycemic episode in the IDeg group over IGlar. Figure 3 shows the estimated Kaplan-Meier curve for time from randomization to first occurrence of EAC-confirmed severe hypoglycaemic episodes by treatment group.

Table 14. Time from Randomization to First Occurrence of EAC Confirmed Severe Hypoglycemic Episodes

Treatment	FAS	First events n	Hazard ratio	95 % CI P-value
IDeg	3818	187		
IGlar	3819	252		0.61, 0.89
IDeg/IGlar			0.74	0.0015

Source: Full Clinical Study Report-Protocol Number EX1250-4080 Table 14.2.127, page 431

Figure 3. Reviewer Kaplan-Meier Plot Time from Randomization to First Occurrence of EAC Confirmed Severe Hypoglycemic Episodes



Source: Statistical Reviewer's Analysis

The analysis for time to first occurrence of EAC confirmed severe hypoglycemic episode was repeated accounting for bolus insulin treatment (Y/N). The results are shown in Table 15. After adjusting for bolus insulin, it was seen that the lower risk of EAC-confirmed severe hypoglycaemia with IDeg relative to IGlar is maintained.

Table 15. Time to First Occurrence of EAC Confirmed Severe Hypoglycaemic Episode Adjusted for Bolus Insulin Usage During Trial Prior to the Episode – FAS

Treatment	FAS	Hazard ratio	95 % CI P-value
IDeg	3818		
IGlar	3819		
Time to first severe hypoglycaemic episode (days)			
IDeg/IGlar		0.74	0.61, 0.89 0.0017

Source: Full Clinical Study Report-Protocol Number EX1250-4080 Table 14.2.128, page 432

Glycemic Control

To evaluate the glycemic control, HbA_{1c} and fasting plasma glucose (FPG) measurements were analyzed. For HbA1c, both treatment groups had a mean HbA1c of 8.4% at baseline. Table 16 shows the results of HbA_{1c} change from baseline to 24-month visit. There was no statistically significant difference seen between the IDeg group and IGlar group. This suggests that the change in HbA_{1c} from baseline at month 24 were similar between two treatment groups.

Table 16. HbA_{1c} Change from Baseline to 24 Month Visit- Post Hoc Analysis - FAS

Treatment	FAS	N	Estimate	95% CI P-value
Change from baseline at 24-month				
IDeg	3818	3707	-0.86	
IGlar	3819	3695	-0.87	
Treatment difference **IDeg - IGlar**			 0.008	-0.05, 0.07 0.7788

Source: Full Clinical Study Report-Protocol Number EX1250-4080 Table 11-4, page 152
Model including interaction between visit and treatment and visit and baseline

The mean FPG at baseline was 9.4 mmol/L in the IDeg group and 9.5 mmol/L in the IGlar group. Table 17 shows the results of FPG change from baseline to month 24. There was a statistically significant difference in FPG change from baseline to month 24 between IDeg and IGlar, in favor of IDeg i.e. a greater reduction on FPG in the IDeg group compared to the IGlar group was observed.

Table 17. FPG Change from Baseline to Month 24 Visit - Post Hoc Analysis- FAS

Treatment	FAS	N	Estimate	95% CI P-value
Change from baseline at 24-month				
IDeg	3818	3505	-2.28	
IGlar	3819	3496	-1.88	
Treatment difference **IDeg - IGlar**			 -0.40	-0.57, 0.23 <0.001

Source: Full Clinical Study Report-Protocol Number EX1250-4080 Table 11-5, page 154

Insulin

A total of 441 subjects were on basal/bolus insulin. Out of those subjects, 100 of them did not have a severe hypoglycemic episode while on basal/bolus insulin. Note, some of these subjects did have a severe hypoglycemic episode while not on basal/bolus insulin. There were 339 subjects that did experience a severe hypoglycemic episode while on basal/bolus insulin, totaling 601 events (Table 18). The characteristics of confirmed severe hypoglycemia are shown in Table 18. There were more events with subjects on basal + bolus premixture insulin than on basal

insulin alone. However, there were less episodes seen in the IDeg group with 226 events compared to IGlar group with 375 events.

Table 18. Characteristics of Confirmed Severe Hypoglycemia

	IDeg N=3818		IGlar N=3819		Total Events
	n (%)	Events	n (%)	Events	
Basal	47 (1.2)	54	60 (1.6)	97	151
Basal+Bolus/Premix	141 (3.7)	226	198 (5.2)	375	601

Source: Statistical Reviewer's Analysis

Table 19 shows the number of events that subjects had while on basal + bolus mixture. There were 339 subjects who had at least one severe hypoglycemic episode while on basal + bolus mixture. Overall, there were less severe hypoglycemic episodes while on bolus insulin in the IDeg group (141 episodes) compared to IGlar (198 episodes).

Table 19. Number of Subjects that had Severe Hypoglycemic Events While on Bolus Insulin by Treatment Group

	Treatment		Total
Number of Events	IDeg N	IGlar N	N
1	99	128	227
2	20	37	57
3	13	11	24
4	6	9	15
5	1	2	3
6	0	3	3
7	0	1	1
8	1	3	4
9	0	1	1
10	0	1	1
11	1	1	2
15	0	1	1

Source: Statistical Reviewer's Analysis
N: Number of subjects

3.3 Evaluation of Safety

Safety evaluations for this submission were evaluated by the Medical Reviewer, Tania Condarco, M.D. Refer to her review for more details regarding the safety findings of IDeg.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

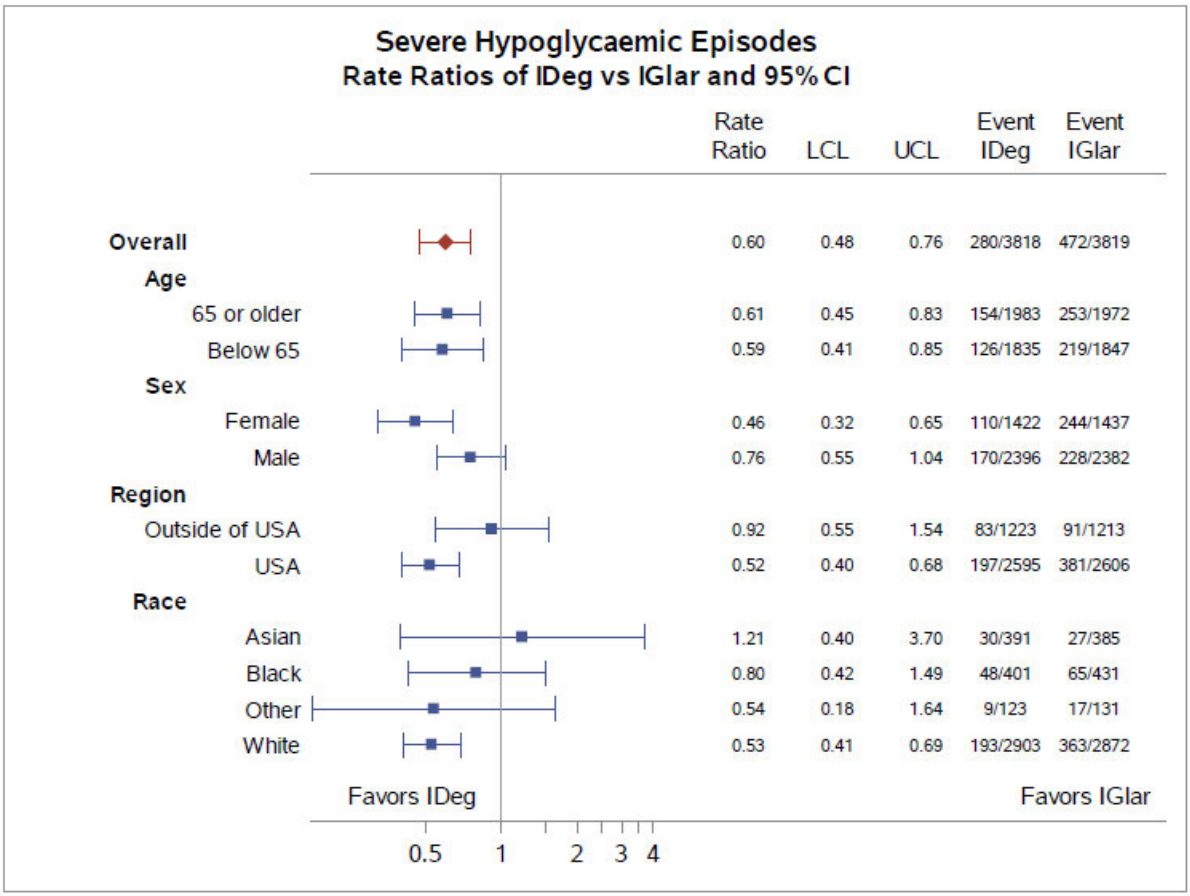
4.1 Gender, Race, Age, and Geographic Region

Subgroup analyses were performed on the confirmatory secondary efficacy endpoint, EAC-confirmed severe hypoglycemic episodes 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. Due to the limitations associated with multiplicity and low power, subgroup analysis results were considered as supportive and exploratory. The forest plot combining all results are presented in Figure 4. All subgroup analyses on the confirmatory secondary endpoint, EAC-confirmed severe hypoglycemic episodes, were performed in the same manner as this confirmatory endpoint.

Subgroup analyses demonstrated consistent decrease in the relative risk of confirmed severe hypoglycemia for IDeg vs. IGlar in all but Asian subgroups. For the Asian subgroup, IDeg is associated with a numerically higher, but not statistically significant increase in the RR of confirmed severe hypoglycemia.

Figure 4: Subgroup Analyses -EAC-confirmed Sever Hypoglycemic Episodes IDeg vs. IGlar

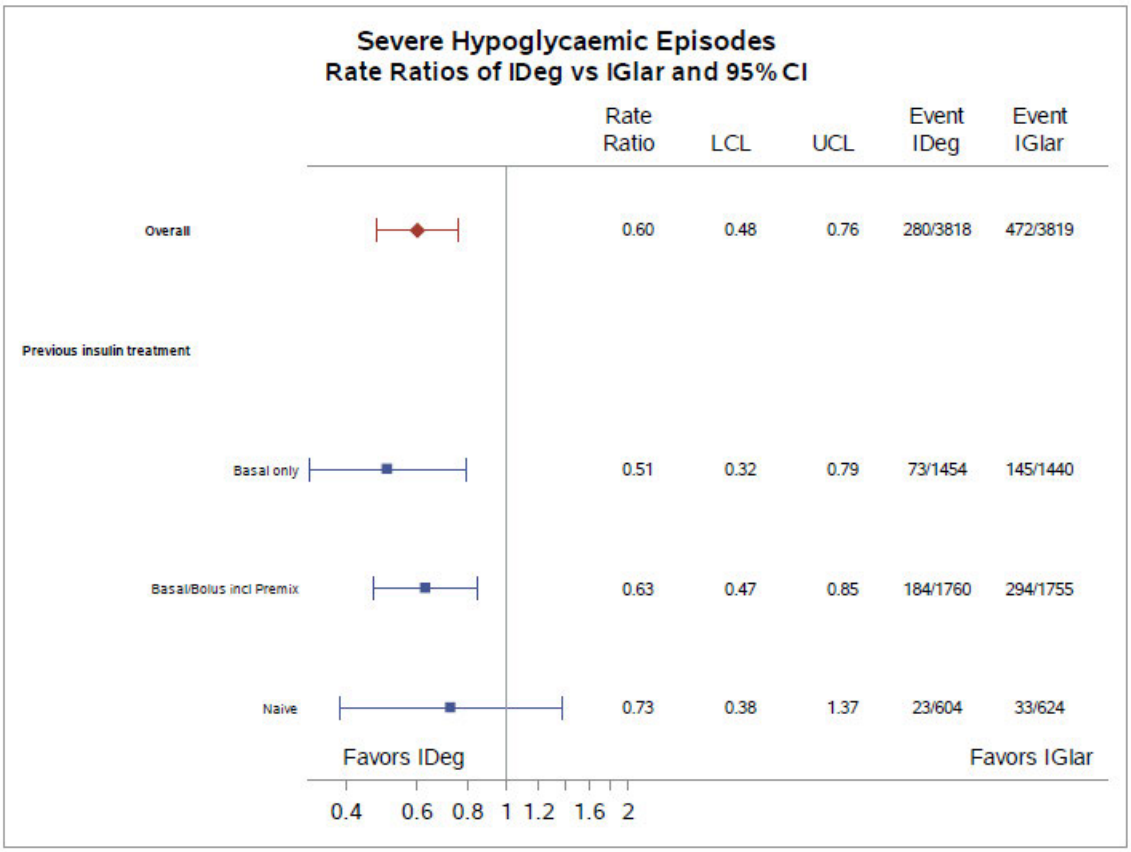


Source: Statistical Reviewer's analysis
UCL: Upper confidence limit; LCL: Lower confidence limit;
Rate Ratio < 1.0 indicates treatment benefit of IDeg

4.2 Other Special/Subgroup Populations

Another subgroup of interest was previous insulin treatment (basal only, basal/bolus incl premix, and naïve). Figure 5 displays the results. The results for the basal/bolus premix subgroup are consistent with the overall results.

Figure 5. Subgroup Analysis - Previous Insulin Treatment



Source: Statistical Reviewer's analysis
UCL: Upper confidence limit; LCL: Lower confidence limit;
Rate Ratio < 1.0 indicates treatment benefit of IDeg

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 were low, about 2%. The tipping point analyses were conducted to evaluate the potential impact of missing data on the results of the confirmatory secondary analyses. For the number of EAC-confirmed severe hypoglycemic episode, 133 more episodes were needed before the tipping point was reached. Out of the 74 non-completers in the IDeg group 25 subjects (34%) would have needed to have an event before the odds ratio was no longer statistically significant compared to none of the 72 non-completers in the IGlar group, estimated

odds ratio and 95% CI: 0.83 (0.69, 1.005)). Refer to the observed incidence rate of 3.7% and 6.3% in two treatment arms respectively; we concluded that the observed superiority in EAC-confirmed severe hypoglycemic episode for IDeg vs. IGlar is robust in the presence of missing values.

5.2 Conclusions and Recommendations

The secondary objective of this study was to assess efficacy of IDeg on markers of glycemic control when compared to IGlar. Efficacy were measured by the secondary confirmatory endpoints, the number of EAC-confirmed severe hypoglycemic episode and occurrence of at least one EAC-confirmed severe hypoglycemic episodes within a subject (yes/no). The superiority was achieved for the first confirmatory endpoint, the number of EAC-confirmed severe hypoglycemic episode since the upper 95% confidence interval was below 1.0. Superiority was also achieved for the second confirmatory secondary endpoint, occurrence of at least one EAC-confirmed severe hypoglycemic episodes within a subject (yes/no), where the 95% confidence interval as below 1.0 as well. In addition, there was an estimated 26% relative risk reduction in time from randomization to first occurrence of EAC confirmed severe hypoglycemic episodes in the IDeg group compared to the IGlar group.

The subgroup analyses and the sensitivity analyses were consistent with the results of the confirmatory endpoints.

There is statistically significant evidence to suggest that IDeg reduces the rate of EAC-confirmed hypoglycemia, compared to IGlar in subjects with T2DM. Based on the evidence reviewed in this document, we conclude that IDeg was associated with a reduction in the rate of EAC-confirmed severe hypoglycemia compared to IGlar in subjects with T2DM.

5.3 Labeling and Recommendations

Based on the review of the submitted data, the following are proposed edits to the label in section 14.

- [redacted] (b) (4)

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

/s/

KIYA HAMILTON
02/16/2018

YUN WANG
02/16/2018

U.S. FOOD & DRUG
ADMINISTRATION

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

CLINICAL STUDIES

NDA / Sequence Number:	203314 / S0135
Drug Name:	Tresiba (insulin degludec injection), for subcutaneous use; Dosages: 100 units/mL (U-100) FlexTouch and 200 units/mL (U-200) Flex Touch
Indications:	Improvement of glycemic control in patients 1 year of age and older with diabetes mellitus
Applicant:	Novo Nordisk
Date(s):	Submission Date: 5/26/2017 PDUFA Date: 3/26/2018
Review Priority:	Standard
Biometrics Division:	Division of Biometrics VII
Statistical Reviewers:	Eugenio Andraca-Carrera, Team Leader (DB7)
Concurring Reviewers:	Mark Levenson, Division Director (DB7)
Medical Division:	Division of Metabolism and Endocrinology Products
Clinical Team:	Medical Officer: Tania Condarco Medical Team Leader: Lisa Yanoff
Project Manager:	Callie Cappel-Lynch
Keywords:	NDA review, Cardiovascular Outcomes Trial

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1 Executive Summary

DEVOTE was a long-term, multi-center, multi-national, 1:1 randomized, double-blinded, parallel group, active-controlled, event-driven trial with a primary objective to confirm cardiovascular safety of IDeg (insulin degludec) compared to IGlar (insulin glargine) when added to standard of care in male and female subjects with type 2 diabetes mellitus at high risk of cardiovascular events. The primary objective of DEVOTE was to show that the hazard ratio of major adverse cardiovascular events (MACE) associated with IDeg is no larger than a pre-specified risk margin of 1.3. MACE is a composite endpoint of cardiovascular death, non-fatal myocardial infarction (MI), and non-fatal stroke.

1.1 Conclusions and Recommendations

Novo Nordisk submitted NDA 203314, supplement 0135, on May 26, 2017 to describe and document the results and analyses of the DEVOTE trial. This review focuses on the evaluation of cardiovascular safety of IDeg compared to IGlar based on the final results of the trial. The primary endpoint of DEVOTE was the time until first adjudicated MACE. In addition to the primary MACE endpoint, pre-specified secondary endpoints related to cardiovascular (CV) safety included the individual components of MACE, all-cause death, unstable angina pectoris (UAP) requiring hospitalization, and heart failure requiring hospitalization. The primary and secondary endpoints were adjudicated by an external independent Event Adjudication Committee (EAC).

A total of 7637 subjects were randomized in DEVOTE: 3818 subjects were randomized to IDeg and 3819 to IGlar. Approximately 97% of subjects in the trial had at least one year and 49.5% had at least two years of on-study follow-up. The median treatment exposure time was approximately 97 weeks in both treatment arms. Vital status at the end of the trial was known for all but 8 randomized subjects in the trial.

A total of 681 subjects experienced at least one adjudicated primary MACE during the trial: 325 subjects randomized to IDeg (4.4 events per 100 person-years) and 356 subjects randomized to IGlar experienced a MACE (4.9 per 100 person-years). The pre-specified Cox proportional hazards model for the primary MACE analysis estimated a hazard ratio (HR) of **0.91** with an associated 95% confidence interval of **(0.78, 1.06)** associated with IDeg. The results of this analysis are summarized in Table 1. The upper bound of the 95 % confidence interval (1.06) ruled out the pre-specified risk margin of 1.3. Analyses of the individual components of MACE and of other pre-specified secondary endpoints related to cardiovascular safety were consistent with the results of the primary analysis of MACE. Subgroup analyses by demographics and baseline cardiovascular risk factors also showed no evidence of an increased risk of MACE associated with IDeg.

In conclusion, the DEVOTE trial met its primary objective of ruling out a hazard ratio margin of MACE larger than 1.3 associated with IDeg. The trial demonstrated that IDeg is not associated with an unacceptable increased cardiovascular risk compared to IGlar.

Table 1. Primary Analysis of MACE

	IDeg N=3818 PY[1]=7366	IGlar N=3819 PY[1]=7326	Hazard Ratio (95% CI)
MACE	325 [4.4]	356 [4.9]	0.91 (0.78, 1.06)
Cardiovascular death	136	142	
Non-fatal MI	144	169	
Non-fatal Stroke	71	79	

[1]Patient-Years based on time to first MACE in the FAS population censored at the time of MACE, death, or trial discontinuation

[ ] incidence rate per 100 person-years based on first observed MACE event

Source: Created by reviewer from dataset adtte xpt

2 INTRODUCTION

2.1 Product Description and Regulatory Bakground

IDeg is a once-daily insulin indicated to improve glycaemic control in patients 1 year of age and older with diabetes mellitus. During the review cycle of the original submissions of NDA 203314 (insulin degludec, IDeg) and NDA 203313 (insulin degludec/insulin aspart, IDegAsp) submitted to the Agency on September 29, 2011, a potential increased cardiovascular risk associated with IDeg was observed in the IDeg/IDegAsp phase 3 development program, based upon a pre-specified meta-analysis to assess the CV risk associated with IDeg/IDegAsp. The meta-analysis was based upon the assessment of 17 randomized, open-label, treat-to-target, non-inferiority clinical trials which were designed primarily for the evaluation of efficacy with prospective capture of key cardiovascular events that underwent adjudication by an independent and blinded committee. The results suggested an increase CV risk associated with IDeg/IDegAsp relative to the pooled comparator arm, using both the pre-specified primary major adverse cardiovascular event (MACE+: composite of CV death, myocardial infarction, stroke and unstable angina pectoris) and a strict MACE endpoint which excluded the unstable angina component from MACE+. A statistical review of this meta-analysis was completed by Dr. Bo Li and signed into DARRTS on 12/13/2012.

On February 8, 2013, the FDA issued a Complete Response Letter to the applicant, which outlined the cardiovascular safety deficiency of insulin degludec and requested additional clinical trial data from a dedicated, double-blind, cardiovascular outcomes trial (CVOT):

> To address the above cardiovascular safety deficiencies, you will need to submit additional clinical trial data from a dedicated, double-blind, cardiovascular outcomes trial using glargine as the comparator. The trial should be powered to exclude an excess cardiovascular risk based on a composite of cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke (MACE), not MACE+. The risk margin to exclude that is necessary for approval should be discussed with

> the Agency at an End-of-Review meeting. At a minimum, the resubmission must include enough MACE events to definitively exclude a hazard of 80% with a reassuring point estimate.

The Applicant met with the Agency on April 4, 2013 to discuss the design and sample size of the new trial. The requirements for the trial are summarized as follows in the meeting minutes:

> While we will accept for resubmission and potentially approve your product based on an interim analysis excluding a CV risk margin of 1.8, assuming a reassuring point estimate and no other countervailing safety signals identified in the resubmission, you will be required to exclude an excess hazard of 30% postmarketing.

The DEVOTE trial initiated in October 2013 to evaluate the CV safety profile of insulin degludec and address the requirements specified in the Complete Response Letter and the meeting minutes. In March, 2015 the Applicant conducted a pre-specified interim analysis after 150 EAC-confirmed MACE had been observed in the trial in order to rule out a risk margin of MACE larger than 1.8 associated with IDeg: 72 MACE were observed among 3818 subjects randomized to IDeg (3.9 MACE per 100 patient years) and 78 MACE were observed among 3820 subjects randomized to IGlar (4.2 MACE per 100 patient years). The estimated hazard ratio of MACE associated with IDeg relative to IGlar based in the interim analysis was 0.92 with a 95% confidence interval (CI) of (0.67, 1.27). A statistical review of this application was signed into DARRTS by Dr. Bo Li in August 2015. Insulin degludec was approved in September 2015 to improve glycemic control in patients with type 1 and type 2 diabetes mellitus.

The DEVOTE trial was designed to continue until 633 MACE had been collected and confirmed. A final analysis would then be performed to further demonstrate non-excessive risk of MACE against a pre-specified risk margin of 1.3. On May 26, 2017, the Applicant submitted NDA 203314, supplement 0135, to document and report the final results of DEVOTE. A total of 681 subjects experienced at least one adjudicated primary MACE during the trial. This review focuses on the assessment of cardiovascular risk of IDeg based on this submission.

2.2 Data Sources

The Applicant submitted electronic documents and analysis datasets in support of NDA 203314, supplement 0135, on May 26, 2017. The CDER Electronic Document Room (EDR) link to the clinical trial report and the analysis datasets of DEVOTE are provided below:

\\CDSESUB1\evsprod\NDA203314\0135

The following analysis datasets were used in this review for the assessment of CV safety of IDeg in DEVOTE:

\\CDSESUB1\evsprod\NDA203314\0135\m5\datasets\ex1250-4080\analysis\adam\datasets\adsl.xpt
\\CDSESUB1\evsprod\NDA203314\0135\m5\datasets\ex1250-4080\analysis\adam\datasets\adadj.xpt
\\CDSESUB1\evsprod\NDA203314\0135\m5\datasets\ex1250-4080\analysis\adam\datasets\adae.xpt
\\CDSESUB1\evsprod\NDA203314\0135\m5\datasets\ex1250-4080\analysis\adam\datasets\adex.xpt
\\CDSESUB1\evsprod\NDA203314\0135\m5\datasets\ex1250-4080\analysis\adam\datasets\adexdur.xpt
\\CDSESUB1\evsprod\NDA203314\0135\m5\datasets\ex1250-4080\analysis\adam\datasets\adtte.xpt

The format, content and documentation of the data submitted in support of this application were adequate to conduct a statistical review of the cardiovascular risk of IDeg.

3 STATISTICAL EVALUATION

3.1 Evaluation of Safety

This review focuses on the evaluation of cardiovascular risk associated with IDeg in the DEVOTE trial. For a complete statistical evaluation of efficacy results, including an assessment of hypoglycemia, please refer to the review authored by Dr. Kiya Hamilton and Dr. Yun Wang.

3.1.1 Study Design

DEVOTE was a long-term, multi-center, multi-national, randomized, double-blinded, parallel group, active-controlled trial designed to evaluate the cardiovascular safety of insulin degludec compared to that of insulin glargine when added to standard of care in male and female subjects with type 2 diabetes mellitus at high risk of cardiovascular events.

DEVOTE planned to randomize a total of 7,500 male and female subjects with T2DM at elevated risk for cardiovascular events based on the following two categories:

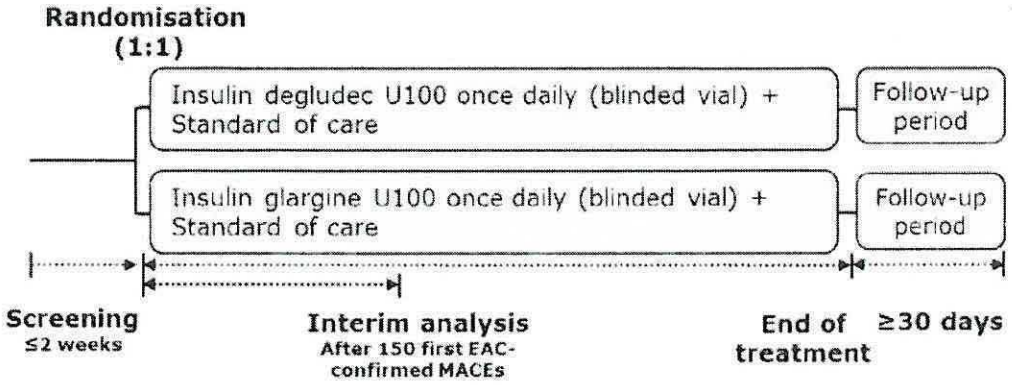
- Subjects aged $\geq$ 50 years with established CV diseases; and,
- Subjects aged $\geq$ 60 years with risk factors for CV diseases.

Subjects were randomized 1:1 in a double-blinded manner to receive one of the investigational products:

- insulin degludec, or
- insulin glargine.

The trial used a "treat-to-target" treatment strategy to target similar glycemic control for all subjects in both arms with titration aimed at reaching an HbA1c < 7%. The trial was event-driven and was designed to continue until at least 633 subjects had experienced a positively adjudicated MACE. The trial was designed to have approximately 91% power to rule out a hazard ratio of MACE larger than 1.3 associated with IDeg under the assumption of a neutral true hazard ratio equal to 1 and an overall 1-sided 2.5% confidence level. The protocol pre-specified that an interim analysis would be conducted to assess the preliminary non-excessive risk of IDeg relative to IGlar for MACE with a risk margin of 1.8 after at least 150 first MACE had been accrued. A single final analysis would be conducted to assess the risk margin of 1.3 after at least 633 had been observed. The trial design is shown schematically in Figure 1 below.

Figure 1. Flow Chart of DEVOTE Study Design



Abbreviations: EAC, external adjudication committee; MACE, major adverse cardiovascular event.

Source: Figure 9-1, page 47, of CSR.

The trial period consisted of a screening period of up to 2 weeks, a randomization visit (V2) at which subjects were randomized to IDeg or IGlar, an estimated treatment period of up to 59 months (depending on actual rate of MACE accrual) and a 30-day post-treatment follow-up period. For each subject, the maximum follow-up in the trial was estimated to be 60.5 months. Randomized subjects were to be followed until the date of trial completion regardless of treatment adherence and compliance. Subjects were scheduled to attend the study site once every month during the first 6 months and every third month during the rest of the trial, and to have monthly phone contacts with the investigator between the site visits. These visits and phone contacts assessed the occurrence of safety and efficacy outcomes, study medication compliance and accountability, and concomitant therapy or intervention.

Safety data collection was limited to serious adverse events (SAEs), adverse events (AEs) associated with drug discontinuation, and episodes of severe hypoglycemia. Non-serious AEs and non-severe hypoglycemic episodes were systematically reported only in Japanese subjects as requested by the Japanese authorities. Adverse events of potential MACE, unstable angina pectoris requiring hospitalization, deaths and episodes of severe hypoglycemia were adjudicated and evaluated by an external event adjudication committee based on predefined diagnostic criteria, in an independent and blinded manner. An EAC charter including event definitions, operational procedures and EAC membership was submitted to the Agency as part of the NDA resubmission package.

An external independent data monitoring committee (DMC) performed ongoing and independent evaluation of accumulated data from the trial. The DMC had access to semi-blinded (e.g., Group A, Group B; decode provided separately in a secured manner) and un-blinded data and was charged with recommending to the Applicant's internal safety committee on whether to continue, modify or terminate the trial. The DMC charter and DMC meeting minutes from all closed and open DMC sessions were submitted to the Agency as part of the NDA application package.

3.1.2 Study Endpoints

3.1.2.1 Primary Composite Endpoint

The pre-specified primary endpoint was the time from randomization to the first occurrence of a Major Adverse Cardiovascular Event (MACE), defined as the composite of cardiovascular death (including deaths of unknown cause), non-fatal myocardial infarction (MI), and non-fatal stroke.

3.1.2.2 Secondary Endpoints

Pre-specified secondary cardiovascular endpoints included the time from randomization to the first occurrence of each of the following EAC-confirmed events:

- 4-point MACE (cardiovascular death, non-fatal MI, non-fatal stroke, and UAP requiring hospitalization)
- Cardiovascular death
- Non-fatal MI
- Non-fatal stroke
- UAP requiring hospitalization
- All-cause death
- Non-cardiovascular death
- Heart failure requiring hospitalization.

3.1.3 Statistical Methodology

3.1.3.1 Analysis Populations

The primary analysis of MACE as well as the analyses of secondary endpoints were conducted in the Full Analysis Set (FAS) population described below:

- Full analysis set (FAS): included all randomized subjects. Subjects were analyzed based on their randomized treatment from the time of randomization until the last recorded contact date on-study, regardless of treatment-adherence. This population follows the intention-to-treat (ITT) principle.

The Applicant conducted sensitivity analyses of MACE (but not of secondary cardiovascular endpoints) in the following populations:

- FAS population with subjects censored at the time of treatment discontinuation.
- FAS population with subjects censored at the time of treatment discontinuation + 30 days.

3.1.3.2 Primary Analysis of MACE

A statistical analysis plan (SAP) dated October 9, 2014/24/2014 documented the pre-specified statistical methods to be used for the final analysis of DEVOTE after 633 MACE had been observed. Statistical methodologies used by the Applicant and additional analyses performed by the statistical reviewer are discussed below. A separate SAP was previously submitted to discuss

the interim analysis of DEVOTE after 150 MACE had been observed. Please refer to Dr. Bo Li's 2015 statistical review for a discussion of the interim analysis and its statistical methodology.

The Applicant summarized graphically the time to first occurrence of an EAC-confirmed MACE associated with IDeg and IGlar through a Kaplan-Meier plot.

The pre-specified primary analysis of time to first MACE used a Cox proportional hazards regression model with treatment (IDeg vs. IGlar) as the only covariate. The estimated hazard ratio for the risk of MACE associated with IDeg and its corresponding 95% confidence interval were reported. Non-inferiority of IDeg relative to IGlar was considered confirmed if the upper bound of the two-sided 95% confidence interval for the HR was smaller than 1.3.

The hypothesis for the primary composite endpoint of MACE was to test non-inferiority of IDeg versus IGlar at the two-sided 5% alpha level:

H0: $HR_{IDeg/IGlar} \geq 1.3$ vs. Ha: $HR_{IDeg/IGlar} < 1.3$

The Statistical Analysis Plan did not pre-specify a test for superiority of IDeg if the risk margin of 1.3 is met.

3.1.3.3 Sensitivity Analyses of the Primary Endpoint

The Applicant conducted the following sensitivity analyses of MACE:

- **Adjustment for baseline covariates.** The Applicant used a Cox proportional hazards model in the FAS population adjusted for the following covariates in addition to treatment: sex (male, female), region (Africa, Asia, Europe, North America, South America), baseline age (regression), smoking status at baseline (never, previous, current smoker), diabetes duration at baseline (regression), cardiovascular risk at baseline (high, medium), insulin-naïve at baseline (yes, no) and renal function eGFR at baseline (regression).

- **Tipping point analysis.** Some subjects withdrew from the trial or were lost to follow-up prior to experiencing an adjudicated MACE. The disposition of all subjects in the trial is discussed in more detail in Section 3.1.4.1 of this review. The Applicant conducted a tipping point analysis to evaluate the potential impact on the estimated hazard ratio of MACE of subjects who were lost to follow-up prior to experiencing an event, under different scenarios of informative missing data.

3.1.3.4 Analyses of Secondary Endpoints

The secondary endpoints listed in Section 3.1.2.2 were analyzed through a Cox proportional hazards model in the FAS population with treatment (IDeg vs. IGlar) as the only covariate. The SAP did not pre-specify a testing hierarchy for secondary endpoints. The Applicant estimated hazard ratios and nominal 95% confidence intervals for the risk of each of the secondary endpoints associated with IDeg uncorrected for multiplicity. Therefore, hazard ratios and confidence intervals for these endpoints are considered exploratory.

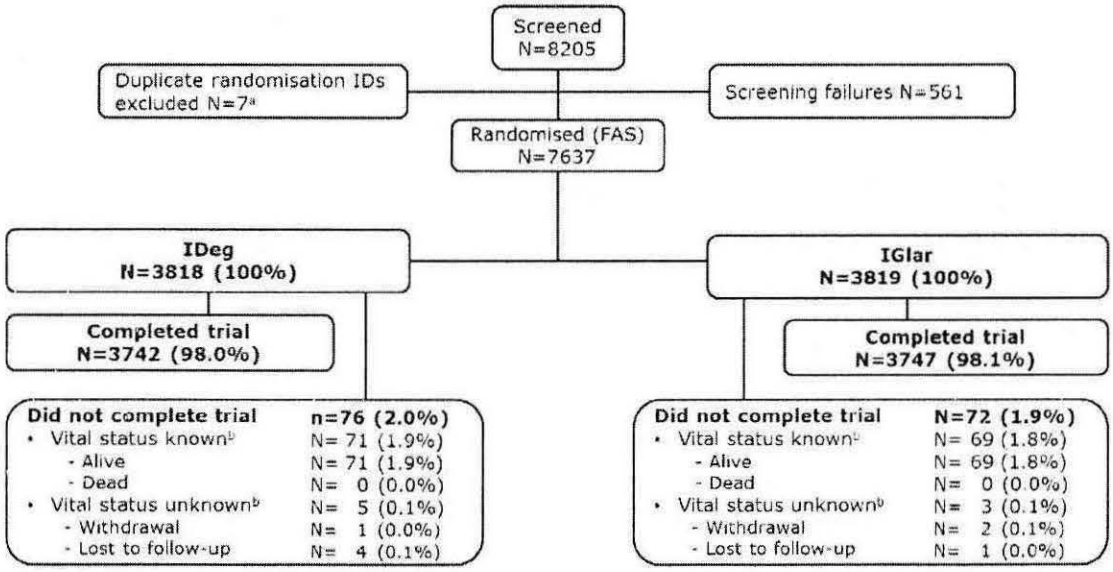
3.1.4 Subject Disposition and Baseline Characteristics

3.1.4.1 Subject Disposition

DEVOTE initiated in October 2013 and recorded the last subject visit on October 16, 2016. A total of 8205 subjects were screened and 7637 were randomized in a 1:1 ratio to receive IDeg (3818 subjects) or IGlar (3819 subjects) which comprise the FAS population used in the primary analysis of MACE. Figure 2 summarizes the final subject disposition in the FAS population.

Of the 7637 randomized subjects in DEVOTE, 98.1% completed the trial. A total of 148 subjects (76 on IDeg and 72 on IGlar) did not complete the trial. Among subjects who did not complete the trial, 10 out of 76 subjects on IDeg and 4 out of 72 subjects on IGlar experienced a non-fatal MACE prior to trial discontinuation. Therefore, 66 subjects randomized to IDeg and 68 subjects randomized to IGlar withdrew from the trial or were lost to follow-up prior to experiencing a MACE. The Applicant obtained the final vital status for all but 8 randomized subjects in the trial (5 on IDeg and 3 on IGlar).

Figure 2. Subject's Disposition On-Trial (FAS Population)



Cross-reference: Modified from EOT Table 14.1.1 and 14.1.4

Note: Completed trial: follow-up visit completed or died during trial. [a]7644 subjects randomised in total; 7 subjects were randomised at 2 different sites; [b]status during trial closure: from the first subject's follow-up visit (29 June 2016) to the actual last patient last visit (16 October 2016).

Abbreviation: N: number of subjects.

Source: Applicant's Clinical Study Report, Figure 10-1. This Figure has been verified by the reviewer using dataset adsl.xpt

The follow-up duration in the FAS population is summarized in Table 2. The mean and median on-study follow-up time were similar in both treatment arms. Approximately 97.2% of subjects had at least one year and 49.5% had 2 or more years of follow-up time. The maximum on-study follow-up duration was 1003 days.

Table 2. Follow-up Time until Death or Trial Discontinuation – FAS Population

	IDeg N=3818 PY=7568	IGlar N=3819 PY=7558
Days of Follow-up		
Mean (SD)	724 (138)	723 (141)
Median	728	728
Max	1003	1003
% Subjects with Follow-up		
≥ 1 year	97.3%	97.1%
≥ 2 years	49.4%	49.5%

Source: Created by the reviewer from dataset adtte xpt

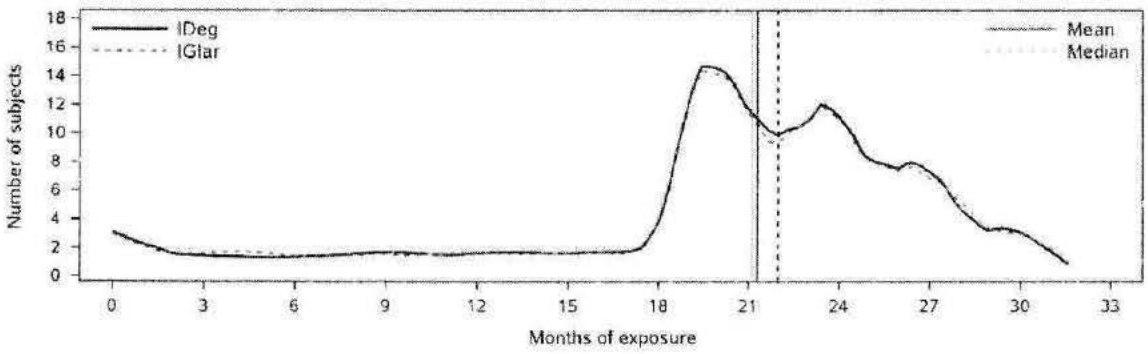
Table 3 summarizes the follow-up time until death or last randomized treatment dose in the FAS population. The median on-treatment follow-up time was similar in both treatment arms (678 days on IDeg and 677 days on IGlar). Figure 3 shows that the distribution of exposure time was similar in both treatment arms. The Applicant did not provide a list of reasons for treatment discontinuation in DEVOTE. The only reason for treatment discontinuation described in the clinical study report and the corresponding datasets was treatment discontinuation due to adverse events. Adverse events leading to permanent discontinuation of randomized treatment were reported in 200 subjects randomized to IDeg (5.2%) and 222 subjects randomized to IGlar (5.8%).

Table 3. Follow-up Time until Death or Last Treatment Dose – FAS Population

	IDeg N=3818 PY=6878	IGlar N=3819 PY=6874
Days of Treatment Exposure		
Mean (SD)	660 (174)	654 (183)
Median	678	677
Max	964	967

Source: Created by the reviewer from dataset adtte xpt

Figure 3. Smoothed Density Plot of Exposure Time - FAS Population



Source: Applicant's Clinical Study Report, Figure 14.2.10. This Figure has been verified by the reviewer using dataset adex.xpt and adexdur.xpt

3.1.4.2 Demographic and Baseline Characteristics

Table 4 summarizes demographics and baseline clinical characteristics for the FAS population in DEVOTE. The characteristics summarized in this table appear balanced between the two randomized treatment arms. Approximately 37.4% of subjects in the trial were female. Most subjects (75.6%) were White, 10.1% were Asian, and 10.9% were Black or African American. The mean age at baseline was 65 years, and most subjects (68.1%) were randomized in the United States.

Baseline clinical characteristics were balanced between both treatment arms: approximately 54.5% of subjects had a baseline HbA1c $\geq$ 8%, 35.4% had moderate or severe renal impairment, 16.1% were insulin naïve, 51% had had diabetes for longer than 15 years, and 78.6% were classified as statin users.

Table 4. Baseline Demographic and Clinical Characteristics

	IDeg N=3818	IGlar N=3819
Sex		
Female	37.2%	37.6%
Male	62.8%	62.4%
Race		
White	76.0%	75.2%
Asian	10.2%	10.1%
Black or African American	10.5%	11.3%
Other	3.3%	3.4%
Age, Mean ± SD	64.9 ± 7.3	65.0 ± 7.5
< 65	48.1%	48.4%
≥ 65	51.9%	51.6%

Country		
United States	68.0%	68.2%
Rest of the World	32.0%	31.8%
HbA1c		
< 8%	44.7%	46.2%
≥ 8%	55.3%	53.8%
Renal Impairment		
Normal / Mild	65.4%	63.8%
Moderate / Severe	34.6%	36.2%
Insulin Naïve		
Yes	15.8%	16.3%
No	84.2%	83.7%
Diabetes Duration		
≤ 15 years	47.6%	50.4%
> 15 years	52.4%	49.6%
Statin Users		
Yes	79.1%	78.1%
No	20.9%	21.9%

Source: Created by reviewer from dataset adtte xpt

3.1.5 Analysis Results

3.1.5.1 Primary Analysis of MACE

Table 5 summarizes the results of the primary analysis of MACE: 325 subjects randomized to IDeg (4.4 MACE per 100 PY) and 356 subjects randomized to IGlar (4.9 MACE per 100 PY) experienced a MACE. The estimated HR based on the pre-specified Cox proportional hazards model was 0.91 with corresponding 95% CI (0.78, 1.06). Based on this result alone, the upper bound of the 95% confidence interval for the hazard ratio of MACE successfully ruled out a hazard ratio margin greater than 1.3 associated with IDeg. Subjects randomized to IDeg observed numerically fewer CV Deaths, non-fatal MIs, and non-fatal strokes than subjects randomized to IGlar.

Table 5. Primary Analysis of MACE – FAS Population

	IDeg N=3818 PY[1]=7366	**IGlar** N=3819 PY[1]=7326	**Hazard Ratio (95% CI)**
MACE	325 [4.4]	356 [4.9]	0.91 (0.78, 1.06)
Cardiovascular death	136	142	
Non-fatal MI	144	169	
Non-fatal Stroke	71	79	

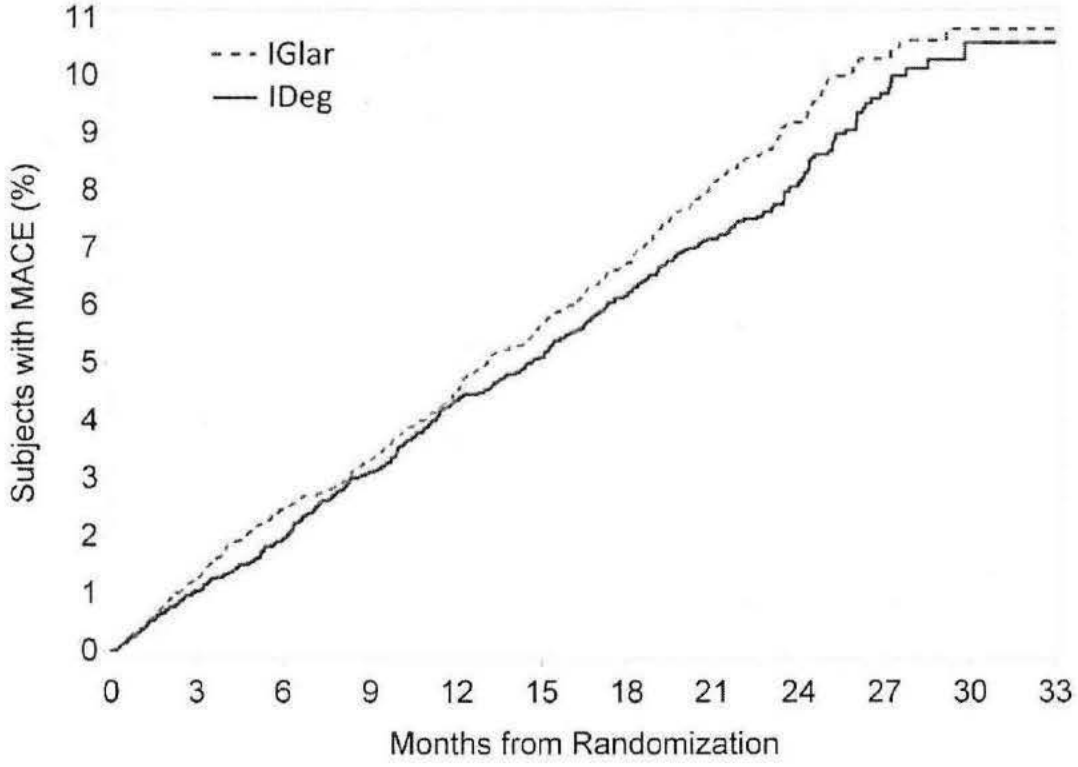
[1]Patient-Years based on time to first MACE in the FAS population censored at the time of MACE, death, or trial discontinuation

[ ] incidence rate per 100 person-years based on first observed MACE event

Source: Created by reviewer from dataset adtte xpt

Figure 4 shows the cumulative probability of experiencing MACE in the two treatment arms. Subjects randomized to IGlar experienced numerically more events than subjects randomized to IDeg throughout the duration of the trial, however the difference between the two curves was not statistically significant (log-rank test p-value: 0.2086).

Figure 4. Cumulative Probability of MACE by Treatment Arm - FAS Population



Source: Created by reviewer from dataset adtte.xpt

3.1.5.2 Sensitivity Analyses of MACE

Sensitivity analyses were conducted to evaluate the effect of treatment discontinuation on the estimated hazard ratio of MACE. Table 6 shows analyses of the primary endpoint MACE in the FAS population under two different censoring schemes: (1) censoring at the earliest of first MACE, treatment discontinuation, or trial completion, and (2) censoring at the earliest of first MACE, treatment discontinuation + 30 days, or trial completion. The on-treatment analysis captured 241 MACE among subjects randomized to IDeg and 273 among subjects randomized to IGlar (compare to 325 events in IDeg and 356 on IGlar in the primary on-study analysis). The estimated hazard ratio and 95% confidence interval, 0.87 (0.73, 1.4), were consistent with the primary analysis. The analysis based on the on-treatment + 30 days censoring scheme estimated a similar hazard ratio and 95% confidence interval, 0.91 (0.78, 1.07).

Table 6. Analyses of MACE – FAS Population, On-Treatment Censoring

Censoring Scheme	IDeg N=3818 PY[1]=6725	IGlar N=3819 PY[1]=6643	Hazard Ratio (95% CI)
On-treatment	241 [3.6]	273 [4.1]	0.87 (0.73, 1.04)
On-treatment + 30 days	294 [4.2]	319 [4.6]	0.91 (0.78, 1.07)

[1]Patient-Years based on time to first MACE in the FAS population censored at the time of treatment discontinuation

[ ] incidence rate per 100 person-years based on first observed MACE event

Source: Created by reviewer from dataset adtte.xpt

Section 3.1.4.1 noted that 66 subjects randomized to IDeg and 68 subjects randomized to IGlar withdrew from the trial or were lost to follow-up without having experienced a MACE. Table 7 shows results of a tipping point analysis that evaluates how the estimated hazard ratio of MACE associated with IDeg could be affected if some of these 66 subjects on IDeg experienced a MACE that was not captured in the trial. The table shows that even if all 66 subjects had experienced a MACE (imputed at the last recorded contact date), the estimated hazard ratio of MACE and its corresponding 95% confidence interval, 1.09 (0.95, 1.26), would still meet the pre-specified risk margin of 1.3.

Table 7. Tipping Point Analysis of MACE – FAS Population

Additional MACE on IDeg Arm	IDeg N=3818	IGlar N=3819	Hazard Ratio (95% CI)
Observed data	325	356	0.91 (0.78, 1.06)
+ 10 MACE	335		0.94 (0.81, 1.09)
+ 33 MACE	358		1.00 (0.86, 1.16)
+ 66 MACE (worst case scenario)	391		1.09 (0.95, 1.26)

Source: Created by reviewer from dataset adtte.xpt

3.1.5.3 Analysis of Secondary Endpoints

Secondary endpoints related to cardiovascular safety and all-cause mortality were collected and adjudicated in DEVOTE in a similar fashion as the primary MACE endpoint. Table 8 summarizes the number of events and the corresponding hazard ratios associated with IDeg for the secondary endpoints listed in Section 3.1.2.2 of this review. The confidence intervals reported in this table are presented at a nominal 95% confidence level and are uncorrected for multiplicity. The estimated hazard ratios and confidence intervals for these endpoints should be interpreted as exploratory.

Subjects randomized to IDeg observed fewer events than subjects randomized to IGlar for all secondary endpoints. The analysis of the pre-specified secondary endpoints shows no evidence of increased risk associated with IDeg.

Table 8. Analysis of Secondary Endpoints - FAS Population

	IDeg N=3818 PY[1]=7568	IGlar N=3819 PY[1]=7558	Hazard Ratio (95% CI)
4-point MACE (MACE + UAP)	386	419	0.92 (0.80, 1.05)
Cardiovascular death[2]	136	142	0.96 (0.76, 1.21)
Non-fatal MI	144	169	0.85 (0.68, 1.06)
Non-fatal Stroke	71	79	0.90 (0.65, 1.23)
UAP requiring hospitalization	71	75	0.95 (0.68, 1.31)
All-cause death	202	221	0.91 (0.76, 1.11)
Non-CV death	66	79	0.84 (0.60, 1.16)
Cardiovascular death[3]	97	106	0.91 (0.69, 1.20)
Heart failure requiring hosp.	296	322	0.91 (0.78, 1.07)

[1]Patient-Years based on time to death in the FAS population censored at the time of death or trial discontinuation
[2]Including undetermined cause of death
[3]Excluding undetermined cause of death
Source: Created by reviewer from dataset adtte xpt

4 Findings in Special/Subgroup Populations

4.1 Subgroup Analyses of MACE

Figure 5 summarizes the risk of MACE associated with IDeg evaluated within subgroups defined by demographic characteristics: sex, age, race, and country of randomization. Figure 6 summarizes the risk of MACE within subgroups defined by baseline clinical characteristics and medication use: HbA1c, renal impairment status, previous exposure to insulin, diabetes duration, and use of statins. Overall, the data summarized in these two forest plots showed no evidence of increased risk of MACE associated with IDeg in any of these subgroups. Interaction tests between treatment and each of the subgroups were all not statistically significant at a nominal level of 0.05 and show no evidence of a potential interaction between treatment and subgroups on the risk of MACE.

Figure 5. Forest Plot of Hazard Ratios of MACE by Demographics Characteristics

Subgroup	IDeg events/N	IGlar events/N	HR (95% CI)
Sex			
Male	226/2396	225/2382	0.99 (0.83, 1.20)
Female	99/1422	131/1437	0.76 (0.59, 0.99)
Race			
White	266/2903	276/2872	0.95 (0.80, 1.12)
Asian	18/391	35/385	0.50 (0.28, 0.89)
Black	26/401	35/431	0.79 (0.49, 1.32)
Age			
Age <= 65	140/1835	167/1847	0.84 (0.67, 1.05)
Age > 65	185/1983	189/1972	0.97 (0.79, 1.19)
Country			
USA	243/2595	251/2606	0.97 (0.81, 1.15)
Non-USA	82/1223	105/1213	0.77 (0.58, 1.03)

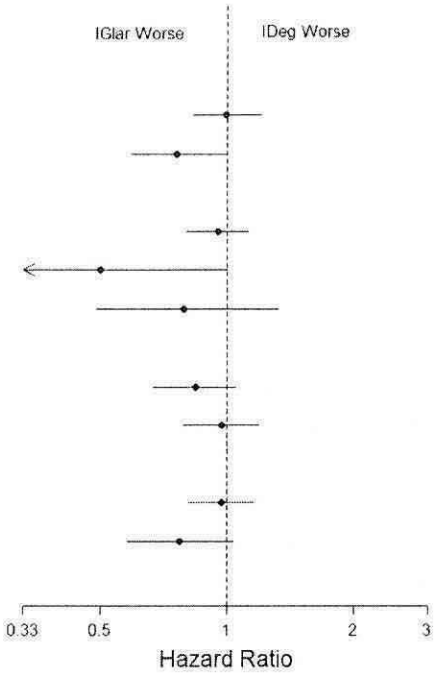
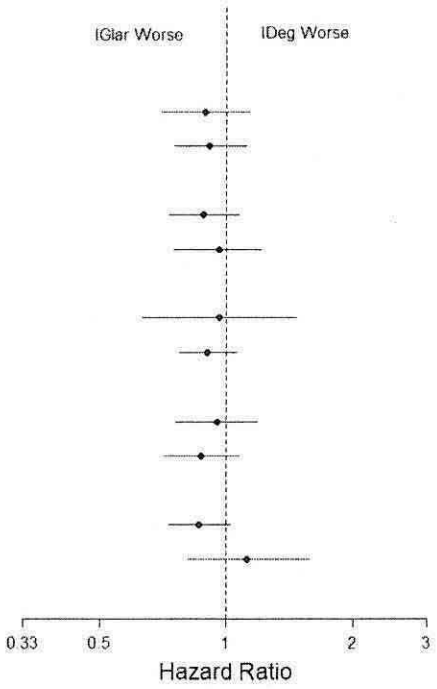


Figure 6. Forest Plot of Hazard Ratios of MACE by Clinical Characteristics and Medication Use at Baseline

Subgroup	IDeg events/N	IGlar events/N	HR (95% CI)
HbA1c			
< 8%	121/1686	141/1745	0.89 (0.70, 1.13)
>= 8%	200/2088	212/2031	0.91 (0.75, 1.11)
Renal Impairment			
Normal / Mild	195/2497	215/2436	0.88 (0.73, 1.07)
Moderate / Severe	130/1321	141/1383	0.96 (0.75, 1.21)
Insulin Naive			
Yes	42/604	45/624	0.96 (0.63, 1.46)
No	283/3214	311/3195	0.90 (0.77, 1.06)
Diabetes Duration			
<= 15 years	149/1817	166/1923	0.95 (0.76, 1.18)
> 15 years	176/2000	190/1895	0.87 (0.71, 1.07)
Statin Users			
Yes	254/3020	289/2983	0.86 (0.73, 1.02)
No	71/798	67/836	1.12 (0.81, 1.57)



Source: Plots created by reviewer from dataset adtte xpt

5 Summary and Conclusions

5.1 Statistical Issues and Collective Evidence

DEVOTE was a long-term, multi-center, multi-national, 1:1 randomized, double-blinded, parallel group, active-controlled, event-driven trial with a primary objective to confirm cardiovascular safety of IDeg (insulin degludec) compared to IGlar (insulin glargine) when added to standard of care in male and female subjects with type 2 diabetes mellitus at high risk of cardiovascular events. The primary objective of DEVOTE was to show that the hazard ratio of MACE associated with IDeg is no larger than a pre-specified risk margin of 1.3.

A total of 7637 subjects were randomized in a 1:1 ratio to receive IDeg (3818 subjects) or IGlar (3819 subjects). The mean and median on-study follow-up time were similar in both treatment arms. Approximately 97.2% of subjects had at least one year and 49.5% had 2 or more years of on-study follow-up time. Of the 7637 randomized subjects in DEVOTE, 98.1% completed the trial. The median on-treatment follow-up time was similar in both treatment arms (678 days on IDeg and 677 days on IGlar).

The pre-specified primary analysis used a Cox proportional hazards model with treatment (IDeg vs. IGlar) as the only covariate to estimate the hazard ratio of MACE associated with IDeg. There were 325 first MACE observed among 3818 subjects randomized to IDeg and 356 first MACE observed among 7558 subjects randomized to IGlar. The estimated hazard ratio of MACE associated with IDeg was 0.91 with 95% confidence interval of (0.78, 1.06). The upper bound of this 95% confidence interval ruled out the pre-specified risk margin of 1.3. Results of the primary analysis of MACE and analyses of pre-specified secondary endpoints are summarized in Table 9. Analyses of secondary endpoints and subgroup analyses of MACE (see Section 4.1 of this review) were consistent with the primary analysis and show no evidence of increased risk associated with IDeg.

Table 9. Analyses of Primary and Secondary Safety Endpoints - FAS Population

	IDeg N=3818 PY[1]=7568	**IGlar** N=3819 PY[1]=7558	**Hazard Ratio (95% CI)**
Primary Endpoint - MACE	325	356	0.91 (0.78, 1.06)
Secondary Endpoints			
4-point MACE (MACE + UAP)	386	419	0.92 (0.80, 1.05)
Cardiovascular death[1]	136	142	0.96 (0.76, 1.21)
Non-fatal MI	144	169	0.85 (0.68, 1.06)
Non-fatal Stroke	71	79	0.90 (0.65, 1.23)
UAP requiring hospitalization	71	75	0.95 (0.68, 1.31)
All-cause death	202	221	0.91 (0.76, 1.11)
Non-CV death	66	79	0.84 (0.60, 1.16)
Cardiovascular death[2]	97	106	0.91 (0.69, 1.20)
Heart failure requiring hosp.	296	322	0.91 (0.78, 1.07)

[1]Patient-Years based on time to death in the FAS population censored at the time of death or trial discontinuation
[2]Including undetermined cause of death
[3]Excluding undetermined cause of death
Source: Created by reviewer from dataset adtte xpt

5.2 Conclusions and Recommendations

The DEVOTE trial was designed to evaluate the cardiovascular safety of IDeg. The pre-specified Cox proportional hazards model obtained an estimated hazard ratio for the primary cardiovascular endpoint MACE of 0.91 with an associated 95% confidence interval of (0.78, 1.06). The upper bound of this confidence interval was smaller than the pre-specified safety margin of 1.3 required by the February 8, 2013 Complete Response Letter. Analyses of secondary safety endpoints related to cardiovascular safety and subgroup analyses of MACE showed no evidence of increased risk associated with IDeg. The conduct, on-study follow-up, and treatment exposure in DEVOTE appear adequate to support the findings of the trial.

In conclusion, the final results from the DEVOTE trial addressed the deficiencies related to cardiovascular safety associated with IDeg outlined in the FDA Complete Response Letter.

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/s/

EUGENIO ANDRACA-CARRERA
02/09/2018

MARK S LEVENSON
02/09/2018

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203314Orig1s008

OTHER REVIEW(S)

Division of Metabolism and Endocrinology Products

REGULATORY PROJECT MANAGER LABELING REVIEW

Application Number:
NDA 203314/S-008

Name of Drug:
Tresiba (insulin degludec injection) 100 units/mL and 200 units/mL

Applicant: Novo Nordisk Inc.

Material Reviewed:

Submission Date	Receipt Date	Document Type
March 13, 2018	March 13, 2018	PI

Background and Summary

Tresiba (insulin degludec) was approved on September 25, 2015, under NDA 203314, to improve glycemic control in adults with diabetes mellitus. Two post marketing requirements were included in the approval letter and are listed below.

2954-1 An open-label, 26-week, randomized, controlled efficacy and safety trial comparing Tresiba (insulin degludec injection) with insulin detemir in pediatric patients with type 1 diabetes ages 1 to 17 years (inclusive) using insulin aspart at each meal, followed by a 26-week safety extension.

2954-2 Conduct a randomized, double-blind, active-controlled trial evaluating the effect of Tresiba (insulin degludec injection) on the incidence of major adverse cardiovascular events (MACE) in subjects with type 2 diabetes mellitus. The primary objective of the trial should be to demonstrate that the upper bound of the 2-sided 95% confidence interval for the estimated risk ratio comparing the incidence of adjudicated MACE (non-fatal myocardial infarction, non-fatal stroke, cardiovascular death) observed with Tresiba to that observed in the comparator group is less than 1.3.

The final study report and efficacy supplement, S-003, for 2954-1 was received on February 16, 2016, and was approved on December 16, 2016.

On May 26, 2017, the sponsor submitted the final study report and efficacy supplement, S-008, for 2954-2.

Review

The prescribing information (PI) submitted on March 13, 2018, was compared to the currently approved PI, approved on December 16, 2016 (S-003). The following significant changes were noted:

In highlights, the RECENT MAJOR CHANGES and DOSAGE AND ADMINISTRATION sections were updated to reflect changes to the dosage and administration section of the full PI.

In highlights, the DRUG INTERATIONS section was updated to reflect changes to the drug interactions section of the full PI.

Under section 2.1 of DOSAGE AND ADMINISTRATION, the following statement was added:

Use TRESIBA with caution in patients with visual impairment that may rely on audible clicks to dial their dose.

Updates were made to section 2.2 of DOSAGE AND ADMINISTRATION for clarity. Please see the attached comparison document for details.

Under section 3 DOSAGE FORMS AND STRENGTHS, the first statement was changed from:
TRESIBA is available as a clear, and colorless solution for injection in:

To:
Injection: TRESIBA is available as a clear and colorless solution:

Under section 5.4 of WARNINGS AND PRECAUTIONS, the second paragraph was updated for clarity. Please see attached comparison for details.

Under section 6, ADVERSE REACTIONS, the following bullet was added:

Medication errors *[see Warnings and Precautions (5.4)]*

Section 6.1 of ADVERSE REACTIONS, was updated to reflect the data provided in this supplement. Please see attached comparison document for details.

Under section 6.1 of ADVERSE REACTIONS, under the heading lipodystrophy, the following statement was removed:

Rotate insulin injection sites within the same region to reduce the risk of lipodystrophy.

Under section 6.2 of ADVERSE REACTIONS, the following statement was removed:
The presence of antibodies that affect clinical efficacy may necessitate dose adjustments to correct for tendencies toward hyper or hypoglycemia.

Under section 8.5 of USE IN SPECIAL POPULATIONS, the following statement was added:

In the safety outcomes trial (DEVOTE), a total of 1983 (52%) of the 3818 TRESIBA-treated patients with type 2 diabetes were 65 years or older and 381 (10%) were 75 years or older. Differences in safety or effectiveness were not observed in these subgroup analyses.

Under section 8.6 of USE IN SPECIAL POPULATIONS, the following statement was added:

In the safety outcomes trial (DEVOTE), a total of 1429 (37.4%) of the 3818 TRESIBA-treated patients with type 2 diabetes had an eGFR less than 60 mL/min/1.73 m2, and 108 (2.8%) subjects had an eGFR less than 30 mL/min/1.73 m2. Differences in safety or effectiveness were not observed in the subgroup analyses.

Section 14.4 Safety Outcomes Trial, was added under the section CLINICAL STUDIES, to present the data from DEVOTE (NCT01959529) "Cardiovascular Outcomes Trial of TRESIBA Administered Once-Daily Between Dinner and Bedtime in Combination with Standard of Care in Subjects with Type 2 Diabetes and Atherosclerotic Cardiovascular Disease."

The following reviewers have cleared this document:
Clinical: Tania Condarco, Monika Houstoun, Patrick Archdeacon and Lisa Yanoff
Statistics: Kiya Hamilton and Yun Wang
Safety Statistics: Eugenio Andraca-Carrera
OPDP: Ankur Kalola

Conclusion

The changes made to the PI were found acceptable. An approval letter for this supplement should be issued.

No changes were made to the patient package insert, or IFUs. Therefore, the currently approved versions of these labeling pieces will be attached to the approval letter.

Callie Cappel-Lynch	March 15, 2018
Regulatory Project Manager	Date
Julie Van der Waag	March 15, 2018
Chief, Project Management Staff	Date

Summary
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CALLIE C CAPPEL-LYNCH
03/15/2018

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: March 5, 2018

To: Callie Cappel-Lynch, Regulatory Project Manager
Division of Metabolism and Endocrinology Products (DMEP)

From: Ankur Kalola, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Melinda McLawhorn, Team Leader, OPDP

Subject: OPDP Labeling Comments for TRESIBA® (insulin degludec injection), for subcutaneous use

NDA: 203314 / Supplement 8

In response to DMEP's consult request dated June 1, 2017, OPDP has reviewed the proposed product labeling (PI) for Tresiba. This supplement (S8) provides for changes to PI based on the DEVOTE study.

OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DMEP (Callie Cappel-Lynch) on February 23, 2018, and are provided below.

Thank you for your consult. If you have any questions, please contact Ankur Kalola at (301) 796-4530 or Ankur.Kalola@fda.hhs.gov.

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/s/

ANKUR S KALOLA
03/05/2018

Clinical Inspection Summary

Date	2/8/2018
From	Cynthia F. Kleppinger, M.D., Senior Medical Officer Janice Pohlman, M.D., M.P.H., Team Leader Kassa Ayalew, M.D., M.P.H., Branch Chief Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	Tania Condarco, M.D., Medical Officer Lisa B. Yanoff, M.D., Clinical Team Leader Patrick Archdeacon, M.D., MPhil, Clinical Team Leader Callie Cappel-Lynch, Regulatory Project Manager Division of Metabolism and Endocrinology Products (DMEP)
NDA/BLA #	NDA 203314/s008
Applicant	Novo Nordisk Inc.
Drug	insulin degludec
NME (Yes/No)	No
Therapeutic Classification	Antidiabetic
Proposed Indication(s)	Treatment of diabetes mellitus
Consultation Request Date	7/12/2017
Summary Goal Date	2/26/2018
Action Goal Date	3/26/2018
PDUFA Date	3/26/2018

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The inspection for this sNDA consisted of four domestic clinical sites as well as the sponsor. The inspection of one clinical investigator listed below revealed regulatory violations. The inspection of the sponsor and the remaining clinical investigators revealed no regulatory violations.

In general, based on the inspections of the four clinical sites and the sponsor, the inspectional findings support validity of data as reported by the sponsor under this sNDA.

The classification for Dr. Wood is Voluntary Action Indicated (VAI). Although regulatory violations were noted (as described below), they are unlikely to significantly impact primary safety and efficacy analyses. Reliability of data from this site is acceptable for use in support of the indication for this application. The full Establishment Inspection Report (EIR) was submitted for review.

The classification for Drs. Agaiby, Harris, and Thrasher is No Action Indicated (NAI). Data from these sites are considered reliable based on the available information. The full EIR for Drs. Agaiby and Harris was submitted for review. The full EIR for Dr. Thrasher was not available for review. Preliminary inspection results were communicated by the FDA ORA field investigator.

The classification for Novo Nordisk is NAI. Data from this sponsor are considered reliable based on the available information. The full EIR was not available for review. Preliminary inspection results were communicated by the FDA ORA field investigator.

All classifications are considered preliminary until the final communication letter is sent to the inspected entity. An inspection summary addendum will be generated if conclusions change upon receipt and review of the pending EIRs.

II. BACKGROUND

Novo Nordisk submitted a supplemental application with a postmarketing requirement (PMR 2954-2) to NDA 203314 for Tresiba® (insulin degludec injection, IDeg), a long-acting basal human insulin analogue, approved on September 25, 2015.

To fulfill the PMR, Novo Nordisk completed the cardiovascular outcomes trial EX1250-4080 (DEVOTE) entitled "*A trial comparing cardiovascular safety of insulin degludec versus insulin glargine in subjects with type 2 diabetes at high risk of cardiovascular events*".

The trial was conducted at 438 sites in 20 countries, with 271 sites from the US. The trial began October 29, 2013 and completed October 16, 2016. A total of 8205 subjects were screened, 7637 subjects were randomized and 7489 subjects completed the trial. A total of 82 subjects were randomized in error.

The primary endpoint was time from randomization to first occurrence of an Event Adjudication Committee (EAC)-confirmed three-component major adverse cardiovascular event (MACE): cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke.

Inspections were requested. Sites were chosen based on the Office of Scientific Investigations (OSI) site selection tool. Only domestic sites were chosen as there was sufficient domestic data. Sites were chosen that had larger than average enrollment, large numbers of adjudicated hypoglycemic events compared to other sites, and no inspectional history or no recent inspectional history.

III. RESULTS (by Site):

Name of CI/ Address Site#	Number of Subjects Randomized	Inspection Date	Classification
John Agaiby 6121 Green Bay Road Suite 150 Kenosha, WI 53142 Site 18637/763	18 subjects	08/03 – 08/10/2017	No Action Indicated (NAI)
Ronald Harris 675 Baltimore Drive Wilkes-Barre, PA 18702 Site 2168/942	31 subjects	09/25 – 09/29/2017	No Action Indicated (NAI)
James Thrasher 500 South University Avenue Suite 615 Little Rock, AR 72205 Site 39303/928	44 subjects	12/18 – 12/22/2017	No Action Indicated (NAI)*
Robert Wood 200 Clinic Drive Madisonville, KY 42431 Site 15705/761	28 subjects	10/30 – 11/08/2017	Voluntary Action Indicated (VAI)
Novo Nordisk A/S Vandtaarnsvej 114 DK-2860 Soeborg Denmark	N/A	11/06 – 11/10/2017	No Action Indicated (NAI)*

Key to Compliance Classifications
NAI = No deviation from regulations
VAI = Deviation(s) from regulations
OAI = Significant deviations from regulations; data unreliable.
*Pending = Preliminary classification based on information in 483 (if applicable) and preliminary communication with the field; final classification is pending letter to site.

NOTE: Site inspections focused on 100% review of informed consent documents (ICDs), institutional review board (IRB)/ ethics committee (EC) correspondences, 1572s/investigator agreements, financial disclosures, training records, CVs and licenses, delegation of duties, monitoring logs and reports, inclusion/exclusion criteria, enrollment logs, subject source documents including medical history records, drug accountability, concomitant medication records, and adverse event reports. Source records were compared to the sponsor's data line listings.

1. John Agaiby/ Site 18637/763

There were 21 subjects screened and 18 subjects enrolled into the study; 17 subjects completed the study. Fourteen of the subject's files were reviewed. This site also absorbed the 10 subjects from Dr. Jain's study site (841) located in Milwaukee, WI. Two of the subjects from Dr. Jain's site came for visits and continued with treatment in the study. Files for these two subjects (b) (6) and one subject (b) (6) that initially agreed to be seen at this site but discontinued, were also reviewed during the inspection.

The central institutional review board used for the study was Sterling Institutional Review Board (IRB).

Dr. Agaiby is Vice President-Medical Affairs for Clinical Investigation Specialists, Inc. (CIS). His wife is the president and owner of the company. CIS has three other locations in Illinois. Dr. Agaiby also works at Aurora Healthcare clinic. Study subjects were recruited from his private practice patients, from the CIS database, through IRB approved advertisements, radio ads, and referrals from other physicians.

All enrolled subjects met inclusion criteria and none of the exclusion criteria. Source records were compared to the sponsor's data line listings and there were no discrepancies. All MACE, serious adverse events, adverse events, deviations, and deaths were reported accurately. The primary endpoint was verifiable. Subject diaries and source documents were also reviewed for hypoglycemic events. All subject-experienced hypoglycemic events that required assistance were reported.

The inspection revealed adequate adherence to the regulations and the investigational plan. There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, issued.

2. Ronald Harris/ Site 2168/942

There were 33 subjects screened and 31 subjects enrolled into the study; 31 subjects completed the study. There were 31 subject records reviewed.

Dr. Harris is an endocrinologist with the Department of Endocrinology, Geisinger Clinic. The subjects were recruited from the Geisinger Health patient population. He also served as a sub-investigator at another Geisinger Medical Center site. Additionally, in December 2015, Dr. Harris temporarily transferred principal investigator responsibility to one of the sub-investigators, Brian Jameson, DO. Dr. Harris resumed his role as principal investigator in April 2016.

The IRB of record was the Geisinger Institutional Review Board.

Most of the source documents were electronic medical records in the Geisinger Health electronic medical record system, EPIC. The records were generally organized, legible and

complete. All randomized subjects met the inclusion/exclusion criteria. Source records were compared to the sponsor's data line listings and there were no discrepancies except for two minor transcription errors in insulin units reported. There was no evidence of under-reporting of adverse events. The primary efficacy endpoint data were verifiable. Subject diaries and source documents were also reviewed for hypoglycemic events. All subject-experienced hypoglycemic events that required assistance were reported.

At this site, there was a drug storage temperature excursion that affected several subjects. From 8/3-18/2015, the study drugs were exposed to temperatures below the lower limit of the required range of 2°C to 8°C. The temperature monitoring system sent alarm notices by email to study personnel in real time but those staff were no longer employed. The deviation went unnoticed until a monitor reviewed the electronic temperature records at a monitoring visit on 9/9/2015. The subjects were immediately notified. Subjects (b) (6) used the affected insulin degludec/insulin glargine and were provided with marketed product until the site received replacement study drugs. There were no adverse events attributed to the temperature excursion. The temperature excursions were reported to the IRB and listed as protocol deviations.

The inspection revealed adequate adherence to the regulations and the investigational plan. There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, issued.

3. James Thrasher/ Site 39303/928

There were 46 subjects screened and 44 subjects enrolled into the study; 44 subjects completed the study. There were 44 subject records reviewed.

Subject (b) (6) was randomized prior to receiving medical records, which stated that the patient had not been in remission from prostate cancer for at least 5 years, a per protocol exclusion criterion. This was listed as a protocol deviation.

Source records were compared to the sponsor's data line listings and there were no discrepancies. All MACE, serious adverse events, adverse events, deviations, and deaths were reported accurately. The primary endpoint was verifiable. Subject diaries and source documents were also reviewed for hypoglycemic events. All subject-experienced hypoglycemic events that required assistance were reported.

The inspection revealed adequate adherence to the regulations and the investigational plan. There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, issued.

4. Robert Wood/ Site 15705/761

There were 33 subjects screened and 28 subjects enrolled into the study; 27 subjects completed the study; one subject was lost to follow-up. There were 28 subject records reviewed.

The Clinical Research Unit was under ownership of Baptist Health and was operational from 2001 until July 7, 2017 when, due to budget restraints, the unit was closed. One staff person was retained to assist with closing out all clinical studies. Dr. Wood maintains a private practice in the same building on a different floor. Study subjects were recruited from his private practice patients, from the site's database, through IRB approved advertisements, radio ads, and referrals from other physicians

The central institutional review board used for the study was Sterling Institutional Review Board (IRB).

The majority of medical records supporting the study were generated from the hospital's (Baptist Health) electronic medical record system. All clinical study records are stored in a locked room in the basement of the building. All records were available for inspectional review. Source records were compared to the sponsor's data line listings. Subject diaries and source documents were also reviewed for hypoglycemic events. The primary endpoint data was verifiable.

At the conclusion of the inspection, a Form FDA-483, Inspectional Observations, was issued for failure to follow the protocol.

- During review of the source documents including diaries and medical records, seven severe hypoglycemic events were not reported. (Subject (b) (6) randomized to IGlar [two events], Subject (b) (6) randomized to IGlar [two events], Subject (b) (6) randomized to IDeg [two events], and Subject (b) (6) randomized to IDeg [one event])
  <u>OSI Reviewer Comment</u>*: This was a secondary endpoint. These events were missed on diary review by clinic staff.*
- Seven subjects were randomized and administered the investigational product prior to the investigator confirming eligibility. Three of these subjects ((b) (6) (b) (6) 1) failed to meet inclusion/exclusion criteria.
  <u>OSI Reviewer Comment</u>*: These three subjects were listed as protocol deviations.*

Dr. Woods submitted a response to the inspectional observations. No corrective actions were made as the site is closed to research. Although regulatory violations were noted as described above, they are unlikely to significantly impact primary safety and efficacy analyses. Data from this site appear acceptable.

5. Novo Nordisk/ Sponsor

The inspection consisted of reviewing the organizational structure and responsibilities, transfer of obligations, contractual agreements, selection of sites, training, investigational product accountability, the evaluation of the adequacy of monitoring and corrective actions taken by the sponsor/monitor/CRO, deviations related to key safety and efficacy endpoints, quality assurance and audits, adverse events evaluation and reporting, 1572s and investigator agreements, the interactive voice/web response system, financial disclosures, standard operating procedures (SOPs), trial master file review, record retention, selection criteria for all committee members, oversight of committees, data management, escalation of issues, and clinical trial oversight.

There were three individuals who had leadership roles in the DEVOTE trial (Chair of Steering Committee, member of Steering Committee, Chair of Data Monitoring Committee) who were also faculty members at the University of Texas Southwestern Medical Center. There was a strict firewall set up with acceptable procedures to maintain independence and ensure integrity of the data. All Data Monitoring Committee (DMC) files were on a separate secure network that only the Chair could access; no records were maintained in his office. DMC related documents were encrypted and password protected. No discussions of the study were allowed in the offices and all DMC phone calls were taken off-site.

The potential unblinding of the interim analysis data that was reported to FDA October 17, 2016 was also evaluated. Per the DEVOTE Data Access Management Plan (DAMP), all unblinded documents from the DEVOTE study were only to be accessible to individuals specified in the log of the DEVOTE Interim Reporting Team (IDRT). The sponsor had set up a very good firewall between the interim analysis team and the blinded study team. All staff were trained. Staff was sequestered to a separate building, had a separate email account, had a separate network folder and space with restricted access and had no contact with the blinded study staff. Review of the audit trail with the interim analysis data showed no unauthorized staff had any access to the folder.

A new staff person in the Regulatory Affairs Department was tasked to submit the interim analysis data to the FDA through the Novo Nordisk eCTD viewing tool, which he proceeded to do on October 3, 2016. This person had been trained on the procedures for submission of documents. However, in the process, he did not keep the submission folder restricted (by checking a box). The restricted DEVOTE interim analysis sequences in NDA 203313 and 203314 (containing unblinded DEVOTE data) became available to all staff in the Regulatory Affairs Department. Of note, Last-Patient-Last-Visit (LPLV) occurred on September 5, 2016.

There were 49 Novo Nordisk employees within the Regulatory Affairs Department that potentially had access to the data. A separate staff person who periodically tests folders discovered that she could access the restricted submission folder on October 11, 2016. She immediately alerted her supervisor who confirmed that the data was viewable and had the folder locked. Upper management was made aware and the supervisor who saw the data

was sent home and was sequestered until database lock. During the inspection, the submission folder activity was available, showing activity by four Regulatory Affairs Department staff, but there was no audit trail to determine who may have viewed the interim analysis data. However, interviews with sponsor staff and review of documents did not indicate that there were any other staff who inappropriately reviewed the interim analysis data. Sponsor took appropriate corrective actions and put into place preventive actions to avoid a similar event in the future.

The inspection revealed adequate adherence to the regulations and the investigational plan. There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, issued.

The audit did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data. Data from this sponsor appear acceptable.

{See appended electronic signature page}

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