CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

206073Orig1s021

Trade Name: **GLYXAMBI**

Generic Name: Empagliflozin and Linagliptin

Sponsor: Boehringer Ingelheim Pharmaceuticals, Inc.

Approval Date: 03/30/20

Indications: GLYXAMBI is a combination of empagliflozin, a sodium-glucose cotransporter 2 (SGLT2) inhibitor and linagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor, indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

Empagliflozin is indicated to reduce the risk of cardiovascular death in adults with type 2 diabetes mellitus and established cardiovascular disease.

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APPROVAL LETTER

NDA 201280/S-020
NDA 201281/S-024
NDA 206073/S-021
NDA 208026/S-012

SUPPLEMENT APPROVAL

Boehringer Ingelheim Pharmaceuticals, Inc.
Attention: Charles Mazzarella
Director, Regulatory Affairs; and
Madhuri Jerfy, M.S.
Associate Director, Regulatory Affairs
900 Ridgebury Road, P.O. Box 368
Ridgefield, CT 06877

Dear Mr. Mazzarella and Ms. Jerfy:

Please refer to your supplemental new drug applications (sNDAs) dated and received May 30, 2019 (NDA 201280) and June 6, 2019 (NDA 201281, NDA 206073, NDA 208026), and your amendments, submitted under section 505(b) and pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Tradjenta (linagliptin) tablets, Jentadueto (linagliptin and metformin hydrochloride) tablets, Glyxambi (empagliflozin and linagliptin) tablets, and Jentadueto XR (linagliptin and metformin hydrochloride extended-release) tablets.

These Prior Approval supplemental new drug applications provide for revisions to the prescribing information to include information based on Study 1218.74 entitled, *A multicenter, international, randomized parallel group, double-blind trial to evaluate cardiovascular safety of linagliptin versus glimepiride in patients with T2DM at high cardiovascular risk. The CAROLINA trial*.

APPROVAL & LABELING

We have completed our review of these applications, as amended. They are approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

WAIVER OF ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

Please note that we have previously granted a waiver of the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of Prescribing Information.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information and Medication Guide), 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 *SPL Standard for Content of Labeling Technical Qs and As*.[2]

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for these NDAs, 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 Microsoft Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), 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 applications, you are exempt from this requirement.

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm
[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

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 Prescribing Information 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 *Providing Regulatory Submissions in Electronic and Non-Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[3]

You must submit final promotional materials and Prescribing Information, 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 FDA.gov.[4] Information and Instructions for completing the form can be found at FDA.gov.[5] For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see FDA.gov.[6]

REPORTING REQUIREMENTS

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

[3] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

[4] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf
[6] http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm

If you have any questions, call Richard Whitehead, Regulatory Project Manager, at (301) 796-4945.

Sincerely,

{See appended electronic signature page}

Patrick Archdeacon, M.D.
Associate Director for Therapeutics (Acting)
Division of Diabetes, Lipid Disorders, and Obesity
Office of Cardiology, Hematology, Endocrinology, and Nephrology
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
  - Prescribing Information
  - Medication Guides

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

PATRICK ARCHDEACON
03/30/2020 12:55:09 PM

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

GLYXAMBI® (empagliflozin and linagliptin tablets), for oral use
Initial U.S. Approval: 2015

----------RECENT MAJOR CHANGES----------

Indications and Usage (1)	3/2020
Warnings and Precautions	
Pancreatitis (5.1)	7/2019
Ketoacidosis (5.4)	1/2020
Increased Low-Density Lipoprotein Cholesterol (LDL-C) – Removed	3/2020
Bullous Pemphigoid (5.12)	7/2019
Macrovascular Outcomes – Removed	7/2019

----------INDICATIONS AND USAGE----------

GLYXAMBI is a combination of empagliflozin, a sodium-glucose co-transporter 2 (SGLT2) inhibitor and linagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor, indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus

Empagliflozin is indicated to reduce the risk of cardiovascular death in adults with type 2 diabetes mellitus and established cardiovascular disease. (1)

Limitations of Use
- Not recommended for patients with type 1 diabetes or for the treatment of diabetic ketoacidosis (1)
- Has not been studied in patients with a history of pancreatitis (1)

----------DOSAGE AND ADMINISTRATION----------
- The recommended dose of GLYXAMBI is 10 mg empagliflozin/ 5 mg linagliptin once daily, taken in the morning, with or without food (2.1)
- Dose may be increased to 25 mg empagliflozin/5 mg linagliptin once daily (2.1)
- Assess renal function before initiating GLYXAMBI. Do not initiate GLYXAMBI if eGFR is below 45 mL/min/1.73 m^2 (2.2)
- Discontinue GLYXAMBI if eGFR falls persistently below 45 mL/min/1.73 m^2 (2.2)

----------DOSAGE FORMS AND STRENGTHS----------

Tablets:
10 mg empagliflozin/5 mg linagliptin
25 mg empagliflozin/5 mg linagliptin (3)

----------CONTRAINDICATIONS----------
- Severe renal impairment, end-stage renal disease, or dialysis (4)
- Hypersensitivity to empagliflozin, linagliptin, or any of the excipients in GLYXAMBI (4, 5.10)

----------WARNINGS AND PRECAUTIONS----------
- *Pancreatitis* There have been reports of acute pancreatitis, including fatal pancreatitis. If pancreatitis is suspected, promptly discontinue GLYXAMBI. (5.1)
- *Heart Failure* Heart failure has been observed with two other members of the DPP-4 inhibitor class. Consider risks and benefits of GLYXAMBI in patients who have known risk factors for heart failure. Monitor for signs and symptoms. (5.2)
- *Hypotension* Before initiating GLYXAMBI assess and correct volume status in patients with renal impairment, the elderly, in patients with low systolic blood pressure, and in patients on diuretics. Monitor for signs and symptoms during therapy. (5.3)
- *Ketoacidosis* Assess patients who present with signs and symptoms of metabolic acidosis for ketoacidosis, regardless of blood glucose level. If suspected, discontinue GLYXAMBI, evaluate and treat promptly. Before initiating GLYXAMBI, consider risk factors for ketoacidosis. Patients on GLYXAMBI may require monitoring and temporary discontinuation of therapy in clinical situations known to predispose to ketoacidosis. (5.4)
- *Acute Kidney Injury* Consider temporarily discontinuing in settings of reduced oral intake or fluid losses. If acute kidney injury occurs, discontinue and promptly treat. Monitor renal function during therapy. (5.5)
- *Urosepsis and Pyelonephritis* Evaluate patients for signs and symptoms of urinary tract infections and treat promptly, if indicated (5.6)
- *Hypoglycemia* Consider lowering the dose of insulin secretagogue or insulin to reduce the risk of hypoglycemia when initiating GLYXAMBI (5.7)
- *Necrotizing Fasciitis of the Perineum (Fournier's Gangrene)* Serious, life-threatening cases have occurred in both females and males. Assess patients presenting with pain or tenderness, erythema, or swelling in the genital or perineal area, along with fever or malaise. If suspected, institute prompt treatment. (5.8)
- *Genital Mycotic Infections* Monitor and treat as appropriate (5.9)
- *Hypersensitivity Reactions* Serious hypersensitivity reactions (e.g., anaphylaxis, angioedema, and exfoliative skin conditions) have occurred with empagliflozin and linagliptin. If hypersensitivity reactions occur, discontinue GLYXAMBI, treat promptly, and monitor until signs and symptoms resolve. (5.10)
- *Arthralgia* Severe and disabling arthralgia has been reported in patients taking DPP-4 inhibitors. Consider as a possible cause for severe joint pain and discontinue drug if appropriate. (5.11)
- *Bullous Pemphigoid* There have been reports of bullous pemphigoid requiring hospitalization. Tell patients to report development of blisters or erosions. If bullous pemphigoid is suspected, discontinue GLYXAMBI. (5.12)

----------ADVERSE REACTIONS----------
- The most common adverse reactions associated with GLYXAMBI (a 5% or greater incidence) were urinary tract infections, nasopharyngitis, and upper respiratory tract infections (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Boehringer Ingelheim Pharmaceuticals, Inc. at 1-800-542-6257 or 1-800-459-9906 TTY, or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------USE IN SPECIFIC POPULATIONS----------
- *Pregnancy* Advise females of the potential risk to a fetus especially during the second and third trimesters (8.1)
- *Lactation* GLYXAMBI is not recommended when breastfeeding (8 2)
- *Pediatric Patients*: Safety and effectiveness of GLYXAMBI in pediatric patients have not been established (8.4)
- *Geriatric Patients* Higher incidence of adverse reactions related to volume depletion and reduced renal function (5.3, 5.5, 8.5)
- *Renal Impairment* Higher incidence of adverse reactions related to reduced renal function (2.2, 5.5, 8.6)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 3/2020

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

GLYXAMBI is a combination of empagliflozin and linagliptin indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

Empagliflozin is indicated to reduce the risk of cardiovascular death in adults with type 2 diabetes mellitus and established cardiovascular disease *[see Clinical Studies (14.2)]*.

Limitations of Use

GLYXAMBI is not recommended for patients with type 1 diabetes or for the treatment of diabetic ketoacidosis *[see Warnings and Precautions (5.4)]*.

GLYXAMBI has not been studied in patients with a history of pancreatitis. It is unknown whether patients with a history of pancreatitis are at an increased risk for the development of pancreatitis while using GLYXAMBI *[see Warnings and Precautions (5.1)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended dose of GLYXAMBI is 10 mg empagliflozin/5 mg linagliptin once daily in the morning, taken with or without food. In patients tolerating GLYXAMBI, the dose may be increased to 25 mg empagliflozin/5 mg linagliptin once daily.

In patients with volume depletion, correcting this condition prior to initiation of GLYXAMBI is recommended *[see Warnings and Precautions (5.3), Use in Specific Populations (8.5) and Patient Counseling Information (17)]*.

No studies have been performed specifically examining the safety and efficacy of GLYXAMBI in patients previously treated with other oral antihyperglycemic agents and switched to GLYXAMBI. Any change in therapy of type 2 diabetes should be undertaken with care and appropriate monitoring as changes in glycemic control can occur.

2.2 Patients with Renal Impairment

Assessment of renal function is recommended prior to initiation of GLYXAMBI and periodically thereafter.

GLYXAMBI should not be initiated in patients with an eGFR less than 45 mL/min/1.73 m^2.

No dose adjustment is needed in patients with an eGFR greater than or equal to 45 mL/min/1.73 m^2.

GLYXAMBI should be discontinued if eGFR is persistently less than 45 mL/min/1.73 m^2 *[see Warnings and Precautions (5.3, 5.5) and Use in Specific Populations (8.6)]*.

3 DOSAGE FORMS AND STRENGTHS

GLYXAMBI is a combination of empagliflozin and linagliptin. GLYXAMBI is available in the following dosage forms and strengths:

- 10 mg empagliflozin/5 mg linagliptin tablets are pale yellow, arc triangular, flat-faced, bevel-edged, film-coated tablets. One side is debossed with the Boehringer Ingelheim company symbol; the other side is debossed with "10/5".

- 25 mg empagliflozin/5 mg linagliptin tablets are pale pink, arc triangular, flat-faced, bevel-edged, film-coated tablets. One side is debossed with the Boehringer Ingelheim company symbol; the other side is debossed with "25/5".

4 CONTRAINDICATIONS

GLYXAMBI is contraindicated in patients with:

- Severe renal impairment, end-stage renal disease, or dialysis *[see Use in Specific Populations (8.6)]*.
- Hypersensitivity to empagliflozin, linagliptin, or any of the excipients in GLYXAMBI, reactions such as anaphylaxis, angioedema, exfoliative skin conditions, urticaria, or bronchial hyperreactivity have occurred *[see Warnings and Precautions (5.10) and Adverse Reactions (6)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Pancreatitis

Acute pancreatitis, including fatal pancreatitis, has been reported in patients treated with linagliptin. In the CARMELINA trial *[see Clinical Studies (14.3)]*, acute pancreatitis was reported in 9 (0.3%) patients treated with linagliptin and in 5 (0.1%) patients treated with placebo. Two patients treated with linagliptin in the CARMELINA trial had acute pancreatitis with a fatal outcome. There have been postmarketing reports of acute pancreatitis, including fatal pancreatitis, in patients treated with linagliptin.

Take careful notice of potential signs and symptoms of pancreatitis. If pancreatitis is suspected, promptly discontinue GLYXAMBI and initiate appropriate management. It is unknown whether patients with a history of pancreatitis are at increased risk for the development of pancreatitis while using GLYXAMBI.

5.2 Heart Failure

An association between DPP-4 inhibitor treatment and heart failure has been observed in cardiovascular outcomes trials for two other members of the DPP-4 inhibitor class. These trials evaluated patients with type 2 diabetes mellitus and atherosclerotic cardiovascular disease.

Consider the risks and benefits of GLYXAMBI prior to initiating treatment in patients at risk for heart failure, such as those with a prior history of heart failure and a history of renal impairment, and observe these patients for signs and symptoms of heart failure during therapy. Advise patients of the characteristic symptoms of heart failure and to immediately report such symptoms. If heart failure develops, evaluate and manage according to current standards of care and consider discontinuation of GLYXAMBI.

5.3 Hypotension

Empagliflozin causes intravascular volume contraction. Symptomatic hypotension may occur after initiating empagliflozin *[see Adverse Reactions (6.1)]* particularly in patients with renal impairment, the elderly, in patients with low systolic blood pressure, and in patients on diuretics. Before initiating GLYXAMBI, assess for volume contraction and correct volume status if indicated. Monitor for signs and symptoms of hypotension

after initiating therapy and increase monitoring in clinical situations where volume contraction is expected *[see Use in Specific Populations (8.5)]*.

5.4 Ketoacidosis

Reports of ketoacidosis, a serious life-threatening condition requiring urgent hospitalization have been identified in postmarketing surveillance in patients with type 1 and type 2 diabetes mellitus receiving sodium glucose co-transporter-2 (SGLT2) inhibitors, including empagliflozin. Fatal cases of ketoacidosis have been reported in patients taking empagliflozin. GLYXAMBI is not indicated for the treatment of patients with type 1 diabetes mellitus *[see Indications and Usage (1)]*.

Patients treated with GLYXAMBI who present with signs and symptoms consistent with severe metabolic acidosis should be assessed for ketoacidosis regardless of presenting blood glucose levels, as ketoacidosis associated with GLYXAMBI may be present even if blood glucose levels are less than 250 mg/dL. If ketoacidosis is suspected, GLYXAMBI should be discontinued, patient should be evaluated, and prompt treatment should be instituted. Treatment of ketoacidosis may require insulin, fluid and carbohydrate replacement.

In many of the postmarketing reports, and particularly in patients with type 1 diabetes, the presence of ketoacidosis was not immediately recognized and institution of treatment was delayed because presenting blood glucose levels were below those typically expected for diabetic ketoacidosis (often less than 250 mg/dL). Signs and symptoms at presentation were consistent with dehydration and severe metabolic acidosis and included nausea, vomiting, abdominal pain, generalized malaise, and shortness of breath. In some but not all cases, factors predisposing to ketoacidosis such as insulin dose reduction, acute febrile illness, reduced caloric intake, surgery, pancreatic disorders suggesting insulin deficiency (e.g., type 1 diabetes, history of pancreatitis or pancreatic surgery), and alcohol abuse were identified.

Before initiating GLYXAMBI, consider factors in the patient history that may predispose to ketoacidosis including pancreatic insulin deficiency from any cause, caloric restriction, and alcohol abuse.

For patients who undergo scheduled surgery, consider temporarily discontinuing GLYXAMBI for at least 3 days prior to surgery *[see Clinical Pharmacology (12.2, 12.3)]*.

Consider monitoring for ketoacidosis and temporarily discontinuing GLYXAMBI in other clinical situations known to predispose to ketoacidosis (e.g., prolonged fasting due to acute illness or post-surgery). Ensure risk factors for ketoacidosis are resolved prior to restarting GLYXAMBI.

Educate patients on the signs and symptoms of ketoacidosis and instruct patients to discontinue GLYXAMBI and seek medical attention immediately if signs and symptoms occur.

5.5 Acute Kidney Injury

Empagliflozin causes intravascular volume contraction *[see Warnings and Precautions (5.3)]* and can cause renal impairment *[see Adverse Reactions (6.1)]*. There have been postmarketing reports of acute kidney injury, some requiring hospitalization and dialysis, in patients receiving SGLT2 inhibitors, including empagliflozin; some reports involved patients younger than 65 years of age.

Before initiating GLYXAMBI, consider factors that may predispose patients to acute kidney injury including hypovolemia, chronic renal impairment, heart failure and concomitant medications (diuretics, ACE inhibitors, ARBs, NSAIDs). Consider temporarily discontinuing GLYXAMBI in any setting of reduced oral intake (such as acute illness or fasting) or fluid losses (such as gastrointestinal illness or excessive heat exposure); monitor

patients for signs and symptoms of acute kidney injury. If acute kidney injury occurs, discontinue GLYXAMBI promptly and institute treatment.

Empagliflozin increases serum creatinine and decreases eGFR. Patients with hypovolemia may be more susceptible to these changes. Renal function abnormalities can occur after initiating GLYXAMBI *[see Adverse Reactions (6.1)]*. Renal function should be evaluated prior to initiation of GLYXAMBI and monitored periodically thereafter. More frequent renal function monitoring is recommended in patients with an eGFR below 60 mL/min/1.73 m^2. Use of GLYXAMBI is not recommended when eGFR is persistently less than 45 mL/min/1.73 m^2 and is contraindicated in patients with an eGFR less than 30 mL/min/1.73 m^2 *[see Dosage and Administration (2.2), Contraindications (4) and Use in Specific Populations (8.6)]*.

5.6 Urosepsis and Pyelonephritis

There have been postmarketing reports of serious urinary tract infections including urosepsis and pyelonephritis requiring hospitalization in patients receiving SGLT2 inhibitors, including empagliflozin. Treatment with SGLT2 inhibitors increases the risk for urinary tract infections. Evaluate patients for signs and symptoms of urinary tract infections and treat promptly, if indicated *[see Adverse Reactions (6)]*.

5.7 Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues

Insulin and insulin secretagogues are known to cause hypoglycemia. The use of empagliflozin or linagliptin in combination with an insulin secretagogue (e.g., sulfonylurea) or insulin was associated with a higher rate of hypoglycemia compared with placebo in a clinical trial. Therefore, a lower dose of the insulin secretagogue or insulin may be required to reduce the risk of hypoglycemia when used in combination with GLYXAMBI.

5.8 Necrotizing Fasciitis of the Perineum (Fournier's Gangrene)

Reports of necrotizing fasciitis of the perineum (Fournier's gangrene), a rare but serious and life-threatening necrotizing infection requiring urgent surgical intervention, have been identified in postmarketing surveillance in patients with diabetes mellitus receiving SGLT2 inhibitors, including empagliflozin. Cases have been reported in both females and males. Serious outcomes have included hospitalization, multiple surgeries, and death.

Patients treated with GLYXAMBI presenting with pain or tenderness, erythema, or swelling in the genital or perineal area, along with fever or malaise, should be assessed for necrotizing fasciitis. If suspected, start treatment immediately with broad-spectrum antibiotics and, if necessary, surgical debridement. Discontinue GLYXAMBI, closely monitor blood glucose levels, and provide appropriate alternative therapy for glycemic control.

5.9 Genital Mycotic Infections

Empagliflozin increases the risk for genital mycotic infections *[see Adverse Reactions (6.1)]*. Patients with a history of chronic or recurrent genital mycotic infections were more likely to develop genital mycotic infections. Monitor and treat as appropriate.

5.10 Hypersensitivity Reactions

There have been postmarketing reports of serious hypersensitivity reactions in patients treated with linagliptin (one of the components of GLYXAMBI). These reactions include anaphylaxis, angioedema, and exfoliative skin conditions. Onset of these reactions occurred predominantly within the first 3 months after initiation of treatment with linagliptin, with some reports occurring after the first dose.

Angioedema has also been reported with other dipeptidyl peptidase-4 (DPP-4) inhibitors. Use caution in a patient with a history of angioedema to another DPP-4 inhibitor because it is unknown whether such patients will be predisposed to angioedema with GLYXAMBI.

There have been postmarketing reports of serious hypersensitivity reactions, (e.g., angioedema) in patients treated with empaglifozin (one of the components of GLYXAMBI).

If a hypersensitivity reaction occurs, discontinue GLYXAMBI, treat promptly per standard of care, and monitor until signs and symptoms resolve. GLYXAMBI is contraindicated in patients with a previous serious hypersensitivity reaction to linagliptin or empagliflozin *[see Contraindications (4)]*.

5.11 Severe and Disabling Arthralgia

There have been postmarketing reports of severe and disabling arthralgia in patients taking DPP-4 inhibitors. The time to onset of symptoms following initiation of drug therapy varied from one day to years. Patients experienced relief of symptoms upon discontinuation of the medication. A subset of patients experienced a recurrence of symptoms when restarting the same drug or a different DPP-4 inhibitor. Consider as a possible cause for severe joint pain and discontinue drug if appropriate.

5.12 Bullous Pemphigoid

Bullous pemphigoid was reported in 7 (0.2%) patients treated with linagliptin compared to none in patients treated with placebo in the CARMELINA trial *[see Clinical Studies (14.3)]*, and 3 of these patients were hospitalized due to bullous pemphigoid. Postmarketing cases of bullous pemphigoid requiring hospitalization have been reported with DPP-4 inhibitor use. In reported cases, patients typically recovered with topical or systemic immunosuppressive treatment and discontinuation of the DPP-4 inhibitor. Tell patients to report development of blisters or erosions while receiving GLYXAMBI. If bullous pemphigoid is suspected, GLYXAMBI should be discontinued and referral to a dermatologist should be considered for diagnosis and appropriate treatment.

6 ADVERSE REACTIONS

The following important adverse reactions are described below and elsewhere in the labeling:

- Pancreatitis *[see Warnings and Precautions (5.1)]*
- Heart Failure *[see Warnings and Precautions (5.2)]*
- Hypotension *[see Warnings and Precautions (5.3)]*
- Ketoacidosis *[see Warnings and Precautions (5.4)]*
- Acute Kidney Injury *[see Warnings and Precautions (5.5)]*
- Urosepsis and Pyelonephritis *[see Warnings and Precautions (5.6)]*
- Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues *[see Warnings and Precautions (5.7)]*
- Necrotizing Fasciitis of the Perineum (Fournier's Gangrene) *[see Warnings and Precautions (5.8)]*
- Genital Mycotic Infections *[see Warnings and Precautions (5.9)]*
- Hypersensitivity Reactions *[see Warnings and Precautions (5.10)]*
- Severe and Disabling Arthralgia *[see Warnings and Precautions (5.11)]*
- Bullous Pemphigoid *[see Warnings and Precautions (5.12)]*

6.1 Clinical Trials Experience

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

Empagliflozin and Linagliptin

The safety of concomitantly administered empagliflozin (daily dose 10 mg or 25 mg) and linagliptin (daily dose 5 mg) has been evaluated in a total of 1363 patients with type 2 diabetes treated for up to 52 weeks in active-controlled clinical trials. The most common adverse reactions with concomitant administration of empagliflozin and linagliptin based on a pooled analyses of these studies are shown in Table 1.

Table 1 Adverse Reactions Reported in ≥5% of Patients Treated with Empagliflozin and Linagliptin

	GLYXAMBI 10 mg/5 mg n=272	**GLYXAMBI 25 mg/5 mg n=273**
	n (%)	**n (%)**
Urinary tract infection[a]	34 (12.5)	31 (11.4)
Nasopharyngitis	16 (5.9)	18 (6.6)
Upper respiratory tract infection	19 (7.0)	19 (7.0)

[a]Predefined adverse event grouping, including, but not limited to, urinary tract infection, asymptomatic bacteriuria, cystitis

Empagliflozin

Adverse reactions that occurred in ≥2% of patients receiving empagliflozin and more commonly than in patients given placebo included (10 mg, 25 mg, and placebo): urinary tract infection (9.3%, 7.6%, and 7.6%), female genital mycotic infections (5.4%, 6.4%, and 1.5%), upper respiratory tract infection (3.1%, 4.0%, and 3.8%), increased urination (3.4%, 3.2%, and 1.0%), dyslipidemia (3.9%, 2.9%, and 3.4%), arthralgia (2.4%, 2.3%, and 2.2%), male genital mycotic infections (3.1%, 1.6%, and 0.4%), and nausea (2.3%, 1.1%, and 1.4%).

Thirst (including polydipsia) was reported in 0%, 1.7%, and 1.5% for placebo, empagliflozin 10 mg, and empagliflozin 25 mg, respectively.

Empagliflozin causes an osmotic diuresis, which may lead to intravascular volume contraction and adverse reactions related to volume depletion. Events related to volume depletion (hypotension and syncope) were reported in 3 patients (1.1%) treated with GLYXAMBI plus metformin.

Linagliptin

Adverse reactions reported in ≥2% of patients treated with linagliptin 5 mg and more commonly than in patients treated with placebo included: nasopharyngitis (7.0% and 6.1%), diarrhea (3.3% and 3.0%), and cough (2.1% and 1.4%).

Other adverse reactions reported in clinical studies with treatment of linagliptin monotherapy were hypersensitivity (e.g., urticaria, angioedema, localized skin exfoliation, or bronchial hyperreactivity) and myalgia.

In the clinical trial program, pancreatitis was reported in 15.2 cases per 10,000 patient year exposure while being treated with linagliptin compared with 3.7 cases per 10,000 patient year exposure while being treated with comparator (placebo and active comparator, sulfonylurea). Three additional cases of pancreatitis were reported following the last administered dose of linagliptin.

Hypoglycemia
Table 2 summarizes the reports of hypoglycemia with empagliflozin and linagliptin over a treatment period of 52 weeks.

Table 2 Incidence of Overall[a] and Severe[b] Hypoglycemic Adverse Reactions

Add-on to Metformin (52 weeks)	**GLYXAMBI 10 mg/5 mg (n=136)**	**GLYXAMBI 25 mg/5 mg (n=137)**
Overall (%)	2.2%	3.6%
Severe (%)	0%	0%

[a]Overall hypoglycemic events: plasma or capillary glucose of less than or equal to 70 mg/dL or requiring assistance
[b]Severe hypoglycemic events: requiring assistance regardless of blood glucose

Laboratory Tests
Empagliflozin and Linagliptin
Changes in laboratory findings in patients treated with the combination of empagliflozin and linagliptin included increases in cholesterol and hematocrit compared to baseline.

Empagliflozin
Increase in Low-Density Lipoprotein Cholesterol (LDL-C): Dose-related increases in low-density lipoprotein cholesterol (LDL-C) were observed in patients treated with empagliflozin. LDL-C increased by 2.3%, 4.6%, and 6.5% in patients treated with placebo, empagliflozin 10 mg, and empagliflozin 25 mg, respectively. The range of mean baseline LDL-C levels was 90.3 to 90.6 mg/dL across treatment groups.

Increase in Hematocrit: Median hematocrit decreased by 1.3% in placebo and increased by 2.8% in empagliflozin 10 mg and 2.8% in empagliflozin 25 mg treated patients. At the end of treatment, 0.6%, 2.7%, and 3.5% of patients with hematocrits initially within the reference range had values above the upper limit of the reference range with placebo, empagliflozin 10 mg, and empagliflozin 25 mg, respectively.

Linagliptin
Increase in Uric Acid: Changes in laboratory values that occurred more frequently in the linagliptin group and ≥1% more than in the placebo group were increases in uric acid (1.3% in the placebo group, 2.7% in the linagliptin group).

Increase in Lipase: In a placebo-controlled clinical trial with linagliptin in type 2 diabetes mellitus patients with micro- or macroalbuminuria, a mean increase of 30% in lipase concentrations from baseline to 24 weeks was observed in the linagliptin arm compared to a mean decrease of 2% in the placebo arm. Lipase levels above 3 times upper limit of normal were seen in 8.2% compared to 1.7% patients in the linagliptin and placebo arms, respectively.

Increase in Amylase: In a cardiovascular safety study comparing linagliptin versus glimepiride in patients with type 2 diabetes mellitus, amylase levels above 3 times upper limit of normal were seen in 1.0% compared to 0.5% of patients in the linagliptin and glimepiride arms, respectively.

The clinical significance of elevations in lipase and amylase with linagliptin is unknown in the absence of other signs and symptoms of pancreatitis *[see Warnings and Precautions (5.1)]*.

6.2 Postmarketing Experience

Additional adverse reactions have been identified during postapproval use of linagliptin and empagliflozin. Because these reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Acute Pancreatitis, including Fatal Pancreatitis *[see Indications and Usage (1)]*
- Ketoacidosis
- Urosepsis and Pyelonephritis
- Necrotizing Fasciitis of the Perineum (Fournier's gangrene)
- Hypersensitivity Reactions including Anaphylaxis, Angioedema, and Exfoliative Skin Conditions
- Severe and Disabling Arthralgia
- Bullous Pemphigoid
- Skin Reactions (e.g., rash, urticaria)
- Mouth Ulceration, Stomatitis
- Rhabdomyolysis

7 DRUG INTERACTIONS

7.1 Drug Interactions with Empagliflozin

Diuretics

Coadministration of empagliflozin with diuretics resulted in increased urine volume and frequency of voids, which might enhance the potential for volume depletion *[see Warnings and Precautions (5.3)]*.

Positive Urine Glucose Test

Monitoring glycemic control with urine glucose tests is not recommended in patients taking SGLT2 inhibitors as SGLT2 inhibitors increase urinary glucose excretion and will lead to positive urine glucose tests. Use alternative methods to monitor glycemic control.

Interference with 1,5-anhydroglucitol (1,5-AG) Assay

Monitoring glycemic control with 1,5-AG assay is not recommended as measurements of 1,5-AG are unreliable in assessing glycemic control in patients taking SGLT2 inhibitors. Use alternative methods to monitor glycemic control.

7.2 Drug Interactions with Linagliptin

Inducers of P-glycoprotein or CYP3A4 Enzymes

Rifampin decreased linagliptin exposure, suggesting that the efficacy of linagliptin may be reduced when administered in combination with a strong P-gp or CYP3A4 inducer. Therefore, use of alternative treatments is strongly recommended when linagliptin is to be administered with a strong P-gp or CYP3A4 inducer *[see Clinical Pharmacology (12.3)]*.

7.3 Insulin or Insulin Secretagogues

Coadministration of GLYXAMBI with an insulin secretagogue (e.g., sulfonylurea) or insulin may require lower doses of the insulin secretagogue or insulin to reduce the risk of hypoglycemia *[see Warnings and Precautions (5.7)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on animal data showing adverse renal effects from empagliflozin, GLYXAMBI is not recommended during the second and third trimesters of pregnancy.

The limited available data with GLYXAMBI, linagliptin, or empagliflozin in pregnant women are not sufficient to determine 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).*

In animal studies, adverse renal changes were observed in rats when empagliflozin was administered during a period of renal development corresponding to the late second and third trimesters of human pregnancy. Doses approximately 13-times the maximum clinical dose caused renal pelvic and tubule dilatations that were reversible. No adverse developmental effects were observed when the combination of linagliptin and empagliflozin was administered to pregnant rats during the period of organogenesis at exposures approximately 253- and 353-times the clinical exposure *(see Data).*

The estimated background risk of major birth defects is 6% to 10% in women with pre-gestational diabetes with a HbA1c >7 and has been reported to be as high as 20% to 25% in women with 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% to 4% and 15% to 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, and delivery complications. Poorly controlled diabetes increases the fetal risk for major birth defects, stillbirth, and macrosomia related morbidity.

Data

Animal Data

The combined components administered during the period of organogenesis were not teratogenic in rats up to and including a combined dose of 700 mg/kg/day empagliflozin and 140 mg/kg/day linagliptin, which is 253- and 353-times the clinical exposure. A pre- and post-natal development study was not conducted with the combined components of GLYXAMBI.

Empagliflozin: Empagliflozin dosed directly to juvenile rats from postnatal day (PND) 21 until PND 90 at doses of 1, 10, 30, and 100 mg/kg/day caused increased kidney weights and renal tubular and pelvic dilatation at 100 mg/kg/day, which approximates 13-times the maximum clinical dose of 25 mg, based on AUC. These findings were not observed after a 13-week drug-free recovery period. These outcomes occurred with drug exposure during periods of renal development in rats that correspond to the late second and third trimester of human renal development.

In embryo-fetal development studies in rats and rabbits, empagliflozin was administered for intervals coinciding with the first trimester period of organogenesis in humans. Doses up to 300 mg/kg/day, which approximates 48-times (rats) and 128-times (rabbits) the maximum clinical dose of 25 mg (based on AUC), did not result in adverse developmental effects. In rats, at higher doses of empagliflozin causing maternal toxicity, malformations of limb bones increased in fetuses at 700 mg/kg/day or 154-times the 25 mg maximum clinical dose. Empagliflozin crosses the placenta and reaches fetal tissues in rats. In the rabbit, higher doses of

empagliflozin resulted in maternal and fetal toxicity at 700 mg/kg/day, or 139-times the 25 mg maximum clinical dose.

In pre- and postnatal development studies in pregnant rats, empagliflozin was administered from gestation day 6 through to lactation day 20 (weaning) at up to 100 mg/kg/day (approximately 16-times the 25 mg maximum clinical dose) without maternal toxicity. Reduced body weight was observed in the offspring at greater than or equal to 30 mg/kg/day (approximately 4-times the 25 mg maximum clinical dose).

Linagliptin: No adverse developmental outcome was observed when linagliptin was administered to pregnant Wistar Han rats and Himalayan rabbits during the period of organogenesis at doses up to 240 mg/kg/day and 150 mg/kg/day, respectively. These doses represent approximately 943-times (rats) and 1943-times (rabbits) the 5 mg maximum clinical dose, based on exposure. No adverse functional, behavioral, or reproductive outcome was observed in offspring following administration of linagliptin to Wistar Han rats from gestation day 6 to lactation day 21 at a dose 49-times the maximum recommended human dose, based on exposure.

Linagliptin crosses the placenta into the fetus following oral dosing in pregnant rats and rabbits.

8.2 Lactation

Risk Summary

There is no information regarding the presence of GLYXAMBI, or its individual components in human milk, the effects on the breastfed infant, or the effects on milk production. Empagliflozin and linagliptin are present in rat milk *(see Data).* Since human kidney maturation occurs *in utero* and during the first 2 years of life when lactational exposure may occur, there may be risk to the developing human kidney.

Because of the potential for serious adverse reactions in a breastfed infant, including the potential for empagliflozin to affect postnatal renal development, advise patients that use of GLYXAMBI is not recommended while breastfeeding.

Data

Empagliflozin was present at a low level in rat fetal tissues after a single oral dose to the dams at gestation day 18. In rat milk, the mean milk to plasma ratio ranged from 0.634 to 5, and was greater than one from 2 to 24 hours post-dose. The mean maximal milk to plasma ratio of 5 occurred at 8 hours post-dose, suggesting accumulation of empagliflozin in the milk. Juvenile rats directly exposed to empagliflozin showed a risk to the developing kidney (renal pelvic and tubular dilatations) during maturation.

8.4 Pediatric Use

Safety and effectiveness of GLYXAMBI in pediatric patients under 18 years of age have not been established.

8.5 Geriatric Use

GLYXAMBI

Empagliflozin is associated with osmotic diuresis, which could affect hydration status of patients age 75 years and older.

Empagliflozin

No empagliflozin dosage change is recommended based on age *[see Dosage and Administration (2)]*. A total of 2721 (32%) patients treated with empagliflozin were 65 years of age and older, and 491 (6%) were 75 years of age and older. Empagliflozin is expected to have diminished efficacy in elderly patients with renal impairment *[see Use in Specific Populations (8.6)]*. The risk of volume depletion-related adverse reactions increased in patients who were 75 years of age and older to 2.1%, 2.3%, and 4.4% for placebo, empagliflozin 10 mg, and empagliflozin 25 mg. The risk of urinary tract infections increased in patients who were 75 years of age and

older to 10.5%, 15.7%, and 15.1% in patients randomized to placebo, empagliflozin 10 mg, and empagliflozin 25 mg, respectively *[see Warnings and Precautions (5.3) and Adverse Reactions (6.1)]*.

Linagliptin
There were 4040 type 2 diabetes patients treated with linagliptin 5 mg from 15 clinical trials of linagliptin; 1085 (27%) were 65 years and over, while 131 (3%) were 75 years and over. Of these patients, 2566 were enrolled in 12 double-blind placebo-controlled studies; 591 (23%) were 65 years and over, while 82 (3%) were 75 years and over. No overall differences in safety or effectiveness were observed between patients 65 years and over and younger patients. Therefore, no dose adjustment is recommended in the elderly population. While clinical studies of linagliptin have not identified differences in response between the elderly and younger patients, greater sensitivity of some older individuals cannot be ruled out.

8.6 Renal Impairment
Empagliflozin
The efficacy and safety of empagliflozin have not been established in patients with severe renal impairment, with ESRD, or receiving dialysis. Empagliflozin is not expected to be effective in these patient populations *[see Dosage and Administration (2.2), Contraindications (4) and Warnings and Precautions (5.3, 5.5)]*.

The glucose lowering benefit of empagliflozin 25 mg decreased in patients with worsening renal function. The risks of renal impairment *[see Warnings and Precautions (5.5)]*, volume depletion adverse reactions and urinary tract infection-related adverse reactions increased with worsening renal function.

8.7 Hepatic Impairment
GLYXAMBI may be used in patients with hepatic impairment *[see Clinical Pharmacology (12.3)]*.

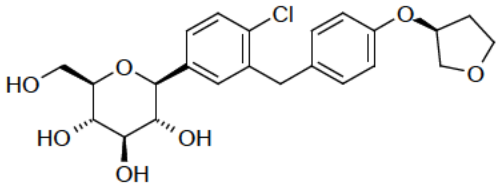
10 OVERDOSAGE
In the event of an overdose with GLYXAMBI, contact the Poison Control Center. Removal of empagliflozin by hemodialysis has not been studied, and removal of linagliptin by hemodialysis or peritoneal dialysis is unlikely.

11 DESCRIPTION
GLYXAMBI tablets contain two oral antihyperglycemic drugs used in the management of type 2 diabetes: empagliflozin and linagliptin.

Empagliflozin
Empagliflozin is an orally-active inhibitor of the sodium-glucose co-transporter 2 (SGLT2).

The chemical name of empagliflozin is D-Glucitol,1,5-anhydro-1-C-[4-chloro-3-[[4-[[(3S)-tetrahydro-3-furanyl]oxy]phenyl]methyl]phenyl]-, (1S).

The molecular formula is $C_{23}H_{27}ClO_7$ and the molecular weight is 450.91. The structural formula is:

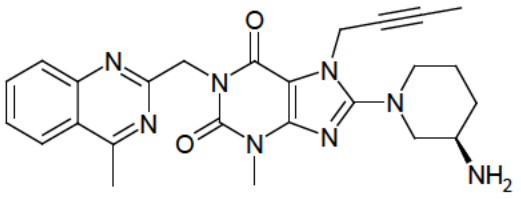


Empagliflozin is a white to yellowish, non-hygroscopic powder. It is very slightly soluble in water, sparingly soluble in methanol, slightly soluble in ethanol and acetonitrile, soluble in 50% acetonitrile/water, and practically insoluble in toluene.

Linagliptin
Linagliptin is an orally-active inhibitor of the dipeptidyl peptidase-4 (DPP-4) enzyme.

The chemical name of linagliptin is 1H-Purine-2,6-dione, 8-[(3R)-3-amino-1-piperidinyl]-7-(2-butyn-1-yl)-3,7-dihydro-3-methyl-1-[(4-methyl-2-quinazolinyl)methyl]-

The molecular formula is $C_{25}H_{28}N_8O_2$ and the molecular weight is 472.54. The structural formula is:



Linagliptin is a white to yellowish, not or only slightly hygroscopic solid substance. It is very slightly soluble in water. Linagliptin is soluble in methanol, sparingly soluble in ethanol, very slightly soluble in isopropanol, and very slightly soluble in acetone.

GLYXAMBI
GLYXAMBI tablets for oral administration are available in two dosage strengths containing 10 mg or 25 mg empagliflozin in combination with 5 mg linagliptin. The inactive ingredients of GLYXAMBI are the following: Tablet Core: mannitol, pregelatinized starch, corn starch, copovidone, crospovidone, talc and magnesium stearate. Coating: hypromellose, mannitol, talc, titanium dioxide, polyethylene glycol and ferric oxide, yellow (10 mg/5 mg) or ferric oxide, red (25 mg/5 mg).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

GLYXAMBI
GLYXAMBI combines 2 antihyperglycemic agents with complementary mechanisms of action to improve glycemic control in patients with type 2 diabetes: empagliflozin, a sodium-glucose co-transporter 2 (SGLT2) inhibitor, and linagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor.

Empagliflozin
Sodium-glucose co-transporter 2 (SGLT2) is the predominant transporter responsible for reabsorption of glucose from the glomerular filtrate back into the circulation. Empagliflozin is an inhibitor of SGLT2. By inhibiting SGLT2, empagliflozin reduces renal reabsorption of filtered glucose and lowers the renal threshold for glucose, and thereby increases urinary glucose excretion.

Linagliptin
Linagliptin is an inhibitor of DPP-4, an enzyme that degrades the incretin hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). Thus, linagliptin increases the concentrations of active incretin hormones, stimulating the release of insulin in a glucose-dependent manner and decreasing the levels of glucagon in the circulation. Both incretin hormones are involved in the physiological regulation of glucose homeostasis. Incretin hormones are secreted at a low basal level throughout the day and levels rise immediately after meal intake. GLP-1 and GIP increase insulin biosynthesis and secretion from pancreatic beta

cells in the presence of normal and elevated blood glucose levels. Furthermore, GLP-1 also reduces glucagon secretion from pancreatic alpha cells, resulting in a reduction in hepatic glucose output.

12.2 Pharmacodynamics

Empagliflozin

Urinary Glucose Excretion

In patients with type 2 diabetes, urinary glucose excretion increased immediately following a dose of empagliflozin and was maintained at the end of a 4-week treatment period averaging at approximately 64 grams per day with 10 mg empagliflozin and 78 grams per day with 25 mg empagliflozin once daily. Data from single oral doses of empagliflozin in healthy subjects indicate that, on average, the elevation in urinary glucose excretion approaches baseline by about 3 days for the 10 mg and 25 mg doses.

Urinary Volume

In a 5-day study, mean 24-hour urine volume increase from baseline was 341 mL on Day 1 and 135 mL on Day 5 of empagliflozin 25 mg once daily treatment.

Cardiac Electrophysiology

In a randomized, placebo-controlled, active-comparator, crossover study, 30 healthy subjects were administered a single oral dose of empagliflozin 25 mg, empagliflozin 200 mg (8 times the maximum recommended dose), moxifloxacin, and placebo. No increase in QTc was observed with either 25 mg or 200 mg empagliflozin.

Linagliptin

Linagliptin binds to DPP-4 in a reversible manner and increases the concentrations of incretin hormones. Linagliptin glucose-dependently increases insulin secretion and lowers glucagon secretion, thus resulting in a better regulation of the glucose homeostasis. Linagliptin binds selectively to DPP-4 and selectively inhibits DPP-4, but not DPP-8 or DPP-9 activity *in vitro* at concentrations approximating therapeutic exposures.

Cardiac Electrophysiology

In a randomized, placebo-controlled, active-comparator, 4-way crossover study, 36 healthy subjects were administered a single oral dose of linagliptin 5 mg, linagliptin 100 mg (20 times the recommended dose), moxifloxacin, and placebo. No increase in QTc was observed with either the recommended dose of 5 mg or the 100-mg dose. At the 100-mg dose, peak linagliptin plasma concentrations were approximately 38-fold higher than the peak concentrations following a 5-mg dose.

12.3 Pharmacokinetics

GLYXAMBI

The results of the bioequivalence study in healthy subjects demonstrated that GLYXAMBI (25 mg empagliflozin/5 mg linagliptin) combination tablets are bioequivalent to coadministration of corresponding doses of empagliflozin and linagliptin as individual tablets. Administration of the fixed-dose combination with food resulted in no change in overall exposure of empagliflozin or linagliptin; however, the peak exposure was decreased 39% and 32% for empagliflozin and linagliptin, respectively. These changes are not likely to be clinically significant.

Absorption

Empagliflozin

The pharmacokinetics of empagliflozin has been characterized in healthy volunteers and patients with type 2 diabetes and no clinically relevant differences were noted between the two populations. After oral administration, peak plasma concentrations of empagliflozin were reached at 1.5 hours post-dose. Thereafter, plasma concentrations declined in a biphasic manner with a rapid distribution phase and a relatively slow terminal phase. The steady-state mean plasma AUC and C_{max} were 1870 nmol·h/L and 259 nmol/L,

respectively, with 10 mg empagliflozin once daily treatment, and 4740 nmol·h/L and 687 nmol/L, respectively, with 25 mg empagliflozin once daily treatment. Systemic exposure of empagliflozin increased in a dose-proportional manner in the therapeutic dose range. The single-dose and steady-state pharmacokinetic parameters of empagliflozin were similar, suggesting linear pharmacokinetics with respect to time.

Administration of 25 mg empagliflozin after intake of a high-fat and high-calorie meal resulted in slightly lower exposure; AUC decreased by approximately 16% and C_{max} decreased by approximately 37%, compared to fasted condition. The observed effect of food on empagliflozin pharmacokinetics was not considered clinically relevant and empagliflozin may be administered with or without food.

Linagliptin
The absolute bioavailability of linagliptin is approximately 30%. High-fat meal reduced C_{max} by 15% and increased AUC by 4%; this effect is not clinically relevant. Linagliptin may be administered with or without food.

Distribution
Empagliflozin
The apparent steady-state volume of distribution was estimated to be 73.8 L based on a population pharmacokinetic analysis. Following administration of an oral [^{14}C]-empagliflozin solution to healthy subjects, the red blood cell partitioning was approximately 36.8% and plasma protein binding was 86.2%.

Linagliptin
The mean apparent volume of distribution at steady-state following a single intravenous dose of linagliptin 5 mg to healthy subjects is approximately 1110 L, indicating that linagliptin extensively distributes to the tissues. Plasma protein binding of linagliptin is concentration-dependent, decreasing from about 99% at 1 nmol/L to 75% to 89% at ≥30 nmol/L, reflecting saturation of binding to DPP-4 with increasing concentration of linagliptin. At high concentrations, where DPP-4 is fully saturated, 70% to 80% of linagliptin remains bound to plasma proteins and 20% to 30% is unbound in plasma. Plasma binding is not altered in patients with renal or hepatic impairment.

Metabolism
Empagliflozin
No major metabolites of empagliflozin were detected in human plasma and the most abundant metabolites were three glucuronide conjugates (2-O-, 3-O-, and 6-O-glucuronide). Systemic exposure of each metabolite was less than 10% of total drug-related material. *In vitro* studies suggested that the primary route of metabolism of empagliflozin in humans is glucuronidation by the uridine 5'-diphospho-glucuronosyltransferases UGT2B7, UGT1A3, UGT1A8, and UGT1A9.

Linagliptin
Following oral administration, the majority (about 90%) of linagliptin is excreted unchanged, indicating that metabolism represents a minor elimination pathway. A small fraction of absorbed linagliptin is metabolized to a pharmacologically inactive metabolite, which shows a steady-state exposure of 13.3% relative to linagliptin.

Elimination
Empagliflozin
The apparent terminal elimination half-life of empagliflozin was estimated to be 12.4 h and apparent oral clearance was 10.6 L/h based on the population pharmacokinetic analysis. Following once-daily dosing, up to 22% accumulation, with respect to plasma AUC, was observed at steady-state, which was consistent with empagliflozin half-life. Following administration of an oral [^{14}C]-empagliflozin solution to healthy subjects, approximately 95.6% of the drug-related radioactivity was eliminated in feces (41.2%) or urine (54.4%). The

majority of drug-related radioactivity recovered in feces was unchanged parent drug and approximately half of drug-related radioactivity excreted in urine was unchanged parent drug.

Linagliptin
Following administration of an oral [^{14}C]-linagliptin dose to healthy subjects, approximately 85% of the administered radioactivity was eliminated via the enterohepatic system (80%) or urine (5%) within 4 days of dosing. Renal clearance at steady-state was approximately 70 mL/min.

Specific Populations
Renal Impairment
GLYXAMBI: Studies characterizing the pharmacokinetics of empagliflozin and linagliptin after administration of GLYXAMBI in renally impaired patients have not been performed *[see Dosage and Administration (2.2)]*.

Empagliflozin: In patients with mild (eGFR: 60 to less than 90 mL/min/1.73 m^2), moderate (eGFR: 30 to less than 60 mL/min/1.73 m^2), and severe (eGFR: less than 30 mL/min/1.73 m^2) renal impairment and subjects with kidney failure/end stage renal disease (ESRD) patients, AUC of empagliflozin increased by approximately 18%, 20%, 66%, and 48%, respectively, compared to subjects with normal renal function. Peak plasma levels of empagliflozin were similar in subjects with moderate renal impairment and kidney failure/ESRD compared to patients with normal renal function. Peak plasma levels of empagliflozin were roughly 20% higher in subjects with mild and severe renal impairment as compared to subjects with normal renal function. Population pharmacokinetic analysis showed that the apparent oral clearance of empagliflozin decreased, with a decrease in eGFR leading to an increase in drug exposure. However, the fraction of empagliflozin that was excreted unchanged in urine, and urinary glucose excretion, declined with decrease in eGFR.

Linagliptin: An open-label pharmacokinetic study evaluated the pharmacokinetics of linagliptin 5 mg in male and female patients with varying degrees of chronic renal impairment. The study included 6 healthy subjects with normal renal function (creatinine clearance [CrCl] ≥80 mL/min), 6 patients with mild renal impairment (CrCl 50 to <80 mL/min), 6 patients with moderate renal impairment (CrCl 30 to <50 mL/min), 10 patients with type 2 diabetes and severe renal impairment (CrCl <30 mL/min), and 11 patients with type 2 diabetes and normal renal function. Creatinine clearance was measured by 24-hour urinary creatinine clearance measurements or estimated from serum creatinine based on the Cockcroft-Gault formula.

Under steady-state conditions, linagliptin exposure in patients with mild renal impairment was comparable to healthy subjects.

In patients with moderate renal impairment under steady-state conditions, mean exposure of linagliptin increased ($AUC_{\tau,ss}$ by 71% and C_{max} by 46%) compared with healthy subjects. This increase was not associated with a prolonged accumulation half-life, terminal half-life, or an increased accumulation factor. Renal excretion of linagliptin was below 5% of the administered dose and was not affected by decreased renal function. Patients with type 2 diabetes and severe renal impairment showed steady-state exposure approximately 40% higher than that of patients with type 2 diabetes and normal renal function (increase in $AUC_{\tau,ss}$ by 42% and C_{max} by 35%). For both type 2 diabetes groups, renal excretion was below 7% of the administered dose.

These findings were further supported by the results of population pharmacokinetic analyses.

Hepatic Impairment
GLYXAMBI: Studies characterizing the pharmacokinetics of empagliflozin and linagliptin after administration of GLYXAMBI in hepatically impaired patients have not been performed.

Empagliflozin: In subjects with mild, moderate, and severe hepatic impairment according to the Child-Pugh classification, AUC of empagliflozin increased by approximately 23%, 47%, and 75% and C_{max} increased by approximately 4%, 23%, and 48%, respectively, compared to subjects with normal hepatic function.

Linagliptin: In patients with mild hepatic impairment (Child-Pugh class A) steady-state exposure ($AUC_{\tau,ss}$) of linagliptin was approximately 25% lower and $C_{max,ss}$ was approximately 36% lower than in healthy subjects. In patients with moderate hepatic impairment (Child-Pugh class B), AUC_{ss} of linagliptin was about 14% lower and $C_{max,ss}$ was approximately 8% lower than in healthy subjects. Patients with severe hepatic impairment (Child-Pugh class C) had comparable exposure of linagliptin in terms of AUC_{0-24} and approximately 23% lower C_{max} compared with healthy subjects. Reductions in the pharmacokinetic parameters seen in patients with hepatic impairment did not result in reductions in DPP-4 inhibition.

Effects of Age, Body Mass Index, Gender, and Race

Empagliflozin: Based on the population PK analysis, age, body mass index (BMI), gender and race (Asians versus primarily Whites) do not have a clinically meaningful effect on pharmacokinetics of empagliflozin *[see Use in Specific Populations (8.5)]*.

Linagliptin: Based on the population PK analysis, age, body mass index (BMI), gender and race do not have a clinically meaningful effect on pharmacokinetics of linagliptin *[see Use in Specific Populations (8.5)]*.

Pediatric

Studies characterizing the pharmacokinetics of empagliflozin or linagliptin after administration of GLYXAMBI in pediatric patients have not been performed.

Drug Interactions

Pharmacokinetic drug interaction studies with GLYXAMBI have not been performed; however, such studies have been conducted with the individual components of GLYXAMBI (empagliflozin and linagliptin).

Empagliflozin

In vitro Assessment of Drug Interactions

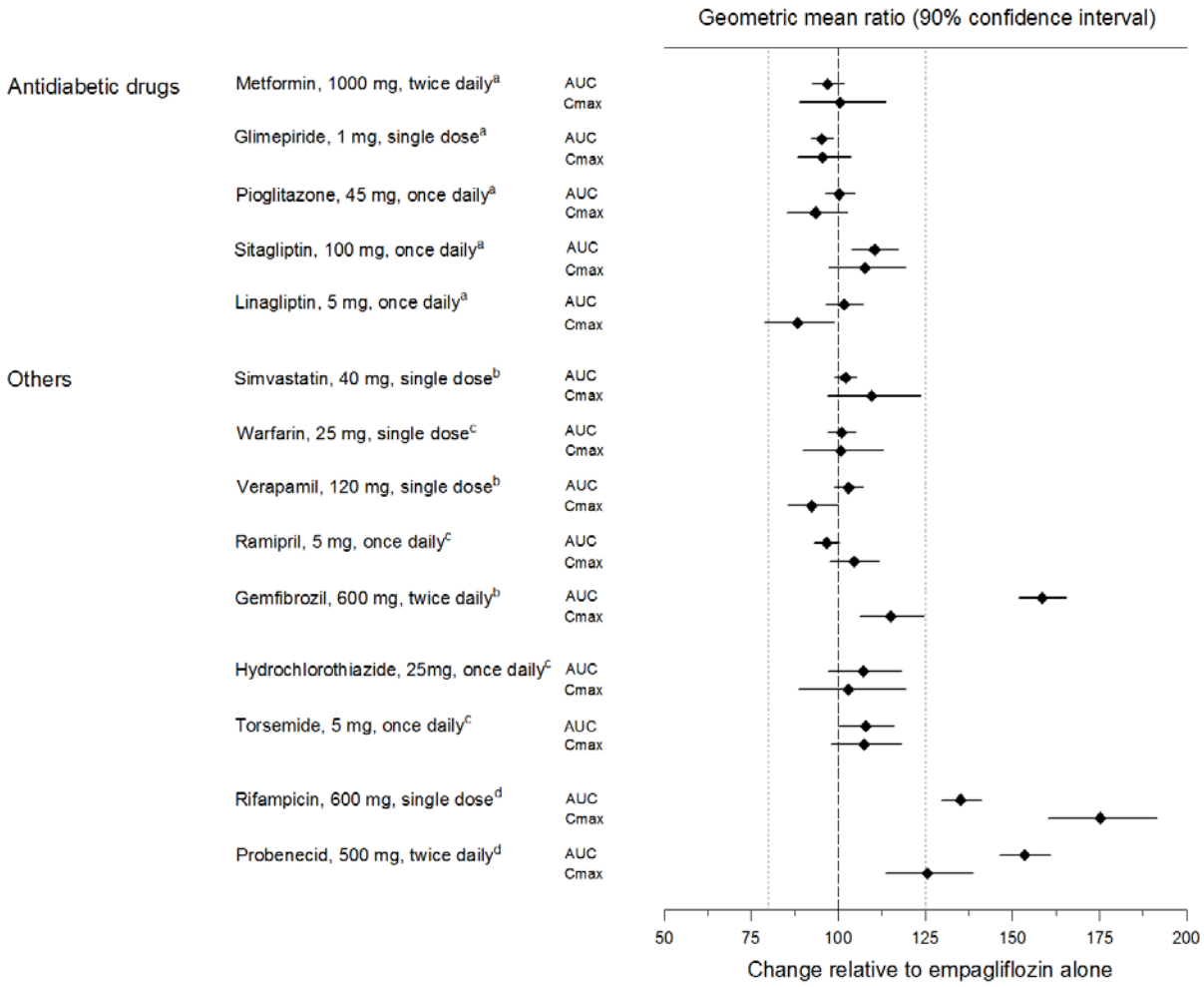
In vitro data suggest that the primary route of metabolism of empagliflozin in humans is glucuronidation by the uridine 5'-diphospho-glucuronosyltransferases UGT2B7, UGT1A3, UGT1A8, and UGT1A9. Empagliflozin does not inhibit, inactivate, or induce CYP450 isoforms. Empagliflozin also does not inhibit UGT1A1. Therefore, no effect of empagliflozin is anticipated on concomitantly administered drugs that are substrates of the major CYP450 isoforms or UGT1A1. The effect of UGT induction (e.g., induction by rifampicin or any other UGT enzyme inducer) on empagliflozin exposure has not been evaluated.

Empagliflozin is a substrate for P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP), but it does not inhibit these efflux transporters at therapeutic doses. Based on *in vitro* studies, empagliflozin is considered unlikely to cause interactions with drugs that are P-gp substrates. Empagliflozin is a substrate of the human uptake transporters OAT3, OATP1B1, and OATP1B3, but not OAT1 and OCT2. Empagliflozin does not inhibit any of these human uptake transporters at clinically relevant plasma concentrations and, therefore, no effect of empagliflozin is anticipated on concomitantly administered drugs that are substrates of these uptake transporters.

In vivo Assessment of Drug Interactions

Empagliflozin pharmacokinetics were similar with and without coadministration of metformin, glimepiride, pioglitazone, sitagliptin, linagliptin, warfarin, verapamil, ramipril, and simvastatin in healthy volunteers and with or without coadministration of hydrochlorothiazide and torsemide in patients with type 2 diabetes (see Figure 1). In subjects with normal renal function, coadministration of empagliflozin with probenecid resulted in a 30% decrease in the fraction of empagliflozin excreted in urine without any effect on 24-hour urinary glucose excretion. The relevance of this observation to patients with renal impairment is unknown.

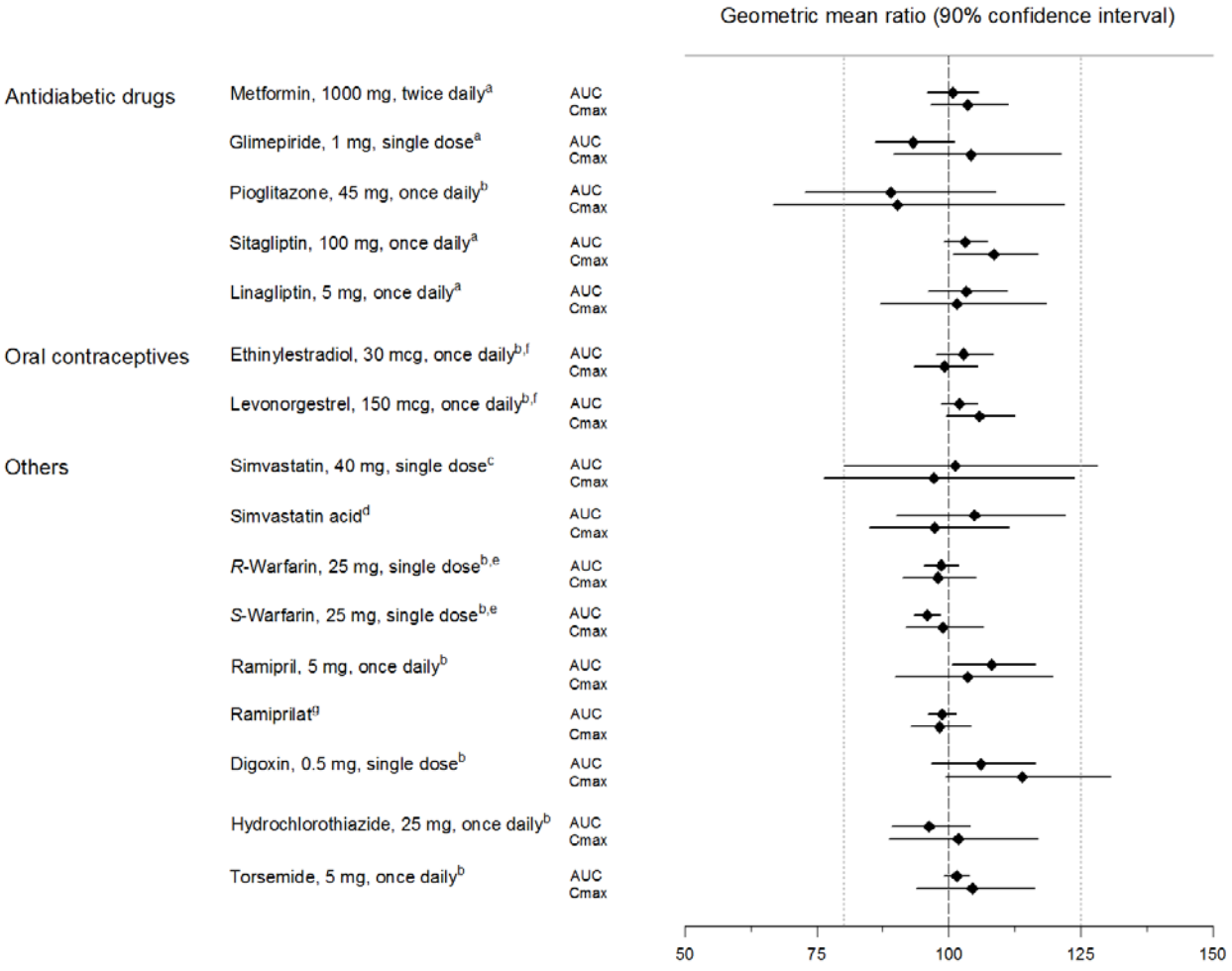
Figure 1 Effect of Various Medications on the Pharmacokinetics of Empagliflozin as Displayed as 90% Confidence Interval of Geometric Mean AUC and C_{max} Ratios [reference lines indicate 100% (80% - 125%)]



[a]empagliflozin, 50 mg, once daily; [b]empagliflozin, 25 mg, single dose; [c]empagliflozin, 25 mg, once daily; [d]empagliflozin, 10 mg, single dose

Empagliflozin had no clinically relevant effect on the pharmacokinetics of metformin, glimepiride, pioglitazone, sitagliptin, linagliptin, warfarin, digoxin, ramipril, simvastatin, hydrochlorothiazide, torsemide, and oral contraceptives when coadministered in healthy volunteers (see Figure 2).

Figure 2 Effect of Empagliflozin on the Pharmacokinetics of Various Medications as Displayed as 90% Confidence Interval of Geometric Mean AUC and C_{max} Ratios [reference lines indicate 100% (80% - 125%)]



[a]empagliflozin, 50 mg, once daily; [b]empagliflozin, 25 mg, once daily; [c]empagliflozin, 25 mg, single dose; [d]administered as simvastatin; [e]administered as warfarin racemic mixture; [f]administered as Microgynon®; [g]administered as ramipril

Linagliptin

In vitro Assessment of Drug Interactions

Linagliptin is a weak to moderate inhibitor of CYP isozyme CYP3A4, but does not inhibit other CYP isozymes and is not an inducer of CYP isozymes, including CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, and 4A11.

Linagliptin is a P-glycoprotein (P-gp) substrate, and inhibits P-gp mediated transport of digoxin at high concentrations. Based on these results and *in vivo* drug interaction studies, linagliptin is considered unlikely to cause interactions with other P-gp substrates at therapeutic concentrations.

In vivo Assessment of Drug Interactions

Strong inducers of CYP3A4 or P-gp (e.g., rifampin) decrease exposure to linagliptin to subtherapeutic and likely ineffective concentrations *[see Drug Interactions (7.2)]*. *In vivo* studies indicated evidence of a low propensity for causing drug interactions with substrates of CYP3A4, CYP2C9, CYP2C8, P-gp and organic cationic transporter (OCT).

Table 3 Effect of Coadministered Drugs on Systemic Exposure of Linagliptin

Coadministered Drug	Dosing of Coadministered Drug[a]	Dosing of Linagliptin[a]	Geometric Mean Ratio (ratio with/without coadministered drug) No effect = 1.0	
			AUC[d]	C_{max}
Metformin	850 mg TID	10 mg QD	1.20	1.03
Glyburide	1.75 mg[c]	5 mg QD	1.02	1.01
Pioglitazone	45 mg QD	10 mg QD	1.13	1.07
Ritonavir	200 mg BID	5 mg[c]	2.01	2.96
Rifampin[b]	600 mg QD	5 mg QD	0.60	0.56

[a]Multiple dose (steady-state) unless otherwise noted
[b]For information regarding clinical recommendations *[see Drug Interactions (7.2)]*.
[c]Single dose
[d]AUC = AUC(0 to 24 hours) for single dose treatments and AUC = AUC(TAU) for multiple-dose treatments
QD = once daily
BID = twice daily
TID = three times daily

Table 4 Effect of Linagliptin on Systemic Exposure of Coadministered Drugs

Coadministered Drug	Dosing of Coadministered Drug[a]	Dosing of Linagliptin[a]	Geometric Mean Ratio (ratio with/without coadministered drug) No effect = 1.0		
				AUC[c]	C_{max}
Metformin	850 mg TID	10 mg QD	metformin	1.01	0.89
Glyburide	1.75 mg[b]	5 mg QD	glyburide	0.86	0.86
Pioglitazone	45 mg QD	10 mg QD	pioglitazone metabolite M-III metabolite M-IV	0.94 0.98 1.04	0.86 0.96 1.05
Digoxin	0.25 mg QD	5 mg QD	digoxin	1.02	0.94
Simvastatin	40 mg QD	10 mg QD	simvastatin simvastatin acid	1.34 1.33	1.10 1.21
Warfarin	10 mg[b]	5 mg QD	R-warfarin S-warfarin INR PT	0.99 1.03 0.93[d] 1.03[d]	1.00 1.01 1.04[d] 1.15[d]
Ethinylestradiol and levonorgestrel	ethinylestradiol 0.03 mg and levonorgestrel 0.150 mg QD	5 mg QD	ethinylestradiol levonorgestrel	1.01 1.09	1.08 1.13

[a]Multiple dose (steady-state) unless otherwise noted
[b]Single dose
[c]AUC = AUC(INF) for single dose treatments and AUC = AUC(TAU) for multiple dose treatments
[d]AUC=AUC(0-168) and $C_{max} = E_{max}$ for pharmacodynamic end points
INR = International Normalized Ratio
PT = Prothrombin Time
QD = once daily
TID = three times daily

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

GLYXAMBI

No animal studies have been conducted with the combination of empagliflozin and linagliptin to evaluate carcinogenesis, mutagenesis, or impairment of fertility. General toxicity studies in rats up to 13 weeks were performed with the combined components. These studies indicated that no additive toxicity is caused by the combination of empagliflozin and linagliptin.

Empagliflozin

Carcinogenesis was evaluated in 2-year studies conducted in CD-1 mice and Wistar rats. Empagliflozin did not increase the incidence of tumors in female rats dosed at 100, 300, or 700 mg/kg/day (up to 72 times the exposure from the maximum clinical dose of 25 mg). In male rats, hemangiomas of the mesenteric lymph node were increased significantly at 700 mg/kg/day or approximately 42 times the exposure from a 25 mg clinical dose. Empagliflozin did not increase the incidence of tumors in female mice dosed at 100, 300, or 1000 mg/kg/day (up to 62 times the exposure from a 25 mg clinical dose). Renal tubule adenomas and carcinomas were observed in male mice at 1000 mg/kg/day, which is approximately 45 times the exposure of the maximum clinical dose of 25 mg. These tumors may be associated with a metabolic pathway predominantly present in the male mouse kidney.

Empagliflozin was not mutagenic or clastogenic with or without metabolic activation in the *in vitro* Ames bacterial mutagenicity assay, the *in vitro* L5178Y $tk^{+/-}$ mouse lymphoma cell assay, and an *in vivo* micronucleus assay in rats.

Empagliflozin had no effects on mating, fertility or early embryonic development in treated male or female rats up to the high dose of 700 mg/kg/day (approximately 155 times the 25 mg clinical dose in males and females, respectively).

Linagliptin

Linagliptin did not increase the incidence of tumors in male and female rats in a 2-year study at doses of 6, 18, and 60 mg/kg. The highest dose of 60 mg/kg is approximately 418 times the clinical dose of 5 mg/day based on AUC exposure. Linagliptin did not increase the incidence of tumors in mice in a 2-year study at doses up to 80 mg/kg (males) and 25 mg/kg (females), or approximately 35- and 270-times the clinical dose based on AUC exposure. Higher doses of linagliptin in female mice (80 mg/kg) increased the incidence of lymphoma at approximately 215-times the clinical dose based on AUC exposure.

Linagliptin was not mutagenic or clastogenic with or without metabolic activation in the Ames bacterial mutagenicity assay, a chromosomal aberration test in human lymphocytes, and an *in vivo* micronucleus assay.

In fertility studies in rats, linagliptin had no adverse effects on early embryonic development, mating, fertility, or bearing live young up to the highest dose of 240 mg/kg (approximately 943-times the clinical dose based on AUC exposure).

14 CLINICAL STUDIES

14.1 GLYXAMBI Glycemic Control Studies

Add-on Combination Therapy with Metformin

A total of 686 patients with type 2 diabetes participated in a double-blind, active-controlled study to evaluate the efficacy and safety of empagliflozin 10 mg or 25 mg in combination with linagliptin 5 mg compared to the individual components.

Patients with type 2 diabetes inadequately controlled on at least 1500 mg of metformin per day entered a single-blind placebo run-in period for 2 weeks. At the end of the run-in period, patients who remained inadequately controlled and had an HbA1c between 7% and 10.5% were randomized 1:1:1:1:1 to one of 5 active-treatment arms of empagliflozin 10 mg or 25 mg, linagliptin 5 mg, or linagliptin 5 mg in combination with 10 mg or 25 mg empagliflozin as a fixed dose combination tablet.

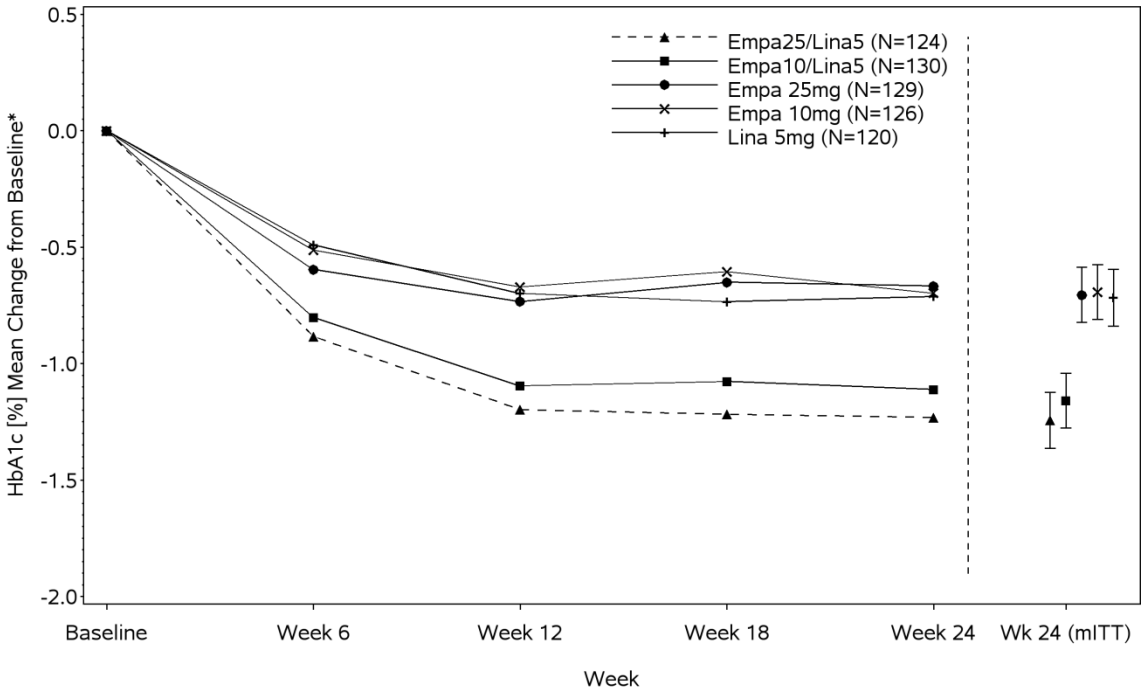
At Week 24, empagliflozin 10 mg or 25 mg used in combination with linagliptin 5 mg provided statistically significant improvement in HbA1c (p-value <0.0001) and FPG (p-value <0.001) compared to the individual components in patients who had been inadequately controlled on metformin (see Table 5, Figure 3). Treatment with GLYXAMBI 25 mg/5 mg or GLYXAMBI 10 mg/5 mg daily also resulted in a statistically significant reduction in body weight compared to linagliptin 5 mg (p-value <0.0001). There was no statistically significant difference compared to empagliflozin alone.

Table 5 Glycemic Parameters at 24 Weeks in a Study Comparing GLYXAMBI to the Individual Components as Add-on Therapy in Patients Inadequately Controlled on Metformin

	GLYXAMBI 10 mg/5 mg	GLYXAMBI 25 mg/5 mg	Empagliflozin 10 mg	Empagliflozin 25 mg	Linagliptin 5 mg
HbA1c (%)					
Number of patients	n=135	n=133	n=137	n=139	n=128
Baseline (mean)	8.0	7.9	8.0	8.0	8.0
Change from baseline (adjusted mean)	-1.1	-1.2	-0.7	-0.6	-0.7
Comparison vs empagliflozin 25 mg or 10 mg (adjusted mean) (95% CI)[a]	-0.4 (-0.6, -0.2)[d]	-0.6 (-0.7, -0.4)[d]	--	--	--
Comparison vs linagliptin 5 mg (adjusted mean) (95% CI)[a]	-0.4 (-0.6, -0.2)[d]	-0.5 (-0.7, -0.3)[d]	--	--	--
Patients [n (%)] achieving HbA1c <7%[b]	74 (58)	76 (62)	35 (28)	43 (33)	43 (36)
FPG (mg/dL)					
Number of patients	n=133	n=131	n=136	n=137	n=125
Baseline (mean)	157	155	162	160	156
Change from baseline (adjusted mean)	-33	-36	-21	-21	-13
Comparison vs empagliflozin 25 mg or 10 mg (adjusted mean) (95% CI)[a]	-12 (-18, -5)[d]	-15 (-22, -9)[d]	--	--	--
Comparison vs linagliptin 5 mg (adjusted mean) (95% CI)[a]	-20 (-27, -13)[d]	-23 (-29, -16)[d]	--	--	--
Body Weight					
Number of patients	n=135	n=134	n=137	n=140	n=128
Baseline (mean) in kg	87	85	86	88	85
% change from baseline (adjusted mean)	-3.1	-3.4	-3.0	-3.5	-0.7
Comparison vs empagliflozin 25 mg or 10 mg (adjusted mean) (95% CI)[c]	0.0 (-0.9, 0.8)	0.1 (-0.8, 0.9)	--	--	--
Comparison vs linagliptin 5 mg (adjusted mean) (95% CI)[c]	-2.4 (-3.3, -1.5)[d]	-2.7 (-3.6, -1.8)[d]	--	--	--

[a]Full analysis population (observed case) using MMRM. MMRM model included treatment, renal function, region, visit, visit by treatment interaction, and baseline HbA1c.
[b]Patients with HbA1c above 7% at baseline: GLYXAMBI 25 mg/5 mg, n=123; GLYXAMBI 10 mg/5 mg, n=128; empagliflozin 25 mg, n=132; empagliflozin 10 mg, n=125; linagliptin 5 mg, n=119. Non-completers were considered failures (NCF).
[c]Full analysis population using last observation carried forward. ANCOVA model included treatment, renal function, region, baseline weight, and baseline HbA1c.
[d]$p<0.001$ for FPG; $p<0.0001$ for HbA1c and body weight

Figure 3 Adjusted Mean HbA1c Change at Each Time Point (Completers) and at Week 24 (mITT population)



*Mean change from baseline adjusted for baseline HbA1c, geographical region, and eGFR at baseline.

14.2 Empagliflozin Cardiovascular Outcome Study in Patients with Type 2 Diabetes Mellitus and Atherosclerotic Cardiovascular Disease

Empagliflozin is indicated to reduce the risk of cardiovascular death in adults with type 2 diabetes mellitus and established cardiovascular disease. The effect of empagliflozin on cardiovascular risk in adult patients with type 2 diabetes and established, stable, atherosclerotic cardiovascular disease is presented below.

The EMPA-REG OUTCOME study, a multicenter, multi-national, randomized, double-blind parallel group trial compared the risk of experiencing a major adverse cardiovascular event (MACE) between empagliflozin and placebo when these were added to and used concomitantly with standard of care treatments for diabetes and atherosclerotic cardiovascular disease. Coadministered antidiabetic medications were to be kept stable for the first 12 weeks of the trial. Thereafter, antidiabetic and atherosclerotic therapies could be adjusted, at the discretion of investigators, to ensure participants were treated according to the standard care for these diseases.

A total of 7020 patients were treated (empagliflozin 10 mg = 2345; empagliflozin 25 mg = 2342; placebo = 2333) and followed for a median of 3.1 years. Approximately 72% of the study population was Caucasian, 22% was Asian, and 5% was Black. The mean age was 63 years and approximately 72% were male.

All patients in the study had inadequately controlled type 2 diabetes mellitus at baseline (HbA1c greater than or equal to 7%). The mean HbA1c at baseline was 8.1% and 57% of participants had diabetes for more than 10 years. Approximately 31%, 22% and 20% reported a past history of neuropathy, retinopathy and nephropathy to investigators respectively and the mean eGFR was 74 mL/min/1.73 m^2. At baseline, patients were treated with one (~30%) or more (~70%) antidiabetic medications including metformin (74%), insulin (48%), sulfonylurea (43%) and dipeptidyl peptidase-4 inhibitor (11%).

All patients had established atherosclerotic cardiovascular disease at baseline including one (82%) or more (18%) of the following: a documented history of coronary artery disease (76%), stroke (23%) or peripheral

artery disease (21%). At baseline, the mean systolic blood pressure was 136 mmHg, the mean diastolic blood pressure was 76 mmHg, the mean LDL was 86 mg/dL, the mean HDL was 44 mg/dL, and the mean urinary albumin to creatinine ratio (UACR) was 175 mg/g. At baseline, approximately 81% of patients were treated with renin angiotensin system inhibitors, 65% with beta-blockers, 43% with diuretics, 77% with statins, and 86% with antiplatelet agents (mostly aspirin).

The primary endpoint in EMPA-REG OUTCOME was the time to first occurrence of a Major Adverse Cardiac Event (MACE). A major adverse cardiac event was defined as occurrence of either a cardiovascular death or a non-fatal myocardial infarction (MI) or a non-fatal stroke. The statistical analysis plan had pre-specified that the 10 and 25 mg doses would be combined. A Cox proportional hazards model was used to test for non-inferiority against the pre-specified risk margin of 1.3 for the hazard ratio of MACE and superiority on MACE if non-inferiority was demonstrated. Type-1 error was controlled across multiples tests using a hierarchical testing strategy.

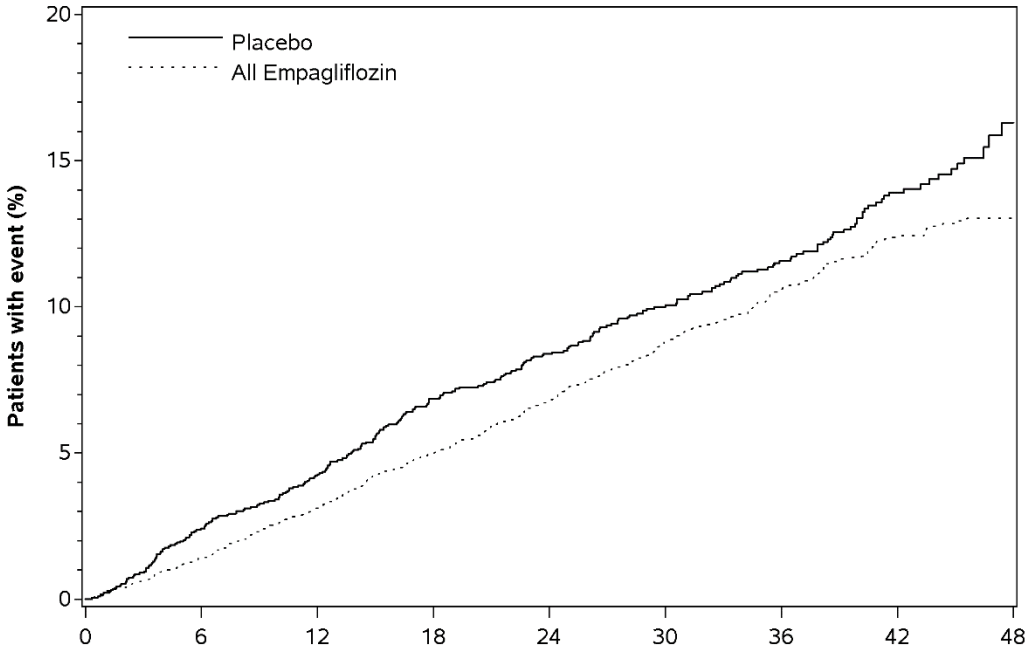
Empagliflozin significantly reduced the risk of first occurrence of primary composite endpoint of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke (HR: 0.86; 95% CI 0.74, 0.99). The treatment effect was due to a significant reduction in the risk of cardiovascular death in subjects randomized to empagliflozin (HR: 0.62; 95% CI 0.49, 0.77), with no change in the risk of non-fatal myocardial infarction or non-fatal stroke (see Table 6 and Figures 4 and 5). Results for the 10 mg and 25 mg empagliflozin doses were consistent with results for the combined dose groups.

Table 6 Treatment Effect for the Primary Composite Endpoint, and its Components[a]

	Placebo N=2333	**Empagliflozin N=4687**	**Hazard ratio vs placebo (95% CI)**
Composite of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke (time to first occurrence)[b]	282 (12.1%)	490 (10.5%)	0.86 (0.74, 0.99)
Non-fatal myocardial infarction[c]	121 (5.2%)	213 (4.5%)	0.87 (0.70, 1.09)
Non-fatal stroke[c]	60 (2.6%)	150 (3.2%)	1.24 (0.92, 1.67)
Cardiovascular death[c]	137 (5.9%)	172 (3.7%)	0.62 (0.49, 0.77)

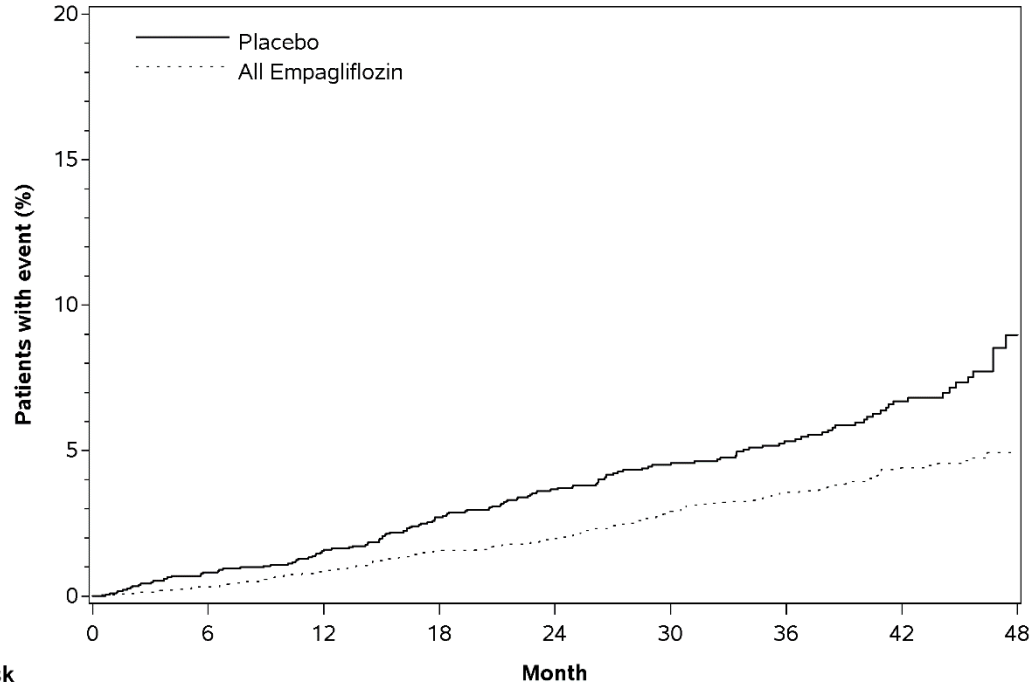
[a]Treated set (patients who had received at least one dose of study drug)
[b]p−value for superiority (2−sided) 0.04
[c]Total number of events

Figure 4 Estimated Cumulative Incidence of First MACE



Subjects at risk									
Placebo	2333	2256	2194	2112	1875	1380	1161	741	166
All Empagliflozin	4687	4580	4455	4328	3851	2821	2359	1534	370

Figure 5 Estimated Cumulative Incidence of Cardiovascular Death



Subjects at risk									
Placebo	2333	2303	2280	2243	2012	1503	1281	825	177
All Empagliflozin	4687	4651	4608	4556	4128	3079	2617	1722	414

The efficacy of empagliflozin on cardiovascular death was generally consistent across major demographic and disease subgroups.

Vital status was obtained for 99.2% of subjects in the trial. A total of 463 deaths were recorded during the EMPA-REG OUTCOME trial. Most of these deaths were categorized as cardiovascular deaths. The non-cardiovascular deaths were only a small proportion of deaths, and were balanced between the treatment groups (2.1% in patients treated with empagliflozin, and 2.4% of patients treated with placebo).

14.3 Linagliptin Cardiovascular Safety Trials

CARMELINA

The cardiovascular risk of linagliptin was evaluated in CARMELINA, a multi-national, multi-center, placebo-controlled, double-blind, parallel group trial comparing linagliptin (N=3494) to placebo (N=3485) in adult patients with type 2 diabetes mellitus and a history of established macrovascular and/or renal disease. The trial compared the risk of major adverse cardiovascular events (MACE) between linagliptin and placebo when these were added to standard of care treatments for diabetes and other cardiovascular risk factors. The trial was event driven, the median duration of follow-up was 2.2 years and vital status was obtained for 99.7% of patients.

Patients were eligible to enter the trial if they were adults with type 2 diabetes, with HbA1c of 6.5% to 10%, and had either albuminuria and previous macrovascular disease (39% of enrolled population), or evidence of impaired renal function by eGFR and Urinary Albumin Creatinine Ratio (UACR) criteria (42% of enrolled population), or both (18% of enrolled population).

At baseline the mean age was 66 years and the population was 63% male, 80% Caucasian, 9% Asian, and 6% Black. Mean HbA1c was 8.0% and mean duration of type 2 diabetes mellitus was 15 years. The trial population included 17% patients ≥75 years of age and 62% patients with renal impairment defined as eGFR <60 mL/min/1.73 m^2. The mean eGFR was 55 mL/min/1.73 m^2 and 27% of patients had mild renal impairment (eGFR 60 to 90 mL/min/1.73 m^2), 47% of patients had moderate renal impairment (eGFR 30 to <60 mL/min/1.73 m^2) and 15% of patients had severe renal impairment (eGFR <30 mL/min/1.73 m^2). Patients were taking at least one antidiabetic drug (97%), and the most common were insulin and analogues (57%), metformin (54%) and sulfonylurea (32%). Patients were also taking antihypertensives (96%), lipid lowering drugs (76%) with 72% on statin, and aspirin (62%).

The primary endpoint, MACE, was the time to first occurrence of one of three composite outcomes which included cardiovascular death, non-fatal myocardial infarction or non-fatal stroke. The study was designed as a non-inferiority trial with a pre-specified risk margin of 1.3 for the hazard ratio of MACE. A total of 434 patients on linagliptin and 420 patients on placebo experienced MACE. The incidence rate of MACE in both treatment arms: 56.3 MACE per 1000 patient-years on placebo vs. 57.7 MACE per 1000 patient-years on linagliptin. The estimated hazard ratio for MACE associated with linagliptin relative to placebo was 1.02 with a 95% confidence interval of (0.89, 1.17). The upper bound of this confidence interval, 1.17, excluded the risk margin of 1.3.

CAROLINA

The cardiovascular risk of linagliptin was evaluated in CAROLINA, a multi-center, multi-national, randomized, double-blind parallel group trial comparing linagliptin (N=3023) to glimepiride (N=3010) in adult patients with type 2 diabetes mellitus and a history of established cardiovascular disease and/or multiple cardiovascular risk factors. The trial compared the risk of major adverse cardiovascular events (MACE) between linagliptin and glimepiride when these were added to standard of care treatments for diabetes and other cardiovascular risk factors. The trial was event driven, the median duration of follow-up was 6.23 years and vital status was obtained for 99.3% of patients.

Patients were eligible to enter the trial if they were adults with type 2 diabetes with insufficient glycemic control (defined as HbA1c of 6.5% to 8.5% or 6.5% to 7.5% depending on treatment-naïve, on monotherapy or on combination therapy), and were defined to be at high cardiovascular risk with previous vascular disease, evidence of vascular related end-organ damage, age ≥70 years, and/or two cardiovascular risk factors (duration of diabetes >10 years, systolic blood pressure >140 mmHg, current smoker, LDL cholesterol ≥135 mg/dL).

At baseline the mean age was 64 years and the population was 60% male, 73% Caucasian, 18% Asian, and 5% Black. The mean HbA1c was 7.15% and mean duration of type 2 diabetes was 7.6 years. The trial population included 34% patients ≥70 years of age and 19% patients with renal impairment defined as eGFR <60 mL/min/1.73 m^2. The mean eGFR was 77 mL/min/1.73 m^2. Patients were taking at least one antidiabetic drug (91%) and the most common were metformin (83%) and sulfonylurea (28%). Patients were also taking antihypertensives (89%), lipid lowering drugs (70%) with 65% on statin, and aspirin (47%).

The primary endpoint, MACE, was the time to first occurrence of one of three composite outcomes which included cardiovascular death, non-fatal myocardial infarction or non-fatal stroke. The study was designed as a non-inferiority trial with a pre-specified risk margin of 1.3 for the hazard ratio of MACE. A total of 356 patients on linagliptin and 362 patients on glimepiride experienced MACE. The incidence rate of MACE in both treatment arms: 20.7 MACE per 1000 patient-years on linagliptin vs. 21.2 MACE per 1000 patient-years on glimepiride. The estimated hazard ratio for MACE associated with linagliptin relative to glimepiride was 0.98 with a 95% confidence interval of (0.84, 1.14). The upper bound of this confidence interval, 1.14, excluded the risk margin of 1.3.

16 HOW SUPPLIED/STORAGE AND HANDLING

GLYXAMBI (empagliflozin and linagliptin) tablets are available in 10 mg/5 mg and 25 mg/5 mg strengths as follows:

10 mg/5 mg tablets: pale yellow, arc triangular, flat-faced, bevel-edged, film-coated tablets. One side is debossed with the Boehringer Ingelheim company symbol; the other side is debossed with "10/5".

Bottles of 30 (NDC 0597-0182-30)
Bottles of 90 (NDC 0597-0182-90)
Cartons containing 3 blister cards of 10 tablets each (3 x 10) (NDC 0597-0182-39), institutional pack.

25 mg/5 mg tablets: pale pink, arc triangular, flat-faced, bevel-edged, film-coated tablets. One side is debossed with the Boehringer Ingelheim company symbol; the other side is debossed with "25/5".

Bottles of 30 (NDC 0597-0164-30)
Bottles of 90 (NDC 0597-0164-90)
Cartons containing 3 blister cards of 10 tablets each (3 x 10) (NDC 0597-0164-39), institutional pack.

If repackaging is required, dispense in a tight container as defined in USP.

Storage
Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Pancreatitis

Inform patients that acute pancreatitis has been reported during use of linagliptin. Inform patients that persistent severe abdominal pain, sometimes radiating to the back, which may or may not be accompanied by vomiting, is the hallmark symptom of acute pancreatitis. Instruct patients to discontinue GLYXAMBI promptly and contact their physician if persistent severe abdominal pain occurs *[see Warnings and Precautions (5.1)]*.

Heart Failure

Inform patients of the signs and symptoms of heart failure. Before initiating GLYXAMBI, patients should be asked about a history of heart failure or other risk factors for heart failure including moderate to severe renal impairment. Instruct patients to contact their healthcare provider as soon as possible if they experience symptoms of heart failure, including increasing shortness of breath, rapid increase in weight or swelling of the feet *[see Warnings and Precautions (5.2)]*.

Hypotension

Inform patients that hypotension may occur with GLYXAMBI and advise them to contact their healthcare provider if they experience such symptoms *[see Warnings and Precautions (5.3)]*. Inform patients that dehydration may increase the risk for hypotension, and to have adequate fluid intake.

Ketoacidosis

Inform patients that ketoacidosis is a serious life-threatening condition and that cases of ketoacidosis have been reported during use of empagliflozin, sometimes associated with illness or surgery among other risk factors. Instruct patients to check ketones (when possible) if symptoms consistent with ketoacidosis occur even if blood glucose is not elevated. If symptoms of ketoacidosis (including nausea, vomiting, abdominal pain, tiredness, and labored breathing) occur, instruct patients to discontinue GLYXAMBI and seek medical attention immediately *[see Warnings and Precautions (5.4)]*.

Acute Kidney Injury

Inform patients that acute kidney injury has been reported during use of empagliflozin. Advise patients to seek medical advice immediately if they have reduced oral intake (such as due to acute illness or fasting) or increased fluid losses (such as due to vomiting, diarrhea, or excessive heat exposure), as it may be appropriate to temporarily discontinue GLYXAMBI use in those settings *[see Warnings and Precautions (5.5)]*.

Monitoring of Renal Function

Inform patients that renal function should be assessed prior to initiation of GLYXAMBI and monitored periodically thereafter *[see Warnings and Precautions (5.5)]*.

Serious Urinary Tract Infections

Inform patients of the potential for urinary tract infections, which may be serious. Provide them with information on the symptoms of urinary tract infections. Advise them to seek medical advice if such symptoms occur *[see Warnings and Precautions (5.6)]*.

Hypoglycemia

Inform patients that the incidence of hypoglycemia is increased when empagliflozin, linagliptin, or GLYXAMBI is added to a sulfonylurea or insulin and that a lower dose of the sulfonylurea or insulin may be required to reduce the risk of hypoglycemia *[see Warnings and Precautions (5.7)]*.

Necrotizing Fasciitis of the Perineum (Fournier's Gangrene)
Inform patients that necrotizing infections of the perineum (Fournier's gangrene) have occurred with empagliflozin, a component of GLYXAMBI. Counsel patients to promptly seek medical attention if they develop pain or tenderness, redness, or swelling of the genitals or the area from the genitals back to the rectum, along with a fever above 100.4°F or malaise *[see Warnings and Precautions (5.8)]*.

Genital Mycotic Infections in Females (e.g., Vulvovaginitis)
Inform female patients that vaginal yeast infections may occur and provide them with information on the signs and symptoms of vaginal yeast infections. Advise them of treatment options and when to seek medical advice *[see Warnings and Precautions (5.9)]*.

Genital Mycotic Infections in Males (e.g., Balanitis or Balanoposthitis)
Inform male patients that yeast infection of penis (e.g., balanitis or balanoposthitis) may occur, especially in uncircumcised males and patients with chronic and recurrent infections. Provide them with information on the signs and symptoms of balanitis and balanoposthitis (rash or redness of the glans or foreskin of the penis). Advise them of treatment options and when to seek medical advice *[see Warnings and Precautions (5.9)]*.

Hypersensitivity Reactions
Inform patients that serious allergic reactions, such as anaphylaxis, angioedema, and exfoliative skin conditions, have been reported during postmarketing use of linagliptin or empagliflozin, components of GLYXAMBI. If symptoms of allergic reactions (such as rash, skin flaking or peeling, urticaria, swelling of the skin, or swelling of the face, lips, tongue, and throat that may cause difficulty in breathing or swallowing) occur, patients must stop taking GLYXAMBI and seek medical advice promptly *[see Warnings and Precautions (5.10)]*.

Severe and Disabling Arthralgia
Inform patients that severe and disabling joint pain may occur with this class of drugs. The time to onset of symptoms can range from one day to years. Instruct patients to seek medical advice if severe joint pain occurs *[see Warnings and Precautions (5.11)]*.

Bullous Pemphigoid
Inform patients that bullous pemphigoid has been reported during use of linagliptin. Instruct patients to seek medical advice if blisters or erosions occur *[see Warnings and Precautions (5.12)]*.

Laboratory Tests
Inform patients that elevated glucose in urinalysis is expected when taking GLYXAMBI.

Pregnancy
Advise pregnant women, and females of reproductive potential of the potential risk to a fetus with treatment with GLYXAMBI *[see Use in Specific Populations (8.1)]*. Instruct females of reproductive potential to report pregnancies to their physicians as soon as possible.

Lactation
Advise women that breastfeeding is not recommended during treatment with GLYXAMBI *[see Use in Specific Populations (8.2)]*.

Missed Dose
Instruct patients to take GLYXAMBI only as prescribed. If a dose is missed, it should be taken as soon as the patient remembers. Advise patients not to double their next dose.

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IT5885SC272020

MEDICATION GUIDE
GLYXAMBI® (glik-SAM-bee)
(empagliflozin and linagliptin tablets)
for oral use

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

GLYXAMBI can cause serious side effects, including:

- **Inflammation of the pancreas (pancreatitis)** which may be severe and lead to death. Certain medical problems make you more likely to get pancreatitis.

  Before you start taking GLYXAMBI, tell your doctor if you have ever had:
  - o inflammation of your pancreas (pancreatitis)
  - o a history of alcoholism
  - o stones in your gallbladder (gallstones)
  - o high blood triglyceride levels

  Stop taking GLYXAMBI and call your doctor right away if you have pain in your stomach area (abdomen) that is severe and will not go away. The pain may be felt going from your abdomen to your back. The pain may happen with or without vomiting. These may be symptoms of pancreatitis.
- **Heart failure**. Heart failure means your heart does not pump blood well enough.

  Before you start taking GLYXAMBI, tell your doctor if you have ever had heart failure or have problems with your kidneys. Contact your doctor right away if you have any of the following symptoms:
  - o increasing shortness of breath or trouble breathing, especially when you lie down
  - o swelling or fluid retention, especially in the feet, ankles or legs
  - o an unusually fast increase in weight
  - o unusual tiredness

  These may be symptoms of heart failure.
- **Dehydration.** GLYXAMBI can cause some people to become dehydrated (the loss of body water and salt). Dehydration may cause you to feel dizzy, faint, light-headed, or weak, especially when you stand up (orthostatic hypotension).

  You may be at higher risk of dehydration if you:
  - o have low blood pressure
  - o are on low sodium (salt) diet
  - o are 65 years of age or older
  - o take medicines to lower your blood pressure, including diuretics (water pills)
  - o have kidney problems

  Talk to your doctor about what you can do to prevent dehydration including how much fluid you should drink on a daily basis.

What is GLYXAMBI?

- GLYXAMBI is a prescription medicine that contains 2 diabetes medicines, empagliflozin (JARDIANCE) and linagliptin (TRADJENTA). GLYXAMBI can be used:
  - o along with diet and exercise to lower blood sugar in adults with type 2 diabetes,
  - o in adults with type 2 diabetes who have known cardiovascular disease when empagliflozin (JARDIANCE), one of the medicines in GLYXAMBI, is needed to reduce the risk of cardiovascular death.
- GLYXAMBI is not for people with type 1 diabetes.
- GLYXAMBI is not for people with diabetic ketoacidosis (increased ketones in the blood or urine).
- If you have had pancreatitis in the past, it is not known if you have a higher chance of getting pancreatitis while you take GLYXAMBI.
- It is not known if GLYXAMBI is safe and effective in children under 18 years of age.

Who should not take GLYXAMBI?

Do not take GLYXAMBI if you:

- have severe kidney problems, end stage renal disease, or are on dialysis.
- are allergic to linagliptin (TRADJENTA), empagliflozin (JARDIANCE) or any of the ingredients in GLYXAMBI. See the end of this Medication Guide for a complete list of ingredients in GLYXAMBI.

  Symptoms of a serious allergic reaction to GLYXAMBI may include:
  - skin rash, itching, flaking or peeling
  - raised red patches on your skin (hives)
  - swelling of your face, lips, tongue and throat that may cause difficulty in breathing or swallowing
  - difficulty with swallowing or breathing

If you have any of these symptoms, stop taking GLYXAMBI and call your doctor right away or go to the nearest hospital emergency room.

What should I tell my doctor before taking GLYXAMBI?

Before taking GLYXAMBI, tell your doctor about all of your medical conditions, including if you:

- have kidney problems.
- have liver problems.

- have a history of infection of the vagina or penis.
- have a history of urinary tract infection or problems with urination.
- are going to have surgery. Your doctor may stop your GLYXAMBI before you have surgery. Talk to your doctor if you are having surgery about when to stop taking GLYXAMBI and when to start it again.
- are eating less, or there is a change in your diet.
- have or have had problems with your pancreas, including pancreatitis or surgery on your pancreas.
- drink alcohol very often, or drink a lot of alcohol in the short term ("binge" drinking).
- have type 1 diabetes. GLYXAMBI should not be used to treat people with type 1 diabetes.
- are pregnant or plan to become pregnant. GLYXAMBI may harm your unborn baby. If you become pregnant while taking GLYXAMBI, tell your doctor as soon as possible. Talk with your doctor about the best way to control your blood sugar while you are pregnant.
- are breastfeeding or plan to breastfeed. GLYXAMBI may pass into your breast milk and may harm your baby. Talk with your doctor about the best way to feed your baby if you are taking GLYXAMBI. Do not breastfeed while taking GLYXAMBI.

Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

GLYXAMBI may affect the way other medicines work, and other medicines may affect how GLYXAMBI works.

Especially tell your doctor if you take:

- insulin or other medicines that can lower your blood sugar
- diuretics (water pills)
- rifampin (Rifadin, Rimactane, Rifater, Rifamate), an antibiotic that is used to treat tuberculosis

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

How should I take GLYXAMBI?

- Take GLYXAMBI exactly as your doctor tells you to take it.
- Take GLYXAMBI 1 time each day in the morning, with or without food.
- If you miss a dose, take it as soon as you remember. If you do not remember until it is time for your next dose, skip the missed dose and go back to your regular schedule. Do not take two doses of GLYXAMBI at the same time.
- Your doctor may tell you to take GLYXAMBI along with other diabetes medicines. Low blood sugar can happen more often when GLYXAMBI is taken with certain other diabetes medicines. See **"What are the possible side effects of GLYXAMBI?"**
- If you take too much GLYXAMBI, call your doctor or local poison control center or go to the nearest hospital emergency room right away.
- Check your blood sugar as your doctor tells you to.
- When taking GLYXAMBI, you may have sugar in your urine, which will show up on a urine test.
- Your doctor will do blood tests to check how well your kidneys are working before and during your treatment with GLYXAMBI.

What are the possible side effects of GLYXAMBI?

GLYXAMBI may cause serious side effects, including:

- See **"What is the most important information I should know about GLYXAMBI?"**
- **Ketoacidosis (increased ketones in your blood or urine).** Ketoacidosis has happened in people who have **type 1 diabetes or type 2 diabetes,** during treatment with empagliflozin, one of the medicines in GLYXAMBI. Ketoacidosis has also happened in people with diabetes who were sick or who had surgery during treatment with GLYXAMBI. Ketoacidosis is a serious condition, which needs to be treated in a hospital. Ketoacidosis may lead to death. **Ketoacidosis can happen with GLYXAMBI even if your blood sugar is less than 250 mg/dL. Stop taking GLYXAMBI and call your doctor right away or go to the nearest hospital emergency room if you get any of the following symptoms:**
  - nausea
  - vomiting
  - stomach-area (abdominal) pain
  - tiredness
  - trouble breathing

  If you get any of these symptoms during treatment with GLYXAMBI, if possible, check for ketones in your urine, even if your blood sugar is less than 250 mg/dL**.**
- **Kidney problems.** Sudden kidney injury has happened to people taking GLYXAMBI. Talk to your doctor right away if you:
  - reduce the amount of food or liquid you drink for example, if you are sick or cannot eat or
  - start to lose liquids from your body for example, from vomiting, diarrhea or being in the sun too long
- **Serious urinary tract infections.** Serious urinary tract infections that may lead to hospitalization have happened in people who are taking empagliflozin, one of the medicines in GLYXAMBI. Tell your doctor if you have any signs or symptoms of a urinary tract infection such as a burning feeling when passing urine, a need to urinate often, the

need to urinate right away, pain in the lower part of your stomach (pelvis), or blood in the urine. Sometimes people also may have a fever, back pain, nausea or vomiting.

- **Low blood sugar (hypoglycemia).** If you take GLYXAMBI with another medicine that can cause low blood sugar, such as a sulfonylurea or insulin, your risk of getting low blood sugar is higher. The dose of your sulfonylurea medicine or insulin may need to be lowered while you take GLYXAMBI. Signs and symptoms of low blood sugar may include:
  - o headache
  - o irritability
  - o confusion
  - o dizziness
  - o drowsiness
  - o hunger
  - o shaking or feeling jittery
  - o sweating
  - o weakness
  - o fast heartbeat
- **A rare but serious bacterial infection that causes damage to the tissue under the skin (necrotizing fasciitis) in the area between and around the anus and genitals (perineum).** Necrotizing fasciitis of the perineum has happened in women and men who take empagliflozin, one of the medicines in GLYXAMBI. Necrotizing fasciitis of the perineum may lead to hospitalization, may require multiple surgeries, and may lead to death. **Seek medical attention immediately if you have a fever or you are feeling very weak, tired or uncomfortable (malaise), and you develop any of the following symptoms in the area between and around your anus and genitals:**
  - o pain or tenderness
  - o swelling
  - o redness of skin (erythema)
- **Vaginal yeast infection.** Women who take GLYXAMBI may get vaginal yeast infections. Symptoms of a vaginal yeast infection include:
  - o vaginal odor
  - o vaginal itching
  - o white or yellowish vaginal discharge (discharge may be lumpy or look like cottage cheese)
- **Yeast infection of the penis (balanitis).** Men who take GLYXAMBI may get a yeast infection of the skin around the penis. Men who are not circumcised may have swelling of the penis that makes it difficult to pull back the skin around the tip of the penis. Other symptoms of a yeast infection of the penis include:
  - o redness, itching, or swelling of the penis
  - o rash of the penis
  - o foul smelling discharge from the penis
  - o pain in the skin around penis

  Talk to your doctor about what to do if you get symptoms of a yeast infection of the vagina or penis. Your doctor may tell you to use an over-the-counter antifungal medicine. Talk to your doctor right away if you use an over-the-counter antifungal medicine and your symptoms do not go away.
- **Allergic (hypersensitivity) reactions.** Serious allergic reactions have happened in people who are taking GLYXAMBI. Symptoms may include:
  - o swelling of your face, lips, throat, and other areas on your skin
  - o difficulty with swallowing or breathing
  - o raised, red areas on your skin (hives)
  - o skin rash, itching, flaking, or peeling

  If you have any of these symptoms, stop taking GLYXAMBI and call your doctor right away or go to the nearest hospital emergency room.
- **Joint pain.** Some people who take medicines called DPP-4 inhibitors, one of the medicines in GLYXAMBI, may develop joint pain that can be severe. Call your doctor if you have severe joint pain.
- **Skin reaction.** Some people who take medicines called DPP-4 inhibitors, one of the medicines in GLYXAMBI, may develop a skin reaction called bullous pemphigoid that can require treatment in a hospital. Tell your doctor right away if you develop blisters or the breakdown of the outer layer of your skin (erosion). Your doctor may tell you to stop taking GLYXAMBI.

The most common side effects of GLYXAMBI include:

- stuffy or runny nose and sore throat
- upper respiratory tract infection

Tell your doctor if you have any side effect that bothers you or that does not go away.
These are not all the possible side effects of GLYXAMBI. For more information, ask your doctor or pharmacist.
Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store GLYXAMBI?

- Store GLYXAMBI at room temperature between 68°F to 77°F (20°C to 25°C).

Keep GLYXAMBI and all medicines out of the reach of children.

General information about the safe and effective use of GLYXAMBI.

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

What are the ingredients in GLYXAMBI?

Active ingredients: empagliflozin and linagliptin

Inactive ingredients: mannitol, pregelatinized starch, corn starch, copovidone, crospovidone, talc and magnesium stearate. The film coating contains the following inactive ingredients: hypromellose, mannitol, talc, titanium dioxide, polyethylene glycol.
10 mg/5 mg tablets also contain yellow ferric oxide.
25 mg/5 mg tablets also contain red ferric oxide.

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For more information about GLYXAMBI including current prescribing information and Medication Guide, go to www.glyxambi.com, or scan the code below, or call Boehringer Ingelheim Pharmaceuticals, Inc. at 1-800-542-6257 or (TTY) 1-800-459-9906.

This Medication Guide has been approved by the U.S. Food and Drug Administration. Revised: March 2020

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206073Orig1s021

CROSS DISCIPLINE TEAM LEADER REVIEW

CDTL Review
Division Summary Memo for Regulatory Action

Date	March 30, 2020
From	Patrick Archdeacon, M.D.
NDA #	sNDA 201280/S-020 (linked to sNDA 201281/S-024 [linagliptin +metformin], sNDA 208026/S-012 [linagliptin+metformin extended-release], sNDA 206073/S-021 [empagliflozin+linagliptin])
Applicant	Boehringer Ingelheim Pharmaceuticals, Inc.
Date of Submission Receipt	May 30, 2019
PDUFA Goal Date	March 30, 2020
Established (USAN) names	Linagliptin (linagliptin, linagliptin+metformin HCl, linagliptin+metformin extended release, empagliflozin+linagliptin)
Trade names	Tradjenta, Jentadueto, Jentadueto XR, Glyxambi
Dosage forms / Strength	Oral tablets, 5 mg
Proposed Indication	As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
Recommended Action	Approval of negotiated labeling changes

1. Introduction

This document serves as the 'Summary Basis for Regulatory Action' memo for sNDAs seeking to add information to the Prescribing Information (PI) for Tradjenta (linagliptin; NDA 201280), Jentadueto (linagliptin + metformin; NDA 201281), Jentadueto XR (linagliptin + metformin extended-release; NDA 209026), and Glyxambi (empagliflozin + linagliptin; NDA 207073) based on the results of Trial 1218.74 (CAROLINA) trial.

CAROLINA was a multicenter, international, randomized, parallel group, double-blind, active-control study to evaluate the cardiovascular safety of linagliptin versus glimepiride in patients with type 2 diabetes at high cardiovascular risk.

Based on the results of CAROLINA, the Applicant proposed new labeling for Section 14 of the PIs to report that CAROLINA did not detect an increased risk of major adverse cardiovascular events (MACE) associated with linagliptin in comparison to glimepiride. (b) (4) [redacted]

As detailed below, the FDA review team has concluded that the clinical data submitted suffice to add new information in Section 14 related to the MACE data from the CAROLINA trial to the Tradjenta, Jentadueto, Jentadueto XR, and Glyxambi PIs. (b) (4) [redacted] The FDA review team did recommend updating the PIs to reflect new information about hypoglycemia. In addition, the FDA team also recommended updates to the medication guides (MGs) of the four products.

This memo references the following documents/sources:

Subject	Author	Date
Clinical Efficacy and Safety Review (DMEP)	Hyon (KC) Kwon	March 26, 2020
Statistical (DBVII) review	Bo Li	February 20, 2020
DMEPA labeling review	Ariane Conrad	October 4, 2019
Patient Labeling Team	Nyedra Booker	March 20, 2020
OPDP labeling review	Meena Savani	March 19, 2020
OSI summary review	Cynthia Kleppinger, Min Lu, Kassa Ayalew	February 6, 2020
DMEP: Division of Metabolism and Endocrinology Products **DBVII:** Division of Biometrics VII **DMEPA:** Division of Medication Error Prevention and Analysis **OSI:** Office of Scientific Investigations **OPDP:** Office of Prescription Drug Promotion		

2. Background

Linagliptin was approved under the trade name Tradjenta by the FDA on May 2, 2011 as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM). It is administered as an oral tablet at a dose of 5 mg once daily. The mechanism of action of linagliptin is delayed inactivation of incretin hormones (e.g., GLP-1 and GIP) due to inhibition of DPP-4; the delayed inactivation of the incretin hormones results in decreased glucagon levels and increased glucose-dependent insulin secretion. Linagliptin has also been approved as a component of Jentadueoto, a fixed-dose combination product (FDCP) containing linagliptin and metformin, of Jentadueto XR, a FDCP containing linagliptin and metformin extended release, and of Glyxambi, a FDCP containing empagliflozin and linagliptin. Trijardy XR, a FDCP containing linagliptin, empagliflozin, and metformin extended release was approved on January 27, 2020. As Trijardy XR was approved after the submission of the sNDAs for the other linagliptin-containing products, no sNDA based on the results of the CAROLINA trial has yet been submitted to the Trijardy XR NDA

In December 2008, FDA issued a Guidance for Industry[1] on "Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes." In this guidance, FDA indicated that the development programs of new type 2 antidiabetic therapies should demonstrate that the therapy will not result in an unacceptable increase in cardiovascular risk. Specifically, the guidance stated that, prior to approval, sponsors should demonstrate that the estimated risk ratio of important cardiovascular events occurring with the investigation agent compared to placebo is less than 1.8 and that, post-market, sponsors should demonstrate that the estimated risk ratio is less than 1.3.

The Applicant started CAROLINA with the intent of relying on the trial to fulfill Tradjenta's postmarketing requirement (PMR) to demonstrate cardiovascular safety as described in the 2008 Guidance. The Applicant was advised, however, to conduct a placebo-controlled cardiovascular outcome trial (CVOT) as specified in PMR 1766-4 for Tradjenta rather than rely on CAROLINA due to concerns about the uncertainty of CV risk associated with glimepiride, the active comparator in CAROLINA. The Applicant therefore conducted a placebo-controlled CVOT of linagliptin (CARMELINA). Supplemental NDAs for CARMELINA were submitted to Tradjenta (linagliptin; NDA 201280), Jentadueto (linagliptin + metformin; NDA 201281), Jentadueto XR (linagliptin + metformin extended-release; NDA 209026), and Glyxambi (empagliflozin + linagliptin; NDA 207073) on September 5, 2018. The CARMELINA sNDAs were approved on July 3, 2019, discharging PMR 1766-4. The Applicant elected to continue CAROLINA, despite no longer intending to rely on the trial to fulfill the Tradjenta PMR.

In general, based on the inspections of five domestic and two foreign clinical sites, the inspectional findings of FDA's Office of Scientific Investigations support the validity of the data reported by the Applicant (see the Clinical Inspection Summary of Dr. Cynthia Kleppinger for additional details).

[1] https://www.fda.gov/downloads/Drugs/Guidances/ucm071627.pdf

Reference ID: 4583309

3. CMC/Device

The submission does not contain new CMC data.

4. Nonclinical Pharmacology/Toxicology

The submission does not contain new nonclinical pharmacology/toxicology data.

5. Clinical Pharmacology/Biopharmaceutics

The submission does not contain new clinical pharmacology data.

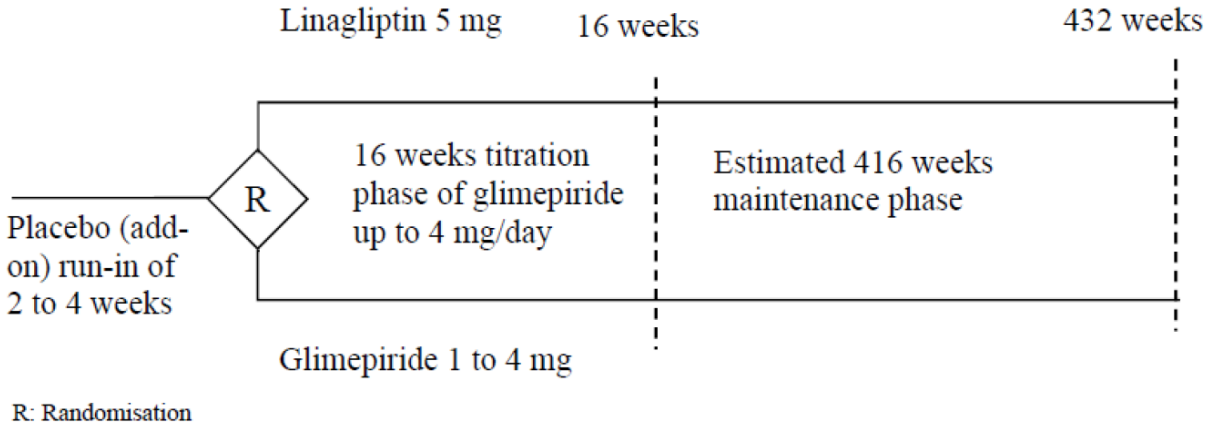
6. Clinical/Statistical- Efficacy

Dr. Bo Li, the statistical reviewer from the Office of Biostatistics (OB), Division of Biometrics VII (DBVII), and Hyon (KC) Kwon, the clinical reviewer from the Office of New Drugs, Division of Metabolism and Endocrinology Products (DMEP), reviewed the Major Adverse Cardiovascular Event (MACE) results from CAROLINA. The pre-specified primary endpoint of CAROLINA was the time from randomization to first MACE, defined as any of the following adjudication-confirmed events: cardiovascular death, non-fatal myocardial infarction (MI), or non-fatal stroke. The statistical analysis plan (SAP) for CARMELINA called for first testing the primary MACE endpoint against the 1.3 risk margin specified by the 2008 FDA Guidance on cardiovascular outcomes trials (CVOT); the SAP allowed for testing for superiority of the non-inferiority margin was met. Both Dr. Li and Dr. Kwon concluded that the data demonstrated the noninferiority of linagliptin compared to glimepiride: for the primary MACE endpoint, the hazard ratio (95% CI) was 0.98 (0.84, 1.14). Both Dr. Li and Dr. Kwon also concluded that the data did not demonstrate the superiority of linagliptin compared to glimepiride.

CAROLINA was a multi-center, randomized, double-blind, active controlled trial conducted to evaluate the effect of linagliptin relative to glimepiride on MACE when added to standard of care in patients with type 2 diabetes at high risk of cardiovascular death (see Figure 1). After a placebo run-in period, patients were randomized to linagliptin 5 mg daily or an initial dose of glimepiride 1 mg daily which could be up-titrated in 4 week intervals during the first 16 weeks

of treatment. The trial was to continue until at least 631 subjects experienced an adjudicated MACE event.

Figure 1: Study Design of CAROLINA



Source: FDA Statistical Review

The pre-specified primary endpoint was the time from randomization to the first occurrence of any adjudication-confirmed 3-point MACE (cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke). The SAP specified several secondary endpoints of interest for the assessment of CV safety including: 4-point MACE (3-point MACE + unstable angina); hospitalization for heart failure; hospitalization for heart failure or CV death; all-cause death. A hierarchical testing procedure was applied to the primary endpoint and key secondary endpoints. After testing for non-inferiority of linagliptin versus glimepiride for the primary endpoint, the second step in the hierarchical testing procedure was to test for superiority of linagliptin versus glimepiride for the primary endpoint.

A total of 6042 patients were randomized, with a total of 6033 patients taking at least one dose of study drug. A total of 5794 (96%) of randomized patients were followed until the completion of the study or until a primary MACE event or death. 239 subjects discontinued participation prior to study completion. Final vital status was known for over 99% of patients enrolled in the trial. Baseline demographics were well balanced across treatment arms. The mean age was 64 years. Around three-fourths of the enrolled patients were White, around 18% were Asian, around 5% were Black, and around 4% were classified as other race categories or as “missing”. Almost 50% of were enrolled at European trial sites. Mean follow-up duration was 5.7 years. Similar proportions of subjects discontinued the investigative treatment across the study arms at all timepoints of the trial. Please see Dr. Kwon’s review for details regarding baseline demographics and subject disposition.

The primary MACE endpoint was analyzed in the 6033 patients who received at least one dose of study drug (the Treated Set), using an “on study” censoring strategy. A total of 719 adjudicated first MACE events were observed. The analysis was based on a Cox proportional hazards model including a fixed effect for treatment. The estimated hazard ratio of MACE associated with linagliptin relative to glimepiride was 0.98 with a 95.47% confidence interval of (0.84, 1.14). See Table 1. Overall, the hazard ratios for the individual components of the

Reference ID: 4583309

MACE composite endpoint were consistent with the findings for the composite endpoint. See Table 2.

Table 1: Primary Analysis Results of MACE (TS, on study)

	Linagliptin *N=3023* *PY= 17205.4*	Glimepiride *N=3010* *PY= 17103.7*
MACE [IR/100PY]	356 [2.1]	362 [2.1]
$HR_{linagliptin/glimepiride}$ (95.47% CI) *	0.98 (0.84, 1.14)	

*: Hazard ratio was estimated based upon a Cox model including a fixed effect for treatment.

Source: FDA Statistical Review

Table 2: Analysis Results for Components of MACE (TS, on study)

	Linagliptin *N= 3023*	Glimepiride *N= 3010*	Hazard Ratio* (95.47% CI)
MACE	356 (11.8%)	362 (12.0%)	**0.98 (0.84, 1.14)**
Component event:			
CV Death	169 (5.6%)	168 (5.6%)	**1.00 (0.80, 1.24)**
Non-fatal MI	145 (4.8%)	142 (4.7%)	**1.01 (0.80, 1.28)**
Non-fatal Stroke	91 (3.0%)	104 (3.5%)	**0.87 (0.65, 1.16)**

*: Hazard ratios were estimated based upon a Cox model including a fixed effect for treatment.

Source: FDA Statistical Review

Formal statistical testing stopped at step 2 of the hierarchical testing procedure, as superiority was not demonstrated for the primary MACE endpoint. Dr.Li, however, considered the results for several key secondary endpoints including all-cause death, hospitalization for heart failure, and hospitalization for heart failure or death from heart failure. Because alpha was not preserved for formal statistical testing of these endpoints, these analyses are presented and discussed in Section 7 (Safety).

I concur with the findings of Dr. Li and Dr. Kwon regarding their conclusions that the data from CAROLINA demonstrated the noninferiority (but not the superiority) of linagliptin compared to glimepiride for the primary MACE endpoint. Additional details regarding the study design and execution of the cardiovascular risk assessment of CARMELINA may be found in the reviews of Dr. Li and Dr. Kwon.

7. Safety

In addition to analyzing the primary endpoint of MACE, Dr. Kwon completed a review of all the safety data collected by CAROLINA. This included endpoints related to all cause death and cardiovascular outcomes (heart failure as well as MACE), in addition to safety endpoints such as adverse events, hypoglycemia, and adverse events of special interest (hypersensitivity reactions, skin lesions, hepatic events, renal events, pancreatitis, pancreatic cancer, malignancies, immunologic reactions, and arthralgia). Dr. Kwon concluded, and I concur, that the data from CAROLINA related to hypersensitivity, skin lesions, hepatic events, renal events, pancreatitis, pancreatic cancer, malignancies, and immunologic reactions are consistent with the current labeling of linagliptin containing products. (b) (4)

The median exposure to study drug was about 5.8 years in both treatment groups; the median time subjects stayed in the study was 6.25 years in both treatment groups (see Table 3). The overall mean dose of glimepiride received by patients in the glimepiride treatment arm was 2.9 mg: by the end of the titration phase, 49% of patients were receiving the 4 mg dose, 14% were receiving the 3 mg dose, 16% were receiving the 2 mg dose, and 21% were receiving the 1 mg dose. Similar proportions of patients across study arms discontinued study drug due to AEs (13.7% for linagliptin, 14.9% for glimepiride).

Table 3: Exposure to Study Drug and Time in Study (TS)

	Linagliptin (N=3023)	Glimepiride (N=3010)
Exposure (years)		
Mean (SD)	4.90 (2.19)	4.7 (2.17)
Median	5.86	5.86
Subjects on treatment, N (%)		
≥16 weeks	2895 (95.8)	2875 (95.5)
≥64 weeks	2649 (87.6)	2654 (88.2)
≥160 weeks	2342 (77.5)	2303 (76.5)
≥208 weeks (~4 years)	2196 (72.6)	2167 (72.0)
≥256 weeks (~5 years)	2089 (69.1)	2035 (67.6)
≥304 weeks (~6 years)	1679 (55.5)	1626 (54.0)
≥352 weeks	375 (12.4)	341 (11.3)
≥368 weeks	90 (3.0)	77 (2.6)
≥400 weeks	0	0
Time in study (years)		
Mean (SD)	6.07 (1.12)	6.05 (1.12)
Median	6.25	6.25
Subjects in study under observation, N (%)		
≥16 weeks	3016 (99.8)	3005 (99.8)
≥64 weeks	2983 (98.7)	2970 (98.7)
≥160 weeks	2903 (96.0)	2884 (95.8)
≥256 weeks (~5 years)	2789 (92.3)	2762 (91.8)
≥304 weeks (~6 years)	2474 (81.8)	2405 (79.9)
≥352 weeks	657 (21.7)	618 (20.5)
≥368 weeks	218 (7.2)	215 (7.1)
≥400 weeks	0	0

*Exposure=date of last study drug intake or date of death minus date of first study drug intake+1;
Time in study=date of last contact or date of death minus date of randomization+1
Source: CSR 1218.74, Table 15.1.5:1, 15.1.5:2

All Cause Death

Reference ID: 4583309

Vital status at the end of the study was obtained for 99.3% of all patients enrolled in CAROLINA. As shown in Table 4, numerically fewer patients randomized to linagliptin died compared to patients randomized to glimepiride.

Table 4: Time-to-event Analysis Results of All Cause Death (TS, on study)

	Linagliptin *N = 3023* *PY = 18336.2*	**Glimepiride** *N = 3010* *PY = 18212.2*
Death [IR/100PY]	308 [1.7]	336 [1.8]
$HR_{linagliptin/glimepiride}$ (95% CI)*	**0.91 (0.78, 1.06)**	

*: Hazard ratio was estimated based upon a Cox model including a fixed effect for treatment.
Source: FDA Statistics Review

CDTL comment: Kaplan-Meier curves for all cause death were similar for the two treatment groups for the first 5 years, then showed slight separating favoring linagliptin. The cause of the numeric imbalance favoring linagliptin for the outcome of all cause death in unclear. However, the observed data is reassuring for linagliptin.

Heart failure

Hospitalization for heart failure and hospitalization for death from heart failure were adjudicated endpoints. Unlike in CARMELINA (the placebo controlled linagliptin CVOT), a higher proportion of patients in CAROLINA randomized to linagliptin experienced hospitalization for heart failure compared to patients randomized to glimepiride. However, when combined with competing events like death from heart failure, CV death, and all cause death, the HRs were more reassuring for linagliptin – in the case of the composite endpoint of hospitalization for heart failure or all-cause death, the HR numerically favored linagliptin over glimepiride.

Table 5: Time-to-event Analysis Results of Heart Failure Endpoints

	Linagliptin (N=3023)			Glimepiride (N=3010)			Hazard ratio vs glimepiride (95% CI)[1]
	N	%	IR	N	%	IR	
HHF	112	3.7	6.4	92	3.1	5.3	1.21 (0.92, 1.59)
HHF or death from heart failure	115	3.8	6.6	97	3.2	5.6	1.18 (0.90, 1.54)
HHF or CV death	236	7.8	13.4	234	7.8	13.4	1.00 (0.84, 1.20)
HHF or All-cause death	372	12.3	21.1	392	13.0	22.3	0.94 (0.82, 1.09)

HHF=hospitalization for heart failure; N=number of subjects; IR=Incidence rate per 1000 years at risk
[1]Hazard ratio and CI derived from Cox's proportional hazards model with factor treatment.
Source: FDA Clinical Review

(b) (4)

(b) (4)

[redacted]

Arthralgia

The proportion of patients reporting AE terms associated with arthralgia were comparable across treatment groups in CAROLINA (23.9% among patients randomized to linagliptin versus 24.2% among patients randomized to glimepiride). Similarly, the proportion of patients with SAEs related to arthralgia were balanced (2.9% among patients randomized to linagliptin versus 3.0% of patients randomized to glimepiride). The number of patients discontinued from study treatment due to arthralgia was 4 in each treatment arm.

(b) (4)

[redacted]

Hypoglycemia

More hypoglycemic events were observed in the glimepiride treatment arm than the linagliptin treatment arm. The pattern was repeated for a variety of definitions of hypoglycemia (see Table 6). The observation is consistent with the known safety profile of glimepiride.

Table 6: Frequency of Subjects with Hypoglycemia and Characteristics of Hypoglycemia by Treatment Group

	Linagliptin (N=3014)	Glimepiride (N=3000)
Subjects with any hypoglycemia	456 (15.1)	1407 (46.9)
PG ≤70 mg/dL or severe#	394 (13.1)	1328 (44.3)
PG <54 mg/dL or severe#	96 (3.2)	530 (17.7)
Subjects with symptomatic* hypoglycemic AEs	258 (8.6)	1023 (34.1)
PG ≤70 mg/dL or severe#	195 (6.5)	927 (30.9)
PG <54 mg/dL or severe#	56 (1.9)	443 (14.8)
Minimum glucose level <54 mg/dL (worst episode) of hypoglycemia	93 (3.1)	514 (17.1)
Severe# hypoglycemia	10 (0.3)	65 (2.2)
Number of hypoglycemia episodes per subject		
≥1	456 (15.1)	1407 (46.9)
≥3	159 (5.3)	841 (28.0)
≥5	99 (3.3)	634 (21.1)
≥10	47 (1.6)	367 (12.2)

PG=plasma glucose; AEs=adverse events
*Symptomatic hypoglycemia=hypoglycemia adverse event reported with typical symptoms of hypoglycemia
#Severe hypoglycemia=hypoglycemia requiring assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions.
Source: CSR, Table 15.3.1.4.1:7

8. Advisory Committee Meeting

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

9. Pediatrics

The sNDA does not support any new indication and did not trigger the Pediatric Research Equity Act (PREA).

10. Labeling

Ariane Conrad from the Division of Medication Error Prevention and Analysis (DMEPA) reviewed the revised PIs and medication guides (MGs) for Tradjenta (linagliptin), Jentadueto (linagliptin and metformin), Jentadueto XR (linagliptin and metformin extended-release), and Glyxambi (empagliflozin and linagliptin). The DMEPA review concluded (and I concur) that the revisions to the PIs and MGs were acceptable from a medication error perspective.

Meena Savani from the Office of Prescription Drug Promotion (OPDP) reviewed the revisions to the PIs and MGs. OPDP provided recommendations regarding final language used to describe the patient population of the CAROLINA trial in section 14 of the PIs for the various linagliptin containing products. The recommendations were adopted.

In addition to minor edits to the PIs to modernize and/or harmonize labeling, the Applicant's proposals for revisions to the linagliptin-containing PIs (including Tradjenta, Jentadueoto, Jentadueto XR, and Glyxambi) were modified and/or addressed as follows:

- (b) (4)
- (b) (4)
- Clinical Studies Section 14.2: Information from the CAROLINA study, including study design and the primary MACE outcome, was added
- Hypoglycemia: (b) (4) ection 6.1 (Adverse Reactions, Clinical Trial Experience) was modified to add new information about hypoglycemia from CAROLINA

Nyedra Booker from the Division of Medical Policy Programs (DMPP) and from the Office of Prescription Drug Promotion (OPDP) reviewed the revisions to the MGs. DMPP provided recommendations to revise the MGs to harmonize with the language used in the Trijardy XR MG (the most recently approved linagliptin containing product). I concur with the recommendations from DMPP.

11. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

Approval: The sNDAs (sNDA 201280/S-018 for Tradjenta/linagliptin; sNDA 201281/S-022 for Jentadueto/linagliptin +metformin; sNDA 208026/S-008 for Jentadueto XR/linagliptin+metformin extended-release; sNDA 206073/S-017 for Glyxambi/empagliflozin+linagliptin) should be approved with regard to updating the labeling for respective products (see Section 10, Labeling for details).

Recommendation for Postmarketing Risk Evaluation and Management Strategies

None

Recommendation for other Postmarketing Requirements and Commitments

None

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/s/

PATRICK ARCHDEACON
03/30/2020 12:27:45 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206073Orig1s021

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	Supplemental New Drug Application (sNDA)
Application Number(s)	sNDA 201280/S-020 (linked to sNDA 201281/S-024 [linagliptin +metformin], sNDA 208026/S-012 [linagliptin+metformin extended-release], sNDA 206073/S-021 [empagliflozin+linagliptin])
Priority or Standard	Standard
Submit Date(s)	May 30, 2019
Received Date(s)	May 30, 2019
PDUFA Goal Date	March 30, 2020
Division/Office	Division of Metabolism and Endocrinology Products (DMEP)
Reviewer Name(s)	Hyon Kwon, PharmD, MPH
Review Completion Date	See electronic signature stamp
Established/Proper Name	Linagliptin
(Proposed) Trade Name	Tradjenta, Jentadueto, Jentadueto XR, Glyxambi
Applicant	Boehringer Ingelheim Pharmaceuticals, Inc.
Dosage Form(s)	Oral tablets
Applicant Proposed Dosing Regimen(s)	5 mg once daily
Applicant Proposed Indication(s)/Population(s)	As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
Recommendation on Regulatory Action	Approval pending labeling negotiations
Recommended Indication(s)/Population(s) (if applicable)	Not applicable

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Glossary

AC	advisory committee
ACE	angiotensin-converting enzyme
AE	adverse event
AESI	adverse event of special interest
ALT	alanine transaminase
ARB	angiotensin receptor blocker
ASA	acetylsalicylic acid
AST	aspartate transaminase
AR	adverse reaction
BMI	body mass index
BRF	Benefit Risk Framework
CDER	Center for Drug Evaluation and Research
CDTL	Cross-Discipline Team Leader
CEC	Clinical Event Committee
CFR	Code of Federal Regulations
CI	confidence interval
CISST	Clinical Investigator Site Selection Tool
CMC	chemistry, manufacturing, and controls
CRF	case report form
CSR	clinical study report
CV	cardiovascular
CVD	cardiovascular disease
CVOT	cardiovascular outcomes trial
DMC	data monitoring committee
DPP-4	dipeptidyl-peptidase-4
ECG	electrocardiogram
eCTD	electronic common technical document
eGFR	estimated glomerular filtration rate
EOT	end of treatment
FDA	Food and Drug Administration
FDCP	fixed-dose combination product
FPG	fasting plasma glucose
GCP	good clinical practice
GIP	glucose-independent insulinotropic polypeptide
GLP-1	glucagon-like peptide-1
HBGM	home blood glucose monitoring

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HF	heart failure
HHF	hospitalization for heart failure
HLT	High Level Term
HR	hazard ratio
ICH	International Council for Harmonization
IND	Investigational New Drug Application
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MACE	major adverse cardiovascular events
MDRD	Modification of Diet in Renal Disease Study
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
mITT	modified intent to treat
NDA	new drug application
NME	new molecular entity
NYHA	New York Heart Association
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OS	on-treatment set
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PPS	per protocol set
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
PT	Preferred Term
PY	person-years
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SC	Steering Committee
SGLT-2	sodium-glucose co-transporter 2

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SMQ	Standardized Medical Query
SOC	System Organ Class
SU	sulfonylurea
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus
TEAE	treatment emergent adverse event
TIA	transient ischemic attack
TS	treated set
UACR	urine albumin-to-creatinine ratio
ULN	upper limit of normal

Reference ID: 4581802

1. Executive Summary

1.1. Product Introduction

Linagliptin (Tradjenta) belongs to the class of antihyperglycemic medications known as dipeptidyl-peptidase-4 (DPP-4) inhibitors. Tradjenta was approved by the FDA on May 2, 2011 as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM) and is administered at the dose of 5 mg once daily. On January 30, 2012, Jentadueto, a fixed-dose combination product (FDCP) containing linagliptin and metformin HCl was approved, and on May 27, 2016, Jentadueto XR, a FDCP containing linagliptin and extended release metformin was approved. Glyxambi, a FDCP containing linagliptin and empagliflozin, was approved on January 30, 2015. Trijardy XR, a FDCP containing linagliptin, empagliflozin, and extended release metformin was approved on January 27, 2020. Aside from linagliptin, there are three other US-approved DPP-4 inhibitors, sitagliptin (Januvia), saxagliptin (Onglyza), and alogliptin (Nesina).

DPP-4 inhibitors' mechanism of action for lowering blood glucose is thought to be through inhibition of the DPP4 enzyme, resulting in delayed inactivation of incretin hormones (e.g., glucagon-like peptide-1 [GLP-1] and glucose-independent insulinotropic polypeptide [GIP]) and an increase in incretin blood levels. This is followed by a decrease in glucagon levels and an increase in glucose-dependent insulin secretion from pancreatic beta-cells.

Metformin, which is a component of the FDCP Jentadueto, Jentadueto XR, and Trijardy XR is an oral antihyperglycemic medication indicated as an adjunct to diet and exercise to improve glycemic control in adults with T2DM. It decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. Metformin improves glucose tolerance in patients with T2DM, lowering both basal and postprandial plasma glucose. Metformin is available as immediate-release, extended-release, and combination product formulations, including in combination with linagliptin.

Empagliflozin, which is a component of the FDCP Glyxambi and Trijardy XR, is an oral antihyperglycemic medication indicated as an adjunct to diet and exercise to improve glycemic control in adults with T2DM, and to reduce the risk of cardiovascular death in adult patients with T2DM and established cardiovascular disease. Empagliflozin is a sodium glucose co-transporter 2 (SGLT2) inhibitor and improves glycemic control by reducing renal reabsorption of filtered glucose and as a result increasing urinary glucose excretion.

The Applicant submitted this supplement to revise the prescribing information of Tradjenta and the linagliptin-containing FDCPs (except Trijardy since this was recently approved) to include

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results of a cardiovascular outcomes trial (CVOT), Study 1218.74. Trial 1218.74 was a multicenter, international, randomized, parallel group, double-blind, active-control study to evaluate **car**di**o**vascular safety of **lina**gliptin versus glimepiride in patients with type 2 diabetes mellitus at high cardiovascular risk, or CAROLINA trial. The primary objective of CAROLINA was to establish that the upper bound of the 2-sided 95% confidence interval (CI) for the estimated risk ratio comparing the incidence of major cardiovascular events (MACE) observed with Tradjenta (linagliptin) tablets to that observed in glimepiride is less than 1.3 to establish non-inferiority.

The Applicant proposes to add the results of the trial, CAROLINA, to show that linagliptin was not associated with an unacceptable increased in the cardiovascular (CV) risk compared to glimepiride to Section 14, Clinical Studies of labeling. (b) (4)

1.2. Conclusions on the Substantial Evidence of Effectiveness

CAROLINA trial showed that linagliptin compared to glimepiride, both added to standard background therapy, did not increase CV risk in patients with type 2 diabetes mellitus at high CV risk. The risk of MACE was evaluated using a composite of CV death, non-fatal myocardial infarction (MI) or non-fatal stroke. The estimated hazard ratio (HR) of linagliptin compared to glimepiride for MACE was 0.98 (95% CI: 0.84, 1.14), with the upper found of the 95% CI <1.3 as pre-specified. Both treatment groups were well balanced in demographic and clinical disease characteristics at baseline. Vital status was obtained in 99.3% of subjects. The robustness of the primary endpoint was supported by the overall low extent of missing data for MACE (4%).

1.3. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

Type 2 diabetes mellitus (T2DM) is a condition of chronic impaired glucose homeostasis leading to chronic hyperglycemia and an increased risk for microvascular (e.g., retinopathy, nephropathy, and neuropathy) and macrovascular (e.g., myocardial infarction, stroke) complications. For patients with T2DM, the presence of microvascular and macrovascular disease is independently associated with an increased 10-year risk of death, major adverse cardiovascular events (myocardial infarction, stroke, or CV death), and major clinical microvascular events (end-stage renal disease, death due to renal disease, retinal photocoagulation, or diabetes-related blindness). Patients with diabetes are twice as likely to have cardiovascular disease (CVD) or stroke as non-diabetic individual and at an earlier age. Diabetes was the 7th leading cause of death in 2015, and CVD remains a major cause of death among diabetic patients.

There are currently 12 pharmacologic classes of antihyperglycemic medications (generally with multiple members within each class) which are approved to improve glycemic control in patients with T2DM. Many of these are also approved as fixed-dose combination drug products (FCDP). While all approved antihyperglycemic medications have been shown to improve glycemic control, not all products have been evaluated for macrovascular outcome. Based on the results of dedicated CVOTs, however, canagliflozin (an SGLT2 inhibitor) and three GLP-1 receptor agonists (liraglutide, semaglutide, and dulaglutide) have been labeled for reducing the risk of major adverse cardiovascular events (MACE: cardiovascular death, myocardial infarction, and stroke) in patients with T2DM and established CV disease. Empagliflozin, an SGLT2 inhibitor, is labeled for reducing the risk of CV death and dapagliflozin, another SGLT2 inhibitor, is labeled for reducing the risk of hospitalization for heart failure in patients with T2DM and established CV disease. Dapagliflozin and two other GLP-1 receptor agonists (exenatide and lixisenatide) did not show an increased risk of MACE but also did not show MACE benefit in their dedicated CVOTs. Two other DPP-4 inhibitors, saxagliptin and alogliptin, also did not show an increase in the risk of MACE nor MACE benefit in a dedicated CVOT, but there was some evidence of increased risk of heart failure (HF) with saxagliptin (3.5% vs 2.8% with placebo) and alogliptin (3.9% vs 3.3% with placebo), which led to class labeling of DPP-4 inhibitors, including linagliptin, to warn about the risk of heart failure. Linagliptin itself did not show an increase in the risk of CV events nor CV benefit when compared to placebo, both added to standard of care, in a dedicated CVOT, CARMELINA, and did not show an increased risk of heart failure when linagliptin was compared to placebo. The hazard ratio (HR) for hospitalization for heart failure observed in CARMELINA was 0.90 (95% CI: 0.74, 1.08).

CAROLINA was a prospective, randomized, double-blind, active-controlled, CV outcomes trial in 6042 randomized subjects with T2DM and at high CV risk comparing linagliptin and glimepiride. After a mean follow-up of ~6 years, compared to glimepiride, linagliptin ruled out a 30% relative increase in MACE ($p<0.0001$), but did not show a MACE benefit ($p=0.38$). The HR for time-to-event analysis of MACE defined as CV

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death, non-fatal MI or non-fatal stroke was 0.98 (95% CI: 0.84, 1.14).

In CAROLINA, there was an imbalance in the proportion of subjects experiencing hospitalization for heart failure not favoring linagliptin (3.7%) compared to glimepiride (3.1%). The time-to-event analysis for hospitalization of heart failure showed that the HR was >1 (HR 1.21), although the 95% confidence interval crossed 1 (95% CI: 0.92, 1.59). The HR for heart failure was similar to that seen in sitagliptin's CVOT (SAVOR; HR 1.27 [95% CI: 1.07, 1.51]) and alogliptin's CVOT (EXAMINE; HR 1.19 [95% CI: 0.90, 1.58]).

Aside from those events related to HF, the adverse events observed with linagliptin compared to glimepiride in CAROLINA were largely reflective of known safety profile of linagliptin established during clinical development, other subsequent Phase 3 glycemic control trials and the previous placebo-controlled linagliptin CVOT (CARMELINA) in patients with T2DM. The incidences of hypoglycemia were higher with glimepiride compared to linagliptin, in both the overall hypoglycemia (15.1% linagliptin versus 46.9% glimepiride) and severe hypoglycemia (0.3% linagliptin, 2.2% glimepiride); this is not unexpected since sulfonylureas (SUs) are known to have a higher risk for hypoglycemia.

In summary, the overall data from CAROLINA provided evidence that linagliptin does not increase MACE risk compared to glimepiride in patients with T2DM at high MACE risk. The data regarding HF from CAROLINA, however, was not as reassuring as those from CARMELINA. I believe that the overall benefit-risk for these subjects was favorable and that the safety concerns with the use of linagliptin is already adequately labeled. Thus, I concur with adding the results of CAROLINA trial to inform healthcare professionals that linagliptin treatment compared to glimepiride is not expected to increase the CV risk [redacted] (b) (4) See Section 10.1 for labeling recommendations and rationale.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Type 2 diabetes mellitus (T2DM) is a condition of chronic impaired glucose homeostasis leading to chronic hyperglycemia and an increased risk for microvascular (e.g., retinopathy, nephropathy, and neuropathy) and macrovascular (e.g., myocardial infarction,	Type 2 diabetes mellitus is a serious and life-threatening condition that if left untreated leads to an increased risk for morbidity and mortality.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	stroke) complications. The Center for Disease Control (CDC) estimates that there are nearly 30 million patients with T2DM in the United States.	
Current Treatment Options	• Patients with diabetes mellitus are at an increased risk of microvascular (e.g., retinopathy, nephropathy) and macrovascular (e.g., myocardial infarction, stroke) complications. For patients with T2DM, the presence of microvascular and macrovascular diseases is independently associated with a 10-year risk of death, major adverse cardiovascular events (myocardial infarction, stroke, or CV death), and major clinical microvascular events (end-stage renal disease, death due to renal disease, retinal photocoagulation, or diabetes-related blindness). Diabetes remains a leading cause of kidney failure, adult-onset blindness, and non-traumatic lower limb amputations in the U.S. In addition, patients with diabetes are twice as likely to have cardiovascular disease (CVD) or stroke as non-diabetic individual and at an earlier age. Diabetes was the 7th leading cause of death in 2015, and CVD remains a major cause of death among diabetic patients. • There are currently 12 pharmacologic classes of antihyperglycemic medications (generally with multiple members within each class), approved to improve glycemic control in patients with T2DM. Many of these are also approved as fixed combination drug products (FCDP). • While all approved antihyperglycemic medications have shown to improve glycemic control, not all products have been evaluated for macrovascular outcome.	Despite many available treatment options for glycemic control, many patients continue to have difficulty with achieving the desired degree of glycemic control. In addition, T2DM is a progressive disorder and patients typically need additional agents as the disease progresses over time. CVOTs have shown MACE benefit in patients with T2DM at high CV risk and MACE benefit is labeled for four antihyperglycemic agents. CVOTs showed CV death benefit in one and hospitalization for heart failure in two other antihyperglycemic agents. CVOTs did not show MACE risk or MACE benefit for five other antihyperglycemic agents. CVOTs for two DPP-4 inhibitors suggested an increased risk for heart failure. However, linagliptin's CVOT trial, CARMELINA, did not show an increased risk of heart failure when linagliptin was compared to placebo. The

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Three SGLT2 inhibitors (empagliflozin, dapagliflozin, and canagliflozin) and liraglutide (a GLP-1 receptor agonist) showed CV benefit in a dedicated CVOT and have been labeled for CV indication in patients with T2DM and established CV disease. • Two other GLP-1 receptor agonist, exenatide and lixisenatide, did not show an increased risk of CV events but also did not show CV benefit in a dedicated CVOT. • Two other DPP-4 inhibitors, saxagliptin and alogliptin, did not show an increase in the risk of CV events but also did not show CV benefit in a dedicated CVOT; more events of heart failure (HF) were observed with saxagliptin (3.5% vs 2.8%) and alogliptin (2.2% vs 1.3% in those without history of HF), when both were compared against placebo. • Linagliptin itself did not shown an increase in the risk of CV events compared to placebo but also did not show CV benefit in a dedicated CVOT; the hospitalization for heart failure was not increased with linagliptin (7.9%) compared to placebo (8.8%).	hazard ratio (HR) for hospitalization for heart failure was 0.90 (95% CI: 0.74, 1.08) in CARMELINA.
Benefit	• The results of CAROLINA showed that linagliptin compared to glimepiride, when added to standard of care, did not increase the risk of MACE. • Risk for heart failure was imbalanced not favoring linagliptin compared to glimepiride in CAROLINA.	CAROLINA demonstrated that treatment with linagliptin compared to glimepiride did not lead to an unacceptable increased risk of MACE in patients with T2DM at high CV risk, and the upper bound of hazard ratio CV risk margin was <1.3 as described in the 2008 FDA Guidance on establishing cardiovascular safety of antidiabetic products. CAROLINA did not show CV benefit with linagliptin compared to glimepiride. Hospitalization for heart failure

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		showed imbalance not favoring linagliptin compared to glimepiride in CAROLINA. The HR for hospitalization for heart failure was 1.21 (95% CI: 0.92, 1.59).
Risk and Risk Management	• The risks associated with the use of linagliptin in subjects with T2DM at high CV risk are consistent with those reported in approved labeling of linagliptin. • No risk evaluation and mitigation strategy is recommended.	The adverse reactions and safety profile of linagliptin added to background of standard care in patients with T2DM at high CV risk is adequately labeled to communicate safety concerns seen in CAROLINA.

1.4. Patient Experience Data

Not applicable. Patient experience data (e.g., information about patients' experiences with a disease or condition, including the impact of such disease or condition, or a related therapy, on patients' lives; and patient preferences with respect to treatment of such disease or condition) were not submitted nor reviewed as part of this sNDA.

Patient Experience Data Relevant to this Application (check all that apply)

□	The patient experience data that was submitted as part of the application include:	Section where discussed, if applicable
	□ Clinical outcome assessment (COA) data, such as	[e.g., Sec 6.1 Study endpoints]
	□ Patient reported outcome (PRO)	
	□ Observer reported outcome (ObsRO)	
	□ Clinician reported outcome (ClinRO)	
	□ Performance outcome (PerfO)	
	□ Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
	□ Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Sec 2.1 Analysis of Condition]
	□ Observational survey studies designed to capture patient experience data	
	□ Natural history studies	
	□ Patient preference studies (e.g., submitted studies or scientific publications)	
	□ Other: (Please specify)	
□	Patient experience data that were not submitted in the application, but were considered in this review:	
	□ Input informed from participation in meetings with patient stakeholders	
	□ Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Current Treatment Options]
	□ Observational survey studies designed to capture patient experience data	
	□ Other: (Please specify)	
□	Patient experience data was not submitted as part of this application.	

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2. Therapeutic Context

2.1. Analysis of Condition

Diabetes mellitus is characterized by chronic hypoglycemia and includes different metabolic disorders due to deficiencies in insulin production, insulin secretion, insulin action or a combination of these processes. There are two main types of diabetes mellitus: type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM). Type 1 diabetes is characterized by autoimmune destruction of pancreatic beta-cells leading to loss of insulin secretion. Type 2 diabetes is a complex, progressive metabolic disorder characterized by a combination of insulin resistance and relative insulin deficiency, with gradual deterioration in insulin secretion and beta-cell function over time. Type 2 diabetes accounts for about 90-95% of all cases of diabetes and is an increasingly prevalent disease.

Patients with T1DM may present with classic symptoms of hyperglycemia (e.g., polyuria, polydipsia, nocturia, blurred vision, and diabetic ketoacidosis), while patients with T2DM may present similarly but can be asymptomatic. Patients with diabetes mellitus are at an increased risk of microvascular (e.g., retinopathy, nephropathy) and macrovascular (e.g., myocardial infarction, stroke) complications. For patients with T2DM, the presence of microvascular and macrovascular disease is independently associated with an increased 10-year risk of death, major adverse cardiovascular events (myocardial infarction, stroke, or CV death), and major clinical microvascular events (end-stage renal disease, death due to renal disease, retinal photocoagulation, or diabetes-related blindness). Diabetes remains a leading cause of kidney failure, adult-onset blindness, and non-traumatic lower limb amputations in the U.S. In addition, patients with diabetes have 2- to 4-fold increase in the risk for CV disease (CVD). Diabetes was the 7th leading cause of death in 2015, and CVD remains a major cause of death among diabetic patients.[1]

2.2. Analysis of Current Treatment Options

Type 2 diabetes mellitus can be treated with a combination of proper diet, exercise, and one or more of the drug products presented in Table 1. Fixed-combination drug products (FCDP) and injectable insulin plus non-insulin FCDPs are not shown.

[1] National Diabetes Statistics Report, 2017. Estimates of diabetes and its burden in the United States. Atlanta, GA: National Center for Chronic Disease Prevention and Health Promotion, Division of Diabetes Translation, 2017. https://www.cdc.gov/diabetes/pdfs/data/statistics/national-diabetes-statistics-report.pdf

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Table 1: Approved Drug Products for the Management of Type 2 Diabetes Mellitus

Pharmacologic Class	Antihyperglycemic Drug Products*
ALPHA-GLUCOSIDASE INHIBITORS	Acarbose; Meglitol
AMYLIN MIMETICS	Pramlintide
BIGUANIDES	Metformin
BILE ACID SEQUESTRANTS	Colesevelam
DOPAMINE-2 AGONISTS	Bromocriptine
DPP-4 INHIBITORS	Alogliptin; Linagliptin; Saxagliptin; Sitagliptin
GLP-1 RECEPTOR AGONISTS	Albiglutide; Dulaglutide; Exenatide; Exenatide extended release; Liraglutide; Lixisenatide, Semaglutide
INSULINS AND INSULIN ANALOGUES	Inhaled insulin human; Insulin aspart: Insulin aspart protamine plus insulin aspart; Insulin degludec; Insulin degludec plus insulin aspart; Insulin detemir; Insulin glargine; Insulin glulisine; Insulin isophane (NPH); Insulin isophane plus regular; Insulin lispro; Insulin lispro protamine plus insulin lispro; Insulin regular (human); Premixed insulins (various)
MEGLITINIDES	Nateglinide; Repaglinide
SGLT2 INHIBITORS	Canagliflozin; Dapafliflozin; Empagliflozin, Ertugliflozin
SULFONYLUREAS	Chlorpropamide; Glimepiride; Glipizide; Glipizide extendedrelease; Glyburide; Tolazamide; Tolbutamide
THIAZOLIDINEDIONES	Pioglitazone; Rosiglitazone

Source: Drugs@FDA: FDA Approved Drug Products, available at: http://www.accessdata.fda.gov/scripts/cder/daf/.
Abbreviations: DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; and SGLT2, sodium-glucose cotransporter 2.

Despite the armamentarium of pharmacologic therapies available for the treatment of T2DM, a substantial portion of patients either remain under poor glycemic control or experience deterioration of glycemic control after an initial period of successful treatment with an antidiabetic therapy. Progressive beta-cell dysfunction in patients with T2DM may lead to secondary treatment failures over time. In addition to diabetes disease progression, nonadherence to the prescribed antihyperglycemic regimen may influence the potential to achieve/maintain adequate glycemic control. Further, many pharmacologic classes may not be tolerated or have limited usefulness in certain populations. For example, metformin and SGLT2 inhibitors are contraindicated in patients with severe renal dysfunction, and DPP-4 inhibitors carry a class warning for severe/disabling arthralgia. As type 2 diabetes is a heterogenous disease in both pathogenesis and clinical manifestations, there remains a need for new

antihyperglycemic treatment options.

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Linagliptin was approved by the FDA on May 2, 2011. Jentadueto (NDA 201-281), a FCDP containing linagliptin and metformin HCl, was approved by the FDA on January 30, 2012. Jentadueto XR (NDA 208-026), a FCDP containing linagliptin and metformin extended-release, was approved by the FDA on May 27, 2016. Glyxambi (NDA 206-073), a FCDP containing linagliptin and empagliflozin, was approved by the FDA on January 30, 2015. Trijardy XR, a FDCP containing linagliptin, empagliflozin, and extended release metformin was approved on January 27, 2020. All linagliptin and linagliptin-containing products are indicated as an adjunct to diet and exercise to improve glycemic control in adults with T2DM.

Some of the recently approved labeling changes include:

- Supplement 011 approved on July 28, 2015 to include terms 'mouth ulcerations' and 'stomatitis' to *Adverse Reactions; Postmarketing Experience* section;
- Supplement 012 approved on August 28, 2015 to include DPP-4 inhibitor class labeling related to severe and disabling arthralgia, added to *Warnings and Precautions* and *Adverse Reactions; Postmarketing Experience* sections, as well as to the Patient Counseling and Medication Guide; it should be noted that a Drug Safety Communication on arthralgia was posted on August 28, 2015;
- Supplement 014 approved on March 14, 2017 to include 'lipase increased' in *Adverse Reactions, Clinical Experience* under *Laboratory Tests*, and to align with the content and format requirements per Pregnancy and Lactation labeling;
- Supplement 015 approved on December 23, 2016 to include DPP-4 inhibitor class labeling related to postmarketing cases of bullous pemphigoid reported in patients with DPP-4 inhibitors, which was added to *Warnings and Precautions*, *Adverse Reactions, Postmarketing Experience*, as well as to the Patient Counseling and Medication Guide;
- Supplement 016 approved on August 10, 2017 to include DPP-4 inhibitor class labeling related to an increased risk of heart failure in patients treated with DPP-4 inhibitor products based on clinical trial data for saxagliptin and alogliptin, two products in this class. This information was added to *Warnings and Precautions* as well as to the Patient Counseling and Medication Guide;
- Supplement 021 approved July 1, 2019 to add 'rhabdomyolysis' to the *Adverse Reactions; Postmarketing Experience* section; this was a DPP-4 inhibitor class labeling;
- Supplement 018 approved on July 3, 2019 to include study results of CARMELINA, a dedicated CV outcomes trial that was conducted to show that linagliptin was not associated

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with an unacceptable increase in CV risk compared to placebo, to *Clinical Studies* section.

3.2. Summary of Presubmission/Submission Regulatory Activity

Trial 1218.74, or CAROLINA, was originally planned to fulfill Tradjenta's postmarketing requirement (PMR) to assess cardiovascular safety per 2008 Draft Guidance for Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes which asked that Applicants show that new antidiabetic therapies do not result in an unacceptable increase in cardiovascular risk.

Trial 1218.74 was initiated in October 2010. During a teleconference in March 2011, we requested a placebo-controlled CVOT to address the PMR rather than CAROLINA because of concerns about the uncertainty of the CV risk associated with the active control, glimepiride. In the approval letter for Tradjenta dated May 2, 2011, PMR 1766-4 described a placebo-controlled study to assess the CV safety of linagliptin. The Applicant continued with the ongoing active-controlled study (CAROLINA) and conducted a placebo-controlled CV study (CARMELINA) to satisfy PMR 1766-4. Supplemental NDAs adding the results of CARMELINA to the labels of Tradjenta, Jentadueto, Jentadueto XR and Glyxambi were submitted by the Applicant on September 5, 2018 and approved on July 3, 2019.

On December 20, 2018 we provided a written response to technical aspects related to the Applicant's planned submission of Trial 1218.74, which included agreement to rely on the final clinical report as a basis for presentation of efficacy and safety results given that the supplement is based on the results of a single outcome study. We also asked that they submit CRFs and narratives for subjects who experienced thyroid neoplasms.

3.3. Foreign Regulatory Actions and Marketing History

Since U.S. approval on May 2, 2011, linagliptin has been approved in over 100 countries worldwide including Europe and other regions.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

CAROLINA was a multinational trial conducted at 607 sites in 43 countries.

OSI audit was requested for CAROLINA and per discussion with Dr. Cynthia Kleppinger from OSI, both domestic and foreign sites were determined appropriate for audit. After discussion with

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Dr. Kleppinger, three domestic and two foreign sites were requested for inspection as listed in Table 2.

Table 2: List of Sites Inspected

Investigator Location	Site #	# of subjects randomized	Rationale for site selection	Inspection date
Ana Fandino Miami, FL	1226	6	Ranked #11 in CISST; site closed by sponsor for non-compliance in 2013; history of several previous complaints; Warning Letter issued 2013	October 8, 2019
Leon Fogelfeld Chicago, IL	1063	31	Ranked #55 in CISST; second highest US enrolled; never been inspected	December 10-13, 2019
Elena Henkel Germany	49014	50	Ranked #7 in CISST; Enrolled most screened subjects; higher than average AEs	October 21-25, 2019
Francisco Munoz Elizabeth, NJ	1241	20	Ranked #8 in CISST; enrolled all screened; high discontinuation rate; site never inspected	September 30, October 10, 2019
W.W. van Kempen The Netherlands	31012	82	Ranked #1 in CISST; highest enroller; higher than average discontinuation and adverse events; never been inspected	October 28-November 1, 2019

Abbreviations: CISST=Clinical Investigator Site Selection Tool

Dr. Fandino's site was one of 10 that was closed in March 2013 due to non-compliance. During inspection, it was found that six subjects in Dr. Fandino's site were transferred to Dr. Luigi Meneghini's site (sub-investigator for Site 1191/Bresta Miranda), and since all records were transferred, Dr. Miranda's site was also inspected.

In addition, during the inspection of Site 121 (Dr. Munoz), it was found that subjects had been transferred from a previous site (Dr. Mandeep Oberoi/Site 1118) and that Dr. Munoz did not enroll his own subjects. Therefore, Dr. Oberoi's site (Site 1118) was also inspected.

Dr. Oberoi's site received Form FDA-483, Inspectional Observations, for investigational records not retained for a period of 2 years after approval of drug's marketing application, as original

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records for one subject were not retained. Except for Dr. Oberoi's site, no other Form FDA-483 was issued.

The Applicant, Boehringer Ingelheim, was also inspected on December 9-12, 2019 as follow-up based on some issues found at clinical sites such as transfer of subjects that was not mentioned in the CSR. At conclusion of inspection, Form FDA-483 was issues for the following:

- Failure to notify FDA of the ending, for-cause, of an investigator's participation in an investigation;
- Failure to ensure that an investigation was conducted in accordance with the general investigational plan and protocols as specified in the IND;
- Records and reports were not retained for two years after discontinuance of the investigation and notification of FDA.

The Applicant sent a written response to these observations on December 20, 2019 and a follow-up response on January 2, 2020, which was deemed acceptable.

Dr. Kleppinger concluded that overall, based on the inspections, findings support the validity of the Applicant's data for this supplement and the study data are considered acceptable. The inspection of one clinical investigator showed deficiencies (Dr. Oberoi), but Dr. Kleppinger determined that they are unlikely to have significantly impact the overall results. The inspection of other clinical investigators showed no violations.

Please refer to Dr. Kleppinger's review dated February 6, 2020 for full details and discussion of the inspection findings.

4.2. Product Quality

Not applicable.

4.3. Clinical Microbiology

Not applicable.

4.4. Nonclinical Pharmacology/Toxicology

Nonclinical studies were not submitted in this supplement.

4.5. Clinical Pharmacology

No new clinical pharmacology studies were submitted in this supplement.

4.6. Devices and Companion Diagnostic Issues

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Not applicable as companion device or diagnostic was not included in this supplement.

4.7. Consumer Study Reviews

Not applicable.

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

One Phase 4 trial, CAROLINA, that is pertinent for evaluation of efficacy and safety is summarized in Table 3.

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Table 3: Efficacy and Safety Clinical Trial Relevant for this NDA

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
Trial Number: 1218.74 **Title:** A multicenter, international, randomized, parallel group, double-blind study to evaluate **Car**di**o**vascular safety of **lina**gliptin versus glimepiride in patients with type 2 diabetes mellitus at high cardiovacular risk. The **CAROLINA** Trial.	NCT01243424	Multicenter, randomized, double-blind, 2-arm, parallel-group, active-controlled	Linagliptin 5 mg once daily versus glimepiride 4 mg once daily, both to be taken orally	**Primary:** Time to first occurrence of adjudicated composite endpoint (3-point Major Adverse Cardiovascular Events [MACE]) of CV death, non-fatal myocardial infarction, or non-fatal stroke **Key secondary:** Time to first occurrence of 3-point MACE or hospitalization for unstable angina pectoris	2-4 weeks of placebo run-in period; Estimated 432 weeks of treatment period, depending on observed number of primary endpoint events (631 primary events needed); 7 days of follow-up period	Linagliptin: 3023 Glimepiride: 3010	Male or female 40-85 years of age, inclusive; T2DM, HbA1c 6.5-8.5% or 6.5-7.5% depending on background anti-diabetic therapy; BMI ≤45 kg/m^2; stable anti-diabetic background therapy for at least 8 weeks; High risk of CV event, defined as either: A) Previous vascular disease, or B) Evidence of vascular related end-organ damage, or C) Age ≥70 years, or D) At least 2 CV risk factors. (see Section 6.1.1, Study Design for full Inclusion/Exclusion criteria)	607 sites; 43 countries

5.2. Review Strategy

The efficacy and safety findings in this review were from a single clinical trial, CAROLINA, that the Applicant conducted and submitted for inclusion in the product labeling. In this review, I will primarily present the results of the Applicant's analyses along with my comments and interpretations of data for efficacy review; please refer to the Statistical Review by Dr. Bo Li, who confirmed and supplemented the Applicant's efficacy analyses. See Section 8.1 for safety review approach.

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. CAROLINA (Trial 1218.74)

6.1.1. Study Design

Overview and Objective

Trial 1218.74 was a multicenter, international, randomized, parallel group, double-blind, active-control study to evaluate **car**di**o**vascular safety of **lina**gliptin versus glimepiride in patients with type 2 diabetes mellitus at high cardiovascular risk, or the CAROLINA trial. The main purpose of the trial was to evaluate the long-term impact of linagliptin 5 mg compared to glimepiride (1 to 4 mg), both given on a background of standard care, on CV morbidity and mortality in patients with T2DM at elevated CV risk.

The primary objective was to demonstrate that linagliptin compared to glimepiride, as add-on to metformin and standard of care, is not associated with an unacceptable increase in MACE risk in patients with T2DM. To meet this objective, the trial was to show non-inferiority of treatment with linagliptin compared to glimepiride by demonstrating that the upper bound of the 2-sided 95% confidence interval for estimated risk ratio comparing time to the first occurrence of 3-point MACE (3-P MACE included CV death, non-fatal MI, or non-fatal stroke) observed with linagliptin to glimepiride is <1.3, in accordance with the FDA Diabetes Guidance of 2008.[2]

After establishing non-inferiority, time to the first occurrence of 3-P MACE was to be tested for superiority to assess the MACE benefit for linagliptin compared to glimepiride.

This was followed by the following key secondary objectives that were tested in the following

[2] FDA Guidance for Industry: Diabetes Mellitus, Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes, December 200.

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sequential order:

- Superiority of linagliptin compared to glimepiride on time to first 4P-MACE (3P-MACE plus hospitalization for unstable angina pectoris);
- Equality between treatment with respect to the composite endpoint of treatment sustainability[3] without 2% weight gain and without any moderate/severe hypoglycemic episodes[4] during the maintenance phase (i.e., Weeks 16 to the end of study).
- Equality between treatment with respect to the composite endpoint of treatment sustainability and without >2% weight gain during the maintenance phase (i.e., Weeks 16 to the end of study).

CAROLINA began on November 11, 2010 and completed on August 21, 2018, with the trial database locked on September 27, 2018.

Trial Design

CAROLINA was a multicenter, multinational, randomized, double-blind, parallel group, active-controlled trial comparing the treatment with linagliptin (5 mg once daily) versus glimepiride (1 to 4 mg once daily) on the composite MACE endpoint in subjects with T2DM who are at elevated CV risk and added on to standard of care. Subjects were predominantly on background metformin therapy.

About 6000 patients were to be randomized 1:1 ratio to one of two treatment groups, and treatment was double-blinded. Randomization was stratified by center. The trial was event-driven and was to run until 631 subjects had adjudication-confirmed primary endpoint events. Treatment duration was estimated to be about 432 weeks for the first randomized subject. See Figure 1 for an overview of trial design.

[3] Defined as the proportion of subjects that maintain glycemic control (i.e., HbA1c ≤7%) at the end of study and are on study drug without requiring rescue therapy during the maintenance phase (i.e., Week 16 to the Final Visit).
[4] For the assessment of efficacy, moderate hypoglycemia was defined as documented symptomatic hypoglycemia (without need for external assistance) with plasma glucose ≤70 mg/dL; and severe hypoglycemia was defined as documented hypoglycemia requiring assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions.

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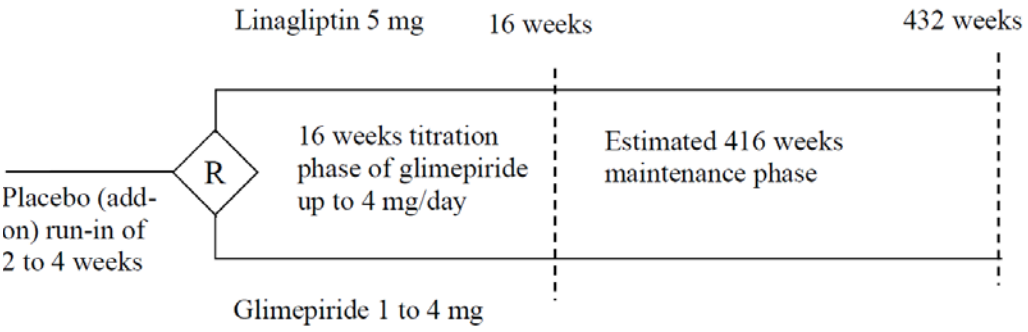
Figure 1: CAROLINA Trial Design



Source: CSR, Figure 9.1:1

Eligible subjects entered an open-label placebo run-in period of 2 to 4 weeks before randomization. Subjects completing at least 2 weeks of placebo run-in period with treatment compliance between 80 and 120% were randomized to either linagliptin or glimepiride. Any sulfonylurea or glinide was to be discontinued before randomization visit. Randomized subjects entered 16 weeks of titration phase followed by maintenance phase.

During the titration phase (i.e., the first 16 weeks after randomization), study visits occurred at 4, 8, 12, and 16 weeks. Subsequently, maintenance phase followed, where study visits occurred every 16 weeks until the End of Treatment visit. All subjects, including those who prematurely discontinue treatment, were to be followed until the end of the trial and were to be contacted by the investigator at regular intervals. Subjects who prematurely discontinued study drug during the maintenance phase were allowed to restart the study drug at any time.

Treatment goal for HbA1c in this trial was ≤7% based on clinical guidelines for treatment of T2DM. During the trial, rescue therapy with additional antidiabetic drugs was allowed for additional glycemic control if HbA1c was >7.5% during the maintenance phase of the trial, as appropriate per local treatment guidelines.

Investigators were also encouraged to treat all other CV risk factors (e.g., lipid levels, blood pressure, smoking, unhealthy lifestyle, and micro/macroalbuminuria) according to local guidance for primary or secondary CV prevention.

Reviewer's comment: *The overall trial design is consistent with other cardiovascular outcomes trials.*

Choice of Control Group:

Glimepiride, a sulfonylurea, was active comparator in CAROLINA to evaluate the long-term CV

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effect of linagliptin in patients with T2DM at increased CV risk. Metformin is currently recommended as first-line therapy with lifestyle intervention when patients are newly diagnosed with T2DM. Both DPP-4 inhibitors such as linagliptin and SUs such as glimepiride are second-line treatment options after metformin.

Reviewer's comment: *Most CV outcome trials with anti-diabetic agents are usually done against placebo and against active comparator. The long-term CV effect of SUs including glimepiride has not been fully evaluated in a prospective large outcomes trial and is unknown.*

Trial Location:

The trial was conducted in 607 centers in 43 countries in Africa, Asia, Europe, North America, Latin America, Australia, and New Zealand.

Inclusion Criteria:

- Documented diagnosis of T2DM, with insufficient glycemic control and at high risk of CV events;
- Insufficient glycemic control defined as:
    A) HbA1c 6.5-8.5% if treatment naïve (if intolerant or contraindicated to first line anti-diabetic drug) or on monotherapy treatment with either metformin, alpha-glucosidase inhibitor, or combination of metformin and alpha-glucosidase inhibitor monotherapy;
    B) HbA1c 6.5-7.5% while treated with monotherapy with SU or glinide, or the following combination maximal up to 5 years:
        - Metformin + SU
        - Metformin + glinide
        - SU + alpha-glucosidase inhibitor
        - Glinide + alpha-glucosidase inhibitor.
- High risk of CV events defined as any one or more of the following:
    A) Previous vascular disease:
        - MI >6 weeks;
        - Documented coronary artery disease (≥50% luminal diameter narrowing of left main coronary artery or ≥50% in at least 2 major coronary arteries in angiogram[5] [e.g., left anterior descending, circumflex, or right coronary artery]);
        - Percutaneous coronary intervention (PCI) >6 weeks before informed consent;
        - Coronary artery by-pass grafting (CABG) >4 years before informed

[5] CT or MRI detection will not suffice for inclusion; only invasive angiography.

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consent or with recurrent angina after surgery;
- Ischemic or hemorrhagic stroke >3 months;
- Peripheral occlusive arterial disease; previous limb bypass surgery, stenting or percutaneous transluminal angioplasty; previous limb or foot amputation due to circulatory insufficiency, angiographic or ultrasound detected significant vessel stenosis (>50%) of major limb arteries, history of intermittent claudication with an ankle:arm blood pressure ratio <0.90 on at least one side.

B) Evidence of vascular related end-organ damage:
- Moderately impaired renal function with estimated glomerular filtration rate (eGFR) of 30-59 mL/min/1.73 m^2 using MDRD formula;
- Random spot urinary albumin: creatinine ratio ≥30 µg/mg in 2 of 3 unrelated specimen past 12 months;
- Proliferative retinopathy defined as retinal neovascularization or previous retinal laser coagulation therapy;

C) Age ≥70 years;

D) At least 2 of the following CV risk factors:
- T2DM duration >10 years at screening;
- Systolic blood pressure >140 mmHg (or on at least one blood pressure lowering treatment);
- Current daily cigarette smoker;
- LDL cholesterol ≥135 mg/dL within past 6 months;

Note: if a subject fulfills more than one CV category, s/he was allocated to the highest CV category, with category A the highest category followed by B, C, and D. To ensure appropriate distribution of subjects from different CV risk categories worldwide, the trial was monitored for the proportion of subjects being recruited into the categories at trial level, region and/or country, and recruitment of a particular category could occur in consultation with the SC.

- Body mass index ≤45 kg/m^2 at beginning of run-in period;
- Age 40-85 years at screening;
- Stable anti-diabetic background drug (unchanged daily dose) for at least 8 weeks before Visit 1a and without short-term use of insulin. Background drug should also be stable during screening/run-in phase.

Reviewer's comment: *Similar to other CVOTs, CAROLINA enriched the study population by enrolling patients at high risk for CV events.*

Exclusion Criteria:
- Type 1 diabetes mellitus;

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- History and/or concurrent treatment with other antidiabetic drugs before informed consent;
- Treatment with anti-obesity drugs past 3 months;
- Uncontrolled hyperglycemia with fasting glucose >240 mg/dL during placebo run-in that is confirmed by a second measurement on a different day;
- Active liver disease or impaired hepatic function, defined by either ALT, AST, or alkaline phosphatase >3x ULN;
- Any previous or planned bariatric surgery or intervention (gastric sleeve) in the next 12 months;
- Pre-planned coronary artery re-vascularization (PCI, CABG) within next 6 months or any PCI/CABG ≤6 weeks prior;
- Hypersensitivity or allergy to study drugs;
- Congestive heart failure of NYHA class 3 or 4;
- Acute or chronic metabolic acidosis;
- Hereditary galactose intolerance;
- Alcohol or drug abuse within past 3 months;
- Current treatment or planned therapy with systemic glucocorticosteroids;
- Change in dose of thyroid hormones within past 6 weeks;
- Participation in another trial within past 2 months;
- Pre-menopausal women (last menstruation ≤1 year before informed consent) who are either nursing, of child-bearing potential and not practicing an acceptable form of birth control, or do not plan to continue use of acceptable method of birth control during trial participation and did not agree to periodic pregnancy testing during the trial;
- Life expectancy of <5 years for non-CV causes, or patients with cancer other than non-melanoma skin cancer within past 3 years;
- Acute coronary syndrome ≤6 weeks;
- Stroke or TIA ≤3 months.

Study Treatment:

After the placebo run-in period, subjects were randomly assigned in a double-blind, double-dummy way in a 1:1 ratio to either linagliptin 5 mg (plus glimepiride placebo) or an initial dose of glimepiride 1 mg (plus linagliptin placebo).

During the first 16 weeks of treatment period (i.e., titration phase), glimepiride or glimepiride placebo was subsequently up-titrated every 4 weeks to the next dose, if FPG values were >110 mg/dL during study visits at Weeks 4, 8, and 12, unless there was an increased risk for hypoglycemia, up to the maximum dose of 4 mg/day.

Subjects who were previously on glimepiride may continue their previous glimepiride dose, and

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after randomization will start glimepiride/glimepiride placebo at their pre-trial glimepiride dose. If previous glimepiride dose was ≥4 mg/day, s/he will start glimepiride/glimepiride placebo dose of 4 mg/day at randomization combined with linagliptin/linagliptin placebo 5 mg/day.

At any time during the trial, glimepiride/glimepiride placebo can be down titrated to prevent recurrent hypoglycemic events and can be up-titrated again to the potential maximum dose of glimepiride/glimepiride placebo 4 mg/day with linagliptin/linagliptin placebo 5 mg/day.

Background Therapy:

Subjects were to continue their background metformin therapy (preferably ≥1500 mg/day) during the trial without changing the dose unless for reasons of safety.

The investigators were also encouraged to treat all other CV risk factors for primary or secondary CV prevention, such as lipid levels, blood pressure, micro/macroalbuminuria, lifestyle and smoking to optimally treat per local/regional standard of care. This included liberal use of statins, ACE-inhibitors, angiotensin receptor blockers, aspirin, beta-blockers, calcium channel blockers, etc.

Rescue Therapy:

Use of rescue therapy was allowed with either pioglitazone, metformin, alpha-glucosidase inhibitor or basal insulin (i.e., intermediate or long-acting insulin), if one or more of the following criteria were met:

- During the titration phase (i.e., randomization to Week 16): FPG >240 mg/dL;
- During the maintenance phase (i.e., Week 16 to end of study): FPG >180 mg/dL or HbA1c >7.5%.

Short-acting insulin were allowed for up to 2 weeks in combination with the study drug in certain situations (e.g., hospitalization).

The dose of rescue therapy was dictated by local labeling at the investigator's discretion.

Restrictions:

Use of other antidiabetic agents other than background therapy and rescue therapy (as defined above) such as other oral agents, short-acting insulin (unless given as rescue for up to 2 weeks) or injectable GLP-1 analogue/agonists were not allowed during the trial.

Treatment with anti-obesity drugs were also prohibited.

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Subject Discontinuation:

Subjects who discontinued the study drug prematurely were encouraged to remain in the trial and continued to be observed until the trial end. At least a telephone call (preferably every 6 months; minimum yearly) and a telephone call at trial end was required to document the occurrence of outcome events and vital status. If subjects could not be followed-up until the trial end and vital status was unavailable, s/he was recorded as lost to follow-up (LTFU).

Subjects who prematurely discontinued the study drug were allowed to restart the study drug at any time if appropriate. Subjects were allowed to have multiple study drug interruptions.

If pancreatitis was suspected, study drug was to be stopped. If subject becomes pregnant, the study drug was to be stopped and subject was to be followed until birth or otherwise termination of the pregnancy.

Administrative Structure:

There were several committees associated with this trial:

- Steering Committee (SC) was composed of university and sponsor-based scientist with clinical and methodological expertise, and had a scientific and clinical advisory function in the trial;
- Data Monitoring Committee (DMC) reviewed unblinded safety and efficacy data to recommend whether to continue, modify, or stop the trial. The DMC analyses and operation were formally separated from the Applicant, the investigators and SC;
- Clinical Event Committee (CEC) was an independent, blinded, external committee that prospectively adjudicated all cardiovascular and cerebrovascular trigger events. A separate independent, blinded, external committee adjudicated pancreatic events, and an independent Oncology Assessment Committee assessed solid malignancies including pancreatic cancer.

Procedures and Schedules:

All subjects were provided with home blood glucose monitoring equipment and supplies for use at home, and weekly finger stick glucose measurements were recommended with additional measurements to be done as needed and for hypo- or hyperglycemia symptoms.

After randomization, study visits occurred every 4 weeks until Week 16, and then every 16 weeks until the End of Treatment (EOT) visit. A follow-up visit took place 7 days after the EOT visit. See Table 4 for Flow Chart showing study visits and procedures for each study visit.

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Table 4: CAROLINA Trial Flow Chart

Trial Period	**Screening**	**Placebo run-in**	**Treatment phase (titration)**			
Visit	**1a**	**1b[A]**	**2**	**3**	**4**	**5**
Trial week		**-4 / -2**	**0**	**4**	**8**	**12**
Days from randomisation	**-35/ -15**	**-28 / -14**	**0**	**28**	**56**	**84**
Time window (days)[J]				**±7**	**±7**	**±7**
Informed Consent	X					
In-/exclusion criteria	X	X	X[C]			
Medical History/ Concomitant diagnoses	X					
Demographics[O]	X	X				
Physical examination		X[M]				
Vital signs		X[M]	X	X	X	X
Height		X[I]				
Weight		X[I]	X			
Waist circumference		X	X			
12-lead-ECG			X[M]			
Diet and exercise counselling	X		X	X	X	X
Pregnancy Test[F]	X		X			
Fasted Home Blood Glucose Monitoring (HBGM)[G]		X	X[L]	X	X	X
Safety lab Tests (Urine and Blood)[H]	X		X			
Glomerular filtration rate[K]	X		X			
Fasting Plasma Glucose[B]		X	X	X	X	X
HbA_{1c}	X		X[C]			
Biomarkers Fasted proinsulin[B] C-Peptide Autoantibodies			X[D]			
PG sampling [E]			X			
Lipid profile			X			
Cognitive function tests and CES-D questionnaire[L]			X			
Adverse events		X	X	X	X	X
Concomitant Therapy	X	X	X	X	X	X
Dispense placebo run-in medication (via IXRS)		X				
Randomisation (via IXRS)			X			
Dispense double-blind medication			X	X	X	X
Medication compliance check			X	X	X	X

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Trial Period	**Treatment phase (maintenance)**											
Visit	**6**	**7/8**	**9**	**10/ 11**	**12**	**13/ 14**	**15**	**16/ 17**	**18**	**19/ 20**	**21**	**22/ 23**
Trial week	**16**	**32/ 48**	**64**	**80/ 96**	**112**	**128/ 144**	**160**	**176/ 192**	**208**	**224/ 240**	**256**	**272/ 288**
Days from randomisation	**112**	**224/336**	**448**	**560/672**	**784**	**896/ 1008**	**1120**	**1232/ 1344**	**1456**	**1568/ 1680**	**1792**	**1904/ 2016**
Time window (days)	**±7**	**±14**	**±14**	**±14**	**±14**	**±14**	**±14**	**±14**	**±14**	**±14**	**±14**	**±14**
Physical examination	X		X		X		X		X		X	
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X
Weight	X	X	X	X	X	X	X	X	X	X	X	X
Waist circumference	X		X		X		X		X		X	
12-lead-ECG	X		X		X		X		X		X	
Diet and exercise counselling	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy Test[F]	X	X	X	X	X	X	X	X	X	X	X	X
Fasted Home Blood Glucose Monitoring (HBGM)[G]							X[L]					
Safety lab Tests (Urine and Blood)	X	X	X	X	X	X	X	X	X	X	X	X
Glomerular filtration rate[K]	X	X	X	X	X	X	X	X	X	X	X	X
Fasting Plasma Glucose[B]	X	X	X	X	X	X	X	X	X	X	X	X
HbA_{1c}	X	X	X	X	X	X	X	X	X	X	X	X
Cognitive function tests and CES-D questionnaire[L]							X					
Lipid profile	X		X		X		X		X		X	
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Therapy	X	X	X	X	X	X	X	X	X	X	X	X
Dispense double-blind medication	X	X	X	X	X	X	X	X	X	X	X	X
Medication compliance check	X	X	X	X	X	X	X	X	X	X	X	X

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Trial Period	**Treatment phase (maintenance)**							**Follow-up**
Visit	**24**	**25/ 26**	**27**	**28/ 29**	**30**	**31**	**32 EOT[N]**	**33**
Trial week	**304**	**320/ 336**	**352**	**368/ 384**	**400**	**416**	**432**	**436**
Days from randomisation	**2128**	**2240/ 2352**	**2464**	**2576/ 2688**	**2800**	**2912**	**3024**	**3054**
Time window (days)	**±14**	**±14**	**±14**	**±14**	**±14**	**±14**	**±14**	**+7**
Physical examination	X		X		X		X	
Vital signs	X	X	X	X	X	X	X	X
Weight	X	X	X	X	X	X	X	
Waist circumference	X		X		X		X	
12-lead-ECG	X		X		X		X	
Diet and exercise counselling	X	X	X	X	X	X	X	
Pregnancy Test[F]	X	X	X	X	X	X	X	
Fasted Home Blood Glucose Monitoring (HBGM)[G]							X[L]	
Safety lab Tests (Urine and Blood)	X	X	X	X	X	X	X	X
Glomerular filtration rate[K]	X	X	X	X	X	X	X	X
Fasting Plasma Glucose[B]	X	X	X	X	X	X	X	X
HbA_{1c}	X	X	X	X	X	X	X	
Biomarkers: Fasted proinsulin[B] C-Peptide Autoantibodies								
Lipid profile	X		X		X		X	
Cognitive function tests and CES-D questionnaire[L]							X[L]	
Adverse events	X	X	X	X	X	X	X	X
Concomitant Therapy	X	X	X	X	X	X	X	X
Dispense double-blind medication	X	X	X	X	X	X		
Medication compliance check	X	X	X	X	X	X	X	

[A] Visit 1b to be performed within 1 week from Visit 1a
[B] Overnight fasting (10 h no food and only water)
[C] HbA_{1c} measured at Visit 1a was used for inclusion
[D] Biomarkers samples (proinsulin, C-peptide, autoantibodies) were collected from all sites in North America and Europe (approximately 3000 patients).
[E] To allow possible retrospective pharmacogenetic (PG) analyses, all patients eligible for randomisation were asked for a blood sample with a separate informed consent. The PG sample was preferably to be taken at Visit 2 but could also be taken at any later visit, pending on availability of respective informed consent. Please note: PG sampling was voluntary and not a prerequisite for participation in the trial.
[F] For female patients (local urine pregnancy test in women of child bearing potential). More frequent testing could be done if required by local regulations/authorities.
[G] Home blood glucose monitoring (HBGM) device provided at Visit 1b. The patient was to be instructed to bring their HBGM device to the clinic at least at the specified visits for an additional measurement of fasted glucose.
[H] Visit 1a safety laboratory only included ALT, AST, alkaline phosphatase, serum creatinine, urine analysis and urine albumin and creatinine, in addition to HbA_{1c}; fasted state was not necessary.
[I] Body Mass Index was calculated automatically.
[J] Maximal time window between two visits during titration phase was 5 weeks and during maintenance phase 18 weeks.
[K] Calculated based on MDRD formula (see TSAP, Appendix 16.1.9).

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[L] Cognitive function tests (MMSE, TMT, VFT) were implemented in all countries/sites using the Latin alphabet and were done in approximately 4000 to 5000 patients (e.g. based on availability of validated questionnaires and/or any language constraints). Patients who completed cognition tests also completed a self-reporting depression questionnaire (CES-D) at the same visit. Prior to completion of cognitive tests, FPG was to be measured by using HBGM at the particular visit. In case glucose level was not within the range including 4 to 13 mmol/L
(72 – 234 mg/dL) the cognitive test procedures were to be postponed (at least one hour [in case FPG was 3-4 mmol/L or 13-18 mmol/L] or 1-7 days [in case FPG <3 mmol/L or >18 mmol/L]) in order to ensure that glucose levels at time of psychometric testing were in a range not believed to confound the test results.
The CES-D questionnaire was to be completed prior to the cognition questionnaires. The MMSE was to be administrated as first of the cognition questionnaires. If MMSE score was <24 at Visit 2, no further cognitive assessments were needed at Visit 2 and further visits.

[M] Clinically relevant abnormalities found at physical examination, vital signs or ECG that were not pre-existing prior to signing of informed consent (trial inclusion) were to be reported as adverse event. If such abnormalities already pre-exist prior trial inclusion they were considered as baseline conditions.

[N] The End of Treatment Visit (EOT) activities were performed when a patient discontinued trial medication treatment permanently. A follow-up visit took place 30 days after the EOT visit. Patients who discontinued trial drug prematurely were to be observed until trial end as if they were still receiving blinded trial medication, but no (safety) laboratory sampling (including pregnancy test), ECG or vital signs were required. If a patient who prematurely discontinued trial drug was not willing to return at the pre-defined regular visit schedule, the patient will be asked for an at minimum yearly telephone call and a telephone call at trial end (through the patient or alternative person designated by the patient) to document the occurrence of outcome events and vital status. If possible, also other AE's and concomitant therapy changes since last visit were to be recorded.
In some situations, it could have been necessary to interrupt trial medication temporarily. Patients were encouraged to re-start trial medication after an interruption if appropriate in the opinion of the investigator and if not contraindicated. In case the patient was re-instituted on trial medication, the preferred dosage for glimepiride/glimepiride placebo was the dose used before stopping treatment (unless hypoglycaemia was the reason to temporarily stop treatment). In case there was a need for further adjustments after this re-institution the guidance for treatment initiation was to be followed.

[O] Race of patients was collected because T2DM treatment results maybe race sensitive. Furthermore, the renal function was assessed using the MDRD formula. This formula considers the race as an adjustment factor; therefore, the race had to be known for accurate estimation.

Source: CSR 1218.74, Table 9.5.1:1

Study Endpoints

All the components for the primary and key secondary endpoints were centrally adjudicated by an independent CEC as discussed above. The CEC Charter appears to be acceptable.

The primary endpoint in CAROLINA was a cardiovascular safety endpoint and was time to the first occurrence of adjudicated composite 3-point MACE, where MACE was defined as CV death, non-fatal MI, or non-fatal stroke. The pre-specified definitions used for adjudication of CV events were established to conform to the 2010[6] version of the FDA Standardized Definitions for Cardiovascular Outcomes Trials.

Silent MI was an investigator reported endpoint and was a trigger term for central adjudication for CV events. Any investigator reported silent MI that was adjudicated and confirmed as being an MI by CEC was counted as MI.

The key secondary efficacy endpoints were:

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

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1) Time to the first occurrence of 3-point MACE or hospitalization for unstable angina pectoris (i.e., 4-point MACE);
2) Composite endpoint of treatment sustainability without >2% weight gain and without any moderate/severe hypoglycemic episodes between Week 16 and the Final Visit (i.e., maintenance phase of treatment period);
3) Composite endpoint of treatment sustainability without >2% gain between Week 16 and the Final Visit (i.e., maintenance phase of treatment period).

Treatment sustainability was defined as the proportion of subjects that maintain glycemic control (i.e., HbA1c ≤7%) at the end of study and are on study drug without requiring rescue therapy during the maintenance phase of treatment period.

For the purpose of efficacy assessment, moderate hypoglycemic episode was defined as documented symptomatic hypoglycemia (without need for external assistance) with plasma glucose ≤70 mg/dL. Severe hypoglycemic episode was defined as documented hypoglycemia requiring assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. See Section 8.3.2 for definitions of hypoglycemia for safety assessments.

All the primary endpoint and the first key secondary CV endpoints were based on centrally adjudicated data.

Reviewer's comment: *The clinical relevance of Applicant's secondary composite endpoint of 'treatment sustainability' that include weight gain and hypoglycemic episodes have not been established for the purpose of regulatory decision or labeling.*

Statistical Analysis Plan

For a detailed review of the statistical analysis plan for this Application, please refer to Dr. Bo Li's Statistical Review. The Trial Statistical Analysis Plan (TSAP) was finalized (March 16, 2018) before the database was locked.

The primary endpoint was time to first 3P-MACE, and the first key secondary endpoint was time to first 4P-MACE. For the analysis of the primary and first key secondary endpoint, a Cox proportional hazard regression model was used to compare the effect of linagliptin versus glimepiride. The second and third key secondary endpoint of treatment sustainability were analyzed using a Chi-square test.

The primary objective was to demonstrate non-inferiority of treatment with linagliptin compared to glimepiride for the time to 3P-MACE in subjects with T2DM. The non-inferiority margin was 1.3 in accordance with the FDA Diabetes Guidance of 2008.[7]

[7] FDA Guidance for Industry: Diabetes Mellitus, Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes, December 2008.

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A 5-step hierarchical testing procedure was done for the primary and key secondary endpoints to control multiplicity, where the hypothesis in the next step was to be tested after the null hypothesis was rejected with significance in the following order:

- **Step 1:** Non-inferiority in the time to first 3P-MACE;
- **Step 2:** Superiority with the time to first 3P-MACE;
- **Step 3:** Superiority with the first key secondary endpoint (i.e., time to first 4P-MACE);
- **Step 4:** Equality with the second key secondary endpoint (i.e., composite endpoint of treatment sustainability without >2% weight gain and without any moderate/severe hypoglycemic episodes during the maintenance phase of treatment period);
- **Step 5:** Equality with the third key secondary endpoint (i.e., composite endpoint of treatment sustainability without >2% weight gain during the maintenance phase of treatment period).

The analysis sets were:

- Treated Set (TS): All subjects treated with at least one dose of study drug; TS was the basis for all efficacy and safety analyses;
- Per protocol set (PPS): Subjects without important protocol deviation; PPS was mostly used for sensitivity analyses;
- On-treatment set (OS): The 30-days-treatment set included all randomized subjects with a minimum treatment duration of 30 days; used for sensitivity analyses.

The primary analysis was an intention-to-treat analysis (as randomized) on the TS. Subjects without occurrence of a primary endpoint event were considered censored at their last documented trial visit.

DMC was to perform two formal interim analyses of the primary endpoint for non-inferiority and superiority, in order to determine whether the trial should be terminated early. Study personnel outside of DMC (e.g., Applicant, investigators, the SC) remained blinded during the trial. The first interim analysis of the primary endpoint was to be done on a minimum number of 190 subjects with adjudicated primary CV outcome events with a minimum duration of 1.5 years after first subject was randomized. The second interim analysis was to be done after about 411 subjects had primary CV outcome events. To prevent an inflation of the significance level, O'Brien & Fleming's sequential design alpha-spending approach was used. At each interim analysis, the trial was to be stopped if superiority for linagliptin was seen with CV outcome, or if superiority for glimepiride was seen prematurely with regard to MACE, or if it seemed that the 1.3 risk margin may not be met.

Protocol Amendments

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The original protocol was issued on August 17, 2010. In total, there were 6 global amendments to the protocol and 8 local amendments for the main trial (1 amendment each in Canada, India, Japan, South Africa, and France, and 3 amendments in Germany).

Key important changes in each amendment are briefly summarized here.

Amendment 1 (July 21, 2011):

- Specified that clinically relevant abnormalities found at physical exam, vital signs, or ECG that were not pre-existing before informed consent were to be reported as AEs.
- To avoid unblinding CV outcome events, they were exempt from expedited and unblinded SUSAR reporting;
- Treatment naïve T2DM patients were to be offered first line therapy (metformin) before included in the trial unless they had contraindications for use. Subjects on glimepiride treatment were to start randomization phase at the same dose of glimepiride;
- Subjects were allowed to participate if they are on background SU and an alpha-glucosidase inhibitor or glinide and an alpha-glucosidase inhibitor. Background therapy was to remain stable during screening/run-in phase. Alpha-glucosidase inhibitors were allowed as rescue therapy;
- Following changes were made to inclusion/exclusion criteria:
  - Documented coronary artery disease was included as high-risk CV event for inclusion;
  - Clarified that peripheral occlusive arterial disease also included stenting;
  - Added BMI ≤45 kg/m^2 as inclusion criterion;
  - Blood pressure and LDL cholesterol added to CV risk factors;
  - Added stable anti-diabetic drug for at least 8 weeks before screening as inclusion criterion;
  - Exclusion of pre-planned coronary artery re-vascularization (PCI, CABG) within 6 months or any previous PCI ≤6 months or any previous CABG <3 months before study participation;
  - Exclusion of acute coronary syndrome ≤6 weeks and stroke or TIA ≤3 months;
- Exclude the short-term use (up to 2 weeks) of basal insulin from being counted as rescue.

Amendment 2 (March 6, 2012):

- Excluded silent MI from the primary endpoint and made it a tertiary CV endpoint; removal of stable angina as endpoint; added any transitions in albuminuria classes and changes from baseline in albuminuria as secondary diabetes-related endpoints; time to rescue and proportion of subjects with rescue intake added as tertiary endpoints; proportion of subjects with hypoglycemia and time to first hypoglycemia added; all-cause mortality removed as other endpoint;

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- Allowed to give short-acting insulin as rescue for up to 2 weeks in combination with the study drug;
- Concurrent treatment with systemic corticosteroids added as exclusion;
- Temporary discontinuation of study drug was allowed.

Amendment 3 (August 1, 2012):

- The time to first occurrence of any of the adjudicated components of 3P-MACE was defined as first key secondary endpoint instead of secondary endpoint, and the other key secondary endpoints moved down in the testing hierarchy;
- Clarified that if subjects did not experience a primary endpoint event, they were considered censored at their last documented trial visit; subjects were also censored at death if s/he died and had no primary outcome event;
- Added adjudication of pancreatic events and adjudication committee was set up;
- Hepatic injury was to be reported as SAE.

Amendment 4 (April 23, 2013):

- Pancreatitis was added as a reason to stop study drug;

Amendment 5 (September 14, 2015):

- Pancreatic cancer was defined as an adverse event of special interest (AESI);
- The follow-up period was changed from 7 to 30 days.

Amendment 6 (April 20, 2016):

- The testing hierarchy was changed after a request from SC. The primary endpoint was changed from 4P-MACE to 3P-MACE, and the 4P-MACE was defined as first key secondary endpoint. This change was based on emerging evidence that 3P-MACE was preferred for assessment of CV outcome by regulators and would be consistent with other outcome trials.[8] This required adjustment of the alpha level and the amendment clarified that a Bonferroni adjustment was to be applied. The SC clarified that there will be 2 interim analyses based on about 190 and 411 primary endpoint events;
- The first key secondary endpoint was to be tested hierarchically with a superiority hypothesis;
- Two additional visits added as the estimated study duration was increased to 432 weeks.

6.1.2. Study Results

[8] Marx N, MgGuire DK, Perkovic V, et al. Composite primary end points in cardiovascular outcomes trials involving type 2 diabetes patients: should unstable angina be included in the primary end point? Diabetes Care 2017;40(9):1144-1151.

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Compliance with Good Clinical Practices

The Applicant stated that the trial 1218.74 was conducted in accordance with the principles of the Declaration of Helsinki, the International Council for Harmonization (ICH) Good Clinical Practice (GCP) guidelines, and in accordance with applicable regulatory requirements. During 64 on-site audits by the Applicant, 10 sites were closed for non-compliance: sites #01126, #01117, #30004, #01021, #01115, #01025, #01226, #01014, #0103, and #01124. Data analysis of subjects from closed sites were pre-specified in the TSAP and are summarized in Table 5 below.

Table 5: Ten Closed Trial Sites Due to Non-Compliance

Closed site	Description	Included in analysis
#01126	Site enrolment was put on hold because suspected non-compliance was reported in another BI trial. On-site audits in May and June 2012 confirmed lack of PI supervision and identified concerns of data quality and integrity. As a result, the site was closed in May 2013.	No, but AE data listed.
#01117	Because of potential clinical trial misconduct, a for-cause audit was conducted in Aug 2012. The audit confirmed serious non-compliance with good clinical practice. The site was closed in Jun 2013.	Yes, but data excluded from PPS.
#30004	In Mar 2012, the site was informed about detected source data discrepancies. As the site failed to implement the requested corrective actions, the site was closed in Jan 2013.	Yes, but data excluded from PPS.
#01021	Because non-compliance and quality issues were detected, a for-cause audit was conducted in Aug 2013. The audit confirmed multiple instances of fraud and clinical trial misconduct. As a result, the site was closed in Nov 2013.	No, but AE data listed.
#01115	Monitoring visits in 2012 revealed lack of PI supervision and suspected trial misconduct. A for-cause audit confirmed significant non-compliances in Sep 2012. The site was closed in May 2013.	No, but AE data listed.
#01025	The sponsor was informed in Dec 2013 that the PI and his/her deputy were indicted for medicare fraud (unrelated to this trial). The site was closed in the same month, in Dec 2013.	Yes, all data included.
#01226	Monitoring revealed serious non-compliances in May 2012. Continuous non-compliance with good clinical practice was confirmed in a for-cause audit in Jul 2012 and a subsequent monitoring visit. The site was closed in Mar 2013.	Yes, but data excluded from PPS. AE data listed.
#01014	The PI failed to inform the sponsor of activities by the Drug Enforcement Administration (DEA); controlled substances had been prescribed illegitimately by the PI since Jul 2014. The contract breach led to site closure in May 2015.	Yes, data included.
#01038	Trial activity stopped because partnership between the site management organisation (New England Center for Clinical Research, NECCR) and PI ended; attempts to continue the activities failed. The contract breach led to site closure in Jun 2012.	Yes, data included.
#01124	Trial supplies (e.g. trial medication and records) were relocated without approval when business agreement between site management organisation (Iconic Clinical Trials, ICON) and PI ended. The contract breach led to site closure in Jun 2013.	Yes, data included.

Sites #01126 and #01117 also enrolled duplicate subjects.
Source: CSR 1218.74, Table 9.6:1

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Financial Disclosure

In accordance with 21 CFR 54.4, the Applicant submitted Form 3454 for Trial 1218.74, certifying that they had not entered into any financial arrangements with principal investigators/sub-investigators that could affect the outcome of the study as defined in 21 CFR 54.2.

There were 4 principal investigators and 2 sub-investigators who held financial interests requiring disclosure:

- (b) (6), a sub-investigator from (b) (6) received funding for a separate research project; his site enrolled (b) (6);
- (b) (6), a sub-investigator from (b) (6), received fees for lecturing and advising work; his site enrolled (b) (6);
- (b) (6), a principal investigator from (b) (6) received fees for consultation; the number of subjects randomized at this site was (b) (6);
- (b) (6), a principal investigator from (b) (6)., received a total sum of $119,807.50 for consulting and speaker fees, but the payment was not made to the representative but to the International Diabetes Center; his site enrolled (b) (6)
- (b) (6), a principal investigator from (b) (6) receive more than $25,000 per year for presentation and consulting services; his site enrolled (b) (6) into the trial;
- (b) (6), a principal investigator from (b) (6) stated that the study will be sponsored by Boehringer Ingelheim; his site enrolled (b) (6);
- (b) (6), sub-investigator in (b) (6), received $40,000 for speaking; (b) (6) (b) (6) was at same study site (b) (6).

Given that Trial 1218.74 was a large trial that randomized 6042 subjects, the number of subjects recruited from these sites are low and unlikely to have had a significant impact on the overall outcome of the trial. In addition, since trial 1218.74 was a randomized, double-blind study with primary and key secondary endpoints adjudicated by an independent external committee, potential for bias is minimized.

Patient Disposition

A total 10,606 subjects were screened, 6423 subjects started the placebo run-in period, and 6042 subjects were randomized. Subjects were randomized at 607 sites from 43 countries in Africa, Asia, Europe, North America, Latin America, Australia, and New Zealand. By region, the largest proportion of randomized subjects were from Europe (n=2826; 46.8% of randomized).

Of 6042 randomized subjects, 6033 subjects were treated with double-blind study drug. Nine subjects were not treated.

A slightly larger proportion of subjects prematurely discontinued the study drug in the

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glimepiride group (39.1%) compared to the linagliptin group (37.3%), mostly due to adverse events (linagliptin 15.1% versus glimepiride 17.4%).

Premature discontinuation from trial was not notably different between treatment groups (4.1% with linagliptin and 3.8% with glimepiride).

About 96% of subjects had completed MACE status or died, with similar percentage between treatment groups (95.9% with linagliptin versus 96.2% with glimepiride). Final vital status was obtained in 99.3% of subjects and was unknown in 23 subjects (0.8%) and 22 subjects (0.7%) in the linagliptin and glimepiride groups respectively.

Table 6 provides a summary of subject disposition in CAROLINA.

Table 6: Subject Disposition in CAROLINA

	Linagliptin	Glimepiride	Total
Randomized	**3028**	**3014**	**6042**
Not treated	5	4	9
Treated subjects (Treated Set)	**3023**	**3010**	**6033**
Did not prematurely discontinued from study drug	1896 (62.7%)	1832 (60.9%)	3728 (61.8%)
Prematurely discontinued the study drug	1127 (37.3%)	1178 (39.1%)	2305 (38.2%)
Adverse Events	457 (15.1%)	523 (17.4%)	980 (16.2%)
Refusal to continue the study drug (not due to AE)	309 (10.2%)	328 (10.9%)	637 (10.6%)
Lack of efficacy	61 (2.0%)	41 (1.4%)	102 (1.7%)
Non-compliance	46 (1.5%)	47 (1.6%)	93 (1.5%)
Lost-to-follow-up with study drug	24 (0.8%)	28 (0.9%)	52 (0.9%)
Other	230 (7.6%)	211 (7.0%)	441 (7.3%)
Completed MACE status or died	2899 (95.9%)	2895 (96.2%)	5794 (96.0%)
Prematurely discontinued from the trial	124 (4.1%)	115 (3.8%)	239 (4.0%)
Consent withdrawn	63 (2.1%)	49 (1.6%)	112 (1.9%)
Final vital status known	**3000 (99.2%)**	**2988 (99.3%)**	**5988 (99.3%)**
Alive	2692 (89.1%)	2652 (88.1%)	5344 (88.6%)
Dead	308 (10.2%)	336 (11.2%)	644 (10.7%)
Lost to follow-up	23 (0.8%)	22 (0.7%)	45 (0.7%)

MACE=major adverse cardiac events
Source: Adapted from CSR 1218.74, Table 10.1:2

Protocol Violations/Deviations

Important protocol violations were defined in the TSAP. In CAROLINA, 87 subjects had at least one important protocol violations.

Of these, 82 subjects had violations related to evaluation of primary/key secondary endpoints. The two most common reasons were that there was serious non-compliance potentially affecting primary endpoint (33 subjects; 17 subjects in linagliptin and 16 subjects in glimepiride), and glinide or SU were not stopped until 35 days after first study drug intake (28

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subjects; 14 subjects in each treatment group).

Five subjects had violations related to rights or safety where informed consent was obtained too late.

Also, 24 subjects enrolled at more than one site. This occurred at 10 sites, and 2 of those 10 sites were close due to non-compliance. Of 24 duplicate subjects, 19 were treated. The duplicate subjects were excluded from TS_D. Handling of duplicate subjects are summarized in Table 7.

Table 7: Handling of Subjects Enrolled at More than One Site in TS and TS_D

	Patient set	
	TS	TS_D
Total number of patients, N	6033	6014
Linagliptin group, N	3023	3014
Glimepiride group, N	3010	3000
Are data for patients with >1 trial site entry included?	Yes, for 19 patients.	No.
How were the data consolidated?	A unique patient number was assigned to the 19 patients with >1 entry and the AE episodes were consolidated for SAEs, trigger and adjudicated events[1]. Baseline information was used for the variables age, sex, region, and country.	-
Which analyses were performed?	Analyses on overall population (e.g. safety); subgroups for age, sex, and region; SAEs, including serious AESIs[2]	Analyses on overall population (other than SAEs and adjudicated events), diabetes-related endpoints (overall and subgroup), other subgroups

[1] All cardio/cerebrovascular trigger events for adjudication by the CEC, all pancreatic trigger events for adjudication by the CECP, and all oncological trigger events for assessment by the Oncology Assessment Committee.
[2] Please note this is a simplified explanation focusing on the rules for duplicate patients. A general rule for subgroup analyses of CV endpoints on the TS was that patients with missing baseline variables for a certain subgroup were excluded from the Cox regression analysis.
Source: CSR 1218.74, Table 9.8.2.4:1

Table of Demographic Characteristics

The baseline demographic characteristics are summarized in Table 8. About 60% of overall subjects were male, the majority were White (73%), and the mean age of the study population was 64.0 years. About 50% of subjects were <65 years old of age.

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Table 8: Baseline Demographic Characteristics - Treated Set

Demographic Parameter	Linagliptin (N=3023)	Glimepiride (N=3010)	Total (N=6033)
Gender, n (%)			
Male	1838 (60.8)	1781 (59.2)	3619 (60.0)
Female	1185 (39.2)	1229 (40.8)	2414 (40.0)
Age, mean (SD) years	63.9 (9.5)	64.2 (9.5)	64.0 (0.5)
Age Group, n (%)			
<65 years	1556 (51.5)	1502 (49.9)	3058 (50.7)
≥ 65 to <75 years	1057 (35.0)	1072 (35.6)	2129 (35.3)
≥ 75 to <85 years	405 (13.4)	430 (14.3)	835 (13.8)
≥ 85 years	5 (0.2)	6 (0.2)	11 (0.2)
Race, n (%)			
White	2217 (73.3)	2190 (72.8)	4407 (73.0)
Asian	531 (17.6)	530 (17.6)	1061 (17.6)
Black or African American	155 (5.1)	169 (5.6)	324 (5.4)
American Indian/Alaska Native	106 (3.5)	108 (3.6)	214 (3.5)
Hawaiian/Pacific Islander	5 (0.2)	3 (0.1)	8 (0.1)
Missing	9 (0.3)	10 (0.3)	19 (0.3)
Ethnicity, n (%)			
Not Hispanic or Latino	2495 (82.5)	2487 (82.6)	4982 (82.6)
Hispanic or Latino	519 (17.2)	513 (17.0)	1032 (17.1)
Missing	9 (0.3)	10 (0.3)	19 (0.3)
Smoking history			
Never smoked	1356 (44.9)	1442 (47.9)	2798 (46.4)
Ex-smoker	1051 (34.8)	977 (32.5)	2028 (33.6)
Currently smokes	607 (20.1)	581 (19.3)	1188 (19.7)
Weight (kg), mean (SD)	84.30 (17.97)	83.59 (17.89)	83.94 (17.93)
BMI (kg/m^2), mean (SD)	30.17 (5.2)	29.99 (5.1)	30.08 (5.1)

Source: CSR 1218.74, Table 15.1.4.1:1

Reviewer's Comment: *Overall, the baseline demographic characteristics appear to be balanced between treatment groups.*

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

The baseline disease characteristics for study population are summarized in Table 9. The mean baseline HbA1c was 7.15% and the mean FPG was 140 mg/dL in subjects without notable differences between treatment groups. Subjects had T2DM for about 7.6 years on average, and 40% of study population had diabetes ≤5 years. About 28.6% of subjects had microvascular disease and ~42% of subjects had macrovascular disease at baseline. The majority (90%) of study population had hypertension and ~32% of subjects had coronary artery disease. A very small proportion of subjects reported history of heart failure (4.5%). The majority (74%) of

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subjects had normal albuminuria, and about half (~58%) of subjects had mild renal impairment (eGFR 60 to <90 mL/min/1.73 m^2).

Table 9: Baseline Disease Characteristics of the Treated Set, N (%)

	Linagliptin (N=3023)	Glimepiride (N=3010)	Total (N=6033)
HbA1c (%), mean (SD)	**7.15 (0.56)**	**7.16 (0.58)**	**7.15 (0.57)**
HbA1c category, n (%)			
<6.5%	211 (7.0)	207 (6.9)	418 (6.9)
6.5 to <7%	1044 (34.5)	1021 (33.9)	2065 (34.2)
7 to <7.5%	966 (32.0)	984 (32.7)	1950 (32.3)
7.5 to <8%	512 (16.9)	502 (16.7)	1014 (16.8)
8 to ≤8.5%	234 (7.7)	226 (7.5)	460 (7.6)
>8.5%	46 (1.5)	60 (2.0)	106 (1.8)
T2D duration (years), mean (SD)	**7.7 (6.2)**	**7.5 (6.1)**	**7.6 (6.1)**
T2D duration category, n (%)			
≤5 years	1224 (40.5)	1212 (40.3)	2436 (40.4)
>5 to <10 years	848 (28.1)	861 (28.6)	1709 (28.3)
≥10 years	942 (31.2)	927 (30.8)	1869 (31.0)
FPG (mg/dL), mean (SD)	140.1 (30.7)	139.8 (30.4)	140.0 (30.5)
UACR (mg/g creatinine), mean (SD)	81.1 (368.4)	63.2 (274.3)	72.2 (325.0)
UACR category, n (%)			
<30 mg/g (normal)	2228 (73.7)	2234 (74.2)	4462 (74.0)
30 to ≤300 mg/g (microalbuminuria)	645 (21.3)	630 (20.9)	1275 (21.1)
>300 mg/g (macroalbuminuria)	134 (4.4)	124 (4.1)	258 (4.3)
eGFR (MDRD) (mL/min/1.73 m^2), mean (SD)	**76.5 (19.7)**	**77.0 (19.8)**	**76.8 (19.8)**
eGFR (MDRD) category, n (%)			
≥90 mL/min/1.73 m^2	693 (22.9)	722 (24.0)	1415 (23.5)
60 to <90 mL/min/1.73 m^2	1726 (57.1)	1740 (57.8)	3466 (57.5)
30 to <60 mL/min/1.73 m^2	576 (19.1)	525 (17.4)	1101 (18.2)
<30 mL/min/1.73 m^2	16 (0.5)	13 (0.4)	29 (0.5)
Microvascular disease[1], n (%)	847 (28.0)	881 (29.3)	1728 (28.6)
Diabetic retinopathy, n (%)	212 (7.0)	236 (7.8)	448 (7.4)
Diabetic nephropathy, n (%)	352 (11.6)	372 (12.4)	724 (12.0)
Diabetic neuropathy, n (%)	515 (17.0)	495 (16.4)	1010 (16.7)
Diabetic foot, n (%)	50 (1.7)	40 (1.3)	90 (1.5)
Macrovascular disease[2], n (%)	1272 (42.1)	1250 (41.5)	2522 (41.8)
Coronary artery disease, n (%)	968 (32.0)	937 (31.1)	1905 (31.6)
Peripheral arterial occlusive disease, n (%)	207 (6.8)	200 (6.6)	407 (6.7)
Cerebrovascular disease, n (%)	371 (12.3)	356 (11.8)	727 (12.1)
History of hypertension, n (%)	2720 (90.0)	2698 (89.6)	5418 (89.8)
History of heart failure, n (%)	122 (4.0)	19 (5.0)	271 (4.5)

FPG=fasting plasma glucose; MDRD=Modification of Diet in Renal Disease; n=number of subjects; SD=standard deviation; UACR=Urine Albumin Creatinine Ratio

[1]defined as diabetic retinopathy, nephropathy, and neuropathy.

[2]defined as coronary artery disease, peripheral artery occlusive disease, and cerebrovascular disease

Source: CSR 1218.74, modified from Tables 15.1.4.2:1, 15.1.4.2:2, 15.1.4.1:10

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As discussed in Inclusion Criteria in Section 6.1.1, Study Design, subjects with T2DM with high CV risk were enrolled in CAROLINA. Overall, about 35% of subjects had previous vascular disease (Risk category A), and very small portion of subjects (13.6%) had evidence of vascular related end-organ damage (Risk category B). Risk category D, which required at least 2 CV risk factors such as hypertension, current smoking, dyslipidemia, >10 years of T2DM, was most frequent (79.7% of subjects) but 37.2% of these subjects were only in risk category D.

Table 10: Subjects [N (%)] by Cardiovascular Risk Factors at Baseline – Treated Set

	Linagliptin (N=3023)	Glimepiride (N=3010)	Total (N=6033)
Risk A: Previous vascular disease	**1051 (34.8)**	**1038 (34.5)**	**2089 (34.6)**
Myocardial infarction	445 (14.7)	393 (13.1)	838 (13.9)
Coronary artery disease	523 (17.3)	511 (17.0)	1034 (17.1)
Previous PCI or CABG	454 (15.0)	455 (15.1)	909 (15.1)
Stroke	249 (8.2)	219 (7.3)	468 (7.8)
Peripheral arterial occlusive disease	163 (5.4)	169 (5.6)	332 (5.5)
Missing	9 (0.3)	10 (0.3)	19 (0.3)
Risk B: Evidence of vascular related end-organ damage	**400 (13.2)**	**418 (13.9)**	**818 (13.6)**
Moderate impaired renal function	265 (8.8)	253 (8.4)	518 (8.6)
Albumin: creatinine ratio ≥30 µg/mg	102 (3.4)	126 (4.2)	228 (3.8)
Proliferative retinopathy	91 (3.0)	91 (3.0)	182 (3.0)
Missing	9 (0.3)	10 (0.3)	19 (0.3)
Risk C: Age ≥70 years (N [%])	**1005 (33.2)**	**1025 (34.1)**	**2030 (33.6)**
Risk D: At least 2 of multiple CV risk factors (hypertension, current smoking, dyslipidemia, T2DM >10 years)	**2416 (79.9)**	**2394 (79.5)**	**4810 (79.7)**
Risk B without Risk A	**258 (8.5)**	**254 (8.4)**	**512 (8.5)**
Risk C without Risk A or B	**566 (18.7)**	**592 (19.7)**	**1158 (19.2)**
Only Risk D	**1132 (37.4)**	**1111 (36.9)**	**2243 (37.2)**
Risk missing	**16 (0.5)**	**15 (0.5)**	**31 (0.5)**

CAD=coronary artery disease; UACR=urine albumin creatinine ratio; eGFR=estimated glomerular filtration rate;
*Includes all subjects in risk category 2 that are not in risk category 1.
Source: CSR 1218.74; modified from Table 15.1.4.1:2

Reviewer's comment: *Overall, the baseline disease characteristics including cardiovascular risk factors were generally balanced without any notable differences between treatment groups.*

Most subjects (~83%) were taking anti-diabetic therapy at screening, and the majority were on monotherapy (~66%). The most frequent baseline antidiabetic therapy was metformin (~83%) followed by sulfonylurea (~28%). The most common monotherapy was metformin (58.7%) and the most common combination therapy was metformin with SU (21.5%). The types of background antidiabetic therapy at screening were similar treatment groups, as summarized in Table 11.

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Table 11: Summary of Background Antidiabetic Therapy at Screening in Treated Set

	Linagliptin (N=3023)	Glimepiride (N=3010)	Total (N=6033)
Subjects not on antidiabetic therapy	274 (9.1)	272 (9.0)	546 (9.1)
Antidiabetic therapies			
Metformin	2510 (83.0)	2510 (83.4)	5020 (83.2)
Sulfonylurea	869 (28.7)	846 (28.1)	1715 (28.4)
Glitazone	1 (0.0)	2 (0.1)	3 (0.0)
Alpha-glucosidase inhibitor	97 (3.2)	92 (3.1)	189 (3.1)
Glinide	28 (0.9)	38 (1.3)	6 (1.1)
DPP-4 inhibitor	4 (0.1)	2 (0.1)	6 (0.1)
Insulin	2 (0.1)	0	2 (0.0
Other	5 (0.2)	5 (0.2)	10 (0.2)
No information available	9 (0.3)	10 (0.3)	19 (0.3)
Monotherapy	1984 (65.6)	1982 (65.8)	3966 (65.7)
Metformin	1765 (58.4)	1774 (58.9)	3539 (58.7)
Sulfonlyurea	189 (6.3)	171 (5.7)	360 (6.0
Alpha-glucosidase inhibitor	18 (0.6)	29 (1.0)	47 (0.8)
Glinide	11 (0.4)	8 (0.3)	19 (0.3)
Other	1	0	1
Dual therapy	736 (24.3)	725 (24.1)	1461 (24.2)
Metformin +SU	650 (21.5)	645 (21.4)	1295 (21.5)
Metformin +alpha glucosidase inhibitor	50 (1.7)	34 (1.1)	84 (1.4)
Metformin +glinide	16 (0.5)	29 (1.0)	45 (0.7)
SU +alpha-glucosidase inhibitor	9 (0.3)	10 (0.3)	19 (0.3)
Triple therapy	20 (0.7)	21 (0.7)	41 (0.7)
Metformin + SU +alpha-glucosidase inhibitor	19 (0.6)	19 (0.6)	38 (0.6)
Metformin + SU + other	1	1	2
Metformin + Glinide + other	0	1	1

Source: CSR 1218.74, modified from Table 15.1.4.2:3

In terms of other important concomitant therapy at screening, the proportion of subjects taking antihypertensive therapy, lipid-lowering therapy, and aspirin were similar between treatment groups, as summarized in Table **12**. The majority (89%) of subjects were taking antihypertensives (mainly ACE inhibitors/ARBs, ~74%) and about 70% of enrolled subjects were also taking lipid-lowering drugs (mostly statins, ~65%). Acetylsalicylic acid (ASA) was used in about 42% of subjects.

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Table 12: Summary of Concomitant Therapies at Screening (excluding Antidiabetic Therapy) in Treated Set

	Linagliptin (N=3023)	Glimepiride (N=3010)	Total (N=6033)
Antihypertensives	**2662 (88.3)**	**2682 (89.4)**	**5344 (88.9)**
Beta-blockers	1193 (39.6)	1159 (38.6)	2352 (39.1)
Diuretics	1099 (36.5)	1137 (37.9)	2236 (37.2)
ACE inhibitors/ARBs	2228 (73.9)	2213 (73.8)	4441 (73.8)
ACE inhibitors	1330 (44.1)	1342 (44.7)	2672 (44.4)
ARBs	956 (31.7)	928 (30.9)	1884 (31.3)
Calcium channel blockers	891 (29.6)	885 (29.5)	1776 (29.5)
Other	224 (7.4)	236 (7.9)	40 (7.6)
Lipid lowering drugs	**2083 (69.1)**	**2134 (71.1)**	**4217 (70.1)**
Statins	1913 (63.5)	197 (66.2)	3900 (64.8)
Fibrates	187 (6.2)	173 (5.8)	360 (6.0)
Ezetimibe	112 (3.7)	95 (3.2)	207 (3.4)
Niacin	28 (0.9)	37 (1.2)	65 (1.1)
Other	162 (5.4)	170 (5.7)	332 (5.5)
ASA	**1410 (46.8)**	**1413 (47.1)**	**2823 (46.9)**
Antithrombotics excluding ASA	**509 (16.9)**	**473 (15.8)**	**982 (16.3)**
Platelet aggregation inhibitors excluding heparin & ASA	346 (11.5)	324 (10.8)	670 (11.1)
Clopidogrel	251 (8.3)	243 (8.1)	494 (8.2)
Other platelet aggregation inhibitors excluding heparin & ASA	81 (2.7)	73 (2.4)	154 (2.6)
Vitamin K antagonists	140 (4.6)	121 (4.0)	261 (4.3)
Warfarin	78 (2.6)	65 (2.2)	143 (2.4)

ACE=angiotensin-converting enzyme; ARB=angiotensin receptor blocker; ASA=acetylsalicylic acid;
*Patients can be counted in more than one category; all drugs starting before the day of first study drug are presented.
Source: CSR 1218.74, modified from Table 15.1.4.1:7

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment Compliance:

Treatment compliance was assessed at each study visit, and the frequency of compliant subjects slightly decreased over time but was within acceptable 80-120% and was similar between treatment groups. During Weeks 1-4, treatment compliance was 98.2% with linagliptin and 97.7% with glimepiride; by Weeks 289-304, treatment compliance was 96.2% with linagliptin and 97.2% with glimepiride.

Concomitant Medications and Rescue Medication

During the trial, newly initiated concomitant drugs such as aspirin, antihypertensives, lipid-lowering drugs, anti-coagulants were similar between treatment groups (data not shown here; see Table 15.1.4.1:8 in CSR). About 10% of overall subjects newly initiated ASA, 17.5% newly initiated anti-thrombotics excluding ASA, 4.6% newly initiated antihypertensives, and 9.3%

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newly initiated lipid lowering drugs during the trial.

As discussed in Section 6.1.1., subjects were allowed to take rescue treatments to maintain glucose levels based on HbA1c and FPG with either metformin, alpha-glucosidase inhibitors, pioglitazone, or basal insulin.

About 40% of subjects required initiation of anti-diabetic therapy after first study drug intake, which is summarized in Table 13. The two most commonly initiated new anti-diabetic therapies were insulin (~19%) and glitazone (12%). Although GLP-1 agonists were not allowed during the trial, 67 subjects (1.1%) initiated GLP-1 agonist after randomization.

Table 13: Newly Initiated Anti-Diabetic Therapy After Randomization

	Linagliptin (N=3023)	Glimepiride (N=3010)	Total (N=6033)
Number of newly onset of antidiabetic therapy			
None	1777 (59.0)	1808 (60.3)	3585 (59.6)
1	832 (27.6)	794 (26.5)	1626 (27.0)
2	305 (10.1)	278 (9.3)	583 (9.7)
3	74 (2.5)	93 (3.1)	17 (2.8)
4	23 (0.8)	18 (0.6)	41 (0.7)
5	2 (0.1)	5 (0.2)	7 (0.1)
6	1 (0.0)	2 (0.1)	3 (0.0)
7	0	2 (0.1)	2 (0.0)
Antidiabetic therapies			
Metformin	183 (6.1)	190 (6.3)	373 (6.2)
Sulfonylurea	213 (7.1)	192 (6.4)	405 (6.7)
Glitazone	389 (12.9)	341 (11.4)	730 (12.1)
Alpha-glucosidase inhibitor	159 (5.3)	161 (5.4)	320 (5.3)
Glinide	35 (1.2)	18 (0.6)	53 (0.9)
DPP-4 inhibitor	127 (4.2)	149 (5.0)	276 (4.6)
GLP-1 agonist	32 (1.1)	35 (1.2)	67 (1.1)
Insulin	561 (18.6)	577 (19.2)	1138 (18.9)
Other	73 (2.4)	89 (3.0)	162 (2.7)

Source: CSR 1218.74, modified from Table 15.1.4.2:4

Efficacy Results – Primary Endpoint

The primary efficacy analysis compared the time to the first occurrence of 3P-MACE which included CV death, non-fatal MI or non-fatal stroke from randomization until the trial end.

In total, 356 MACE events were observed in 3023 subjects (11.8%) in the linagliptin and 362 MACE events were observed 3010 subjects (12.0%) in the placebo group. The hazard ratio (HR) for the composite 3P-MACE resulted in a point estimate of 0.98 with the upper bound of

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95.47%[9] confidence interval less than 1.3, establishing non-inferiority (0.84, 1.14).

Table 14: Cox Regression Analysis of Time to First Occurrence of MACE (Treated Set)

	Linagliptin (N=3023)	Glimepiride (N=3010)
Subjects with MACE, n (%)	356 (11.8)	362 (12.0)
Cardiovascular death	129 (4.3)	125 (4.2)
Non-fatal myocardial infarction	141 (4.7)	138 (4.6)
Non-fatal stroke	86 (2.8)	101 (3.4)
Incidence rate of MACE per 1000 years	20.7	21.2
Hazard ratio of MACE versus glimepiride (95.47% CI)[1]	0.98 (0.84, 1.14)	
p-value for HR ≥1.3 (1-sided)	<0.0001	
p-value for HR ≥1.0 (1-sided)	0.3813	
p-value for HR =1.0 (2-sided)	0.7625	

MACE=major adverse cardiovascular event; CI=confidence interval; HR=hazard ratio
[1] Based on a Cox's proportional hazards model with factor treatment
[2] p-value derived from Wald's Chi-square test. HR ≥1.3 corresponds to non-inferiority and HR ≥1.0 to superiority analysis.
Source: CSR 1218.74, Table 11.1.1:1

As discussed in the Statistical Analysis Plan, based on the order of hierarchical hypothesis testing, after confirming non-inferiority, superiority of the primary endpoint (i.e., 3P-MACE) for linagliptin versus glimepiride was to be tested. Since the upper bound of 95.47% CI for HR of 3P-MACE was above 1.0 (p-value of 0.38), linagliptin was not shown to be superior to glimepiride for time to the first occurrence of 3P-MACE, and further hypothesis testing was stopped.

Reviewer's comment: *The results of CARMELINA showed that linagliptin did not unacceptably increase the rate of 3P-MACE compared to glimepiride and excluded a 30% excess increased CV risk in accordance with the FDA 2008 Guidance. The same data provided no evidence that linagliptin is superior to glimepiride in reducing the risk of 3P-MACE.*

The Kaplan-Meier estimates of the time to first occurrence of 3P-MACE for linagliptin compared to placebo is shown in **Figure 2** and shows that the curves appear to be very similar and overlap between two treatment groups.

[9] 95.7% confidence interval was used due to interim analyses that the Applicant had done.

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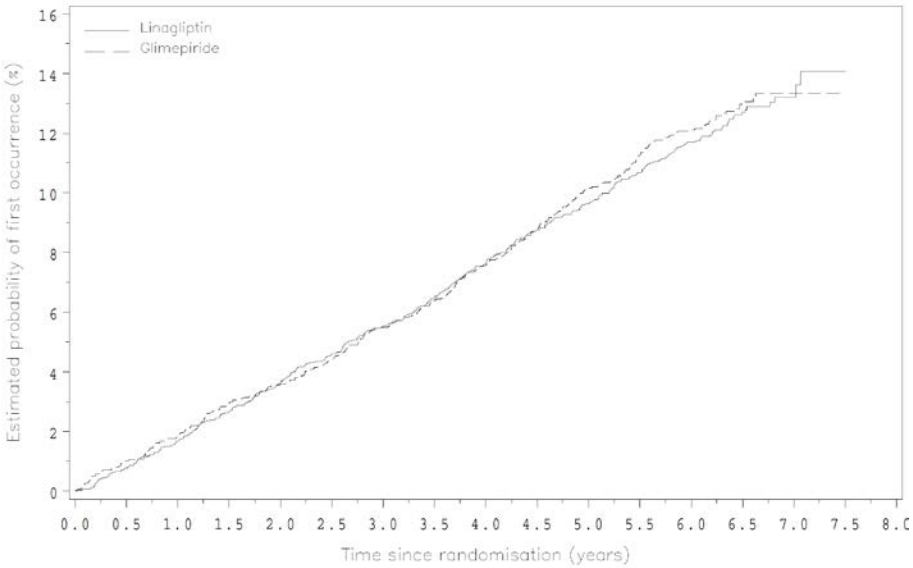
Figure 2: Kaplan-Meier Curve of Time to First Occurrence of 3P-MACE Over Time - TS



Source: CSR 1218.74, Figure 15.2.1.1:1

Sensitivity analyses using various on-treatment censoring approach and different population set appear to be consistent with the results of the primary analysis (data not shown; see Figure 11.1.1:2 in the CSR).

Individual Components of 3P-MACE:

Table 15 summarizes the individual components of 3P-MACE by evaluating both the time to event analyses for each component (i.e., time to first CV death, time to first non-fatal MI, time to first non-fatal stroke), which were pre-specified as tertiary endpoints in this trial. These endpoints are presented here since understanding the MACE components is necessary in an overall assessment of the primary endpoint.

Each individual component for 3P-MACE appear to be consistent with the primary analysis of composite MACE with point estimate of HR around 1. In addition, the 95% confidence intervals for the individual component events of MACE all included the null value of 1.

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Table 15: Analysis of Time to First Occurrence of Each 3P-MACE Component (Treated Set)

	Linagliptin (N=3023)	Glimepiride (N=3010)	Hazard ratio[1] (95% CI)
CV death, N (%)	169 (5.6)	168 (5.6)	1.00 (0.81, 1.24)
MI (fatal and non-fatal), N (%)	153 (5.1)	148 (4.9)	1.03 (0.82, 1.29)
Non-fatal MI, N (%)	145 (4.8)	142 (4.7)	1.01 (0.80, 1.28)
Stroke (fatal and non-fatal), N (%)	104 (3.4)	120 (4.0)	0.86 (0.66, 1.12)
Non-fatal stroke, N (%)	91 (3.0)	104 (3.5)	0.87 (0.66, 1.15)

MACE=major adverse cardiovascular event; CI=confidence interval; MI=myocardial infarction; N=number of subjects
[1] Based on a Cox's proportional hazards model with factor treatment
Source: CSR 1218.74, Table 11.1.2.3.2:1, 11.1.2.3.3:1, 11.1.2.3.4:1

Reviewer's comment: *Each component of MACE was consistent with the overall MACE analysis with the hazard ratio around 1. The point estimate of the HR (1.03) for myocardial infarction is slightly above 1, but the small imbalance is consistent with chance and cannot reasonably be interpreted as an actionable safety signal.*

Data Quality and Integrity

Dr. Bo Li, Statistical Reviewer, found the submitted data adequate to conduct a statistical evaluation. She did not note any notable data quality or analysis issues in the electronic submission that may impact the study results.

Efficacy Results – Secondary and other relevant endpoints

Key secondary endpoint related to CV safety (i.e., 4-point composite MACE and hospitalization for heart failure) are discussed in this section, as they are relevant endpoints for assessing the overall CV and glycemic benefit with linagliptin.

As discussed above, the trial failed to show superiority for time to first 3P-MACE with linagliptin compared to glimepiride (Step 2), and therefore aside from 4P-MACE, other key secondary endpoints will not be further discussed (i.e., composite endpoint of treatment sustainability with weight gain).

<u>4P-MACE:</u>

The first key secondary endpoint was the time to first 4P-MACE, which included the time to the first occurrence of CV death, non-fatal MI, non-fatal stroke, or hospitalization for unstable angina. In total, 398 subjects (13.2%) had a 4P-MACE event in the linagliptin group and 401 subjects (13.3%) in the glimepiride group. The HR for linagliptin compared to glimepiride was 0.99 (95% CI: 0.86, 1.14) and the 95% confidence interval included the null value of 1. The

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proportion of subjects with each event type that comprise 4P-MACE was generally balanced between the treatment groups. The results are summarized in Table 16.

Table 16: Time-to-event Analysis of 4P-MACE (Treated Set)

	Linagliptin (N=3023)	**Glimepiride (N=3010)**
Subjects with 4P-MACE, n (%)	398 (13.2)	401 (13.3)
Cardiovascular death	124 (4.1)	122 (4.1)
Non-fatal myocardial infarction	134 (4.4)	129 (4.3)
Non-fatal stroke	84 (2.8)	99 (3.3)
Hospitalization for unstable angina pectoris	56 (1.9)	53 (1.8)
Incidence rate of MACE per 1000 years	23.4	23.7
Hazard ratio of MACE versus glimepiride (95.47% CI)[1]	0.99 (0.86, 1.14)	
p-value for HR ≥1.3 (1-sided)	<0.0001	
p-value for HR ≥1.0 (1-sided)	0.4334	
p-value for HR =1.0 (2-sided)	0.8668	

4P-MACE=4 point major adverse cardiovascular event, which included cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, and hospitalization for unstable angina pectoris; CI=confidence interval; HR=hazard ratio
[1] Based on a Cox's proportional hazards model with factor treatment
[2] p-value derived from Wald's Chi-square test. HR ≥1.3 corresponds to non-inferiority and HR ≥1.0 to superiority analysis.
Source: CSR 1218.74, Table 11.1.1:1

Reviewer's comment: *Analysis of 4P-MACE was consistent with the 3P-MACE analysis with the hazard ratio around 1.*

All Cause Death:

Vital status was obtained for 99.3% of all subjects (Table 6). Analysis of time to all-cause mortality for linagliptin compared to glimepiride is shown in **Table 17**. Numerically smaller proportion of subjects in the linagliptin had all-cause death compared to the glimepiride group, 10.2% versus 11.2% respectively, and the HR for linagliptin compared to glimepiride was 0.91 (95% CI: 0.78, 1.06).

Table 17: Time-to-event Analysis of All-Cause Mortality (Treated Set)

	Linagliptin (N=3023)	**Glimepiride (N=3010)**
Subjects with all-cause mortality, n (%)	308 (10.2)	336 (11.2)
Incidence rate per 1000 years at risk	16.8	18.4
Hazard ratio* of all-cause mortality vs glimepiride (95% CI)	0.91 (0.78, 1.06)	

*Hazard ratio and CI derived from Cox's proportional hazards model with factor treatment
Source: CSR 1218.7, Table 11.1.2.3.6:1

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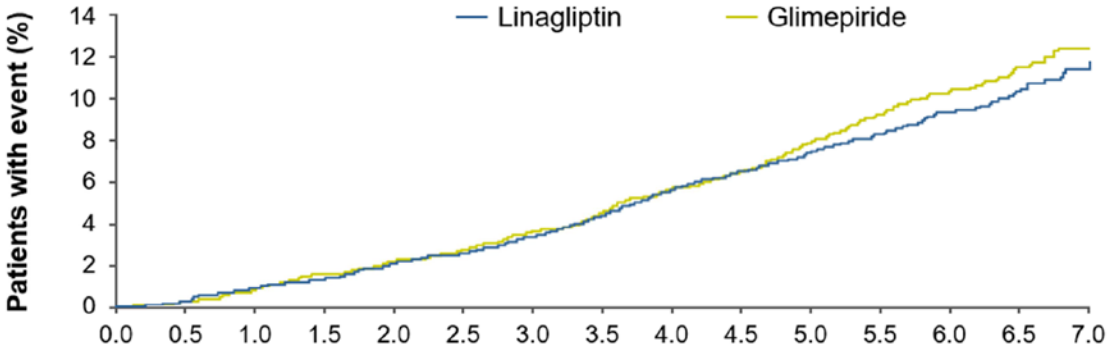
The Kaplan-Meier estimation of time to all-cause death for linagliptin compared to glimepiride show that the curves are similar between treatment groups for 5 years, although curves start to separate after 5 years not favoring glimepiride and the reason for this is unclear (Figure 3).

Figure 3: Kaplan-Meier Estimation of Time to All-Cause Mortality Over Time (TS)



No. of patients															
Linagliptin (N)	3023	3009	2991	2976	2951	2934	2908	2873	2838	2808	2780	2706	2045	1164	236
Glimepiride (N)	3010	2999	2982	2955	2937	2916	2885	2857	2823	2797	2751	2656	2068	1144	237

Source: CSR 1218.74, Figure 11.1.2.3.6:1

Heart Failure:

Heart failure requiring hospitalization was defined as an event that met the following criteria:

- Hospitalization, defined as admission to an inpatient unit or a visit to an emergency department leading to at least 12 hours of stay, AND
- Clinical manifestations of heart failure including at least one new or worsening dyspnea, orthopnea, paroxysmal nocturnal dyspnea, edema, pulmonary basilar crackles, jugular venous distension, new or worsening third heart sound or gallop rhythm, or radiological evidence of worsening heart failure, AND
- additional/increased therapy (e.g., initiation or up-titration of diuretic or intravenous therapy, initiation of mechanical or surgical intervention).

Reviewer's comment: *The pre-defined definition for hospitalization for heart failure was the same as that used in SAVOR (CVOT for saxagliptin) where an increase in the risk of hospitalization for heart failure was seen with saxagliptin (3.5%) compared to placebo (2.8%) with the HR of 1.27 (95% CI: 1.07, 1.51), which along with data from EXAMINE (CVOT for alogliptin) led to class labeling of heart failure in DPP-4 inhibitors.*

Hospitalization for heart failure, hospitalization for or death from heart failure, and hospitalization for heart failure or CV death were tertiary CV endpoints and were adjudicated.

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In CAROLINA, a numerically larger proportion of subjects in the linagliptin group compared to glimepiride group experienced hospitalization for heart failure, 3.7% (112/3023) versus 3.1% (92/3010) respectively, but the difference was not statistically significant (HR 1.21 [95% CI: 0.92, 1.59]).

In addition, when hospitalization for heart failure (HHF) was combined as a composite endpoint for possible competing risk of HHF and other events like CV death or all-cause death, the HR becomes closer to 1 (**Table 18**). All 95% confidence intervals in **Table 18** include null value of 1.

Table 18: Time-to-Event Analyses for Heart Failure-related Endpoints (Treated Set)

	Linagliptin (N=3023)			Glimepiride (N=3010)			Hazard ratio vs glimepiride (95% CI)[1]
	N	%	IR	N	%	IR	
HHF	112	3.7	6.4	92	3.1	5.3	1.21 (0.92, 1.59)
HHF or death from heart failure	115	3.8	6.6	97	3.2	5.6	1.18 (0.90, 1.54)
HHF or CV death	236	7.8	13.4	234	7.8	13.4	1.00 (0.84, 1.20)
HHF or All-cause death	372	12.3	21.1	392	13.0	22.3	0.94 (0.82, 1.09)

HHF=hospitalization for heart failure; N=number of subjects; IR=Incidence rate per 1000 years at risk
[1]Hazard ratio and CI derived from Cox's proportional hazards model with factor treatment.
Source: CSR 1218.74, Table 11.1.2.3.5:1, Table 11.1.2.3.6:1

Reviewer's comment: *The HR for hospitalization for heart failure with linagliptin compared to glimepiride (1.21 [95% CI: 0.92, 1.59]) was very similar to that seen with saxagliptin compared to placebo in SAVOR (1.27 [95% CI: 1.07, 1.51]), but the 95% confidence interval include null value of 1 with linagliptin.*

The Kaplan-Meier curve of adjudicated hospitalization for heart failure showed that there was some early divergence of curves during the early part of the trial, but the slight separation of curves appears around 2.5 years (**Figure 4**).

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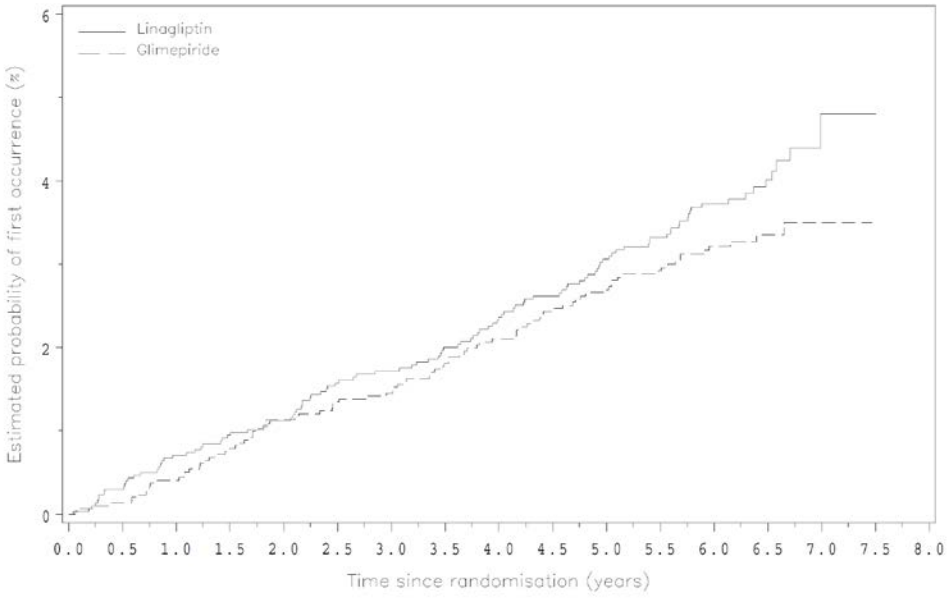
Figure 4: Kaplan-Meier Curve of Adjudicated Hospitalization for Heart Failure Over Time



Source: CSR 1218.74, Figure 15.2.3.:1

Reviewer's comment: (b) (4)

In order to determine whether differences between study populations between CARMELINA and CAROLINA may explain different results for the risk of heart failure with linagliptin, baseline characteristics for study populations are compared in Table 19. Due to different inclusion/exclusion criteria for each study which differently defined CV risk, CAROLINA enrolled slightly younger subjects with better glycemic control as reflected by baseline HbA1c and subjects in CAROLINA did not have T2DM as long as subjects in CARMELINA (average duration of 7.15 versus 14.75 years). Subjects in CAROLINA also had better renal function and had a lower proportion of subjects with history of heart failure.

Table 19: Comparison of Demographics and Baseline Characteristics between CARMELINA and CAROLINA

Demographic Parameter	CARMELINA (N=6,979)	CAROLINA (N=6,033)
Duration of exposure, years	1.9	4.9
Age, mean years (SD)	65.9 (9.1)	64.0 (9.5)
Female, %	37%	40%
BMI (kg/m^2), mean	31.3	30.1
HbA1c (%), mean (SD)	8.0 (1.02)	7.15 (0.57)
T2D duration (years), mean (SD)	14.75 (9.45)	7.6 (6.1)
≤5 years	1074 (15.4%)	2436 (40.4%)
>5 to <10 years	1384 (19.8%)	1709 (38.3%)
≥10 years	4521 (64.8%)	1869 (31.0%)
Diabetic retinopathy	1938 (27.8%)	448 (7.4%)
Diabetic nephropathy	4393 (62.9%)	724 (12.0%)
Diabetic neuropathy	2851 (40.9%)	1010 (16.7%)
eGFR (MDRD) (mL/min/1.73 m^2), mean (SD)	54.6 (25.0)	76.8 (19.8)
eGFR (MDRD) category, n (%)		
≥90 mL/min/1.73 m^2	728 (10.4%)	1415 (23.5%)
60 to <90 mL/min/1.73 m^2	1903 (27.3%)	3466 (57.5%)
30 to <60 mL/min/1.73 m^2	3286 (47.1%)	1101 (18.2%)
<30 mL/min/1.73 m^2	1062 (15.2%)	29 (0.5%)
UACR category, n (%)		
<30 mg/g (normal)	1392 (19.9%)	4462 (74.0%)
30 to ≤300 mg/g (microalbuminuria)	2894 (41.5%)	1275 (21.1%)
>300 mg/g (macroalbuminuria)	2690 (38.5%)	258 (4.3%)
History of hypertension, n (%)	6349 (91.0)	5418 (89.8%)
History of heart failure, n (%)	1873 (26.8%)	271 (4.5%)
Prior myocardial infarction, n (%)	1873 (26.8%)	838 (13.9%)

Reviewer's comment: *CAROLINA appears to have enrolled healthier study population compared to CARMELINA. However, it is unclear if this led to different heart failure results.*

In CARMELINA, which had higher proportion of subjects with a history of heart failure (26.8%), the HR for HHF with linagliptin compared to placebo was observed to be similar in those with or without history of heart failure. Similarly, in saxagliptin's CVOT trial SAVOR, HHF showed an imbalance not favoring saxagliptin group compared to placebo regardless of prior history of heart failure. Subjects in CAROLINA had a very small proportion of subjects with history of heart failure (4.5%).

The higher proportion of subjects with a history of heart failure in study population is consistent with the higher incidences of hospitalization for heart failure observed in CARMELINA, where 6% (27.7/1000 patient-years) of linagliptin group and 6.5% (30.4/1000 patient-years) of placebo group were hospitalized for heart failure compared to those observed in CAROLINA, where 3.7%

(6.4/1000 patient-years) of linagliptin group and 3.1% (5.3/1000 patient-years) of glimepiride group were hospitalized for heart failure.

Based on Dr. Li's analysis, the observed difference in the number of subjects with HHF (112 with linagliptin versus 92 with glimepiride) appear to be largely attributed to subjects who experienced HHF before CV death (24 with linagliptin versus 12 with glimepiride) and subjects who experienced HHF with or after MI (30 with linagliptin versus 15 with glimepiride) (**Table 20**). Therefore, an analysis of a composite CV event rather than individual elements was used to measure the risk for HHF, since death and MI are competing outcomes. In order to assess this, Dr. Li conducted additional post-hoc analysis looking at time to first event of 1) composite endpoint of confirmed HHF or MACE, and 2) composite endpoint of confirmed HHF or death from any cause. **Table 21** summarizes the results of her analyses and showed that there was no meaningful difference between linagliptin and glimepiride when HHF was combined with either MACE or death due to any cause.

Table 20: Timing of MACE and death among subjects who experienced HHF

	Linagliptin (N=3023)	**Glimepiride (N=3010)**
HHF before MACE	30	23
CV death	**24**	**12**
MI	4	7
Stroke	2	4
HHF with/after MACE	38	20
With/after MI	**30**	**15**
With/after stroke	7	5
HHF before non-CV death	2	7
Only HHF	42	42
Total subjects with HHF	112	92

HHF=hospitalization for heart failure; MACE=major adverse cardiovascular event; CI=confidence interval; HR=hazard ratio
Source: Dr. Bo Li's Analysis

Table 21: HHF with MACE or death among subjects who experienced HHF

	Linagliptin (N=3023)	**Glimepiride (N=3010)**	**Hazard ratio (95% CI)**
HHF or MACE	400 (13.2%)	411 (13.7%)	0.97 (0.84, 1.11)
HHF or death from any cause	372 (12.3%)	392 (13.0%)	0.94 (0.82, 1.09)

HHF=hospitalization for heart failure; MACE=major adverse cardiovascular event; CI=confidence interval;
Source: Dr. Bo Li's Analysis

Reviewer's comment: *Analysis of HHF that accounted for competing outcomes such as MACE or death due to any cause showed no evidence of an increased CV risk associated with linagliptin, which is reassuring.*

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Insulin and pioglitazone were allowed as rescue therapy for optimizing glycemic control during the trial. However, both insulin and pioglitazone use have been associated with heart failure. During the trial, numerically larger proportion of subjects in the linagliptin group initiated glitazone (12.9% versus 11.4% in glimepiride) whereas numerically larger proportion of subjects in the glimepiride group newly initiated insulin (19.2% versus 18.6% in linagliptin).

Dr. Li conducted additional analyses to see the incidence of HHF in those who initiated insulin and/or glitazone during the trial (**Table 22**). There was numerically larger proportion of subjects with HHF in linagliptin group due to new use of glitazone (2.5% with linagliptin versus 2.0% with glimepiride), new use of insulin (8.4% with linagliptin and 7.1% with glimepiride), and when new insulin or glitazone users were combined (5.9% with linagliptin versus 5.2% with glimepiride).

Table 22: HHF with Insulin and Glitazone Use

	Linagliptin N=3023	**Glimepiride N=3010**
Subjects with HHH	112	92
New insulin user	558	576
Incidence of HHH in subjects with new insulin use	47/558 (8.4%)	41/576 (7.1%)
New glitazone user	399	353
Incidence of HHF in subjects with new glitazone use	10/399 (2.5%)	7/353 (2.0%)
New insulin or glitazone user	861	834
Incidence of HHF in subjects with new insulin or glitazone use	51/861 (5.9%)	43/834 (5.2%)

HHF=hospitalization for heart failure
Source: Dr. Bo Li's Analysis

Reviewer's comment: *Although there was numerically larger proportion of subjects with HHF in linagliptin due to insulin and/or glitazone use, the overall imbalance is small (5.9% with linagliptin versus 5.2% with glimepiride).*

HbA1c:

The adjusted mean change from baseline in HbA1c over time was compared between treatment groups using an MMRM model in the Treated Set (Observed Cases).

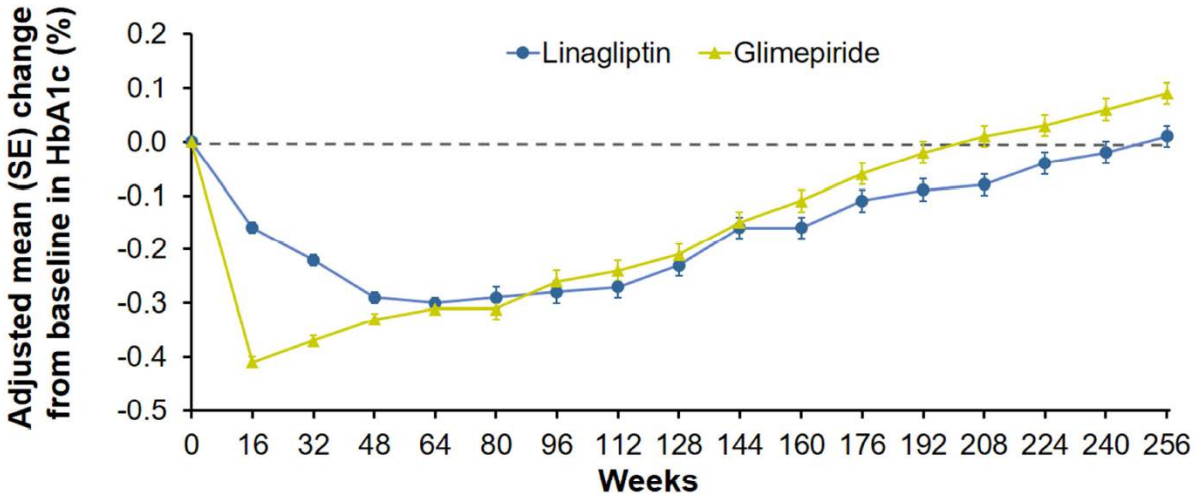
Table 23: Change from Baseline in HbA1c (%) in Treated Set (Observed Cases) – MMRM model

	Linagliptin (N=2951)	Glimepiride (N=2949)
Baseline mean (SE)	7.15 (0.01)	7.16 (0.01)
Final Visit, mean (SE)	7.21 (0.02)	7.30 (0.02)
Adjusted mean change in HbA1c from baseline (SE)	0.06 (0.02)	0.15 (0.02)
Treatment difference (linagliptin vs placebo) (SE) [95% CI]	-0.09 (0.03) [-0.15, -0.03]	

Source: CSR, Table 11.1.2.4.1:1

Change in HbA1c over time showed that there was a larger HbA1c decline in the glimepiride group by the end of Week 16, but over time the HbA1c converged. However, subjects in the linagliptin group initiated rescue therapy earlier than subjects in the glimepiride group (not shown; Figure 15.2.6.19.1:1) and had numerically larger number of subjects who initiated rescue therapy for glycemic control, 49.3% in the linagliptin group compared to 47.1% in the glimepiride group.

Figure 5: Change from Baseline in HbA1c (%) Over Time, MMRM Analysis (TS_D; Observed Cases-All)



Source: CSR, Figure 11.1.2.4.1:1

Reviewer's comment: *Although linagliptin appear to have better glycemic control over time, subjects in the linagliptin group initiated rescue therapy earlier than glimepiride and numerically larger proportion of subjects in the linagliptin group required rescue therapy for additional glycemic control.*

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Body Weight:

At baseline, the average weight was similar between treatment groups, 84.31 kg in the linagliptin group and 83.58 kg in the glimepiride group. At the Final Visit of the study, subjects in the linagliptin lost 2.12 kg (SE 0.11) and subjects in the glimepiride group lost 0.52 kg (SE 0.11).

Dose/Dose Response

Not applicable as only one dose of linagliptin is approved at 5 mg daily.

Durability of Response

Not applicable.

Persistence of Effect

Not applicable.

Additional Analyses Conducted on the Individual Trial

Additional analyses conducted for CAROLINA were discussed in each relevant section throughout results section.

7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

This section is not applicable as only data from one trial, CAROLINA, was submitted in this supplement, and a comprehensive review of efficacy from CAROLINA was presented in Section 6.1.2, Study Results. Therefore, Subsections 7.1.1 through 7.1.5 are deleted from this review.

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Postmarket Setting

CAROLINA evaluated MACE in diabetic patients who are at increased cardiovascular risk. Although about 18% of the overall population was from U.S., the study population was reasonably representative of patients with T2DM and of the U.S. population.

The trial population included a limited number of subjects ≥75 years of age (14%) and enrolled predominantly White subjects (73%), and it is unclear if efficacy and safety findings from this

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trial can be extrapolated to all racial groups or to patients who are 75 years or older. However, we have no reason to believe that the cardiovascular safety seen with linagliptin in CAROLINA (i.e., no increased risk for MACE) would not be applicable to the overall type 2 diabetic patients.

7.2.2. Other Relevant Benefits

As there will be no change in doing schedule or route of administration with this application, this section is not relevant.

7.3. Integrated Assessment of Effectiveness

The Applicant conducted CAROLINA to assess cardiovascular safety of linagliptin compared to glimepiride. CAROLINA was a large, prospective, multicenter, randomized, double-blind, active-controlled trial conducted in 6042 subjects with T2DM at high risk of CV event. Subjects were randomized to either linagliptin (N=3023) or glimepiride (N=3010), both as add-on to standard of care. After a mean follow-up of 6 years and 718 composite primary endpoint of CV death, nonfatal MI or nonfatal stroke, the analysis for the composite MACE endpoint showed a HR point estimate of 0.98 with the upper bound of the CI less than 1.3 (95% CI: 0.84, 1.14). Therefore, compared to glimepiride, linagliptin ruled out a 30% excess CV risk captured using 3 component MACE in accordance with the recommendation from the 2008 Guidance for Industry: Diabetes Mellitus- Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes. Results of sensitivity analyses were consistent with the primary analysis. In addition, each component of the primary MACE was consistent with the primary analysis of composite MACE with point estimate of around 1 and did not raise any clinical or statistical concern. However, linagliptin therapy did not demonstrate MACE benefit compared to glimepiride.

8. Review of Safety

8.1. Safety Review Approach

Endpoints related to cardiovascular outcomes, cerebrovascular, and diabetes-related outcomes were efficacy endpoints in CAROLINA, some of which are discussed in Section 6.1.2, Study Results. Therefore, safety endpoints for CAROLINA included adverse events (AEs), hypoglycemic events, AEs of special interest (i.e., hypersensitivity reactions, skin lesions, hepatic events, renal events, pancreatitis, and pancreatic cancer), other specific AEs (malignancies, immunological reactions, angioedema, arthralgia, bullous conditions), and changes from baseline in electrocardiograms (ECG) and laboratory values, vital signs, and physical examinations.

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8.2. Review of the Safety Database

8.2.1. Overall Exposure

Safety data were analyzed on TS which included all subjects who took at least one dose of study drug or on TS_D which was TS excluding subjects enrolled at more than one site (see Table 7).

The median exposure to study drug was about 5.8 years in both treatment group, and at about 5.8 years (304 weeks), 55.5% of subjects in the linagliptin group and 54% of subjects in the glimepiride group were still taking the study drug. The median time subjects stayed in the study was 6.25 years in both treatment groups. See Table 24 for summary of study drug exposure and follow-up time.

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Table 24: Exposure to Study Drug and Time in Study* - Treated Set

	Linagliptin (N=3023)	Glimepiride (N=3010)
Exposure (years)		
Mean (SD)	4.90 (2.19)	4.7 (2.17)
Median	5.86	5.86
Subjects on treatment, N (%)		
≥16 weeks	2895 (95.8)	2875 (95.5)
≥64 weeks	2649 (87.6)	2654 (88.2)
≥160 weeks	2342 (77.5)	2303 (76.5)
≥208 weeks (~4 years)	2196 (72.6)	2167 (72.0)
≥256 weeks (~5 years)	2089 (69.1)	2035 (67.6)
≥304 weeks (~6 years)	1679 (55.5)	1626 (54.0)
≥352 weeks	375 (12.4)	341 (11.3)
≥368 weeks	90 (3.0)	77 (2.6)
≥400 weeks	0	0
Time in study (years)		
Mean (SD)	6.07 (1.12)	6.05 (1.12)
Median	6.25	6.25
Subjects in study under observation, N (%)		
≥16 weeks	3016 (99.8)	3005 (99.8)
≥64 weeks	2983 (98.7)	2970 (98.7)
≥160 weeks	2903 (96.0)	2884 (95.8)
≥256 weeks (~5 years)	2789 (92.3)	2762 (91.8)
≥304 weeks (~6 years)	2474 (81.8)	2405 (79.9)
≥352 weeks	657 (21.7)	618 (20.5)
≥368 weeks	218 (7.2)	215 (7.1)
≥400 weeks	0	0

*Exposure=date of last study drug intake or date of death minus date of first study drug intake+1;
Time in study=date of last contact or date of death minus date of randomization+1
Source: CSR 1218.74, Table 15.1.5:1, 15.1.5:2

Glimepiride doses during the trial are displayed in Figure 6. The overall mean dose of glimepiride that subjects received during the study was 2.9 mg (SD 1.1 mg). By the end of titration phase (i.e., Week 16), 49% of subjects were receiving 4 mg dose while 21% of subjects were still receiving 1 mg dose, 16% of subjects were receiving 2 mg dose, and 14% of subjects were receiving 3 mg dose, with a mean dose of 2.9 mg (SD 1.2 mg) and median dose of 3 mg. By Week 32, the mean dose of glimepiride was 3 mg (SD 1.2 mg), the median dose was 4 mg, and 52% of subjects were receiving 4 mg dose. The proportion of subjects taking 4 mg dose slightly increased over time.

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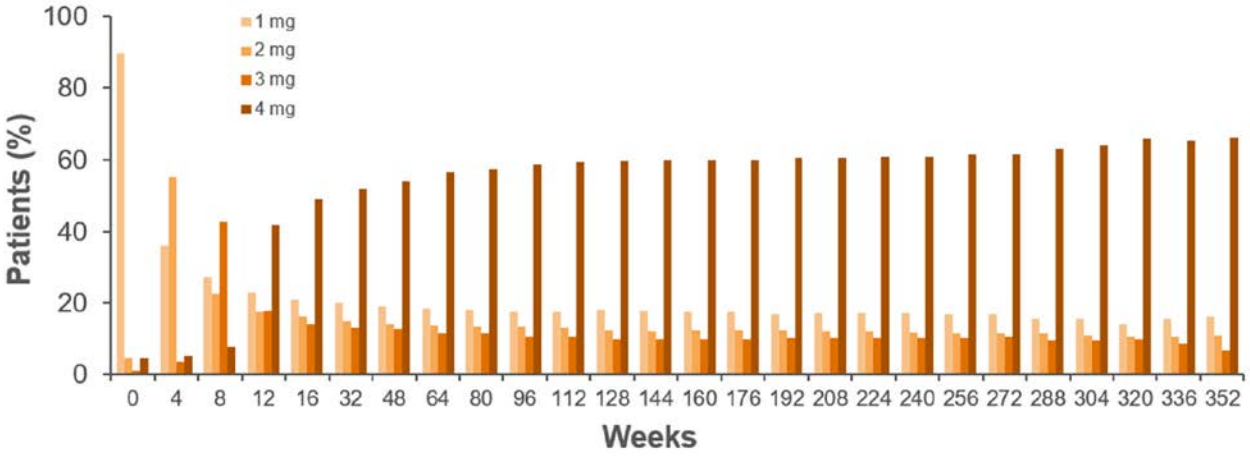
Figure 6: Glimepiride Dose Over Time - TS_D



Source: CSR 1218.74, Figure 10.5:1

8.2.2. Relevant characteristics of the safety population:

Since this supplement only included a single trial, demographics (Table 8) and clinical characteristics (**Table 9**) of the safety population were discussed in Section 6.1.2 Study Results.

8.2.3. Adequacy of the safety database:

CAROLINA was an event-driven trial. The trial continued until sufficient MACE events were observed to have adequate power to establish MACE safety by demonstrating non-inferiority of linagliptin compared to glimepiride for a 3-point MACE composite endpoint in a patient population of subjects with type 2 diabetes and high baseline CV risk. Baseline demographic characteristics of the overall study population showed that non-Whites, Hispanics, and elderly subjects ≥75 years of age were underrepresented in this trial (Table 8), presenting some limitations for generalizing safety findings across races and ages that may receive linagliptin in the clinical setting.

CAROLINA was a global trial and subjects from U.S. represented about 18% of total patients randomized.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

OSI was asked to inspect five investigational sites and Dr. Cynthia Kleppinger from OSI did not identify any findings that may impact the validity of submitted data in this application (see Section 4.1, Office of Scientific Investigation).

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Ten sites were closed due to non-compliance with Good Clinical Practice, but adverse events from these sites were listed.

8.3.2. Categorization of Adverse Events

Adverse events (AEs) were considered treatment-emergent AEs if the onset was after the first dose of study drug and occurred up to a period of 7 days after the last permanent study drug dose. AEs during the on-treatment period were shown by randomized treatment group. AEs that occurred before first intake of randomized study drug were assigned to 'screening/run-in'. AEs occurring after last drug intake +7 days were assigned to 'post-treatment'. AEs reported after trial completion +1 day were assigned to 'post-study'.

As discussed in Section 6.1.2, there were 19 treated subjects who were duplicates. For analysis of AE data in the treated set excluding these 19 subjects, TS_D was used which included 3014 subjects treated with linagliptin and 3000 subjects treated with glimepiride. For analysis of AE data including all subjects, TS was used which included 3023 subjects treated with linagliptin and 3010 subjects treated with glimepiride.

AEs were generally analyzed on TS/TS_D for on-treatment period, but some specific AEs were also analyzed up to the trial end (e.g., malignancies, pancreatic cancer, and pancreatic events) or up to 30 days after treatment stop (e.g., renal and hepatic events).

AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 21.0. AE were based on the number of subjects with AEs (not on the number of AEs).

Adverse events of special interest (AESIs) included the following:

- Hypersensitivity reactions such as angioedema, angioedema-like events, and anaphylaxis;
- Skin lesions such as exfoliative rash, skin necrosis, or bullous dermatitis;
- Hepatic events such as AST and/or ALT ≥3x ULN combined with elevated total bilirubin >2x ULN, hepatitis, hepatic injury, jaundice, and potential Hy's law cases[10];
- Renal events such as acute renal failure;
- Pancreatitis;
- Pancreatic cancer.

These AESIs were searched with groups of coded PTs such as Standardized MedDRA Queries (SMQs) (See corresponding section in 8.5 for search terms used for specific AE of interest). Pancreatic events were adjudicated.

[10] Potential Hy's Law case: AST and/or ALT >3x ULN and total bilirubin >2x ULN and ALP <2x ULN.

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Unless otherwise noted, AESIs were analyzed on the TS_D for the on-treatment period (TS_D+7). For skin lesions, hepatic events, renal events, and pancreatitis, AEs were also analyzed with events occurring up to 30 days after first study drug intake (TS_D+30). For pancreatitis and pancreatic cancer, analysis period was from the first trial intake until individual trial end (TS_D).

In addition, the following AEs were further specified as AE of interest: malignancies, immunological reactions, angioedema, arthralgia, and bullous condition.

Cancers of new histology and exacerbation of existing cancer were to be reported as an SAE regardless of the duration between discontinuation of the drug and the occurrence of the cancer.

All symptomatic hypoglycemic events, all asymptomatic hypoglycemic events with glucose <54 mg/dL, and any asymptomatic hypoglycemic events that were considered as AEs were to be recorded by the investigator as AEs. Hypoglycemic events were to be documented by the investigator according to the following criteria:

- Asymptomatic hypoglycemia: Event not accompanied by typical symptoms of hypoglycemia but with plasma glucose ≤70 mg/dL;
- Confirmed symptomatic hypoglycemia: Event accompanied by typical symptoms of hypoglycemia and with plasma glucose 54-70 mg/dL, inclusive;
- Confirmed symptomatic hypoglycemia with glucose <54 mg/dL: Event accompanied by typical symptoms of hypoglycemia without need for external assistance;
- Severe hypoglycemic episode: Event requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative measures regardless of glucose level; documented severe hypoglycemia.

8.3.3. Routine Clinical Tests

The frequency of all clinical tests can be seen in the Flow Chart (Table 4).

Routine laboratory parameters included clinical chemistry, hematology, and urinalysis. Laboratory analyses were done by a central laboratory. Local pregnancy testing was done in females of child-bearing potential. 12-lead ECGs were centrally analyzed and additional ECGs could be collected by the investigator for safety reasons.

Renal function was assessed by the central lab based on the plasma creatinine value measured, and the glomerular filtration rate was estimated according to the MDRD formula.

All subjects were provided with HBGM equipment and supplies for use at home. Weekly finger stick glucose measurements were recommended, and additional measurements to be done if

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necessary or having hypo- or hyperglycemic symptoms.

8.4. Safety Results

8.4.1. Deaths

All-cause deaths were discussed in Section 6.1.2, Study Results, as it was one of tertiary CV outcome endpoints and related to MACE (**Table 17**); an imbalance between treatment groups was not observed. In addition, all deaths in the randomized subjects were sent for adjudication by cardiovascular CEC to identify potential cardiovascular deaths.

The frequency and overall incidence rates of AEs leading to death were reported for 199 subjects (6.6%) with linagliptin and 204 subjects (6.8%) with glimepiride. Review of reported PT terms did not show a notable difference between treatment groups for a particular System Organ Class or Preferred Terms (data not shown; see Table 15.3.1.1:10).

8.4.2. Serious Adverse Events

The proportion of subjects with serious adverse events (SAEs) was similar between treatment groups: 46.4% of subjects (127.5/1000 patient-years) in the linagliptin group compared to 48.1% of subjects (135/1000 patient-years) in the glimepiride group.

SAEs with a frequency of ≥1% in either linagliptin or glimepiride groups at PT level are summarized in Table 25. The most frequently reported SAEs were pneumonia (2.7% linagliptin, 2.8% glimepiride), unstable angina (1.8% linagliptin, 2.2% glimepiride), myocardial infarction (1.6% linagliptin, 2.1% glimepiride), and osteoarthritis (1.6% linagliptin, 2.1% glimepiride). Hypoglycemia events are discussed in Section 8.5.1.

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Table 25: Serious Adverse Events with a Frequency of ≥1% in Any Treatment Group at PT Level, Sorted SOC (TS+7)

MedDRA System Organ Class (SOC) MedDRA Preferred Term	Linagliptin		Glimepiride	
Number of subjects	3023		3010	
	N (%)	IR	N (%)	IR
Subjects with SAEs	1403 (46.4)	127.5	1448 (48.1)	135.0
Infections and Infestations SOC	275 (9.1)	19.3	30 (10.2)	21.9
Pneumonia	83 (2.7)	5.6	83 (2.8)	5.7
Urinary tract infection	30 (1.0)	2.0	31 (1.0)	2.1
Neoplasms benign, malignant, and unspecified (inclusive cysts and polyps) SOC	251 (8.3)	17.6	273 (9.1)	19.3
Basal cell carcinoma	39 (1.3)	2.6	33 (1.1)	2.3
Prostate cancer	28 (0.9)	1.9	29 (1.0)	2.0
Nervous system disorders SOC	227 (7.5)	15.8	253 (8.4)	17.9
Cerebrovascular accident	51 (1.7)	3.5	61 (2.0)	4.2
Transient ischemic attack	31 (1.0)	2.1	33 (1.1)	2.3
Eye disorders SOC	94 (3.1)	6.4	96 (3.2)	6.7
Glaucoma	29 (1.0)	2.0	31 (1.0)	2.1
Cardiac disorders SOC	396 (13.1)	28.4	429 (14.3)	31.3
Cardiac failure	58 (1.9)	3.9	53 (1.8)	3.6
Angina unstable	54 (1.8)	3.7	65 (2.2)	4.5
Acute myocardial infarction	52 (1.7)	3.5	56 (1.9)	3.8
Myocardial infarction	49 (1.6)	3.3	64 (2.1)	4.4
Coronary artery disease	43 (1.3)	2.9	42 (1.4)	2.9
Atrial fibrillation	39 (1.3)	2.6	48 (1.6)	3.3
Angina pectoris	37 (1.2)	2.5	40 (1.3)	2.7
Cardiac failure congestive	37 (1.2)	2.5	45 (1.5)	3.1
Musculoskeletal and connective tissue disorders SOC	153 (5.1)	10.6	162 (5.4)	11.4
Osteoarthritis	49 (1.6)	3.3	63 (2.1)	4.3
Renal and urinary disorders SOC	132 (4.4)	9.1	116 (3.9)	8.0
Acute kidney injury	47 (1.)	3.2	41 (1.4)	2.8
General disorders and administration site conditions SOC	128 (4.2)	8.8	120 (4.0)	8.3
Chest pain	50 (1.7)	3.4	52 (1.7)	3.6
Injury, poisoning and procedural complications SOC	153 (5.1)	10.6	162 (5.4)	11.3
Fall	31 (1.0)	2.1	44 (1.5)	3.0
Metabolism and nutrition disorders SOC	54 (1.8)	3.7	72 (2.4)	4.9
Hypoglycemia	3 (0.1)	0.2	29 (1.0)	2.0

IR=incidence rate per 1000 patient-years
Source: CSR 1218.74, Table 15.3.1.1:9

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

In CAROLINA, subjects who discontinued study drug for any reason (including an AE) can subsequently re-start the study drug, unless for reasons of safety. The summary of AEs leading to discontinuation of study drug therefore will include subjects with AEs leading to a temporary discontinuation.

The proportion of subjects with AEs leading to study drug discontinuation was similar between treatment groups: 414 subjects (13.7%) in the linagliptin group and 448 subjects (14.9%) in the placebo group had at least one AE leading to study drug discontinuation.

Review of AEs leading to study drug discontinuation by SOC and PT did not show any notable imbalance between treatment groups, as all PTs except hypoglycemia were <1% and difference between treatment group was ≤0.1% for all AEs (not shown here; Table 15.3.1.1:8 in CSR). Hypoglycemia was the only AE leading to discontinuation of study drug in more than 1% of subjects in either treatment group and was lower in the linagliptin group (0.2%) compared to glimepiride group (2.7%). Hypoglycemic events are discussed in Section 8.5.1.

There were 8 cases of pancreatitis with linagliptin and 5 with glimepiride, 4 cases of acute pancreatitis with linagliptin and 6 with glimepiride, 2 cases of chronic pancreatitis with linagliptin and 1 with glimepiride that led to study drug discontinuation. Also, 25 subjects (0.8%) in the linagliptin versus 11 subjects (0.4%) in the glimepiride group had increased lipase and 14 subjects (0.5%) in the linagliptin versus 9 subjects (0.3%) in the glimepiride group had increase amylase that led to study drug discontinuation. Pancreatitis is further discussed in Section 8.5.6.

8.4.4. Significant Adverse Events

Adverse events that are considered significant and of interest are discussed in Section 8.5, Analysis of Submission-Specific Safety Issue. Categorization of AEs, definitions, and search strategy used by the Applicant were described in Section 8.3.2, Categorization of Adverse Events.

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

All TEAEs reported in at least 5% of subjects in either treatment group are summarized in Table 26.

AEs with treatment difference of at least 1% and occurred at higher incidence in the linagliptin group compared to glimepiride were diarrhea (12.2% linagliptin, 11.0% glimepiride) and lipase increased (7.0% linagliptin, 5.2% glimepiride).

Reference ID: 4581802

Table 26: Summary of Treatment-Emergent Adverse Events with Frequency of ≥5% Preferred Term in Either Treatment Group, by SOC and PT (TS_D+7)

MedDRA System Organ Class (SOC)/ MedDRA Preferred Term (PT)	Linagliptin (N=3014)		Glimepiride (N=3000)	
	N (%)	IR	N (%)	IR
Subjects with any AEs	2821 (93.6)	1218.6	2855 (95.2)	1445.2
Infections and infestations SOC	1802 (59.8)	235.5	1838 (61.3)	242.0
Nasopharyngitis	530 (17.6)	41.4	518 (17.3)	40.6
Urinary tract infection	336 (11.1)	24.4	335 (11.2)	24.4
Bronchitis	328 (10.9)	23.9	346 (11.5)	25.5
Upper respiratory tract infection	317 (10.5)	23.3	322 (10.7)	23.9
Influenza	269 (8.9)	19.4	249 (8.3)	18.0
Gastroenteritis	162 (5.4)	11.3	148 (4.9)	10.4
Pneumonia	160 (5.3)	11.1	177 (5.9)	12.4
Metabolism and nutrition disorders SOC	1217 (40.4)	116.2	1738 (57.9)	216.6
Hypoglycemia	301 (10.0)	21.9	1080 (36.0)	103.4
Hyperglycemia	428 (14.2)	32.1	489 (16.3)	37.3
Musculoskeletal & connective tissue disorders SOC	1335 (44.3)	136.4	1371 (45.7)	142.3
Back pain	391 (13.0)	29.0	374 (12.5)	27.8
Arthralgia	316 (10.5)	22.9	316 (10.5)	23.2
Osteoarthritis	264 (8.8)	18.9	306 (10.2)	22.3
Pain in extremity	218 (7.2)	15.5	224 (7.5)	16.1
Musculoskeletal pain	152 (5.0)	10.6	182 (6.1)	12.9
Gastrointestinal disorders SOC	1308 (43.4)	129.5	1254 (41.8)	122.3
Diarrhea	368 (12.2)	27.1	329 (11.0)	24.2
Constipation	199 (6.6)	14.0	175 (5.8)	12.3
Nausea	158 (5.2)	11.0	169 (5.6)	12.0
Nervous system disorders SOC	1073 (35.6)	96.4	1228 (40.9)	118.3
Dizziness	292 (9.7)	21.2	361 (12.0)	27.1
Headache	269 (8.9)	19.5	297 (9.9)	21.9
General disorders & administration site conditions SOC	777 (25.8)	63.5	879 (29.3)	75.4
Chest pain	188 (6.2)	13.2	173 (5.8)	12.3
Peripheral edema	152 (5.0)	10.6	195 (6.5)	13.9
Fatigue	118 (3.9)	8.2	163 (5.4)	11.6
Investigations SOC	859 (28.5)	71.9	792 (26.4)	65.6
Lipase increased	211 (7.0)	14.9	155 (5.2)	10.9
Cardiac disorders SOC	778 (25.8)	62.3	787 (26.2)	63.8
Atrial fibrillation	143 (4.7)	9.9	163 (5.4)	11.4
Injury, poisoning and procedural complications SOC	767 (25.4)	61.8	780 (26.0)	64.0
Fall	174 (5.8)	12.1	205 (6.8)	14.5
Respiratory, thoracic and mediastinal disorders SOC	745 (24.7)	60.1	766 (25.5)	63.3
Cough	286 (9.5)	20.6	292 (9.7)	21.3

Vascular disorders SOC	699 (23.2)	56.0	744 (24.8)	61.5
Hypertension	439 (14.6)	33.0	458 (15.3)	35.2
Eye disorders SOC	512 (17.0)	38.9	509 (17.0)	39.2
Cataract	234 (7.8)	16.6	220 (7.3)	15.7
Blood and lymphatic system disorders SOC	336 (11.1)	24.3	310 (10.3)	22.4
Anemia	218 (7.2)	15.4	190 (6.3)	13.4

N=number of subjects; IR=incidence rate/1000 patient-years.
Source: CSR 1218.74, Table 15.3.1.1:3

8.4.6. Laboratory Findings

Standard laboratory tests (i.e., hematology, clinical chemistry, and urinalysis) including lipase were measured for all subjects throughout the study as shown in Table 4.

Laboratory data related to hepatic function are summarized in Section 8.5.4, and laboratory data related to renal function are summarized in Section 8.5.5.

There were no notable findings from baseline to last values on treatment between treatment groups, or transitions relative to reference range, except lipase and amylase. See Section 8.5.6, Pancreatitis, for discussion of lipase and amylase levels.

8.4.7. Vital Signs

Systolic and diastolic blood pressure and pulse rate were measured after 5 minutes at rest in the seated position frequently during the trial as shown in Table 4.

There were no clinically meaningful differences between treatment groups, or any marked changes from baseline for systolic blood pressure, or pulse rate (data not summarized here; see Tables 15.3.3:1 in CSR). As discussed previously, the clinical trial allowed changes in hypertension therapies to optimize blood pressure control per standard of care.

8.4.8. Electrocardiograms (ECGs)

12-lead ECGs were recorded at times shown in Table 4; after baseline, Week 16, ECGs were obtained every 48 weeks during the maintenance phase of the trial. The ECGs were centrally analyzed.

Clinically meaningful abnormal ECG findings were reported as AEs and are summarized in Table 27. Numerically more subjects with linagliptin compared to glimepiride reported 'electrocardiogram abnormal', 8 subjects versus 3 subjects. Also, 12 subjects in the glimepiride group reported 'electrocardiogram QT prolonged' compared to 7 subjects in the linagliptin group. The clinical significance of this finding is unclear, as ECGs were checked for pathological results by the investigator and any ECG abnormalities were carefully monitored. None of the

'electrocardiogram QT prolonged' led to discontinuation.

Table 27: Frequency (N [%]) of ECG-related Adverse Events by Preferred Term (TS_D+7)

Preferred Term	Linagliptin (N=3023)	Glimepiride (N=3010)
Electrocardiogram T wave inversion	12 (0.4)	13 (0.4)
Electrocardiogram abnormal	8 (0.3)	3 (0.1)
Electrocardiogram ST segment depression	8 (0.3)	6 (0.2)
Electrocardiogram QT prolonged	7 (0.2)	12 (0.4)
Electrocardiogram T wave amplitude decreased	6 (0.2)	6 (0.2)
Electrocardiogram T wave abnormal	2 (0.1)	0
Electrocardiogram change	2 (0.1)	3 (0.1)
Electrocardiogram ambulatory abnormal	1	0
Electrocardiogram QRS complex prolonged	1	0
Electrocardiogram ST segment abnormal	1	0
Electrocardiogram T wave biphasic	1	1
Electrocardiogram Q wave abnormal	1	0
Electrocardiogram repolarization abnormality	1	1
Electrocardiogram PR prolongation	1	2
QRS axis abnormal	1	0
ECG signs of myocardial ischemia	1	0
Electrocardiogram QT shortened	0	1
Electrocardiogram ST-T segment abnormal	0	1

Source: CSR 1218.74, adapted from Table 15.3.1.1:3

8.4.9. QT

Not applicable, abnormal ECG findings are summarized in Section 8.4.8, Electrocardiograms.

8.4.10. Immunogenicity

Not applicable.

8.5. Analysis of Submission-Specific Safety Issues

AESI are discussed in this section. The Applicant also analyzed immunological reactions using Immune system disorders SOC (System Organ Class), which is not further discussed in this review as there was no notable findings and some of the events captured were already discussed in hypersensitivity reactions.

8.5.1. Hypoglycemia

Reference ID: 4581802

Categorization of hypoglycemic events reported as an AE by an investigator was discussed in Section 8.3.2.

Table 28 provides a summary of hypoglycemic events reported as AEs in CAROLINA, both any hypoglycemic events reported as an AE by the investigator (i.e., investigator-defined hypoglycemic AEs) but also asymptomatic hypoglycemia that was not reported as AEs but based on low plasma glucose levels. The frequency of subjects having hypoglycemic AEs was lower in the linagliptin group compared to glimepiride across all types of hypoglycemic events. Overall, about 15% of subjects in the linagliptin group and 47% of subjects in the glimepiride group experienced hypoglycemia.

Hypoglycemia with plasma glucose level <54 mg/dL and severe hypoglycemia are considered clinically important by the American Diabetes Association[11]. The proportion of subjects having hypoglycemic events with plasma glucose <54 mg/dL or severe hypoglycemia was less with linagliptin (3.2%) compared to glimepiride (17.7%). Similarly, less subjects in the linagliptin group compared to glimepiride had severe hypoglycemic episodes, 0.3% compared to 2.2%.

Table 28: Frequency [N (%)] of Subjects with Hypoglycemic AEs and Characteristics of Hypoglycemia by Treatment in CAROLINA – Treated Set

	Linagliptin (N=3014)	Glimepiride (N=3000)
Subjects with any hypoglycemia	456 (15.1)	1407 (46.9)
PG ≤70 mg/dL or severe#	394 (13.1)	1328 (44.3)
PG <54 mg/dL or severe#	96 (3.2)	530 (17.7)
Subjects with symptomatic* hypoglycemic AEs	258 (8.6)	1023 (34.1)
PG ≤70 mg/dL or severe#	195 (6.5)	927 (30.9)
PG <54 mg/dL or severe#	56 (1.9)	443 (14.8)
Minimum glucose level <54 mg/dL (worst episode) of hypoglycemia	93 (3.1)	514 (17.1)
Severe# hypoglycemia	10 (0.3)	65 (2.2)
Number of hypoglycemia episodes per subject		
≥1	456 (15.1)	1407 (46.9)
≥3	159 (5.3)	841 (28.0)
≥5	99 (3.3)	634 (21.1)
≥10	47 (1.6)	367 (12.2)

PG=plasma glucose; AEs=adverse events
*Symptomatic hypoglycemia=hypoglycemia adverse event reported with typical symptoms of hypoglycemia
#Severe hypoglycemia=hypoglycemia requiring assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions.
Source: CSR, Table 15.3.1.4.1:7

Reviewer's comment: *The increased incidence of hypoglycemic events with glimepiride*

[11] American Diabetes Association. Standards of Medical Care in Diabetes – 2017. Diabetes Care 2017;40(S1):S48-56R.

Reference ID: 4581802

compared to linagliptin is not surprising given that hypoglycemia is a known adverse effect of sulfonylureas such as glimepiride, whereas DPP-4 inhibitors such as linagliptin has comparatively lower risk of hypoglycemia.

Subgroup Analyses of Hypoglycemia:

Post-hoc subgroup analyses of hypoglycemia were conducted. Consistent with analyses of hypoglycemia in the overall population, the incidence of hypoglycemia was lower in the linagliptin group compared to glimepiride across subgroups of age, race, gender, renal function, prior use of SU or glinide, or use of rescue therapy during the trial. The lower frequency of hypoglycemia in the linagliptin group compared to glimepiride was seen in the overall hypoglycemia as well as in clinically relevant hypoglycemic events such as hypoglycemia with plasma glucose <54 mg/dL and/or severe hypoglycemia across subgroups with similar imbalance favoring linagliptin.

Subgroup analyses of interest such as age, eGFR, prior use of SU or glinide, and rescue therapy are presented in Table 29. There was a trend for more hypoglycemic events in both treatment groups with worsening renal function, but the imbalance continued to be lower in the linagliptin group compared to glimepiride group within each eGFR category.

Interestingly, the incidence of hypoglycemia AEs was similarly low with linagliptin compared to glimepiride in subjects regardless of whether subjects needed rescue therapy during the trial, and the proportion of hypoglycemia was similar with or without rescue therapy. Thus it appears that rescue therapy did not have much impact on the incidence of hypoglycemia.

Reference ID: 4581802

Table 29: Frequency [N (%)] of Subjects with Hypoglycemia by Subgroup – TS_D+7

Subgroup variable	Subgroup category	Hypoglycemia	Linagliptin (N=3014)	Glimepiride (N=3000)
Age	<70	N	2009	1975
		Subjects with hypoglycemia	307 (15.3)	922 (46.7)
		PG <54 mg/dL or severe	62 (3.1)	344 (17.4)
		Severe	5 (0.2)	32 (1.6)
	70 to <80	N	911	922
		Subjects with hypoglycemia	132 (14.5)	438 (47.5)
		PG <54 mg/dL or severe	31 (3.4)	166 (18.0)
		Severe	5 (0.5)	24 (2.6)
	≥80	N	94	103
		Subjects with hypoglycemia	17 (18.1)	47 (45.6)
		PG <54 mg/dL or severe	3 (3.2)	20 (19.4)
		Severe	0	9 (8.7)
eGFR	≥90	N	693	722
		Subjects with hypoglycemia	98 (14.1)	304 (42.1)
		PG <54 mg/dL or severe	21 (3.0)	113 (15.7)
		Severe	3 (0.4)	8 (1.1)
	60 to <90	N	1726	1740
		Subjects with hypoglycemia	250 (14.5)	820 (47.1)
		PG <54 mg/dL or severe	49 (2.8)	301 (17.3)
		Severe	5 (0.3)	30 (1.7)
	30 to <60	N	576	525
		Subjects with hypoglycemia	105 (18.2)	276 (52.6)
		PG <54 mg/dL or severe	26 (4.5)	113 (21.5)
		Severe	2 (0.3)	25 (4.8)
	<30	N	16	13
		Subjects with hypoglycemia	3 (18.8)	7 (53.8)
		PG <54 mg/dL or severe	0	3 (23.1)
		Severe	0	2 (15.4)
Prior use of SU or glinide	Yes	N	897	884
		Subjects with hypoglycemia	172 (19.2)	398 (45.0)
		PG <54 mg/dL or severe	45 (5.0)	153 (17.3)
		Severe	5 (0.6)	21 (2.4)
	No	N	2117	2116
		Subjects with hypoglycemia	284 (13.4)	1009 (47.7)
		PG <54 mg/dL or severe	51 (2.4)	377 (17.8)
		Severe	5 (0.2)	44 (2.1)
Use of rescue therapy	Yes	N	1487	1414
		Subjects with hypoglycemia	230 (15.5)	681 (48.2)
		PG <54 mg/dL or severe	47 (3.2)	240 (17.0)
		Severe	5 (0.3)	31 (2.2)

Reference ID: 4581802

	No	N	1527	1586
		Subjects with hypoglycemia	226 (14.8)	726 (45.8)
		PG <54 mg/dL or severe	49 (3.2)	290 (18.3)
		Severe	5 (0.3)	34 (2.1)

N=number of subjects; PG=plasma glucose
Source: CSR Table 15.3.1.4.2:2, 15.3.1.4.2:9, 15.3.1.4.2:10, 15.3.1.4.2:12

8.5.2. Hypersensitivity Reactions

Hypersensitivity reactions were searched based on the narrow SMQ 'hypersensitivity'.

Hypersensitivity reactions were reported in 13.4% (404/3014) subjects in the linagliptin group and 11.5% (346/3000) of subjects in the glimepiride group. The most frequently reported PTs in hypersensitivity reactions were eczema (2.8% linagliptin, 2.6% glimepiride), rash (2.5% linagliptin, 2.2% glimepiride), and allergic rhinitis (1.8% linagliptin, 1.2% glimepiride). Overall, there was no imbalance between treatment groups for any particular hypersensitivity AE terms (data not shown; see Table 15.3.1.3.1:1 in CSR).

Subjects with serious hypersensitivity reactions by treatment group are summarized in Table 30.

Reference ID: 4581802

Table 30: Frequency [N (%)] and Incidence Rate of Subjects with Serious Hypersensitivity Reactions by Treatment and Preferred Term (TS+7)

MedDRA Preferred Term	Linagliptin		Glimepiride	
	N (%)	IR	N (%)	IR
Total subjects	3023	14853.5	3010	14706.2
Total subjects with serious hypersensitivity reactions	26 (0.9)	1.8	32 (1.1)	2.2
Circulatory collapse	4 (0.1)	0.3	6 (0.2)	0.4
Shock	3 (0.1)	0.2	2 (0.1)	0.1
Drug eruption	3 (0.1)	0.2	0	
Eczema	2 (0.1)	0.1	2 (0.1)	0.1
Hypersensitivity	2 (0.1)	0.1	1	0.1
Angioedema	2 (0.1)	0.1	4 (0.1)	0.3
Bronchospasm	2 (0.1)	0.1	3 (0.1)	0.2
Exfoliative dermatitis	2 (0.1)	0.1	0	
Rash	2 (0.1)	0.1	4 (0.1)	0.3
Urticaria	1	0.1	1	0.1
Anaphylactic reaction	1	0.1	1	0.1
Bullous dermatitis	1	0.1	0	
Eye swelling	1	0.1	0	
Lip swelling	0		1	0.1
Swollen tongue	0		1	0.1
Tongue edema	0		1	0.1
Dermatitis	0		2 (0.1)	0.1
Allergic dermatitis	0		1	0.1
Swelling face	0		1	0.1
Allergy to vaccine	0		1	0.1
Rash macular	0		1	0.1
Rash vesicular	0		1	0.1

N=number of subjects; IR=incidence rate/1000 patient-years
Source: CSR 1218.74, Appendix 16.1.13.1, Table 8.3.1.3

One case of anaphylactic reaction with linagliptin (subject # (b) (6) was temporally related to Augmentin that the subject started due to cholecystitis and not likely related to linagliptin. Three fatal shock cases in the linagliptin group (b) (6)) were unrelated to hypersensitivity reaction.

Two cases of serious exfoliative dermatitis with linagliptin are further discussed in Section 8.5.3, skin lesions.

Reference ID: 4581802

There were 3 cases of serious drug eruption with linagliptin compared to none with glimepiride, and these 3 cases are summarized here:

- Subject (b) (6) (South Africa): A 73-year old man with diabetes with multiple prior history including psoriasis was randomized to linagliptin. On Day 1334, he felt ill and has serious event of **drug eruption**. There was no other concurrent event. Evaluation showed skin lesions covered >30% of body surface area and were disseminated both arms and legs without mucosal involvement. Four days later, he experienced chills and the rash spread all over his body without pruritus, and he was hospitalized for evaluation by a specialist. Linagliptin therapy continued and no other therapy was reported. Two days later, the drug eruption resolved. He completed the trial about 2 years later.

- Subject (b) (6) (New Zealand): A 73-year old man with diabetes with multiple medical history was randomized to linagliptin. On Day 2128, he developed serious **drug eruption** which was morbilliform. He had concurrent urinary tract infection and received Amoxicillin, which was a co-suspect for the event. The rash was disseminated, located in both arms, both legs, and trunk region, covering >30% of body surface area without mucosal involvement. Three days later Amoxicillin was discontinued and trimethoprim was started. Linagliptin was continued, and the event resolved 3 days later after discontinuation of Amoxicillin.

- Subject (b) (6) (Asia): A 54-year old man with diabetes was randomized to linagliptin. On Day 1359, he developed exanthema in the precordium, back, neck, and right-sided intraoral region, and reported serious event of **drug eruption**. He had concurrent pyrexia 4 days before drug eruption and had received drugs for pyrexia (paracetamol and acetaminophen/dihydrocodeine/chlorpheniramine/caffeine), which were considered co-suspect drugs for eruption. The exanthema was localized in the trunk and the face covering less than 10% of the body surface area with mucosal involvement in the mouth. Linagliptin and drugs for pyrexia were stopped and he received steroid therapy for drug eruption. The pyrexia resolved 3 days later, and linagliptin was restarted 6 days after pyrexia resolved. The drug eruption resolved about 2 weeks later. He completed the trial.

Reviewer's comment: *In one subject ((b) (6) drug eruption was likely related to Amoxicillin, and the role of other drugs for drug eruption in another subject ((b) (6) also could not be ruled out, especially since linagliptin was reinitiated and drug eruption resolved. The drug eruption also resolved while linagliptin was continued in the remaining case ((b) (6) making it difficult to determine the role of linagliptin in drug eruption in that subject. It is also notable that in all three cases, drug eruption occurred >3 years after initiation of linagliptin. Typically, hypersensitivity reaction for drugs would not be expected to occur several years after initiation.*

Reference ID: 4581802

Angioedema:

Angioedema was searched using narrow SMQ 'angioedema', and 1.8% of subjects (n=54) in the linagliptin group compared to 1.7% of subjects (n=50) in the glimepiride had angioedema AEs. Four angioedema events (0.1%) in the linagliptin group (2 angioedema, 1 eye swelling, 1 urticaria) and 8 angioedema events (0.3%) in the glimepiride group (4 angioedema, 1 face swelling, 1 lip swelling, 1 tongue swollen, 1 tongue edema, and 1 urticaria) were considered serious.

One case of eye swelling with linagliptin (subject # (b) (6) that was serious occurred during his hospitalization for dizziness and dyspnea and resolved after receiving therapy (unspecified) without discontinuation of linagliptin. Another subject with serious urticaria (subject # (b) (6) had serious urticaria on Day 2093 that resolved after receiving Benadryl; linagliptin was temporarily discontinued and restarted after resolution of urticaria without any issues.

One of 2 angioedema that was serious appear to be related to concurrent enalapril (subject # (b) (6) as angioedema resolved after discontinuation of enalapril and linagliptin was continued. The other case of angioedema with linagliptin is summarized here:

- Subject (b) (6) (Germany): A 69-year old man with diabetes was randomized to linagliptin. On Day 281, he experienced serious angioedema, which was considered life-threatening as swelling of the tongue could have led to choking. No other event was ongoing at the time. He received therapy for angioedema and linagliptin was permanently discontinued on Day 331 due to angioedema.

Reviewer's comment: *Serious angioedema in this subject appear to be possibly related to linagliptin as there was no other etiology.*

Review of narratives of remaining 5 subjects (b) (6) that reported non-serious angioedema while receiving linagliptin showed that the event was confounded by concomitant ACE-inhibitor therapy, which was discontinued while linagliptin continued during the reported angioedema event, with resolution of event.

Reference ID: 4581802

Table 31: Subjects with Angioedema by Treatment Group (TS_D+7)

MedDRA High Level Term (HLT)/ Preferred Term	Linagliptin		Glimepiride	
	N (%)	IR	N (%)	IR
Number of subjects	3014		3000	
Number of subjects with angioedema	54 (1.8)	3.7	50 (1.7)	3.4
Number of subjects with serious angioedema	4 (0.1)	0.3	8 (0.3)	0.5
Allergic conditions NEC HLT	**0**		**1**	**0.1**
Allergic edema	0		1	0.1
Angioedemas HLT	**9 (0.3)**	**0.6**	**7 (0.2)**	**0.5**
Angioedema	7 (0.2)	0.5	4 (0.1)	0.3
Swelling face	2 (0.1)	0.1	3 (0.1)	0.2
Corneal infections, edemas and inflammations HLT	**0**		**1**	**0.1**
Corneal edema	0		1	0.1
Lid, lash and lacrimal	**0**		**4 (0.1)**	**0.3**
Eyelid edema	0		4 (0.1)	0.3
Ocular disorders NEC HLT	**5 (0.2)**	**0.3**	**2 (0.1)**	**0.1**
Eye swelling	4 (0.1)	0.3	1	0.1
Periorbital edema	1	0.1	1	0.1
Edema NEC HLT	**4 (0.1)**	**0.3**	**3 (0.1)**	**0.2**
Face edema	4 (0.1)	0.3	3 (0.1)	0.2
Oral soft tissue swelling and edema HLT	**3 (0.1)**	**0.2**	**5 (0.2)**	**0.3**
Gingival swelling	1	0.1	0	
Lip edema	1	0.1	0	
Mouth swelling	1	0.1	0	
Lip swelling	0		4 (0.1)	0.3
Pharyngeal disorders HLT	**0**		**2 (0.1)**	**0.1**
Pharyngeal edema	0		2 (0.1)	0.1
Tongue signs and symptoms HLT	**0**		**3 (0.1)**	**0.2**
Swollen tongue	0		1	0.1
Tongue edema	0		2 (0.1)	0.1
Urticarias HLT	**33 (1.1)**	**2.2**	**25 (0.8)**	**1.7**
Urticaria	32 (1.1)	2.2	22 (0.7)	1.5
Idiopathic urticaria	1	0.1	0	
Urticaria papular	0		1	0.1
Urticaria chronic	0		3 (0.1)	0.2

HLT=high level term; NEC=not elsewhere classified; N= number of subjects; IR=incidence rate per 1000 patient-years
Source: CSR 1218.74, Table 15.3.1.3.2:5

Reference ID: 4581802

8.5.3. Skin Lesions (including Bullous condition)

AEs of skin lesions were searched based on the narrow SMQ 'severe cutaneous adverse reactions'.

Skin lesions were reported in 9 subjects (0.3%) receiving linagliptin versus 4 subjects (0.1%) receiving glimepiride and the reported AE terms by treatment group are presented in Table 32. The most common PT reported was 'bullous dermatitis' in 3 subjects receiving linagliptin and 2 subjects receiving glimepiride.

Table 32: Frequency [N (%)] and Incidence Rate of Subjects with AE Terms Associated with Skin Lesions by Treatment, High Level Term, and Preferred Term (TS_D+7)

High Level Term/ Preferred Term	Linagliptin		Glimepiride	
	N (%)	IR	N (%)	IR
Total subjects	3014	14838.3	3000	14692.7
Subjects with AEs	**9 (0.3)**	**0.6**	**4 (0.1)**	**0.3**
Bullous conditions	**4 (0.1)**	**0.3**	**2 (0.1)**	**0.1**
Bullous dermatitis	3 (0.1)	0.2	2 (0.1)	0.1
Erythema multiforme	1	0.1	0	
Dermatitis ascribed to specific agent	**2 (0.1)**	**0.1**	**1**	**0.1**
Toxic skin eruption	2 (0.1)	0.1	1	0.1
Exfoliative conditions	**3 (0.1)**	**0.2**	**0**	
Exfoliative dermatitis	2 (0.1)	0.1	0	
Exfoliative rash	1	0.1	0	
Skin vasculitides	**0**		**1**	**0.1**
Cutaneous vasculitis	0		1	0.1

N=number of subjects; IR=incidence rate per 1000 patient-years;
Source: CSR 1218.74, Table 15.3.1.3.1:2

Skin lesions in 3 subjects receiving linagliptin group were serious skin AEs (2 were exfoliative dermatitis, 1 was bullous dermatitis) whereas none in the glimepiride group was serious skin AE.

Two cases of serious exfoliative dermatitis are summarized here:

- Subject (b) (6) (Peru): A 58-year old man with diabetes who was receiving metformin therapy was randomized to linagliptin and about a month later experienced contact dermatitis that resolved 2 months later. About 18 months after linagliptin initiation in 2013, he reported erythematous skin lesions, scaling, and itching on the neck, anterior thorax and inguinal area, and was reported with serious **exfoliative dermatitis**. Few

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months later, lesions disseminated to both arms, both legs, trunk and the head, covering 90% of the body surface area. He received corticosteroid and Cetaphil cream for exfoliative dermatitis and study drug was permanently discontinued 4 months after exfoliative dermatitis began. Later (unspecified), erythema and exfoliative scaling was reduced to 40% of the body surface area. In 2016, the intensity of exfoliative dermatitis was changed from moderate to mild. During the last known contact during phone call in 2017, he reported that he was receiving an unspecified skin cancer treatment. He died of an unknown cause about 3.6 years after study drug was discontinued. Back pain, cellulitis, and exfoliative dermatitis were ongoing AEs at that time. It was unknown whether autopsy was done and further information was not provided.

- Subject (b) (6) (Brazil): A 73-year old woman with diabetes who was receiving metformin therapy was randomized to linagliptin. About 3 years later, she developed exfoliative dermatitis that led to hospitalization. She developed macular stain throughout the body surface, but ciprofloxacin was also considered co-suspect drug for the event as it developed shortly after administration of ciprofloxacin, as well as a 'nose cleaner product'. She received unspecified therapy and study drug was permanently discontinued. About 6 days later, exfoliative dermatitis was reported resolved. About 20 days after resolution, she experienced serious AE of worsening exfoliative erythroderma which led to hospitalization, and ciprofloxacin and the nose cleaner product were considered co-suspect drugs for worsening of skin condition.

Reviewer's comment: *Exfoliative dermatitis in Subject (b) (6) appear to be possibly related to linagliptin, as there was a temporal relationship and no other co-suspect was reported. However, in Subject (b) (6) exfoliative dermatitis was confounded by ciprofloxacin, and recurrent exfoliative dermatitis occurred after discontinuation of study drug, therefore unlikely related to linagliptin.*

One case of bullous dermatitis that was serious is summarized here:

- Subject (b) (6) (U.S.): A 73-year old man with diabetes receiving metformin therapy was randomized to linagliptin; he had a complicated medical history which included seborrheic dermatitis, actinic keratosis, and psoriasis. During a routine dermatology check-up about 76 days after study drug initiation, he has dysplastic nevus which was considered serious. He was found with 2 lesions of 0.6 cm in diameter without any mucosal involvement. He did not receive any therapy and continued the treatment and dysplastic nevus resolved about 2 months later. On 155th day of study drug, he was found with skin lesion of right lower extremity which was considered serious and also had concurrent seborrheic keratosis. He did not receive any therapy and continued the study drug. On 337th day of study drug, he was noted with a spot on his left ear and biopsy showed a basal cell carcinoma of left ear. Two days later, he developed serious

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bullous dermatitis on his 2nd toe left foot due to rubbing of a shoe, which had few segmental lesions without any mucosal involvement. The bullous dermatitis was drained on the same day and he received therapy and continued the study drug. He underwent surgery to remove basal cell carcinoma of his left ear. Bullous dermatitis also resolved about 10 days later.

Reviewer's comment: *The SAE of bullous dermatitis appeared to be unrelated to the study drug in this subject. No labeling change is warranted based on this case.*

Bullous Condition:

Bullous conditions were searched using HLT 'bullous conditions', where some PTs (i.e., bullous dermatitis, erythema multiforme) overlapped with search for skin lesions that were discussed above.

AEs for bullous conditions were reported in 15 subjects (0.5%) receiving linagliptin and 14 subjects (0.5%) receiving glimepiride. The reported AE terms by treatment group are presented in Table 33. Notable imbalance included 5 cases of pemphigoid which were all reported with linagliptin compared to none with glimepiride.

Table 33: Frequency [N (%)] and Incidence Rate of Subjects with AE Terms Associated with Bullous Conditions by Treatment, High Level Term, and Preferred Term (TS_D+7)

High Level Term/ Preferred Term	Linagliptin		Glimepiride	
	N (%)	IR	N (%)	IR
Total subjects	3014	14838.3	3000	14692.7
Subjects with bullous conditions	15 (0.5)	1.0	14 (0.5)	1.0
Bullous conditions	**15 (0.5)**	**1.0**	**14 (0.5)**	**1.0**
Blister	6 (0.2)	0.4	9 (0.3)	0.6
Pemphigoid	5 (0.2)	0.3	0	
Bullous dermatitis	3 (0.1)	0.2	2 (0.1)	0.1
Blood blister	1	0.1	1	0.1
Erythema multiforme	1	0.1	0	
Diabetic bullosis	0		1	0.1
Blister rupture	0		1	0.1

N=number of subjects; IR=incidence rate per 1000 patient-years;
Source: CSR 1218.74, Table 15.3.1.3.2:7

Four cases were serious bullous conditions (3 cases of pemphigoid, 1 case of bullous dermatitis that was described above) which were all reported with linagliptin, and 3 pemphigoid cases (2

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of which were also SAE) led to discontinuation in the linagliptin group. None of the bullous conditions led to discontinuation in the glimepiride group.

Reviewer's comment: *Bullous pemphigoid is a labeled event for DPP-4 inhibitors based on postmarketing cases. Also, labeling about bullous pemphigoid for linagliptin was updated with approval of CARMELINA due to an imbalance in bullous pemphigoid not favoring linagliptin compared to placebo with some leading to hospitalization. The incidence of pemphigoid with linagliptin in CAROLINA was similar to CARMELINA (0.2%), and some of the pemphigoid also led to hospitalization. No pemphigoid events had fatal outcome. Review of all cases of pemphigoid did not shown any new safety issue that is not already labeled. Therefore, the current labeling adequately describes the risk of bullous pemphigoid associated with linagliptin.*

8.5.4. Hepatic Events

Hepatic events were flagged using the narrow sub-SMQ 'hepatitis, non-infectious', the narrow sub-SMQ 'hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions', the narrow sub-SMQ 'liver related investigations, signs and symptoms', the narrow sub-SMQ 'cholestasis and jaundice of hepatic origin'.

Hepatic events were reported in 7.7% of subjects receiving linagliptin and 8.7% of subjects receiving glimepiride. The reported AE terms by treatment group are presented in Table 34. There was no notable imbalance of hepatic event terms between treatment groups. The most commonly reported event was hepatic steatosis, 2.6% in the linagliptin and 3.0% in the glimepiride group.

Table 34: Frequency [N (%)] and Incidence Rate of Subjects with AE Terms Associated with Hepatic Adverse Events by Treatment, High Level Term, and Preferred Term (TS_D+7)

High Level Term/ Preferred Term	Linagliptin		Glimepiride	
	N (%)	IR	N (%)	IR
Total subjects	3014	14838.3	3000	14692.7
Subjects with hepatic AEs	233 (7.7)	16.5	261 (8.7)	18.8
Subjects with serious hepatic AEs	37 (1.2)	2.5	39 (1.3)	2.7
Subjects with hepatic AEs leading to discontinuation	10 (0.3)	0.7	18 (0.6)	1.2
Cholestasis and jaundice	**4 (0.1)**	**0.3**	**6 (0.2)**	**0.4**
Cholestatic jaundice	3 (0.1)	0.2	0	
Cholestasis	1	0.1	2 (0.1)	0.1
Jaundice	1	0.1	1	0.1
Hyperbilirubinemia	0		3 (0.1)	0.2
Gastric and esophageal hemorrhages	**0**		**2 (0.1)**	**0.1**
Esophageal varices hemorrhage	0		1	0.1

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Portal hypertensive gastropathy	0		1	0.1
Hepatic and hepatobiliary disorders NEC	**10 (0.3)**	**0.7**	**14 (0.5)**	**1.0**
Abnormal hepatic function	7 (0.2)	0.5	13 (0.4)	0.9
Hypertransaminasemia	3 (0.1)	0.2	1	0.1
Hepatic failure and associated disorders	**1**	**0.1**	**3 (0.1)**	**0.2**
Hepatic failure	1	0.1	1	0.1
Acute hepatic failure	0		2 (0.1)	0.1
Hepatic fibrosis and cirrhosis	**6 (0.2)**	**0.4**	**7 (0.2)**	**0.5**
Hepatic cirrhosis	3 (0.1)	0.2	6 (0.2)	0.4
Hepatic fibrosis	3 (0.1)	0.2	1	0.1
Hepatic vascular disorders	**0**		**1**	**0.1**
Portal hypertension	0		1	0.1
Hepatobiliary imaging procedures	**0**		**1**	**0.1**
Ultrasound liver abnormal	0		1	0.1
Hepatobiliary signs and symptoms	**9 (0.3)**	**0.6**	**6 (0.2)**	**0.4**
Hepatomegaly	8 (0.3)	0.5	4 (0.1)	0.3
Hepatic pain	1	0.1	0	
Hepatic congestion	0		1	0.1
Hepatosplenomegaly	0		1	0.1
Hepatocelluar damage and hepatitis NEC	**89 (3.0)**	**6.1**	**97 (3.2)**	**6.7**
Hepatic steatosis	79 (2.6)	5.4	89 (3.0)	6.2
Hepatitis	2 (0.1)	0.1	2 (0.1)	0.1
Acute hepatitis	2 (0.1)	0.1	0	
Drug-induced liver injury	2 (0.1)	0.1	0	
Hepatocellular injury	1	0.1	1	0.1
Non-alcoholic steatohepatitis	1	0.1	0	
Cholestatic liver injury	1	0.1	0	
Hepatic steato-fibrosis	1	0.1	0	
Autoimmune hepatitis	0		1	0.1
Chronic hepatitis	0		1	0.1
Ischemic hepatitis	0		1	0.1
Non-alcoholic hepatitis	0		3 (0.1)	0.2
Liver injury	0		1	0.1
Liver function analyses	**127 (4.2)**	**8.8**	**146 (4.9)**	**10.3**
Gamma-glutamyltransferase increased	74 (2.5)	5.1	84 (2.8)	5.8
Alanine aminotransferase increased	34 (1.1)	2.3	48 (1.6)	3.3
Aspart aminotransferase increased	24 (0.8)	1.6	32 (1.1)	2.2
Hepatic enzyme increased	15 (0.5)	1.0	11 (0.4)	0.8
Liver function test increased	7 (0.2)	0.5	6 (0.2)	0.4
Liver function test abnormal	6 (0.2)	0.4	5 (0.2)	0.3
Transaminases increased	4 (0.1)	0.3	5 (0.2)	0.3
Aspartate aminotransferase abnormal	2 (0.1)	0.1	0	
Blood bilirubin increased	1	0.1	6 (0.2)	0.4

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Esophageal varices	**0**		**2 (0.1)**	**0.1**
Esophageal varices	0		2 (0.1)	0.1
Peritoneal and retroperitoneal disorders	**2 (0.1)**	**0.1**	**6 (0.2)**	**0.4**
Ascites	2 (0.1)	0.1	6 (0.2)	0.4

NEC=not elsewhere classified; N=number of subjects; IR=incidence rate per 1000 patient-years
Source: CSR 1218.74, Table 15.3.1.3.1:3, 12.1.4.3:1

The incidence of SAEs of hepatic events was similar between treatment groups, which occurred in 1.2% (2.5/1000 PY) of subjects in the linagliptin group and 1.3% (2.7/1000 PY) in the glimepiride group. There was less hepatic AEs leading to discontinuation of study drug in the linagliptin group (0.3%) compared to glimepiride group (0.6%).

There were 2 cases of drug-induced liver injury reported with linagliptin with serious outcome compared to none with glimepiride. Review of these cases showed that in one case (subject # (b) (6) the SAE of drug-induced liver injury occurred on Day 1 of the study drug initiation, and subject's baseline hepatic enzymes were already elevated and were thought to be due to concomitant anti-inflammatory therapy. Study drug continued and drug-induced liver injury was considered resolved. In the other subject ((b) (6) drug-induced liver injury was considered to be related to antibacterial drugs (clindamycin and cefozopran) that was initiated for treatment of infective spondylitis. Study drug was continued, and hepatic event resolved after discontinuation of antibacterial drugs.

Also, 2 of 3 cholestatic jaundice cases with linagliptin had serious outcome compared to no cases with glimepiride. Review of these cases showed that in one case, the cholestatic jaundice was due to her final diagnosis of cholangiocarcinoma (subject (b) (6) cholangiocarcinoma discussed in Section 8.5.7). In another SAE of cholestatic jaundice (subject (b) (6) he had obstructive jaundice concurrent with bacteremia, cholangitis, and had biliary stones undergoing cholecystectomy; it resolved without discontinuation of study drug, and his cholestatic jaundice was likely due to biliary stones.

Ten subjects (0.3% or 0.7/1000 PY) in the linagliptin group and 18 subjects (0.6% or 1.2/1000 PY) in the glimepiride group discontinued the study drug due to hepatic AEs, and there was no notable imbalance between treatment groups in hepatic AEs leading to study drug discontinuation (not shown here; see Appendix 16.1.13.1, Table 8.3.3.3).

Laboratory tests for hepatic function:

Laboratory measure such as elevated liver enzymes, elevated AST and/or ALT (≥3x ULN) in combination with elevated total bilirubin (>2x ULN) measured in the same blood draw sample, as well as laboratory tests consistent with potential Hy's Law cases were AESI.

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The incidence of subjects with elevated liver enzyme by treatment group is summarized in Table 35. Overall, there was a numerically smaller proportion of subjects in the linagliptin compared to glimepiride with elevated liver enzymes.

Table 35: Frequency [N (%)] of Subjects with Elevated Liver Enzymes (TS_D+7)

	Linagliptin (N=3014)	Glimepiride (N=3000)
ALT and/or AST ≥3x ULN	66 (2.2)	72 (2.4)
ALT and/or AST ≥5x ULN	13 (0.4)	22 (0.7)
ALT and/or AST ≥10x ULN	4 (0.1)	5 (0.2)
ALT and/or AST ≥20x ULN	0	0
ALT and/or AST ≥3x ULN with total bilirubin ≥2x ULN	3 (0.1)	1
Alkaline phosphatase* ≤2x ULN	0	0
Alkaline phosphatase* >2x ULN	3 (0.1)	1

AST=aspartate transaminase; ALT=alanine transaminase; ULN=upper limit of normal
*alkaline phosphatase was the maximum value in the 30 day period.
Source: CSR 121.7, Table 15.3.2:10

During the treatment period, 3 subjects in the linagliptin group and 1 subject in the glimepiride group has AST and/or ALT ≥3x ULN in combination with elevated total bilirubin ≥2x ULN measured in the same blood draw or within 30 days after the elevation. However, none of these subjects met the criteria for Hy's Law cases, which is defined by any on-treatment value of ALT/AST ≥3x UNL with total bilirubin ≥2x ULN without initial finding of cholestasis (i.e., alkaline phosphatase ≤2x ULN). Review of 3 subjects in the linagliptin group showed that 2 subjects had concurrent cholelithiasis (subjects (b) (6) also reported with cholangiocarcinoma; cholangiocarcinoma discussed in Section 8.5.7), and the remaining subject ((b) (6) also had history of cholelithiasis and had elevated liver enzymes concurrent renal impairment. One subject in the glimepiride group ((b) (6) was found to have pancreatic carcinoma which likely caused elevated liver enzymes.

Reviewer's comment: *There was no hepatic safety concerns with linagliptin from CAROLINA trial.*

8.5.5. Renal Adverse Events

Renal events were identified using narrow SMQ 'acute renal failure'.

A total of 178 subjects (5.9%) in the linagliptin group and 156 subjects (5.2%) in the glimepiride group reported renal AEs. The reported AE terms by treatment group are presented in Table 36. Numerically larger proportion of subjects in the linagliptin group compared to glimepiride reported renal impairment (3.1% versus 2.5%), but similar proportion of subjects in each

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treatment group had SAE of renal impairment, 8 subjects (0.3%) in the linagliptin and 10 subjects (0.3%) in the glimepiride group. There were 3 cases of oliguria with linagliptin but none were serious or led to discontinuation.

The overall frequency of serious renal AEs was similar between treatment groups (2.4% linagliptin, 2.1% glimepiride) as well as renal AEs leading to study drug discontinuation (0.6% linagliptin, 0.7% glimepiride).

Table 36: Frequency [N (%)] and Incidence Rate of Subjects with AE Terms Associated with Renal Adverse Events by Treatment, High Level Term, and Preferred Term (TS_D+7)

High Level Term/ Preferred Term	Linagliptin		Glimepiride	
	N (%)	IR	N (%)	IR
Total subjects	3014	14838.3	3000	14692.7
Subjects with renal AEs	178 (5.9)	12.3	156 (5.2)	10.9
Subjects with serious renal AEs	73 (2.4)	4.9	64 (2.1)	4.4
Subjects with renal AEs leading to discontinuation	19 (0.6)	1.3	20 (0.7)	1.4
Renal failure and impairment	**175 (5.8)**	**12.1**	**153 (5.1)**	**10.7**
Renal impairment	92 (3.1)	6.3	76 (2.5)	5.2
Acute kidney injury	47 (1.6)	3.2	41 (1.4)	2.8
Renal failure	40 (1.3)	2.7	40 (1.3)	2.7
Oliguria	3 (0.1)	0.2	0	
Prerenal failure	1	0.1	2 (0.1)	0.1
Anuria	0		1	0.1
Renal failure complications	**3 (0.1)**	**0.2**	**3 (0.1)**	**0.2**
Azotemia	3 (0.1)	0.2	3 (0.1)	0.2

AE=adverse event; N=number of subjects; IR=incidence rate/1000 patient-years
Source: CSR 1218.74, Table 15.3.1.3.1:4, Table 12.1.4.4:1, Appendix 16.1.13.1, Table 8.3.4.3

Reviewer's comment: *There was no notable imbalances in renal adverse events between treatment groups.*

Subgroup analyses showed that the frequency of renal AEs increased in elderly subjects and in those with decreasing renal function with lower eGFR, see summary in Table 37. The increasing incidence of renal AEs with increasing age and worsening eGFR was similarly seen in both treatment groups with no notable difference between treatment groups.

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Table 37: Incidence of subjects with renal AEs by Age and eGFR subgroup and treatment (TS_D+7)

	Linagliptin			Glimepiride		
	N	n (%)	IR	N	n (%)	IR
Age (years) subgroup						
<70	2009	86 (4.3)	8.7	1975	81 (4.1)	8.3
70 to <80	911	78 (8.6)	18.6	922	63 (6.8)	15.2
≥80	94	14 (14.9)	40.3	103	12 (11.7)	30.0
eGFR (mL/min/1.73 m^2) subgroup						
≥90	693	8 (1.2)	2.3	722	13 (1.8)	3.5
60 to <90	1726	90 (5.2)	10.6	1740	80 (4.6)	9.5
30 to <60	576	76 (13.2)	30.4	525	60 (11.4)	27.5
<30	16	4 (25.0)	100.3	13	3 (23.1)	81.5

AE=adverse event; eGFR=estimated glomerular filtration rate, estimated using MDRD
Source: CSR 1218.74, Appendix 16.1.13.1, Table 8.3.4.7

Laboratory tests for renal function:

Renal function changes were evaluated by serum creatinine, eGFR (using MDRD), and UACR.

The changes from baseline in serum creatinine, eGFR, and UACR were not notably different between linagliptin and glimepiride groups (see Table 38).

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Table 38: Change from Baseline of Serum Creatinine, eGFR, and UACR (TS_D)

	Linagliptin	Glimepiride
Creatinine (mg/dL), N	2917	2898
Baseline, mean (SE)	0.95 (0.01)	0.94 (0.00)
Final visit, mean (SE)	1.04 (0.01)	1.03 (0.01)
Change from baseline, adjusted mean (SE)	0.08 (0.01)	0.09 (0.01)
Comparison vs glimepiride, adjusted mean (SE), [95% CI]	-0.01 (0.01) [-0.03, 0.01]	
eGFR (MDRD, mL/min/1.73 m^2), N	2917	2898
Baseline, mean (SE)	76.5 (0.4)	77.1 (0.4)
Final visit, mean (SE)	72.6 (0.4)	72.1 (0.4)
Change from baseline, adjusted mean (SE)	-4.0 (0.3)	-5.0 (0.3)
Comparison vs glimepiride, adjusted mean (SE), [95% CI]	1.0 (0.4) [0.2, 1.8]	
UACR (mg/g), N	2904	2880
Baseline, gMean (gCV)	14.47 (2.79)	13.56 (2.59)
Final visit, gMean (gCV)	21.83 (3.88)	21.49 (3.54)
Change from baseline, adjusted gMean ratio (gCV)	1.52 (1.83)	1.57 (1.83)
Comparison vs glimepiride, adjusted ratio of gMean ratios [95% CI]	0.97 [0.91, 1.03]	

N=number of subjects with baseline and on-treatment results; eGFR=estimated glomerular filtration rate; UACR=urine albumin creatinine ratio
Source: CSR 1218.74, Table 11.1.2.4.1:1, Table 15.2.6.9.1:1

In the analysis of safety laboratory tests, doubling of serum creatinine compared to baseline occurred in 3.6% (107 subjects) and 2.9% (87 subjects) in the linagliptin and glimepiride groups respectively. The proportion of subjects with shifts from normal baseline to a value >ULN at the last treatment value were similar in both treatment groups, 10.4% with linagliptin and 10.0% with glimepiride.

The sustained reduction of eGFR defined as ≥40% from baseline occurred in 5.2% (10.4/1000 PY) of subjects in the linagliptin group compared to 4.5% (8.9/1000 PY) of subjects in the glimepiride group.

The transitions in UACR categories were similar between treatment groups (data not shown; see CSR 1218.74, Table 15.2.6.9.3:2). About 58.4% of linagliptin subjects had normal UACR at baseline (i.e., <30 mg/g) and at the final study visit, while 14.1% transitioned to microalbuminuria (30 to 300 mg/g, inclusive) and 1.4% had macroalbuminuria (>300 mg/g). In the glimepiride group, 57.7% of subjects had normal UACR at baseline and at final visit, while 16.0% transitioned to microalbuminuria and 1.4% transitioned to macroalbuminuria.

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8.5.6. Pancreatitis

Pancreatitis events were adjudicated by an independent CEC. AEs triggering adjudication were reported in 522 subjects (17.3%) in the linagliptin and 464 subjects (15.4%) in the glimepiride group, and subjects with confirmed pancreatitis events are summarized in Table 39.

Acute pancreatitis was reported in 0.5% of subjects in both treatment groups; one subject in the linagliptin group and 2 subjects in the glimepiride group reported acute pancreatitis with organ failure, and one of two organ failure with glimepiride reported a fatal outcome. Chronic pancreatitis was reported in 3 subjects in the linagliptin group and none in the glimepiride group. Subjects with asymptomatic pancreatic hyperenzymemia occurred in numerically higher proportion of subjects in the linagliptin group (5.7%) compared to glimepiride (3.6%). Four events were not assessable in each treatment group. Pancreatic malignancy will be further discussed in Section 8.5.7.

Table 39: CEC Confirmed Pancreatic Events by Treatment (TS)

	Linagliptin	Glimepiride
Number of subjects	3023	3010
Subjects with acute pancreatitis	15 (0.5)	16 (0.5)
Without organ failure	14 (0.5)	15 (0.5)
With organ failure	1	2
Subjects with chronic pancreatitis	3 (0.1)	0
Subjects with asymptomatic pancreatic hyperenzymemia	171 (5.7)	108 (3.6)
Subjects with pancreatic malignancy	16 (0.5)	24 (0.8)
Subjects with not assessable events	4 (0.1)	4 (0.1)

Source: CSR 1218.74, Table 15.3.1.5:1

In 2 of 3 chronic pancreatitis cases with linagliptin, subjects had their last dose of study drug about 2 years (subject # (b) (6) and 4 years (subject # (b) (6) before the event. Third subject reporting chronic pancreatitis (subject # (b) (6) had a history of alcohol consumption.

Necrotizing pancreatitis was reported in one subject ((b) (6) in the linagliptin group, which was adjudicated as acute pancreatitis without organ failure by CEC:

- Subject (b) (6) (U.S.): A 40-year old male with diabetes and medical history of depression, chronic pancreatitis, erectile dysfunction, dyspepsia, hypercholesterolemia, and hypertension was randomized to linagliptin. He did not smoke but had history of alcohol consumption with estimated average daily amount of 7000 mL (45%), he reportedly consumed 8-12 oz beers 3x week and 1 L of rum daily. About 10 months after starting linagliptin, he had nausea, vomiting, diarrhea and abdominal pain. CT scan of the abdomen showed necrotizing pancreatitis and he was hospitalized in a status of

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agitation secondary of delirium. Lipase was 1229 U/L (normal 32-219 U/L). Initial abdominal ultrasound showed normal gallbladder with normal bile ducts and severe fatty liver. Abdominal CT scan showed decreased enhancement of pancreatic tail consistent with pancreatic necrosis without biliary dilatation. Triglyceride level was greater than 4000 (unit and reference range not provided). He received therapy and was discharged with a diagnosis of acute pancreatitis secondary to elevated triglycerides. Two days later, he had concurrent event of alcohol withdrawal syndrome and experienced chronic abdominal pain. Necrotizing pancreatitis and delirium resolved.

Reviewer's comment: *The role of linagliptin to necrotizing pancreatitis in this subject was confounded by concurrent elevated triglyceride level and/or alcohol consumption, which may have likely led to necrotizing pancreatitis.*

It is interesting to note that there was no particular imbalance for pancreatitis between linagliptin and glimepiride, as linagliptin and other DPP-4 inhibitors have been linked with cases of pancreatitis, particularly acute pancreatitis, whereas glimepiride is not known to be associated with the risk for pancreatitis.

Laboratory Tests: Lipase and Amylase

There was a small increase of both lipase and amylase values from baseline to the last value on treatment in both treatment groups, but numerical increase for both lipase and amylase during treatment was larger in the linagliptin group compared to glimepiride (Table 40). The median lipase levels at baseline were similar between treatment groups, 40 U/L in the linagliptin group and 41 U/L in the glimepiride group, and the median amylase levels were 67 U/L in the linagliptin group and 68 U/L in the glimepiride group. From baseline to the last value on treatment, there was a 12 U/L increase (26%) in lipase levels in the linagliptin group versus a 3 U/L (6%) in the glimepiride group, and there was a 6 U/L increase (8%) in amylase levels in the linagliptin group versus a 2 U/L increase (3%) in the glimepiride group.

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Table 40: Change from Baseline of Lipase and Amylase (TS_D+7)

	Linagliptin (N=3014)	Glimepiride (N=3000)
Lipase, U/L		
Baseline, mean (SD)	47 (30)	47 (31)
Last value on treatment, mean (SD)	59 (69)	50 (36)
Difference from baseline, mean (SD)	12 (66)	3 (39)
Amylase, U/L		
Baseline, mean (SD)	73 (31)	73 (28)
Last value on treatment, mean (SD)	79 (38)	75 (32)
Difference from baseline, mean (SD)	6 (28)	2 (26)

Source: CSR 1218.74, Table 15.3.2:1

Analyses of shifts from normal range at baseline to >ULN at last value on treatment showed more occurring in the linagliptin group (18.5%; 441/2384) compared to glimepiride (13.0%; 308/2373). Similar trend for shifts from normal range at baseline to >ULN at last value on treatment was seen with amylase levels, 7.3% in the linagliptin group compared to 5.6% with glimepiride.

During the trial, overall frequency of subjects with baseline lipase values <3x ULN and shifts to maximum lipase values of ≥3x ULN post-baseline during treatment was 12.1% of subjects in the linagliptin group and 8.4% of subjects in the glimepiride group. The overall frequency of subjects with baseline amylase values <3x ULN and shifts to maximum amylase values of ≥3x ULN post-baseline during treatment was 1.0% in the linagliptin group and 0.6% in the glimepiride group (data not shown here; see CSR 121.74, Table 15.3.2:12).

Reviewer's comment: *There was a numerically larger increase in lipase and amylase levels during treatment with linagliptin compared to glimepiride, and the magnitude of increase was larger with lipase and smaller with amylase. The clinical significance of this numerical increase in lipase and/or amylase levels with linagliptin is unclear as an imbalance in pancreatitis was not seen with linagliptin compared to glimepiride. Increase in lipase is already labeled for linagliptin. The Applicant proposed to add the increase in amylase in labeling with this supplement; however, I do not believe that this small numerical increase in amylase with linagliptin warrants adding it to the labeling, especially since lipase has higher sensitivity to detect acute pancreatitis compared to amylase.*

8.5.7. Oncological Adverse Events

Malignancies reported by the investigator were analyzed using narrow SMQs 'malignant tumors' and 'tumors of unspecified malignancy'. This search showed similar proportion of subjects reported at least one malignancy, 9.3% (280 subjects) in the linagliptin group and

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10.1% (303 subjects) in the glimepiride group. Review of incidence of these cases by SOC and PT did not show notable imbalance between treatment groups in any specific site (data not shown; see Appendix 16.1.13.1, Table 8.3.8.1).

A separate, independent, blinded, external committee (Oncology Assessment Committee) reviewed all suspected solid cancers and evaluated whether cancer was possibly related, not related to the study drug, or not assessable. Of malignancy AEs reported by the investigator, 266 (8.8%) were solid tumors in linagliptin group and 285 (9.5%) in the glimepiride group that were sent for assessment. Most events were evaluated as not related in both treatment groups, and 2.8% (84 subjects) in the linagliptin group and 3.7% (111 subjects) in the glimepiride group had cancer events that were assessed as possibly related to the study drug.

Thyroid cancer:

One subject in the linagliptin group (thyroid cancer PT) and 3 subjects in the glimepiride group (1 thyroid cancer PT, 2 papillary thyroid cancer PT) reported thyroid neoplasms. Of these only one case of thyroid cancer with glimepiride was assessed as possibly treatment related by treatment by the committee.

Pancreatic cancer:

Pancreatic cancer was one of AESI specified in the protocol and adjudicated by independent committee, Clinical Event Committee Pancreatic (CECP). Pancreatic events other than pancreatic malignancy were discussed in Section 8.5.6, Pancreatitis, and pancreatic malignancy will be discussed here.

AE search of pancreatic cancer using 'pancreatic neoplasms' showed that there was no imbalance between treatment groups, with 19 subjects (0.6%) in the linagliptin group and 23 subjects (0.8%) in the glimepiride group reporting pancreatic cancer. Of these, 3 subjects in the linagliptin and 2 subjects in the glimepiride group reported pancreatic cancer with exposure <6 months; with minimum exposure of 6 months, 16 subjects (0.6%) in the linagliptin group and 21 subjects (0.7%) in the glimepiride group reported pancreatic cancer.

As discussed in Section 8.5.6, 16 subjects (0.5%) in the linagliptin group and 24 subjects (0.8%) in the glimepiride group had at least one CECP-adjudicated pancreatic malignancy. The Oncology Assessment Committee determined that 9 subjects (0.3%) in the linagliptin group and 13 subjects (0.4%) in the glimepiride group with pancreatic cancer was assessed as possibly related to the study drug.

Reviewer's comment: *No imbalance was observed in the overall malignancies or types of cancers including thyroid cancer or pancreatic cancer with linagliptin compared to glimepiride.*

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Cholangiocarcinoma:

Cholangiocarcinoma is a new potential safety concern identified with DPP-4 inhibitors.[12] In CAROLINA, there was no imbalance between treatment groups for bile duct cancer, see Table 41.

Table 41: Frequency [N(%), IR] of Subjects with Bile Duct Cancer (TS)

HLT/Preferred Term	Linagliptin		Glimepiride	
	N (%)	IR	N (%)	IR
Bile duct neoplasm malignant HLT	5 (0.2)	0.3	4 (0.1)	0.2
Cholangiocarcinoma	3 (0.1)	0.2	2 (0.1)	0.1
Bile duct cancer	2 (0.1)	0.1	1	0.1
Bile duct adenocarcinoma	0		1	0.1

HLT=high level term; N=number of subjects; IR=incidence rate/1000 patient-years; TS=treated set
Source: CSR 1218.74, Appendix 16.1.13.1, Table 8.3.8.1

8.5.8. Arthralgia

Arthralgia is a labeled event for DPP-4 inhibitors as a class based on postmarketing reports of severe and disabling arthralgia, as discussed in Section 3.1.

In CAROLINA, 23.9% (721 subjects) in the linagliptin group and 24.2% (727 subjects) in the glimepiride group reported AE terms associated with arthralgia based on HLGT 'join disorders' search which include arthralgia PT. The most commonly reported PT was arthralgia without any imbalance between treatment groups (10.5% in both treatment groups).

Overall, 2.9% (87 subjects) in the linagliptin group and 3.0% (90 subjects) in the glimepiride group had an SAE of arthralgia-related event, and 4 subjects (0.1% in each) in each treatment group discontinued the study drug due to AE associated with arthralgia.

Reviewer's comment: *In CAROLINA, there was no imbalance between treatment groups in the incidence of overall AEs, SAEs, or discontinuations due to arthralgia-related events.*

Additional analyses by Applicant:

The Applicant provided additional analyses of arthralgia based on their clinical trials and safety database, because they believe that the data is insufficient to establish arthralgia with linagliptin.

[12] Abrahami D, Douros A, Yin H, et al. Incretin based drugs and risk of cholangiocarcinoma among patients with type 2 diabetes: population based cohort study. BMJ 2018;363:k480.

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The clinical trials database included a pooled data from placebo-controlled studies in T2DM patients (7136 subjects treated with linagliptin and 4936 subjects treated with placebo), CARMELINA trial (3494 subjects treated with linagliptin and 3485 subjects treated with placebo with a mean follow-up of 2.2 years), and CAROLINA trial. The safety database included cumulative cases for all linagliptin-containing products up to December 31, 2018, retrieved irrespective of causality, seriousness, or type of report.

In the pooled placebo-controlled clinical trials of linagliptin, there was no imbalance in the overall frequency of joint disorders between linagliptin (3.9%) and placebo (4.7%), or arthralgia (linagliptin 2.07% versus placebo 2.55%). In CARMELINA, the frequency of joint disorders was also similar between linagliptin (6.2%) and placebo (5.7%).

The postmarketing search for Tradjenta identified 297 arthralgia-related events from 258 cases, and 16.5% (49 of 297) were serious. Twelve events, including 7 PT arthralgia events, were reported as serious due to disability. There was one 'disabling' event of PT arthritis with positive rechallenge from a 74-year old man.

Reviewer's comment: *All DPP-4 inhibitors were labeled with a warning for the risk of severe arthralgia based on the DPV's review of post-marketing cases of arthralgia associated with DPP-4 inhibitors, which identified 33 patients experiencing severe and disabling arthralgia with positive temporal relationship with one of DPP-4 inhibitors (see Debra Ryan's Pharmacovigilance Review dated July 14, 2014). It was noted that most of the cases were associated with sitagliptin (28 cases) and only 2 cases were associated with linagliptin. The symptoms of these cases were severe and debilitating, with the majority of patients being treated with immunosuppressive agents to control symptoms rather than discontinuation of DPP-4 inhibitors. Based on DPV's review, DMEP concluded that the data provided strong evidence to support a causal association between DPP-4 inhibitors and severe arthralgia (see Dr. Pippin's Memo dated August 27, 2015 for discussion).*

The Applicant provided additional clinical trials data and postmarketing cases associated with joint disorders/arthralgia (b) (4) [redacted] *Their postmarketing data did identify cases of arthralgia with serious outcome, some disabling and some with positive rechallenge with linagliptin.* (b) (4) [redacted]

8.6. Safety Analyses by Demographic Subgroups

Subgroup analyses for the overall summary of AE by SOC and PT did not show any meaningful imbalance between linagliptin and placebo groups across various subgroups such as age, BMI, race, gender, renal disease, metformin use at baseline, etc (data not shown here; see Table 15.3.1.2.2 to 15.3.1.2.16 in CSR). However, this single trial was not adequately powered to reach meaningful conclusions regarding subgroup analyses.

Subgroup analysis for hypoglycemia was discussed in Section 8.5.1.

8.7. Specific Safety Studies/Clinical Trials

As previously discussed, CAROLINA was a cardiovascular safety study to evaluate CV outcomes in patients with type 2 diabetes mellitus.

8.8. Additional Safety Explorations

8.8.1. Human Carcinogenicity or Tumor Development

Oncological adverse events of interest were discussed in Section 8.5.7.

8.8.2. Human Reproduction and Pregnancy

Women who are pregnant or nursing were excluded from study participation, and women of child-bearing potential were screened for pregnancy before enrollment and during their participation in the trial.

During a follow-up call, a subject ((b) (6) receiving linagliptin was found to be pregnant and delivered about 3.5 years after treatment discontinuation. The outcome of pregnancy was not reported by the investigator. She completed the trial 1.5 years after estimated date of delivery.

8.8.3. Pediatrics and Assessment of Effects on Growth

Not applicable as CAROLINA only enrolled adults.

8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Not applicable.

8.9. Safety in the Postmarket Setting

8.9.1. Safety Concerns Identified Through Postmarket Experience

The most recent Periodic Benefit-Risk Evaluation Report (PBRER) was submitted on July 9, 2019,

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covering May 3, 2018 to May 2, 2019.

On July 1, 2019, the labeling for all DPP-4 inhibitors including linagliptin was updated to include 'rhabdomyolysis' to the postmarketing section of the labeling based on review of postmarketing cases.

As discussed in Section 8.5.7, cholangiocarcinoma is a new safety concern for incretins including DPP-4 inhibitors based on a published population-based cohort study. CAROLINA did not show an increased incidence of cholangiocarcinoma with linagliptin compared to glimepiride (Table 41).

8.9.2. Expectations on Safety in the Postmarket Setting

The approval of this supplement would not expand the patient population from what is currently approved, as the indication will not change based on the current supplement. The results of CAROLINA will be labeled to inform healthcare professionals that the use of linagliptin is not associated with an unacceptable increase in CV risk compared to glimepiride. I expect that the safety in the postmarketing setting will remain similar if this supplement is approved.

8.9.3. Additional Safety Issues From Other Disciplines

At the time of this review, no additional safety issues were identified by the other review disciplines.

8.10. Integrated Assessment of Safety

Treatment-emergent AEs with linagliptin in CAROLINA that occurred at ≥1% higher incidence compared to glimepiride were diarrhea (12.2% linagliptin, 11.0% glimepiride) and increased lipase (7.0% linagliptin, 5.2% glimepiride). All-cause deaths and CV deaths were evaluated as safety endpoint and did not show an increased risk. Reported AEs for deaths did not show an imbalance between treatment groups. The overall incidence of SAEs (46.4% linagliptin, 48.1% glimepiride) and AEs leading to discontinuation (13.7% linagliptin, 14.9% glimepiride) were similar between treatment arms.

The incidences of any hypoglycemia (15.1% linagliptin, 46.9% glimepiride) and severe hypoglycemia (0.3% linagliptin, 2.2% glimepiride) were higher with glimepiride compared to linagliptin. This is not unexpected as sulfonylureas are known to have higher risk for hypoglycemia.

Other adverse events of special interest (AESI) that were evaluated with a pre-specified MedDRA queries included hypersensitivity reaction including angioedema, skin lesions including bullous conditions, hepatic events, renal adverse events, pancreatitis, pancreatic cancer and

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other malignancies, and arthralgia. Pancreatitis and all solid cancers were adjudicated by an independent adjudication committee.

The data regarding HF from CAROLINA was not as reassuring as there was an imbalance in the proportion of subjects experiencing hospitalization for heart failure not favoring linagliptin (3.7%) compared to glimepiride (3.1%) with HR >1 (HR 1.21 [95% CI: 0.92, 1.59]).

9. Advisory Committee Meeting and Other External Consultations

Not applicable, as Advisory Committee meeting was not held for this supplement.

10. Labeling Recommendations

10.1. Prescription Drug Labeling

The proposed labeling for linagliptin conform to the final rule governing the "Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products" released on January 24, 2006, available at: https://www.fda.gov/ohrms/dockets/98fr/06-545.pdf.

The relevant labeling revisions proposed by the Applicant that are the subject of this review include:

- (b) (4)
- (b) (4)

- Adding 'Increase in Amylase' in Section 6.1, Clinical Trials Experience, Laboratory Tests: Although there was a small imbalance in increase of amylase levels with linagliptin compared to glimepiride in CAROLINA, the Applicant would like to include this imbalance in labeling to inform healthcare provider.

- Add CAROLINA study results in Section (b) (4) Clinical Studies: I agree with including the results of CAROLINA in this section, and the final language will be negotiated.

- (b) (4) . However, we are negotiating to include the incidence of hypoglycemia from CAROLINA in the Hypoglycemia section under Section 6.1, Clinical Trials Experience. We propose to include only severe hypoglycemia since this is an active comparator trial.

10.2. Nonprescription Drug Labeling

Not applicable.

11. Risk Evaluation and Mitigation Strategies (REMS)

Given the favorable safety profile of this drug, there are no additional risk management strategies required beyond the recommended labeling.

12. Postmarketing Requirements and Commitments

No postmarketing requirement (PMRs) or commitments (PMCs) are recommended.

13. Appendices

13.1. References

References are cited throughout the document in footnotes.

13.2. Financial Disclosure

CAROLINA was a covered trial. The Applicant has adequately disclosed financial arrangements with clinical investigators as recommended in the guidance for industry Financial Disclosure by

Reference ID: 4581802

Clinical Investigators

Covered Clinical Study (Name and/or Number): CAROLINA/1218.74

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 607		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 6		
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: 6 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator: 0 Sponsor of covered study: Boehringer Ingelheim		
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) _____		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

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/s/

HYON J KWON
03/26/2020 03:11:32 PM

PATRICK ARCHDEACON
03/26/2020 03:41:57 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206073Orig1s021

PHARMACOLOGY REVIEW(S)

Pharmacology/Toxicology
Memo to File

Date:	August 22, 2019
NDA #s	201280 – Supplement 20 201281 – Supplement 24 206073 – Supplement 21 208026 – Supplement 12
Sponsor:	Boehringer Ingelheim
Drug:	Linagliptin (Tradjenta®) tablets Linagliptin-containing FDC drugs
Reviewer:	David B. Carlson, Ph.D.

Summary:

Efficacy supplements for linagliptin and linagliptin-containing FDCs were submitted based on results of the completed CAROLINA post-market cardiovascular outcomes trial (CVOT) which investigated linagliptin and glimepiride treatment in type 2 diabetes mellitus patients. Supplements include updated prescribing information in clinical sections of the various drug labels with results of the CAROLINA trial.

Nonclinical review of the proposed label changes confirmed no changes to Nonclinical (Section 13) or Pregnancy/Pediatric (Section 8) sections of any of the listed drug labels.

No action is indicated from a nonclinical perspective on any of the proposed linagliptin-containing NDA Supplements.

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20903
www.fda.gov

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

DAVID B CARLSON
08/22/2019 02:44:58 PM
Linagliptin CVOT 'CAROLINA' supplements -- NAI for nonclinical

TODD M BOURCIER
08/22/2019 02:50:56 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206073Orig1s021

OTHER REVIEW(S)

REGULATORY PROJECT MANAGER
PHYSICIAN LABELING RULE (PLR) FORMAT REVIEW
OF THE PRESCRIBING INFORMATION and RPM LABELING REVIEW

Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements

Application: NDA 206073/S- 021

Application Type: Efficacy Supplement (type SE-8)

Drug Name(s)/Dosage Form(s): Glyxambi (empagliflozin and linagliptin tablets)

Applicant: Boehringer Ingelheim Pharmaceuticals, Inc.

Receipt Date: June 6, 2019

Goal Date: April 6, 2020

1. Regulatory History and Applicant's Main Proposals

Glyxambi (empagliflozin and linagliptin) tablets is a fixed dose combination product comprising empagliflozin, a selective inhibitor of sodium-dependent glucose co-transporter-2 (SGLT-2), and linagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor, both developed by Boehringer Ingelheim Pharmaceuticals, Inc. (BI). Both empagliflozin (NDA 204629), proprietary name Jardiance, and linagliptin (NDA 201280), proprietary name Tradjenta, were previously approved and marketed in the United States prior to the approval of Glyxambi, NDA 206073, on January 30, 2015.

Supplements to Glyxambi which have updated its labeling include the following: S-001 addressed the risk of arthralgia with the use of DPP-4 inhibitors and was approved on August 28, 2015; S-003 addressed the risks of ketoacidosis and urosepsis with the use of SGLT-2 inhibitors and was approved on December 4, 2015; S-006 added statements on fatal cases of ketoacidosis with empagliflozin and a statement about thirst and was approved on July 8, 2016; S-007 updated the label with results of the cardiovascular safety study 1245.25, the EMPA-REG OUTCOME trial, and brought the prescribing information (PI) into compliance with the Pregnancy and Lactation Labeling Rule and was approved concurrently on December 23, 2016, with S-009 that informed of the risk of bullous pemphigoid with DPP-4 inhibitors; S-008 added information about increased lipase observed during linagliptin clinical studies and was approved on March 14, 2017; S-011 updated the presentation of the trade name and logo for selected Glyxambi carton and containers and was approved on August 10, 2017, the same day S-013 was approved to address the risk of heart failure with DPP-4 inhibitor products; S-012 updated the PI and Medication Guide with information about hypersensitivity reactions and was approved on December 13, 2017; S-019 provided information on the risk of necrotizing fasciitis of the perineum, also known as Fournier's gangrene, and was approved on October 26, 2018; S-022 updated the PI to inform of the risk of rhabdomyolysis and was approved on July 1, 2019; S-017 updated the PI and Medication Guide based on the results of cardiovascular safety and renal microvascular outcome study 1218.22, the CARMELINA trial, and was approved on July 3, 2019; and S-023 updated the PI and Medication Guide on the risk of risk of peri-/post-operative diabetic ketoacidosis and was approved on January 24, 2020.

Reference ID: 4582111

RPM PLR Format Review of the Prescribing Information

The supplement that is the focus of this PLR review, S-021, is an SE-8 type efficacy supplement that was received on June 6, 2019. S-021 proposes revisions to the PI and Medication Guide based on the results of study 1218.74 entitled, " A multicentre, international, randomised, parallel group, double blind study to evaluate Cardiovascular safety of linagliptin versus glimepiride in patients with type 2 diabetes mellitus at high cardiovascular risk.," (CAROLINA). Corollary supplements were also submitted to BI's other linagliptin containing products: NDA 201280/S-020 Tradjenta (linagliptin) tablets, NDA 201281/S-024 Jentadueto (linagliptin and metformin) tablets, and NDA 208026/S-012 Jentadueto XR (linagliptin and metformin extended-release) tablets. The version of the Glyxambi PI that was reviewed below was submitted by BI via email as part of labeling negotiations on March 26, 2020.

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI) provided by email during labeling negotiations on March 26, 2020. The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements of Prescribing Information (SRPI)" checklist (see Section 4 of this review).

The major change to the PI is the addition of a CAROLINA study results subsection to Section 14.3 Linagliptin Cardiovascular Safety Trials. Additional prominent changes to the PI include:

- the removal of former Section 5.11 Warnings and Precautions on Increased Low Density Lipoprotein Cholesterol (LDL-C);
- the addition of event number data on volume depletion to the *Empagliflozin* subsection of Section 6.1 Clinical Trials Experience;
- the addition of an *Increase in Amylase* subsection to the Section 6.1 Clinical Trial *Laboratory Tests* Linagliptin subsection;
- the removal of language from Section 12.3 Pharmacokinetics that recommended no dose adjustment of empagliflozin or linagliptin with coadministration of other products which appeared in the *In vivo* Assessment of Drug Interactions sections of both the *Empagliflozin* and *Linagliptin* subsections, respectively; and
- the removal of Table 7 and Figure 6 in the Section 14.3 Linagliptin Cardiovascular Safety subsection on CARMELINA and the replacement of that information with new, simplified text.

The Division also took the opportunity to remove a qualifying statement from Highlights, Section 1 Indications and Usage, and Clinical Studies Section 14.2 which had stated that "the effectiveness of Glyxambi on reducing the the risk of cardiovascular death in adults with type 2 diabetes mellitus and cardiovascular disease has not been established."

Other additional minor changes are also made throughout the PI.

For additional details, and changes to the Medication Guide, see the attached comparison of the last approved Glyxambi labeling (S-023 approved on January 24, 2020) to BI draft labeling for S-021 emailed as part of labeling negotiations on March 26, 2020.

3. Conclusions/Recommendations

No SRPI format deficiencies were identified in the review of this PI. There are no additional recommendations.

Reference ID: 4582111

4. Selected Requirements of Prescribing Information

The Selected Requirement of Prescribing Information (SRPI) is a 41-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

See Appendix for a sample tool illustrating Highlights format.

HIGHLIGHTS GENERAL FORMAT

YES 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment:

YES 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. Instructions to complete this item: If the length of the HL is one-half page or less, select "YES" in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select "NO" unless a waiver has been granted.

Comment: *Waiver previously granted.*

YES 3. A horizontal line must separate:

- HL from the Table of Contents (TOC), **and**
- TOC from the Full Prescribing Information (FPI).

Comment:

YES 4. All headings in HL (from Recent Major Changes to Use in Specific Populations) must be **bolded** and presented in the center of a horizontal line. (Each horizontal line should extend over the entire width of the column.) The HL headings (from Recent Major Changes to Use in Specific Populations) should be in UPPER CASE letters. See Appendix for HL format.

Comment:

YES 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix for HL format.

Comment:

YES 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment:

YES 7. Headings in HL must be presented in the following order:

Heading	Required/Optional
• **Highlights Heading**	Required
• **Highlights Limitation Statement**	Required
• **Product Title**	Required

Reference ID: 4582111

Selected Requirements of Prescribing Information

• **Initial U.S. Approval**	Required
• **Boxed Warning**	Required if a BOXED WARNING is in the FPI
• **Recent Major Changes**	Required for only certain changes to PI*****
• **Indications and Usage**	Required
• **Dosage and Administration**	Required
• **Dosage Forms and Strengths**	Required
• **Contraindications**	Required (if no contraindications must state "None.")
• **Warnings and Precautions**	Not required by regulation, but should be present
• **Adverse Reactions**	Required
• **Drug Interactions**	Optional
• **Use in Specific Populations**	Optional
• **Patient Counseling Information Statement**	Required
• **Revision Date**	Required

* RMC only applies to five labeling sections in the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES 8. At the beginning of HL, the following heading, **"HIGHLIGHTS OF PRESCRIBING INFORMATION"** must be **bolded** and should appear in all UPPER CASE letters.

Comment:

Highlights Limitation Statement

YES 9. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert NAME OF DRUG PRODUCT) safely and effectively. See full prescribing information for (insert NAME OF DRUG PRODUCT).**" The name of drug product should appear in UPPER CASE letters.

Comment:

Product Title in Highlights

YES 10. Product title must be **bolded**.

Comment:

Initial U.S. Approval in Highlights

YES 11. Initial U.S. Approval must be **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment:

Boxed Warning (BW) in Highlights

N/A 12. All text in the BW must be **bolded**.

Comment:

N/A 13. The BW must have a title in UPPER CASE, following the word "**WARNING**" and other words to identify the subject of the warning. Even if there is more than one warning, the term "**WARNING**" and not "**WARNINGS**" should be used. For example: "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**". If there is more than one warning in the

Reference ID: 4582111

BW title, the word "and" in lower case can separate the warnings. The BW title should be centered.

Comment:

N/A 14. The BW must always have the verbatim statement "***See full prescribing information for complete boxed warning***." This statement must be placed immediately beneath the BW title, and should be centered and appear in *italics*.

Comment:

N/A 15. The BW must be limited in length to 20 lines. (This includes white space but does not include the BW title and the statement "***See full prescribing information for complete boxed warning.***")

Comment:

Recent Major Changes (RMC) in Highlights

YES 16. RMC pertains to only five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. Labeling sections for RMC must be listed in the same order in HL as they appear in the FPI.

Comment:

YES 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Warnings and Precautions, Acute Liver Failure (5.1) --- 8/2015."

Comment:

YES 18. A changed section must be listed under the RMC heading for at least one year after the date of the labeling change and must be removed at the first printing subsequent to the one year period. (No listing should be one year older than the revision date.)

Comment:

Dosage Forms and Strengths in Highlights

N/A 19. For a product that has more than one dosage form (e.g., capsules, tablets, injection), bulleted headings should be used.

Comment:

Contraindications in Highlights

YES 20. All contraindications listed in the FPI must also be listed in HL. If there is more than one contraindication, each contraindication should be bulleted. If no contraindications are known, must include the word "None."

Comment:

Adverse Reactions in Highlights

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YES 21. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's U.S. phone number which should be a toll-free number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**"

Comment: *FDA web addressed is hyperlinked and italicized.*

Patient Counseling Information Statement in Highlights

YES 22. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- **See 17 for PATIENT COUNSELING INFORMATION**

If a product **has (or will have)** FDA-approved patient labeling:

- **See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**
- **See 17 for PATIENT COUNSELING INFORMATION and Medication Guide**

Comment:

Revision Date in Highlights

YES 23. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., "**Revised: 8/2015** ").

Comment:

Contents: Table of Contents (TOC)

See Appendix for a sample tool illustrating Table of Contents format.

YES 24. The TOC should be in a two-column format.

Comment:

YES 25. The following heading must appear at the beginning of the TOC: **"FULL PRESCRIBING INFORMATION: CONTENTS."** This heading should be in all UPPER CASE letters and **bolded**.

Comment:

N/A 26. The same title for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.

Comment:

YES 27. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.

Comment:

YES 28. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (for, of, to) and articles (a, an, the), or conjunctions (or, and)].

Comment:

YES 29. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.

Comment:

YES 30. If a section or subsection required by regulation [21 CFR 201.56(d)(1)] is omitted from the FPI, the numbering in the TOC must not change. The heading "**FULL PRESCRIBING INFORMATION: CONTENTS***" must be followed by an asterisk and the following statement must appear at the end of the TOC: "*Sections or subsections omitted from the full prescribing information are not listed."

Comment:

Reference ID: 4582111

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

YES 31. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. (Section and subsection headings should be in UPPER CASE and title case, respectively.) If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation (if not required to be in Pregnancy and Lactation Labeling Rule (PLLR) format, use "**Labor and Delivery**")
8.3 Females and Males of Reproductive Potential (if not required to be in PLLR format, use "**Nursing Mothers**")
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

YES 32. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, "*[see Warnings and Precautions (5.2)]*."

Comment:

Reference ID: 4582111

YES 33. For each RMC listed in HL, the corresponding new or modified text in the FPI must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

YES 34. The following heading "**FULL PRESCRIBING INFORMATION"** must be **bolded,** must appear at the beginning of the FPI, and should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

N/A 35. All text in the BW should be **bolded**.

Comment:

N/A 36. The BW must have a title in UPPER CASE, following the word "**WARNING**" and other words to identify the subject of the warning. (Even if there is more than one warning, the term, "**WARNING**" and not "**WARNINGS**" should be used.) For example: "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**". If there is more than one warning in the BW title, the word "and" in lower case can separate the warnings.

Comment:

CONTRAINDICATIONS Section in the FPI

N/A 37. If no Contraindications are known, this section must state "None."

Comment:

ADVERSE REACTIONS Section in the FPI

YES 38. When clinical trials adverse reactions data are included (typically in the "Clinical Trials Experience" subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions from clinical trials:

> "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."

Comment:

YES 39. When postmarketing adverse reaction data are included (typically in the "Postmarketing Experience" subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions:

"The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure."

Comment: *The following acceptable modifications of the above standard statement was made: "Additional" replaces "The following" at the beginning of the first sentence. Also in the first sentence, "post-approval" is dehyphenated to "postapproval".*

Reference ID: 4582111

Selected Requirements of Prescribing Information

In the second sentence "it is not always possible" is replaced by "it is generally not possible".

PATIENT COUNSELING INFORMATION Section in the FPI

YES 40. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION). The reference statement should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide). Recommended language for the reference statement should include one of the following five verbatim statements that is most applicable:

- Advise the patient to read the FDA-approved patient labeling (Patient Information).
- Advise the patient to read the FDA-approved patient labeling (Instructions for Use).
- Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).
- Advise the patient to read the FDA-approved patient labeling (Medication Guide).
- Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Comment: *Statement for only referring to a Medication Guide used.*

YES 41. FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide) must not be included as a subsection under Section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Reference ID: 4582111

Appendix: Highlights and Table of Contents Format

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

PROPRIETARY NAME (non-proprietary name) dosage form, route of administration, controlled substance symbol
Initial U.S. Approval: YYYY

WARNING: TITLE OF WARNING
See full prescribing information for complete boxed warning.

- **Text (4)**
- **Text (5.x)**

----------RECENT MAJOR CHANGES----------
Section Title, Subsection Title (x.x) M/201Y
Section Title, Subsection Title (x.x) M/201Y

----------INDICATIONS AND USAGE----------
PROPRIETARY NAME is a (insert FDA established pharmacologic class text phrase) indicated for … (1)

Limitations of Use: Text (1)

----------DOSAGE AND ADMINISTRATION----------
- Text (2.x)
- Text (2.x)

----------DOSAGE FORMS AND STRENGTHS----------
Dosage form(s): strength(s) (3)

----------CONTRAINDICATIONS----------
- Text (4)
- Text (4)

----------WARNINGS AND PRECAUTIONS----------
- Text (5.x)
- Text (5.x)

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence > x%) are text (6.x)

To report SUSPECTED ADVERSE REACTIONS, contact name of manufacturer at toll-free phone # or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
- Text (7.x)
- Text (7.x)

----------USE IN SPECIFIC POPULATIONS----------
- Text (8.x)
- Text (8.x)

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

Revised: M/201Y

FULL PRESCRIBING INFORMATION: CONTENTS*

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

Reference ID: 4582111

Attachment: Labeling comparison

Labeling comparison of the Prescribing Information and Medication Guide between the last approved Glyxambi labeling (S-023 approved on January 24, 2020) to BI draft labeling for S-021 emailed as part of labeling negotiations on March 26, 2020. Comparison made using the Microsoft Word comparison function.

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

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MICHAEL G WHITE
03/27/2020 01:07:40 AM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	October 2, 2019
Requesting Office or Division:	Division of Metabolism and Endocrinology Products (DMEP)
Application Type and Number:	NDA 201280/S-020 NDA 201281/S-024 NDA 208026/S-012 NDA 206073/S-021
Product Name and Strength:	Tradjenta (linagliptin) tablet, 5 mg Jentadueto (linagliptin and metformin) tablet, 2.5 mg/500 mg, 2.5 mg/850 mg, 2.5 mg/1000 mg Jentadueto XR (linagliptin and metformin extended-release) tablet, 5 mg/1000 mg and 2.5 mg/1,000 mg Glyxambi (empagliflozin and linagliptin) tablet, 10 mg/5 mg and 25 mg/5 mg
Applicant/Sponsor Name:	Boehringer Ingelheim Pharmaceuticals
OSE RCM #:	2019-1307
DMEPA Safety Evaluator:	Ariane O. Conrad, PharmD, BCACP, CDE
DMEPA Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

Boehringer Ingelheim submitted efficacy supplements for each product containing linagliptin to propose revised labeling on May 30, 2019, June 6, 2019, and July 17, 2019. They propose revisions based on the results of Study 1218.74 entitled "A multicenter, international, randomized parallel group, double-blind trial to evaluate cardiovascular safety of linagliptin versus glimepiride in patients with T2DM at high cardiovascular risk. The CAROLINA trial." Thus, they have proposed changes to various sections of the prescribing information (Highlights of Prescribing Information-Warnings and Precautions; Full Prescribing Information-Section 5

Reference ID: 4500783

Warnings and Precautions, Section 6 Adverse Reactions, Section 14 Clinical Studies, and Section 17 Patient Counseling Information) for each product containing linagliptin.

We reviewed the revised prescribing information (PI) and medication guides for Tradjenta (linagliptin), Jentadueto (linagliptin and metformin), Jentadueto XR (linagliptin and metformin extended-release), and Glyxambi (empagliflozin and linagliptin) to determine if they are acceptable from a medication error perspective.

2 CONCLUSION

We defer to the review team for analysis of the proposed changes to the various sections of the prescribing information. The revised prescribing information and medication guides for Tradjenta, Jentadueto, Jentadueto XR, and Glyxambi are acceptable from a medication error perspective. We have no further recommendations at this time.

APPENDIX A. LABELING SUBMITTED BY BOEHRINGER INGELHEIM RECEIVED ON JULY 17, 2019

Tradjenta Prescribing Information

- \\cdsesub1\evsprod\nda201280\0231\m1\us\proposed.doc

Jentadueto Prescribing Information

- \\cdsesub1\evsprod\nda201281\0153\m1\us\proposed.doc

Jentadueto XR Prescribing Information

- \\cdsesub1\evsprod\nda208026\0066\m1\us\proposed.doc

Glyxambi Prescribing Information

- \\cdsesub1\evsprod\nda206073\0127\m1\us\proposed.doc

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ARIANE O CONRAD
10/02/2019 04:46:01 PM

HINA S MEHTA
10/04/2019 11:49:59 AM

Clinical Inspection Summary

Date	2/05/2020
From	Cynthia F. Kleppinger, M.D., Senior Medical Officer Min Lu, 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	Hyon J. Kwon, Pharm.D., M.P.H., Senior Clinical Analyst Patrick Archdeacon, M.D., M.Phil., Clinical Team Leader Richard Whitehead, M.S., Regulatory Project Manager Division of Metabolism and Endocrinology Products (DMEP)
NDA	201280s020
Applicant	Boehringer Ingelheim Pharmaceuticals, Inc.
Drug	Linagliptin (Tradjenta®)
NME	No
Therapeutic Classification	Antidiabetic Agents, Non-Insulin
Proposed Indication	Type 2 diabetes mellitus
Consultation Request Date	7/30/2019
Summary Goal Date	2/1/2020 (extended to 2/7/2020)
Action Goal Date	3/30/2020
PDUFA Date	3/30/2020

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The inspection for this supplemental new drug application (sNDA) consisted of five domestic and two foreign clinical sites in addition to the sponsor.

The inspection of one clinical investigator revealed regulatory deficiencies, which are unlikely to have a significant impact on overall results. The inspection of the remaining clinical investigators revealed no regulatory violations.

In addition, there were previous for-cause inspections of four clinical sites that were closed prematurely by the sponsor for GCP non-compliance.

The inspection of the sponsor revealed regulatory deficiencies (as described below). Of note, the Clinical Study Report Appendix 16.1.4 *List and description of investigators and sites* has listed the number of enrolled subjects per site. "Enrolled" are those subjects who were screened at each site. It was determined from the site inspections and subsequent sponsor inspection that this list is incorrect for sites that had transferred subjects but correct for all sites that were not involved with any transferring of subjects. During the inspection of the sponsor, the statistical staff walked

Reference ID: 4557422

through the analyses of several subjects and confirmed that data in the analyses reflected only one subject and not any duplicated data. Although the CSR Appendix 16.1.4 enrollment (screened) numbers are incorrect, the analyses that were done on all randomized subjects appear to have the correct number of subjects.

Based on the inspections, the study data generated are considered acceptable and may be used in support of this NDA.

II. BACKGROUND

Boehringer Ingelheim Pharmaceuticals, Inc. submitted a supplement to NDA 201280 to propose revisions to the Tradjenta® prescribing label to include information based on results of Study 1218.74, entitled: *A multicenter, international, randomized, parallel group, double blind study to evaluate **Car**di**o**vascular safety of **lina**gliptin versus glimepiride in patients with type 2 diabetes mellitus at high cardiovascular risk.* The CAROLINA Trial (c23238241-01).

Linagliptin (BI 1356, Tradjenta®, Trayenta®, Trazenta®, Trajenta®), an oral once daily DPP-4 inhibitor, received its first marketing approval May 2, 2011, and is approved in over 100 countries worldwide including the United States, Europe, and other regions.

This was a multicenter, multinational, randomized, double-blind, double-dummy, parallel group, comparator-controlled study of linagliptin versus glimepiride, predominantly on metformin background treatment. Patients with a documented diagnosis of type 2 diabetes mellitus (T2DM) with insufficient glycemic control and at high risk of cardiovascular (CV) events prior to informed consent could be enrolled in the trial.

After a 2 to 4 weeks placebo run-in, subjects were randomly assigned at Visit 2 in a double-blind, double-dummy way to either 5 mg linagliptin (plus glimepiride placebo) or an initial dose of 1 mg /day of glimepiride (plus linagliptin placebo). After the starting dose of 1 mg/day, glimepiride or glimepiride placebo was uptitrated in 4-week intervals during the first 16 weeks of treatment to the next dose. The potential maximum dose of glimepiride was 4 mg/day.

The primary endpoint was time to first occurrence of any of the following adjudicated components of the primary composite endpoint: cardiovascular (CV) death (including fatal stroke and fatal myocardial infarction [MI]), non-fatal stroke, or non-fatal MI (excluding silent MI) (also referred to as ‘time to first 3-point Major Adverse Cardiovascular Events [3P-MACE]’).

Study 1218.74 was conducted at 607 sites that screened at least one subject in 43 countries. There were 10,606 subjects screened (enrolled), 6423 subjects started the placebo run-in period, 6042 subjects were randomized, and 6033 subjects were treated. There were 5794 subjects that completed endpoint status or died. The trial was conducted from November 11, 2010 to August 21, 2018. Database lock was on September 27, 2018.

Reference ID: 4557422

III. RESULTS (by Site)

NOTE: Site inspections focused on 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. **Ana Fandino, M.D.**
   2955 Southwest Eight Street
   Miami, FL 33135
   Site: 1226

Dates of inspection: October 8, 2019

Dr. Fandino's site was chosen for inspection because her site was one of 10 that was closed/early terminated for non-compliance. A meeting took place at Dr. Fandino's private practice located at: 10300 Sunset Dr. Suite 430, Miami, FL 33173.

During an attempted inspection of Site 1226, it was discovered that no study files were available. The inspectional operation (Op12) was converted to an investigational operation (Op13) because Dr. Fandino has ceased research operations since 2014; the study site where the research took place (Swiss Medical Research, LLC.) is no longer operational; Dr. Fandino is no longer conducting clinical research; and she did not have and could not locate any records for the study.

Boehringer Ingelheim terminated Site 1226 from the CAROLINA Trial on 1/11/2013. Per the Clinical Study Report (CSR), monitoring revealed serious non-compliance in May 2012. Continuous noncompliance with good clinical practice was confirmed with a for-cause audit in July 2012 and a subsequent monitoring visit. The site was closed in March 2013. There were no monitoring reports, letters, or any other documents at the site to substantiate the reasons for the closing.

[Note: Subsequently, at the sponsor inspection, monitoring reports were reviewed. There were **23** subjects screened and 11 subjects randomized; one discontinued. Four of seven active subjects (b) (6) were potentially "duplicate subjects" enrolled/entered in the same trial at other sites. CSR Appendix 16.1.4 *List and description of investigators and sites* states that Site 1226 enrolled (screened) **23** subjects; footnote says **6** subjects transferred to Site 01191.

The site had hired two people as study coordinators who were found to be diverting controlled substances for another study at the site. Both staff members left when confronted. Of note, this site had a break-in not long after starting the CAROLINA trial in the fall of 2011 shortly after the site initiation visit. It was noted that the eRT ECG machine for the 1218.74 study that was provided by the sponsor was stolen. The site reported the break-in, the incident was escalated to Boehringer

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Ingelheim, and the police report was sent to Boehringer Ingelheim. Additionally, about 900 Schedule 2 investigational product (IP) used for another study was also stolen, along with computers, centrifuge, and other equipment. It was confirmed that the only Study 1218.74 item affected was the stolen ECG machine.

Follow-up monitoring reports at Boehringer Ingelheim mention that some subjects at the site were consented using the incorrect language version of the informed consent form (ICF). Eight out of 15 subjects were SPANISH ONLY but were consented using the English version of the ICF. Seven of these subjects were screen failed, while one remained active (Subject 29751).

Site was audited July 26 – 27, 2012 and had a follow-up monitoring visit November 6-8, 2012. No Spanish diaries had been provided to Spanish speaking subjects. The cognitive scales were available in Spanish; however, they were not used. There was limited demonstration of oversight by Dr. Fandino. For example, Subject (b) (6) (V3) fasting blood sugar results were elevated, and the laboratory report noted that the test was to be repeated; however, there was no evidence that the test was repeated; (V5) was >110 mg/dl but there was no evidence the subject was up-titrated as required by the protocol. Several subjects were consented on the wrong version of the informed consent. Dr. Fandino failed to ensure the primary care physicians were notified of subjects' participation in the clinical trial, although the subjects agreed to the notification. In addition, 4 of 7 active subjects were potentially enrolled/entered in same trial at other sites (same date of birth and initials). It was decided in a management meeting on December 5, 2012 to close the site for-cause. Initial management decision was not to transfer the subjects.]

Per Dr. Fandino and the supporting emails that were in her possession, all 6 subjects at her site and the study records, including all the source documents and regulatory binders, were transferred on 4/3/2013 by the contract research organization (CRO) (b) (4) to Dr. Luigi Meneghini's site. Dr. Meneghini is listed in the application as a sub-investigator for Site 1191/ Bresta Miranda. Dr. Fandino did not have any records for the CAROLINA Trial in her possession. (The original records appear to be lost as only copies were found at Dr. Miranda's site during inspection. There is the possibility that the CRO (b) (4) retained the originals).

Dr. Fandino explained that in May of 2013 she was audited by FDA for 2 different protocols and she received a Form FDA 483, Inspectional Observations. This inspection was conducted on 5/6 – 22 /2013. Dr. Fandino received a Warning Letter on 4/30/2014 due to violations of the FD&C Act and inadequate response to the Agency. Per Dr. Fandino, she chose to forgo clinical research altogether and "concentrate on growing" her private practice. Dr. Fandino was cooperative with the investigation and agreed to sign an FDA 463a, Affidavit, attesting to the facts and the statement that she was no longer involved in clinical research nor had any intentions to do clinical research in the future.

Boehringer Ingelheim determined that the site's data could be used in analyses but would be excluded from the per protocol set (PPS). Adverse event (AE) data are listed.

Since all records had been transferred, an amendment to the inspection assignment was made to inspect Site 1191/ Bresta Miranda (see information below).

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2. **Bresta Y. Miranda, M.D.**
   University of Miami
   Diabetes Research Institute
   1450 NW 10th Ave
   Miami, Florida 33136
   Site: 1191

Dates of inspection: October 16 – 30, 2019

There were **2** subjects screened and 2 subjects were randomized into the study. There were 6 subjects transferred from Site 1226; 2 of these subjects did not continue in the study but their records were available for review. Five subjects completed the study. There were 8 subject records reviewed. Clinical Study Report Appendix 16.1.4 *List and description of investigators and sites* incorrectly states that Site 1191 enrolled (screened) **6** subjects; footnote says **2** subjects transferred to Site 1046.

Dr. Miranda divides her time between private practice/academia 90% and research 10%. She serves as an Assistant Professor of Clinical Medicine at the University of Miami, Diabetes Research Institute and as the Director, Clinical Research Center at University of Miami School of Medicine. She was originally a sub-investigator for the study and took over as the site investigator on 1/24/2014. The original investigator was Dr. Luigi Meneghini from 11/21/2011 – 1/16/2014. Subjects were recruited by the site's internal database, doctor referrals, and institutional review board (IRB) approved advertisements.

The IRB of record was University of Miami Human Subjects Research Office.

Dr. Miranda/Dr. Meneghini was contacted by the sponsor in April 2013 regarding a transfer of 6 subjects to their site from another site in Miami, Site 1226. The source documents for the transferred subjects were copies sent by Site 1226. Per Dr. Miranda, they never received original source. There is communication between Dr. Miranda's site and the sponsor where the sponsor states that they would "request the site copy the records and send to your site." During the current inspection, University of Miami staff contacted the sponsor to request the original records for the transferred subjects and the sponsor was unable to provide the original source or the location. The sponsor stated that the records could be in permanent storage in Iron Mountain but never confirmed or delivered the original source to the inspected site. The only original source for these transferred subjects was for the source created once the subjects were consented with Dr. Miranda through the end of the study phone follow-up.

Dr. Miranda maintained original and adequate custody of study records for the subjects that were originally enrolled at her site and for the subjects that were transferred to her site for all tasks that were completed after transfer. Source records were compared to the sponsor data line listings. There were no discrepancies. There was no under-reporting of adverse events. The primary efficacy endpoint was verifiable.

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Out of the 6 transferred subjects, only 4 signed an ICF for Dr. Miranda and agreed to be followed-up via phone contact for vital status (Subjects (b) (6)). These 4 transferred subjects were no longer on investigational product (IP). There were several discrepancies noted with the subjects that were originally enrolled at Site 1226 and transferred to Dr. Miranda (Site 1191). These findings pertain to Site 1226 and not for Dr. Miranda but were discussed at the closing meeting:

- Three out of 6 subjects were on prohibited medication when randomized and therefore did not meet inclusion criteria but were included in the study.
    - Subject (b) (6) was on glimepiride (prohibited medication) during the study. Per source from Site 1226, the subject did not disclose this information until Visit 6. This deviation was submitted to the IRB by Site 1226.
    - Subject (b) (6) was on insulin (prohibited medication) during the study and while on active IP at the original site (Site 1226) but the insulin was not reported. Dr. Miranda submitted a protocol deviation for the subject being on prohibited medication during the study.
    - Subject (b) (6) was on glyburide (prohibited medication) during the study and while on active IP at the original Site 1226 but glyburide was not reported. Dr. Miranda submitted a protocol deviation for the subject being on prohibited medication during the study.
- One out of 6 subjects were given an ICF in a language not understood by the subject.
- One out of 6 subjects were given rescue medication during the study, but the concomitant medication source was never updated. Subject (b) (6) was prescribed rescue medication, Acarbose 25 mg.
- Source documents were not contemporaneous for at least 5 out of 6 subjects (chart notes written several weeks after the visit).
- No original study source documents were available for the subjects from Site 1226 (only copies of documents were available).

Per Dr. Miranda, the sponsor wanted the site to use (b) (4), a 3rd party vendor that traces lost to follow-up subjects, to contact the two subjects from Site 1226, even though the site did not have IRB approval to use this vendor. The UM IRB provided guidance to Dr. Miranda that no further contact should be made with subjects that had not enrolled at their site/signed an ICF. Dr. Miranda informed the sponsor that she would not make further attempts to reach the subjects since she did not have an ICF from the subjects. Per sponsor instructions, Dr. Miranda transferred these 2 subjects (Subject (b) (6)) to Dr. Julio Rosenstock (Coordinating Investigator and Steering Committee member), Site 1046, located at: 7777 Forest Lane, Suite C-685, Dallas, TX 75230

The inspection revealed adequate adherence by Dr. Miranda to the regulations and the investigational plan. There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, issued.

Since there was confusion with transferring of subjects and their records, an amendment to the inspection assignment was made to inspect the sponsor (see information below later in report).

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3. Leon A. Fogelfeld, M.D.
Cook County Health and Hospitals Systems
1950 W. Polk Street, Suite 4811
Chicago, IL, 60612
Site: 1063

Dates of inspection: December 10 – 13, 2019

There were **48** subjects screened and 31 subjects were randomized into the study. There were 31 subject records reviewed. No subjects transferred from another site to this site. Clinical Study Report Appendix 16.1.4 *List and description of investigators and sites* correctly states that Site 1063 enrolled (screened) **48** subjects.

Dr. Fogelfeld is the Chairman, Division of Endocrinology, Department of Medicine, at John H. Stroger, Jr. Hospital of Cook County. There were multiple Statement of Investigator, Form FDA 1572, at the site signed by Dr. Fogelfeld to add and remove sub-investigators as many residents and fellows participated in the study.

Study procedures for the protocol were performed at the John H. Stroger Jr. Hospital of Cook County and the Cook County Health and Hospitals Systems Clinics. The clinic that was mainly used during the study was located at the Fantus Health Center, 621 S. Winchester Street. The Fantus Health Center building no longer exists. Dr. Fogelfeld recruited patients from the medical practice at the Cook County Health and Hospitals System. Approximately 3000 patients are seen at the clinic each year. There were no advertisements used.

The IRB of record was Cook County Health and Hospital Systems IRB.

Source records included electronic medical records and paper source worksheets. Source data was organized, accurate, and legible. There was adequate documentation that all subjects were alive and available during their participation in the study. Study coordinators transcribed data from the source documents into the electronic case report form (eCRF) database.

Subjects (b) (6) and (b) (6) were not on a stable dose of anti-diabetic medication for at least 8 weeks prior to visit V1a (an inclusion criterion) and Subject (b) (6) was not on a stable dose of thyroid medication for 6 weeks prior to informed consent (an exclusion criterion). These deviations were found by a study monitor and reported by the site. Study documentation reports the deviations were an oversight by study staff. These deviations are reported in the Inclusion and Exclusion Criteria data listing. In addition, Subject (b) (6)'s medication was not titrated in accordance with the protocol at one visit.

Source records reviewed were compared to the sponsor data line listings. There were no discrepancies, except as noted below. There was no under-reporting of adverse events. The primary efficacy endpoint was verifiable.

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Of note, for some subjects the FDA inspectors could not reconcile the final date included in the BIMO listings Table 3 "Discontinuations" and in Table 8 "Efficacy Endpoints".

- Subject (b) (6) was randomized and received test article on 7/18/2011. Source documentation indicated that the subject withdrew from the study on Visit 7, which occurred on March 1, 2012. The eCRF also indicated the last contact was March 1, 2012. However, the study completion date on Table 3 "Discontinuations" and on Table 8 "Efficacy Endpoints" indicates that the last date is on 2/5/2018. The "value" given on Table 8 is 2395 days, which represents the time period of when first study drug was given on 7/18/2011 to 2/5/2018. The study site could not explain the 2/5/2018 date reported by the sponsor.
  OSI Reviewer Comment: The sponsor may have had additional public records available to confirm the subject was alive, but this was not documented at the site.
- Subject (b) (6) was randomized and received test article on 5/2/2012. Source documentation indicates that the subject was last seen at the site during Visit 3 on 6/1/2012. The site completed the EOT/Final Visit worksheet via phone on 6/29/2012. The study completion date on Table 3 "Discontinuations" and on Table 8 "Efficacy Endpoints" indicates that the last date is on 5/2/2018. The "value" given on Table 8 is 2192 days. The study site could not explain the 5/2/2018 date reported by the sponsor.
  OSI Reviewer Comment: The sponsor may have had additional public records available to confirm the subject was alive, but this was not documented at the site.
- Subject (b) (6) was randomized and received test article on 5/4/12. Source documentation indicates that the subject was last seen at the site during Visit 5 on 7/27/2012. The site tried to contact the subject by mail and telephone but was unsuccessful. The site reviewed the local hospital records and found that the subject picked up off-study medication on 1/28/13. This was considered by the clinical site as the last known date alive. The eCRF also indicated the last contact was on or prior to 1/28/13. This information was documented in a Note-to-File dated 10/18/13. The study completion date on Table 3 "Discontinuations" and the Table 8 "Efficacy Endpoints" indicates that the last date was on 6/25/2018. The "value" on Table 8 is 2244 days. The study site could not explain the 6/25/18 date reported by the sponsor.
  OSI Reviewer Comment: The sponsor may have had additional public records available to confirm the subject was alive, but this was not documented at the site.

As this was an outcome study, subjects who discontinued from treatment after randomization were followed up until the end of the study to record endpoints and other clinical status when feasible. The sponsor used (b) (4) a 3rd party vendor that traces lost to follow-up subjects. It is assumed that the dates recorded in the application represent information gathered by this vendor. If this cannot be confirmed with reviewing of additional data in the application, it is recommended that the review team contact the sponsor to confirm the source of the discrepant dates for the three subjects.

Other than the observations described above, the inspection revealed adequate adherence to the investigational plan. There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, issued.

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4. Elena Henkel, M.D.
MVZ Rudi
Rosenbergstraße 14
01277 Dresden
Germany

(b) (4)

(b) (4)

Dates of inspection: October 21 – 25, 2019

There were **63** subjects screened and 50 subjects were randomized into the study; 45 subjects completed the study (20 subjects off treatment and 5 deaths). There were 26 subject records reviewed. Clinical Study Report Appendix 16.1.4 *List and description of investigators and sites* correctly states that **63** subjects were enrolled (screened).

A translator was present throughout the inspection.

(b) (4)

Dr. Henkel is (b) (4) a private practice physician. Subjects were recruited from Dr. Henkel's patient population or her colleagues' patient population.

The IRB of record was the Ethik-Kommission der Landesärztekammer Hessen (Ethik-Kommission der Landesärztekammer Hessen, Im vogelsgesang 3 Frankfurt 60488 Germany). All informed consents were in German. The site was a non-IND site.

The study documents were organized and appeared to be complete. The subject's hardcopy CRF source documents were in English, but comments were written in German. The subject's diaries, protocol-specified questionnaires (i.e., the MMSE), medical history documents, progress notes, and related correspondence were in German. Translations were requested as much as possible.

Source records were compared to the sponsor data line listings. There were no

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discrepancies. There was no under-reporting of adverse events. The primary efficacy endpoint was verifiable.

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.

5. Francisco Munoz, M.D.
824 Elizabeth Avenue
Elizabeth, NJ 7201
Site: 1241

Dates of inspection: September 30 – October 10, 2019

During the start of the inspection of Site 1241 (Dr. Munoz), it was discovered that subjects had been transferred from a previous site (Dr. Mandeep Oberoi/ Site 1118) and that Dr. Munoz did not enroll any subjects on his own. This is in conflict with the Clinical Study Report Appendix 16.1.4 *List and description of investigators and sites* which incorrectly states that Site 1241 enrolled (screened) **20** subjects; footnote says 21 subjects transferred to Site 1241 from Site 1118 and 1 subject transferred back from Site 1241 to Site 1118.

Dr. Munoz was contacted by Boehringer Ingelheim to take over the clinical study from Dr. Mandeep Oberoi, Site1118. Dr. Munoz stated that he was told that almost all the study subjects had completed the active phase of care and that he would have to follow-up the health status of the study subjects by telephone. In February of 2015, he was given photocopies of previous medical records transferred from Dr. Oberoi's site. Dr. Munoz was given a new study site number and Dr. Oberoi's site was reportedly closed.

The IRB of record was Schulman IRB. Responsibilities were migrated from Schulman IRB to Advarra Contract IRB, Columbia, MD on June 15, 2018. The IRB allowed for consenting the subjects via mail; the site contacted the subjects by telephone to explain the ICF and obtained verbal consent to continue in the study and receive the ICF by mail.

Subject Screening and Enrollment Log for study subjects under Dr. Munoz' care reflects that there were 21 subjects that were transferred from Dr. Oberoi to Dr. Munoz. However, the file for Subject (b) (6) was empty, except for a photocopy of a Transfer Request reflecting that the subject had declined to transfer their records over to Dr. Munoz, and in a hand-written note on the transfer of records request, had withdrawn their consent to participate in the study.

The FDA inspector conducted a 100% review of the ICFs for each of the 20 study subjects. There were no original ICF forms from Dr. Oberoi's office in the study subjects' charts; photocopies of ICFs were in all 20 subjects' files. There were two active study subjects, (b) (6) and (b) (6) that were given investigational drug at Dr. Munoz's clinical site. They had original signed ICFs at Dr. Munoz's office prior to treatment by Dr. Munoz. One other

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study subject, (b) (6) also signed an ICF at Dr. Munoz's office. Study Subjects (b) (6) (b) (6) returned signed ICFs by mail. Five other subjects had expired.

Study Subjects (b) (6), and (b) (6) presented for follow-up, and in the case of Subjects (b) (6) and (b) (6) for treatment. The others were followed by phone and questioned about their health. Study Subjects (b) (6), and (b) (6) withdrew consent from the study.

Copies of the source records and all original source records were compared to the sponsor data line listings. There were no discrepancies noted other than what was in the CSR Appendix 16.1.4 regarding enrollment numbers. There was no under-reporting of adverse events. The primary efficacy endpoint was verifiable.

The inspection revealed adequate adherence by Dr. Munoz to the regulations and the investigational plan. There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, issued.

An amendment to the inspection assignment was made to inspect Site 1118/ Mandeep Oberoi and the sponsor (see information below later in report).

6. Mandeep Singh Oberoi, M.D.
1010 Coolidge Road
Elizabeth, NJ 07202-1004
Site: 1118

Dates of inspection: December 20 – January 10, 2020

There were **31** subjects screened and 21 subjects were randomized into the study. There were 30 subject records reviewed. This is in conflict with the Clinical Study Report Appendix 16.1.4 *List and description of investigators and sites* which states incorrectly that Site 1118 enrolled **11** subjects; footnote says 21 subjects transferred to Site 1241 and 1 subject was transferred back to Site 1118.

When Dr. Oberoi was contacted by the FDA inspector for the inspection, he was working in Pennsylvania and his study records were in a locked storage facility in Elizabeth, NJ. Dr. Oberoi arranged for the records to be examined at the office of Dr Sukhjender S. Goraya, who had purchased Dr. Oberoi's practice at 240 Williamson Street, Suite 305, in Elizabeth, NJ. Dr. Oberoi is maintaining 1010 Coolidge Ave., Elizabeth, NJ as his official address. He provided the medical records from his storage facility and provided copies of requested documents.

Dr. Oberoi started his practice in Internal Medicine in Elizabeth, NJ in 2008 and started clinical trial research soon after in the same year. Dr. Oberoi sold his practice in 2015. He now teaches and practices internal medicine at Penn State Medical School in central Pennsylvania. He stated that he is no longer involved in clinical trial research after selling

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his practice in 2015.

The IRB of record was Shulman Institutional Review Board.

Dr. Oberoi transferred copies of all medical records from the study subjects in the CAROLINA trial to another clinical investigator Francisco Munoz, M.D. in September of 2015. He kept control of the original clinical study records and placed them in storage.

The study subject records were in a state of general disarray. According to Dr. Oberoi, the files were taken apart in order to make copies for transfer to Dr. Munoz. The charts were made up of paper records with a two-hole punch on the top of each paper record and were fastened within each chart by a metal clip attached to the inside-top of each chart. The charts were disassembled for copying, but not reassembled to their original state. One file demonstrated some degree of water damage to the file jacket.

Source records were available except that records for Subject (b) (6) were missing. The chart for Subject (b) (6) was empty and none of the study subject's documents were present. These documents included the informed consent forms, drug dispensing records and laboratory test results.

One informed consent form for Subject (b) (6) demonstrated an issue. The ICF, version date 2/18/2013, was signed by the subject's grand-daughter instead of the subject on 4/15/2013. This error was identified, captured in a Note-to-File, reported to the IRB, and corrected on the next subject visit on 7/22/2013. This subject had 4 previous signed ICFs.

All randomized subjects reviewed met the inclusion criteria and none of the subjects exhibited any of the exclusion criteria. Study Subject (b) (6) was randomized and assigned medication but withdrew consent shortly after randomization.

Source records were compared to the sponsor data line listings. There were no discrepancies. There was no under-reporting of adverse events. The primary efficacy endpoint was verifiable.

At the conclusion of the inspection, a Form FDA-483, Inspectional Observations, was issued for investigational records not retained for a period of two years following approval of a drug's marketing application. Specifically, records for Study Subject (b) (6) were not retained.

OSI Reviewer Comment: A copy of the records were transferred to Dr Munoz' site.

7. **W.W. van Kempen M.D.,**
   Schieweg 52a
   Rotterdam, 3039 BD
   The Netherlands
   Site: 31012

Reference ID: 4557422

Dates of inspection: October 28 – November 1, 2019

There were **28** subjects screened and 14 subjects were randomized into the study; 13 subjects completed the study (9 completed treatment). There were 27 subject records reviewed (including 11 transferred records). Clinical Study Report Appendix 16.1.4 *List and description of investigators and sites* incorrectly states that **96** subjects were enrolled (screened) at the site; footnote says 8 subjects transferred from Site 31011, 11 subjects transferred from Site 31013, 11 subjects transferred from Site 31014, 6 subjects transferred from Site 31015, and 32 subjects transferred from Site 31016.

Dr. van Kempen's site closed on 9/27/2018, so the inspection was conducted at a hotel in Rotterdam (Hotel van der Valk Blijdorp, Energieweg 2, 3041 JC, Rotterdam, The Netherlands).

Karina E. van Wonderen, Senior Inspector, Health Care Inspectorate, Ministry of Health, Welfare and Sport was present throughout the inspection and acted as translator.

Dr. van Kempen was affiliated with Andromed B.V. since December 2001. Andromed B.V. was a Site Management Organization (SMO) that was founded in 1996. Andromed B.V. had a database of potential subjects that it amassed by advertising in newspapers and working with general practitioners. Andromed B.V. also recruited potential subjects from a laboratory in Groningen and the Vascular Medicine Department of the Erasmus University Rotterdam Medical Center. Andromed B.V. had 7 clinical sites in The Netherlands for Protocol 1218.0074. Dr. van Kempen currently works for an Occupational Health company.

All Andromed B.V. sites, including Dr. van Kempen's site (Site 31012), are now closed due to lack of clinical studies business. As of 2018, Andromed B.V. does not exist anymore as a company, but all study subject documents for Protocol 1218.0074 are maintained by an archive company in Rotterdam.

The IRB of record was Aan de Medisch Ethische Commissie (E2-170/172, Academisch Medisch Centrum, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands). The site was a non-IND site.

On or about April 2015, 5 of the 7 clinical sites in The Netherlands for Protocol 1218.0074 were voluntarily closed. Subjects from 4 of the 5 closed sites were transferred to Site 31012. The total number of subjects transferred at that time to Site 31012 was 36. Of the 36 subject that were transferred to Site 31012, 15 subjects completed treatment and the study, one subject expired while on treatment and in the study, and 20 subjects completed the study but not treatment.

On or about May 2018, a 6th site in The Netherlands closed (Site 31016), and 32 subjects from that site were transferred to Site 31012. At that time, Site 31012 was the only remaining open clinical site in The Netherlands for Protocol 1218.0074. Of the 32 subjects

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that were transferred to Site 31012, 12 subjects completed treatment and the study, and 20 subjects completed the study but not treatment.

Towards the end of the study on or about May 2018, the total number of subjects at Site 31012 was 82 (i.e., 14 subjects at Site 31012, 36 subjects transferred on or about April 2015, and 32 subjects transferred on or about May 2018).

During the inspection, the study subject files were locked and maintained in a restricted access room in the Hotel van der Valk Blijdorp. All 82 treated/randomized study subject source documents were available for review. All screen failed study subject source documents from Dr. van Kempen's site and the closed sites were also available for review.

Study documents were organized and appeared to be complete. Most of the subjects' hardcopy CRF source documents were in English, but comments were written in Dutch. The subject's diaries, protocol-specified questionnaires (i.e., the MMSE), medical history documents, progress notes, and related correspondence were in Dutch. The translator was used as much as possible. Source records were compared to the sponsor data line listings. There were no discrepancies. There was no under-reporting of adverse events. The primary efficacy endpoint was verifiable.

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.

8. Boehringer Ingelheim Pharmaceuticals, Inc.
900 Ridgebury Rd/P.O. Box 368
Ridgefield, CT 06877-0368
Sponsor

Dates of inspection: December 9 – 12, 2019

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.

Due to the issues found at the sites, the sponsor site was inspected. There is no discussion in the body of the CSR regarding transfer of subjects. In Appendix 16.1.4 *List and description of investigators and sites*, it lists the number of subjects enrolled (screened) at each site with a footnote of each site that transferred subjects. It was determined from the site inspections that this

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list is incorrect for sites that had transferred subjects but correct for all sites that were not involved with any transferring of subjects. This list was generated by clinical operations and was not checked by the statistical staff before placement in the CSR. During the inspection, the statistical staff walked through the analyses of several subjects and confirmed that data in the analyses reflected only one subject and not any duplicated data. Although the CSR Appendix enrollment (screened) numbers were incorrect, the analyses that were done on all randomized subjects appeared to have the correct number of subjects.

From the audit trail of (b) (4), Boehringer Ingelheim staff determined that 327 subjects transferred to another site, with 389 occurrences of transfers during the study (some subjects transferred more than once). Out of the 389 occurrences, there were 104 subjects that were on study drug at the time of the transfer.

Of note, there were also several "back transfers" where the subject was transferred to a site in remote data capture (RDC) in error and was then transferred back to the original site in RDC.

1. Site 01072/Dr. Thrasher: Site 01204/Dr. Harrell was closed on 14 June 2013. At the time of site closure, it was planned that Subjects (b) (6) would transfer to Site 01072/Dr. Thrasher. However, it was later identified that Drs. Thrasher and Harrell only spoke about Subjects (b) (6) and (b) (6) and did not speak about Subject (b) (6) Therefore, Subject (b) (6) was transferred back to Dr. Harrell in the RDC for vital status reporting.
2. Site 01241/Dr. Munoz: Site 01118/Dr. Oberoi was closed on 25 March 2015. At the time of site closure, it was planned that all subjects would transfer to Site 01241/Dr. Munoz. However, it was later identified that Subject (b) (6) did not agree to be transferred; therefore, Subject (b) (6) was transferred back to Dr. Oberoi in the RDC for vital status reporting.
3. Site 84235/Dr. Amato: Dr. Amato agreed to take over the care of Subjects (b) (6) (b) (6). The site was created in the RDC database, but the site was never initiated; the subjects were transferred back to Site 01013/Dr. Carlos in RDC for vital status reporting.

As reported in the CSR, 24 subjects were enrolled at more than one site in the US. Initial discovery and subsequent handling of these duplicate subjects was investigated. An overview was created on the trial level to investigate the finding from a global perspective. It appeared that the site investigators were unaware of their subjects enrolling at multiple sites. There is a flag in the subject data set indicating how subjects were to be considered for analysis; for all original subject ID of a duplicate subject, the flag would indicate that these subjects are not considered for analysis; for the new subject ID the flag indicates that this subject is considered for analysis.

Boehringer Ingelheim dismissed the CRO (b) (4) initially hired to monitor sites in the US due to poor performance and brought the monitoring in-house with their own Monitoring Plan.

During the trial, Boehringer Ingelheim did have drug supply issues. By March 2012, it was noted that there were several "forced randomizations" in France, due to late acknowledgements of

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medication shipments by sites. In total, there were 98 cases of forced randomization in the study between March 10, 2011 and March 27, 2012. Five subjects were force-randomized into the linagliptin treatment group and 93 subjects were force-randomized into the glimepiride treatment group. Study sites were not aware of a forced randomization, as the system automatically, without prior notification, force-randomized the subject into the treatment group with available medication stock during the randomization visit. From a quality point of view the number of forced randomizations should be kept to a minimal. Therefore, further forced randomizations were stopped. The study team would not allow further forced randomizations in the IXRS due to late medication shipments confirmations, i.e., subjects could not be randomized anymore if medication was not "available" (in the IXRS system) on site. After this decision, a gap in protocol required medication occurred in 191 cases. The time off treatment ranged from 1 day – 368 days.

Although there was lack of IP, it was determined that subject safety was not affected by the IP interruption as there were various alternative ways for the investigator to manage the subjects T2DM outside the scope of the trial (i.e., by prescribing commercially available medication). Data integrity was considered not adversely affected by the failure to supply IP as the protocol allows for temporary discontinuation of IP. Boehringer Ingelheim failed to fulfill their commitment to subjects to supply IP, although other treatment options were available to subjects. In summary, the number of subjects that stopped medication then were restarted for any reason were 232 subjects, 115 for Glimepiride and 117 for Linagliptin.

At the conclusion of the inspection, a Form FDA-483, Inspectional Observations, was issued for the following deficiencies:

1. Failure to notify FDA of the ending, for-cause, of an investigator's participation in an investigation.

Specifically, the sponsor terminated Site 1220/ Dr. Jonathan Wise, on June 14, 2012, due to a lack of clinical investigator oversight, being unresponsive to sponsor's requests, delinquent remote data capture, and failure to complete training on Protocol 1218.74. The sponsor did not notify FDA of the end of the clinical investigator's participation in the investigation. This site enrolled 3 subjects.

Participation of the clinical investigator at Site 1205/ Dr. Samuel Teniola was terminated by the sponsor on May 19, 2015, due to poor oversight by the investigator. The sponsor did not notify FDA of the end of the clinical investigator's participation in the investigation. This site enrolled 13 subjects; 5 subjects transferred to Site 1172.

A hold was placed on enrollment and randomization of the clinical investigator at Site 1035/ Dr. Clarita Ketel on November 11, 2011, related to concerns of Good Clinical Practice (GCP) noncompliance. The investigator's participation in the study ended on May 14, 2012. The sponsor did not notify FDA of the ending of the clinical investigator's participation in the investigation. The site enrolled 8 subjects.

<u>OSI Reviewer Comment</u>: Although the CSR listed 10 sites that were closed for-cause, there were 16 sites closed. During the investigation of the additional sites found in the sponsor files, it was

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discovered that three other sites had been reported to the FDA but not listed in the CSR (1173, 1066, 1218). There was initial discussion regarding the closing of Site 1035. Although the investigator voluntarily closed the site, communications between the sponsor staff confirmed that they had already decided to terminate the site. It was discussed that this was a non-compliant site and FDA would want to be aware of their actions. Boehringer Ingelheim acknowledged the deficiency in their internal process for accurately documenting sites closed for-cause and also the lack of reporting to the FDA and reporting in the CSR.

2. Failure to ensure that an investigation was conducted in accordance with the general investigational plan and protocols as specified in the IND.

Specifically, there is no discussion in the protocol regarding transfer of subjects to an alternative site.

There is no discussion in the Monitoring Plan regarding transfer of subjects to an alternative site.

In the BRAVE Version 2.0 for the Electronic Data Capture System, section Subject Transfer, it states, "If a subject relocates from one city to another during an ongoing trial this subject can remain in the trial, **if the new location of the subject has another site nearby**. In this situation the subject needs to be transferred from the old site to the new site in BRAVE – as well as in IRT and BICTMS."

The study Operations Manual Version 2, Final 22 April 2013, Section 2.3 describes the Patient Site Transfer Process. There is no mention of transferring of subjects to a **remote** site that is not geographically near the subject. There is no mention how subjects will be handled if an adverse event develops and a clinic visit is needed, how laboratory testing will be accomplished, or how any procedure needing subject contact with the clinical site will be accomplished.

There were 10 sites that accepted 27 subjects that were not geographically located in the same state as the clinical investigator. This included having subjects transferred to the Protocol Coordinating Investigator, who was a member of the Steering Committee. The sites and locations are listed below:

Study Subjec	original Site	Original city	Original	New Site	new city	new state
(b) (6)	01150	Harleysvill	Pennsylvan	1007	Avon	Indiana
	01158	Bristol	Tennessee	1183	Brownsbur	Indiana
	01156	Davie	Florida	1183	Brownsbur	Indiana
	01156	Davie	Florida	1183	Brownsbur	Indiana
	01204	Little	Arkansas	1183	Brownsbur	Indiana
	01013	Mobile	Alabama	1183	Brownsbur	Indiana

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(b) (6)

01013	Mobile	Alabama	1183	Brownsbur	Indiana
01013	Mobile	Alabama	1183	Brownsbur	Indiana
01191	Miami	Florida	1046	Dallas	Texas
01191	Miami	Florida	1046	Dallas	Texas
01040	Tulsa	Oklahoma	1046	Dallas	Texas
01183	Brownsbur	Indiana	1150	Harleysvill	Pennsylvan
01008	Minneapol	Minnesota	1155	Jonesboro	Arkansas
01098	Kalamazo	Michigan	1072	Little	Arkansas
01151	Jacksonvil	Florida	1200	Mesa	Arizona
01047	Tucson	Arizona	1196	Midvale	Utah
01047	Tucson	Arizona	1196	Midvale	Utah
01047	Tucson	Arizona	1196	Midvale	Utah
01047	Tucson	Arizona	1196	Midvale	Utah
01155	Jonesboro	Arkansas	1008	Minneapol	Minnesota
01173	Austin	Texas	84234	Tucson	Arizona
01173	Austin	Texas	84234	Tucson	Arizona
01196	Midvale	Utah	84234	Tucson	Arizona
01196	Midvale	Utah	84234	Tucson	Arizona
01196	Midvale	Utah	84234	Tucson	Arizona
01196	Midvale	Utah	84234	Tucson	Arizona
01031	New Braunfe	Texas	84234	Tucson	Arizona

The sponsor had subjects transferred to Site 1046/Dr. Julio Rosenstock (Coordinating investigator and Chairman, Steering Committee). As noted in the Steering Committee Charter, members must be independent of the persons and/or organizations with a vested interest in the study conduct or outcome, so that any potential conflict of interest is avoided.

In addition, there was no documentation of IRB approval of the transfer of 8 subjects and no documentation at the firm that all subjects were reconsented.

OSI Reviewer Comment: It was stressed to Boehringer Ingelheim staff that there were several concerns with the transferring of the subjects to remote sites hundreds of miles from the subjects' homes: (1) there was no mention in the protocol that such arrangements could be made (2) there was no mention in the CSR about such transfers (3) there were no written procedures in place to address transferring subjects to a remote site (4) there were safety concerns with subjects not having easy access to the clinical site if they were to need assessment and/or treatment (5) subjects

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needed to be reconsented by the accepting investigator site and there was no discussion in the protocol for the ability to consent remotely and there were no procedures in place for remote consenting.

Furthermore, the appearance of a potential conflict of interest was discussed with the transferring of subjects to Dr. Rosenstock's site.

The sponsor staff acknowledged the lack of clarity with their procedures and the potential appearance of a conflict of interest.

3. Records and reports were not retained for two years after discontinuance of the investigation and notification of FDA. Specifically, the sponsor failed to produce the 23 Data Monitoring Committee (DMC) Closed Meeting Minutes for FDA review during the inspection.

OSI Reviewer Comment: Open and closed data monitoring committee meetings were conducted during Study 1218.74 to review safety and efficacy data and make recommendations as to whether to continue the study, continue the study with modifications, or terminate the study. Closed DMC session included only DMC members and an independent statistician. The study DMC chair maintained the records for the closed session meetings to ensure blinding. The closed DMC meeting minutes were to be forwarded to the sponsor by the DMC chair at the end of study completion in order to avoid unblinding. These closed DMC meeting minutes were not forwarded and, therefore, not retained in the trial master file at the conclusion of the study. Sponsor staff was unaware of these meeting minutes missing and was in the process of contacting the DMC chair to obtain.

Boehringer Ingelheim sent a written response to the 483 observations on December 20, 2019 and a follow-up response on January 24, 2020. The DMC closed meeting minutes were submitted as well as Corrective and Preventive Action (CAPA) plans. The response was deemed acceptable.

It is acknowledged that Study 1218.74 was a very large trial. Issues did occur but the sponsor staff generally dealt with them appropriately and in a timely manner. There had also been a lot of process improvement and development of improved procedures since the beginning of the trial. Although regulatory violations were noted as described above, they are unlikely to significantly impact primary safety and efficacy analyses. Data from this sponsor appear acceptable.

ADDITIONAL INFORMATION
The following four (#9-#12) previous for-cause inspections were conducted prior to submission of the supplemental application. None of the inspections led to any regulatory actions.

9. Percy Conrad May, Jr., M.D.
3857 West Washington Blvd.
Suburban Clinical Research
Chicago, IL 60624
Site: 1115

Reference ID: 4557422

Dates of inspection: February 20 – May 4, 2015 (with two interruptions)

There were 32 subjects screened and 7 subjects enrolled into the study. There were 32 subject records reviewed. All subjects discontinued the study when the sponsor closed the study site.

Boehringer Ingelheim made the decision to close this site early following a sponsor audit that revealed non-compliance, citing (1) study participation of enrolled subjects that could not be reconstructed (2) a lack of contemporaneous and complete study documentation in which they concluded the data was unsubstantiated and deemed unreliable and (3) lack of investigator oversight.

It was noted during the inspection that there were multiple citations in the monitoring letters that the CRFs were not being completed in a timely manner, there was missing subject data, missing regulatory documents, missing ECG reports and incomplete investigational product (IP) accountability logs. There was also a lot of research staff turnover.

The site was placed on administrative hold October 10, 2012. The sponsor did a site audit November 2012. On February 5, 2013 Boehringer Ingelheim sent a notification of study site closure for-cause. The letter was also sent to the FDA.

At the conclusion of the inspection, a Form FDA-483, Inspectional Observations, was issued for not following the protocol. Four of seven subjects enrolled subjects did not meet the enrollment criteria. It was also noted in discussions with the site that there were several notes that were not dated, several documents without the investigator's signature, documents missing from the Regulatory folder, and missing IP.

Dr. May provided a written response dated May 14, 2015, to the Form FDA 483 and provided a corrective action plan.

Boehringer Ingelheim determined that the site's data was not to be used in analyses, but adverse event data was to be listed.

10. Debra Carter-Miller, M.D
Mapleton Medical Center
101 East 34th Street
Indianapolis, Indiana 46205-3408
Site: 1014

Dates of inspection: May 6 - June 11, 2015

There were 3 subjects screened and 2 subjects enrolled into the study; no subjects completed the study. The two subjects were discontinued from the study because they refused to change sites after site closure and were taking prohibited medication. There were 3 subject records reviewed.

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This inspection of Debra Carter-Miller, M.D. was conducted for-cause in response to Boehringer Ingelheim's report of non-compliance. Boehringer Ingelheim reported the termination of Dr. Carter-Miller's conduct of Protocol 1218.74. The sponsor's decision to terminate Dr. Carter-Miller in May 2015 was based on the sponsor's understanding that the site was under investigation by the Drug Enforcement Administration (DEA) for prescribing controlled substances without a legitimate medical purpose. In addition, the sponsor's report indicated that Dr. Carter-Miller was unresponsive to sponsor's request to discuss the DEA case.

At the conclusion of the inspection, a Form FDA-483, Inspectional Observations, was issued for the following deficiencies:

1. Investigation was not conducted in accordance with the investigational plan
2. Failure to assure that an IRB complying with applicable regulatory requirements was responsible for the initial and continuing review and approval of a clinical study
3. Failure to prepare or maintain adequate and accurate case histories
4. Failure to report promptly to the IRB all unanticipated problems involving risk to human subjects or others
5. Inadequate drug disposition records
6. Failure to permit an authorized officer or employee of FDA to have access to, copy, and verify records

Boehringer Ingelheim determined that the site's data could be used in analyses.

11. Fernandez-Miro Humberto, MD
401 Miracle Mile, Suite 302
Coral Gables, FL 33134
Site: 1117

Dates of inspection: April 5 - 13, 2017.

There were 75 subjects screened and 29 subjects enrolled into the study; no subjects completed the study because the sponsor terminated the site. There were 25 subject records reviewed.

The firm where the clinical trial took place was Doral Research Center previously located at 10454 NW 31st Terrace, Doral, FL 33172. As of 4/4/17, when the inspection began, the site is no longer operational.

Dr. Fernandez-Miro began working at Doral Research Center in August 2011, taking over for the previous Clinical Investigator, Dr. Jose Nunez, for whom Dr. Fernandez-Miro was not a sub-investigator. At the time he took over from Dr. Nunez, Dr. Fernandez-Miro stated he didn't realize that Dr. Nunez was convicted for Medicare fraud. Boehringer Ingelheim became aware that Dr. Nunez was found guilty of Medicare Fraud, and issued an enrollment hold and conducted a for-cause audit of the investigator site on August 14, 2012. Dr. Fernandez-Miro was informed that the sponsor was shutting down his site's participation in the study on September 27, 2012 due to his failure to inform the sponsor or IRB about Dr. Nunez's indictment for Medicaid fraud, a lack of documentation for study entry criteria to include previous patient medical records, and lack of documented evidence of investigator oversight and inappropriate delegation of trial related

Reference ID: 4557422

activities. Twenty-nine (29) subjects were enrolled based on their HbA1c result only, with no other study entry criteria documented and without any exclusionary condition being reported. Multiple instances were found where Dr. Fernandez-Miro signed source documents before he was approved by the IRB as the Site Investigator.

At the conclusion of the inspection, a Form FDA-483, Inspectional Observations, was issued for failure to follow the protocol and not all changes in research activity were approved by an Institutional Review Board prior to implementation. Dr. Fernandez-Miro began taking over the role of Investigator from Dr. Nunez prior to IRB approval. In addition, two subjects had inconsistencies with the signatures on their ICFs. Subject (b) (6) appeared to have two different signatures on the 4/1/11 and 12/12/11 ICF and Subject (b) (6) had the 9/15/11 ICF signed on 2/21/12 while the subject's final follow-up visit occurred on 11/1/11.

Dr. Fernandez-Miro submitted a written response dated April 26, 2017 and included corrective actions.

Boehringer Ingelheim determined that the site's data could be used in analyses but would be excluded from the per protocol set (PPS).

12. Walter Fowler, M.D.
Novant Medical Group
4205 Ben Franklin Boulevard
Durham, NC 27704
Site: 1021

Dates of inspection: May 27 - June 3, 2014, and October 14 - 15, 2014

There were 8 subjects screened and 6 subjects enrolled into the study; no subjects completed the study. There were 6 subject records reviewed.

This inspection was conducted in response to Boehringer Ingelheim's report (dated September 24, 2013) of non-compliance. The report indicated that Dr. Fowler's site participation was terminated September 18, 2013 based on a sponsor audit (August 2013) that revealed the following noncompliance issues during the conduct of Protocol 1218.74:

- fraudulent activities
  - discrepancy between subject signatures on original informed consent documents (ICDs), hospital records, and updated versions of ICDs
  - sub-investigator's signatures appear to be incorrect or falsified/altered on laboratory reports
  - inconsistent subject's handwriting on home glucose monitoring diary logs
  - subjects reported that site staff did not complete a series of blood pressure readings; however, sponsor has records suggesting otherwise.
- poor clinical trial oversight
- protocol deviations

Reference ID: 4557422

- inadequate adverse event reporting within the required timeframe

At the conclusion of the inspection, a Form FDA-483, Inspectional Observations, was issued for failure to follow the protocol and inadequate record keeping. Discrepancies with study documentation occurred during the tenure of an ex-study coordinator who was terminated in May 2013.

Boehringer Ingelheim determined that the site's data was not to be used in analyses, but adverse event data was to be listed.

The data analysis from subjects of closed sites was prespecified in the trial's Statistical Analysis Plan and summarized in the Clinical Study Report.

{See appended electronic signature page}

Cynthia F. Kleppinger, M.D.
Senior Medical Officer
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE: *{See appended electronic signature page}*

Min Lu, M.D., M.P.H.
Team Leader
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Office of Scientific Investigations

CONCURRENCE: *{See appended electronic signature page}*

Kassa Ayalew, M.D., M.P.H
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

Reference ID: 4557422

cc:

Central Doc. Rm./ NDA 201280/s020
DMEP/Acting Division Director/ Lisa Yanoff
DMEP /Acting Deputy Director/William Chong
DMEP/Team Lead/Patrick Archdeacon
DMEP/Clinical Reviewer/ Hyon J. Kwon
DMEP /Regulatory Project Manager/Rich Whitehead
OSI/DCCE/Division Director/Ni Aye Khin
OSI/DCCE/GCPAB/Branch Chief/Kassa Ayalew
OSI/DCCE/GCPAB/Team Leader/Min Lu
OSI/DCCE/GCPAB Reviewer/Cynthia Kleppinger
OSI/DCCE/GCPAB/Program Analyst/Yolanda Patague
OSI/DCCE/Database Project Manager/Dana Walters

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/s/

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KASSA AYALEW
02/06/2020 10:37:37 AM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: March 19, 2020

To: Richard Whitehead, Regulatory Project Manager
Division of Metabolism and Endocrinology Products (DMEP)

LaiMing Lee, Associate Director for Labeling, DMEP

From: Meena Savani, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Samantha Bryant, Regulatory Review Officer, OPDP

CC: Melinda McLawhorn, Team Leader, OPDP

Subject: OPDP Labeling Comments for TRADJENTA® (linagliptin) tablets, for oral use, JENTADUETO® (linagliptin and metformin hydrochloride) tablets, for oral use, JENTADUETO® XR (linagliptin and metformin hydrochloride extended-release) tablets, for oral use, and GLYXAMBI® (empagliflozin and linagliptin) tablets, for oral use

NDA: 201280/Supplement 020
201281/Supplement 024
208026/Supplement 012
206073/Supplement 021

In response to DMEP's consult request dated June 6, 2019, OPDP has reviewed the proposed product labeling (PI) and Medication Guides for Tradjenta, Jentadueto, Jentadueto XR, and Glyxambi. These supplements (S020, S024, 012, 021) provide for changes to the labeling based on the results of the CAROLINA study.

PI and Medication Guide: OPDP's comments on the proposed labeling are based on the draft PIs and Medication Guides received by electronic mail from DMEP (Richard Whitehead) on March 16, 2020 and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed Medication Guides will be sent under separate cover

Thank you for your consult. If you have any questions, please contact Meena Savani at (240) 402-1348 (Meena.Savani@fda.hhs.gov) or Samantha Bryant at (301) 348-1711 (Samantha.Bryant@fda.hhs.gov).

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SAMANTHA E BRYANT
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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs

PATIENT LABELING REVIEW

Date:	March 20, 2020
To:	Richard Whitehead, MS Senior Regulatory Project Manager **Division of Metabolism and Endocrinology Products (DMEP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Marcia Williams, PhD Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Nyedra W. Booker, PharmD, MPH Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Samantha Bryant, PharmD, BCPS Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)** Meena Savani, PharmD, RAC **Regulatory Review Officer** **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name), Dosage Form and Route, Application Type/Number and Supplement Number:	TRADJENTA (linagliptin tablets), for oral use, NDA 201280/S-020 JENTADUETO (linagliptin and metformin tablets), for oral use, NDA 201281/S-024 JENTADUETO XR (linagliptin and metformin hydrochloride extended-release tablets), for oral use, NDA 208026/S-012

	GLYXAMBI (empagliflozin and linagliptin tablets), for oral use, NDA 206073/S-021
Applicant:	Boehringer Ingelheim Pharmaceuticals, Inc.

1 INTRODUCTION

On May 30, 2019 Boehringer Ingelheim Pharmaceuticals, Inc. submitted for the Agency's review a Supplemental New Drug Application (sNDA)(Efficacy)-Trial 1218.74 for TRADJENTA (linagliptin tablets), for oral use (NDA 201280/S-020) and the following linagliptin combination products: JENTADUETO (linagliptin and metformin tablets), for oral use (NDA 201281/S-024), JENTADUETO XR (linagliptin and metformin hydrochloride extended-release tablets), for oral use, (NDA 208026/S-012) and GLYXAMBI (empagliflozin and linagliptin tablets), for oral use (NDA 206073 S-021).

The purpose of these sNDAs is to propose revisions to the prescribing information (PI) for TRADJENTA and linagliptin combination products JENTADUETO, JENTADUETO XR and GLYXAMBI based on results of a multi-center, international, randomized parallel group, double-blind study to evaluate cardiovascular safety of linagliptin versus glimepiride in patients with type 2 diabetes mellitus (T2DM) at high cardiovascular risk (The CAROLINA Trial).

This collaborative review is written by Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Metabolism and Endocrinology Products (DMEP) on June 6, 2019 for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for TRADJENTA (linagliptin tablets), for oral use, JENTADUETO (linagliptin and metformin tablets), for oral use, JENTADUETO XR (linagliptin and metformin hydrochloride extended-release tablets), for oral use and GLYXAMBI (empagliflozin and linagliptin tablets), for oral use.

2 MATERIAL REVIEWED

- Draft TRADJENTA (linagliptin tablets), for oral use, JENTADUETO (linagliptin and metformin tablets), for oral use, JENTADUETO XR (linagliptin and metformin hydrochloride extended-release tablets), for oral use and GLYXAMBI (empagliflozin and linagliptin tablets), for oral use MGs received on May 30, 2019, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on March 16, 2020.
- Draft TRADJENTA (linagliptin tablets), for oral use, JENTADUETO (linagliptin and metformin tablets), for oral use, JENTADUETO XR (linagliptin and metformin hydrochloride extended-release tablets), for oral use and GLYXAMBI (empagliflozin and linagliptin tablets), for oral use PIs received on May 30, 2019, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on March 16, 2020.
- Approved TRIJARDY XR (empagliflozin, linagliptin, and metformin hydrochloride extended-release tablets), for oral use comparator labeling dated January 27, 2020.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the MGs we have:

- simplified wording and clarified concepts where possible
- ensured that the MGs are consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MGs are free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MGs meet the Regulations as specified in 21 CFR 208.20
- ensured that the MGs meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MGs are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our review of the MGs is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MGs.

Please let us know if you have any questions.

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/s/

NYEDRA W BOOKER
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MEENA R SAVANI
03/20/2020 04:03:38 PM

SAMANTHA E BRYANT
03/23/2020 08:33:56 AM

MARCIA B WILLIAMS
03/23/2020 08:45:16 AM

LASHAWN M GRIFFITHS
03/23/2020 08:53:06 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206073Orig1s021

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 206073 SUPPL # 021 HFD # 510

Trade Name Glyxambi

Generic Name empagliflozin and linagliptin

Applicant Name Boehringer Ingelheim Pharmaceuticals, Inc.

Approval Date, If Known March 30, 2020

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

SE8

b) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☐ NO ☒

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

This submission proposes revisions to the TRADJENTA prescribing information to include information based on results of Study 1218.74, entitled: A multicentre, international, randomised, parallel group, double blind study to evaluate Cardiovascular safety of linagliptin versus glimepiride in patients with type 2 diabetes mellitus at high

Reference ID: 4583048

cardiovascular risk. The CAROLINA Trial

c) Did the applicant request exclusivity?

YES ☒ NO ☐

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

Three years of exclusivity was claimed in NDA201280/S-020 (this submission is cross-referenced) under 21 CFR 314.l 08(b)(5) (i) New Clinical Investigations, (ii) Essential to Approval, and (iii) Conducted or Sponsored By

d) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☐ NO ☐

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If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☒ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 206073	Glyxambi (empagliflozin and linagliptin) tablets
NDA# 201280	Tradjenta (linagliptin) tablets
NDA# 201281	Jentadueto (linagliptin and metformin hydrochloride) tablets
NDA# 208026	Jentadueto XR (linagliptin and metformin hydrochloride extended-release) tablets

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed

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only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☒ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☒ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☒

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☐

If yes, explain:

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(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☒

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Study 1218.74- A multicentre, international, randomised, parallel group, double blind study to evaluate Cardiovascular safety of linagliptin versus glimepiride in patients with type 2 diabetes mellitus at high cardiovascular risk. The CAROLINA Trial (c23238241-01)

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES ☒ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

Study 1218.74 in NDA 201280/S-020 Tradjenta (approved concurrently on March 30, 2020)

PLEASE NOTE that the following four SE8 supplements were approved concurrently for changes which were supported by Study 1218.74 (CAROLINA):

- NDA 201280/S-020 Tradjenta (linagliptin) tablets
- NDA 201281/S-024 Jentadueto (linagliptin and metformin hydrochloride) tablets
- NDA 206073/S-021 Glyxambi (empagliflozin and linagliptin) tablets
- NDA 208026/S-012 Jentadueto XR (linagliptin and metformin hydrochloride extended-release) tablets
-

Supplement NDA 201280/S-020 containing Study 1218.74 was received on May 30, 2019. Supplements NDA 201281/S-024, NDA 206073/S-021, and NDA 208026/S-012 were received on June 5, 2019 and contained cross-references to Study 1218.74 in NDA 201280/S-020. All four supplements were approved concurrently on March 30, 2020, using a single combined approval letter.

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES ☐	NO ☒
Investigation #2	YES ☐	NO ☐

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial

support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1: IND 070963 on June 13, 2019 (Sequence 0555, Serial Number 0750)

IND # 070963	YES ☒	NO ☐ Explain:

Investigation #2		
IND #	YES ☐	NO ☐ Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	
YES ☐ Explain:	NO ☐ Explain:

Investigation #2	
YES ☐ Explain:	NO ☐ Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to

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the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☒

If yes, explain:

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Name of person completing form: Richard Whitehead, M.S.
Title: Senior Regulatory Project Manager
Date: March 30, 2020

Name of Division Director signing form: Lisa B. Yanoff, M.D.
Title: Director (Acting)
Signed by: Patrick Archdeacon, M.D., Clinical Team Lead/CDTL, on behalf of Dr. Yanoff

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

RICHARD E WHITEHEAD
03/30/2020 09:10:19 AM

PATRICK ARCHDEACON
03/30/2020 12:52:30 PM
On behalf of Lisa Yanoff