CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

206073Orig1s017

Trade Name: **GLYXAMBI**

Generic Name: Empagliflozin and Linagliptin

Sponsor: Boehringer Ingelheim Pharmaceuticals, Inc.

Approval Date: 07/03/2019

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. However, the effectiveness of GLYXAMBI on reducing the risk of cardiovascular death in adults with type 2 diabetes mellitus and cardiovascular disease has not been established (1)

CENTER FOR DRUG EVALUATION AND RESEARCH

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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APPROVAL LETTER

NDA 201280/S-018
NDA 201281/S-022
NDA 206073/S-017
NDA 208026/S-008

SUPPLEMENT APPROVAL
FULFILLMENT OF POSTMARKETING REQUIREMENT

Boehringer Ingelheim Pharmaceuticals, Inc.
Attention: Joerg Schnitzler, Ph.D. and Madhuri Jerfy, M.S.
Senior Associate Director and Associate Director, Regulatory Affairs
900 Ridgebury Road, P.O. Box 368
Ridgefield, CT 06877

Dear Dr. Schnitzler and Ms. Jerfy:

Please refer to your supplemental new drug applications (sNDAs) dated and received September 5, 2018, for NDA 201280 and September 12, 2018, for NDA 201281, NDA 206073, and 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 sNDAs provide for changes to the Prescribing Information and Medication Guides based on results of study 1218.22 entitled, "A Multicenter, International, Randomized, Parallel Group, Double-blind, Placebo-Controlled Cardiovascular Safety and Renal Microvascular Outcome Study with Linagliptin, 5 mg Once Daily in Patients with Type 2 Diabetes Mellitus at High Vascular Risk," (CARMELINA). The CARMELINA trial was conducted to fulfill PMR 1766-4 for NDA 201280.

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 this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in 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 application, 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.

FULFILLMENT OF POSTMARKETING REQUIREMENT

The supplemental application for NDA 201280 contained the final report for the following postmarketing requirement listed in the May 2, 2011, approval letter for NDA 201280.

1766-4 A randomized, double-blind, placebo-controlled trial evaluating the effect of Tradjenta (linagliptin) tablets on the incidence of major adverse cardiovascular events in patients with type 2 diabetes mellitus.

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

We remind you that there is a postmarketing requirement listed in the December 22, 2017, postapproval postmarketing requirement letter that is still open for NDA 201280.

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]

[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.

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).

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

Sincerely,

{See appended electronic signature page}

Lisa B. Yanoff, M.D.
Director (Acting)
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling (Prescribing Information and Medication Guides) for Tradjenta, Jentadueto, Glyxambi, and Jentadueto XR

[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

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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/

LISA B YANOFF
07/03/2019 03:08:51 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206073Orig1s017

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----------

Warnings and Precautions	
Pancreatitis (5.1)	7/2019
Necrotizing Fasciitis of the Perineum (Fournier's Gangrene) (5.8)	10/2018
Bullous Pemphigoid (5.13)	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. However, the effectiveness of GLYXAMBI on reducing the risk of cardiovascular death in adults with type 2 diabetes mellitus and cardiovascular disease has not been established (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 such as anaphylaxis, angioedema, exfoliative skin conditions, urticaria, or bronchial hyperreactivity (4)

----------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 and Impairment in Renal Function* 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* Discontinue GLYXAMBI, treat promptly, and monitor until signs and symptoms resolve. (5.10)
- *Increased LDL-C* Monitor and treat as appropriate (5.11)
- *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. (5.12)
- *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. (5.13)

----------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: 7/2019

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)]*. However, the effectiveness of GLYXAMBI on reducing the risk of cardiovascular death in adults with type 2 diabetes mellitus and cardiovascular disease has not been established.

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 such as anaphylaxis, angioedema, exfoliative skin conditions, urticaria, or bronchial hyperreactivity *[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 due to illness or 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. In patients treated with GLYXAMBI consider monitoring for ketoacidosis and temporarily discontinuing GLYXAMBI in clinical situations known to predispose to ketoacidosis (e.g., prolonged fasting due to acute illness or surgery).

5.5 Acute Kidney Injury and Impairment in Renal Function

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 insufficiency, congestive 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 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 Increased Low-Density Lipoprotein Cholesterol (LDL-C)

Increases in LDL-C can occur with empagliflozin *[see Adverse Reactions (6.1)]*. Monitor and treat as appropriate.

5.12 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.

5.13 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 and Impairment in Renal Function *[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)]*
- Increased Low-Density Lipoprotein Cholesterol (LDL-C) *[see Warnings and Precautions (5.11)]*
- Severe and Disabling Arthralgia *[see Warnings and Precautions (5.12)]*
- Bullous Pemphigoid *[see Warnings and Precautions (5.13)]*

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.

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 *[see Warnings and Precautions (5.11)]*. 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.

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 6-10% in women with pre-gestational diabetes with a HbA1c >7 and has been reported to be as high as 20-25% in women with HbA1c >10. The estimated background risk of miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk: Poorly controlled diabetes in pregnancy increases the maternal risk for diabetic ketoacidosis, pre-eclampsia, spontaneous abortions, preterm delivery, 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 -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

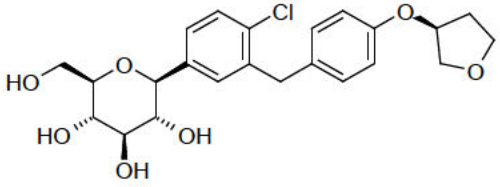
GLYXAMBI tablets contain two oral antihyperglycemic drugs used in the management of type 2 diabetes: empagliflozin and linagliptin.

Empagliflozin

Empagliflozin is an orally-active inhibitor of the sodium-glucose co-transporter (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:



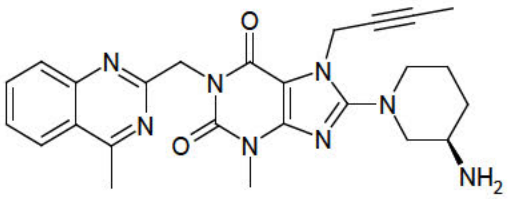
Empagliflozin is a white to yellowish, non-hygroscopic powder. It is very slightly soluble in water, sparingly soluble in methanol, slightly soluble in ethanol and acetonitrile; soluble in 50% acetonitrile/water; and practically insoluble in toluene.

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.

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

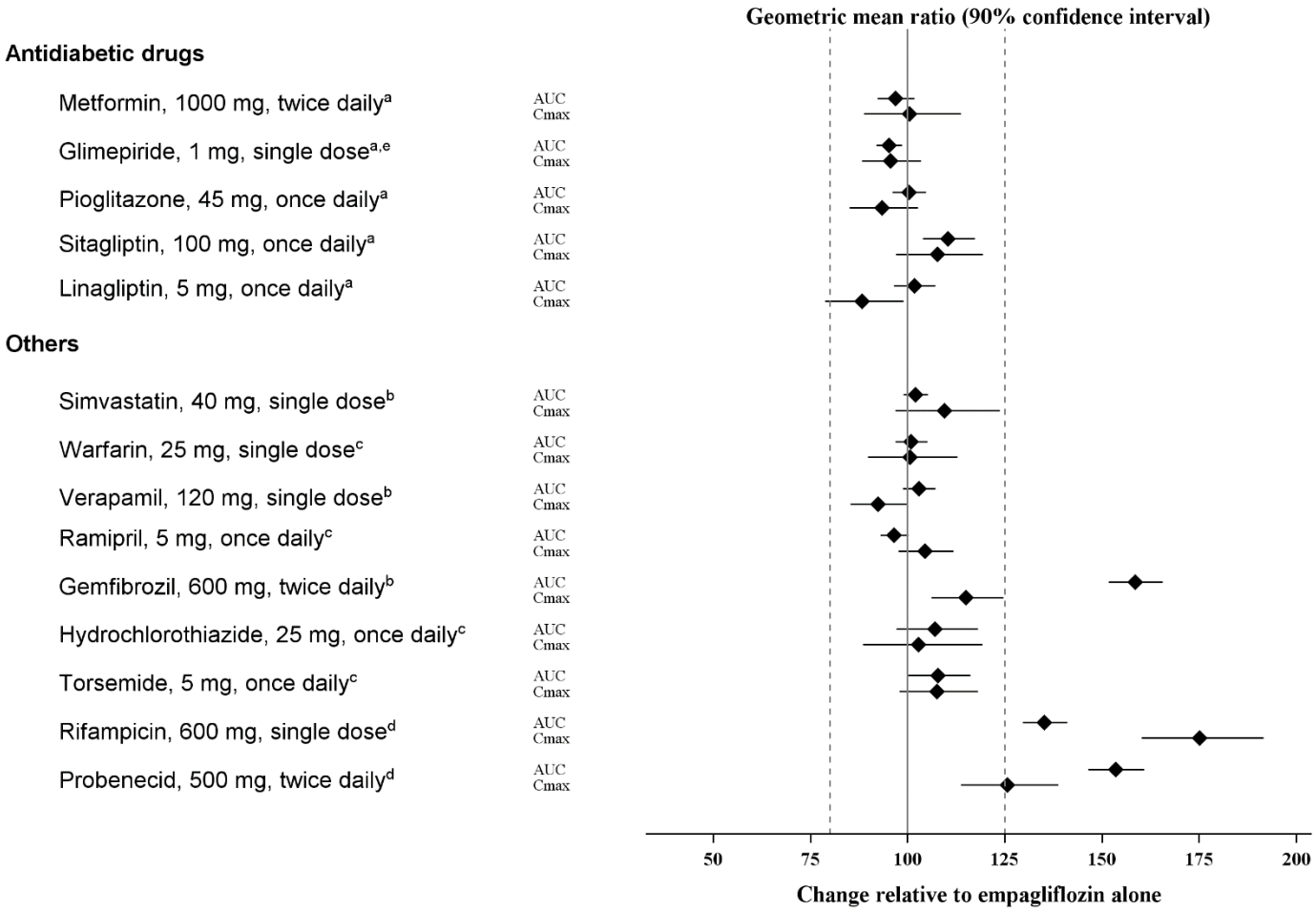
In vitro data suggest that the primary route of metabolism of empagliflozin in humans is glucuronidation by the uridine 5'-diphospho-glucuronosyltransferases UGT2B7, UGT1A3, UGT1A8, and UGT1A9. Empagliflozin does not inhibit, inactivate, or induce CYP450 isoforms. Empagliflozin also does not inhibit 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

No dose adjustment of empagliflozin is recommended when coadministered with commonly prescribed medicinal products based on results of the described pharmacokinetic studies. 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). The observed increases in overall exposure (AUC) of empagliflozin following coadministration with gemfibrozil, rifampicin, or probenecid are not clinically relevant. 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%)]

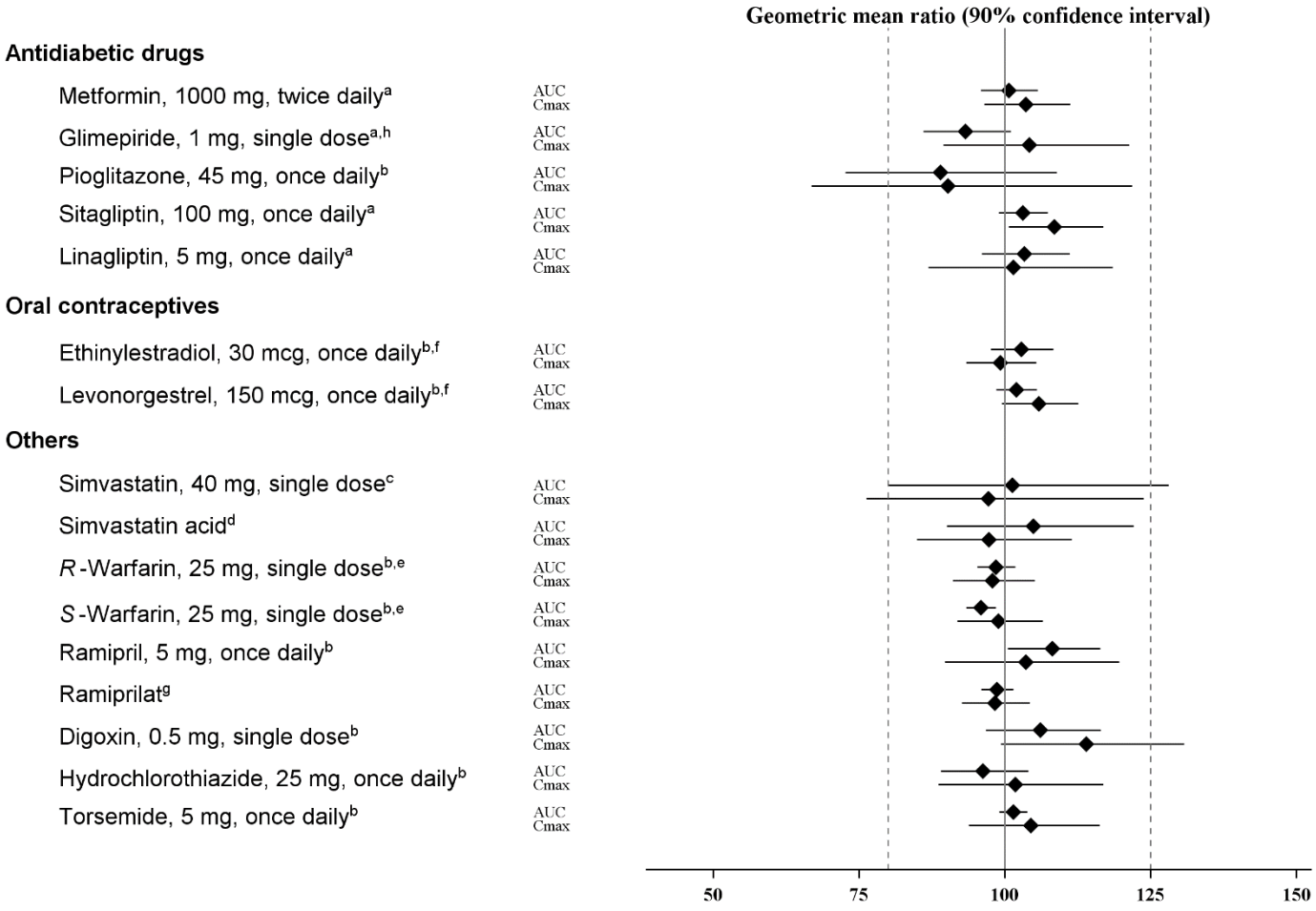


[a]empagliflozin, 50 mg, once daily; [b]empagliflozin, 25 mg, single dose; [c]empagliflozin, 25 mg, once daily; [d]empagliflozin, 10 mg, single dose

[e]Coadministration of empagliflozin 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) and Drug Interactions (7.3)]*.

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
[h]Coadministration of empagliflozin 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) and Drug Interactions (7.3)]*.

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. For patients requiring use of such drugs, an alternative to linagliptin is

strongly recommended. *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). No dose adjustment of linagliptin is recommended based on results of the described pharmacokinetic studies.

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[e]	C_{max}
Metformin	850 mg TID	10 mg QD	1.20	1.03
Glyburide[b]	1.75 mg[d]	5 mg QD	1.02	1.01
Pioglitazone	45 mg QD	10 mg QD	1.13	1.07
Ritonavir	200 mg BID	5 mg[d]	2.01	2.96
Rifampin[c]	600 mg QD	5 mg QD	0.60	0.56

[a]Multiple dose (steady state) unless otherwise noted
[b]Coadministration of linagliptin 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) and Drug Interactions (7.3)]*.
[c]For information regarding clinical recommendations *[see Drug Interactions (7.2)]*.
[d]Single dose
[e]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[d]	C_{max}
Metformin	850 mg TID	10 mg QD	metformin	1.01	0.89
Glyburide[b]	1.75 mg[c]	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[c]	5 mg QD	R-warfarin S-warfarin INR PT	0.99 1.03 0.93[e] 1.03[e]	1.00 1.01 1.04[e] 1.15[e]
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]Coadministration of linagliptin 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) and Drug Interactions (7.3)]*.
[c]Single dose
[d]AUC = AUC(INF) for single dose treatments and AUC = AUC(TAU) for multiple dose treatments
[e]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.

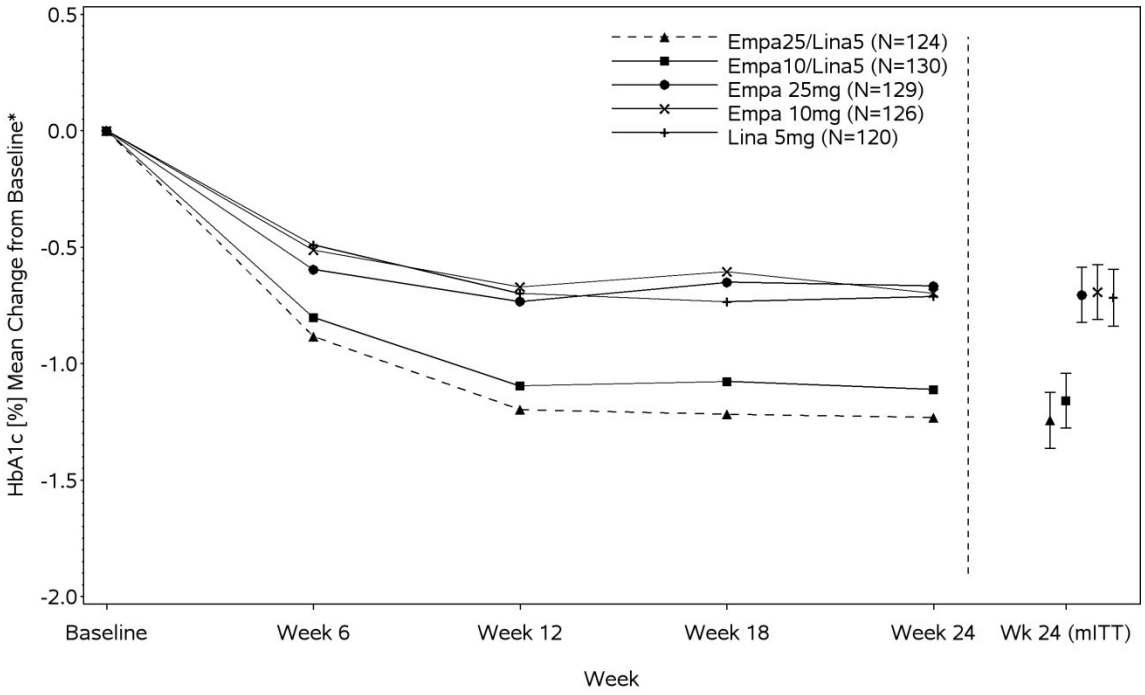
At Week 24, empagliflozin 10 mg or 25 mg used in combination with linagliptin 5 mg provided statistically significant improvement in HbA1c (p-value <0.0001) and FPG (p-value <0.001) compared to the individual components in patients who had been inadequately controlled on metformin (see Table 5, Figure 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. However, the effectiveness of GLYXAMBI on reducing the risk of cardiovascular death in adults with type 2 diabetes mellitus and established cardiovascular disease has not been established. 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 nonfatal myocardial infarction (MI) or a nonfatal 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.

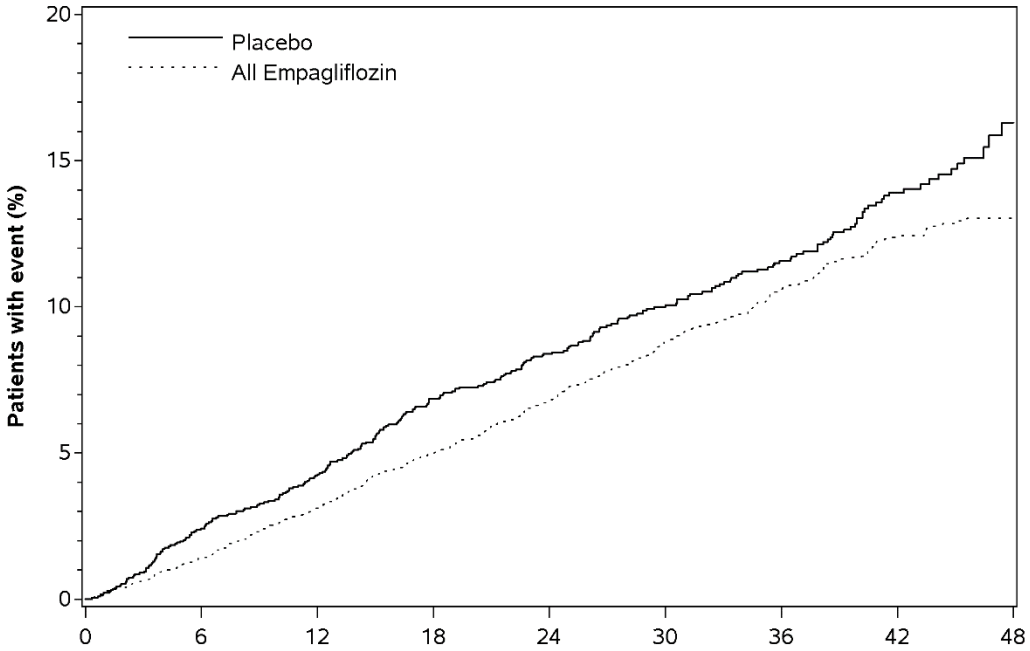
Empagliflozin significantly reduced the risk of first occurrence of primary composite endpoint of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke (HR: 0.86; 95% CI 0.74, 0.99). The treatment effect was due to a significant reduction in the risk of cardiovascular death in subjects 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 Figure 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)

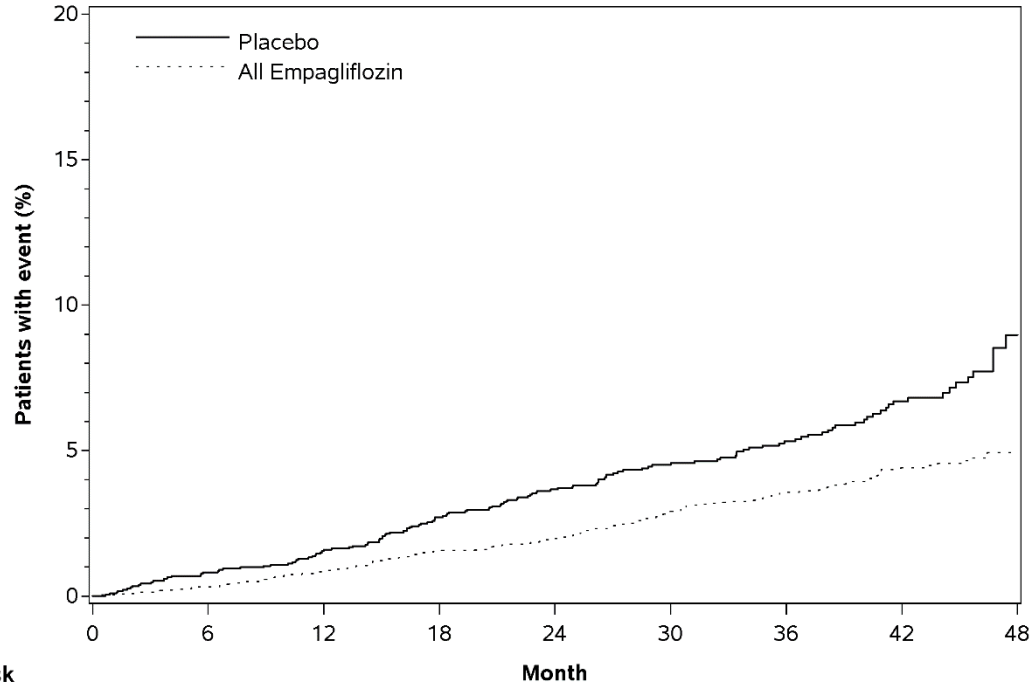
[a]Treated set (patients who had received at least one dose of study drug)
[b]p−value for superiority (2−sided) 0.04
[c]Total number of events

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 Trial

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 drugs (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, nonfatal myocardial infarction or nonfatal 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.

The results of CARMELINA, including the contribution of each component to the primary composite endpoint, are shown in Table 7. 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. The Kaplan-Meier curve depicting time to first occurrence of MACE is shown in Figure 6.

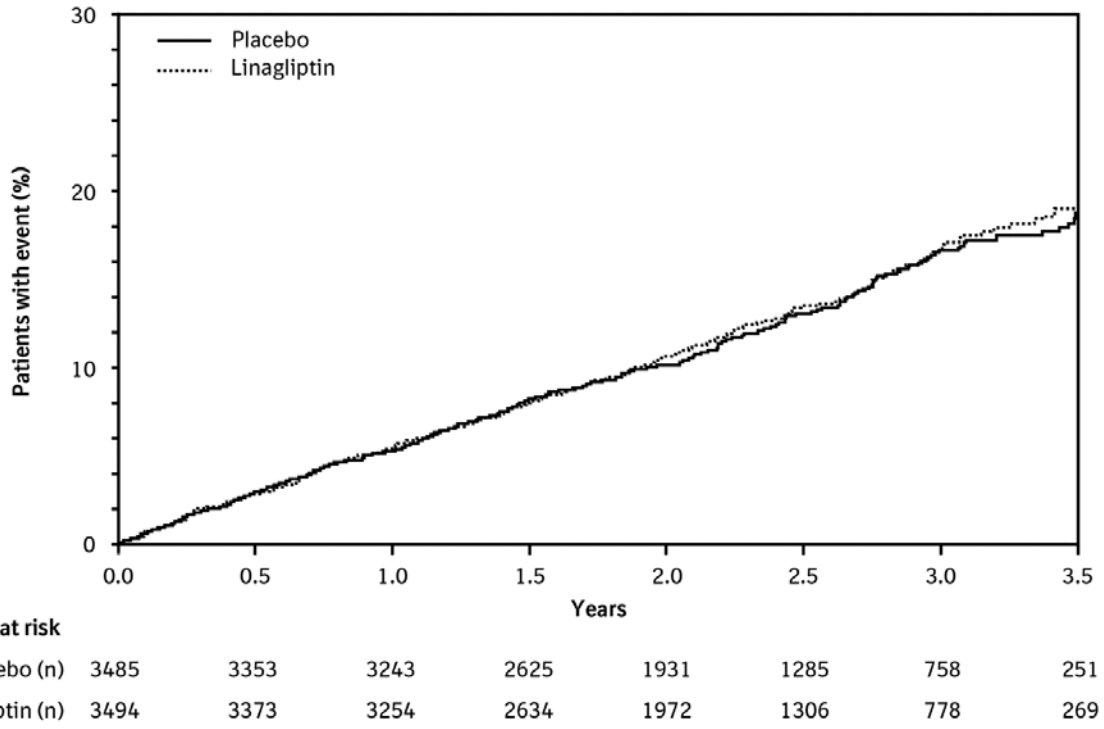
Table 7 Major Adverse Cardiovascular Events (MACE) by Treatment Group in the CARMELINA Trial

	Linagliptin 5 mg n = 3494		Placebo n = 3485		Hazard Ratio
	Number of Subjects (%)	Incidence Rate per 1000 PY[a]	Number of Subjects (%)	Incidence Rate per 1000 PY[a]	(95% CI)
Composite of first event of CV death, non-fatal myocardial infarction (MI), or non-fatal stroke (MACE)	434 (12.4)	57.7	420 (12.1)	56.3	1.02 (0.89, 1.17)
CV death[b]	255 (7.3)	32.6	264 (7.6)	34.0	0.96 (0.81, 1.14)
Non-fatal MI[b]	156 (4.5)	20.6	135 (3.9)	18.0	1.15 (0.91, 1.45)
Non-fatal stroke[b]	65 (1.9)	8.5	73 (2.1)	9.6	0.88 (0.63, 1.23)

[a]PY=patient years

[b]A patient may have experienced more than one component; therefore, the sum of the components is larger than the number of patients who experienced the composite outcome.

Figure 6 Kaplan-Meier: Time to First Occurrence of MACE in the CARMELINA Trial



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 25°C (77°F); excursions permitted to 15°-30°C (59°-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. Cases of ketoacidosis have been reported during use of empagliflozin. 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 advice 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 (5.12)]*.

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 (5.13)]*.

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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MEDICATION GUIDE
GLYXAMBI® (glik-SAM-bee)
(empagliflozin and linagliptin)
Tablets

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

Serious side effects can happen to people taking GLYXAMBI, 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:
  - inflammation of your pancreas (pancreatitis)
  - a history of alcoholism
  - stones in your gallbladder (gallstones)
  - 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:
  - increasing shortness of breath or trouble breathing, especially when you lie down
  - swelling or fluid retention, especially in the feet, ankles or legs
  - an unusually fast increase in weight
  - unusual tiredness

  These may be symptoms of heart failure.

- **Dehydration.** GLYXAMBI can cause some people to have dehydration (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:
- have low blood pressure
- are on low sodium (salt) diet
- are 65 years of age or older
- take medicines to lower your blood pressure, including diuretics (water pills)
- have kidney problems

- **Vaginal yeast infection.** Women who take GLYXAMBI may get vaginal yeast infections. Symptoms of a vaginal yeast infection include:
  - vaginal odor
  - vaginal itching
  - white or yellowish vaginal discharge (discharge may be lumpy or look like cottage cheese)
- **Yeast infection of the penis (balanitis or balanoposthitis).** 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 yeast infection of the penis include:
  - redness, itching, or swelling of the penis
  - foul smelling discharge from the penis
  - rash of the penis
  - 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.

What is GLYXAMBI?

GLYXAMBI is a prescription medicine that contains 2 diabetes medicines, empagliflozin (JARDIANCE) and linagliptin (TRADJENTA). GLYXAMBI can be used:
- along with diet and exercise to lower blood sugar in adults with type 2 diabetes,
- in adults with type 2 diabetes who have known cardiovascular disease when both empagliflozin (JARDIANCE) and linagliptin (TRADJENTA) is appropriate and empagliflozin (JARDIANCE) 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 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 tell your doctor or go to the nearest hospital emergency room right away.

What should I tell my doctor before taking GLYXAMBI?

Before you take 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
- are eating less due to illness, surgery, or 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)
- 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.
- When your body is under some types of stress, such as fever, trauma (such as a car accident), infection, or surgery, the amount of diabetes medicine that you need may change. Tell your doctor right away if you have any of these conditions and follow your doctor's instructions.
- Check your blood sugar as your doctor tells you to.
- Stay on your prescribed diet and exercise program while taking GLYXAMBI.
- Talk to your doctor about how to prevent, recognize and manage low blood sugar (hypoglycemia), high blood sugar (hyperglycemia), and complications of diabetes.
- Your doctor will check your diabetes with regular blood tests, including your blood sugar levels and your hemoglobin A1C.
- 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 is a serious condition, which may need 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 if you get any of the following symptoms**:
  - o nausea
  - o vomiting
  - o stomach-area (abdominal) pain
  - o tiredness
  - o 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:
  - o reduce the amount of food or liquid you drink for example, if you are sick or cannot eat or
  - o 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 drowsiness
  - o weakness
  - o irritability
  - o hunger
  - o fast heartbeat
  - o confusion
  - o shaking or feeling jittery
  - o dizziness
  - o sweating
- **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)
- **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 these symptoms, stop taking GLYXAMBI and tell your doctor or go to the nearest hospital emergency room right away.
- **Increased fats in your blood (cholesterol)**
- **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.
This Medication Guide summarizes the most important information about GLYXAMBI. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about GLYXAMBI that is written for health professionals.
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.

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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This Medication Guide has been approved by the U.S. Food and Drug Administration. Revised: July 2019

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206073Orig1s017

CROSS DISCIPLINE TEAM LEADER REVIEW

CDTL Review
Division Summary Memo for Regulatory Action

Date	July 1, 2019
From	Patrick Archdeacon, M.D.
NDA #	sNDA 201280/S-018 (linked to sNDA 201281/S-022 [linagliptin +metformin], sNDA 208026/S-008 [linagliptin+metformin extended-release], sNDA 206073/S-017 [empagliflozin+linagliptin])
Applicant	Boehringer Ingelheim Pharmaceuticals, Inc.
Date of Submission Receipt	September 5, 2019
PDUFA Goal Date	July 5, 2019
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 and Fulfillment of PMR 1766-4

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 the CARMELINA trial (b) (4)

CARMELINA (full title: "A multicenter, international, randomized, parallel group, double-blind, placebo-controlled CArdiovasular safety and Renal Microvascular outcome study with LINAgliptin, 5 mg once daily in patients with type 2 diabetes mellitus at high vascular risk") was conducted to fulfill Postmarketing Requirement 1766-4 issued to NDA 201280 to evaluate the effects of Tradjenta (linagliptin) tablets on cardiovascular events, immunological and hypersensitivity reactions (including serious skin and/or mucosal reactions), neoplasms, serious hypoglycemia, pancreatitis, and renal safety.

As detailed below, the FDA review team has concluded that the clinical data submitted suffice to fulfill PMR 1766-4 and to add information to the Tradjenta, Jentadueto, Jentadueto XR, and Glyxambi PIs.

(b) (4)

This memo references the following documents/sources:

Subject	Author	Date
Clinical Efficacy and Safety Review (DMEP)	Hyon (KC) Kwon	June 21, 2019
Statistical (DBVII) review	Bo Li	May 24, 2019
DMEPA labeling review	Ariane Conrad	February 1, 2019
Patient Labeling Team	Aman Sarai, Samantha Bryant	June 21, 2019
OSI summary review	Cynthia Kleppinger, Min Lu, Kassa Ayalew	May 22, 2019

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

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 dipeptidyl peptidase-4 (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 Jentadueto, a fixed-dose combination drug product (FCDP) containing linagliptin and metformin, of Jentadueto XR, a FCDP containing linagliptin and metformin extended release, and of Glyxambi, a FCDP containing empagliflozin and linagliptin.

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.

In keeping with this 2008 Guidance, the Agency issued PMR 1766-4 at the time of approval of NDA 201280: PMR 1766-4 required "a randomized, double-blind, placebo-controlled trial evaluating the effect of Tradjenta (linagliptin) tablets on the incidence of major adverse cardiovascular events in patients with type 2 diabetes mellitus. The primary objective of this trial is to establish that the upper bound of the 2-sided 95% confidence interval for the estimated risk ratio comparing the incidence of major adverse cardiovascular events observed with Tradjenta (linagliptin) tablets to that observed in the control group is less than 1.3. Secondary objectives must include an assessment of the long-term effects of Tradjenta (linagliptin) tablets on immunological and hypersensitivity reactions (including serious skin and/or mucosal reactions), neoplasms, serious hypoglycemia, pancreatitis, and renal safety. For hypersensitivity reactions, especially angioedema, reports should include detailed information on concomitant use of an angiotensin-converting enzyme inhibitor or an angiotensin-receptor blocker. For cases of pancreatitis, serum amylase and/or lipase concentrations with accompanying normal ranges and any imaging reports should be included in the narratives."

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

The Applicant conducted the CARMELINA trial to address the requirements of PMR 1766-4. The trial began on July 29, 2013 and completed on January 18, 2018. In general, based on the inspections of the six 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.

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

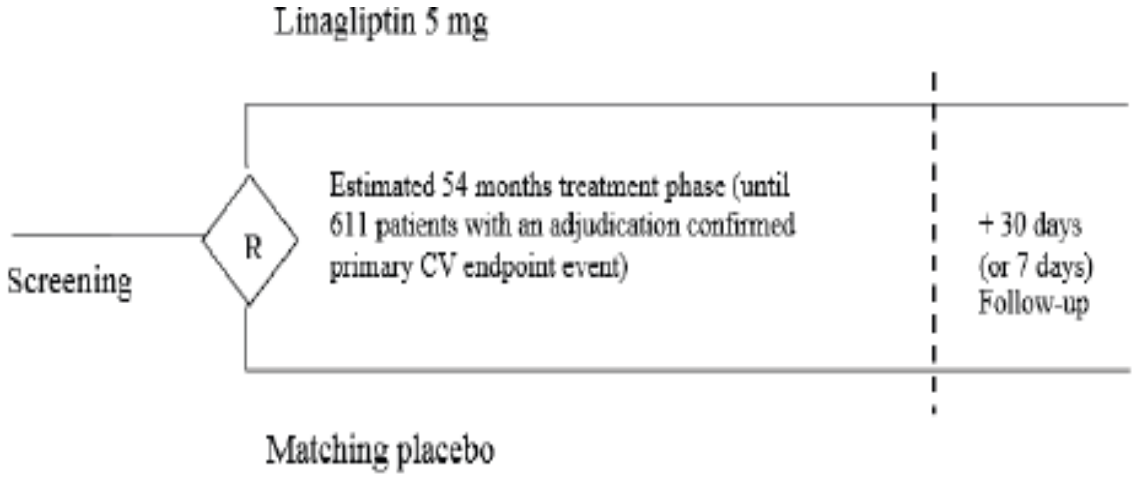
Dr. Bo Li, the statistical reviewer from the Office of Biostatistics (OB), Division of Biometrics VII (DBVII), and Hyon Kwon, the clinical reviewer from the Office of New Drugs, Division of Metabolism and Endocrinology Products (DMEP), reviewed the Major Adverse Cardiovascular Event (MACE) results from CARMELINA. The pre-specified primary endpoint of CARMELINA 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 if the non-inferiority margin was met. Both Dr. Li and Dr. Kwon concluded that the data demonstrated the noninferiority of linagliptin compared to placebo: for the primary MACE endpoint, the hazard ratio (95% CI) was 1.02 (0.89, 1.17). Both Dr. Li and Dr. Kwon also concluded that the data did not demonstrate the superiority of linagliptin compared to placebo.

I concur with the findings of Dr. Li and Dr. Kwon. Based on these results, I also conclude that these results fulfill the primary objective of PMR 1766-4 (i.e., "to establish that the upper bound of the 2-sided 95% confidence interval for the estimated risk ratio comparing the incidence of major adverse cardiovascular events observed with Tradjenta (linagliptin) tablets to that observed in the control group is less than 1.3"). 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.

Study Overview

CARMELINA is a multi-center, randomized, double-blind, parallel group placebo-controlled trial that compared the effect of linagliptin with placebo as an add-on therapy to standard of care treatment in patients with type 2 diabetes on cardiovascular outcomes. CARMELINA was designed as an event-driven trial – it was to continue until at least 611 positively adjudicated MACE events accrued (the number sufficient to discharge the 1.3 risk margin). Study visits occurred at Week 12, then every 24 weeks until the End of Treatment visit.

Figure 1: Study Design of CARMELINA



Source: FDA Statistical Review

The pre-specified primary endpoint was the time from randomization to the first occurrence of any adjudication-confirmed MACE (CV death, non-fatal MI, or non-fatal stroke). A key secondary endpoint, intended to demonstrate benefit on chronic kidney disease in diabetes patients, was defined as the time from randomization to first occurrence of any adjudication-confirmed component of a composite renal endpoint: renal death, end-stage renal disease (ESRD), or sustained decrease of 40% or more in eGFR. Additional endpoints assessed included adjudication-confirmed 4-component MACE+ (CV death, non-fatal MI, non-fatal stroke, or hospitalization with unstable angina pectoris); individual adjudication-confirmed CV events (CV death, MI, fatal MI, non-fatal MI, stroke, fatal stroke, non-fatal stroke, and hospitalization with unstable angina pectoris); all-cause death, as reported in the electronic case report form (eCRF); adjudication-confirmed hospitalization for heart failure; adjudication-confirmed CV death or hospitalization for heart failure; and all-cause death or adjudication-confirmed hospitalization for heart failure. The adjudications were performed by an independent, blinded external Clinical Event Committee (CEC).

The SAP specified that if the pre-specified criteria for demonstrating the non-inferiority for MACE were met, a sequential rejective multiple test procedure would be applied to test in parallel for superiority of the primary MACE endpoint and to assess for superiority of the key secondary renal endpoint. The initial one-sided α levels were set at $0.2*\alpha$ for MACE and $0.8*\alpha$ for the composite renal endpoint; if superiority was concluded for either endpoint, α could be recycled to the other test.

A total of 6991 subjects were randomized (3499 assigned to linagliptin and 3491 assigned to placebo). Of these, 3494 subjects randomized to the linagliptin arm and 3485 subjects randomized to the placebo arm took at least one dose of study drug and were included in the "Treated Set". A total of 3458 (99.0%) of the linagliptin arm subjects and 3430 (98.4%) of the placebo arm subjects were followed until study completion or until occurrence of a first MACE. A total of 91 subjects were lost to follow-up for MACE, including 36 subjects (1.0%) assigned to linagliptin and 55 subjects (1.6%) assigned to placebo. A total of 6958 (99.7%) of subjects had vital status collected at the study end; vital status was not available for 7 (0.2%) subjects assigned to linagliptin and 14 (0.4%) subjects assigned to placebo.

Table 1: Patient Disposition in CARMELINA

	Linagliptin	Placebo	Total
Randomized	**3499**	**3492**	**6991**
Not treated	5	7	12
Treated subjects (Treated Set)	**3494**	**3485**	**6979**
Did not prematurely discontinued from study drug	2660 (76.1%)	2530 (72.6%)	5190 (74.4%)
Prematurely discontinued the study drug	834 (23.9%)	955 (27.4%)	1789 (25.6%)
Adverse Events	362 (10.4%)	402 (11.5%)	764 (10.9%)
Patient refused to continue study drug	281 (8.0%)	333 (9.6%)	614 (8.8%)
Other	176 (5.0%)	196 (5.6%)	372 (5.3%)
Non-compliance	15 (0.4%)	24 (0.7%)	39 (0.6%)
Completed the trial or died*	3458 (99.0%)	3430 (98.4%)	6888 (98.7%)
Lost to follow-up for 3P-MACE*	36 (1.0%)	55 (1.6%)	91 (1.3%)
Prematurely discontinued from the trial	39 (1.1%)	59 (1.7%)	98 (1.4%)
Consent withdrawn	19 (0.5%)	34 (1.0%)	53 (0.8%)
Lost to follow-up	20 (0.6%)	25 (0.7%)	45 (0.6%)
Final vital status			
Alive	3120 (89.3%)	3098 (88.9%)	6218 (89.1%)
Dead	367 (10.5%)	373 (10.7%)	740 (10.6%)
Lost to follow-up	0	4 (0.1%)	4 (0.1%)
Missing	7 (0.2%)	10 (0.3%)	17 (0.2%)

CV=cardiovascular; MACE=major adverse cardiac events
*Subject who has no visit information (except date of non-CV death) after trial close out and has no confirmed 3P-MACE is included in the line "Lost to follow-up for 3P-MACE". "Completed the trial or died" included all subjects with 3P-MACE event.

Source: FDA Clinical Review

The primary MACE endpoint was assessed multiple population sets: the randomized population, the "treated set", the "per protocol set" (all subjects in the treated set except those with important protocol violations), and the "on treatment set" (all subjects who received trial medication for at least a cumulative duration of 30 days). The primary analysis was conducted in the treated set; sensitivity analyses were conducted in the per protocol set and the on-treatment set.

Table 2: Study Populations Assessed in CARMELINA

Study Populations	linagliption	Placebo	Total
Randomized Set (RS)	3499	3492	6991
Treated Set (TS)	3494 (100%)	3485 (100%)	6979 (100%)
Per Protocol Set (PPS)	3466 (99.2%)	3459 (99.3%)	6925 (99.2%)
On-treatment Set (OS)	3453 (98.8%)	3433 (98.5%)	6886 (98.7%)

Source: FDA Statistical Review

The mean ages of the patient populations were 66.1 years in the linagliptin arm and 65.6 years in the placebo arm. The majority of patients enrolled in CARMELINA were male (62.9%) and white (80.2%). To help accrue MACE events, CARMELINA was enriched with patients at high-risk of cardiovascular events and with evidence of impaired renal function: all patients had either evidence of microalbuminuria AND previous macrovascular disease ("Risk Category 1") or evidence of impaired renal function as measured by eGFR of 15-<45

ml/min/1.73 m^2 or macroalbuminuria and eGFR of 45-75 ml/min/1.73 m^2 ("Risk Category 2"). 57% of patients had history of macrovascular disease at baseline; 27% had history of heart failure at baseline. The mean baseline HbA1c was 8%, the mean duration of diabetic disease was 14.8 years. Most patients (96.8%) were taking antidiabetic therapy at baseline: the most frequent baseline antidiabetic therapy were insulin and analogs (57.3%) followed by metformin (54%) and sulfonylureas (31.9%).

Table 3: Baseline Demographic Characteristics of the Treated Set

Demographic Parameter	Linagliptin (N-3494)	Placebo (N=3485)	Total (N=6979)
Gender, n (%)			
Male	2148 (61.5)	2242 (64.3)	4390 (62.9)
Female	1346 (38.5)	1243 (35.7)	2589 (37.1)
Age			
Mean years (SD)	66.1 (9.05)	65.6 (9.14)	65.9 (9.10)
Age Group			
<65 years	1467 (42.0)	1501 (43.1)	2968 (42.5)
≥ 65 to <75 years	1405 (40.2)	1395 (40.0)	2800 (40.1)
≥ 75 to <80 years	402 (11.5)	397 (11.4)	799 (11.4)
≥ 80 years	220 (6.3)	192 (5.5)	412 (5.9)
Race, n (%)			
White	2827 (80.9)	2769 (79.5)	5596 (80.2)
Black or African American	194 (5.6)	217 (6.2)	411 (5.9)
Asian	307 (8.8)	333 (9.6)	640 (9.2)
American Indian or Alaska Native	159 (4.6)	156 (4.5)	315 (4.5)
Native Hawaiian or Other Pacific Islander	7 (0.2)	10 (0.3)	17 (0.2)
Ethnicity, n (%)			
Hispanic or Latino	1227 (35.1)	1274 (36.6)	2501 (35.8)
Not Hispanic or Latino	2267 (64.9)	2211 (63.4)	4478 (64.2)
Region			
North America	593 (17.0)	587 (16.8)	1180 (16.9)
United States	528 (15.1)	528 (15.2)	1056 (15.1)
Latin America	1156 (33.1)	1154 (33.1)	2310 (33.1)
Europe	1473 (42.2)	1461 (41.9)	2934 (42.0)
Asia	272 (7.8)	283 (8.1)	555 (8.0)
Weight (kg), mean (SD)	86.4 (18.00)	86.9 (18.26)	86.6 (18.13)
BMI (kg/m^2), mean (SD)	31.2 (5.29)	31.3 (5.37)	31.3 (5.33)

Source: FDA Clinical Review

Table 4: Cardiovascular Risk Factors at Baseline - Treated Set

	Linagliptin (N-3494)	Placebo (N=3485)	Total (N=6979)
Albuminuria and previous macrovascular disease (Risk category 1)	**2011 (57.6)**	**1986 (57.0)**	**3997 (57.3)**
Confirmed history of MI	942 (27.0)	921 (26.4)	1863 (26.7)
Advanced CAD	594 (17.0)	556 (16.0)	1150 (16.5)
High-risk single-vessel CAD	73 (2.1)	70 (2.0)	143 (2.0)
History of ischemia or hemorrhagic stroke	467 (13.4)	494 (14.2)	961 (13.8)
Presence of carotid artery disease	177 (5.1)	175 (5.0)	352 (5.0)
Presence of peripheral artery disease	269 (7.7)	266 (7.6)	535 (7.7)
Evidence of impaired renal function with predefined UACR (Risk category 2)*	**1462 (41.8)**	**1457 (41.8)**	**2919 (41.8)**
eGFR 15 to <45 mL/min/1.73 m^2	1157 (33.1)	1160 (33.3)	2317 (33.2)
eGFR 45 to <75 mL/min/1.73 m^2 with UACR >200 mg/g creatinine	317 (9.1)	304 (8.7)	621 (8.9)
No albuminuria and previous macrovascular disease (Risk category 1) and no evidence of impaired renal function (Risk category 2)	**21 (0.6)**	**40 (1.1)**	**61 (0.9)**
Missing albuminuria and previous macrovascular disease and impaired renal function	**0**	**2 (0.1)**	**2 (0.0)**

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: FDA Clinical Review

The primary efficacy analysis was conducted in the "treated set" patient population using an "on study" censoring strategy where all first primary MACE were included. A total of 864 adjudication-confirmed first MACE were identified – 434 in the linagliptin arm (5.8 per 100 patient years) and 420 in the placebo arm (5.6 per 100 patient years). As shown in Table 5, the estimated hazard ratio (HR) of linagliptin compared to placebo for MACE is 1.02 and the 95% confidence interval (CI) of the HR is (0.89, 1.17); the upper bound of the 95% CI met the pre-specified risk margin of 1.3.

Table 5: Cox Regression Analysis of Time to First Occurrence of MACE (Treated Set)

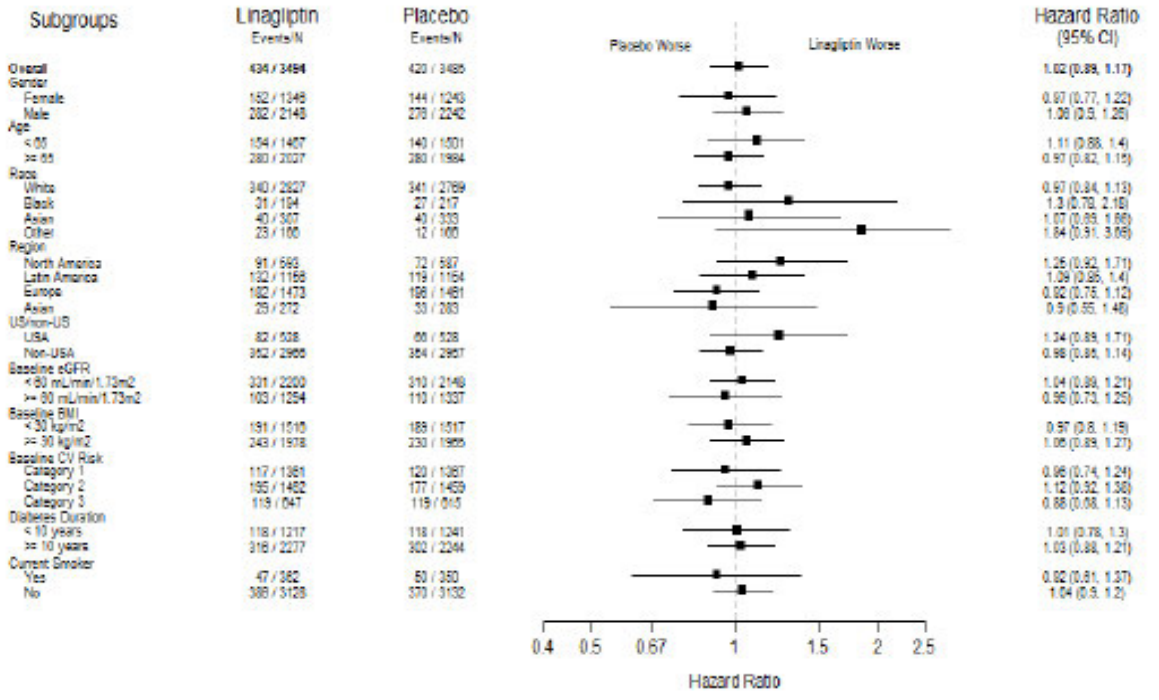
	Linagliptin (N=3494)	Placebo (N=3485)
Subjects with MACE, n (%)	**434 (12.4)**	**420 (12.1)**
Cardiovascular death	221 (6.3)	225 (6.5)
Non-fatal myocardial infarction	154 (4.4)	132 (3.8)
Non-fatal stroke	59 (1.7)	63 (1.8)
Incidence rate of MACE per 1000 years, (95% CI)[1]	**57.7 (52.38, 63.37)**	**56.3 (51.08, 61.99)**
Hazard ratio of MACE (compared to placebo)[2]	**1.02**	
95% CI; alpha=2.5%	0.89, 1.17	
99% CI; alpha=0.5%	0.86, 1.22	
p-value for HR ≥1.3 (1-sided)	0.0002	
p-value for HR ≥1.0 (1-sided)	0.6301	

MACE=major adverse cardiovascular event; CI=confidence interval; HR=hazard ratio
[1] 95% CI was calculated based on the Exact Poisson method for the number of patients.
[2] Based on a Cox regression model with terms for treatment group (p=0.7398), region (p=0.7878)

Source: FDA Clinical Review

As detailed in Dr. Li's review, the sensitivity analyses (using a variety of censoring schemes and analysis populations) all returned results that are consistent with those of the primary analysis. In addition, the primary MACE endpoint was also evaluated across a range of subgroups: analyses were performed based on categories of race, gender, age, geographic region, renal function, CV risk category, duration of diabetes, and tobacco use. In general, the subgroup analyses also returned similar treatment effects as the treatment effect observed in the overall population.

Figure 2: Forest Plot of Hazard Ratios for MACE by Baseline Subgroup (Treated Set, on study)



Source: FDA Statistical Review

7. Safety

In addition to analyzing the primary endpoint of MACE, Dr. Kwon completed a review of all the safety data collected by CARMELINA. Overall, Dr. Kwon concluded that the adverse events observed in association with linagliptin were largely reflective of the known safety profile of linagliptin, that no new safety signal was identified in the patient population, and that the safety concerns with the use of linagliptin are adequately labeled. Finally, while Dr. Kwon noted that prospectively collected and appropriate adjudicated events of hospitalization for heart failure did not support an increased risk for heart failure events with linagliptin, she also noted that the Applicant notified FDA during the course of the review of conflicting results from another recently completed CVOT comparing linagliptin and glimepiride (CAROLINA). (b) (4)

I concur with the findings and recommendations of Dr. Kwon. Based on the analyses of the safety data collected in CARMELINA, I also conclude that the secondary objectives (i.e., to assess the long-term effects of linagliptin on immunological and hypersensitivity reactions, neoplasms, serious hypoglycemia, pancreatitis, and renal safety) of PMR 1766-4 have been fulfilled.

In summary, the safety evaluation of CARMELINA included review of the individual components of MACE, additional CV risk data (e.g., adjudicated data related to hospitalization for heart failure), the renal composite endpoint data, adverse event data (including the data related to adverse events of special interest such as hypoglycemia events, pancreatitis, and pancreatic carcinomas), laboratory data, physical examination data, and EKG data. The Safety population was defined the same as the "Treated Set" population: all subjects who took at least one dose of the randomized study drug. The mean exposure to study drug was similar between treatment groups, with both having mean exposure of 1.9 years. The number of patients experiencing all-cause deaths or serious adverse events (SAE) were similar across treatment groups. Additional details regarding these safety analyses are found in the clinical review by Dr. Kwon.

CV death, non-fatal MI, non-fatal Stroke

In addition to considering the primary MACE endpoint, Dr. Kwon assessed other metrics of CV safety, including the individual components of the composite MACE endpoint and various analysis related to hospitalization for heart failure. Dr. Kwon concluded, and I concur, that the results of the individual components of MACE were consistent with the overall MACE analysis.

Table 6: Analysis Results for MACE components (Treated Set, on study)

	Linagliptin N= 3494	Placebo N= 3485	Hazard Ratio* (95% CI)
MACE	434 (12.4%)	420 (12.1%)	1.02 (0.89, 1.17)
Component event:			
CV Death	255 (7.3%)	264 (7.6%)	0.96 (0.81, 1.14)
Non-fatal MI	156 (4.5%)	135 (3.9%)	1.15 (0.91, 1.45)
Non-fatal Stroke	65 (1.9%)	73 (2.1%)	0.88 (0.63, 1.23)

*: Hazard ratios were estimated based upon a Cox model including a fixed effect for treatment and region as a covariate.
Source: FDA Statistical Review

CDTL comment: The hierarchical statistical testing pre-specified by the SAP did not support formal hypothesis testing related to the individual MACE components. Nonetheless, consistent with precedents set with the labeling of MACE results from other CVOTs of anti-diabetic agents, I concur with the recommendations of the FDA statistical and clinical reviewers to include the nominal HRs and CIs associated with CV death, non-fatal MI, and non-fatal stroke in section 14 of the PI: the CIs are especially helpful to signal to providers and patients that any nominal differences observed between linagliptin and placebo do not necessarily indicate a treatment effect.

Hospitalization for Heart Failure

Given that linagliptin-containing products carry a Warning and Precaution related to heart failure due to observations from CVOTs conducted with two other DPP-4 drug products (saxagliptin and alogliptin), data from events related to heart failure hospitalization were carefully collected and adjudicated in CARMELINA. Dr. Kwon concluded, and I concur, that a numerically lower proportion of subjects in the linagliptin group (6.0%) compared to the placebo group (6.5%) experienced hospitalization for heart failure. Sensitivity analyses for this endpoint included assessing the composite endpoints of "hospitalization for heart failure or CV death" and "hospitalization for heart failure or all-cause death" to avoid confounding due to censoring of heart failure events due to death.

Table 7: Time-to-Event analysis for heart failure-related endpoints (Treated Set)

	Linagliptin (N=3494)			Placebo (N=3485)			Hazard ratio vs placebo (95% CI)
	N	%	IR	N	%	IR	
Hospitalization for heart failure	209	6.0	27.7	226	6.5	30.4	0.90* (0.74, 1.08)
Hospitalization for heart failure or CV death	406	11.6	53.7	422	12.1	56.6	0.94* (0.82, 1.08)
Hospitalization for heart failure or all-cause mortality	499	14.3	65.9	518	14.9	69.4	0.95# (0.84, 1.07)

N=number of subjects; IR=Incidence rate per 1000 years at risk
*Based on Cox regression model with terms for treatment group, region, and history of heart failure;
Based on Cox regression model with terms for treatment group and region
Source: CSR, Table 11.1.3.5:1

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

Renal Safety

As discussed previously, a key secondary endpoint of CARMELINA compared the time to first occurrence of a composite renal endpoint (renal death, ESRD, or sustained decrease of 40% or more eGFR from baseline). In total, 633 subjects had events included in this analysis, including 327 (9.4%) of subjects in the linagliptin arm and 306 subjects in the placebo group. The results of the Cox proportional hazards model analysis prespecified in the SAP did not support either a benefit or a risk associated with linagliptin with regards to renal safety.

Table 8: Cox proportional hazards model analysis of composite renal endpoint (Treated Set)

	Linagliptin (N=3494)	Placebo (N=3485)
Subjects with composite renal endpoint, n (%)	327 (9.4)	306 (8.8)
Incidence rate per 1000 subject-years	48.9	46.6
Hazard ratio of renal endpoint (vs placebo)	1.04	
95% CI; alpha level=2.5%	0.89, 1.22	
96% CI; alpha level=2.0%	0.88, 1.23	
p-value for HR ≥1.0 (1-sided)	0.6918	

Source: CSR, Table 11.1.2.1:1

In addition to the data from the key secondary endpoint, Dr. Kwon also assessed the AE, SAE, and laboratory data collected in CARMELINA related to renal safety. She concluded, and I concur, that there were no new signals related to renal safety present in the CARMELINA data.

Immunologic/hypersensitivity Reactions

Seven cases of bullous pemphigoid (including four events that were classified as SAEs) were observed in the linagliptin treatment group, compared to none in the placebo treatment group. One of the four SAEs of bullous pemphigoid was likely related to exposure to clopidogrel, but the role of linagliptin could not be excluded for the other three SAEs.

Due to a Tracked Safety Issue for DPP-4 inhibitors related to inflammatory bowel disease (IBD), Dr, Kwon investigated the CARMELINA data for evidence of an association between linagliptin and IBD. While Dr. Kwon found a small imbalance for non-specific events of colitis, she did not find events of IBD associated with linagliptin exposure.

CDTL comment: As Dr. Kwon observed in her review, bullous pemphigoid is already a labeled event associated with DPP-4 inhibitors based on postmarketing events. I concur with Dr. Kwon's recommendation to add the clinical trial data related to bullous pemphigoid to the PIs of linagliptin-containing products.

Hypoglycemia

Dr. Kwon concluded, and I concur, that the incidence of hypoglycemia events was similar across treatment groups in CARMELINA. In considering these data, it is important to acknowledge that a larger proportion of patients in the placebo treated group initiated additional antidiabetic therapies after randomization, including insulin: 14.6% of subjects randomized to linagliptin initiated insulin after randomization, compared to 18.0% of subjects randomized to placebo.

Table 9: Frequency of subjects with hypoglycemia - Treated Set

	Linagliptin (N=3494)	Placebo (N=3485)
Subjects with any investigator defined hypoglycemia adverse event	1036 (29.7%)	1024 (29.4%)
Hypoglycemia with PG ≤70 mg/dL or any severe# hypoglycemia	946 (27.1%)	928 (26.6%)
Hypoglycemia with PG <54 mg/dL or any severe# hypoglycemia	557 (15.9%)	572 (16.4%)
Subjects with symptomatic* hypoglycemia or severe# hypoglycemia	880 (25.2%)	887 (25.5%)
Symptomatic hypoglycemia with PG ≤70 mg/dL or any severe# hypoglycemia	843 (24.1%)	845 (24.2%)
Symptomatic hypoglycemia with PG <54 mg/dL or any severe# hypoglycemia	484 (13.9%)	512 (14.7%)
Severe# hypoglycemia	106 (3.0%)	108 (3.1%)
Number of hypoglycemia episodes per subject		
≥1	1036 (29.7%)	1024 (29.4%)
≥3	541 (15.5%)	539 (15.5%)
≥5	334 (9.6%)	335 (9.6%)
≥10	174 (5.0%)	175 (5.0%)

PG=plasma glucose
*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 12.1.4:1

CDTL comment: While it is true that a higher proportion of patients in the placebo group initiated additional antidiabetic therapies after randomization, it is also true that glycemic control as measured by HbA1c was nominally better in the group of patients randomized to linagliptin compared to the group of patients randomized to placebo. Overall, the data suggest that the use of linagliptin in patients with type 2 diabetes is not associated with increased hypoglycemia when compared to standard of care for patients with type 2 diabetes.

Pancreatitis and Pancreatic Cancer

Pancreatic events were adjudicated by the CEC. In total, 2.6% of patients randomized to linagliptin and 1.5% of patients randomized to placebo experienced a pancreatic event. The most common pancreatic event was asymptomatic pancreatic enzyme elevation (hyperenzymemia). However, imbalances not favoring linagliptin were also observed for acute pancreatitis and pancreatic malignancy.

Table 10: Pancreatic events confirmed by the Clinical Event Committee - Treated Set

	Linagliptin (N=3494)	Placebo (N=3485)
Subjects with at least one pancreatic event	92 (2.6%)	53 (1.5%)
Subjects with asymptomatic pancreatic hyperenzymemia	72 (2.1%)	41 (1.2%)
Subjects with pancreatic malignancy	11 (0.3%)	4 (0.1%)
Acute pancreatitis	9 (0.3%)	5 (0.1%)
Without organ failure	5 (0.1%)	5 (0.1%)
With organ failure	4 (0.1%)	0
Chronic pancreatitis	2 (0.1%)	3 (0.1%)

Source: CSR, Table 15.3.1.5.3

Of the nine patients who experienced acute pancreatitis observed in association with linagliptin, four developed organ failure and two of these subsequently died. None of the five patients who experienced acute pancreatitis in the placebo group developed organ failure and none died.

Eleven patients randomized to linagliptin were adjudicated with pancreatic malignancy compared with four patients randomized to placebo. While the absolute number of events is small, the observed imbalance is concerning due to as some lines of research have suggested a possible link between incretin mimetics and pancreatic cancer (see the discussion in Section 8.5.7. of Dr. Kwon's clinical review for details). Aware that other large CVOT studying linagliptin (CAROLINA) had recently closed and locked its database, Dr. Kwon issued an Information Request (IR) regarding the observed events of pancreatic cancer in CAROLINA (a trial that enrolled a similar number of patients but had a longer duration of follow-up that CARMELINA). While CAROLINA used the same data collection and adjudication procedures for pancreatic cancer cases as CARMELINA, the pancreatic cancer data from CAROLINA was much more favorable to linagliptin: in CAROLINA, 16/3023 (0.5%) of subjects experienced an event of pancreatic cancer in the linagliptin arm compared to 24/3010 (0.8%) of subjects in the glimepiride arm.

CDTL comment: Dr. Kwon concluded that, while current linagliptin labeling already includes a Warning and Precaution related to pancreatitis based on postmarketing reports, the CARMELINA data related to pancreatitis should be added to the Warning and Precaution. Given the small number of cases and relatively short duration of follow-up and the discordant results from CAROLINA, Dr. Kwon concluded that the numeric imbalance in pancreatic cancer cases seen in CARMELINA was likely due to chance and did not recommend new labeling related to pancreatic cancer. I concur with clinical conclusions and the labeling recommendations of Dr. Kwon regarding pancreatitis and pancreatic neoplasms. Further follow up of this issue will occur when CAROLINA is submitted for Agency review.

Other Neoplasia

Overall, 3.3% of patients randomized to linagliptin and 3.8% of patients randomized to placebo were observed to experience cancer events. Dr. Kwon reviewed the incidence of the cases by SOC and PT and did not observe notable imbalances by types of events. Two subjects

in the linagliptin treatment arm and one subject in the placebo treatment arm reported benign thyroid neoplasms. One subject in the placebo group experienced papillary thyroid cancer.

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 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.

Aman Sarai from the Division of Medical Policy Programs (DMPP) and Samantha Bryant from the Office of Prescription Drug Promotion (OPDP) reviewed the revisions to the Medication Guides. The joint Patient Labeling Review concluded (and I concur) that the revisions to the MGs were acceptable.

In addition to edits to the PIs to modernize and/or harmonize labeling (including 'streamlining' the glycemic control indication statement for the FCDPs that DMEP is intending for these types of products), the Applicant's proposals for revisions to the linagliptin-containing PIs (including Tradjenta, Jentadueto, Jentadueto XR, and Glyxambi) were modified and/or addressed as follows:

- Section 5.1: Pancreatitis: Added clinical trial data related to pancreatitis from CARMELINA
- (b) (4)
- (b) (4) Bullous Pemphigoid: Added clinical trial data related to bullous pemphigoid from CARMELINA
- (b) (4)
- (b) (4) Add MACE results from CARMELINA

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 regards to discharging PMR 1766-4 and 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

The data contained in the sNDA 201280/S-018 fulfills post-marketing requirement 1766-4.

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
07/03/2019 12:30:31 PM

LISA B YANOFF
07/03/2019 01:02:46 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206073Orig1s017

MEDICAL REVIEW(S)

Clinical Review
Hyon Kwon, PharmD, MPH
sNDA 201280/S-018
Tradjenta (linagliptin)

CLINICAL REVIEW

Application Type	Supplemental New Drug Application (sNDA)
Application Number(s)	sNDA 201280/S-018 (linked to sNDA 201281/S-022 [linagliptin +metformin], sNDA 208026/S-008 [linagliptin+metformin extended-release], sNDA 206073/S-017 [empagliflozin+linagliptin])
Priority or Standard	Standard
Submit Date(s)	September 5, 2018
Received Date(s)	September 5, 2018
PDUFA Goal Date	July 5, 2019
Division/Office	Division of Metabolism and Endocrinology Products (DMEP)
Reviewer Name(s)	Hyon Kwon, PharmD, MPH
Review Completion Date	
Established/Proper Name	Linagliptin, linagliptin+metformin HCl, linagliptin+metformin extended release, empagliflozin+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
AE	adverse event
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CEC	Clinical Event Committee
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
CRF	case report form
CSR	clinical study report
CV	Cardiovascular
CVOT	Cardiovascular outcome trial
DMC	data monitoring committee
DPP-4	Dipeptidyl peptidase-4
ECG	electrocardiogram
eCTD	electronic common technical document
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
FDCP	Fixed-dose combination product
GCP	good clinical practice
GLP-1	glucagon-like petide-1
GRMP	good review management practice
IBD	inflammatory bowel disease
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
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality

OSE	Office of Surveillance and Epidemiology
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
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SOC	standard of care
TEAE	treatment emergent adverse event
TS	Treated Set

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. 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 and Jentadueto 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, 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 fulfill a post-marketing requirement (PMR) 1766-4, specified in the approval letter for Tradjenta dated May 2, 2011 as following:

> **PMR 1766-4:** A randomized, double-blind, placebo-controlled trial evaluating the effect of Tradjenta (linagliptin) tablets on the incidence of major adverse cardiovascular events

in patients with type 2 diabetes mellitus."

The primary objective of this trial is to establish that the upper bound of the 2-sided 95% confidence interval (CI) for the estimated risk ratio comparing the incidence of major adverse cardiovascular events (MACE) observed with Tradjenta (linagliptin) tablets to that observed in the control group is less than 1.3, as specified in the FDA Guidance for Industry: Diabetes Mellitus – Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes, December 2008.

The Applicant proposes to add the results of the trial, CARMELINA, a dedicated cardiovascular outcomes trial (CVOT) that was conducted to show that linagliptin was not associated with an unacceptable increase in cardiovascular (CV) risk compared to placebo, to Section 14, Clinical Studies of labeling. (b) (4)

1.2. Conclusions on the Substantial Evidence of Effectiveness

CARMELINA trial showed that linagliptin compared to placebo, both added to standard background therapy, did not increase cardiovascular risk in patients with type 2 diabetes mellitus at high CV risk. The risk of major cardiovascular events (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 placebo for MACE was 1.02 (95% CI: 0.89, 1.17), with the upper bound 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 99.7% of subjects. The robustness of the primary endpoint was supported by the overall low extent of missing data for MACE (1.4%).

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 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. Two SGLT2 inhibitors (empagliflozin and canagliflozin) and liraglutide (a GLP-1 receptor agonist) showed CV benefit in a dedicated cardiovascular outcomes trial (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. Other DPP-4 inhibitors, saxagliptin and alogliptin, also did not show an increase in the risk of CV events nor CV benefit, but there was an increased risk of heart failure (HF) with saxagliptin (3.5% vs 2.8%) and alogliptin (2.2% vs 1.3% in those without history of HF), which led to class labeling of DPP-4 inhibitors to warn about the risk of heart failure, including linagliptin.

As specified in the 2008 Guidance for Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes, linagliptin was required to conduct a postmarketing cardiovascular outcomes trial to assess cardiovascular risk as part of postmarketing requirement (PMR 1766-4) at the time of approval. CARMELINA was a dedicated cardiovascular outcomes trial conducted by the Applicant to fulfill PMR 1766-4.

CARMELINA was a prospective, randomized, double-blind, placebo-controlled, CV outcomes trial in 6979 randomized subjects with T2DM and at high CV risk. After a mean follow-up of 2.2 years, compared to placebo, linagliptin ruled out a 30% relative increase in CV risk (p=0.0002), but did not show CV benefit (p=0.6301). The hazard ratio for time-to-event analysis of MACE defined as CV death, non-fatal MI or non-fatal stroke was 1.02 (95% CI: 0.89, 1.17). The key secondary efficacy endpoints included composite renal outcome that included renal death, sustained end-stage renal disease (ESRD), or sustained decrease of 40 or more in eGFR from baseline. However, linagliptin was not shown to be beneficial

in this composite renal endpoint, with the hazard ratio of 1.04 and the upper bound of 95% CI greater than 1 (95% CI: 0.88, 1.23).

The time-to-event analysis for hospitalization of heart failure adjusted for history of heart failure showed hazard ratio (HR) of 0.90 (95% CI: 0.74, 1.08) for linagliptin compared to placebo. Thus, unlike SAVOR (a dedicated CVOT for saxagliptin) or EXAMINE (a dedicated CVOT for alogliptin), CARMELINA did not show an increased risk for heart failure with linagliptin compared to placebo as the point estimate was less than 1. However, the Applicant notified us heart failure data from another recent linagliptin trial called CAROLINA, an active-comparator CVOT comparing linagliptin to glimepiride, where the HR for hospitalization of heart failure was 1.21 with 95% CI (0.92, 1.59). Given this discordant result for the risk of heart failure between two linagliptin CVOTs, we will re-assess the risk of heart failure for linagliptin after evaluating CAROLINA.

The adverse events observed in associated with linagliptin in CARMELINA were largely reflective of known safety profile of linagliptin established during clinical development and other subsequent Phase 3 glycemic control trials in subjects with T2DM. This is the first clinical trial to my knowledge that reported cases of bullous pemphigoid with linagliptin, as current safety warnings about bullous pemphigoid in labeling was based on postmarketing reports. CARMELINA also showed a slight imbalance in the overall frequency of acute pancreatitis with linagliptin (9 subjects [0.3%] with linagliptin versus 5 subjects [0.1%] in the placebo group).

In summary, the overall data from CARMELINA provides evidence that linagliptin does not increase CV risk in patients with T2DM at high CV risk. No new safety signal was identified in this patient population. I believe that the overall benefit-risk for these subjects are favorable and that the safety concerns with the use of linagliptin is already adequately labeled. Thus, I concur with adding the results of CARMELINA trial to inform healthcare professionals that linagliptin treatment is not expected to increase the CV risk.

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, stroke) complications. The Center for Disease Control (CDC) estimates that there are nearly 30 million patients with T2DM in the United States.	Type 2 diabetes mellitus is a serious and life-threatening condition that if left untreated leads to an increased risk for morbidity and mortality.
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 disease are 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).	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 CV benefit in patients with T2DM and at high CV risk for three antihyperglycemic agents. CVOTs did not show either a CV risk or CV benefit for four other antihyperglycemic agents; however, the CVOTs suggested an increased risk for heart failure for two of these products.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• While all approved antihyperglycemic medications have shown to improve glycemic control, not all products have been evaluated for macrovascular outcome. • Two SGLT2 inhibitors (empagliflozin and canagliflozin) and liraglutide (a GLP-1 receptor agonist) showed CV benefit in a dedicated cardiovascular outcomes trial 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. • 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; there were more events of heart failure (HF) observed with saxagliptin (3.5% vs 2.8%) and alogliptin (2.2% vs 1.3% in those without history of HF).	
Benefit	• The results of CARMELINA showed that linagliptin compared to placebo, when added to a standard background therapy, did not increase the risk of MACE. • Risk for heart failure was not increased with linagliptin compared to placebo in CARMELINA.	CARMELINA demonstrated that treatment with linagliptin 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 new antidiabetic products. CARMELINA did not show CV benefit with linagliptin compared to placebo. The risk for heart failure was not increased with linagliptin compared to placebo in CARMELINA.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
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 for this sNDA.	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 CARMELINA.

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.			

2. Therapeutic Context

2.1. Analysis of Condition

Diabetes mellitus is a disease of impaired glucose homeostasis that results in chronic hyperglycemia. There are two main types of diabetes mellitus: type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM). Type 2 diabetes is characterized by autoimmune destruction of pancreatic beta-cells and loss of insulin secretion. Type 2 diabetes is characterized by beta-cell destruction and insulin resistance, with inadequate insulin production to maintain euglycemia.

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 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.[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

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. 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 August 10, 2017 to include DPP-4 inhibitor class labeling related to 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.

A recent safety issue related to DPP-4 inhibitors is a potential signal for inflammatory bowel disease (IBD). A new DARRTS Tracked Safety Issue was created for DPP-4 inhibitors regarding a

potential signal for IBD, based on a recent meta-analysis of studies on DPP-4 inhibitors and IBD.[2] See Section 8.4.5, Treatment Emergent Adverse Events and Adverse Reactions for safety data related to IBD in CARMELINA trial.

3.2. Summary of Presubmission/Submission Regulatory Activity

In the 2008 Guidance for Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes, FDA requested that Applicants show that new antidiabetic therapies do not result in an unacceptable increase in cardiovascular risk.

Trial 1218.22, or CARMELINA, was conducted to fulfill a post-marketing requirement (PMR) 1766-4, specified in the approval letter for Tradjenta dated May 2, 2011 as following:

> **PMR 1766-4:** A randomized, double-blind, placebo-controlled trial evaluating the effect of Tradjenta (linagliptin) tablets on the incidence of major adverse cardiovascular events in patients with type 2 diabetes mellitus."
>
> The primary objective of this trial is to establish that the upper bound of the 2-sided 95% confidence interval for the estimated risk ratio comparing the incidence of major adverse cardiovascular events observed with Tradjenta (linagliptin) tablets to that observed in the control group is less than 1.3. Secondary objectives must include an assessment of the long-term effects of Tradjenta (linagliptin) tablets on immunological and, hypersensitivity reactions (including serious skin and/or mucosal reactions), neoplasms, serious hypoglycemia, pancreatitis, and renal safety. For hypersensitivity reactions, especially angioedema, reports should include detailed information on concomitant use of an angiotension-converting enzyme inhibitor or an angiotension-receptor blocker. For cases of pancreatitis, serum amylase and/or lipase concentration with accompanying normal ranges and any imaging reports should be included in the narratives.

The final protocol was submitted on October 31, 2013 and accepted by DMEP on November 7, 2013. This study was to have been completed by October 31, 2018 with the final report submission by May 31, 2019.

On July 29, 2016, we provided a written response to the Applicant's Type C meeting request to discuss ongoing Trial 1218.22. In this meeting, the Applicant asked for concurrence on the following proposed changes to the protocol, and we concurred:

- Changing the protocol definition of the primary and secondary endpoints from 4-point MACE (CV death, non-fatal stroke, non-fatal MI, and hospitalization for

[2] Radel, JA, Pender DN, and Shah SA. Dipeptidyl peptidase-4 inhibitors and inflammatory bowel disease risk: a meta-analysis. Annals of Pharmacotherapy, 2019; 1-8.

unstable angina) to 3-point MACE (CV death, non-fatal stroke, non-fatal MI);
- Dropping a planned interim analysis;
- Changing the key secondary composite renal endpoint; from sustained, confirmed decrease in eGFR from 50% to 40% based on most recent guidelines;
- Changing testing strategy; and
- Stopping recruitment in July 2016 to allow a clinically relevant minimum length of drug-exposure.

We reiterated that we considered the key secondary composite renal endpoint exploratory and therefore results related to the renal composite endpoint are unlikely to be included in the labeling.

On October 17, 2017, we provided a written response to technical aspects related to the Applicant's planned submission of Trial 1218.22, which included agreement that the final clinical report as basis for efficacy and safety results given that the supplement is based on the results of a single outcome study.

3.3. Foreign Regulatory Actions and Marketing History

Since U.S. approval on May 2, 2011, linagliptin has been authorized in 105 countries worldwide. Jentadueto was approved in U.S. on January 30, 2012 and is currently authorized in 91 countries worldwide.

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

4.1. Office of Scientific Investigations (OSI)

CARMELINA was a multinational trial conducted at 660 sites in 27 countries. At the country level, U.S. randomized the largest subjects, and Eastern Europe and Latin America as a region randomized most subjects. OSI audit was requested for CARMELINA and per discussion with Dr. Cynthia Kleppinger from OSI, both domestic and foreign sites were determined appropriate to audit. The list of 6 sites chosen for inspection, reasons for site selection, and the inspection findings are summarized in Table 2.

One of 6 sites audited, Dr. Leslie Forgoshi's site, was determined to be 'Voluntary Action Indicated' due to regulatory violations, but Dr. Kleppinger found data from this site acceptable and unlikely to significantly impact the primary safety and efficacy analyses. The primary efficacy endpoint was verifiable, all adverse events were captured except for a few that did not appear to have a big impact to the safety evaluation (see Dr. Kleppinger's review dated May 22,

2019 for full details). Form FDA-483 was issued, and the investigator submitted a response on March 2, 2019 which was found to be acceptable.

The remaining 5 sites were considered reliable based on the available information (Table 2).

Table 2: List of Sites Inspected

Investigator Location	Site#	# of subjects randomized	Rationale for site selection	Classification* (inspection date)
Diana-Hortensia Barbonta, MD, PhD; Romania	2611	122	Ranked #2 in CISST; Enrolled 122 subjects; Never been inspected	NAI (2/18-3/1/2019)
Iwona Kobielusz-Gembala, MD; Poland	2501	52	Ranked #3 in CISST; Enrolled 52 subjects; History of previous complaint; Never been inspected	NAI (3/11-3/25/2019)
Stanislaw Mazur, MD; Poland	2516	107	Ranked #4 in CISST; Enrolled 107 subjects; Very high safety numbers; Never been inspected	NAI (2/25-3/4/2019)
Robert Anderson, MD; Omaha, NE	4075	20	Ranked #87 in CISST; Enrolled 20 subjects; Very high safety numbers and high discontinuations; Never been inspected	NAI (4/8-4/12/2019)
Leslie B. Forgosh, MD; St Paul, MN	4245	37	Ranked #54 in CISST; Highest US enrolling site with 37 subjects; Slightly higher than average protocol deviations; Never been inspected	VAI
Virginia Savin; Kansas City, MO	4111	36	Ranked #59 in CISST; Very high safety numbers and high discontinuation; Never been inspected	NAI

Abbreviations: CISST=Clinical Investigator Site Selection Tool; NAI=no action indicated (i.e., no deviation from regulations); VAI=voluntary action indicated (i.e., deviation(s) from regulations)
*Pending=Preliminary classification based on information in 483 (if applicable) and preliminary communication with the field; final classification is pending letter to site.
Source: modified from Dr. Cynthia Kleppinger's Clinical Inspection Summary, dated May 22, 2019

Dr. Kleppinger concluded that overall, based on the inspection of these 6 clinical sites, findings support the validity of the Applicant's data for this supplement. I agree with her assessment.

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

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, CARMELINA, that is pertinent for evaluation of efficacy and safety is summarized in Table 3.

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

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Stud
Trial Number: 1218.22 **Title:** A multicenter, international, randomized, parallel group, double-blind, placebo controlled **CA**rdiovascular Safety & **R**enal **M**icrovascular outcom**E** study with **LINA**gliptin, 5 mg once daily in patients with type 2 diabetes mellitus at high vascular risk. CARMELINA	NCT01897532	Multicenter, randomized, double-blind, 2-arm, parallel-group, placebo-controlled	Linagliptin 5 mg once daily versus matching placebo once daily, both to be taken orally	**Primary:** Time to first occurrence of adjudicated composite endpoint (3-point Major Adverse Cardiovascular Events) of CV death, non-fatal myocardial infarction, or non-fatal stroke **Key secondary:** Time to first occurrence of adjudicated composite renal endpoint of renal death, sustained end stage renal disease, or sustained decrease of 40% or more in estimated glomerular filtration rate	2-week screening period; Estimated 54 months treatment period, depending on observed number of primary endpoint events (611 primary events needed); 30 days of follow-up period	Linagliptin: 3499 Placebo: 3492	Male or female T2DM with Hb screening, incl eGFR ≥15 mL/ High risk of CV 1) Albuminuria macrovascular 2) Evidence of with predefine CV co-morbidit (see Section 6. Inclusion/Exclu

5.2. Review Strategy

The efficacy and safety findings in this review was from a single clinical trial, CARMELINA, 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. CARMELINA (Trial 1218.22)

6.1.1. Study Design

Overview and Objective

Trial 1218.22, or CARMELINA (A multicenter, international, randomized, parallel group, double-blind, placebo-controlled, **CA**rdiovascular Safety & **R**enal **M**icrovascular outcom**E** study with **LINA**gliptin, 5 mg once daily in patients with type 2 diabetes mellitus at high vascular risk), was conducted to fulfill the FDA post-marketing requirement (PMR) 1766-4, as discussed in Section 3.2, Summary of Presubmission/Submission Regulatory Activity. The main purpose of this trial was to evaluate the long-term impact of linagliptin compared to placebo, both given on a background of standard of care, on CV morbidity and mortality in type 2 diabetic patients at high cardiovascular risk.

The primary objective was to demonstrate that linagliptin compared to placebo, as add-on to standard of care, is not associated with an unacceptable increase in CV risk in patients with T2DM. To meet this objective, the trial was to establish non-inferiority by demonstrating that the upper bound of the 2-sided 95% confidence interval for the estimated risk ratio comparing the incidence of major adverse cardiovascular events (MACE, which was a 3-point composite that included CV death, non-fatal MI, and non-fatal stroke) observed with linagliptin to the control group is <1.3, in accordance with the FDA Diabetes Guidance of 2008[3].

After establishing non-inferiority, the incidence of MACE was to be tested for superiority to assess CV benefit for linagliptin. In addition, the effect of linagliptin versus placebo was to be evaluated for superiority on the composite renal endpoint, which included renal death,

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

sustained ESRD, and sustained loss in eGFR ≥ 40% from baseline.

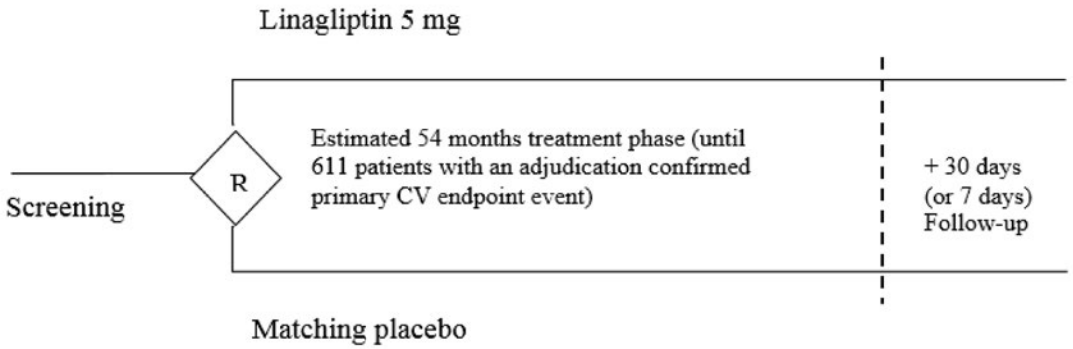
CARMELINA began July 29, 2013 and completed January 18, 2018. The trial database was locked on March 29, 2018.

Trial Design

CARMELINA was a multicenter, multi-national, randomized, double-blind, parallel group, placebo-controlled trial comparing treatment with linagliptin 5 mg once daily versus matching placebo once daily, both as add-on therapy to standard of care, on the composite MACE in subjects with T2DM who are at high risk of CV events.

The trial was event driven and was to run until 611 subjects experienced an adjudicated confirmed primary endpoint event, with about 7000 eligible subjects to be randomized in a 1:1 ratio per treatment group. Randomization was stratified by geographical region. Trial duration was expected to be about 54 months. See Figure 1 for an overview of trial design.

Figure 1: CARMELINA Trial Design



Source: Protocol 1218.22, Figure 3.1:1

After randomization, study visits occurred at 12, 36, 60, and 84 weeks, and thereafter every 24 weeks until the End of Treatment (EOT) visit. A follow-up visit occurred 30 days after the EOT visit. Subjects who discontinued or withdrew from study drug after randomization were to be followed until the end of the trial using the same visit schedule until the end of the trial.

Reviewer's comment: *The overall trial design is consistent with other cardiovascular outcomes trials which have been reviewed by the Division.*

Choice of Control Group:

CARMELINA was a placebo-controlled design, and the trial allowed changes in the background treatment regimen to maintain or obtain adequate glycemic control per local and regional

guidelines and at the investigator's discretion according to standard of care in both arms of the trial.

Treatment goal for HbA1c in this trial was ≤7%, using open-label titration and addition of non-trial antihyperglycemic therapies in both arms to achieve this goal throughout the trial.

The protocol also encouraged investigators to treat all other CV risk factors (e.g, lipid levels, blood pressure, smoking) per local and regional standard of care for primary or secondary CV risk prevention. For example, the investigator could adjust antihypertensive therapy, or other needed therapy, according to clinical guidelines, if better BP control was warranted during the trial.

Background Therapy:

Subjects continued with their standard background antidiabetic therapy during their participation in the trial with dose unchanged unless medical emergencies or other safety reasons (e.g., renal impairment, hypoglycemia, hyperglycemia) required changes, which was left to the discretion of the investigator. Metformin was allowed to be temporarily held according to local/regional guidelines in case of contrast exposure.

Changes to the background antihyperglycemic medication (either dose or drugs) to optimize glycemic control was allowed per standard of care and at the discretion of the investigator during the treatment period, with hypoglycemic targets defined by guidelines, except for DPP4-inhibitors, GLP-1 receptor agonists, and SGLT2 inhibitors which were not allowed.

The use of medication for optimizing glycemic control was advised during the treatment period when subject had FPG >180 mg/dL (confirmed by a minimum of 2 measurements on 2 different days), or the subject had an HbA1c >7.5%. Any additional treatment other than glycemic control was left at the discretion of the investigator.

Trial Location:

This trial was conducted in 660 centers in 27 countries worldwide, which included Argentina, Brazil, Bulgaria, Canada, Chile, China, Colombia, Croatia, Czech Republic, Germany, Hungary, Israel, Japan, Malaysia, Mexico, Netherlands, Poland, Portugal, Romania, Russia, South Africa, South Korea, Spain, Taiwan, Ukraine, United Kingdom, and United States.

Inclusion Criteria:

- Male or female adults (age ≥18 years; age ≥20 years for Japan only) with T2DM who were drug-naïve or pre-treated with any antidiabetic background therapy, except GLP-1

receptor agonists, DPP-4 inhibitors, or SGLT2 inhibitors if ≥7 consecutive days;

- Stable antidiabetic background therapy (unchanged daily dose) for at least 8 weeks before randomization; if on insulin, the average daily insulin dose was not to have changed by more than 10% within 8 weeks before randomization;
- HbA1c of 6.5-10%, inclusive, at screening;
- BMI ≤45 kg/m^2;
- High risk of CV events **(Risk Category 1 and/or 2):**

1. **Albuminuria (UACR ≥30 mg/g creatinine or ≥30 µg/min or ≥30 mg/24 hour in 2 out of 3 unrelated spot urine or timed samples in the last 24 hours before randomization <u>AND</u> previous macrovascular disease, defined as either one or more:**
    a) Confirmed history of MI (>2 months before screening);
    b) Advanced coronary artery disease, defined by any of the following:
        – ≥50% narrowing of the luminal diameter in 2 or more major coronary arteries by coronary angiography, MRI angiography or CT angiography;
        – Left main stem coronary artery with ≥50% narrowing of the luminal diameter by coronary angiography, MRI angiography or CT angiography;
        – Prior percutaneous or surgical revascularization of ≥2 major coronary arteries at least 2 months before screening;
        – Combination of prior percutaneous or surgical revascularization of 1 major coronary artery at least 2 months before screening, and ≥50% narrowing of the luminal diameter by coronary angiography, MRI angiography or CT angiography of at least 1 additional major coronary artery;
    c) High risk single-vessel coronary artery disease (defined as the presence of ≥50% narrowing of the luminal diameter of one major coronary artery by coronary angiography, MRI angiography or CT angiography in patients not vascularized) **<u>AND</u>** at least one of the following:
        – A positive non-invasive stress test, confirmed by either:
            ▪ A positive ECG exercise tolerance test in patients without left bundle branch block, Wolff-Parkinson-White syndrome, left ventricular hypertrophy with repolarization abnormality, or paced ventricular rhythm, atrial fibrillation in case of abnormal ST-T segments;
            ▪ A positive stress echocardiogram showing induced regional systolic wall motion abnormalities;
            ▪ A positive nuclear myocardial perfusion imaging stress test showing stress-induced reversible perfusion abnormality;

        - A positive cardiac stress perfusion MRI showing a stress induced perfusion defect;
    - Patient discharged from hospital with a documented diagnosis of unstable angina pectoris between 2 and 12 months before screening;
  d) History of ischemic or hemorrhagic stroke (>3 months before screening);
  e) Presence of carotid artery disease (symptomatic or not) documented by either:
    - Imaging techniques with at least one lesion estimated to be ≥50% narrowing of the luminal diameter;
    - Prior percutaneous or surgical carotid revascularization;
  f) Presence of peripheral artery disease documented by either:
    - Previous limb angioplasty, stenting or bypass surgery;
    - Previous limb or foot amputation due to microcirculatory insufficiency;
    - Angiographic evidence of peripheral artery stenosis ≥50% narrowing of the luminal diameter in at least one limb;

2. **Evidence of impaired renal function with predefined UACR, with or without CV co-morbidities, defined as follows (and/or criteria):**
  a) Impaired renal function (as defined by MDRD formula) with an eGFR of 15 to <45 mL/min/1.73 m^2 at screening with any UACR;
  b) Impaired renal function (as defined by MDRD formula) with an eGFR of 45 to 75 mL/min/1.73 m^2 at screening with an UACR >200 mg/g creatinine or >200 µg/min or >200 mg/24 hour demonstrated in 2 out of 3 unrelated spot urine or timed samples in t he last 24 months before randomization.

Note: To ensure appropriate representation of patients from different CV risk categories, the trial team monitored the proportion of patients being recruited into these categories (trial level, and by region and/or country if appropriate), and limitation of recruitment of a particular category could have been arranged in consultation with SC to ensure a proper distribution of CV risk categories worldwide.

Reviewer's comment: *As with other CVOTs, a strategy to enrich the population with patients at high risk for CV events was implemented in Inclusion Criteria for 'High risk of CV events'.*

Key Exclusion Criteria:

- Type 1 diabetes mellitus;
- Treatment with GLP-1 receptor agonists, other DPP-4 inhibitors or SGLT2 inhibitors for

≥7 consecutive days;

- eGFR <15 mL/min/1.73 m^2 or need for maintenance dialysis;
- Any previous bariatric surgery or intervention (gastric sleeve), or planned within next 12 months;
- Active liver disease or impaired liver function defined as ALT, AST or alkaline phosphatase ≥3x upper limit of normal (ULN) at screening;
- Pre-planned coronary artery re-vascularization (PCI, CABG) or any previous PCI and/or CABG ≤2 months before informed consent;
- Pre-menopausal women who are either nursing, pregnant, or were of child-bearing potential and were not practicing an acceptable method of birth control or did not plan to continue using acceptable method of birth control during the trial and did not agree to periodic pregnancy testing during trial participation;
- Acute coronary syndrome, diagnosed ≤2 months before screening;
- Stroke or TIA ≤3 months before screening;
- Have a life expectancy less than 5 years for non-CV causes, have cancer other than non-melanoma skin cancer within last 3 years, or has other conditions which, in the opinion of the investigator, would not allow safe participation in the trial.

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.

If subject who prematurely discontinued the study drug was not willing to return at the pre-defined trial visits, a minimum yearly telephone call and a call at the trial end was required to document the occurrence of outcome events and vital status, and also to record other AEs and concomitant therapy changes if possible.

Subjects who prematurely discontinued study drug were allowed to restart the study drug at any time if appropriate and safe. Subjects were allowed to have multiple study drug interruptions, and there was no limit on either the number of study drug interruptions or the maximum length of any study drug interruption.

Study drug was to be stopped if pancreatitis was suspected or if a subject becomes pregnant during the trial.

Early discontinuation of study drug was not a criterion for withdrawal of consent for trial participation.

Administrative Structure:

There were several committees associated with this trial:

- Steering Committee (SC) was comprised of university and sponsor-based scientists with clinical and methodological expertise, and had a scientific and clinical advisory function;
- Data Monitoring Committee (DMC) independently reviewed safety and efficacy data and made recommendation whether to continue or stop the trial;
- Clinical Event Committee (CEC) was an independently, blinded, external committee that prospectively adjudicated all cardio/cerebrovascular trigger events. Additionally, separate independent, blinded, external CECs were set up for adjudication of renal events and pancreatic events. There was also an Oncology Assessment Committee for causality assessment of oncological adverse events.

Procedures and Schedule:

All subjects were provided with home blood glucose monitoring (HBGM) 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. Subjects were also instructed to bring their HBGM device to visits for an additional measurement of fasted glucose.

Subjects were to record the results of HBGM test on a HBGM diary. Subjects were to contact the site if HBGM test showed fasting blood plasma glucose was <70 mg/dL, >180 mg/dL or random glucose >400 mg/dL that was confirmed by a second measure. Subjects were instructed to drink/eat some carbohydrate if blood glucose was <54 mg/dL. HBGM diary was brought to each visit for review and collection.

Study visits occurred at Week 12, 36, 60 and thereafter every 24 weeks until the End of Treatment (EOT) visit. A follow-up visit took place 30 days after the EOT visit. See Table 4 for Flow Chart showing study visits and procedures for each study visit.

Table 4: Trial Flow Chart

Trial period	**Screening**	**Treatment period**						**FU**
Visit	**1**	**2**	**3**	**4**	**5**	**6 to N**	**EOT[3]**	**FU[4]**
Week	**-2**	**0**	**12**	**36**	**60**	**84 to N[2]**	**-**	**-**
Days from randomisation	**-14[1]**	**0**	**84**	**252**	**420**	**588 to N[2]**	**-**	**EOT +30**
Time window (days)[15]	**+13[1]**		**±7**	**±14**	**±14**	**±14**	**±14**	**+7**
Informed consent	X							
In-/exclusion criteria	X	X						
Medical history/ concomitant	X							
Demographics	X							
Physical examination[6]		X		X		X	X	X[4]
Vital signs	X	X	X	X	X	X	X	X[4]
Height	X[E]							
Weight	X[E]			X	X	X	X	
Waist circumference		X		X	X	X	X	
Cognitive function tests/CES-D[7]		X					X	
12-lead-ECG[8]		X		X	X	X	X	X[4]
Pregnancy test[9]		X		X	X	X	X	
Fasted home blood glucose monitoring[10]		X	X	X	X	X	X	
Safety laboratory[11]	X	X	X	X	X	X	X	X[4]
UACR[17]	X	X[1]		X		X[11]	X	X[4]
HbA_{1c}	X	X	X	X	X	X	X	
Lipid panel		X		X		X[11]	X	X[4]
eGFR[12]	X	X	X	X	X	X	X	X[4]
Pharmacogenetic sampling[16]		X						
Adverse events/outcome events[13]	X	X	X	X	X	X	X	X
Concomitant therapy	X	X	X	X	X	X	X	X
Randomisation (IRT)[14]		X						
Dispense trial medication (IRT)[14]		X	X	X	X	X		
Return trial medication/ medication compliance check			X	X	X	X	X	

1 Randomisation could have been done as soon as the Visit 1 (safety) laboratory results and eGFR were known and all other eligibility criteria were met. If the UACR result at Visit 2 was required to fulfil inclusion criterion 8, randomisation could have been postponed until the laboratory results were known. It was not required to repeat Visit 2 assessments if the patient returned to the clinic for randomisation.

2 A clinic visit was scheduled every 24 weeks until trial end.

3 The trial was event driven. The number of confirmed adjudicated primary endpoint events were continuously monitored during the trial. Based on the available number of events the projected number of expected future events was calculated. As soon as the projection reliably suggested that the total number of patients with an adjudication-confirmed primary endpoint event would reach 611, the trial team performed respective actions to stop the trial. From this time point on, all patients were expected to perform their last visit (EOT visit) within the proposed time schedule, communicated via an investigator letter. A follow-up visit took place 30 days after the end of treatment (EOT visit).

Patients who discontinued trial drug prematurely were to continue trial visits until trial end. Trial assessments could have been omitted if a patient was willing to return to the pre-defined trial visits, with the exception of cognitive function tests, collection of adverse events, outcome events, concomitant therapy and laboratory testing of creatinine for the calculation of the eGFR.

If a patient who prematurely discontinued trial drug was not willing to return to the pre-defined trial visits, at minimum a yearly telephone call (preferably every 6 months) and a telephone call at trial end were required, to document the occurrence of outcome events and vital status. If possible, other adverse events and concomitant therapy changes since last visit were to be recorded.

4 All patients were to have a follow-up visit 30 days following regular or premature completion of the treatment period. The follow-up visit could have been performed as a phone visit for patients who did not prematurely discontinue trial medication and who did not have abnormalities at the EOT visit (only adverse events/outcome events and changes in concomitant therapy were to be obtained).

5 Body mass index was calculated automatically.

6 A complete, head-to-toe physical examination (e.g. evaluation of the body and its functions using inspection, palpation, percussion, and auscultation) was done.

7 Cognitive function tests (MMSE, TMT, VFT) were implemented in North America and in all European countries using the Latin alphabet. 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. The CES-D questionnaire was to be completed prior to the cognition questionnaires. The MMSE was to be administrated first of the cognition questionnaires. If the MMSE score was <24 at Visit 2, no further cognitive assessment was needed.

8 In addition to the visits indicated, electrocardiogram (ECG) was to be recorded in case of respective cardiac symptoms (indicating rhythm disorders or cardiac ischaemia).

9 For female patients (local urine pregnancy test in women of child bearing potential). More frequent testing could have been done if required by local regulations/authorities.

10 Distribution of glucometer and testing supplies with instructions at randomisation (Visit 2). During the treatment period, weekly finger stick glucose measurements were recommended (fasted). During the whole trial participation, additional measurements were to be done if necessary and in case of hypo- or hyperglycaemia-related symptoms. The patient was to be instructed to bring their HBGM device and diary to the clinic for an additional measurement (fasted).

11 At Visit 1, safety laboratory included ALT, AST, alkaline phosphatase and creatinine to check for eligibility in addition to lipase, urine albumin, urine creatinine and HbA_{1c} – as specified in the flow chart. At randomisation (Visit 2) baseline laboratory were obtained. As of Visit 6: yearly (every other visit) lipid profile (total cholesterol, HDL cholesterol, LDL cholesterol and triglycerides), urine albumin and urine creatinine.

12 Estimated glomerular filtration rate (eGFR) was calculated using the MDRD formula. This formula considers the race as an adjustment factor, therefore, the race had to be known (and collected) for accurate estimation. In case of an eGFR decrease of ≥40% since baseline (Visit 2) and again in case of an eGFR decrease of ≥50% since baseline (Visit 2) an additional visit 4 to 8 weeks after detection was to be scheduled to collect a blood sample for repeat analysis of creatinine (eGFR). An additional sample of creatinine was also to be taken between the visits if a signal of increasing creatinine was reported to the trial site by others (e.g. GPs from local laboratories).

13 In case of a stroke the reported value from the modified Rankin Scale was collected approximately 1 week after stroke onset and 3 months after stroke onset. This might have required an additional contact.

14 Interactive Response Technology (IRT) allocated medication kit numbers at all trial visits from Visit 2 until trial end. At Visit 2 patients received one treatment box sufficient for 12 weeks treatment (plus 1-week reserve). As of Visit 3 patients received two medication boxes sufficient for 24 weeks treatment (plus 2 weeks reserve).

15 The protocol allowed a time window of ±7 days for Visit 3 and ±14 days for all scheduled visits in the treatment period after Visit 3. To ensure sufficient medication, visits after Visit 3 were to be scheduled within 182 days and Visit 3 was to take place no later than 91 days after Visit 2.

16 To allow possible retrospective pharmacogenetic analyses, all patients eligible for randomisation were asked for a blood sample with a separate informed consent. The pharmacogenetic sample was preferably taken at Visit 2, but could also have been taken at any later visit, depending on availability of the respective informed consent. Pharmacogenetic sampling was voluntary and was not a prerequisite for participation in the trial.

17 Urine Albumin Creatinine Ratio (UACR) was calculated at the central laboratory, and was to be measured on a first morning void specimen wherever possible.

Source: CTR 1218.22, Table 9.5.1:1

Study Endpoints

All the components for the primary and key secondary endpoints, in addition to other cardiovascular tertiary endpoints (such as heart failure), were centrally adjudicated by an independent Clinical Event Committee (CEC) blinded to the treatment assignment, as discussed above. The CEC Charter appears to be acceptable.

The primary endpoint in CARMELINA 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[4] version of the FDA Standardized Definitions for Cardiovascular Outcomes Trials.

Of note, 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 endpoint was time to the first occurrence of adjudicated composite renal endpoint, which included renal death, sustained ESRD, and sustained decrease of 40% or more in eGFR.

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 before the database was locked. The trial database lock was on March 29, 2018, and the final TSAP was signed on December 18, 2017.

The Applicant's analysis population for their primary analysis was the Treated Set (TS), which included all subjects treated with at least one dose of study drug. The primary analysis on the primary composite CV endpoint of time to the first 3-point MACE was done on the TS, and the time to the primary endpoint was derived from the date of randomization. For the primary analysis, a Cox proportional hazard regression model was done to compare the effect of linagliptin versus placebo, and the model included randomized treatment and geographical region as factors. The key secondary composite renal endpoint was analyzed on the TS in the same was as the primary endpoint.

Subjects without occurrence of a specific endpoint (either composite endpoint or individual component) were considered censored at their last day of trial completion.

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

For the primary and key secondary endpoint, an intent-to-treat (ITT) analysis on the TS was done as following:

- The analysis set consisted of TS;
- The allocated trial treatment at randomization was used for the analysis; and
- All adjudicated events which occurred until trial end was taken into account.

Sensitivity analyses was done in Per Protocol Set (PPS) and On-treatment Set (OS). The PPS included all subjects in the TS who had no important protocol violations. The OS included all randomized subjects with a minimum treatment duration of 30 days (cumulative).

For the primary analyses of MACE based on the TS, subjects were censored at their "individual day of trial completion" when subject was last known to be free of an endpoint event of interest. The individual day of trial completion, for those experiencing a non-fatal event, was defined as the latest of either: adverse event/outcome event start dates, onset dates of events sent for adjudication whether confirmed or not, or date of trial completion. For subjects who died, date until which follow-up for non-fatal outcome event was conducted was used for censoring.

Additional analyses for the primary MACE endpoint and other tertiary CV-related endpoints included:

- TS+0: captured the event of interest that occurred while the subject was on the study treatment; subjects who did not experience the event were censored on the last day of treatment, or the day of trial completion, whichever is earlier;
- TS+30: captured the event of interest that occurred while the subject was on the study treatment or within 30 days after the last day of study drug treatment; subjects who did not experience the event were censored on the last day of treatment+30 days, or the day of trial completion, whichever is earlier.

For the hazard ratio of the primary endpoint, non-inferiority was tested by comparing the upper limit of the two-sided 95% CI of the hazard ratio with the non-inferiority margin of 1.3 (i.e., non-inferiority was established if the upper limit was <1.3). The non-inferiority margin was chosen as 1.3 per the *FDA Guidance for Industry – Diabetes Mellitus – Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes*.

After non-inferiority of the primary endpoint was confirmed, the next set of hypotheses (two separate hypothesis tests) were tested: 1) test for superiority on the primary composite CV endpoint, and 2) test for superiority on the secondary composite renal endpoint. To adjust for multiplicity, a sequentially rejective multiple test procedure was used. Both one-sided hypotheses for superiority were tested separately, at the initial alpha-levels of 0.2*alpha (=0.5%) for 3-point MACE and 0.8*alpha (=2%) for the composite renal endpoint. If superiority

for both tests were not confirmed at these initial alpha-levels, the procedure was stopped and superiority could not be established for either endpoints. If superiority for one of these endpoints was shown, the used alpha could then be allotted to the other hypothesis testing at the full alpha-level of 2.5% (one-sided).

This multiple test procedure proposed in the SAP was found to be acceptable for controlling the overall Type 1 error by Dr. Bo Li.

Subgroup Analyses:

The primary endpoint, key secondary endpoint, time to first 4-P MACE event, time to CV death, time to first MI (fatal or non-fatal), time to first stroke (fatal or non-fatal), time to first hospitalization for unstable angina, time to first hospitalization for heart failure, and time to first hospitalization for heart failure or CV death were explored across the subgroups. All subgroup analyses were done on the TS with censoring on the individual day of trial completion.

Subgroup analyses for primary and key secondary endpoints included: region (North America, Latin America, Europe, Asia), age (<65, ≥65 years), systolic and diastolic blood pressure (<140/90 mmHg, ≥140/90 mmHg), gender (male, female), prior anti-diabetic treatment (insulin, no insulin), eGFR <60 mL/min/1.73 m^2 at baseline, prevalent kidney disease defined as eGFR <60 mL/min/1.73 m^2 at baseline and/or UACR >300 mg/g creatinine at baseline.

Missing data:

Subjects with temporary or permanent study drug discontinuation were followed up for CV events.

Missing efficacy data for continuous endpoints for subjects who discontinued the study drug prematurely or missed a visit were estimated by their last observed data. Missing data for binary efficacy endpoints for subjects who discontinued the study drug prematurely were considered as non-responders.

For each time to event analysis, subjects who did not have a particular outcome were censored. For continuous endpoints (i.e., HbA1c, FPG, eGFR, UACR, weight, SBP, DBP, pulse rate, heart rate, waist circumference), all available data were considered and missing data were not replaced. In addition, for continuous endpoint of eGFR over time, all available data obtained on-treatment were used and missing data were not replaced.

Protocol Amendments

The original protocol was dated February 5, 2014, and there were 2 global amendments to the protocol dated October 24, 2013 and November 22, 2016.

Important modifications in Protocol Amendment 1 (October 24, 2013):

- Tertiary endpoints were added: Composite renal endpoint 2 (renal death, sustained ESRD, sustained decrease of 40% or more in eGFR); sustained decrease of 40% or more in eGFR; composite microvascular outcome 2 (40% decrease or more in eGFR, albuminuria progression, requirement for renal replacement therapy or death due to renal failure, use of retinal photocoagulation or intravitreal injection of an anti-VEGF therapy for diabetic retinopathy);
- Lipase added to the laboratory assessments;
- Independent adjudication of pancreatic events was added;
- Information about censoring of CV and renal endpoint was added;
- In inclusion criterion, definitions of albuminuria and UARC were removed to reflect the KDIGO Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease.

Important modifications in Protocol Amendment 2 (November 22, 2106):

- The primary endpoint was changed from 4-point MACE to 3-point MACE, based on review of newly published CV outcomes trials; 4-point MACE became a tertiary endpoint;
- eGFR cut off in the key secondary endpoint for decrease in eGFR was changed to 40% (from 50%) in response to the NIH/FDA scientific workshop on GFR decline as an endpoint for clinical trials in CKD, and current clinical information on decline in eGFR and subsequent risk of end stage renal disease and mortality;
- Interim analysis for efficacy was removed, and the required number of subjects with primary endpoint to achieve 90% of power for non-inferiority was reduced from 625 to 611, and estimated treatment period decreased from 48 to 54 months;
- The hypothesis testing was changed with a higher alpha-level assigned to the composite renal endpoint;
- Additional tertiary endpoints were added: stent thrombosis, TIA, CV death or hospitalization for heart failure, composite renal endpoint 3 (renal death, sustained ESRD, sustained decrease of 30% or more in eGFR), sustained decrease of 30% or more in eGFR, renal death, sustained ESRD, CV death, eGFR slope from baseline to last week on-treatment, eGFR slope from baseline to follow-up, eGFR slope from last value on treatment to follow-up, composite diabetic retinopathy endpoint, composite microvascular outcome 3 (renal death, sustained ESRD, sustained 30% decrease or more in eGFR, albuminuria progression, use of retinal photocoagulation or intravitreal injection of an anti-VEGF therapy for diabetic retinopathy or vitreous hemorrhage or diabetic-related blindness).

Reviewer's comment: *These changes to the protocol were made before database was locked and appear to have been amended appropriately based on updated clinical information in the scientific literature. These modifications to the protocol are unlikely to have affected the integrity or interpretation of the efficacy and safety data.*

It should also be noted that some of the major changes in Amendment 2 such as change in primary endpoint to 3-point MACE, change in the component of renal endpoint from sustained, confirmed decrease in eGFR from 50% to 40%, removing interim analysis, and changing hypothesis testing were found acceptable and agreed upon in our response to their Type C meeting request on July 29, 2016 (see Section 3.2, Summary of Presubmission/Submission Regulatory Activity).

6.1.2. Study Results

Compliance with Good Clinical Practices

The Applicant stated that trial 1218.22 was conducted with the principles of the Declaration of Helsinki, in accordance with the International Council for Harmonization-Good Clinical Practice, and in accordance with applicable regulatory requirements.

The Applicant provided listings of all recorded protocol violations. Distribution of the types of protocol deviations were overall infrequent, similar between treatment arms, and appear to be unlikely to influence overall study integrity.

Financial Disclosure

In accordance with 21 CFR 54.4, the Applicant submitted Form 3454 for Trial 1218.22, 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.

Boehringer Ingelheim is the Applicant, and Eli Lilly was identified as a financial co-funder in the financial disclosure information.

There were 2 principal investigators/sub-investigators who held financial interests requiring disclosure, both for Eli Lilly:

- (b) (6) who was a sub-investigator under Principal Investigator (b) (6), held stocks in Eli Lilly due to previous employment; this site enrolled (b) (6);
- (b) (6) had received speaker fees for Eli Lilly; this site enrolled (b) (6).

Given that Trial 1218.22 a large trial that randomized 6991 subjects, the number of subjects

recruited from these sites are very low and unlikely to have had a significant impact on the overall outcome of this trial. In addition, since Trial 1218.22 was a randomized, double-blind study with primary endpoints and key secondary endpoints adjudicated by an independent, external committee, potential for bias is minimized.

Patient Disposition

A total of 12,280 subjects were screened, of which 5289 subjects (~43%) were not randomized. Most subjects were not randomized because they did not meet the eligibility criteria, such as not at high risk of CV events as defined in the protocol (2467 subjects) and not having HbA1c of 6.5-10% at screening (2234 subjects).

About 57% of those screened (6991 subjects) were randomized. By region, the largest proportion of randomized subjects were from Europe (n=2936; 42% of randomized), followed by Latin America (n=2314; 33% of randomized). At country level, the U.S. had the largest randomized subjects (n=1059; 15% of randomized), followed by Brazil (n=808; 11.6% of randomized) and Argentina (n=787; 11.3% of randomized).

Of 6991 randomized subjects, 6979 subjects were treated with double-blind study drug. Nine subjects were randomized in error and none of these subjects were treated; these 9 subjects were considered to be screen failures because the study site made an administrative mistake in the system leading to subjects being randomized in error. An additional 3 subjects were randomized but not treated.

A slightly larger percentage of subjects prematurely discontinued the study drug in the placebo group (27.4%) compared to linagliptin group (23.9%), mostly due to adverse events or CV outcome events (linagliptin 10.4%, placebo 11.5%).

About 98.7% of subjects completed the trial or died, with similar percentage between treatment groups (99% in the linagliptin vs 98.4% in the placebo group). A total of 1.3% of subjects were lost to follow-up (LTFU) for 3p-MACE, and a slightly higher percentage of placebo subjects were LTFU (1.6%) compared to linagliptin group (1.0%).

Vital status was collected in 99.7% of subjects as either alive or dead, and this was similar in both treatment groups (99.8% in the linagliptin and 99.6% in the placebo group). Final vital status was missing in 21 subjects (7 linagliptin and 14 placebo subjects).

Slightly larger number of subjects in the placebo group (59 subjects; 1.7%) discontinued the study participation compared to the subjects in the linagliptin group (39 subjects; 1.1%), and this was largely due to withdrawal of consent (linagliptin 0.5%, placebo 1.0%).

Table 5 provides a summary of subject disposition in CARMELINA.

Table 5: Subject Disposition in CARMELINA

	Linagliptin	Placebo	Total
Randomized	**3499**	**3492**	**6991**
Not treated	5	7	12
Treated subjects (Treated Set)	**3494**	**3485**	**6979**
Did not prematurely discontinued from study drug	2660 (76.1%)	2530 (72.6%)	5190 (74.4%)
Prematurely discontinued the study drug	834 (23.9%)	955 (27.4%)	1789 (25.6%)
Adverse Events	362 (10.4%)	402 (11.5%)	764 (10.9%)
Patient refused to continue study drug	281 (8.0%)	333 (9.6%)	614 (8.8%)
Other	176 (5.0%)	196 (5.6%)	372 (5.3%)
Non-compliance	15 (0.4%)	24 (0.7%)	39 (0.6%)
Completed the trial or died*	3458 (99.0%)	3430 (98.4%)	6888 (98.7%)
Lost to follow-up for 3P-MACE*	36 (1.0%)	55 (1.6%)	91 (1.3%)
Prematurely discontinued from the trial	39 (1.1%)	59 (1.7%)	98 (1.4%)
Consent withdrawn	19 (0.5%)	34 (1.0%)	53 (0.8%)
Lost to follow-up	20 (0.6%)	25 (0.7%)	45 (0.6%)
Final vital status			
Alive	3120 (89.3%)	3098 (88.9%)	6218 (89.1%)
Dead	367 (10.5%)	373 (10.7%)	740 (10.6%)
Lost to follow-up	0	4 (0.1%)	4 (0.1%)
Missing	7 (0.2%)	10 (0.3%)	17 (0.2%)

CV=cardiovascular; MACE=major adverse cardiac events
*Subject who has no visit information (except date of non-CV death) after trial close out and has no confirmed 3P-MACE is included in the line "Lost to follow-up for 3P-MACE". "Completed the trial or died" included all subjects with 3P-MACE event.
Source: Adapted from CSR 1218.22, Table 10.1:2

Protocol Violations/Deviations

Important protocol violations were predefined in the TSAP. Overall, 54 subjects (0.8%) had at least 1 important protocol violation leading to exclusion from the Per Protocol Set (PPS). The proportion of subjects with important protocol violations was similar between treatment groups (28 subjects [0.8%) in the linagliptin and 26 subjects [0.7%) in the placebo group). Excluding these subjects, 6925 subjects were included in the Per Protocol Set with 3466 in the linagliptin group and 3459 in the placebo group.

Of 54 total subjects with protocol violations, 35 subjects violated exclusion criteria (21 linagliptin vs 14 placebo subjects), 6 subjects took incorrect study drug (2 linagliptin vs 4 placebo subjects), and 20 subjects had trial specific protocol violations (11 linagliptin vs 9 placebo subjects). Review of these small number of protocol violations in the overall study population of CARMELINA did not show any obvious trends or treatment difference that may have affected the interpretation of study results (data not shown here; see Table 10.3:1 in CSR).

Table of Demographic Characteristics

The baseline demographic characteristics are summarized in Table 5. About 62.9% of overall subjects were male, the majority were White (80.2%), and the mean age of the study population was 65.9 years. Most subjects were <65 years old (42.5%) or 65 to <75 years old (40.1%), and a very small proportion of study population was ≥80 years old (5.9%).

Table 6: Baseline Demographic Characteristics of the Treated Set

Demographic Parameter	Linagliptin (N-3494)	Placebo (N=3485)	Total (N=6979)
Gender, n (%)			
Male	2148 (61.5)	2242 (64.3)	4390 (62.9)
Female	1346 (38.5)	1243 (35.7)	2589 (37.1)
Age			
Mean years (SD)	66.1 (9.05)	65.6 (9.14)	65.9 (9.10)
Age Group			
<65 years	1467 (42.0)	1501 (43.1)	2968 (42.5)
≥ 65 to <75 years	1405 (40.2)	1395 (40.0)	2800 (40.1)
≥ 75 to <80 years	402 (11.5)	397 (11.4)	799 (11.4)
≥ 80 years	220 (6.3)	192 (5.5)	412 (5.9)
Race, n (%)			
White	2827 (80.9)	2769 (79.5)	5596 (80.2)
Black or African American	194 (5.6)	217 (6.2)	411 (5.9)
Asian	307 (8.8)	333 (9.6)	640 (9.2)
American Indian or Alaska Native	159 (4.6)	156 (4.5)	315 (4.5)
Native Hawaiian or Other Pacific Islander	7 (0.2)	10 (0.3)	17 (0.2)
Ethnicity, n (%)			
Hispanic or Latino	1227 (35.1)	1274 (36.6)	2501 (35.8)
Not Hispanic or Latino	2267 (64.9)	2211 (63.4)	4478 (64.2)
Region			
North America	593 (17.0)	587 (16.8)	1180 (16.9)
United States	528 (15.1)	528 (15.2)	1056 (15.1)
Latin America	1156 (33.1)	1154 (33.1)	2310 (33.1)
Europe	1473 (42.2)	1461 (41.9)	2934 (42.0)
Asia	272 (7.8)	283 (8.1)	555 (8.0)
Weight (kg), mean (SD)	86.4 (18.00)	86.9 (18.26)	86.6 (18.13)
BMI (kg/m^2), mean (SD)	31.2 (5.29)	31.3 (5.37)	31.3 (5.33)

Source: CSR 1218.22, Table 10.4.1:1

Reviewer's Comment: *Overall, baseline demographic characteristics were balanced between treatment groups.*

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

The baseline clinical disease characteristics for study population are summarized in

Table 7. The mean baseline HbA1c was 8% and the mean FPG was 151 mg/dL in subjects without notable differences between treatment groups. Subjects had T2DM for a mean of 14.75 years and the majority (~65%) of study population had diabetes for ≥10 years. About 63% of subjects had diabetic nephropathy, 41% had diabetic neuropathy, and 28% had diabetic retinopathy.

About 57.2% of subjects had macrovascular disease at baseline, and 26.8% of subjects had history of heart failure.

At baseline, about 40% of subjects had microalbuminuria and about 40% of subjects had macroalbuminuria. The proportion of subjects in each UACR category was balanced at baseline. The mean eGFR was 54.6 mL/min/1.73 m^2, ~30% of subjects had mild renal impairment (eGFR 60 to <90 mL/min/1.73 m^2), and ~60% of subjects had moderate or severe renal impairment (eGFR <60 mL/min/1.73 m^2). According to risk stratification by KDIGO[5] standards, 27.2% of subjects were high risk and 43.4% of subjects were very high risk for adverse kidney events based on their eGFR and albuminuria at baseline.

[5] Levey AS, de Jong PE, Coresh J et al. The definition, classification, and prognosis of chronic kidney disease: a KDIGO controversies conference report. Kidney Int 2011;80(10):17-28.

Table 7: Baseline Clinical Disease Characteristics of the Treated Set, N (%)

	Linagliptin (N-3494)	Placebo (N=3485)	Total (N=6979)
HbA1c (%), mean (SD)	**7.9 (1.00)**	**8.0 (1.01)**	**8.0 (1.02)**
HbA1c category, n (%)			
<7%	614 (17.6)	616 (17.7)	1230 (17.6)
7 to <8%	1301 (37.2)	1239 (35.6)	2540 (36.4)
8 to <9%	948 (27.1)	969 (27.8)	1917 (27.5)
≥9%	631 (18.1)	661 (19.0)	1292 (18.5)
T2D duration (years), mean (SD)	14.97 (9.63)	14.53 (9.25)	14.75 (9.45)
T2D duration category, n (%)			
≤5 years	521 (14.9)	553 (15.9)	1074 (15.4)
>5 to <10 years	696 (19.9)	688 (19.7)	1384 (19.8)
≥10 years	2277 (65.2)	2244 (64.4)	4521 (64.8)
Diabetic retinopathy	970 (27.8)	968 (27.8)	1938 (27.8)
Diabetic nephropathy	2229 (63.8)	2164 (62.1)	4393 (62.9)
Diabetic neuropathy	1457 (41.7)	1394 (40.0)	2851 (40.9)
FPG (mg/dL), mean (SD)	151.2 (45.95)	151.2 (45.95)	151.2 (45.95)
UACR (mg/g creatinine)			
Mean	683.8	727.8	705.8
median	161.5	162.0	163.0
UACR category, n (%)			
<30 mg/g (normal)	696 (19.9)	696 (20.0)	1392 (19.9)
30 to ≤300 mg/g (microalbuminuria)	1463 (41.9)	1431 (41.1)	2894 (41.5)
>300 mg/g (macroalbuminuria)	1333 (38.2)	1357 (38.9)	2690 (38.5)
eGFR (MDRD) (mL/min/1.73 m^2), mean (SD)	**54.7 (25.09)**	**54.5 (24.92)**	**54.6 (25.00)**
eGFR (MDRD) category, n (%)			
≥90 mL/min/1.73 m^2	363 (10.4)	365 (10.5)	728 (10.4)
60 to <90 mL/min/1.73 m^2	931 (26.6)	972 (27.9)	1903 (27.3)
45 to <60 mL/min/1.73 m^2	690 (19.7)	658 (18.9)	1348 (19.3)
30 to <45 mL/min/1.73 m^2	994 (28.4)	944 (27.1)	1938 (27.8)
15 to <30 mL/min/1.73 m^2	505 (14.5)	536 (15.4)	1041 (14.9)
<15 mL/min/1.73 m^2	11 (0.3)	10 (0.3)	21 (0.3)
KDIGO risk categories for prognosis of CKD*			
Low risk	232 (6.6)	252 (7.2)	484 (6.9)
Moderately increased risk	766 (21.9)	795 (22.8)	1561 (22.4)
High risk	995 (28.5)	905 (26.0)	1900 (27.2)
Very high risk	1499 (42.9)	1533 (44.0)	3032 (43.4)
Established renal disease[#], n (%)	2109 (60.4)	2074 (59.5)	4183 (59.9)
Prevalent kidney disease[+], n (%)	2606 (74.6)	2541 (72.9)	5147 (73.7)
Macrovascular disease, n (%)	2008 (57.5)	1982 (56.9)	3990 (57.2)
History of hypertension, n (%)	3171 (90.8)	3178 (91.2)	6349 (91.0)
History of heart failure, n (%)	952 (27.2)	921 (26.4)	1873 (26.8)

FPG=fasting plasma glucose; MDRD=Modification of Diet in Renal Disease; n=number of subjects; SD=standard deviation; UACR=Urine Albumin Creatinine Ratio
*Low risk: eGFR ≥60 and UACR <30; Moderately increased risk: eGFR ≥45 to <60 and UACR <30, or eGFR ≥60 and UACR ≥30 to ≤300; High risk: eGFR ≥30 to <45 and UACR <30, or eGFR ≥45 to <60 and UACR ≥30 to ≤300, or eGFR ≥60 and UACR >300; Very high risk: eGFR <30 with any UACR, eGFR ≥30 to ≤45 and UACR ≥30, or eGFR ≥45 to <60 and UACR >300.
#Defined as impaired renal function with either eGFR 15 to <45 mL/min/1.73 m^2 with any UACR or eGFR 45 to 75 mL/min/1.73 m^2 with an UACR >200 mg/g;
+Defined as baseline eGFR <60 mL/min/1.73 m^2 or macroalbuminuria UACR >300 mg/g.
Source: CSR 1218.22, modified from Table 10.4.2:1, Table 15.1.4.1, Table 15.1.4.28, Table 16.1.13.2.1

Subjects with T2DM who had high cardiovascular risk were enrolled in CARMELINA, as discussed in Inclusion Criteria in Section 6.1.1, Study Design. Overall, about 57% of subjects had albuminuria and previous macrovascular disease (Risk category 1), and about 42% of subjects had evidence of impaired renal function with predefined UACR (Risk category 2). Subjects with each type of cardiovascular risk factors were well balanced between treatment groups (Table 8).

Table 8: Frequency of Subjects [N (%)] With Cardiovascular Risk Factors at Baseline – Treated Set

	Linagliptin (N-3494)	Placebo (N=3485)	Total (N=6979)
Albuminuria and previous macrovascular disease (Risk category 1)	**2011 (57.6)**	**1986 (57.0)**	**3997 (57.3)**
Confirmed history of MI	942 (27.0)	921 (26.4)	1863 (26.7)
Advanced CAD	594 (17.0)	556 (16.0)	1150 (16.5)
High-risk single-vessel CAD	73 (2.1)	70 (2.0)	143 (2.0)
History of ischemia or hemorrhagic stroke	467 (13.4)	494 (14.2)	961 (13.8)
Presence of carotid artery disease	177 (5.1)	175 (5.0)	352 (5.0)
Presence of peripheral artery disease	269 (7.7)	266 (7.6)	535 (7.7)
Evidence of impaired renal function with predefined UACR (Risk category 2)*	**1462 (41.8)**	**1457 (41.8)**	**2919 (41.8)**
eGFR 15 to <45 mL/min/1.73 m^2	1157 (33.1)	1160 (33.3)	2317 (33.2)
eGFR 45 to <75 mL/min/1.73 m^2 with UACR >200 mg/g creatinine	317 (9.1)	304 (8.7)	621 (8.9)
No albuminuria and previous macrovascular disease (Risk category 1) and no evidence of impaired renal function (Risk category 2)	**21 (0.6)**	**40 (1.1)**	**61 (0.9)**
Missing albuminuria and previous macrovascular disease and impaired renal function	**0**	**2 (0.1)**	**2 (0.0)**

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, modified from Table 10.4.4:1

Reviewer's comment: *Overall, the baseline disease characteristics including cardiovascular risk*

factors were balanced without any notable differences between treatment groups.

Most subjects (96.8%) were taking antidiabetic therapy at baseline, and the majority were either on monotherapy (50.8%) or dual therapy (40.6%). The most frequent baseline antidiabetic therapy were insulins and analogues (57.3%) followed by metformin (54%) and sulfonylurea (31.9%). The types of background antidiabetic therapy at baseline were similar between treatment groups, as summarized in Table 9.

Table 9: Summary of Background Antidiabetic Therapy at Baseline in Treated Set

	Linagliptin N=3494 n (%)	Placebo N-3484 n (%)	Total N=6979 n (%)
Subjects with at least one antidiabetic therapy	3378 (96.7)	3376 (96.9)	6754 (96.8)
Number of antidiabetic therapy			
Monotherapy	1764 (50.5)	1778 (51.0)	3542 (50.8)
Insulins and analogues	1084 (31.0)	1031 (29.6)	2115 (30.3)
Metformin	450 (12.9)	498 (14.3)	948 (13.6)
Sulfonylureas	202 (5.8)	226 (6.5)	428 (6.1)
Dual therapy	1419 (40.6)	1414 (40.6)	2833 (40.6)
Insulin and analogues & metformin	621 (17.8)	612 (17.6)	1233 (17.7)
Metformin & sulfonylureas	593 (17.0)	612 (17.6)	1205 (17.3)
Insulins and analogues & sulfonylureas	110 (3.1)	110 (3.2)	220 (3.2)
Triple therapy	189 (5.4)	177 (5.1)	366 (5.2)
Insulins and analogues & metformin & sulfonylureas	132 (3.8)	130 (3.7)	262 (3.8)
Types of antidiabetic therapy			
Insulin and analogies	2033 (58.2)	1963 (56.3)	3996 (57.3)
Metformin	1865 (53.4)	1903 (54.6)	3768 (54.0)
Sulfonylurea	1095 (31.3)	1132 (32.5)	2227 (31.9)
Alpha-glucosidase inhibitors	79 (2.3)	73 (2.1)	152 (2.2)
Thiazolidinediones	61 (1.7)	50 (1.4)	111 (1.6)
Meglitinides	50 (1.4)	35 (1.0)	85 (1.2)
Other antidiabetic drugs	8 (0.2)	9 (0.3)	17 (0.2)
DPP-4 inhibitors	2 (0.1)	0	2 (0.0)

Source: CSR, modified from Table 10.4.7.1:1

In terms of other important concomitant therapy at baseline, the proportion of subjects taking antihypertensive therapy, lipid-lowering therapy, and aspirin was similar between treatment groups, as summarized in Table 10. The majority (98%) of enrolled subjects were taking antihypertensives, about 75% of enrolled subjects were taking lipid-lowering drugs (mostly

statin, ~72%), and about 62% of subjects were taking aspirin at baseline.

Table 10: Summary of Background* Antithrombotics, Antihypertensives, or Lipid Lowering Therapies at Baseline in Treated Set

	Linagliptin N=3494 n (%)	Placebo N-3484 n (%)	Total N=6979 n (%)
Antihypertensives	3429 (97.9)	3420 (98.1)	6840 (98.0)
Beta-blockers	2080 (59.5)	2073 (59.5)	4153 (59.5)
Diuretics	1892 (54.1)	1936 (55.6)	3828 (54.9)
ACE inhibitors/ARBs	2860 (81.9)	2798 (80.3)	5658 (81.1)
ACE inhibitors	1574 (45.0)	1562 (44.8)	3136 (44.9)
ARBs	1382 (39.6)	1308 (37.5)	2690 (38.5)
Renin inhibitors	5 (0.1)	4 (0.1)	9 (0.1)
Calcium channel blockers	1433 (41.0)	1446 (41.5)	2879 (41.3)
Lipid lowering drugs	2623 (75.1)	2646 (75.9)	5269 (75.5)
Statins	2495 (71.4)	2523 (72.4)	5018 (71.9)
Fibrates	311 (8.9)	340 (9.8)	651 (9.3)
Ezetimibe	73 (2.1)	85 (2.4)	158 (2.3)
Niacin	12 (0.3)	12 (0.3)	24 (0.3)
ASA	2166 (62.0)	2178 (62.5)	4344 (62.2)
Antithrombotics other than ASA	1007 (28.8)	1051 (30.2)	2058 (29.5)
Platelet aggregation inhibitors excluding heparin and ASA			
Clopidogrel	584 (16.7)	601 (17.2)	1185 (17.0)
Other platelet aggregation inhibitors excluding heparin and ASA	179 (5.1)	178 (5.1)	357 (5.1)
Dipyridamole	3 (0.1)	6 (0.2)	9 (0.1)
Direct factor Xa inhibitors	33 (0.9)	54 (1.5)	87 (1.2)
Direct thrombin inhibitors	27 (0.8)	24 (0.7)	51 (0.7)
Vitamin K antagonists	245 (7.0)	256 (7.3)	501 (7.2)
Warfarin	149 (4.3)	145 (4.2)	294 (4.2)
Thrombolytic agents	2 (0.1)	1 (0.0)	3 (0.0)
Other antithrombotic agents	11 (0.3)	12 (0.3)	23 (0.3)

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, modified from Table 10.4.7.2

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment Compliance:

Treatment compliance was evaluated at each study visit by counting dispensed and returned study drug, and subjects were considered to be compliant if their adherence rates were between 80 to 120%. The overall non-compliance rate was about 4% at Week 60, 2.6% at Week 132, and was similar between treatment groups throughout the trial (data not shown; see Table 15.1.6 of Clinical Study Report).

Concomitant Medications: Antidiabetic Therapy

During the trial, 98.4% of subjects (linagliptin 98.2%, placebo 98.6%) used at least one concomitant antidiabetic drugs; of these, about 64.2% of subjects (linagliptin 63.9%, placebo 64.4%) used insulins and analogues, and about 57.3% of subjects (linagliptin 56.2%, placebo 58.4%) used metformin.

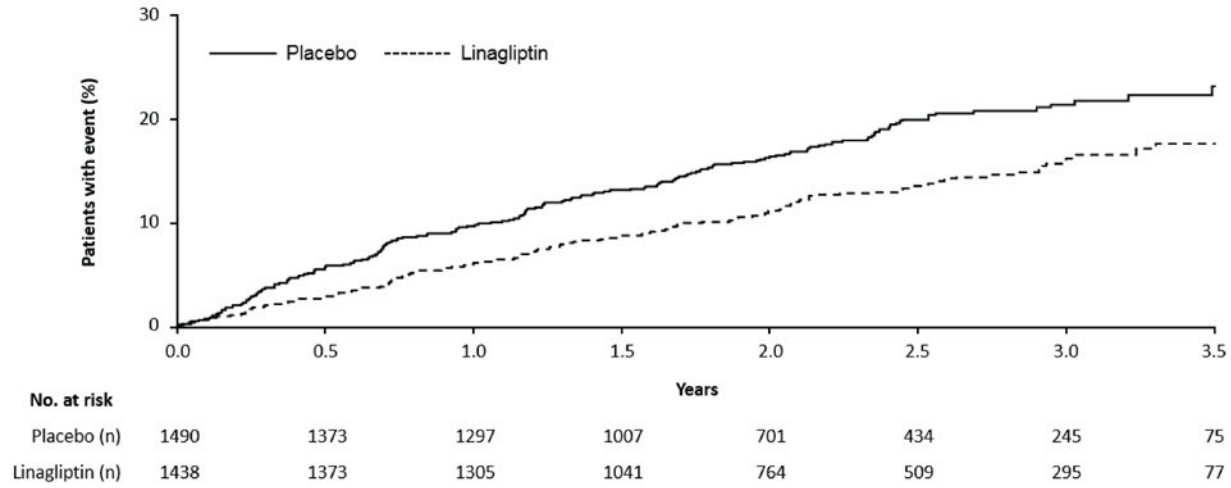
During the study, a slightly higher proportion of subjects in the placebo group started a new antidiabetic therapy (22.4% [783/3494] of subjects in the linagliptin group versus 27.8% [970/3484] of subjects in the placebo group). Insulin was the most frequently introduced antidiabetic therapy at a numerically higher proportion of subjects in the placebo group (14.6% [509/3494] linagliptin vs 18.0% [626/3484] placebo), followed by metformin (2.6% [91/3494] linagliptin vs 3.3% [116/3484] placebo).

Reviewer's comment: *It is perhaps not surprising that more subjects in the placebo group needed to start new antidiabetic therapy, as these subjects are likely requiring additional therapy for glycemic control compared to those who were receiving active treatment (i.e., linagliptin).*

Initiation/intensification of insulin

A Kaplan-Meier curve of time to first initiation of insulin therapy in subjects not on insulin at baseline for linagliptin compared to placebo is shown in Figure 2. The curves show that larger number of subjects on placebo compared to linagliptin initiated insulin therapy shortly after starting study and through the study duration.

Figure 2: Kaplan-Meier Estimate of Time to First Initiation of Insulin for Subjects Not On Insulin at Baseline – Treated Set



Source: CSR, Figure 11.1.4.6:1

Concomitant Medications: Aspirin/Antithrombotics, Antihypertensives, or Lipid Lowering Drugs

About 51.7% of subjects started aspirin, other antithrombotics, antihypertensives, or lipid lowering drugs after first dose of study drug, including those that may have been taking a therapy at baseline that was stopped and reintroduced later in the trial. The proportions of subjects initiating antihypertensives, lipid-lowering drugs, aspirin, and antithrombotics other than aspirin were similar between treatment groups.

Table 11: Summary of Subjects Initiating Antihypertensive, Lipid-Lowering Drugs, Aspirin, or other Antithrombotics After the First Dose of Study Drug

	Linagliptin N=3494 n (%)	Placebo N-3484 n (%)	Total N=6979 n (%)
Subjects with at least one drug	1811 (51.8)	1794 (51.5)	3605 (51.7)
Antihypertensives	1188 (34.0)	1231 (35.3)	2419 (34.7)
Lipid lowering drugs	499 (14.3)	499 (14.3)	998 (14.3)
ASA	170 (4.9)	164 (4.7)	334 (4.8)
Antithrombotics other than ASA	393 (11.2)	406 (11.6)	799 (7.1)

ASA=aspirin
Source: CSR, adapted from Table 10.4.8.2:2

Efficacy Results – Primary Endpoint

The primary efficacy analysis compared the time to the first occurrence of major cardiovascular

outcome event (MACE), defined as cardiovascular death, non-fatal myocardial infarction or non-fatal stroke from randomization until the trial end. In total, 854 subjects had a MACE event, 434 subjects (12.4%) in the linagliptin group and 420 subjects (12.1%) in the placebo group. The hazard ratio for the composite MACE resulted in a point estimate of 1.02 with the upper bound of 95% confidence interval less than 1.3 (0.89., 1.17; p=0.0002 for non-inferiority).

Table 12: Cox Regression Analysis of Time to First Occurrence of MACE (Treated Set)

	Linagliptin (N=3494)	**Placebo (N=3485)**
Subjects with MACE, n (%)	**434 (12.4)**	**420 (12.1)**
Cardiovascular death	221 (6.3)	225 (6.5)
Non-fatal myocardial infarction	154 (4.4)	132 (3.8)
Non-fatal stroke	59 (1.7)	63 (1.8)
Incidence rate of MACE per 1000 years, (95% CI)[1]	**57.7 (52.38, 63.37)**	**56.3 (51.08, 61.99)**
Hazard ratio of MACE (compared to placebo)[2]	**1.02**	
95% CI; alpha=2.5%	0.89, 1.17	
99% CI; alpha=0.5%	0.86, 1.22	
p-value for HR ≥1.3 (1-sided)	0.0002	
p-value for HR ≥1.0 (1-sided)	0.6301	

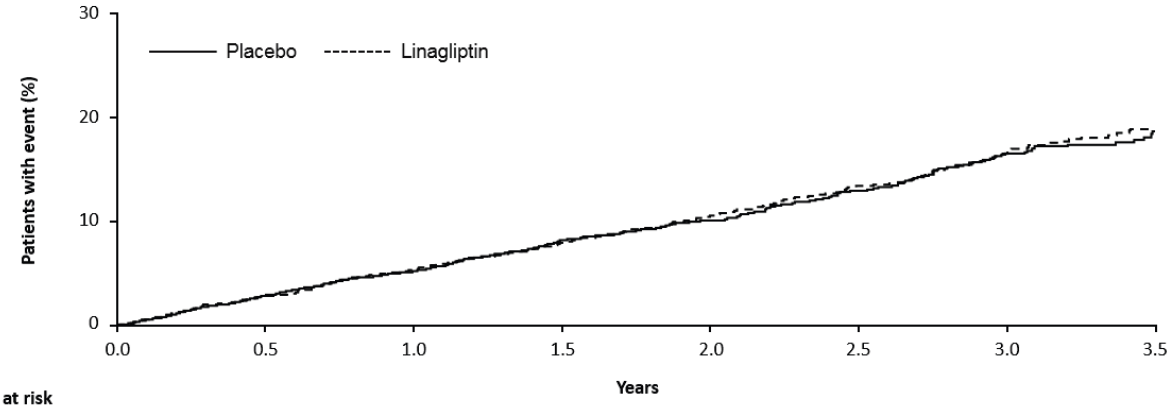
MACE=major adverse cardiovascular event; CI=confidence interval; HR=hazard ratio
[1] 95% CI was calculated based on the Exact Poisson method for the number of patients.
[2] Based on a Cox regression model with terms for treatment group (p=0.7398), region (p=0.7878)
Source: CSR 1218.22, Table 11.1.1.1:1

As discussed in the Statistical Analysis Plan, based on the order of hierarchical hypothesis testing, superiority of the primary endpoint was to be tested after non-inferiority of the primary endpoint at 0.2% of alpha. Since the upper bound of 99% CI was above 1.0 (p-value of 0.63), linagliptin was not shown to be superior to placebo.

Reviewer's comment: *The results of CARMELINA showed that linagliptin did not unacceptably increase the rate of MACE compared to placebo and excluded a 30% excess increased CV risk in accordance with the FDA 2008 Guidance. The same data provides no evidence that linagliptin is superior to placebo (i.e., that it reduces the risk of MACE).*

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

Figure 3: Kaplan-Meier Estimates of Time to First Occurrence of MACE (Treated Set)



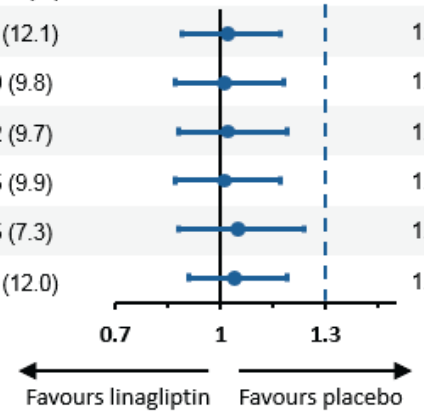
No. at risk								
Placebo (n)	3485	3353	3243	2625	1931	1285	758	251
Linagliptin (n)	3494	3373	3254	2634	1972	1306	778	269

Source: CSR 1218.22, Figure 11.1.1.1:1

Sensitivity analyses using various on-treatment censoring approach and different analysis population appear to be consistent with the result of the primary analysis, as shown in Figure 3.

Figure 4: Forest Plot for time to MACE and Sensitivity Analysis

	Linagliptin (n = 3494)	Placebo (n = 3485)	HR (95% CI)[1]
	Patients with Events, N (%)		
Primary analysis (TS)	434 (12.4)	420 (12.1)	1.02 (0.89, 1.17)
Per-protocol set[2]	353 (10.2)	339 (9.8)	1.01 (0.87, 1.18)
On-treatment set[3]	350 (10.1)	332 (9.7)	1.02 (0.88, 1.19)
TS +30 days censoring approach	357 (10.2)	345 (9.9)	1.01 (0.87, 1.17)
TS +0 days censoring approach	275 (7.9)	255 (7.3)	1.05 (0.88, 1.24)
TS +additional covariates[4]	433 (12.4)	418 (12.0)	1.04 (0.91, 1.19)



CI = confidence interval; HR = hazard ratio; T2DM = type 2 diabetes mellitus; HbA_{1c} = glycosylated haemoglobin; eGFR = estimated glomerular filtration rate; UACR = urine albumin to creatinine ratio; SBP = systolic blood pressure; DBP = diastolic blood pressure; BMI = body mass index.
1 Cox regression model with terms for treatment group and region.
2 Per-protocol set: n = 3466 for linagliptin and n = 3459 for placebo.
3 On-treatment set: n = 3453 for linagliptin and n = 3433 for placebo.
4 Cox regression model with terms for treatment group, region, baseline age, time since diagnosis of T2DM, HbA_{1c}, eGFR (MDRD), UACR, SBP, DBP, and BMI.
Source: CSR, Figure 11.1.1.2:1

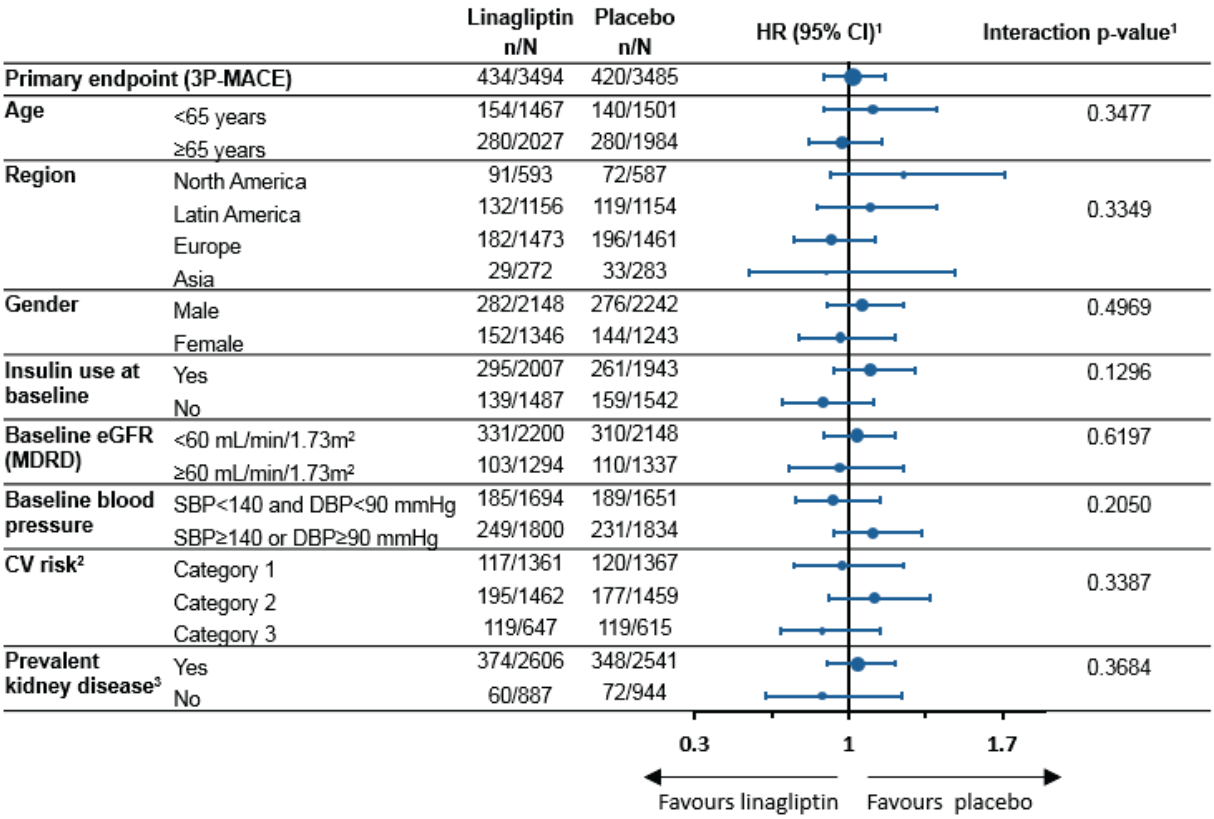
Subgroup Analyses:

The primary endpoint was analyzed for subgroups, some of which are shown in Figure 4. These analyses were done without adjustment for multiplicity and are considered exploratory.

Although some of the point estimate of HR for MACE was numerically larger than 1.0, most appear to be due to uncertainty in HR estimate given smaller number of subjects making up each subgroup. For example, the HR for MACE in North America was 1.25 with wide confidence interval (95% CI: 0.92, 1.71), and it is notable that only about 17% of overall study population were from North America. In addition, none of the p-values for interaction showed significance.

Dr. Bo Li also conducted subgroup analysis of MACE by U.S. and non-U.S. The estimated HR using Cox model with a fixed effect for treatment was 1.24 (95% CI: 0.89, 1.71) among subjects randomized to U.S., and 0.98 (95% CI: 0.85, 1.14) among subjects randomized outside of U.S (see Table 19 of Dr. Li's Statistical Review). Dr. Li did not find evidence of interaction with treatment (p-value=0.21).

Figure 5: Subgroup Analysis for MACE



CI = confidence interval; CV = cardiovascular; HR = hazard ratio; eGFR = estimated glomerular filtration rate; UACR = urine albumin to creatinine ratio.
1 Cox regression model with terms for treatment group, region, subgroup, and treatment-by-subgroup interaction.
2 Categories: (1) Established macrovascular disease and albuminuria without established renal disease (2) Established renal disease without macrovascular and albuminuria disease (3) Established macrovascular disease and albuminuria and established renal disease.
3 Defined as: eGFR <60 mL/min/1.73 m² or macroalbuminuria UACR >300 mg/g.
N, total number of patients in the subgroup; n, number of patients with event; the bubble size for the HR point estimate is proportional to the number of patients in the subgroup.
Source: CSR, Figure 11.1.1.3:1

Reviewer's comment: *Subgroup analyses were generally consistent with the primary analysis of MACE. It is particularly reassuring that the HR for MACE was consistent in different categories of CV risk based on established macrovascular disease, albuminuria, and established renal disease.*

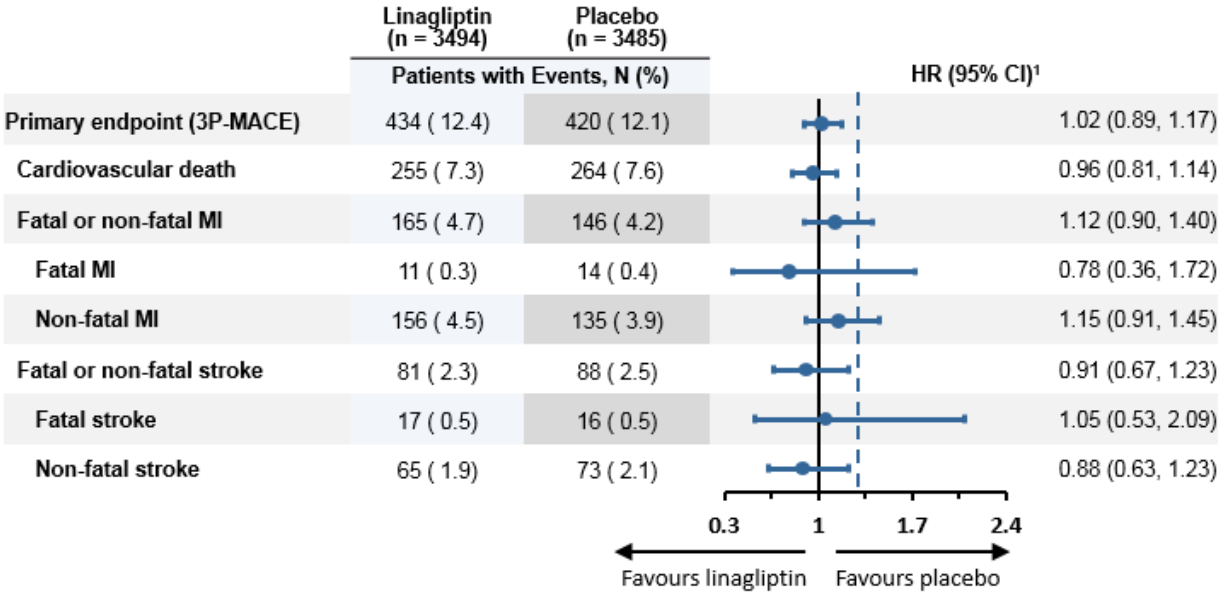
Discussion of Individual Components of MACE:

This section presents the individual components of MACE by evaluating both the time to event analyses for each component (i.e., time to first non-fatal myocardial infarction, time to first non-fatal stroke, and time to cardiovascular death), which were pre-specified as tertiary

endpoints in this trial. These endpoints are discussed here rather than in the other endpoints section since understanding the MACE components is necessary in an overall assessment of the primary endpoint.

Figure 5 shows forest plot of subjects who experienced individual components, even if not specifically contributing to the primary analysis of MACE, and HR for each component that make up MACE. Most individual component appear to be consistent with the primary analysis of composite MACE with point estimate of around 1. In addition, the 95% confidence intervals for the individual component events of MACE all included the null value of 1.

Figure 6: Forest Plot of Time to 3P-MACE and Time to MACE Components (Treated Set)



CI = confidence interval; HR = hazard ratio; MI = myocardial infarction.
1 Cox regression model with terms for treatment group and region.
Source: CSR, Figure 11.1.1.4:1

Reviewer's comment: *Each component of MACE was consistent with the overall MACE analysis with the hazard ratio around 1. Myocardial infarction had slight elevation above 1 with HR of 1.12 which appeared to be mostly due to non-fatal MI. It is not uncommon to see a slight increase in a MACE component in CVOTs, and this slight increase does not appear to be concerning since it is not a significant increase above 1 and we have no scientific reason to be concerned about MI with linagliptin specifically or DPP-4 inhibitors as a class.*

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 confirmatory endpoint, other tertiary endpoint related to CV safety (i.e., 4-point composite MACE, all-cause mortality, and hospitalization for unstable angina pectoris), hospitalization for heart failure, and other glycemic endpoints are discussed in this section, as they are relevant endpoints for assessing the overall CV and glycemic benefit with linagliptin.

As discussed below, the trial failed to show superiority for renal composite endpoint with linagliptin, and thus individual components of the renal composite endpoint are not further discussed. In addition, there were other tertiary and exploratory endpoints related to microvascular and renal-related endpoints, which are also not further discussed in this review, as they were exploratory endpoints, did not show adverse outcome with linagliptin, and do not directly contribute to the macrovascular CV benefit for linagliptin.

Key Secondary Endpoint:

The results of the key secondary analysis compared the time to first occurrence of composite renal endpoint (defined as renal death, sustained ESRD, or sustained decrease of 40% or more eGFR from baseline) using a Cox proportional hazards models. In total, 633 subjects had composite renal endpoint, which included 327 subjects (9.4%) from the linagliptin group and 306 subjects (8.8%) from the placebo group. The hazard ratio for the composite renal endpoint was 1.04 (96% CI: 0.88, 1.23; p-value=0.69). Therefore, linagliptin was not shown to be superior to placebo in the composite renal endpoint. Results are summarized in Table 8.

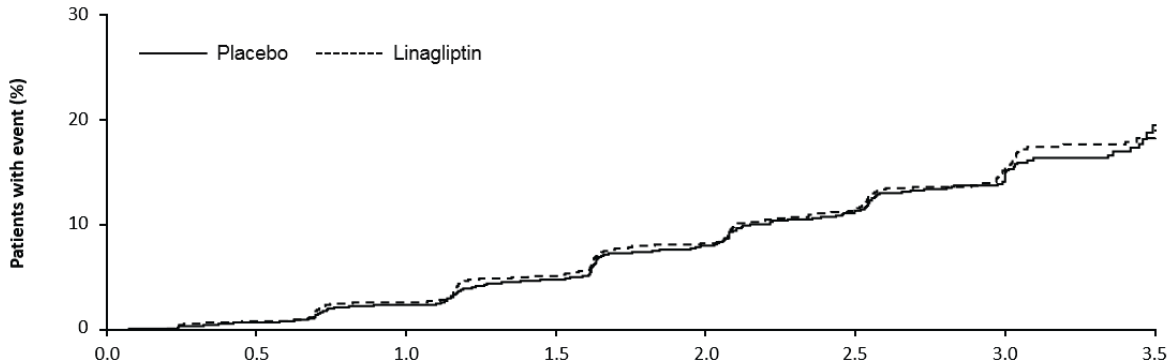
Table 13: Time-to-event Analysis of Composite Renal Endpoint (Treated Set)

	Linagliptin (N=3494)	**Placebo (N=3485)**
Subjects with composite renal endpoint, n (%)	327 (9.4)	306 (8.8)
Incidence rate per 1000 subject-years	48.9	46.6
Hazard ratio of renal endpoint (vs placebo)	1.04	
95% CI; alpha level=2.5%	0.89, 1.22	
96% CI; alpha level=2.0%	0.88, 1.23	
p-value for HR ≥1.0 (1-sided)	0.6918	

Source: CSR, Table 11.1.2.1:1

The Kaplan-Meier estimates of time to occurrence of composite renal endpoint is shown in Figure 5, which show that the curves between treatment groups appear to overlap without much separation of curves.

Figure 7: Kaplan-Meier Estimate of Time to First Occurrence of Composite Renal Endpoint (Treated Set)



No. at risk								
Placebo (n)	3485	3213	2995	2298	1608	1005	496	103
Linagliptin (n)	3494	3227	3018	2345	1675	1040	518	109

Source: CSR, Figure 11.1.2.1:1

The sensitivity analyses of the key secondary endpoint were consistent with the main analysis (data not shown; see Figure 11.1.2.2:1 in CSR).

Other CV Tertiary Endpoints:

All further tertiary and other endpoint analyses were conducted without adjustment for multiplicity and therefore are considered exploratory. All statistical tests and confidence intervals were 2-sided with a significance level of 5% and was analyzed in Treated Set.

The following tertiary endpoints that are relevant to the primary composite MACE endpoint are shown in Table 9: 4 point-MACE (defined as CV death, non-fatal MI, non-fatal stroke, or hospitalization for unstable angina pectoris), all-cause death, and hospitalization for unstable angina pectoris. These analyses showed that the HR for these tertiary endpoints did not show a significant treatment difference between linagliptin and placebo group, as the point estimate for the HR was around 1 or less than 1, and the 95% confidence intervals all included the null value of 1.

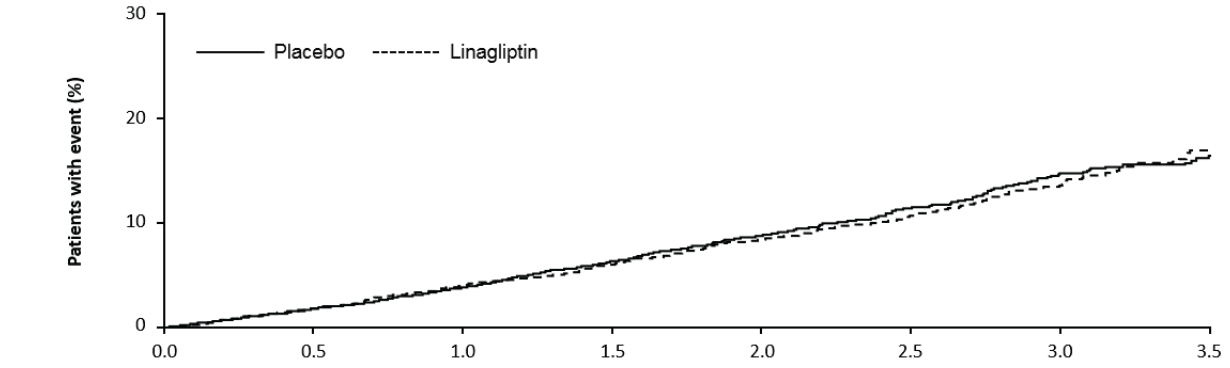
Table 14: Time-to-event Analysis* of 4 point-MACE, All-Cause Mortality, and Hospitalization for Unstable Angina (Treated Set)

	Linagliptin (N=3494)	Placebo (N=3485)	Hazard ratio (95% CI)
Subjects with 4 point-MACE**, n (%)	463 (13.3)	459 (13.2)	1.00 (0.88, 1.13)
Subjects with all cause-mortality, n (%)	367 (10.5)	373 (10.7)	0.98 (0.84, 1.13)
Subjects with hospitalization for unstable angina pectoris, n (%)	42 (1.2)	48 (1.4)	0.87 (0.57, 1.31)

*Based on Cox regression model with terms for treatment group and region; 95% CI was calculated based on the Exact Poisson method for the number of patients;
**4 point-MACE included CV death, non-fatal MI, non-fatal stroke, or hospitalization for unstable angina pectoris
Source: CSR, Table 11.1.3.1:1, Table 11.1.3.2:1, Table 11.1.3.3:1

The Kaplan Meier estimation of time to all-cause mortality for linagliptin compared to placebo show that the curves are similar between treatment groups (Figure 8).

Figure 8: Kaplan-Meier Estimation of Time to Occurrence of All-Cause Mortality (Treated Set)



Source: CSR, Figure 11.1.3.2.2:1

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 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.*

A numerically lower proportion of subjects in the linagliptin group compared to placebo group experienced hospitalization for heart failure, 6.0% (209/3494) versus 6.5% (226/3485) respectively. The time-to-event analysis for hospitalization for heart failure was adjusted for history of heart failure and the HR was <1 (HR: 0.90 [95% CI: 0.74, 1.08]), indicating that the risk for hospitalization for heart failure was not increased with linagliptin treatment compared to placebo in CARMELINA (Table 15).

Since death can confound the analyses of nonfatal events, hospitalization for heart failure was also combined with CV death and all deaths. Both the HR for composite endpoint of 'hospitalization for heart failure or CV death' and 'hospitalization for heart failure or all-cause mortality' were also <1 (Table 15), which is reassuring.

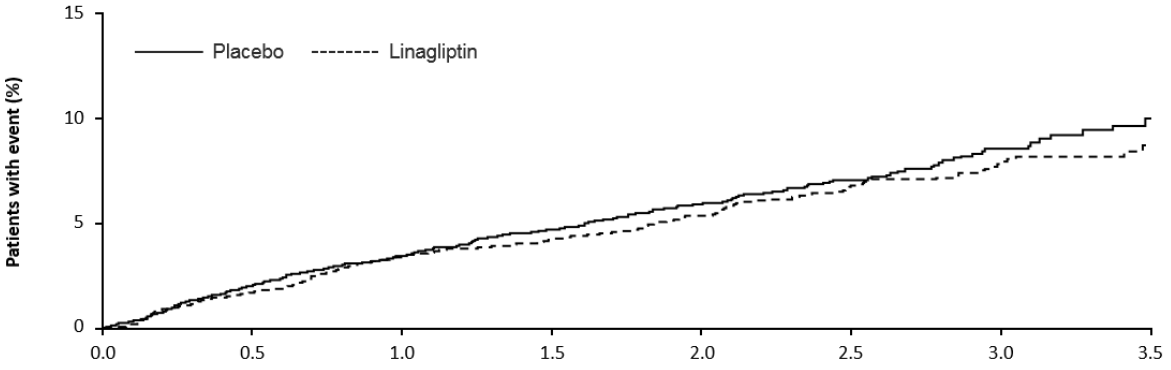
Table 15: Time-to-Event Analyses for Heart Failure-related Endpoints (Treated Set)

	Linagliptin (N=3494)			Placebo (N=3485)			Hazard ratio vs placebo (95% CI)
	N	%	IR	N	%	IR	
Hospitalization for heart failure	209	6.0	27.7	226	6.5	30.4	0.90* (0.74, 1.08)
Hospitalization for heart failure or CV death	406	11.6	53.7	422	12.1	56.6	0.94* (0.82, 1.08)
Hospitalization for heart failure or all-cause mortality	499	14.3	65.9	518	14.9	69.4	0.95# (0.84, 1.07)

N=number of subjects; IR=Incidence rate per 1000 years at risk
*Based on Cox regression model with terms for treatment group, region, and history of heart failure;
Based on Cox regression model with terms for treatment group and region
Source: CSR, Table 11.1.3.5:1

The Kaplan-Meier estimate of time to first occurrence of hospitalization for heart failure is shown in Figure 7, and curves overall appear to be similar between treatment groups.

Figure 9: Kaplan-Meier Estimate of Time to First Hospitalization for Heart Failure (Treated Set)



No. at risk								
Placebo (n)	3485	3336	3222	2621	1923	1285	767	258
Linagliptin (n)	3494	3361	3243	2647	1979	1317	787	280

Source: CSR, Figure 11.1.3.5.1:1

Recurrent hospitalization for heart failure did not show a treatment effect. Overall, 60 subjects in the linagliptin group and 78 subjects in the placebo group had more than one hospitalization for heart failure (data not shown; see Table 11.1.3.5.1:2 in CSR).

Reviewer's comment: *In CARMELINA, linagliptin compared to placebo did not appear to increase the risk for hospitalization for heart failure, with hazard ratio of 0.90 (95% CI: 0.74, 1.08). Hospitalization for heart failure was an adjudicated tertiary endpoint.*

Subgroup analyses for time to first hospitalization for heart failure are shown in Figure 8. There appeared to be some regional differences, with HR of 0.47 (95% CI: 0.24, 0.95) in Asia and HR of 0.65 (95% CI: 0.44, 0.97) in North America, and the p-value for interaction for region was nominally significant at 0.0368. However, the proportion of subjects in North America (~17%) and Asia (~8%) was a small fraction of overall study population.

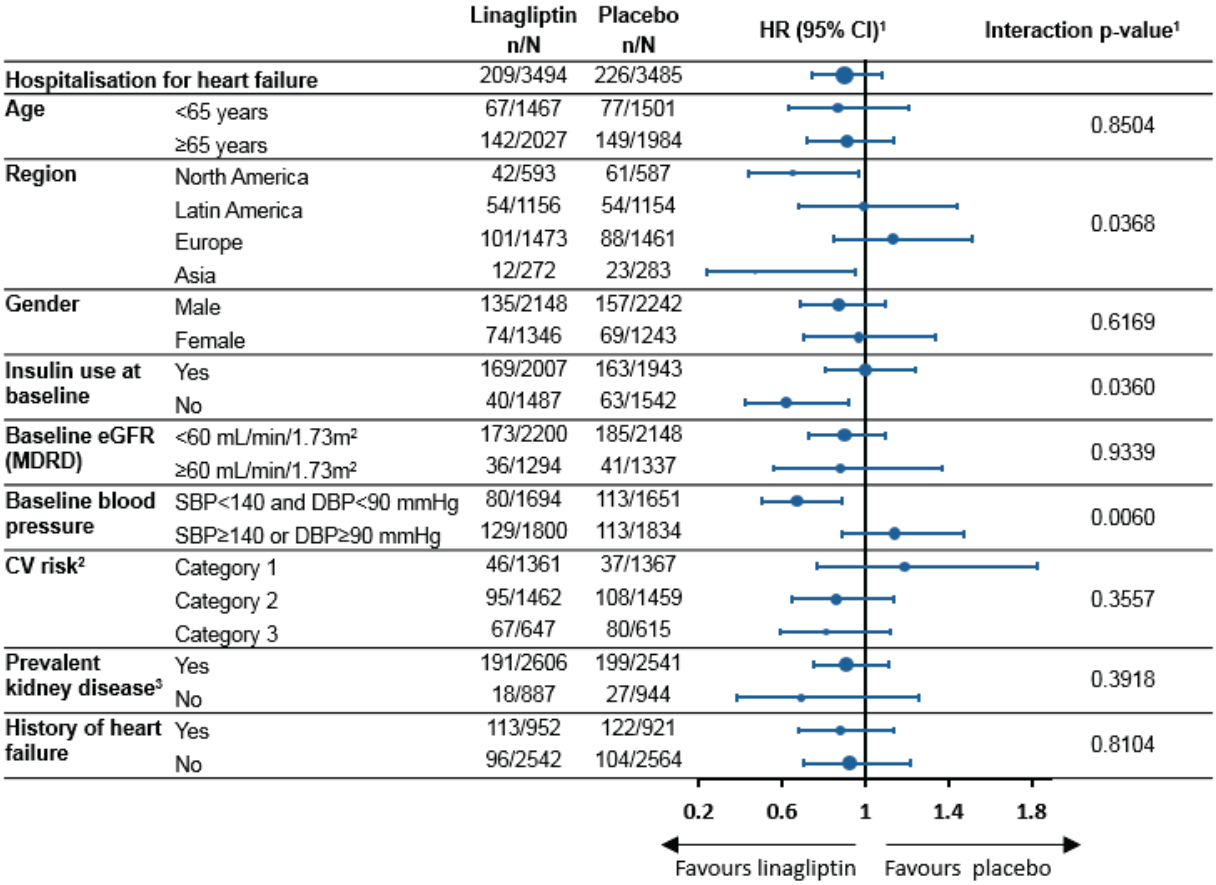
A significant subgroup by treatment interaction was also seen in subjects with or without insulin at baseline (p-value for interaction=0.0360), with subjects without insulin at baseline showing HR of 0.62 (95% CI: 0.42, 0.92) whereas subjects with insulin had HR of 1.00 (95% CI: 0.81, 1.24).

The p-value for treatment interaction was also significant (0.0060) in SBP and DBP category, where the HR was 0.67 (95% CI: 0.50, 0.89) in subjects with baseline SBP/DBP <140/90 mmHg compared to HR of 1.14 (95% CI: 0.89, 1.47) in subjects with baseline SBP/DBP ≥140/90 mmHg. Since hypertension is an independent major risk factor for heart failure, it is possible that this subgroup finding may not be related to the study drug itself.

Notably, no treatment interaction was seen for the subgroup of history of heart failure. The HR for hospitalization of heart failure with linagliptin compared to placebo was similar in those with or without history of heart failure (HR of 0.88 [95% CI: 0.68, 1.14] versus 0.92 [95% CI: 0.70, 1.22] respectively; Figure 10).

Reviewer's comment: *Although the p-value for subgroup by treatment interaction was nominally significant with p-value <0.05 for subgroup analyses for region, insulin use at baseline, and blood pressure category, subgroup analyses are considered exploratory as they are likely to be of chance finding and not controlled for Type 1 error. It is reassuring that no treatment interaction was seen for the subgroup by history of heart failure, and that the HR for heart failure was <1 in both subjects with or without history of heart failure.*

Figure 10: Subgroup Analyses for Time to First Hospitalization for Heart Failure (Treated Set)



CI = confidence interval; CV = cardiovascular; HR = hazard ratio; eGFR = estimated glomerular filtration rate, SBP = systolic blood pressure DBP = diastolic blood pressure; CV = cardiovascular; N = total number of patients in the subgroup; n = number of patients with event.

1 Cox regression model with terms for treatment group, region, subgroup, and treatment-by-subgroup interaction.

2 Categories: (1) Established macrovascular disease and albuminuria without established renal disease, (2) Established renal

disease without macrovascular and albuminuria disease, (3) Established macrovascular disease and albuminuria and established renal disease.
3 Defined as: eGFR <60 mL/min/1.73 m² or macroalbuminuria UACR >300 mg/g.
The bubble size for the HR point estimate is proportional to the number of patients in the subgroup.
Source: CSR, Figure 11.1.3.5.1:2

Heart Failure Adverse Events:

For complete discussion of heart failure, heart failure AEs will be discussed here. Heart failure AEs were investigator-reported and grouped based on narrow SMQ 'cardiac failure'. A smaller proportion of subjects in the linagliptin group reported heart failure AEs compared to the placebo group, 7.9% versus 8.8% respectively. The HR for heart failure AEs was <1 (HR 0.89 [95% CI: 0.76, 1.05]) as summarized in Table 10, which was similar to HR for hospitalization for heart failure.

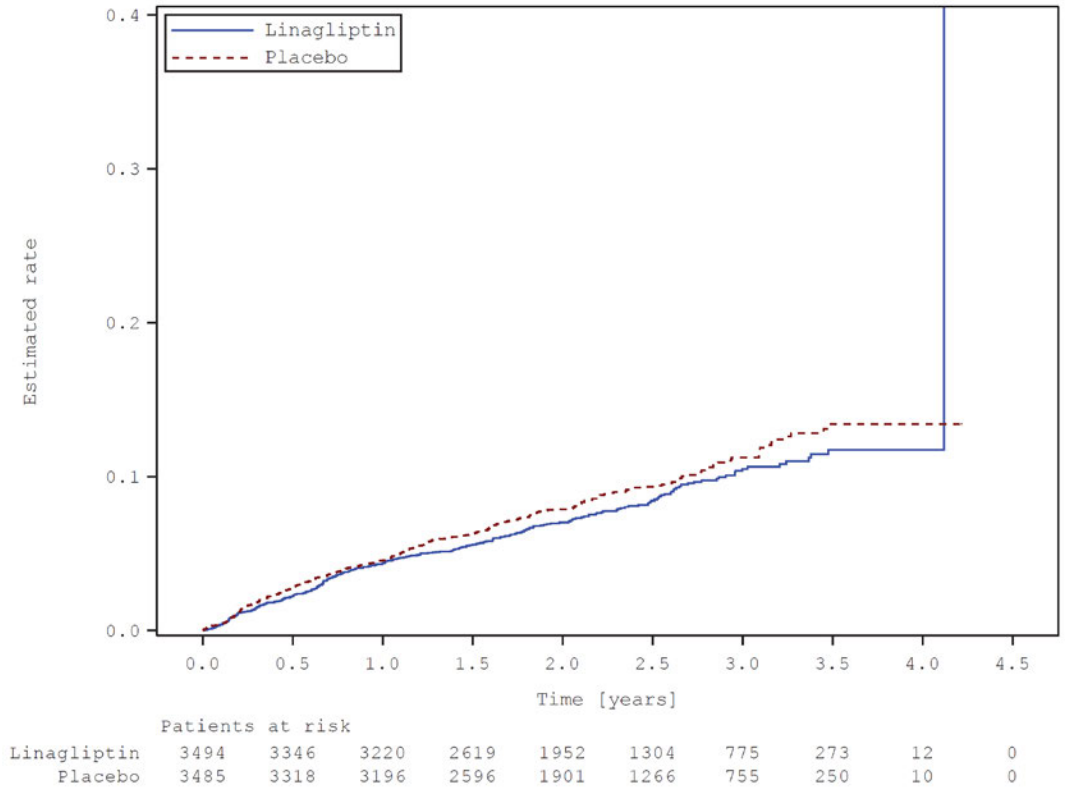
Table 16: Cox Regression of Heart Failure Adverse Events (based on SMQ Cardiac Failure) – Treated Set

	Linagliptin (N=3494)	Placebo (N=3485)
Subjects with heart failure AE, n (%)	**276 (7.9)**	**305 (8.8)**
Incidence rate per 1000 subject-years	36.9	41.1
Hazard ratio (versus placebo)	0.89 (0.76, 1.05)	
p-value	0.1697	

Source: CSR, Table 11.1.3.5.4:1

The Kaplan-Meier curve for heart failure AEs is shown in Figure 9, and shows that the rate of heart failure AEs in the linagliptin group is either lower or similar to the placebo group during the treatment period.

Figure 11: Kaplan-Meier Plot of Time to First Occurrence of Heart Failure Adverse Events (Treated Set)



Source: CSR, Figure 15.2.30.4

Reviewer's comment: *Investigator-reported heart failure is not adjudicated and therefore likely to be less rigorous than adjudicated 'hospitalization for heart failure' events. However, it is reassuring that the evaluation of heart failure AEs using MedDRA grouping strategy appear to show similar results as adjudicated heart failure events. Less proportion of subjects in the linagliptin group (7.9%) reported heart failure AEs compared to the placebo group (8.8%).*

Heart Failure in CAROLINA Trial:

On April 12, 2019, in their response to an Information Request (IR) for further information about pancreatic cancer, the Applicant also voluntarily submitted heart failure data from another linagliptin trial called CAROLINA. The Applicant stated that they submitted "the relevant heart failure data resulting from the CAROLINA study for transparency to FDA while the decision related to heart failure and linagliptin is being evaluated."

Briefly, CAROLINA (**CAR**diovascular **O**utcome study of **LINA**agliptin versus glimepiride in

patients with type 2 diabetes) is an active-comparator cardiovascular outcomes study comparing linagliptin to glimepiride. The Applicant plans to submit CAROLINA as a supplemental NDA sometime in mid-2019 since the study has been completed and they are completing data analyses and CSR.

The Applicant noted that the adjudication process for heart-failure related cases was the same in the CAROLINA study as it was in CARMELINA. And in addition to the analyses of adjudicated heart failure endpoints, the occurrence of and time to first investigator-reported heart failure based on narrow SMQ 'cardiac failure' was a tertiary cardiovascular endpoint in CAROLINA. The Applicant submitted a Table summarizing heart failure data from CAROLINA as shown in Table 17, but did not provide any further information or interpretation about these heart failure results.

Table 17: Heart Failure-related Endpoints in CAROLINA

	Linagliptin (N=3023)			Glimepiride (N=3010			Hazard ratio vs glimepiride (95% CI)
	N	%	IR	N	%	IR	
Hospitalization for heart failure	112	3.7	6.4	92	3.1	5.3	1.21 (0.92, 1.59)
Hospitalization for or death from heart failure	115	6.6	1.18	97	3.2	5.6	1.18 (0.90, 1.54)
Hospitalization for heart failure or CV death*	236	7.8	13.4	234	7.8	13.4	1.00 (0.84, 1.20)
Hospitalization for heart failure or all-cause mortality*	372	12.3	21.1	392	13.0	22.3	0.94 (0.82, 1.09)
Investigator-reported heart failure (non-adjudicated)	166	5.5	9.5	155	5.2	9.0	1.06 (0.85, 1.32)

N=number of subjects; IR=Incidence rate per 1000 years at risk
*Post hoc analysis
Source: Applicant's Response to Information Request, 4/12/2019 under NDA 201280

Reviewer's comment: *In contrast to CARMELINA where the HR for hospitalization for heart failure endpoints were <1 (Table 17), the HR for hospitalization for heart failure was >1 with linagliptin compared to placebo in CAROLINA. Given that neither the data nor study reports for CAROLINA have been submitted, it is difficult to understand or interpret discordant results about the risk for heart failure between two linagliptin studies. One major notable difference between two trials is that linagliptin is compared to placebo in one trial (CARMELINA) whereas linagliptin is compared to glimepiride in the other trial (CAROLINA), but we have no reason to believe that glimepiride would affect heart failure outcomes.*

Based on these new results about heart failure from CAROLINA trial, (b) (6) [redacted]

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). At each measured time point, the reduction in adjusted mean HbA1c was statistically significant for linagliptin compared to placebo (see Table 11 summary of baseline and at Week 180).

Table 18: Change from Baseline in HbA1c (%) in Treated Set (Observed Cases) – MMRM model

	Linagliptin (N=3494)	Placebo (N=3485)
Baseline mean	7.94	7.96
Adjusted mean HbA1c at Week 180 (SE)	7.72 (0.05)	7.97 (0.05)
Adjusted mean change in HbA1c from baseline (SE)	-0.21 (0.05)	0.04 (0.05)
Treatment difference (linagliptin vs placebo) (SE) [95% CI]	-0.26 (0.07) [-0.40, -0.11] p=0.0006	

Source: CSR, Table 11.1.4.1:1

The proportion of subjects who at the end of the study visit achieve glycemic control (HbA1c ≤7%) without adding additional antidiabetic drug or increasing background antidiabetic drug was significantly higher in the linagliptin group (22.3% [780/3494]) compared to placebo group (13.9% [483/3485]) ($p<0.0001$ using Chi-test). Similarly, the proportion of subjects who achieved glycemic control at the end of the study was higher with linagliptin (29% [1012/3494]) compared to placebo (19.7% [685/3485]), regardless of background antidiabetic drug.

Reviewer's comment: *It is unclear what factors may have influenced the difference in HbA1c between treatment arms. The difference in HbA1c between treatment groups is somewhat surprising, given that change in background antidiabetic medications were allowed per standard of care and more subjects in the placebo group started insulin and other antidiabetic medications. However, other CVOTs have shown similar differences related to HbA1c.*

Body Weight:

During the study, there was no clinically meaningful changes in body weight in either treatment group. By Week 180, subjects in the linagliptin lost 1.25 kg (SE 0.25) and subjects in the placebo group lost 1.29 kg (SE 0.26).

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

None.

7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

This section is not applicable as only data from one trial, CARMELINA, was submitted in this supplement, and a comprehensive review of efficacy from CARMELINA was presented in Section 6.1.2, Study Results.

7.1.1. Primary Endpoints

Not applicable, see Section 6.

7.1.2. Secondary and Other Endpoints

Not applicable, see Section 6.

7.1.3. Subpopulations

Not applicable, see Section 6.

7.1.4. Dose and Dose-Response

Not applicable.

7.1.5. Onset, Duration, and Durability of Efficacy Effects

Not applicable.

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Postmarket Setting

CARMELINA evaluated the major cardiovascular adverse event in patients who are at increased cardiovascular risk, and enrolled patients who either have evidence of macrovascular disease with albuminuria and/or evidence of impaired renal function. Although about 15% 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 and enrolled predominantly White subjects (80%), and it is unclear if efficacy and safety findings from this trial can be extrapolated to all racial groups or for patients who are 75 years or older. However, it is reassuring that the subgroup analysis did not find any significant interactions, and we have no reason to believe that the cardiovascular safety seen with linagliptin in CARMELINA (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

To demonstrate cardiovascular safety of linagliptin, the Applicant conducted a dedicated cardiovascular outcomes trial, CARMELINA. This trial was conducted to satisfy a post-marketing requirement.

CARMELINA was a large, prospective, multicenter, randomized, double-blind, placebo-controlled trial conducted in 6979 subjects with T2DM and at high risk of CV event. Subjects were randomized to either linagliptin (N=3494) or placebo (N=3485), both as add-on to standard of care. After a mean follow-up of ~2.2 years and 845 composite primary endpoint of CV death, nonfatal MI or nonfatal stroke, the analysis for the composite MACE endpoint resulted in a HR point estimate of 1.02 with the upper bound of the CI less than 1.3 (95% CI: 0.89, 1.17). Therefore, compared to placebo, linagliptin successfully ruled out a 30% excess CV risk captured using 3 component MACE endpoint 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 endpoint 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 CV benefit.

8. Review of Safety

8.1. Safety Review Approach

The safety evaluation for this supplement was based on the clinical safety data for a single trial 1218.22, also called CARMELINA. The safety evaluation in the trial included adverse events (including adverse events [AEs] of special interest, hypoglycemic events, and changes from baseline in electrocardiogram (ECG) and physical examination documented as AEs), changes from baseline in safety laboratory parameters, vital signs, and ECG. As discussed in Section 6.1.1 Study Design, an independent committee adjudicated renal and pancreatic events, and an Oncology Assessment Committee reviewed oncology adverse events for causality assessment.

CV outcomes were primary efficacy endpoints in CARMELINA and were already discussed in Section 6.1.2, Study Results.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

Safety population was defined as all subjects who took at least one dose of randomized study drug, and safety data are presented according to the randomized treatment group. In total, 6979 randomized subjects took at least one dose of study drug, with 3494 subjects in the linagliptin and 3485 subjects in the placebo group. The mean and median exposure to study drug was similar between treatment groups, with both treatment groups having a mean exposure to study drug of 1.9 years (Table 13). About 87% of subjects received the study drug for about 1 year, and about 48% of subjects received the study drug for about 2 years.

Table 19: Exposure to Study Drug - Treated Set

	Linagliptin (N=3494)	Placebo (N=3485)
Duration of exposure (years)		
Mean (SD)	1.9 (0.90)	1.9 (0.90)
Median	1.9	1.8
Cumulative exposure	6766.2	6585.0
Exposure categories, n (%)		
≥6 months	3284 (94.0%)	3241 (93.0%)
≥12 months	3059 (87.6%)	3030 (86.9%)
≥18 months	2381 (68.1%)	2302 (66.1%)
≥24 months	1713 (49.0%)	1611 (46.2%)
≥30 months	1088 (31.1%)	1026 (29.4%)
≥36 months	636 (18.2%)	586 (16.8%)
≥42 months	139 (4.0%)	135 (3.9%)

Source: CSR, modified from Table 10.5:1

The mean follow-up duration in trial was about 2.2 years for each treatment group.

8.2.2. Relevant characteristics of the safety population:

Since this supplement only included a single trial, demographics (Table 5) and clinical characteristics (Table 6) of the study population were discussed in Section 6.1.2 Study Results.

8.2.3. Adequacy of the safety database:

CARMELINA was event-driven trial to have sufficient power to establish CV safety by demonstrating non-inferiority in composite MACE endpoints and enrolled diabetic subjects at high CV risk. Baseline demographic data showed that non-Whites and elderly subjects ≥75 years of age were underrepresented in this trial (Table 5); these represented some of the limitations for generalizing safety findings across races and ages that may receive linagliptin in the clinical setting. Also, CARMELINA was a global trial and subjects from U.S represented about 15% of total patient population.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

Issues related to data quality or integrity issues that may affect the safety review were not identified. OSI was asked to inspect 6 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).

8.3.2. Categorization of Adverse Events

Treatment-emergent adverse events (TEAE) included all events with an onset after the first dose of study drug up to 7 days after last permanent study drug dose. All adverse events (AE) with an onset after the first dose of study drug up to a period of 7 days after the last dose of study drug were assigned to the treatment phase for evaluation; all AEs after the first dose of study drug were displayed by randomized treatment group. AEs that occurred before first intake of randomized study drug were assigned to 'screening'. The Applicant provided accurate definitions of AEs and serious adverse events (SAEs) in the protocol (see Section 5.2.2.1 of the protocol).

AEs were coded using MedDRA version 20.1.

The intensity of the AE was judged as:

- Mild: Awareness of sign(s) or symptom(s) that are easily tolerated;
- Moderate: Enough discomfort to cause interference with usual activity;
- Severe: Incapacitating or causing inability to work or to perform usual activities.

Causal relationship was assessed using medical judgement, considering all relevant factors including patterns of reaction, temporal relationship, de-challenge or re-challenge, confounding factors such as concomitant medication, concomitant diseases and relevant history, as following:

- Yes – There is a reasonable causal relationship between the study drug and the AE;
- No – There is no reasonable causal relationship between the study drug and the AE.

Rather than a yes or no for assessing causality of the AE to the study drug, it may have been more helpful to have pre-defined classification of causality such as 'probable', 'possible', 'unlikely'.

Worsening of underlying disease or other pre-existing conditions are to be recorded as an (S)AE. In addition, changes in vital signs, ECG, physical examination and laboratory test results are to be recorded as an (S)AE if judged to be clinically relevant by the investigator.

All symptomatic hypoglycemic events, all asymptomatic events with glucose <54 mg/dL, a nd all asymptomatic hypoglycemic events that are considered as adverse event by the investigator were to be recorded as an adverse event.

Any hypoglycemic event reported as an AE by investigator were classified as:

- Symptomatic or asymptomatic: based on typical signs and symptoms of hypoglycemia;
- Severe: event requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions;
- Confirmed: if hypoglycemia was accompanied by a lower plasma glucose (≤70 mg/dL) or criteria for severe hypoglycemia were met.

The following events were considered as an adverse events of special interest (AESI), and the Applicant created custom MedDRA Queries to identify AESI from a list of pre-specified PTs or Standardized MedDRA Queries (SMQs), which are further discussed in Section 8.5:

- Hypersensitivity reactions such as angioedema, angioedema-like events, and anaphylaxis (see Section 8.5.2);
- Skin lesions such as exfoliative rash, skin necrosis, or bullous dermatitis (see Section 8.5.3);
- Hepatic events such as ≥3x ULN of AST/ALT, hepatitis, hepatic injury, jaundice, and potential Hy's Law cases (≥3x ULN of AST/ALT and total bilirubin ≥2x ULN and alkaline phosphatase ≤2x ULN) (see Section 8.5.4);
- Renal adverse events such as acute renal failure (see Section 8.5.5);
- Pancreatitis (see Section 8.5.6);
- Thyroid neoplasm (benign) (see Section 8.5.7);

- Thyroid cancer (see Section 8.5.7);
- Pancreatic cancer (see Section 8.5.7).

These specified AESIs were to be reported on an SAE form in an expedited manner similar to that used to report SAEs even if they do not meet any of the SAE seriousness criteria.

Renal events, pancreatic events, and oncologic events were adjudicated by an independent adjudication committee.

8.3.3. Routine Clinical Tests

The frequency of all clinical tests can be seen in the Flow Chart (Table 3).

Routine laboratory parameters included clinical chemistry, renal function, and urine analysis. Pregnant testing was also done in female subjects of child-bearing potential. 12-lead ECGs were centrally analyzed, and additional ECGs can be collected by the investigator for safety reasons. Vital signs were measured after 5 minutes at rest in the seated position and a head-to-toe physical examination wad done.

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 necessary or having hypo- or hyperglycemia symptoms.

8.4. Safety Results

8.4.1. Deaths

All-cause deaths were discussed in Section 6.1.2, Study Results (Table 9) and did not show an imbalance between treatment groups. In addition, all deaths in the randomized subjects were sent for adjudication by the cardiovascular CEC to identify potential cardiovascular deaths. The majority of deaths (519 deaths; 70% of all deaths) were confirmed by CEC as CV deaths, and there was no imbalance in CV death between treatment groups (Figure 6). TEAEs leading to death by treatment group showed that there was no notable imbalance in the reported Preferred Terms reported as AEs leading to death (data not shown; see Table 15.3.1.3.22).

8.4.2. Serious Adverse Events

The proportion of subjects with serious adverse events (SAE) was similar between treatment groups: 37% of subjects in the linagliptin arm versus 38.5% of subjects in the placebo group experienced at least one SAE. The fatal and non-fatal SAEs with a frequency of ≥1% in either linagliptin or placebo groups are summarized in Table 12. The most frequent SAEs reported were in 'Cardiac disorders' and 'Infections and infestations'.

Table 20: Serious Adverse Events with a Frequency of ≥1% in Any Treatment Group at PT Level, Sorted by Frequency and SOC (Treated Set)

MedDRA SOC	Linagliptin		Placebo	
MedDRA PT	N (%)	Rate/100 pt-yrs	N (%)	Rate/100 pt-yrs
Number of patients	3494 (100.0)		3485 (100.0)	
Number of patients with at least one SAE	1293 (37.0)	23.63	1343 (38.5)	25.56
Cardiac disorders	518 (14.8)	8.16	509 (14.6)	8.26
Cardiac failure	104 (3.0)	1.54	104 (3.0)	1.59
Cardiac failure congestive	77 (2.2)	1.14	98 (2.8)	1.49
Angina unstable	77 (2.2)	1.14	70 (2.0)	1.06
Acute myocardial infarction	78 (2.2)	1.15	59 (1.7)	0.89
Myocardial infarction	47 (1.3)	0.69	54 (1.5)	0.82
Angina pectoris	42 (1.2)	0.62	25 (0.7)	0.38
Atrial fibrillation	34 (1.0)	0.50	26 (0.7)	0.39
Infections and infestations	286 (8.2)	4.34	349 (10.0)	5.50
Pneumonia	99 (2.8)	1.46	121 (3.5)	1.85
Urinary tract infection	30 (0.9)	0.44	41 (1.2)	0.62
Cellulitis	22 (0.6)	0.32	38 (1.1)	0.57
Renal and urinary disorders	255 (7.3)	3.86	244 (7.0)	3.79
Acute kidney injury	96 (2.7)	1.43	100 (2.9)	1.53
End stage renal disease	38 (1.1)	0.56	45 (1.3)	0.68
Chronic kidney disease	49 (1.4)	0.72	32 (0.9)	0.48
Nervous system disorders	186 (5.3)	2.79	188 (5.4)	2.90
Ischaemic stroke	61 (1.7)	0.90	49 (1.4)	0.74
Metabolism and nutrition disorders	127 (3.6)	1.89	131 (3.8)	2.01
Hypoglycaemia	28 (0.8)	0.41	38 (1.1)	0.58
Investigations	54 (1.5)	0.80	47 (1.3)	0.71
Glomerular filtration rate decreased	36 (1.0)	0.53	30 (0.9)	0.45

MedDRA=Medical dictionary for drug regulatory activities; PT=Preferred Term; pt-yrs=patient-years; SOC=system organ class; MedDRA Version 20.1 was used to code adverse events.
Source: CSR, Table 12.2.2:1

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

In CARMELINA, 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: 359 subjects (10.3%) in the linagliptin group and 402 subjects (11.5%) 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 were <1% and difference between treatment group was ≤0.1% for all AEs (Table 15.3.1.3.22 in CSR), except for cardiac arrest (0.6% [21 subjects] versus 0.4% [13 subjects] in the linagliptin vs placebo) and acute myocardial infarction (0.4% [15 subjects] versus 0.2% [8 subjects] the linagliptin vs placebo).

8.4.4. Significant Adverse Events

Adverse events that are considered significant 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

A summary of all TEAEs reported in at least 1% of subjects with a higher proportion in the linagliptin group during treatment period is presented in Table 13. Some of the known AEs associated with linagliptin occurred in numerically higher proportion of subjects receiving linagliptin, such as diarrhea (3.5% linagliptin, 3.1% placebo) and increased lipase (4.2% linagliptin, 2.7% placebo).

Table 21: Summary of Treatment-Emergent Adverse Events with a Frequency of ≥1% in the Linagliptin Group and at Higher Proportion Compared to Placebo, by SOC and PT

SOC/PT	Linagliptin (N=3494)	Placebo (N=3485)
Metabolism and nutrition disorders SOC		
Hypoglycemia	1031 (29.5%)	1016 (29.2%)
Hypertriglyceridemia	57 (1.6%)	47 (1.3%)
Gout	55 (1.6%)	42 (1.2%)
Infections and infestations SOC		
Urinary tract infection	221 (6.3%)	192 (5.5%)
Cardiac disorders		
Atrial fibrillation	105 (3.0%)	82 (2.4%)
Angina pectoris	86 (2.5%)	67 (1.9%)
Angina unstable	77 (2.2%)	70 (2.0%)
Acute myocardial infarction	78 (2.2%)	59 (1.7%)
Coronary artery disease	37 (1.1%)	30 (0.9%)
Investigations SOC		
Glomerular filtration rate decreased	233 (6.7%)	226 (6.5%)
Lipase increased	146 (4.2%)	93 (2.7%)
Blood creatinine increased	36 (1.0%)	33 (0.9%)
Nervous system disorders SOC		

Ischemic stroke	61 (1.7%)	49 (1.4%)
Gastrointestinal disorders SOC		
Diarrhea	123 (3.5%)	109 (3.1%)
Renal and urinary disorders SOC		
Chronic kidney disease	91 (2.6%)	71 (2.0%)
Renal failure	69 (2.0%)	62 (1.8%)
Musculoskeletal & connective tissue disorders SOC		
Back pain	111 (3.2%)	91 (2.6%)
Osteoarthritis	81 (2.3%)	62 (1.8%)
Vascular disorders SOC		
Hypotension	46 (1.3%)	35 (1.0%)
General disorders and administration site conditions SOC		
Asthenia	63 (1.8%)	54 (1.5%)
Injury, poisoning & procedural complications SOC		
Limb injury	52 (1.5%)	45 (1.3%)
Contusion	41 (1.2%)	34 (1.0%)
Eye disorders SOC		
Diabetic retinopathy	50 (1.4%)	42 (1.2%)
Blood and lymphatic system disorders SOC		
Anemia	143 (4.1%)	114 (3.3%)
Psychiatric disorders SOC		
Depression	56 (1.6%)	46 (1.3%)
Insomnia	42 (1.2%)	38 (1.1%)
Hepatobiliary disorders SOC		
Cholelithiasis	34 (1.0%)	27 (0.8%)
Reproductive system and breast disorders SOC		
Benign prostatic hyperplasia	41 (1.2%)	40 (1.1%)

SOC=system organ class; PT=preferred term
Source: CSR, Modified from Table 15.3.1.2.1.1

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 CARMELINA, 217 subjects (6.2%) in the linagliptin arm and 198 subjects (5.7%) in the placebo arm reported AEs related to arthralgia based on HLGT 'Joint disorders' search. Of these, 26 subjects (0.7%) in the linagliptin arm and 24 subjects (0.7%) in the placebo arm had an SAE of arthralgia-related event, with osteoarthritis most commonly reported without much imbalance between treatment groups (0.4% [n=15] linagliptin vs 0.5% [n=17] placebo). Three subjects in the placebo arm and no subjects in the linagliptin arm discontinued study drug due to arthralgia-related event.

Reviewer's comment: *In CARMELINA, there was no imbalance between treatment groups in the incidence of overall AEs, SAEs, or discontinuations due to arthralgia-related events.*

Bullous pemphigoid:

Seven cases of pemphigoid were reported in the linagliptin arm whereas none were reported with placebo. Four of 7 events were serious but in one case, the event did not appear to be related to the study drug based on concomitant drugs:

- In one subject ([(b) (6)] pemphigoid appeared to be related to clopidogrel that was started about 2 weeks before the onset of skin lesions that was found to be 'bullous pemphigoid' based on histological examination and skin biopsy; this occurred about 771 days after starting linagliptin and he continued linagliptin for another 2 months to finish the study without any further problem.

In the remaining 3 SAEs, the role of linagliptin on bullous pemphigoid cannot be excluded, and in 2 cases bullous pemphigoid led to study drug discontinuation:

- Subject [(b) (6)] was hospitalized due to SAE of bullous pemphigoid on 899th day after starting linagliptin and was diagnosed with SAE of basal cell carcinoma (BCC) on the same day. She stopped linagliptin about a month after the event, and the events pemphigoid and BCC were not resolved at the time of report.

- Subject [(b) (6)] was a 68 years old man from Brazil and was hospitalized due to bullous pemphigoid after about 18 months on study drug (linagliptin). Study drug was permanently discontinued on 648th day after first intake of study drug. Pemphigoid resolved about 45 days later with treatment.

- Subject [(b) (6)] was a 75-year old man who experienced pemphigoid on Day 712 after starting the study drug and discontinued the study drug due to pemphigoid. Signs and symptoms of pemphigoid progressed despite discontinuation of pemphigoid, and 12 days after the study drug was discontinued, the intensity of the event became serious and he was hospitalized for observation and biopsy. He received treatment for pemphigoid and recovered.

Reviewer's comment: *Bullous pemphigoid is a labeled event for DPP-4 inhibitors based on postmarketing cases. I recommend adding that bullous pemphigoid has been seen in CARMELINA with linagliptin, with onset ranging from 18 to 30 months after initiating linagliptin.*

Inflammatory Bowel Disease:

As discussed in Section 3.1, U.S. Regulatory Actions and Marketing History, new DARRTS

Tracked Safety Issue was created for DPP-4 inhibitors regarding a potential signal for IBD, based on a recent meta-analysis of studies on DPP-4 inhibitors and IBD where a 3-fold risk of IBD with DPP-4 inhibitors was suggested using a fixed-effects model (RR=3.01; 95% CI: 2.30, 3.93).

I searched the AE data using the same MedDRA search terms that was used to search SAVOR (CVOT for saxagliptin) and EXAMINE (CVOT for alogliptin), and although there was a numerical imbalance between treatment groups, imbalances were related to unspecified 'colitis' terms and neither Crohn's Disease nor ulcerative colitis were reported(Table 22).

Table 22: Inflammatory Bowel Disease-related Events in CARMELINA

Preferred Term (PT)	Linagliptin N=3494	Placebo N=3485
# of subjects (%)	**18 subjects (0.5%)**	**11 subjects (0.3%)**
Colitis	**11**	**3**
Colitis ischaemic	**4**	**1**
Colitis microscopic	0	1
Enteritis	1	1
Enterocolitis	1	3
Enterocolitis haemorrhagic	1	0
Gastrointestinal inflammation	0	2

Event onset >180 days (6 months)

Preferred Term (PT)	Linagliptin N=3494	Placebo N=3485
# of subjects (%)	**8 subjects (0.2%)**	**6 subjects (0.2%)**
Colitis	5	1
Colitis ischaemic	2	0
Colitis microscopic	0	1
Enterocolitis	0	3
Enterocolitis haemorrhagic	1	0
Gastrointestinal inflammation	0	1

Source: ADAE, generated by reviewer

8.4.6. Laboratory Findings

Standard laboratory tests (i.e., hematology, clinical chemistry, and urinalysis) including lipase were measured for all subjects at baseline, Week 12, Week 36, Week 84 and every 24 weeks thereafter, as shown in Table 3. Lipid panel was obtained at baseline, Week 36, Week 84 and yearly (every other visit) thereafter. Laboratory values after the first dose of study drug up to a period of 7 days after the last dose of study drug were assigned to the on-treatment period.

Laboratory findings were analyzed by descriptive statistics, transition relative to reference range (low, normal, high), and for possibly clinically significant abnormalities.
For most of laboratory values, there was no notable findings from baseline to last values on treatment between treatment groups, or transition relative to reference range, except for lipase and creatinine. See Section 8.5.5, Renal Adverse Events, for discussion of changes in creatinine levels. See Section 8.5.6, Pancreatitis, for discussion of lipase levels.

8.4.7. Vital Signs

Blood pressure was obtained at baseline, Week 12, Week 36, Week 60, and every 24 weeks thereafter until the end of trial visit, as well as at 30-day follow-up visit.

There were no clinically meaningful differences between treatment groups, or any marked changes from baseline for systolic blood pressure, pulse, or heart rate (data not summarized here; see Tables 15.3.3.1 and 15.3.3.2 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 obtained at baseline, Week 36, Week 60, and every 24 weeks thereafter until the end of trial visit, as well as at 30-day follow-up visit. In addition to these visits, ECG was to be recorded in case of cardiac symptoms indicating rhythm disorders or cardiac ischemia.

Clinically meaningful abnormal ECG findings were reported as AEs and are summarized in Table 14. There were no clinically meaningful differences between treatment groups for abnormal ECG findings.

Table 23: Frequency of Electrocardiogram-related Adverse Events by Preferred Terms – Treated Set

Preferred Term	Linagliptin (N=3494)		Placebo (N=3485)	
	N (%)	Incidence rate	N (%)	Incidence rate
Electrocardiogram QT prolonged	11 (0.3)	0.16	18 (0.5)	0.27
Electrocardiogram T wave inversion	6 (0.2)	0.09	4 (0.1)	0.06
Electrocardiogram T wave abnormal	3 (0.1)	0.04	4 (0.1)	0.06
ECG signs of myocardial ischemia	1	0.01	2	0.03
Electrocardiogram PR prolongation	1	0.01	1	0.02
Electrocardiogram ST-T change	1	0.01	1	0.02
Electrocardiogram abnormal	0	0	1	0.02
Electrocardiogram QRS complex prolonged	1	0.01	0	0
Electrocardiogram ST segment depression	0	0	1	0.02
Electrocardiogram ST-T segment abnormal	0	0	1	0.02
Electrocardiogram ST-T segment depression	1	0.01	0	0
Electrocardiogram T wave biphasic	0	0	1	0.02

*Incidence rate=1/100 patient-year exposure
Source: CSR, adapted from Table 15.3.1.2.1.1

8.4.9. QT

Not applicable in this supplement. Abnormal ECG findings were summarized in Section 8.4.8, Electrocardiograms.

8.4.10. Immunogenicity

Not applicable.

8.5. Analysis of Submission-Specific Safety Issues

As discussed in Section 8.3.2, the Applicant evaluated the following AESI related to known safety findings and concerns associated with linagliptin and other DPP-4 inhibitors and will be discussed further in this section: hypersensitivity reactions, skin lesions, hepatic events, renal adverse events, pancreatitis, thyroid neoplasm, thyroid cancer, and pancreatic cancer.

Unless otherwise specified, analysis of AESIs were done on the Treated Set for on-treatment events (those occurring from first study drug intake up to last intake plus 7 days).

8.5.1. Hypoglycemia

As discussed in section 8.3.2, Categorization of Adverse Event, any hypoglycemic event reported as an AE by investigator were classified as symptomatic or asymptomatic, severe, and/or confirmed.

Table 13 provide a summary of hypoglycemic events reported as AEs in CARMELINA. The incidence of hypoglycemia events with plasma glucose <54 mg/dL or severe were similar between treatment groups, with 15.9% and 16.4% in the linagliptin and placebo groups respectively. Severe hypoglycemia was also balanced between treatment groups (3.0% linagliptin vs 3.1% placebo). There also did not appear to be an increased number of hypoglycemic episodes with linagliptin compared to placebo.

Table 24: Frequency [N (%)] of Subjects with Hypoglycemia and Characteristics of Hypoglycemia by Treatment – Treated Set

	Linagliptin (N=3494)	Placebo (N=3485)
Subjects with any investigator defined hypoglycemia adverse event	1036 (29.7%)	1024 (29.4%)
Hypoglycemia with PG ≤70 mg/dL or any severe[#] hypoglycemia	946 (27.1%)	928 (26.6%)
Hypoglycemia with PG <54 mg/dL or any severe[#] hypoglycemia	557 (15.9%)	572 (16.4%)
Subjects with symptomatic* hypoglycemia or severe[#] hypoglycemia	880 (25.2%)	887 (25.5%)
Symptomatic hypoglycemia with PG ≤70 mg/dL or any severe[#] hypoglycemia	843 (24.1%)	845 (24.2%)
Symptomatic hypoglycemia with PG <54 mg/dL or any severe[#] hypoglycemia	484 (13.9%)	512 (14.7%)
Severe[#] hypoglycemia	106 (3.0%)	108 (3.1%)
Number of hypoglycemia episodes per subject		
≥1	1036 (29.7%)	1024 (29.4%)
≥3	541 (15.5%)	539 (15.5%)
≥5	334 (9.6%)	335 (9.6%)
≥10	174 (5.0%)	175 (5.0%)

PG=plasma glucose
*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 12.1.4:1

However, this doesn't take into account a larger number of subjects in the placebo group compared to linagliptin group initiating insulin therapy throughout the study (Figure 2), as more subjects in the placebo group initiated insulin therapy shortly after staring therapy and throughout the study duration (see Section 6.1.2, Study Results). Insulin was the most frequently introduced antidiabetic therapy after randomization, at a higher proportion of

subjects in the placebo group compared to linagliptin (14.6% [509/3494] linagliptin vs 18.0% [626/3484] placebo).

Reviewer's comment: *Although it is reassuring that the incidence of hypoglycemia was not increased in the linagliptin group compared to placebo group in CARMELINA where investigators were allowed to change background antidiabetic therapy per standard of care, treatment difference in hypoglycemic events may not be reliably estimated in CARMELINA due to difference in usage of background antidiabetic therapy between treatment groups which can potentially affect hypoglycemic events.*

8.5.2. Hypersensitivity Reactions

Hypersensitivity reactions such as angioedema, angioedema-like events, and anaphylaxis were considered AESI and narrow SMQ of 'Hypersensitivity' was used to flag these reports.

Hypersensitivity reactions were reported in 114 subjects (3.3%) in the linagliptin group and 109 subjects (3.1%) in the placebo group. Rash was most frequently reported PT terms and was balanced between treatment groups (0.6% [n=22; 0.22/100 PYE] linagliptin vs 0.6% [n=21; 0.11/100 PYE] placebo). Other reported PTs were comparable between treatment groups (not shown here; see Table 15.2.1.7.1.1).

Of these, 15 subjects (0.4%) in the linagliptin group versus 7 subjects (0.2%) in the placebo group reported hypersensitivity SAEs with the following PTs:

- Linagliptin group reported angioedema (2), circulatory collapse (2), hypersensitivity (2), bullous dermatitis, exfoliative generalized dermatitis, rash, skin necrosis, swelling face, toxic epidermal necrolysis, drug hypersensitivity, immune thrombocytopenic purpura, laryngeal edema, mouth edema, and tongue edema;

- Placebo group reported angioedema, maculo-papular rash, circulatory collapse, distributive shock, shock, immune thrombocytopenic purpura, bronchospasm.

Two cases of circulatory collapse reported with linagliptin did not appear to be related to the study drug, as one was reported with respiratory failure and the other with pneumonia that likely led to circulatory collapse.

Toxic epidermal necrolysis and drug hypersensitivity were both reported in a 77-year old woman (b) (6) and appear to be related to Bactrim which was started for an ear infection rather than related to linagliptin. She had been taking linagliptin for over 8 months before these reactions occurred and 'blistering of rash, body aches, and skin necrosis' occurred the day she received Bactrim for an ear infection. She experienced toxic epidermal necrolysis when family physician prescribed the same drug about 2 weeks later, and she died 9 days later.

8.5.3. Skin Lesions

Skin lesions such as exfoliative rash, skin necrosis, or bullous dermatitis were flagged using the narrow SMQ 'Severe Cutaneous Adverse Reactions'.

Five patients in the linagliptin group and one subject in the placebo group reported skin lesions, all under SOC of 'Skin and Subcutaneous Tissue Disorders'. These cases reported bullous dermatitis, exfoliative generalized dermatitis, skin necrosis, and toxic epidermal necrolysis, and were included under Section 8.5.1, Hypersensitivity Reactions.

Of these, 4 SAEs were reported with linagliptin (bullous dermatitis, exfoliative dermatitis, skin necrosis, and toxic epidermal necrolysis) and two events reported with linagliptin (skin necrosis and toxic epidermal necrolysis [already discussed in Section 8.5.2]) led to study drug discontinuation. The skin necrosis in a subject ((b) (6) that led to study discontinuation occurred in an 80 year old man with history of vascular disease and cellulitis of the lower leg; skin necrosis occurred about 746 days after initiating linagliptin and appeared to be due to diabetic neuropathy rather than study drug.

8.5.4. Hepatic Events

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

Hepatic events were reported in 2.4% (n=85) in the linagliptin group and 2.2% (n=75) in the placebo group, of which 13 subjects (0.4%) in the linagliptin and 8 subjects (0.2%) in the placebo group reported serious hepatic events. In both the overall AEs and SAEs, the incidence rates of reported PTs were similar between treatment groups (data not shown here; see Table 15.3.1.7.3.1, Table 12.1.3.3:1 in CSR). One subjects in the linagliptin and 3 subjects in the placebo group experienced hepatic AEs which led to study drug discontinuation.

<u>Liver enzyme elevations and Hy's Law cases:</u>

Although numerically more subjects receiving linagliptin reported various liver enzyme elevations compared to placebo, there were small number of subjects and did not appear to show concerning differences between treatment groups: 3 subjects receiving linagliptin vs 2 subjects receiving placebo had ALT/AST ≥3x ULN, 2 subjects receiving linagliptin had ALT/AST ≥5x ULN, and 7 subjects receiving linagliptin and 4 subjects receiving placebo had total bilirubin ≥2x ULN.

During the study, 2 subjects receiving linagliptin and one subject receiving placebo met the

laboratory criteria for potential Hy's Law cases. Hy's Law is defined by any on-treatment value of ALT/AST ≥3x ULN with total bilirubin ≥2x ULN. However, review of these cases did not implicate hepatocellular liver injury with linagliptin, as one case [redacted] (b) (6)) with linagliptin was diagnosed with cholelithiasis, and the other case [redacted] (b) (6) with linagliptin had history of hepatic steatosis, dyslipidemia and consumed alcohol before presenting with asymptomatic liver enzyme elevations. Both events resolved while continuing linagliptin.

8.5.5. Renal Adverse Events

Kidney-related events were adjudicated and part of efficacy endpoints in CARMELINA, as discussed in Section 6.1.2, Study Results. Overall, time-to-event analysis showed similar risk for linagliptin compared to placebo in the adjudicated composite renal endpoints which included renal death, sustained ESRD, or sustained decrease of 40% or more in eGFR from baseline (Table 13).

In safety assessment, renal AEs were identified using SMQ of 'acute renal failure'. A total of 242 subjects (6.9%) in the linagliptin group and 260 subjects (7.5%) in the placebo group had renal AEs, and subjects who reported SAE of renal events were balanced between treatment groups (Table 26).

Table 25: Frequency [N (%)] of Renal Events by Treatment and Preferred Terms - Treated Set

	Linagliptin (N=3494)		Placebo (N=3485)	
	All Renal AEs	Serious AEs	All Renal AEs	Serious AEs
Total	**242 (6.9%)**	**151 (4.3%)**	**260 (7.5%)**	**164 (4.7%)**
Acute kidney injury	96 (2.7%)	96 (2.7%)	102 (2.9%)	100 (2.9%)
Renal impairment	86 (2.5%)	24 (0.7%)	93 (2.7%)	27 (0.8%)
Renal failure	69 (2.0%)	32 (0.9%)	62 (1.8%)	31 (0.9%)
Azotemia	2 (0.1%)	1	6 (0.2%)	6 (0.2%)
Nephropathy toxic	1	1	2 (0.1%)	1
Oliguria	0	0	3 (0.1%)	1
Acute prerenal failure	1	1	0	0
Anuria	0	0	1	1

Source: CSR, Table 15.3.1.7.4.1, Table 15.3.1.7.4.15

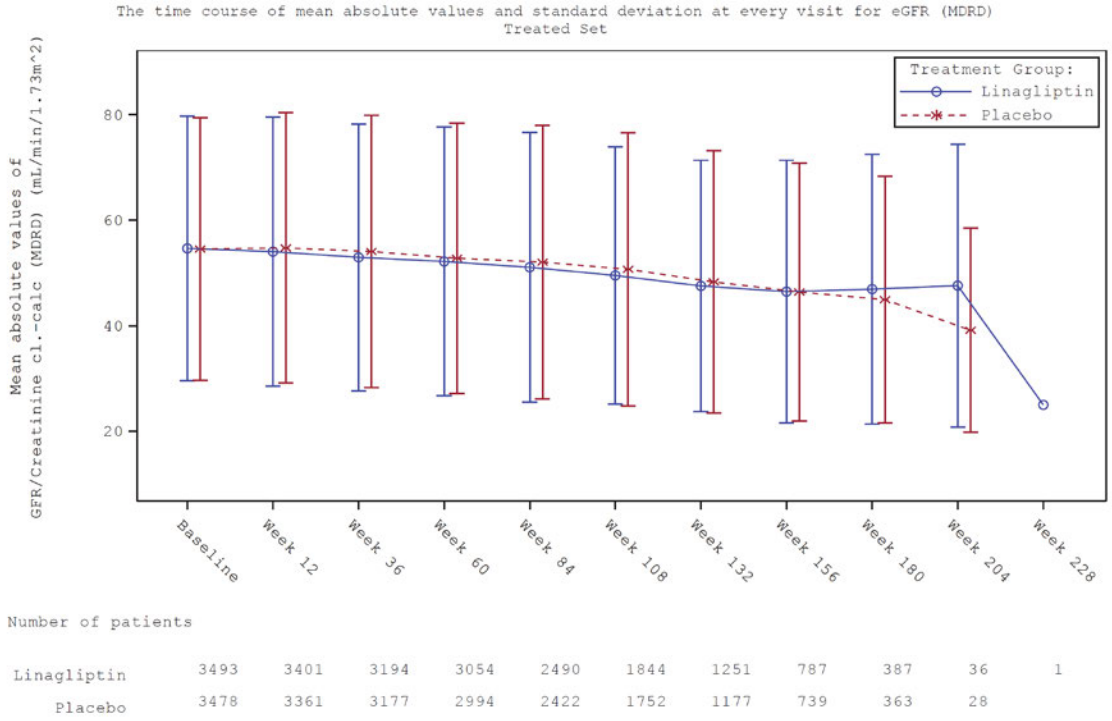
Creatinine and eGFR:

The increase in the mean creatinine from baseline to last value on-treatment was similar between treatment groups (linagliptin 0.28 mg/dL, placebo 0.26 mg/dL).

In both treatment groups, eGFR values declined over time, and although there was a larger absolute decline from baseline in the linagliptin group compared to placebo, the difference

between treatment groups did not appear to be clinically meaningful. At Week 132, eGFR decline from baseline was 6.22 mL/min/1.73 m^2 in the linagliptin group compared to a decline of 5.42 mL/min/1.73 m^2 in the placebo group (adjusted mean treatment difference of -0.79 mL/min/1.73 m^2). Figure 12 show the mean absolute eGFR over time during study.

Figure 12: The Mean Absolute Value and Standard Deviation of eGFR (MDRD) at Every Study Visit for Treated Set



Source: CSR, Figure 15.2.33.44

Analysis of eGFR shifts did not show notable difference between treatment groups in terms of progression or regression of eGFR at the last value on study (data not shown; see Table 11.1.3.7.3:1 in CSR).

8.5.6. Pancreatitis

Pancreatic events were adjudicated by CEC and are summarized in Table 14. In total, 2.6% of subjects in the linagliptin groups compared to 1.5% of subjects in the placebo group had at least one pancreatic event, and most pancreatic events were asymptomatic pancreatic hyperenzymemia (2.1% linagliptin vs 1.2% placebo). Cases of pancreatic malignancy are further discussed in Section 8.5.6, Oncological Adverse Events.

Table 26: Pancreatic Events Confirmed by the Clinical Event Committee [N (%)] - Treated Set

	Linagliptin (N=3494)	Placebo (N=3485)
Subjects with at least one pancreatic event	92 (2.6%)	53 (1.5%)
Subjects with asymptomatic pancreatic hyperenzymemia	72 (2.1%)	41 (1.2%)
Subjects with pancreatic malignancy	11 (0.3%)	4 (0.1%)
Acute pancreatitis	9 (0.3%)	5 (0.1%)
Without organ failure	5 (0.1%)	5 (0.1%)
With organ failure	4 (0.1%)	0
Chronic pancreatitis	2 (0.1%)	3 (0.1%)

Source: CSR, Table 15.3.1.5.3

Of 9 subjects (0.3%) in the linagliptin group and 5 subjects in the placebo group confirmed with acute pancreatitis, 4 in the linagliptin were with organ failure versus none in the placebo group. Two of 4 subject with organ failure died due to pancreatitis ((b) (6) described below). Four subjects who had acute pancreatitis with organ failure, all receiving linagliptin, are discussed briefly below:

- Subject (b) (6) (linagliptin; US; Died): A 63-year old male who had multiple medical history including cholelithiasis, hyperlipidemia, obesity, with estimated average alcohol consumption per week of 100 mL (40%) reported cholecystitis around Day 161. On Day 162, he had an onset of pancreatitis with epigastric abdominal pain, nausea, fever, and lower back pain without vomiting. A CT scan of the abdomen on the same day showed acute pancreatitis, and an abdominal sonogram showed gall bladder sludge, a gallstone, and small 'stone polyps'. The event was specified as acute-on-chronic pancreatitis, likely gallstone pancreatitis. The next day he was admitted for pancreatitis, and gallbladder surgery was scheduled, but the procedure was postponed due to abdominal swelling. Two days later an abdominal X-ray showed distended stomach, and a repeat CT scan showed significant worsening of pancreatitis. He also had dehydration and suffered from acute kidney injury and sepsis. At screening, his lipase was within normal range (42 U/L; reference range 13-60 U/L), which was slightly elevated when he had pancreatitis onset on Day 162 at 86 U/L (reference range, 22-52 U/L) which returned to normal range (22 U/L) 4 days later. No therapy was given for pancreatitis and he was found unresponsive 5 days after the onset and died from pancreatitis.

- Subject (b) (6) (linagliptin; Argentina; Died); A 68-year old male with history of biliary lithiasis and no alcohol use was hospitalized with acute pancreatitis on Day 205 with acute epigastric pain, nausea and vomiting. Study drug was permanently discontinued due to acute pancreatitis, and no imaging tests were available. His lipase value at baseline was slightly elevated at 105 U/L (reference range 13-60 U/L) which did not

increase about 3 months after initiation of study drug (93 U/L), and lipase value was not obtained during his pancreatitis event. He received medical therapy for acute pancreatitis and was transferred to the intensive care unit due to poor progress. On the same day, he died of acute pancreatitis after unsuccessful cardiorespiratory resuscitation. The cause of death was cardiorespiratory arrest due to sepsis as a result of pancreatitis per death certificate.

- Subject (b) (6) (linagliptin; US): A 86-year old female without any history of alcohol consumption arrived at the ER on Day 514 with severe pain in the upper right quadrant along with nausea, vomiting, and dizziness since morning, and was hospitalized due to suspected pancreatitis. She was noted with hypertransaminasemia and elevated amylase (3x normal value; narrative did not show amylase levels), with laboratory values indicating pre-renal kidney injury. An ultrasound showed hydrocholecystitis with an increased pancreatic dissemination and gas in the upper colon. The patient required oxygen support and had an APACHE score of 17 and remained in ICU. No therapy was given for pancreatitis. She recovered from pancreatitis 14 days after onset, and study drug was discontinued due to pancreatitis. She completed the trial. At screening, her lipase was normal (49 U/L; reference range 13-60 U/L) and remained within normal during study, although the lipase values during pancreatitis event was not provided in the narrative.

- Subject (b) (6) (linagliptin; US): A 67-year old man with history of cholelithiasis, hyperlipidemia, and no alcohol consumption was diagnosed with cholelithiasis on Day 325 leading to cholecystectomy. His lipase value at baseline was slightly elevated (107 U/L; reference range 13-60 U/L) and remained elevated during treatment period. Linagliptin was stopped about 19 months after initiation per protocol. About 34 days after discontinuation of linagliptin, he had sepsis secondary to histoplasmosis and acute stroke which led to hospitalization, and he also had end stage renal disease requiring hemodialysis. The same day, he was diagnosed with upper abdominal pain, pneumonia, nephrogenic anemia, constipation, and GERD. He completed the trial but remained in the hospital without resolution of his medical issues at the time of report. ***Reviewer's comment:*** *The Pancreatic Event Committee adjudicated 'upper abdominal pain' as acute pancreatitis with organ failure, but given that the abdominal pain occurred almost a month after study drug discontinuation, it is unlikely that it was related to the study drug.*

The pancreatic events appeared to occur at slightly higher frequency in those with lipase >ULN at baseline compared to those with lipase ≤ULN at baseline (Table 26). For example, 1.4% of subjects in the linagliptin versus 0.8% in the placebo group with normal lipase values at baseline developed at least one pancreatic event, compared to 5.1% and 2.9% of subjects in the

linagliptin and placebo groups who had baseline lipase values >ULN, respectively. Although the proportion of subjects who reported acute pancreatitis do not appear to show much difference between treatment groups with regard to baseline lipase values, reported events are too few to reach a conclusion.

Table 27: Pancreatic Events Confirmed by Clinical Event Committee by Lipase Baseline Value – Treated Set

	Linagliptin (N=3494)	Placebo (N=3485)
Lipase at baseline ≤ULN	N=2014	N=2010
Subjects with at least one pancreatic event	28 (1.4)	16 (0.8)
Subjects with asymptomatic pancreatic hyperenzymemia	20 (1.0)	14 (0.7)
Subjects with pancreatic malignancy	4 (0.2)	1 (0.0)
Acute pancreatitis	4 (0.2)	0
Without organ failure	3 (0.1)	0
With organ failure	1 (0.0)	0
Chronic pancreatitis	1 (0.0)	1 (0.0
Lipase at baseline >ULN	N=629	N=620
Subjects with at least one pancreatic event	32 (5.1)	18 (2.9)
Subjects with asymptomatic pancreatic hyperenzymemia	29 (4.6)	12 (1.9)
Subjects with pancreatic malignancy	0	1 (0.2)
Acute pancreatitis	3 (0.5)	3 (0.5)
Without organ failure	1 (0.2)	3 (0.5)
With organ failure	2 (0.3)	0
Chronic pancreatitis	0	2 (0.3)

Source: CSR, Table 15.3.1.5.4

Reviewer's comment: *Current linagliptin labeling discusses postmarketing reports of acute pancreatitis in Warnings and Precautions Section 5.1, as glycemic control clinical trials have not shown notable imbalance in acute pancreatitis. Since CARMELINA showed a notable imbalance in acute pancreatitis, I recommend adding this clinical trial information to Section 5.1 to inform healthcare professionals.*

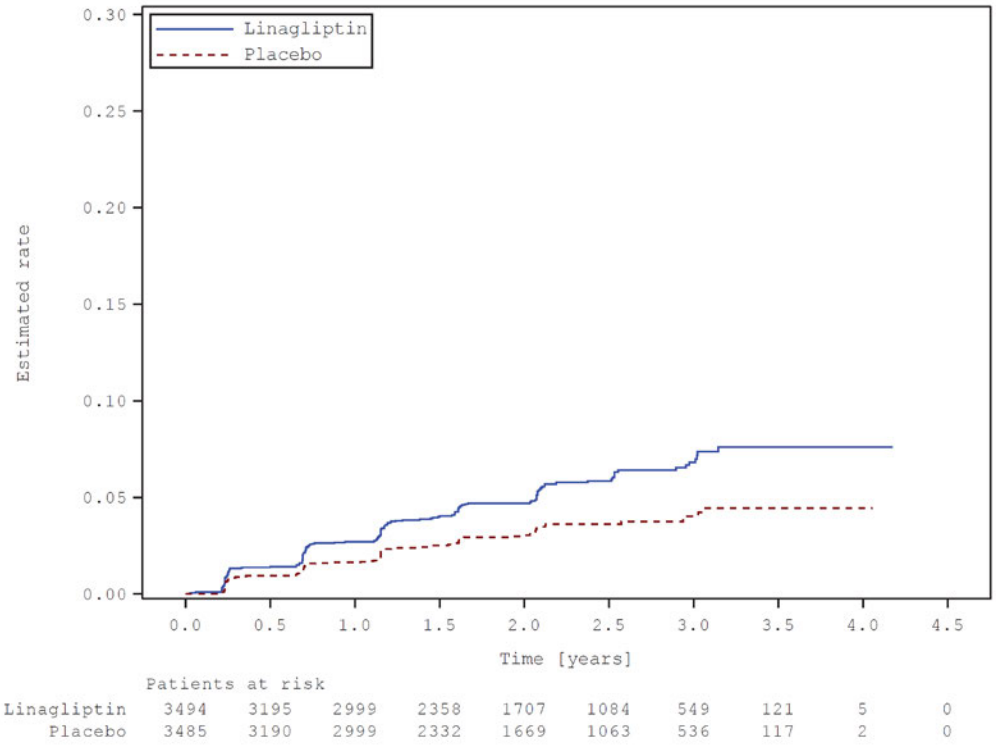
Lipase:

As discussed in Section 3.1, U.S. Regulatory Actions and Marketing History, supplement for 014 was approved on March 14, 2017 to include 'lipase increased' in *Adverse Reactions, Clinical Experience* under *Laboratory Tests* based on the results from study 1218.89 (MARLINA).

In CARMELINA, lipase was 51.7 U/L and 49.9 U/L at baseline in the linagliptin and placebo groups, respectively, and change from baseline to last value on-treatment was 6.2 U/L and 0.6 U/L in the linagliptin and placebo groups, respectively (only subjects with at least one available baseline and one on-treatment value are included for the change from baseline).

The Kaplan Meier estimates of time to first increase of lipase ≥3x ULN showed that a higher proportion of subjects in the linagliptin group compared to placebo experienced first increase of lipase ≥3x ULN at all time points (Figure 12), and the log-rank test p-value was statistically significant between treatment groups (<0.0001).

Figure 13: Kaplan-Meier Plot of Time to First Increase of ≥3x ULN – Treated Set



Source: CSR, Figure 15.3.2.12

Lipase shift from baseline to the maximum value during treatment is summarized in Table 14 by treatment group. Overall, regardless of baseline lipase value, slightly higher proportion of subjects in the linagliptin (7.2%) had maximum lipase level of >3x ULN compared to placebo group (3.9%).

Table 28: Lipase Shift Tables From Baseline To Maximum Value On-Treatment – Treated Set

Linagliptin (N=3494)					
	Post-baseline categories				
Baseline	<LLN	LLN to ULN	ULN to ≤3x ULN	>3x ULN	Total
<LLN	8 (36.4)	13 (59.1)	1 (4.5)	0	22 (100)
LLN to ULN	4 (0.2)	1203 (62.6)	652 (33.9)	62 (3.2)	1921 (100)
ULN to ≤3x ULN	0	61 (10.6)	410 (71.6)	102 (17.8)	573 (100)
>3x ULN	0	4 (10.5)	15 (39.5)	19 (50.0)	38 (100)
Total	12 (0.5)	1281 (50.2)	1078 (42.2)	183 (7.2)	2554 (100)
Placebo (N=3485)					
Baseline	<LLN	LLN to ULN	ULN to ≤3x ULN	>3x ULN	Total
<LLN	12 (37.5)	19 (59.4)	1 (3.1)	0	32 (100)
LLN to ULN	5 (0.3)	1380 (73.2)	464 (24.6)	36 (1.9)	1885 (100)
ULN to ≤3x ULN	0	81 (14.1)	439 (76.5)	54 (9.4)	574 (100)
>3x ULN	0	1 (4.0)	15 (60.0)	9 (36.0)	25 (100)
Total	17 (0.7)	1481 (58.9)	919 (36.5)	99 (3.9)	2516 (100)

LLN=lower limit of normal; ULN=upper limit of normal; n=number of subjects; %=percentage of subjects relative to the total number of subjects with a baseline and post-baseline value, for each specified visit and baseline category.
Source: CSR, adapted from Table 15.3.2.8

As discussed in Section 8.4.5, higher proportion of subjects in the sitagliptin arm reported AE of 'lipase increased' compared to the placebo (4.2% linagliptin, 2.7% placebo; Table 20).

8.5.7. Oncological Adverse Events

Overall, 3.3% (n=116) of linagliptin and 3.8% (n=134) of placebo groups reported cancer. 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 Table 15.3.1.4.4.1 of CSR). Specific cancer of interest such as thyroid and pancreatic cancers are discussed further below in this section.

Thyroid neoplasm (benign):

Two subjects in the linagliptin and one subject in the placebo group reported benign thyroid neoplasms, all related to thyroid gland. No subjects discontinued, and none were considered related to the study drug.

Thyroid cancer:

Only one subject in the placebo group reported thyroid cancer with PT of papillary thyroid

cancer.

Pancreatic cancer:

Pancreatic cancer was one of AESI specified in the protocol, and once identified by an investigator, were to be reported on an SAE form in an expedited manner even if it did not meet any of the SAE seriousness criteria. Clinical Event Committee Pancreatic (CECP) adjudicated events suspected of acute pancreatitis, chronic pancreatitis, asymptomatic pancreatic hyperenzymemia and pancreatic malignancy. Pancreatic events other than pancreatic malignancy were discussed in Section 8.5.6, Pancreatitis, and pancreatic malignancy will be discussed here.

Pancreatic cancer is an ongoing area of interest with incretin mimetics (i.e., DPP-4 inhibitors and GLP-1 receptor agonists). In a 2013 research publication, pancreatic cellular changes, including exocrine cell proliferation and dysplasia and alpha-cell hyperplasia, were reported in a series of patients with diabetes who had been exposed to incretin based therapy (sitagliptin or exenatide) and suggested a potential link between these drugs and abnormal pancreatic exocrine or endocrine cell growth.[6] In a response, FDA and European Medicine Agency (EMA) together conducted a comprehensive review of all clinical, nonclinical and postmarketing data available for incretin mimetics, and concluded that the available data did not support a causal relationship between incretin mimetics and pancreatic toxicity or pancreatic cancer.[7] FDA acknowledged that systemic identification and documentation of new cases of pancreatic cancer in future cardiovascular outcomes trials and other clinical trials could provide additional information in the future. Therefore, pancreatic cancer with linagliptin remains an area of interest, and CARMELINA was a large, randomized controlled trial with follow-up of around 2 years to further inform this safety issue.

Eleven (0.31%) of subjects in the linagliptin group and 4 subjects (0.11%) in the placebo group were adjudicated as having pancreatic malignancy during the study, and these cases are summarized in Table 29. An Oncology Assessment Committee assessed causality and determined that one subject in the linagliptin group ((b) (6) and one subject in the placebo group (25110004) had pancreatic cancer event that was 'possibly related' to study drug.

[6] Butler AE, et al. Marked expansion of exocrine and endocrine pancreas with incretin therapy in humans with increased exocrine pancreas dysplasia and the potential for glucagon-producing neuroendocrine tumors. Diabetes 2013;62(7): 2595-604.
[7] Egan AG, et al. Pancreatic safety of incretin-based drugs – FDA and EMA assessment. NEJM 2014; 370:794-7.

Table 29: Summary of Adjudicated Pancreatic Cancer Cases

Subject ID	Age	Sex	Race	Country	On Study Drug	PT	Onset Months	S/sx	Outcome	Oncology assessment	Smoking	DM duration	Dyslipidemia	Obesity	Alcohol	Family history or ho CA
Linagliptin <1 yr bf onset																
(b) (6)	71	M	African-American	US	No; recvd drug 91 days (3 mo); event 2 months later	Pancreatic carcinoma	5	Wt loss (70 lbs); abdominal pain and anorexia; lipase nl	Tx with chemo; Died	Not related	No	2 yrs	Hyperlipidemia	Yes (34.5)	No	h/o kidney CA
(b) (6)	75	F	White	Ukraine	Yes	Pancreatic carcinoma	8	Had asymptomatic lipase elevation 3 mo after study drug; worsening health with wt loss (10 kg), D/N, and yellowing skin led to US of abd	Died	Not related	No	3 yrs	None	Yes (36.6)	No	None
(b) (6)	71	M	White	Argentina	Yes; completed study and received 15 months of study drug	Pancreatic neoplasm	8	Hospitalized due to wt loss, asthenia, anemia (lipase normal)	Not resolved	Not related	Ex-smoker (40 packs yrs)	8 yrs	Dyslipidemia	Yes (35.3)	No	None
(b) (6)	66	M	White	Chile	No; recvd drug 141 (5 mo); event 4 mo later	Pancreatic carcinoma	9	Drug d/c'd due to gastric issues (flatulence, abd pain); lipase was 2x ULN 7 days bf start study drug	Died	Not related	Ex-smoker (26 pack yrs)	24 yrs	Dyslipidemia	Overwt (29.4)	No	None

								and ULN at start of study drug								
Linagliptin > 1 yr bf onset																
(b) (6)	74	F	White	Poland	No; recvd drug 376 days (12 mo); event 3 mo later	Pancreatic carcinoma	15	Abd pain led to CT of abdomen; lipase nl	Died	Not related	No	7 yrs	Dyslipidemia	Overwt (29.1)	No	None
(b) (6)	56	M	White	Poland	Yes	Adeno-carcinoma pancreas	14	Elevated lipase led to referral to hosp	Died	Not related	Yes (15 pack yrs)	11 yrs	Hyperlipidemia	Overwt (27.8)	50 mL/wk (15%)	Mother h/o breast CA
(b) (6)	68	M	White	Poland	No; 514 days (17 mo), event 2 mo later	Pancreatic carcinoma	19	Hosp due to jaundice and diarrhea for 2-3 days; lipase nl	Died	Not related	No	14 yrs	Dyslipidemia	Yes (32)	750 mL/mo (4.5%)	h/o chondrosarcoma pubic bones
(b) (6)	61	M	White	Argentina	No; received tx for 268 days (9 mo); event occurred 325 days after d/c study drug	Pancreatic carcinoma	20	Hospitalized w/asthenia and jaundice (lipase normal levels)	Died	Not related	Yes (51 pack yrs)	12 yrs	None	No (21.6)	200 mL/day (12%)	None
(b) (6)	65	M	White	Portugal	Yes	Pancreatic carcinoma metastatic	23	Unspecified; lipase above ULN (<1x)	Not resolved; died due to complications	Not related	No	21 yrs	Dyslipidemia	Yes (43.9)	400 mL/day (10%)	None
(b) (6)	77	M	White	Poland	Yes	Pancreatic neoplasm	23	Hosp due to possible lung issue; lipase nl	Not resolved	Not related	Yes (40 pack yrs)	15 yrs	None	Yes (32.9)	None	None
(b) (6)	71	M	White	Argentina	1069 (36 months);	Pancreatic neoplasm	36 months	Experienced abdominal pain,	Not resolved	Possibly related	None	36 yrs	Dyslipidemia	Overwt (25)	None	Brothers h/o

					completed the study		; 8 days after study drug stopped	went to ER due to increase in pain; amylase, lipase normal								laryngeal and prostate CA
Placebo < 1 yr bf onset																
(b) (6)	82	M	Asian	Japan	Yes	Adenocarcinoma pancreas	5 mo	Unspecified; lipase nl at baseline	Not resolved	Not related	Ex-smoker (20 pack yrs)	10 yrs	Hypercholesterol	No (21)	200 mL/wk (5%)	None
(b) (6)	59	F	White	Mexico	Yes	Adenocarcinoma pancreas	10 mo	WU due to abd pain, distension, fatigue, wkness, wt loss	Died	Not related	Ex-smoker (20 pack yrs)	16 yrs	Dyslipidemia	Overwt (25.6)	No	Sibling h/o stomach CA
Placebo > 1 yr bf onset																
(b) (6)	63	F	White	Poland	Yes	Mucinous cystadenocarcinoma of pancreas	18 mo	Unspecified; lipase ULN at bl and remained WNL	Sub-total pancreatectomy w/splenectomy; recovered	Possibly related	No	9 yrs	Hypercholesterol	Yes (41.5)	No	None
(b) (6)	72	F	White	Spain	Yes	Pancreas neoplasm	29 mo	Unspecified; lipase nl	Resolved (no tx recvd)	Not assessable	No	7 yrs	Dyslipidemia	Yes (33.2)	No	No

Source: Reviewer abstracted from narratives

However, upon review of CRF, 2 cases receiving placebo had questionable diagnosis that did not seem to be pancreatic cancer:

- Subject (b) (6) (placebo) had 'mucinous cystadenoma of pancreas' (not cystadenocarcinoma), had resection of pancreas, and histopathology showed no neoplastic cells; CRF stated that 'the reported event is not pancreatic cancer';
- Subject (b) (6) (placebo) was reported as 'pancreas nodule' and not 'pancreatic neoplasm'.

On March 29, 2019, an Information Request (IR) was sent to the Applicant to get further information and clarification about pancreatic cancer cases. We also asked information about the number of pancreatic cancer cases in another large CVOT with linagliptin called CAROLINA, as we were aware that the study has been completed and the Applicant was in the process of getting the study results ready for a submission.

On April 12, 2019, the Applicant submitted the response to question regarding pancreatic cancers cases in the CAROLINA study (along with heart failure data from CAROLINA study, discussed in Section 6.1.2, Study Results):

> *DMEP Request #5: Report how many pancreatic cancer cases have been reported and how many have been confirmed in each treatment group of the CAROLINA study, and whether the same independent adjudication of pancreatic cancer events was implemented in the CAROLINA study.*
>
> Applicant Response to #5: The adjudication process for pancreatic cancer cases was the same in the CAROLINA study as it was in CARMELINA.
>
> The proportion of subjects with investigator-reported pancreatic cancer AEs were 0.6% of linagliptin and 0.8% of glimepiride subjects in CAROLINA. Of these, 16 subjects (0.5% of 3023) in the linagliptin group and 24 subjects (0.8% of 3010) in the glimepiride group had at least 1 CECP-confirmed pancreatic cancer during the trial, and 9 subjects (0.3%) in the linagliptin group and 13 subjects (0.4%) of the glimepiride group with pancreatic cancer was assessed as possibly related to treatment by the Oncology Assessment Committee.
>
> ***Reviewer's comment:*** *It is reassuring that an imbalance in pancreatic cancer was not seen between treatment groups in CAROLINA. CAROLINA had a longer duration of follow-up than CARMELINA (6.25 years).*

On May 16, 2019, the Applicant responded to the remaining questions from March 2018 IR, both request and answers are summarized here:

DMEP Request #1: Upon review of the case report forms, it is not evidence why 2 of the events in placebo group were diagnosed as pancreatic cancers: (b) (6) *and* (b) (6) *Clarify how events in these 2 patients were adjudicated as pancreatic malignancy event by the Oncology Assessment Committee.*

Applicant Response to #1: For subject (b) (6) all CECP adjudicators unanimously confirmed the result 'pancreatic malignancy' including a panel decision regarding the onset date (the Applicant submitted decision report and supporting source document including available clinical information).

For subject (b) (6) the event pancreas nodule was adjudicated by the CECP as not a pancreatic event, but it was inadvertently included in the Table 12.1.5.2:2 (Listing of patients with adjudication-confirmed pancreatic cancer).

The Applicant detected another patient (b) (6) which should have been listed in Table 12.1.5.3:2 but was inadvertently omitted. This patient had 'intraductal papillary mucinous neoplasm' that was confirmed by CECP adjudication as pancreatic malignancy.

The Applicant submitted a corrected version of Table 12.1.5.3:2, which lists 11 subjects with linagliptin and 4 subjects with placebo who had adjudication-confirmed pancreatic cancer.

Reviewer's comment: *The number of subjects did not change since one subject in the placebo was included by error and there was another subject in the placebo that was omitted inadvertently. Based on review of cases, this is acceptable.*

DMEP Request #2: Describe what factors were used to determine causality and how this causality was determined. Submit the Oncology Assessment Committee's documentation related to determining causality assessment for these and all reported pancreatic cancer events.

Applicant's Response to #2: Excluding one subject that was inadvertently omitted (see #1 above), there were 2 cases that was considered 'possibly related to treatment', one in linagliptin and one in placebo group. The WHO-UMC Causality Categories were used as a guide for assessing relationship. The Applicant also submitted the source data packages for CECP adjudication and Oncology assessment.

Reviewer's comment: *The Applicant's response was acceptable.*

DMEP Request #3: Calculate the incidence rate of pancreatic cancer in linagliptin and placebo group among patients followed for >180 days after randomization and had >90 days of drug exposure in CARMELINA. Calculate hazard ratios for linagliptin compared to placebo group with 95% confidence intervals.

Applicant's Response to #3: Summary of incidence rate of pancreatic cancer and HR excluding subject (b) (6) and including subject (b) (6) (as discussed in #1) are summarized in Table 29.

Table 30: Adjudicated Pancreatic Cancer by Treatment – Treated Set

	Linagliptin (N=3494)			Placebo (N=3485)		
	N	%	R*	N	%	R*
Subjects with pancreatic cancer	11	0.3	1.4	4	0.1	0.5
HR vs placebo (95% CI)	2.72 (0.87, 8.55)					
Subjects with pancreatic cancer with >180 days follow-up and >90 days of exposure	10	0.3	1.7	3	0.1	0.5
HR vs placebo (95% CI)	3.29 (1.01, 13.02)					

*Incidence rate per 1000 patient-years
Source: Applicant's response to information request submitted April 12, 2019, NDA 201280

Reviewer's comment: *The HR for pancreatic cancer excluding subjects with cancer with >180 days of follow-up and >90 days of exposure is 3.29 with 95% CI excluding 1 (1.01, 13.02). This is a post hoc analysis and it is unclear whether this is an appropriate cut off to assess pancreatic cancer. The overall HR including all cases was 2.72 with 95% CI crossing 1 (0.87, 8.55). In both cases, the 95% CI is very wide, indicating large uncertainty for the point estimate.*

DMEP Request #4: Provide any additional analyses and/or additional information including your interpretation of finding(s) that you believe would be helpful to evaluate this imbalance of pancreatic cancer.

Applicant's Response to #4: The Applicant summarized pancreatic cancer data from other DPP-4 inhibitor's CVOTs (EXAMINE, SAVOR, and TECOS) which did not show an imbalance in pancreatic cancer between treatment groups. The Applicant also summarized recent literature data indicating no relationship between DPP-4 inhibitors and pancreatic cancer.

To evaluate this imbalance with pancreatic cancer in CARMELINA, data from other CVOTs are important to note and discuss further. In CVOTs for other DPP-4 inhibitors (i.e., saxagliptin/SAVOR, alogliptin/EXAMINE, and sitagliptin/TECOS), there was no imbalance in pancreatic cancer between treatment groups. However, a numerical imbalance of pancreatic

cancer was observed in LEADER, which was a CVOT for liraglutide, a GLP-1 receptor agonist (RA). In LEADER, 4668 subjects were randomized to liraglutide and 4672 were randomized to placebo, and the median time of exposure was about 3.5 years. An external adjudication committee identified cases of malignant pancreatic neoplasms in 13 subjects in liraglutide and 5 subjects in the placebo arm. DMEP consulted our Oncology colleague within FDA, and Dr. Horiba from Division of Oncology Products 2 reviewed and assessed 13 subjects (13/4668, 0.28%) in the liraglutide arm versus 8 subjects (6/4672, 0.17%) in the placebo arm as having reasonably likely to have had pancreatic cancer.[8] Subjects in LEADER reported pancreatic cancer with onset of 1-42 months. Dr. Horiba commented that:

> "Despite the advanced presentation at diagnosis and aggressive clinical course typically observed in patients with pancreatic cancer, quantitative analysis of the timing of genetic evolution suggest that at least a decade takes place between the initial mutation and development of the first malignant (non-metastatic) pancreatic cancer cell and that approximately 5 additional years are required for the primary tumor to develop metastatic potential. This suggests that a direct causal role for GLP-1 RAs in the initial development of pancreatic cancer in patients participating in …the LEADER trial is unlikely given the short (approximately 9 months) latency period between exposure… and diagnosis of pancreatic cancer. There is insufficient information available to elucidate whether GLP-1 RA treatment plays a role in accelerating the evolution of primary or metastatic disease following the occurrence of the initial mutation that will ultimately lead to clinically evident pancreatic cancer, given the relative short follow-up period (median follow-up of…3.5 years for liraglutide)."

Dr. Horiba also commented that "the number of cases is too small to permit conclusions regarding whether this imbalance is due to chance alone, an acceleration in the development of pancreatic cancer due to treatment with GLP-RA, or other patient risk factors" and that "longer follow-up (e.g., 10 years) is recommended to further characterize the relationship between GLP-1 RAs and the development of pancreatic cancer".

Reviewer's comment: *The numerical imbalance in pancreatic cancer seen with linagliptin compared to placebo in CARMELINA was very similar to that seen in LEADER, a CVOT for another incretin mimetics. LEADER compared to CARMELINA enrolled more subjects (9340 vs 6979 subjects) and had longer follow-up (3.5 vs 2.2 years). Based on Dr. Horiba's assessment as discussed above, I believe that this numerical imbalance in pancreatic cancer seen with linagliptin in CARMELINA is likely due to chance, given that the imbalance is based on a small number of cases and duration of trial follow-up is insufficient to fully assess the relationship between the drug product and the development of pancreatic cancer. In addition, an imbalance*

[8] Dr. Margit Horiba review under NDA 022341, dated May 19, 2017

in pancreatic cancer was not seen in another large CVOT with linagliptin, CAROLINA, which had a longer median follow-up compared to CARMELINA (6.25 years).

8.6. Safety Analyses by Demographic Subgroups

Subgroup analyses for the overall summary of AEs 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.

8.7. Specific Safety Studies/Clinical Trials

As previously discussed, CARMELINA 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 were pregnant or breast-feeding were excluded from study participation, and women who are of child-bearing potential were screened for pregnancy before enrollment and during their participation in the trial.

8.8.3. Pediatrics and Assessment of Effects on Growth

Not applicable as only adults were enrolled in CARMELINA.

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 31, 2018, covering May 3, 2015 to May 2, 2018. The changes to the US Prescribing Information and summarized in this PBRER (bullous pemphigoid, arthralgia, increased lipase) were already summarized in Section 3.1.

As discussed previously, inflammatory bowel disease (IBD) is a Tracked Safety Issue (created on May 21, 2018) based on a population-based cohort study that was published in March 2018. CARMELINA did not show an increased incidence of IBD with linagliptin compared to placebo (Table 22).

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 CARMELINA will be labeled to inform healthcare professionals that the use of linagliptin is not associated with an unacceptable increase in CV risk. 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

The most common AEs with linagliptin in CARMELINA were diarrhea (3.5% linagliptin, 3.1% placebo) and increase lipase (4.2% linagliptin, 2.7% placebo). 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 (37% linagliptin, 38.5% placebo) and AEs leading to discontinuation (10.3% linagliptin, 11.5% placebo) were similar between treatment arms.

The incidence of any hypoglycemia (29.7% linagliptin, 29.4% placebo) and severe hypoglycemia (3.0% linagliptin, 3.1% placebo) was not increased in the linagliptin group compared to placebo in CARMELINA. However, slightly higher number of subjects in the placebo group compared to linagliptin initiated insulin and other antidiabetic agents for glycemic control after randomization which makes interpretation of hypoglycemia between treatment groups difficult, since change in concomitant antidiabetic therapy will affect the incidence of hypoglycemia.

Other adverse events of special interest (AESI) that were evaluated with a pre-specified MedDRA queries included hypersensitivity reactions, skin lesions, hepatic events, renal adverse events, pancreatitis, thyroid neoplasm and cancer, and pancreatic cancer. Renal AEs (such as acute renal failure), pancreatitis, thyroid neoplasm and cancer, and pancreatic cancer were all adjudicated by an independent adjudication committee.

There was an imbalance in acute pancreatitis with linagliptin in CARMELINA, with 9 subjects in the linagliptin group and 5 subjects in the placebo group confirmed to have acute pancreatitis. Four acute pancreatitis in the linagliptin group were with organ failure versus none in the placebo group. Higher proportion of subjects in the linagliptin group had maximum lipase value of >3x ULN compared to placebo group (7.2% vs 3.9%). Increase in lipase with linagliptin is adequately labeled. However, imbalance in acute pancreatitis with linagliptin in CARMELINA should be added to the Warnings and Precautions section for pancreatitis, as only postmarketing reports of acute pancreatitis are currently described.

Bullous pemphigoid is a safety issue that have been identified through postmarketing reports. In CARMELINA, 7 cases of bullous pemphigoid were reported in the linagliptin arm compared to none with placebo; 3 of these were SAEs and in 2 cases pemphigoid led to study drug discontinuation. The onset of pemphigoid in these cases ranged from 18 to 30 months after initiating linagliptin. This is the first clinical trial to my knowledge that reported cases of bullous pemphigoid with linagliptin, as current safety warnings about bullous pemphigoid in labeling was based on postmarketing reports. Therefore, I recommend adding the cases of bullous pemphigoid that were reported in CARMELINA to linagliptin labeling.

Heart failure is a labeled safety concern for two other DPP-inhibitors, saxagliptin and alogliptin, based on the increased risk for hospitalizations for heart failure seen in the dedicated cardiovascular outcome trials for these products, SAVOR and EXAMINE respectively. Therefore, evaluation of heart failure was important for linagliptin. In CARMELINA, hospitalization for heart failure was an adjudicated tertiary endpoint and occurred in 435 subjects. Less subjects in the linagliptin arm (6.0%) compared to the placebo arm (6.5%) were hospitalized for heart failure, with a HR point estimate of 0.90 (95% CI: 0.74, 1.08). This indicated that there was no evidence of increased harm for heart failure associated with linagliptin. Although there was no multiplicity adjustment for hospitalization for heart failure, this finding is supported by the large number of events used in the estimation of the risk, the fact that hospitalization for heart failure was a pre-specified endpoint using a standard definition, and events were prospectively collected and adjudicated by an independent, blinded adjudication committee.

Based on the totality of the data, no ‘new’ safety concerns were identified with linagliptin, as the safety profile of linagliptin in patients with T2DM at high CV risk in CARMELINA was overall similar to the known safety profile of linagliptin.

9. Advisory Committee Meeting and Other External Consultations

Not applicable, an 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:

- Section 2.1 Recommended Dosing: (b) (4) [redacted]
- Section 5.1, Pancreatitis: To include pancreatitis information from CARMELINA. I agree with adding pancreatitis information from CARMELINA to this section;
- Section 5.2, Heart Failure: Based on preliminary findings that the Applicant voluntarily submitted about heart failure with linagliptin from CAROLINA trial, (b) (4) [redacted] We will further evaluate heart failure when full data and results from CAROLINA are submitted for review;
- (b) (4) [redacted] Bullous Pemphigoid: To include pemphigoid cases from CARMELINA. I agree with adding clinical trial data here;
- Section 6.1, Clinical Trials Experience: To update this section from CARMELINA, I disagree with inclusion of certain statements and final details to be included will be further negotiated with the Applicant;
- Section 8.6, Renal Impairment: I agree including available information about patients with renal impairment from CARMELINA in this section.
- (b) (4) [redacted] adding the results of CARMELINA trial in Clinical Studies section. I agree with including the results of CARMELINA in this section, final language will be negotiated.

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. Therefore, the subsequent subsections are not applicable for this review and have been omitted.

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

CARMELINA was a covered trial. The Applicant has adequately disclosed financial arrangements with clinical investigators as recommended in the guidance for industry Financial Disclosure by Clinical Investigators.

Covered Clinical Study (Name and/or Number): CARMELINA/1218.22

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 660		
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): 2		
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		

<table>
<tr><td colspan="3">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: _____

Significant payments of other sorts: 1

Proprietary interest in the product tested held by investigator: 0

Significant equity interest held by investigator: 1

Sponsor of covered study: Boehringer Ingelheim; Eli Lilly (Financial co-funder)</td></tr>
<tr><td>Is an attachment provided with details of the disclosable financial interests/arrangements:</td><td>Yes ☒</td><td>No ☐ (Request details from Applicant)</td></tr>
<tr><td>Is a description of the steps taken to minimize potential bias provided:</td><td>Yes ☒</td><td>No ☐ (Request information from Applicant)</td></tr>
<tr><td colspan="3">Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____</td></tr>
<tr><td>Is an attachment provided with the reason:</td><td>Yes ☒</td><td>No ☐ (Request explanation from Applicant)</td></tr>
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206073Orig1s017

OTHER REVIEW(S)

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	July 2, 2019
To:	Lisa Yanoff, M.D. Acting Director **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:	Aman Sarai, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Samantha Bryant, PharmD, BCPS Regulatory Review Officer Office of Prescription Drug Promotion (OPDP)
Subject:	Review of Patient Labeling: Medication Guides (MG)
Drug Name (established name):	JENTADUETO (linagliptin and metformin hydrochloride) NDA 201281 S-022 JENTADUETO XR (linagliptin and metformin hydrochloride extended-release) NDA 208026 S-008 GLYXAMBI (empagliflozin and linagliptin) NDA 206073 S-017
Dosage Form and Route:	tablets, for oral use
Applicant:	Boehringer Ingelheim Pharmaceuticals, Inc.

1 INTRODUCTION

On September 12, 2018, Boehringer Ingelheim Pharmaceuticals, Inc. submitted for the Agency's review a supplemental New Drug Application for for proposed revisions to the prescribing information based on the study results for the Cardiovascular Safety & Renal Microvascular outcome study with linagliptin (CARMELINA).

This collaborative review is written by the 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 October 2, 2018 and September 28, 2018, respectively, for DMPP and OPDP to review the Applicant's proposed Medication Guides (MGs) for JENTADUETO (linagliptin and metformin hydrochloride), JENTADUETO XR (linagliptin and metformin hydrochloride extended-release) and GLYXAMBI (empagliflozin and linagliptin) tablets, for oral use.

2 MATERIAL REVIEWED

- Draft JENTADUETO (linagliptin and metformin hydrochloride), JENTADUETO XR (linagliptin and metformin hydrochloride extended-release) and GLYXAMBI (empagliflozin and linagliptin) MGs received on September 12, 2018, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on June 27, 2019.
- Draft JENTADUETO (linagliptin and metformin hydrochloride), JENTADUETO XR (linagliptin and metformin hydrochloride extended-release) and GLYXAMBI (empagliflozin and linagliptin) Prescribing Information (PI) received on September 12, 2018, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on June 27, 2019.

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:

- 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 meets the Regulations as specified in 21 CFR 208.20
- ensured that the MGs meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MGs are consistent with the approved comparator labeling where applicable.

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 collaborative review of the MGs are 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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SAMANTHA E BRYANT
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FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: July 2, 2019

To: Richard Whitehead, Regulatory Project Manager
Division of Metabolism and Endocrinology Products (DMEP)

Monika Houstoun, Associate Director for Labeling, DMEP

From: Samantha Bryant, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Melinda McLawhorn, Team Leader, OPDP

Subject: OPDP Labeling Comments for 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: 201281/Supplement 022
208026/Supplement 008
206073/Supplement 017

In response to DMEP's consult request dated September 28, 2018, OPDP has reviewed the proposed product labeling (PI), and Medication Guide for Jentadueto, Jentadueto XR, and Glyxambi. These supplements (S022, S008, S017) provide for changes to the labeling based on the results of the CARMELINA 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 June 27, 2019, and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed Medication Guide will be sent under separate cover.

Thank you for your consult. If you have any questions, please contact Samantha Bryant at (301) 348-1711 or Samantha.Bryant@fda.hhs.gov.

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SAMANTHA E BRYANT
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FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: June 21, 2019

To: Richard Whitehead, Regulatory Project Manager
Division of Metabolism and Endocrinology Products (DMEP)

Monika Houstoun, Associate Director for Labeling, DMEP

From: Samantha Bryant, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Melinda McLawhorn, Team Leader, OPDP

Subject: OPDP Labeling Comments for TRADJENTA® (linagliptin) tablets, for oral use

NDA: 201280/Supplement 018

In response to DMEP's consult request dated September 28, 2018, OPDP has reviewed the proposed product labeling (PI), and Medication Guide for Tradjenta. This supplement (S018) provides for changes to the labeling based on the results of the CARMELINA study.

PI and Medication Guide: OPDP's comments on the proposed labeling are based on the draft PI, and Medication Guide received by electronic mail from DMEP (Richard Whitehead) on June 17, 2019, and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed Medication Guide will be sent under separate cover.

Thank you for your consult. If you have any questions, please contact Samantha Bryant at (301) 348-1711 or 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:	June 21, 2019
To:	Lisa Yanoff, M.D. Acting Director **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:	Aman Sarai, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Samantha Bryant, PharmD, BCPS Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	DMPP and OPDP Concurrence with Submitted: Medication Guide (MG)
Drug Name (established name):	TRADJENTA (linagliptin)
Dosage Form and Route:	tablets, for oral use
Application Type/Number:	NDA 201280
Supplement Number:	S-018
Applicant:	Boehringer Ingelheim Pharmaceuticals, Inc.

1 INTRODUCTION

On September 5, 2018, Boehringer Ingelheim Pharmaceuticals, Inc. submitted for the Agency's review a supplemental New Drug Application for for proposed revisions to the prescribing information based on the study results for the Cardiovascular Safety & Renal Microvascular outcome study with linagliptin (CARMELINA). TRADJENTA (linagliptin) tablets is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. On October 2, 2018 and September 28, 2018, respectively, the Division of Metabolism and Endocrinology Products (DMEP) requested that the Division of Medical Policy Programs (DMPP) and Office of Prescription Drug Promotion (OPDP) review the Applicant's proposed Medication Guide (MG) for TRADJENTA (linagliptin) tablets, for oral use.

2 MATERIAL REVIEWED

- Draft TRADJENTA (linagliptin) MG received on September 5, 2018, and received by DMPP and OPDP on June 17, 2019.
- Draft TRADJENTA (linagliptin) Prescribing Information (PI) received on September 5, 2018, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on June 17, 2019.

3 CONCLUSIONS

We find the Applicant's proposed MG is acceptable as submitted.

4 RECOMMENDATIONS

- Consult DMPP and OPDP regarding any additional revisions made to the Prescribing Information (PI) to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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REGULATORY PROJECT MANAGER
PHYSICIAN LABELING RULE (PLR) FORMAT REVIEW
OF THE PRESCRIBING INFORMATION

Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements

Application: NDA 206073/S-017

Application Type: Efficacy Supplement (SE-8)

Drug Name(s)/Dosage Form(s): Glyxambi (empagliflozin and linagliptin) tablets

Applicant: Boehringer Ingelheim Pharmaceuticals, Inc.

Receipt Date: September 12, 2018

Goal Date: July 12, 2019

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; and 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.

The supplement that is the focus of this PLR review, S-017, is an SE-8 type efficacy supplement that was received on September 12, 2018. S-017 proposes revisions to the PI and Medication Guide based on the results of study 1218.22 entitled, "A Multicenter, International, Randomized, Parallel Group, Double-blind, Placebo-controlled Cardiovascular Safety & Renal Microvascular Outcome Study with Linagliptin, 5 mg Once Daily in Patients with Type 2 Diabetes Mellitus at High Vascular Risk," (CARMELINA). Corollary supplements were also submitted to BI's other linagliptin containing products: NDA 201280/S-018 Tradjenta (linagliptin) tablets, NDA 201281/S-022 Jentadueto

(linagliptin and metformin) tablets, and NDA 208026/S-008 Jentadueto XR (linagliptin and metformin extended-release) tablets. The version of the Glyxambi PI that was reviewed below was submitted as an amendment to S-017 on April 11, 2019 (SD-896, eCTD 0119).

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI) received on April 11, 2019 (SD-896). 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).

3. Conclusions/Recommendations

No SRPI format deficiencies were identified in the review of this PI.

In addition, the following labeling issues were identified:

1. Inconsistent amounts of white space in Highlights.
2. Dates for Recent Major Changes and Revised date need to be updated to replace current placeholders.

Other labeling issues identified above will be conveyed to the applicant in during labeling negotiations. The applicant will be asked to correct these issues and resubmit the PI in Word format. The resubmitted PI will be used for further labeling review.

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:

N/A 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: *one-half page 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: *The amount of whites pace between major headings varies. We will attempt to standardize white space amount during labeling negotiations.*

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

Selected Requirements of Prescribing Information

• **Product Title**	Required
• **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 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: *Placeholder for dates "x/xxxx" is used. Dates of changes being enacted by this supplement will be updated just prior to approval.*

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:

Selected Requirements of Prescribing Information

Adverse Reactions in Highlights

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:

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: *Revision date placeholder is used "x/201x". Final revision date will be updated just prior to approval.*

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:

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:

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: *Modification of the standard statement include starting the first sentence with "Additional adverse reactions" instead of "The following adverse reactions" and removing the hyphen from "post-approval" to state "postapproval". Both the established names of linagliptin*

and empagliflozin are listed for the drug names. In the second sentence, the phrase "it is not always possible…" is replaced with "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:

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:

Selected Requirements of Prescribing Information

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.

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
06/20/2019 09:02:15 AM

Clinical Inspection Summary

Date	5/22/2019
From	Cynthia F. Kleppinger, M.D., Senior Medical Officer Min Lu, M.D., Acting 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 Tania Condarco, M.D., Clinical Team Leader Richard Whitehead, M.S., Regulatory Project Manager Division of Metabolism and Endocrinology Products (DMEP)
NDA	NDA 201280/s018 (linked to NDA 201281/s022 [linagliptin and metformin] NDA 206073/s017 [empagliflozin and linagliptin] NDA 208026/s008 [linagliptin and metformin Extended-Release])
Applicant	Boehringer Ingelheim Pharmaceuticals, Inc.
Drug	Linagliptin (Tradjenta®)
NME	No
Therapeutic Classification	Antidiabetic Agents, Non-Insulin (3031400)
Proposed Indication	Post-Marketing Requirement Cardiovascular Risk Study in patients with type 2 diabetes mellitus
Consultation Request Date	11/7/2018
Summary Goal Date	5/27/2019
Action Goal Date	7/5/2019
PDUFA Date	7/5/2019

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The inspection for this supplemental new drug application (sNDA) consisted of three domestic and three foreign clinical sites.

In general, based on the inspections of the six clinical sites, the inspectional findings support validity of data as reported by the sponsor under this NDA.

The compliance classification for Dr. Forgosh is Voluntary Action Indicated (VAI). Although regulatory violations were noted (as described below), they are unlikely to significantly impact primary safety and efficacy analyses. Data from this site is acceptable for use in support of the indication for this application. The full Establishment Inspection Report was submitted for review

The compliance classification for Drs. Barbonta, Kobielusz-Gembala, Mazur, Anderson, and Savin is No Action Indicated (NAI). Data from these sites is considered reliable based on the available information. The full Establishment Inspection Reports for Drs. Barbonta, Mazur, Anderson, and Savin were submitted for review. The full Establishment Inspection Report for Dr. Kobielusz-Gembala was not available for review. Preliminary inspection results were communicated by the FDA ORA field investigator.

All classifications are considered preliminary until the final communication letter is sent to the inspected entity. An inspection summary addendum will be generated if conclusions change upon receipt and review of the pending Establishment Inspection Report.

II. BACKGROUND

Boehringer Ingelheim Pharmaceuticals, Inc. (BI) has submitted a supplement to NDA 201280 to revise the Tradjenta® (linagliptin) prescribing information to include information based on results of Study 1218.22 entitled "A multicenter, international, randomized, parallel group, double-blind, placebo-controlled **CA**rdiovascular Safety & **R**enal **M**icrovascular outcom**E** study with **LINA**gliptin, 5 mg once daily in patients with type 2 diabetes mellitus at high vascular risk" CARMELINA (c22196815-01).

The CARMELINA® trial was conducted to fulfill Post-Marketing Requirement (PMR) 1766-4.

This was a randomized, double-blind, placebo-controlled trial comparing treatment with linagliptin (5 mg once daily) with placebo treatment (matching tablets once daily) as add-on therapy to standard of care background antidiabetic treatment. Subjects with documented diagnosis of type 2 diabetes mellitus (T2DM) at high risk of cardiovascular (CV) events with HbA1c of $\geq$ 6.5% and $\leq$ 10.0% were enrolled.

The trial involved 660 sites in 27 countries. A total of 12,280 subjects signed informed consent; 6991 subjects were randomized; 6888 subjects completed the trial (i.e., were followed up for endpoints up to the end of the observation period in the trial) or died. Overall, 6958 patients had vital status collected; i.e., were reported to be alive or dead at trial end.

The trial began July 29, 2013 and completed January 18, 2018. The trial database was locked on March 29, 2018.

The primary endpoint in this trial was time to the first occurrence of any of the following adjudication-confirmed components of the primary composite endpoint (3-point Major Adverse Cardiovascular Events [MACE]): CV death, non-fatal myocardial infarction (MI) or non-fatal stroke. The key secondary endpoint was time to the first occurrence of any of the following adjudication-confirmed components: renal death, sustained End Stage Renal Disease (ESRD), sustained decrease of 40% or more in the estimated glomerular filtration rate (eGFR) (composite renal endpoint 1).

III. RESULTS (by Site):

Name of CI/ Address Site#	# of Subjects Randomized	Inspection Date	Classification
Diana-Hortensia Barbonta, M.D., Ph.D. SRL, Specialitatea Diabet Zaharat Nutritie si Boli Metabolice Str. Closca nr 6, Bloc 4BCDEF, AP. 70 Cod 510053, Alba lulia, Judet Alba Romania Site 2611	122 subjects	02/18 – 03/01/2019	No Action Indicated (NAI)
Iwona Kobielusz-Gembala, M.D. ul. Plac Kosciuszki 12 Oswiecim, 32-600 Poland Site 2501	52 subjects	03/11 – 03/15/2019	No Action Indicated (NAI)*
Stanislaw Mazur, M.D. Medyk Centrum Medyczne ul. Szopena 1 Rzeszow, 35-055 Poland Site 2516	107 subjects	02/25 – 03/04/2019	No Action Indicated (NAI)
Robert Anderson, M.D. Chief of Endocrinology c/o Omaha VA Medical Center 4101 Woolworth Avenue Omaha, NE 68105 Site 4075	20 subjects	04/08 – 04/12/2019	No Action Indicated (NAI)
Leslie B. Forgosh, M.D. 45 West 10th Street St. Paul, MN 55102 Site 4245	37 subjects	02/19 – 02/27/2019	Voluntary Action Indicated (VAI)*
Virginia Savin VA Medical Center 4810 East Linwood Boulevard Kansas City, MO 64128 Site 4111	36 subjects	01/28 – 01/31/2019	No Action Indicated (NAI)

Key to Compliance Classifications
NAI = No deviation from regulations
VAI = Deviation(s) from regulations
OAI = Significant deviations from regulations; data unreliable.
*Pending = Preliminary classification based on information in 483 (if applicable) and preliminary communication with the field; final classification is pending letter to site.

NOTE: Site inspections focused on 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. Diana-Hortensia Barbonta/ Site 2611

There were 194 subjects screened and 122 subjects enrolled into the study; 112 subjects completed the study (9 deaths and one withdrawal of consent prior to Visit 6/Week 84 End of Treatment). There were 44 subject records reviewed.

A translator was present throughout the inspection.

Dr. Barbonta is the former Head of Department for Diabetes Nutrition and Metabolic Diseases at Alba lulia County Emergency Hospital. She now is the Senior Specialist for Diabetes, Nutrition and Metabolic Diseases at her own Medical Practice.

Study approval and oversight was by the Romanian National Ministry of Health – The National Ethics Committee for the Clinical Study Medicines (NECCSM). The site was a non-IND site.

Source records were organized and available. Data was originally collected on paper source documents and entered into the Oracle Clinical Inform system. Source records were compared to the sponsor data line listings and there were no discrepancies.

Primary and key secondary efficacy endpoints were verifiable and there was no evidence of under-reporting of adverse events. There was no accidental unblinding.

The inspection revealed adequate adherence to the regulations and the investigational plan. There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, issued.

2. Iwona Kobielusz-Gembala/ Site 2501

There were 80 subjects screened and 52 subjects enrolled into the study; 47 subjects completed the study. There were 52 subject records reviewed.

The site was a non-IND site.

Source records were compared to the sponsor data line listings and there were no discrepancies. Primary and key secondary efficacy endpoints were verifiable and there was no evidence of under-reporting of adverse events. There was no accidental unblinding.

The inspection revealed adequate adherence to the regulations and the investigational plan. There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, issued.

3. Stanislaw Mazur/ Site 2516

There were 269 subjects screened and 107 subjects enrolled into the study; 88 subjects completed the study (two subjects' study drug was discontinued by the Investigator, four subjects discontinued due to adverse events, four subjects discontinued by their own decision, and there were nine subject deaths). There were 22 subject records reviewed.

A translator was present during the inspection.

Dr. Mazur has been in medical practice for approximately 29 years. He started the Medyk Centrum Medyczne clinic approximately 25 years ago. The clinic has been doing clinical research since 1999 and has since grown to approximately 25 sites within the local Province. Dr. Mazur is the Director of the clinic and CEO/President of the corporation. The Medyk Centrum Medyczne is comprised of multiple specialties and serves private pay and national insurance patients. The clinics perform free screening tests for multiple health issues and has developed a large database (>36,000) from which they recruited most of the study participants. No advertising was utilized for the study.

Approval and oversight were performed by the Central Ethics Committee Bioethics Committee at the District Medical Chamber in Lublin.

The study site was found to be well organized with adequate controls and security in place to maintain integrity of the test articles and study blinding. All documentation was found and maintained in administrative binders or subject study/medical files. The records were found to be extensive and well organized.

Source documents were compared against the sponsor data line listings. Throughout the inspection there were minor recordkeeping errors (such as years being recorded as 214 instead of 2014) but nothing significant. The primary endpoint was verifiable. There was no under-reporting of adverse events.

The inspection revealed adequate adherence to the regulations and the investigational plan. There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, issued.

4. Robert Anderson/ Site 4075

There were 34 subjects screened and 20 subjects enrolled into the study; 19 subjects completed the study (had outcome data); one subject moved out of the area and there were

4 subject deaths. There were 21 subject records reviewed.

Dr. Anderson has been with the firm in the same position approximately 39 years. Some of his duties include working as a Principal Investigator on clinical trials that include Veterans Administration (VA) cooperative studies. The firm did not do any advertisement for the study other than word of mouth and referrals to the Omaha VA Medical Center.

The IRB of record was the Omaha VA Medical Center IRB.

The VA electronic medical records system is the Computerized Patient Record System (CPRS). Since this was an older study, information was documented on paper documents and transferred to eCRFs into the sponsor's EDC system. The subject records were neat and organized by subject visit. The source records were compared to the sponsor data line listings and there were only a few minor discrepancies.

The primary endpoint was verifiable and there was no under-reporting of adverse events.

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. Leslie Forgosh/ Site 4245

There were 85 subjects screened and 37 subjects enrolled into the study; 30 subjects completed the study. There were 18 subject records reviewed.

Dr. Forgosh has been a practicing non-invasive cardiologist since 1997 and was approached by the sponsor to participate in the study. He practices at Saint Joseph's Hospital, a tertiary, 253-bed hospital that is part of the Health East Care System. All study subject visits and protocol activities were conducted at Health East Heart Care on St. Joseph's Hospital campus. Subjects were recruited from among the hospital's patient population. They were identified by the clinical study coordinators via review of hospital records. Study staff mailed IRB-approved letters and postcards to patients/potential subjects to gauge interest. Referrals from the 21 cardiologists in the group and some Certified Nurse Practitioners also contributed subjects to the study.

The Health East Institutional Review Board provided oversight of the study.

The trial was initiated at the same time the Health East Care System implemented the EPIC electronic medical record in the hospital. It captured all essential health information for the research subjects. Source was compared to the sponsor data line listings and there were only minor discrepancies.

The primary efficacy endpoint was verifiable. All adverse events were captured except a few as noted below.

At the conclusion of the inspection, a Form FDA-483, Inspectional Observations, was issued for failure to follow the protocol. Specifically,

- Subject (b) (6) suffered a stroke but no Rankin scores were done at one week and three months post event as required by the protocol Section 5.3.2.
  OSI Reviewer Comment: The serious adverse event itself was captured. The subject was in a transitional unit and not available for evaluation.
- Subject (b) (6) was seen at their last clinic visit (b) (6). He was reported to have benign prostatic hypertrophy since (b) (6), which was not reported as an AE. Subject was seen in the clinic (b) (6) with a history of allergic reaction and treatment with dapsone, which resulted in nausea, vomiting and shortness of breath that resolved with discontinuation of the medication. This was not reported as an adverse event.
  OSI Reviewer Comment: These were isolated adverse events unrelated to study medication.
- Subject (b) (6) had back pain documented at Visit 5 but this was not reported as an adverse event. No further evaluation of the complaint was documented.
  OSI Reviewer Comment: This was an isolated adverse event unrelated to study medication.
- Not all concomitant medications were captured for Subject (b) (6) (furosemide, hydrochlorothiazide, colchicine, ceftriaxone and piperacillin/tazobactam), Subject (b) (6) (baclofen and clobetasol), Subject (b) (6) (tadalafil, nitroglycerin, iohexol and ondansetron), Subject (b) (6) (benzonatate), Subject (b) (6) (losartan and rosuvastatin calcium) and Subject (b) (6) (erythropoietin and gabapentin).
  OSI Reviewer Comment: Subject population with significant disease on multiple medications during the trial. Staff failed to record a few isolated medications.

The investigator submitted a response to the Form FDA-483 on March 1, 2019 and it was determined to be acceptable.

Although regulatory violations were noted as described above, they are unlikely to significantly impact primary safety and efficacy analyses. Data from this site appear acceptable.

6. Virginia Savin/ Site 4111

There were 63 subjects screened and 36 subjects enrolled into the study; 25 subjects completed the study (eleven subjects discontinued treatment early; four subjects died while on treatment). There were 20 subject records reviewed.

Dr. Savin has been conducting clinical research since 1966.

The IRB responsible for oversight of the study was KC VA Medical Center Human Studies Committee. Full approval was required from the Human Studies Committee, the Research and Development Committee, and the Medical Research Service Office.

Study binders were accurate, contemporaneous, legible, original and attributable. There was adequate documentation to confirm the demographics of the subjects and all inclusion and exclusion criteria, the subject's exposure to the investigational product, lab results and any effects, adverse or otherwise, of the administration of investigational product.

Source records were compared to the sponsor data line listings. There were some minor discrepancies between the concomitant medications and adverse events listed in the subject notes and what was reported to the sponsor but nothing of significance. The primary endpoint was verifiable.

Of note, during the portion of the inspection covering the Investigational Pharmacy, it was discovered that the unblinding envelope was not among the contents of the binder and could not be found. On 2/5/19, the FDA inspector received an email from the pharmacist stating she recalled shredding the unblinding envelope after final IMP accountability was performed by the monitor.

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.

{See appended electronic signature page}

Cynthia F. Kleppinger, M.D.
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.
Acting Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
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

cc:

Central Doc. Rm./ NDA 201280
DMEP/Acting Division Director/ Lisa Yanoff
DMEP /Acting Deputy Director/William Chong
DMEP/Team Lead/ Tania Condarco
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/Acting Team Leader/Min Lu
OSI/DCCE/GCPAB Reviewer/Cynthia Kleppinger
OSI/DCCE/GCPAB/Program Analyst/Yolanda Patague
OSI/DCCE/Database Project Manager/Dana Walters

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/

CYNTHIA F KLEPPINGER
05/22/2019 03:26:14 PM

MIN LU
05/22/2019 03:39:51 PM

KASSA AYALEW
05/22/2019 03:40:40 PM

MEMORANDUM

REVIEW OF REVISED 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:	February 1, 2019
Requesting Office or Division:	Division of Metabolism and Endocrinology Products (DMEP)
Application Type and Number:	NDA 201280/S-018 NDA 201281/S-022 NDA 208026/S-008 NDA 206073/S-017
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/1000 mg Glyxambi (empagliflozin and linagliptin) tablet, 10 mg/5 mg and 25 mg/5 mg
Applicant/Sponsor Name:	Boehringer Ingelheim Pharmaceuticals
FDA Received Date:	September 5, 2018, September 12, 2018, November 9, 2018
OSE RCM #:	2018-2090
DMEPA Safety Evaluator:	Ariane O. Conrad, PharmD, BCACP, CDE
DMEPA Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

The Division of Metabolism and Endocrinology Products (DMEP) requested that we review 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.

Boehringer Ingelheim submitted efficacy supplements to propose revised labeling on September 5, 2018 and September 12, 2018. They propose revisions based on the results of a study entitled "A Multicenter, International, Randomized, Parallel Group, Double-blind, Placebo Controlled Cardiovascular Safety and Renal Microvascular Outcome Study with Linagliptin, 5 mg Once Daily in Patients with Type 2 Diabetes Mellitus at High Vascular Risk," (CARMELINA). The CARMELINA trial was conducted to fulfil PMR 1766-4 for Tradjenta (NDA 201280). Thus, they have proposed changes to various sections of the prescribing information (b) (4)

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 guide 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

Tradjenta Prescribing Information received on September 5, 2018

- \\cdsesub1\evsprod\nda201280\0203\m1\us\proposed.doc

Jentadueto Prescribing Information received on September 12, 2018

- \\cdsesub1\evsprod\nda201281\0141\m1\us\proposed.doc

Jentadueto XR Prescribing Information received on September 12, 2018

- \\cdsesub1\evsprod\nda208026\0053\m1\us\proposed.doc

Glyxambi Prescribing Information received on November 9, 2018

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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/

ARIANE O CONRAD
02/01/2019 03:06:17 PM

HINA S MEHTA
02/01/2019 10:49:10 PM

MEMORANDUM

OSI/DCCE CONSULT: CLINICAL INSPECTIONS REQUEST

CDER's Clinical Investigator Site Selection Tool Generated

Date: 11/7/2018

To: Ni Khin, M.D., Division Director, DCCE
Kassa Ayalew, M.D., M.P.H, Branch Chief, GCPAB

Cynthia Kleppinger, M.D., Senior Medical Officer
Division of Clinical Compliance Evaluation
Office of Scientific Investigations
Office of Compliance/CDER

Through: Hyon J. Kwon, Pharm.D., M.P.H., Senior Clinical Analyst
Tania Condarco, M.D., Clinical Team Leader

From: Richard Whitehead, M.S., Regulatory Project Manager
Division of Metabolism and Endocrinology Products (DMEP)

Subject: Request for Clinical Site Inspections

I. General Information

Application: NDA 201280 S018 (linked to NDA 201281/S-022-Jentadueto [linagliptin and metformin] NDA 206073/S-017 Glyxambi [empagliflozin and linagliptin] NDA 208026/S-008-Jentadueto XR [linagliptin and metformin Extended-Release])

IND 70963
Applicant: Boehringer Ingelheim Pharmaceuticals, Inc.
Phone: 203-798-9988
Regulatory Point of Contact:
Renee Zindell, M.S., RAC, Sr. Associate Director, Regulatory Affairs
Phone: 203-798-5419 Email: renee.zindell@boehringer-inglheim.com

Drug Proprietary Name: Tradjenta
Generic Drug Name: Linagliptin
NME or Original BLA (Yes/No): No
Review Priority (Standard or Priority): Standard

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
FDA.GOV

Study Population includes < 17 years of age (Yes/No): No
Is this for Pediatric Exclusivity (Yes/No): No

Proposed New Indication(s): PMR Cardiovascular Risk Study in patients with Type 2 diabetes mellitus

Submission Date: 5 Sept 2018
PDUFA: 5 July 2019
Action Goal Date: 5 July 2019
Inspection Summary Goal Date: 27 May 2019

II. Protocol/Site Identification

(Name, Address, Phone number, email, fax#)	Site #	Protocol ID	Number of Subjects	Study Title
Robert Anderson 601 North 30th Street Omaha, NE 68131 (b) (6)	4075	1218_0022	20	CARMELINA
Diana-Hortensia Barbonta Str. Closca nr. 6 bl. 4 BCDEF, ap. 70 Alba Iulia, 510053 Romania (b) (6)	2611	1218_0022	122	CARMELINA
Leslie Forgosh 45 West 10th Street St. Paul, MN 55102 (b) (6)	4245	1218_0022	37	CARMELINA
Iwona Kobielusz-Gembala ul. Plac Kosciuszki 12 Oswiecim, 32-600 Poland (b) (6)	2501	1218_0022	52	CARMELINA
Stanislaw Mazur ul. Szopena 1 Rzeszow, 35-055 Poland (b) (6)	2516	1218_0022	107	CARMELINA
Virginia Savin 4810 East Linwood Boulevard Kansas City, MO 64128 (b) (6)	4111	1218_0022	36	CARMELINA

III. Site Selection/Rationale

Site Information

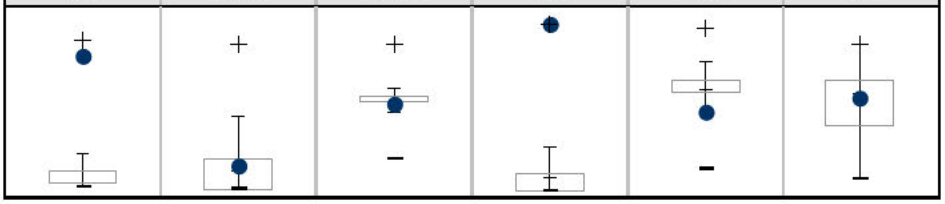
STUDY:	1218_0022	SITEID:	2611

NAME	Barbonta, Diana-Hortensia
LOCATION	Str. Closca nr. 6, bl. 4 BCDEF, ap. 70 Alba Iulia, , ROU 510053
PHONE/FAX	(b) (6)
EMAIL	(b) (6)

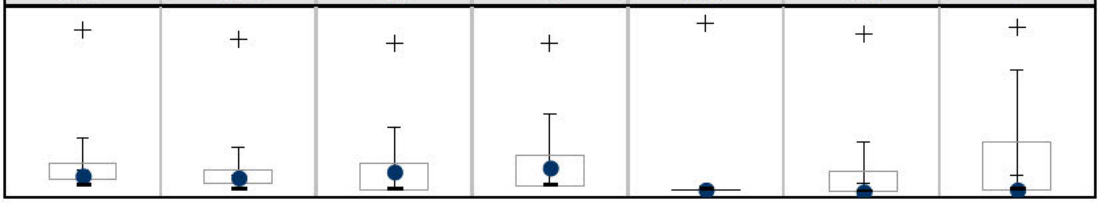
RANK	2	FINLDISC	0	COMPLAINT	0
SITE RISK	13.4	OAI	0	TSLI	3

Site Values vs. Overall Study Results

	ENROLL	TRTEFFR	SITEEFFE	EW_TRTEFFR	EW_SITEEFFE	SCREEN
Max	137	1.00	1.00	19.00	5.00	1.00
Study Rate	12	0.12	0.01	1.44	0.05	.66
Min	1	0.00	-1.00	0.00	-6.21	.06
Site	122	0.16	-0.03	19.00	-1.68	.63



	NSAE	SAE	DEATH	DISCONT	PROTVIOL	INDS	EXPERIENCE
Max	55.00	12.00	1.00	1.00	1.14	12.64	37
Study Rate	5.42	1.03	.11	.12	0.01	0.57	3
Min	0.00	0.00	.00	.00	0.00	0.00	0
Site	2.85	0.89	.12	.12	0.00	0.00	0



Site Memo

Barbonta. Romania. Ranked #2. Enrolled 122. Audited by sponsor. Has never been inspected.

Site Information

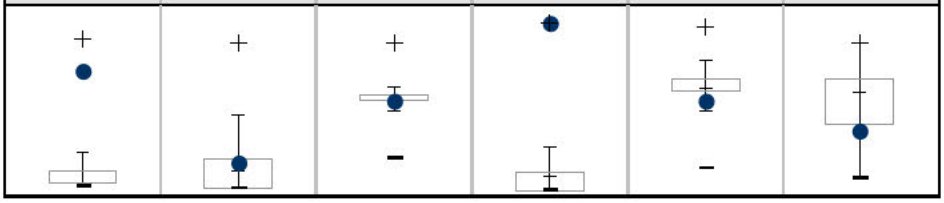
STUDY:	1218_0022	SITEID:	2516

NAME	Mazur, Stanislaw
LOCATION	ul. Szopena 1 Rzeszow, , POL 35-055
PHONE/FAX	(b) (6)
EMAIL	(b) (6)

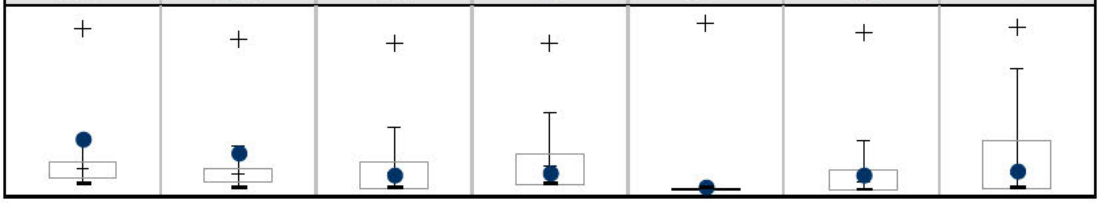
RANK	4	FINLDISC	0	COMPLAINT	0
SITE RISK	12.3	OAI	0	TSLI	3

Site Values vs. Overall Study Results

	ENROLL	TRTEFFR	SITEEFFE	EW_TRTEFFR	EW_SITEEFFE	SCREEN
Max	137	1.00	1.00	19.00	5.00	1.00
Study Rate	12	0.12	0.01	1.44	0.05	.66
Min	1	0.00	-1.00	0.00	-6.21	.06
Site	107	0.18	-0.02	19.00	-0.81	.40



	NSAE	SAE	DEATH	DISCONT	PROTVIOL	INDS	EXPERIENCE
Max	55.00	12.00	1.00	1.00	1.14	12.64	37
Study Rate	5.42	1.03	.11	.12	0.01	0.57	3
Min	0.00	0.00	.00	.00	0.00	0.00	0
Site	15.97	2.79	.08	.08	0.01	1.25	4



Site Memo

Mazur. Poland. Ranked #4. Enrolled 107. Very high safety numbers. Has never been inspected.

Site Information

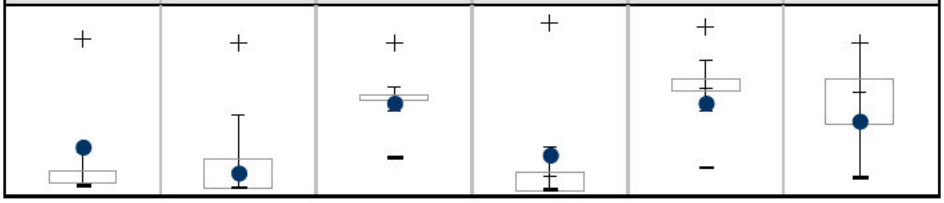
STUDY:	1218_0022	SITEID:	4245

NAME	Forgosh, Leslie
LOCATION	45 West 10th Street St. Paul, MN, USA 55102
PHONE/FAX	(b) (6)
EMAIL	(b) (6)

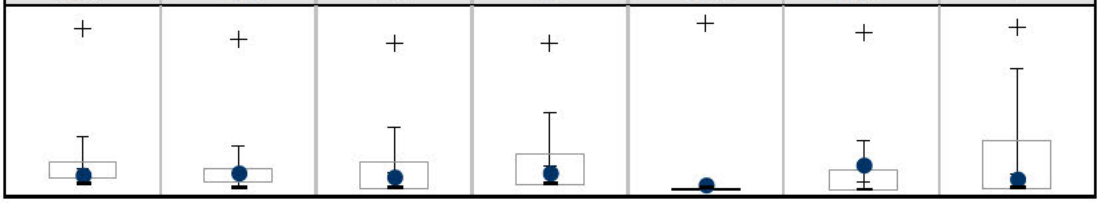
RANK	54	FINLDISC	0	COMPLAINT	0
SITE RISK	5.6	OAI	0	TSLI	3

Site Values vs. Overall Study Results

	ENROLL	TRTEFFR	SITEEFFE	EW_TRTEFFR	EW_SITEEFFE	SCREEN
Max	137	1.00	1.00	19.00	5.00	1.00
Study Rate	12	0.12	0.01	1.44	0.05	.66
Min	1	0.00	-1.00	0.00	-6.21	.06
Site	37	0.11	-0.04	4.00	-0.93	.47



	NSAE	SAE	DEATH	DISCONT	PROTVIOL	INDS	EXPERIENCE
Max	55.00	12.00	1.00	1.00	1.14	12.64	37
Study Rate	5.42	1.03	.11	.12	0.01	0.57	3
Min	0.00	0.00	.00	.00	0.00	0.00	0
Site	3.38	1.24	.08	.08	0.03	2.00	2



Site Memo

Forgosh. US site. Ranked #54. Highest US enrolling site with 37 subjects. Slightly higher than average protocol deviations. Site has never been inspected.

Site Information

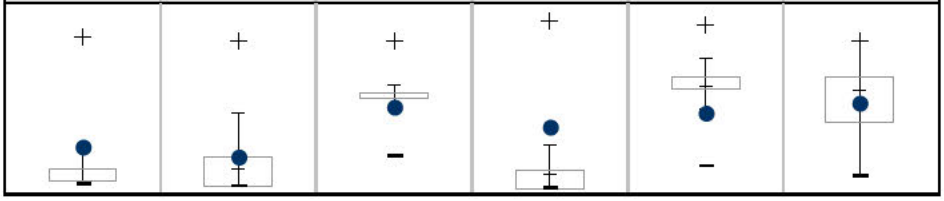
STUDY:	1218_0022	SITEID:	4111

NAME	Savin, Virginia
LOCATION	4810 East Linwood Boulevard Kansas City, MO, USA 64128
PHONE/FAX	(b) (6)
EMAIL	(b) (6)

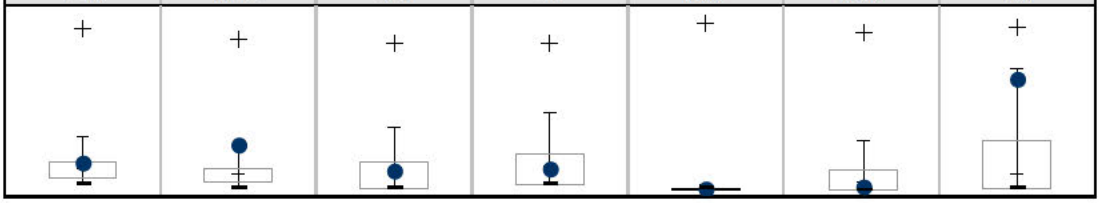
RANK	59	FINLDISC	0	COMPLAINT	0
SITE RISK	5.4	OAI	0	TSLI	3

Site Values vs. Overall Study Results

	ENROLL	TRTEFFR	SITEEFFE	EW_TRTEFFR	EW_SITEEFFE	SCREEN
Max	137	1.00	1.00	19.00	5.00	1.00
Study Rate	12	0.12	0.01	1.44	0.05	.66
Min	1	0.00	-1.00	0.00	-6.21	.06
Site	36	0.19	-0.13	7.00	-2.00	.57



	NSAE	SAE	DEATH	DISCONT	PROTVIOL	INDS	EXPERIENCE
Max	55.00	12.00	1.00	1.00	1.14	12.64	37
Study Rate	5.42	1.03	.11	.12	0.01	0.57	3
Min	0.00	0.00	.00	.00	0.00	0.00	0
Site	7.44	3.42	.11	.11	0.00	0.28	25



Site Memo

Savin. US site. Ranked #59. Second highest US enroller with 36 subjects. Higher than average SAEs. The site has never been inspected.

Site Information

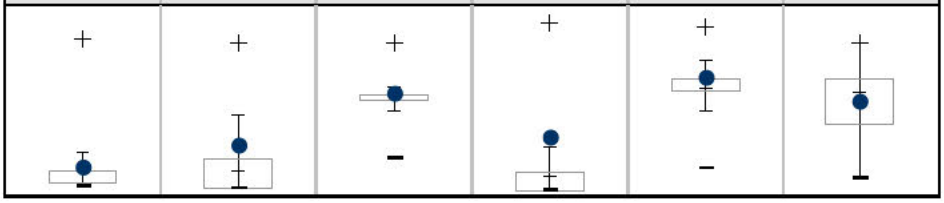
STUDY:	1218_0022	SITEID:	4075

NAME	Anderson, Robert
LOCATION	601 North 30th Street Omaha, NE, USA 68131
PHONE/FAX	(b) (6)
EMAIL	(b) (6)

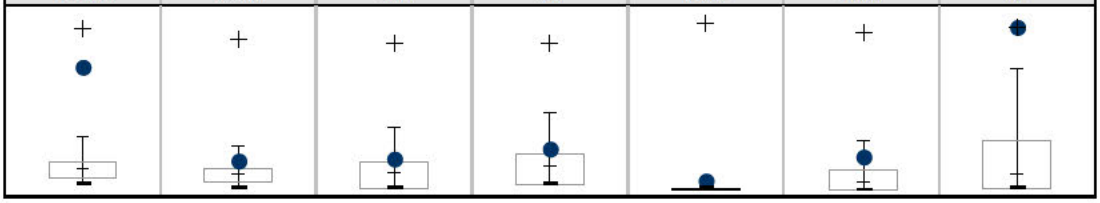
RANK	87	FINLDISC	0	COMPLAINT	0
SITE RISK	4.2	OAI	0	TSLI	3

Site Values vs. Overall Study Results

	ENROLL	TRTEFFR	SITEEFFE	EW_TRTEFFR	EW_SITEEFFE	SCREEN
Max	137	1.00	1.00	19.00	5.00	1.00
Study Rate	12	0.12	0.01	1.44	0.05	.66
Min	1	0.00	-1.00	0.00	-6.21	.06
Site	20	0.30	0.13	6.00	1.00	.61



	NSAE	SAE	DEATH	DISCONT	PROTVIOL	INDS	EXPERIENCE
Max	55.00	12.00	1.00	1.00	1.14	12.64	37
Study Rate	5.42	1.03	.11	.12	0.01	0.57	3
Min	0.00	0.00	.00	.00	0.00	0.00	0
Site	41.55	2.10	.20	.25	0.05	2.59	37



Site Memo

Anderson. US site. Ranked #87. Enrolled 20. Very high safety numbers and high discontinuations. Site has never been inspected.

Site Information

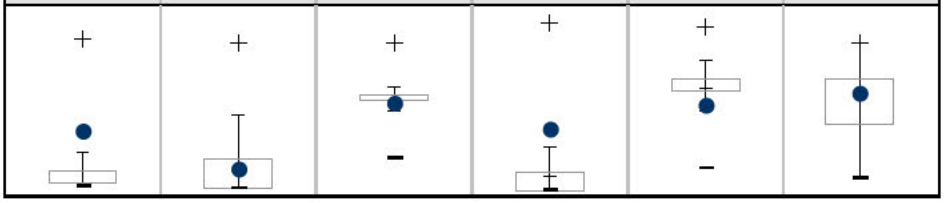
STUDY:	1218_0022	SITEID:	2501

NAME	Kobielusz-Gembala, Iwona
LOCATION	ul. Plac Kosciuszki 12 Oswiecim, , POL 32-600
PHONE/FAX	(b) (6)
EMAIL	(b) (6)

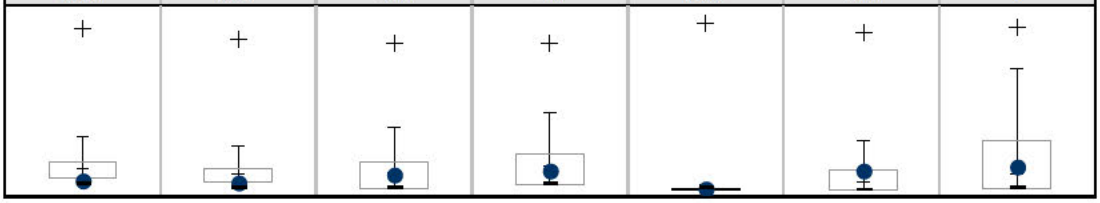
RANK	3	FINLDISC	0	COMPLAINT	1
SITE RISK	12.6	OAI	0	TSLI	3

Site Values vs. Overall Study Results

	ENROLL	TRTEFFR	SITEEFFE	EW_TRTEFFR	EW_SITEEFFE	SCREEN
Max	137	1.00	1.00	19.00	5.00	1.00
Study Rate	12	0.12	0.01	1.44	0.05	.66
Min	1	0.00	-1.00	0.00	-6.21	.06
Site	52	0.13	-0.04	7.00	-1.21	.66



	NSAE	SAE	DEATH	DISCONT	PROTVIOL	INDS	EXPERIENCE
Max	55.00	12.00	1.00	1.00	1.14	12.64	37
Study Rate	5.42	1.03	.11	.12	0.01	0.57	3
Min	0.00	0.00	.00	.00	0.00	0.00	0
Site	0.90	0.37	.10	.10	0.00	1.60	5



Site Memo

Kobielusz-Gembala. Poland. Ranked #3. Enrolled 52. History of previous complaint. Has never been inspected.

Domestic Inspections:

Reasons for inspections (please check all that apply):

- ✓ Enrollment of large numbers of study subjects
- _ High treatment responders (specify):
- _ Significant primary efficacy results pertinent to decision-making
- _ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
- ✓ Other (specify): High safety numbers; history of previous complaint.

International Inspections:

Reasons for inspections (please check all that apply):

- _ There are insufficient domestic data
- _ Only foreign data are submitted to support an application
- _ Domestic and foreign data show conflicting results pertinent to decision-making
- _ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
- ✓ Other (specify): Eastern Europe and Latin America enrolled the most subjects. High enrollment numbers at sites.

Five or More Inspection Sites *(delete this if it does not apply)*:

We have requested these sites for inspection (international and/or domestic) because of the following reasons: Very large multinational trial enrolling 12,280 subjects. Need adequate number of inspected sites to reflect size of trial. The US had the most subjects randomized per country (1056), but Eastern Europe and Latin America had the most by region and, overall, enrolled 4x more subjects.

Note: International inspection requests or requests for five or more inspections require sign-off by the OND Division Director and forwarding through the Director, DCCE.

Should you require any additional information, please contact KC Kwon at 301-796-0190 or Richard Whitehead at 301-796-4945.

Concurrence: (as needed)

_____ Medical Team Leader
_____ Medical Reviewer
_____ Division Director (for foreign inspection requests or requests for 5 or more sites only)

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
11/07/2018

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206073Orig1s017

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 206073 SUPPL # 017 HFD # 510

Trade Name Glyxambi

Generic Name empagliflozin and linagliptin

Applicant Name Boehringer Ingelheim Pharmaceuticals, Inc.

Approval Date, If Known July 3, 2019

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:

The supplement fulfills the objectives of PMR 1766-4 issued to NDA 201280 to evaluate the effects of Tradjenta (linagliptin) tablets on cardiovascular events, immunological and hypersensitivity reactions (including serious skin and/or mucosal

reactions), neoplasms, serious hypoglycemia, pancreatitis, and renal safety. Linagliptin-containing products were updated with new safety data from the trial conducted to address the PMR.

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 NDFA201280/S-018 (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 ☐

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 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:

(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 1218.22 A multicenter, international, randomized, parallel group, doubleblind, placebo-controlled **CA**rdiovascular Safety & **R**enal **M**icrovascular outcom**E** study with **LINA**gliptin, 5 mg once daily in patients with type 2 diabetes mellitus at high vascular risk. CARMELINA

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 1218.22 in NDA 201280/S-18 Tradjenta (approved concurrently on 7/3/2019)

PLEASE NOTE that the following four SE8 supplements were approved concurrently for changes which were supported by Study 1218.22 (CARMELINA):

- NDA 201280/S-018 Tradjenta (linagliptin) tablets
- NDA 201281/S-022 Jentadueto (linagliptin and metformin hydrochloride) tablets
- NDA 206073/S-017 Glyxambi (empagliflozin and linagliptin) tablets
- NDA 208026/S-008 Jentadueto XR (linagliptin and metformin hydrochloride extended-release) tablets

Supplement NDA 201280/S-018 containing Study 1218.22 was received on September 5, 2018. Supplements NDA 201281/S-022, NDA 206073/S-017, and NDA 208026/S-008 were received on September 12, 2018, and contained cross-references to Study 1218.22 in NDA 201280/S-018. All four supplements were approved concurrently on July 3, 2019, 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 Study 1218.22 study report eCTD SEQ 0529 / SN 0745 submitted on September 10, 2018

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 ☐ ! NO ☐

Explain:	! Explain:
Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! 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 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: Michael G. White, Ph.D.
Title: Senior Regulatory Project Manager
Date: July 2, 2019

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
07/03/2019 11:07:19 AM

PATRICK ARCHDEACON
07/03/2019 12:51:31 PM
On behalf of Lisa Yanoff