CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206073Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

BIOPHARMACEUTICS REVIEW ADDENDUM
Office of New Drug Quality Assessment

Application No.:	NDA 206-073	**Reviewer:** Kareen Riviere, Ph.D.	
Submission Date(s):	1/30/14; 6/3/14		
Division:	DMEP	**Secondary Signature:** Tapash Ghosh, Ph.D.	
Applicant:	Boehringer Ingelheim Pharmaceuticals, Inc.	**Supervisor:** Paul Seo, Ph.D.	
Trade Name:	Glyxambi	**Date Assigned:**	1/30/14
Generic Name:	empagliflozin/linagliptin fixed-dose combination tablets	**Date of Review:**	10/15/14
Indication:	adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus	**Type of Submission:** 505(b)(1) New Drug Application	
Formulation/strengths:	IR Tablet; 10 mg/5 mg and 25 mg/5mg		
Route of Administration:	Oral		

In the Biopharmaceutics review dated September 16, 2014, Dr. Kareen Riviere stated that Glyxambi (empagliflozin/linagliptin) 10 mg/5 mg and 25 mg/5mg immediate release tablets are recommended for approval from a Biopharmaceutics standpoint pending the OSI inspection results for the pivotal BE Study 1275.3. In the OSI inspection report for Study 1275.3 dated October 3, 2014, Drs. Seongeun (Julia) Cho and Sripal R. Mada stated:

> *Based on the inspectional outcomes, these reviewers conclude that the clinical and analytical portions of the Study 1275.003 are acceptable for further Agency review.*

Thus, NDA 206-073 for Glyxambi (empagliflozin/linagliptin) 10 mg/5 mg and 25 mg/5mg immediate release tablets is recommended for approval from the Biopharmaceutics perspective.

Kareen Riviere, Ph.D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Tapash Ghosh, Ph.D.
Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

cc: Dr. Paul Seo

Reference ID: 3643612

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/s/

KAREEN RIVIERE
10/15/2014

TAPASH K GHOSH
10/15/2014

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA:	206073
Submission Date(s):	January 30, 2014
Brand Name	Glyxambi
Generic Name	Empagliflozin / Linagliptin FDC
OCP Division	Clinical Pharmacology -2
OND division	Metabolism and Endocrinology Products
Sponsor	Boehringer Ingelheim Pharmaceuticals, Inc.
Submission Type; Code	NDA 505(b)(1); Standard
Formulation; Strength(s)	Tablets: • 10 mg empagliflozin/5 mg linagliptin • 25 mg empagliflozin/5 mg linagliptin
Proposed Indication	• Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when both empagliflozin and linagliptin is appropriate.
Dosage & Administration	• The recommended starting dose of Glyxambi is 10 mg empagliflozin/5 mg linagliptin once daily. • Dose can be increased to 25 mg empagliflozin/5 mg linagliptin once daily in patients who require additional glycemic control. • Glyxambi can be taken with or without food. • Do not initiate Glyxambi if eGFR is below 45 mL/min/1.73 m^2
Clinical Pharmacology Reviewer	Suryanarayana Sista, PhD
Clinical Pharmacology Team Leader (Acting)	Manoj Khurana, PhD

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1 Executive Summary

Boehringer Ingelheim Pharmaceuticals, Incorporated Inc. (BI) is seeking US marketing approval for Glyxambi® tablets under the provisions of Section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act. Glyxambi is a fixed-dose combination (FDC) product of empagliflozin, a sodium-glucose co-transporter 2 (SGLT2) inhibitor, and linagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor. Empagliflozin (Jardiance®, NDA 204629, BI) and linagliptin (Tradjenta®, NDA 201280, BI) were approved by the Agency on 08/01/2014 and 05/02/2011, respectively. The proposed indication of Glyxambi tablets is "adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both empagliflozin and linagliptin is appropriate".

If approved, Glyxambi will be the first SGLT2/DPP-4 FDC to enter the market.

1.1 Recommendation

The Office of Clinical Pharmacology (OCP) has reviewed the clinical pharmacology data submitted under NDA 206073 and finds it acceptable to support the approval.

1.2 Phase IV Commitments

None.

1.3 Summary of Important Clinical Pharmacology Findings

Empagliflozin / linagliptin film-coated tablets, (Glyxambi) are manufactured in strengths of 10 mg / 5 mg, and 25 mg / 5 mg, and contain 10 mg or 25 mg of empagliflozin and 5 mg of linagliptin.

The sponsor has proposed the recommended starting dose of Glyxambi of 10 mg empagliflozin/5 mg linagliptin once daily. In patients who require additional glycemic control, the dose can be increased to 25 mg empagliflozin / 5 mg linagliptin once daily. The sponsor also proposed that Glyxambi can be taken with or without food.

This NDA is supported by data from <u>one</u> bioequivalence (BE) and food-effect trial (Study 1275.3), <u>one</u> multiple-dose relative bioavailability study (Study 1245.3), and <u>one</u> safety and efficacy trial (1275.1).

Evaluation of BE portion of study 1275.3 was conducted by the ONDQA reviewer. The review has concluded that the proposed tablet containing 25 mg empagliflozin and 5 mg linagliptin is bioequivalent to the individual tablets administered together (see review by Dr. Kareen Riviere in DARRTS dated 09/16/2014).

The multiple-dose relative bioavailability study (Study 1245.3) has already been reviewed under NDA 204629 (see Clinical Pharmacology review by Dr. Manoj Khurana in DARRTS dated 11/08/2013). In brief, relative bioavailability of empagliflozin and of linagliptin after concomitant multiple oral administration of 50 mg empagliflozin tablets and 5 mg linagliptin were evaluated in comparison to 50 mg empagliflozin and 5 mg linagliptin given alone. The steady-state bioavailability of 5 mg linagliptin q.d. (based on $AUC_{\tau,ss}$ and $C_{max,ss}$) was not affected by concomitant administration of 50 mg empagliflozin q.d. The 90% confidence intervals of the adjusted geometric mean ratios for linagliptin were completely located within the limits of 80 to 125%. For empagliflozin, the $AUC_{\tau,ss}$ was similar when the drug was given alone and in combination with linagliptin, but $C_{max,ss}$ was reduced by approximately 12% when the drug was co-administered with linagliptin.

The clinical pharmacology review of the food effect portion of study 1275.3 showed that:

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Food decreased the C_{max} of empagliflozin and linagliptin by 39% and 32%, respectively; however, empagliflozin and linagliptin AUCs were similar for fasting and fed treatments. This effect of food on relative BA is consistent with previous findings with Empagliflozin (Jardiance, NDA 20-4629), and Linagliptin (Tradjenta, NDA 201280). In NDA 20-4629, the sponsor reported that reduction in C_{max} of empagliflozin did not influence the amounts of glucose excreted in the urine when empagliflozin was administered in the fed state. In NDA 20-1280, the sponsor reported that despite a reduction of C_{max} under fed conditions, DPP-4 inhibition is comparable for fasted and fed linagliptin dosage regimens. Therefore, the observed food effect for the empagliflozin and linagliptin components of the FDC tablet is unlikely to be of clinical importance.

A Forest plot showing the effect of food on empagliflozin and linagliptin C_{max} and AUC is shown in Figure 1.

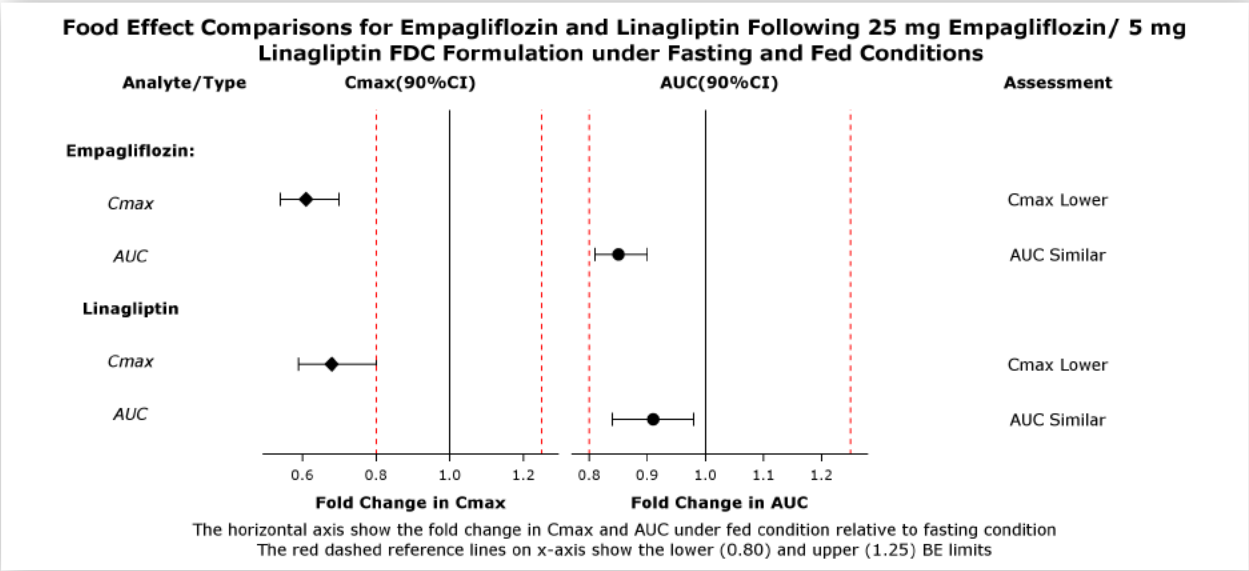

Figure 1: Food-effect Comparison for Empagliflozin and linagliptin following 25 mg Empagliflozin/5 mg Linagliptin FDC Formulation under Fasting and Fed Conditions

The efficacy results from the efficacy/safety trial (1275.1) suggest that, there is a trend for dose dependent reduction in HbA_{1c} from baseline for the FDC treatment from add-on therapy to metformin portion of the trial. There is, however, lack of clear trend for dose dependent reduction in HbA_{1c} from baseline for the FDC treatment in patients without background therapy (treatment naïve). Therefore, the additional benefit for HbA_{1c} reduction from 25 mg empagliflozin/5 mg linagliptin once daily appears to be available only in select treatment settings (add-on to metformin), as demonstrated by the data.

2 *Question-Based Review (QBR)*

2.1 What are the *in vivo* Clinical Pharmacology and Biopharmaceutics studies with PK information submitted in the NDA

The clinical pharmacology and Biopharmaceutics program performed to evaluate the bioequivalence and relative bioavailability of the Glyxambi fixed-dose combination (FDC) compared to the mono components included a single Phase 1 trial conducted in healthy volunteers (Table 1). In addition, trough concentrations of empagliflozin and linagliptin were measured in a Phase 3 trial, which evaluated the safety and efficacy of once daily oral administration of empagliflozin 25 mg/linagliptin 5 mg and

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empagliflozin 10 mg/linagliptin 5 mg FDC tablets compared with the individual components (empagliflozin 25 mg, empagliflozin 10 mg, and linagliptin 5 mg) for 52 weeks in treatment naïve and metformin treated patients with type 2 diabetes mellitus with insufficient glycemic control.

Table 1: Overview of studies with pharmacokinetic assessments relevant to the clinical pharmacology and biopharmaceutics of Glyxambi

Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
Phase I Relative Bioavailability (1275.3)					
(i) to determine the relative bioavailability of a 25 mg empagliflozin / 5 mg linagliptin fixed dose combination (FDC) tablet (formulation A1: 'FDC A1') compared with the individual tablets administered together and a second formulation of the FDC tablet (formulation A3: 'FDC A3') (ii) to assess the effect of food on the bioavailability of the FDC A1 tablet.	Open-label, randomized, single-dose, crossover design (with two 3-way crossover parts). Each subject was to receive 3 of the 4 treatments investigated.	• Treatment A: Empagliflozin 25 mg / linagliptin 5 mg FDC tablet formulation A1 (FDC A1). • Treatment B: Individual tablets of 25 mg empagliflozin and 5 mg linagliptin administered together • Treatment C: 25 mg / linagliptin 5 mg FDC A1 tablet given after a high-fat, high caloric meal. • Treatment D: A second formulation of the FDC tablet (FDC A3) All subjects were planned to receive 3 of the 4 treatments. Of the 42 entered subjects, 18 subjects were to be randomly assigned to 1 of the 6 possible sequences containing Treatments A, B, and C, whereas 24 subjects were to be randomly assigned to 1 of the 6 possible sequences containing Treatments A, B, and D. Each treatment was administered as a single dose followed by a washout phase of at least 35 days.	42 subjects randomized, 41 subjects completed the study	Healthy M or F, age 18-55 years, with a BMI of 18.5 to 29.9 kg/m^2	Treatments A, B, C and D: single-dose The subjects were to undergo 3 treatment periods and were to receive a single dose of trial medication in each treatment period. The 3 drug administrations were separated by washout phases of at least 35 days.
Phase III Safety and Efficacy (1275.1)					
To investigate the efficacy, safety, and tolerability of the fixed-dose combination (FDC) empagliflozin 25 mg/linagliptin 5 mg and of the FDC empagliflozin 10 mg/linagliptin 5	Randomized, double-blind, multi-national, parallel-group comparison study. Screened patients had to undergo a 2-week single-blinded placebo run-in period	Patients who met the eligibility criteria at the end of 2-week placebo run-in period were randomly assigned to 1 of the 5 study treatment groups (FDC empagliflozin 25 mg/linagliptin 5	Enrolled (overall): 2504 patients Entered (overall): 1363 patients	Patients aged ≥18 years with confirmed diagnosis of type 2 diabetes mellitus with insufficient glycemic control, i.e. HbA1c ≥7.0% and	Two-week single-blinded placebo run-in period followed by a 52-week double-blinded treatment period and a 4-week follow-up period

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Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
mg compared with the individual components (empagliflozin 25 mg or 10 mg, and linagliptin 5 mg) given once daily (q.d.) for 52 weeks in treatment naïve and metformin-treated patients with type 2 diabetes mellitus with insufficient glycemic control.	before randomization. Patients who successfully completed this period and who still met the entry criteria were randomized to the double-blinded 52-week treatment period followed by a 4-week follow-up period.	mg, FDC empagliflozin 10 mg/linagliptin 5 mg, empagliflozin 25 mg, empagliflozin10 mg, or linagliptin 5 mg) in a 1:1:1:1:1 ratio. Randomization was performed at Visit 3, and was stratified separately for treatment naïve and for metformin-treated patients by HbA_{1c} at screening (<8.5% or <69.4 mmol/mol, ≥8.5% or ≥69.4 mmol/mol), renal function at screening (eGFR ≥90 mL/min/1.73 m^2, 60 to 89 mL/min/1.73 m^2), and geographical region (North America, South America, Asia, and Europe). To minimize unequal treatment allocation, blocks of 10 were used for randomization, and the blocks were assigned to strata.		≤10.5% (≥53.0 mmol/mol and ≤91.3 mmol/mol); treatment naïve or pre-treated with metformin, unchanged for 12 weeks prior to randomization; and body mass index (BMI) ≤45 kg/m^2	

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2.1.1 What are the highlights of the Glyxambi drug product as they relate to clinical pharmacology review?

Empagliflozin/Linagliptin FDC tablets are arc triangular, flat faced, bevel-edged film-coated tablets. One side will be debossed with the Boehringer Ingelheim company symbol; the other side is debossed with "10/5" or "25/5" for the 10 mg empagliflozin / 5 mg linagliptin, or 25 mg empagliflozin / 5 mg linagliptin strengths, respectively.

2.1.2 What is the composition of to-be-marketed formulation of Glyxambi?

The composition of the formulations for 10 mg empagliflozin / 5 mg linagliptin, and 25 mg empagliflozin / 5 mg linagliptin strengths are shown in Table 2.

Table 2 Qualitative and quantitative composition of empagliflozin / linagliptin film-coated tablets

10 mg empagliflozin / 5 mg linagliptin			
Ingredient	**[mg / tablet]**	**Function**	**Reference to Standards**
Tablet core			
Empagliflozin	10.00	Drug substance	Company standard
Linagliptin	5.00	Drug substance	Company standard
Mannitol	(b) (4)		USP
Pregelatinized starch			NF
Corn starch			NF
Copovidone			NF
Crospovidone			NF
Talc			USP
Magnesium stearate			NF
(b) (4)			USP
Film-coat			
(b) (4)			Company standard
			USP
Total mass of film-coated tablet	**185.0**		
(b) (4)			

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Table 2 (cont.) Qualitative and quantitative composition of empagliflozin / linagliptin film-coated tablets

25 mg empagliflozin / 5 mg linagliptin			
Ingredient	**[mg / tablet]**	**Function**	**Reference to Standards**
Tablet core			
Empagliflozin	25.00	Drug substance	Company standard
Linagliptin	5.00	Drug substance	Company standard
Mannitol	(b) (4)		USP
Pregelatinized starch			NF
Corn starch			NF
Copovidone			NF
Crospovidone			NF
Talc			USP
Magnesium stearate			NF
(b) (4)			USP
Film-coat			
(b) (4)			Company standard
			USP
Total mass of film-coated tablet	**185.0**		
(b) (4)			

(Source: Glyxambi NDA eCTD module 3.2.P.1; Description and Composition 10/5mg (A144065), Table 1, page 2; Description and Composition 25/5mg (A144067), Table 1, , page 2)

2.1.3 What are the proposed mechanism of action and therapeutic indications?

Empagliflozin:

Sodium glucose co-transporter (SGLT2) is the predominant transporter responsible for reabsorption of approximately 90% of glucose from the glomerular filtrate back into the circulation. Empagliflozin inhibits SGLT2 thereby reducing renal reabsorption of glucose. This promotes increased urinary glucose excretion resulting in reduction of blood glucose levels. The amount of excess glucose removed by the kidney is dependent upon the blood glucose concentration and GFR.

A schematic of the mechanism of action of empagliflozin is shown in Figure 2.

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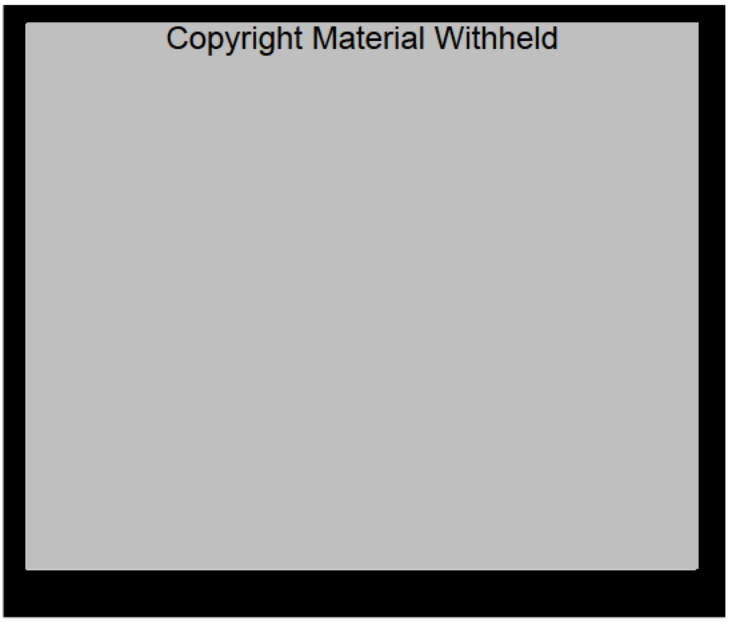

Figure 2: Empagliflozin mechanism of action

(Source: Ferrannini, E. & Solini, A. (2012) SGLT2 inhibition in diabetes mellitus: rationale and clinical prospects Nature Reviews Endocrinology 8, 495-502)

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) (Figure 3). 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.

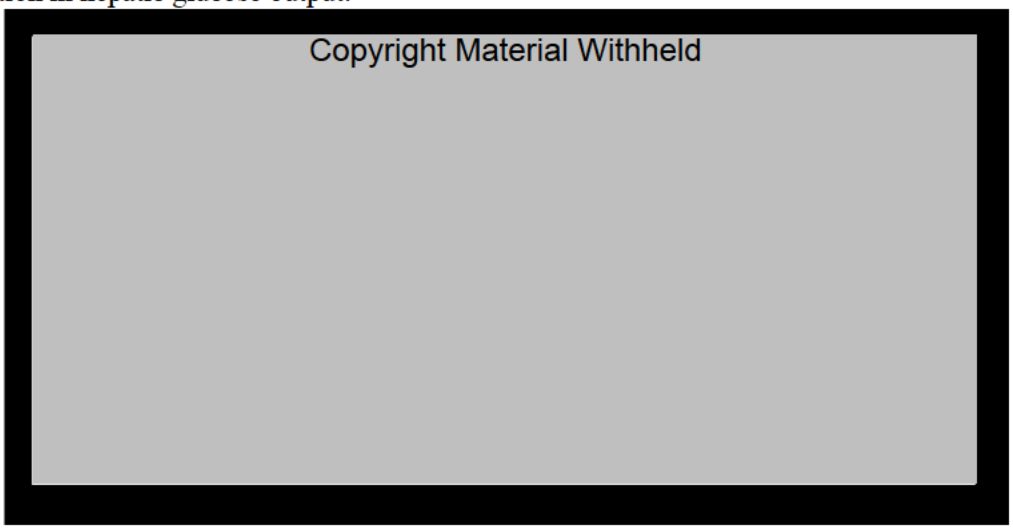

Figure 3: Linagliptin mechanism of action

(Source: May, M (2009), Nature Biotechnology 27, 682 - 685)

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2.1.4 What are the proposed dosages and routes of administration?

The proposed starting dose of Glyxambi is 10 mg empagliflozin/5 mg linagliptin once daily, administered orally. In patients who require additional glycemic control, the dose can be increased to 25 mg empagliflozin/5 mg linagliptin once daily.

2.2 General Clinical Pharmacology

2.2.1 What is known about the PK characteristics of Empagliflozin and Linagliptin following the administration of approved drugs, Jardiance and Tradjenta tablets?

Empagliflozin:

After single dose administration of 10 mg or 25 mg empagliflozin tablet formulations under fasted conditions, empagliflozin was absorbed rapidly with a median T_{max} of 1 hour for both doses. Thereafter, plasma levels declined in a biphasic fashion with a rapid distribution phase and a slower elimination phase. Empagliflozin exposure increased in proportion to the dose. Mean (%CV) AUC_{0-x} was 2360 nmol·h/L (26.7%) for the 10 mg dose and 5550 nmol·h/L (26.0%) for the 25 mg dose. Mean (%CV) C_{max} was 377 nmol/L (26.2%) and 867 nmol/L (26.8%) for the 10 mg and 25 mg dose, respectively.

The apparent steady-state volume of distribution ranged from 180-230 L. Following administration of an oral [^{14}C]-empagliflozin solution (50 mg; ~100µCi) to healthy subjects, the total radioactivity exposure in blood was lower compared to plasma, consistent with moderate red blood cell (RBC) partitioning (28.6% to 36.8%) observed *in vivo*. Protein binding of total radioactivity ranged from 80.3% to 86.2%.

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. O-dealkylation gave rise to metabolite M380/1 (EX 609), an active metabolite of empagliflozin, which was not detected in plasma after single oral doses of 0.5 to 50 mg empagliflozin; only partial profiles were obtained at doses of 100 to 800 mg empagliflozin. At the highest dose level, the EX 609 metabolite exposure (AUC and C_{max}) was approximately 0.12% of the parent drug. The total fraction of EX 609 excreted in urine ranged from 0.02 to 0.05% of the administered empagliflozin dose. *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.

The typical apparent terminal elimination half-life of empagliflozin was 12.4 h and typical apparent oral clearance was 10.6 L/h. Mass balance study showed that overall drug related radioactivity recovered in urine and feces over the 168 h study period was 95.6%. A mean of 54.4% of the dose was excreted in urine and 41.2% was excreted in feces. Approximately 50% of the drug related radioactivity excreted in urine was unchanged parent (28.6%). PKPD studies in subjects with normal renal function in general showed that fraction of empagliflozin dose excreted unchanged ranged from 13- 18%. With once-daily dosing, steady-state plasma concentrations of empagliflozin were reached by the fifth dose. Consistent with half-life, up to 22% accumulation of empagliflozin was observed.

Population pharmacokinetic/pharmacodynamic analyses suggest that dose-adjustments of Empagliflozin is not warranted based on covariates such as eGFR, body weight, age, BMI, race, and gender.

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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. No dose adjustment is needed in patients with an eGFR greater than or equal to 45 mL/min/1.73 m^2. Empagliflozin should not be initiated in patients with an eGFR less than 45 mL/min/1.73 m^2.

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:

Linagliptin follows non-linear PK for doses ranging from 1 mg to 600 mg. Increases in exposures were less than dose proportional for the dose range of 1 mg to 10 mg, more than dose proportional for the dose range of 25 mg to 100 mg, and almost dose proportional for the dose range of 100 mg to 600 mg. The non-linearity in dose range of 1 to 10 mg and long half-life of linagliptin (i.e., >100 hours) may be explained by concentration dependent binding to DPP-4. At concentrations of 1 nM, almost 99% of drug remains bound to DPP-4, which reduced to 70-80% at concentrations of about 100 nM. Following oral administration, T_{max} is reached between 0.5 to 3 h. The accumulation half-life of linagliptin ranged from 8-12 hours.

Metabolism is a minor pathway of elimination for linagliptin. The majority of drug is eliminated unchanged in feces (~85%) and a minor proportion in urine (~4.5%). Enterohepatic circulation contributes to linagliptin elimination. The predominant metabolite, CD1790 (formed by CYP3A4 isoform), is therapeutically inactive.

Co-administration with high-fat meal reduced linagliptin rate of absorption (i.e., C_{max}) by ~15 to 25% but had no effect on AUC. These changes were not considered clinically relevant. • Population PK analysis suggested that the between subject variability on clearance was low (i.e., CV% of 24%). Gamma glutamyl transferase (GGT) was a significant covariate for clearance but had no clinically meaningful effect.

No dose-adjustments are recommended for subjects with renal or hepatic impairment. Age, weight, BMI, and gender had no clinically meaningful effect of linagliptin PK. Linagliptin exposures in subjects with Japanese and Chinese ethnicity were ~25-30% higher than that of Caucasian subjects. This small change was not expected to be clinically meaningful.

2.2.2 Were the active moieties in the plasma appropriately identified and measured to assess the pharmacokinetics?

Yes. Empagliflozin and Linagliptin were appropriately identified and measured in plasma to assess the PK parameters.

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2.3 Intrinsic Factors

2.3.1 What intrinsic factors (e.g., weight, gender, race, age, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

No dedicated study was conducted with Glyxambi to evaluate the pharmacokinetics in special populations such as geriatric, hepatic impaired and renal impaired patients. The Applicant referred to information regarding special population (geriatric and renal) and drug interaction from the NDAs for Jardiance® (Empagliflozin, NDA 204629) and Tradjenta® (Linagliptin, NDA 201280).

2.4 Extrinsic Factors

2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence exposure and/or response and what is the impact of any differences in exposure on pharmacodynamics?

The effects of herbal products, smoking and alcohol on Glyxambi use were not evaluated. The sponsor conducted a specific study to investigate the effect of food on the PK of Glyxambi. This is discussed in the next section below.

2.5 General Biopharmaceutics

The sponsor conducted a relative bioavailability study to evaluate the pharmacokinetics of empagliflozin and linagliptin from the FDC tablet containing 25 mg empagliflozin and 5 mg linagliptin compared to the individual tablets administered together. This study also evaluated a second FDC formulation (A3), however, the data for this formulation will not be discussed in this review since this formulation does not represent the to-be-commercialized formulation.

2.5.1 Was bioequivalence established between Empagliflozin and Linagliptin FDC formulations and individual components?

Bioequivalence portion of this study entitled "Relative bioavailability investigations of a 25 mg empagliflozin / 5 mg linagliptin fixed dose combination (FDC) tablet (formulation A1) including the comparison with its mono-components, the comparison with a second FDC tablet (formulation A3), and the investigation of food (an open-label, randomized, single dose, crossover, Phase I trial in healthy male and female volunteers)" was evaluated by ONDQA. For details, please refer to the review by Dr. Kareen Riviere in DARRTS.

Briefly, the pharmacokinetic data demonstrate that the proposed tablet containing 25 mg empagliflozin and 5 mg linagliptin (formulation A1) is bioequivalent to the co-administered individual components.

Reference ID: 3640237

2.5.2 What is the effect of food on the bioavailability of Empagliflozin and Linagliptin from the FDC

Co-administration of Glyxambi with high-fat high-calorie diet decreased the peak systemic exposure (C_{max}) for both empagliflozin (39% decrease) and linagliptin (32% decrease), however, the extent of exposure of empagliflozin (AUC) and linagliptin was unaffected. This effect of food on relative BA is consistent with previous findings with Empagliflozin (Jardiance, NDA 20-4629), and Linagliptin (Tradjenta, NDA 20-1280). In NDA 20-4629, the sponsor reported that reduction in C_{max} of empagliflozin did not influence the amounts of glucose excreted in the urine when empagliflozin was administered in the fed state. In NDA 20-1280, the sponsor reported that despite a reduction of C_{max} under fed conditions, DPP-4 inhibition is comparable for fasted and fed linagliptin dosage regimens. Therefore, the observed food effect for the empagliflozin and linagliptin components of the FDC tablet is unlikely to be of clinical importance and the FDC can be administered with or without food.

The results of the food effect portion of study 1275.3 on the relative bioavailability of Empagliflozin and Linagliptin from the FDC formulation are summarized below.

Empagliflozin:
Mean concentration-time plots of empagliflozin following administration of the FDC formulation under fasting and fed conditions is presented in Figure 4.

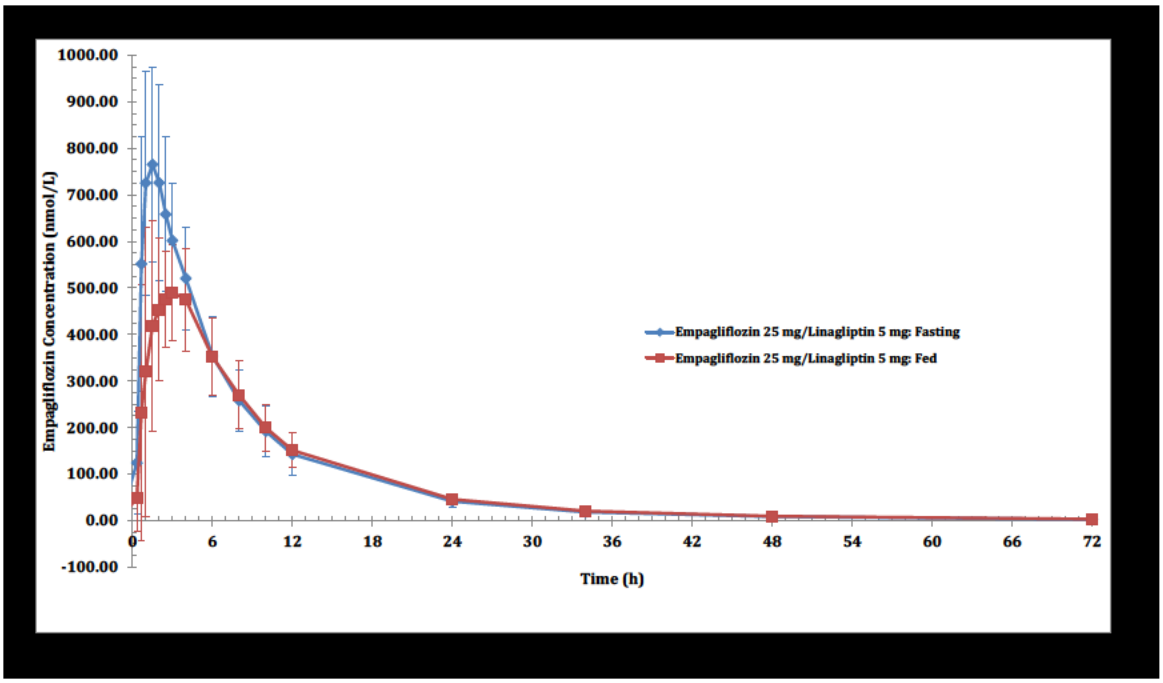

Figure 4: Mean plasma concentration time profile of empagliflozin following FDC formulation consisting of 25 mg empagliflozin and 5 mg linagliptin under fasting and fed conditions

Following administration of the 25/5 FDC tablet, a food effect on Empagliflozin PK was observed. There was a 39% reduction in C_{max} and a 15% and 14% reduction in both $AUC_{(0-t)}$ and $AUC_{(0-\infty)}$, respectively (Table 3). Though the 2 one-sided 90% confidence intervals for empagliflozin C_{max} were outside the standard bioequivalence boundaries of 80 to 125%, the corresponding 2 one-sided 90% confidence intervals for $AUC_{(0-t)}$ and $AUC_{(0-\infty)}$ were contained within the standard bioequivalence boundaries of 80 to 125% (Table 4). Box-plot distribution for the PK parameters, C_{max}, $AUC_{(0-t)}$, and $AUC_{(0-\infty)}$ are shown in Figures 5 - 7.

Reference ID: 3640237

Table 3: Summary Statistics for Empagliflozin Pharmacokinetic Parameters following administration of FDC formulation consisting of 25 mg empagliflozin and 5 mg linagliptin under fasting and fed conditions to healthy subjects

Treatment	Empagliflozin Pharmacokinetic Parameters				
	C_{max} (ng/mL) GM [n] (CV%)	$AUC_{(0-t)}$ (ng.h/mL) GM [n] (CV%)	$AUC_{(0-\infty)}$ (ng.h/mL) GM [n] (CV%)	T_{max} (h) Median [n] (Min-Max)	$t_{1/2}$ (h) Mean [n] (SD)
Fasting	948.8 [18] (24.4)	6333 [18] (16.3)	6406 [18] (16.0)	1.50 [18] (0.67 – 3.00)	13.93 [18] (5.45)
Fed	582.7 [18] (24.4)	5405 [18] (16.9)	5500 [18] (17.3)	2.00 [18] (0.67 – 4.00)	15.51 [18] (6.88)

Abbreviations: GM = geometric mean; n = number of non-missing observations; CV% = coefficient of variation; SD = standard deviation
Fasting: A single oral dose of FDC tablets (one 25-mg dapagliflozin/5 mg linagliptin) administered in the fasting state.
Fed: A single oral dose of FDC tablets (one 25-mg dapagliflozin/5 mg linagliptin) administered in the fed state.
(Source: Report of Study 1275.3; Table 15.6.2.1:5, pages 299-300; Table 15.6.2.1:7, Page 307-308)

Table 4: Bioequivalence and Food Effect Comparisons for Empagliflozin following administration of FDC formulation consisting of 25 mg empagliflozin and 5 mg linagliptin under fasting and fed conditions in healthy subjects

Treatment and Comparison	C_{max} (nmol/L) Adjusted GM (n)	$AUC_{(0-t)}$ (ng.h/mL) Adjusted GM (n)	$AUC_{(0-\infty)}$ (ng h/mL) Adjusted GM (n)
Fasting	948.8 (18)	6333 (18)	6406 (18)
Fed	582.7 (18)	5404 (18)	5500 (18)
Ratio of Adjusted GM (90% CI) [intra-individual CV(%)]			
Fed vs Fasted	61.4 (54.12, 69.74) 21.95	85.3 (80.74, 90.09) 9.41	85.9 (81.29, 90.64) 9.30

GM = geometric mean; n = number of non-missing observations
Fasting: A single oral dose of FDC tablets (one 25-mg dapagliflozin/5 mg linagliptin) administered in the fasting state.
Fed: A single oral dose of FDC tablets (one 25-mg dapagliflozin/5 mg linagliptin) administered in the fed state.
(Source: Analysis performed by reviewer using SAS v9.3)

Reference ID: 3640237

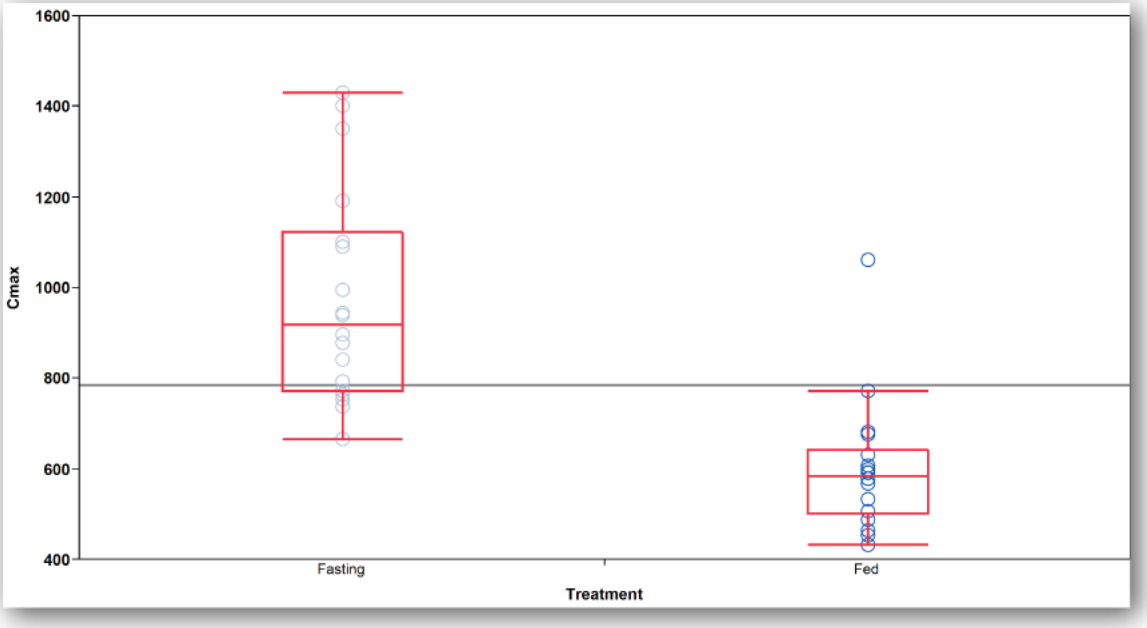

Figure 5: Boxplot of C_{max} vs. Treatment for Empagliflozin

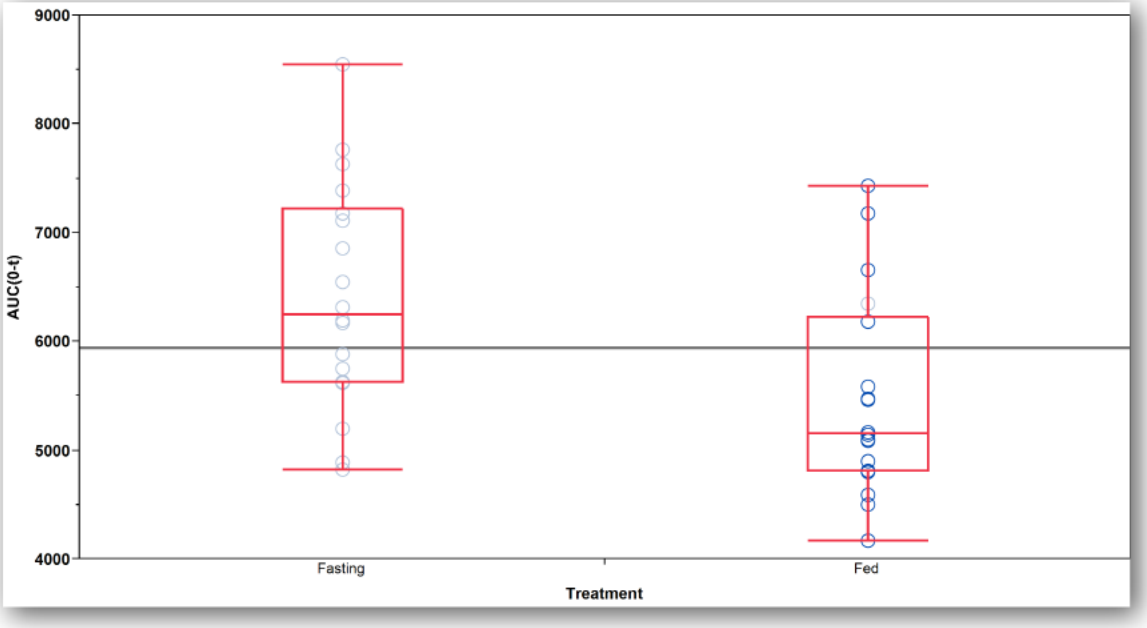

Figure 6: Boxplot of AUC_{0-t} vs. Treatment for Empagliflozin

Reference ID: 3640237

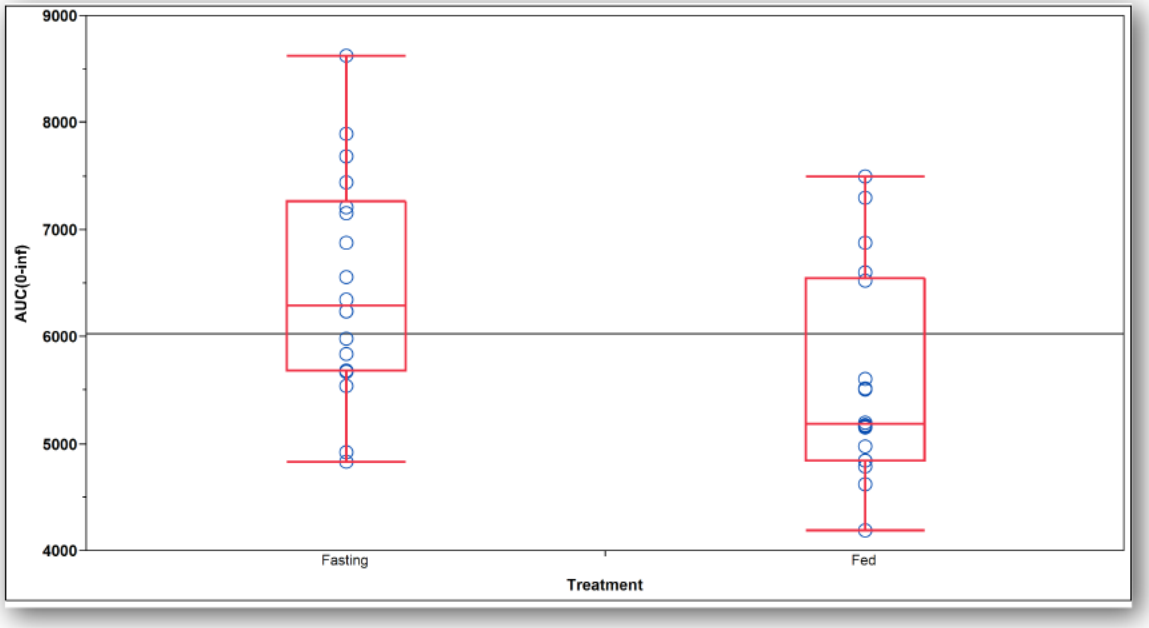

Figure 7: Boxplot of $AUC_{0-\infty}$ vs. Treatment for Empagliflozin

Linagliptin:

Mean concentration-time plot of linagliptin following administration of the FDC formulation under fasting and fed conditions is presented in Figure 8.

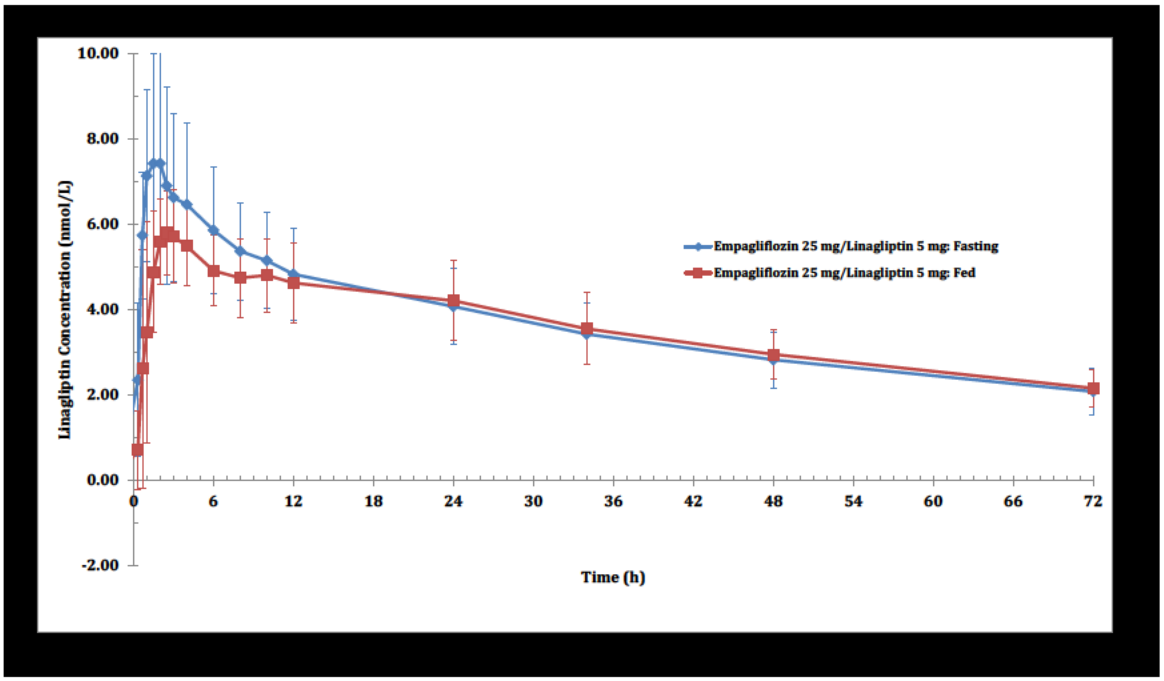

Figure 8: Mean plasma concentration time profile of linagliptin following FDC formulation consisting of 25 mg empagliflozin and 5 mg linagliptin under fasting and fed conditions

Reference ID: 3640237

Following administration of the 25/5 FDC tablet, a food effect on linagliptin PK was observed. There was a 32% reduction in C_{max} and a 9% and 7% reduction in both $AUC_{(0-t)}$ and $AUC_{(0-\infty)}$, respectively (Table 5). Though the 2-one sided 90% confidence intervals for linagliptin C_{max} were outside the standard bioequivalence boundaries of 80 to 125%, the corresponding 2-one sided 90% confidence intervals for $AUC_{(0-t)}$ and $AUC_{(0-\infty)}$ were contained within the standard bioequivalence boundaries of 80 to 125% (Table 6). Box-plot distribution for the PK parameters, C_{max}, $AUC_{(0-t)}$, and $AUC_{(0-\infty)}$ are shown in Figures 9 - 11.

Table 5: Summary Statistics for Linagliptin Pharmacokinetic Parameters following administration of FDC formulation consisting of 25 mg empagliflozin and 5 mg linagliptin under fasting and fed conditions to healthy subjects

Treatment	Linagliptin Pharmacokinetic Parameters				
	C_{max} (ng/mL) GM [n] (CV%)	$AUC_{(0-t)}$ (ng.h/mL) GM [n] (CV%)	$AUC_{(0-\infty)}$ (ng.h/mL) GM [n] (CV%)	T_{max} (h) Median [n] (Min-Max)	$t_{1/2}$ (h) Mean [n] (SD)
Fasting	8.97 [18] (38.4)	275.15 [18] (21.7)	451.67 [18] (23.9)	1.26 [18] (0.33 – 6.03)	55.1 [18] (9.44)
Fed	6.14 [18] (16.3)	250.21 [18] (19.4)	420.90 [18] (18.2)	2.25 [18] (1.00 – 4.00)	55.8 [18] (12.8)

Abbreviations: GM = geometric mean; n = number of non-missing observations; CV% = coefficient of variation; SD = standard deviation
Fasting: A single oral dose of FDC tablets (one 25-mg dapagliflozin/5 mg linagliptin) administered in the fasting state.
Fed: A single oral dose of FDC tablets (one 25-mg dapagliflozin/5 mg linagliptin) administered in the fed state.
(Source: Report of Study 1275.3; Table 15.6.2.1:1, pages 285-286; Table 15.6.2.1:3, Page 293-294)

Table 6: Bioequivalence and Food Effect Comparisons for Linagliptin following administration of FDC formulation consisting of 25 mg empagliflozin and 5 mg linagliptin under fasting and fed conditions in healthy subjects

Treatment and Comparison	C_{max} (nmol/L) Adjusted GM (n)	$AUC_{(0-t)}$ (ng.h/mL) Adjusted GM (n)	$AUC_{(0-\infty)}$ (ng h/mL) Adjusted GM (n)
Fasting	8.97 (18)	275.1 (18)	451.7 (18)
Fed	6.14 (18)	250.2 (18)	420.9 (18)
Ratio of Adjusted GM (90% CI) [intra-individual CV(%)]			
Fed vs Fasted	68.5 (58.63, 80.08) 27.16	91.0 (84.26, 98.23) 13.17	93.2 (85.03, 102.08) 15.67

GM = geometric mean; n = number of non-missing observations
Fasting: A single oral dose of FDC tablets (one 25-mg dapagliflozin/5 mg linagliptin) administered in the fasting state.
Fed: A single oral dose of FDC tablets (one 25-mg dapagliflozin/5 mg linagliptin) administered in the fed state.
(Source: Analysis performed by reviewer using SAS v 9.3)

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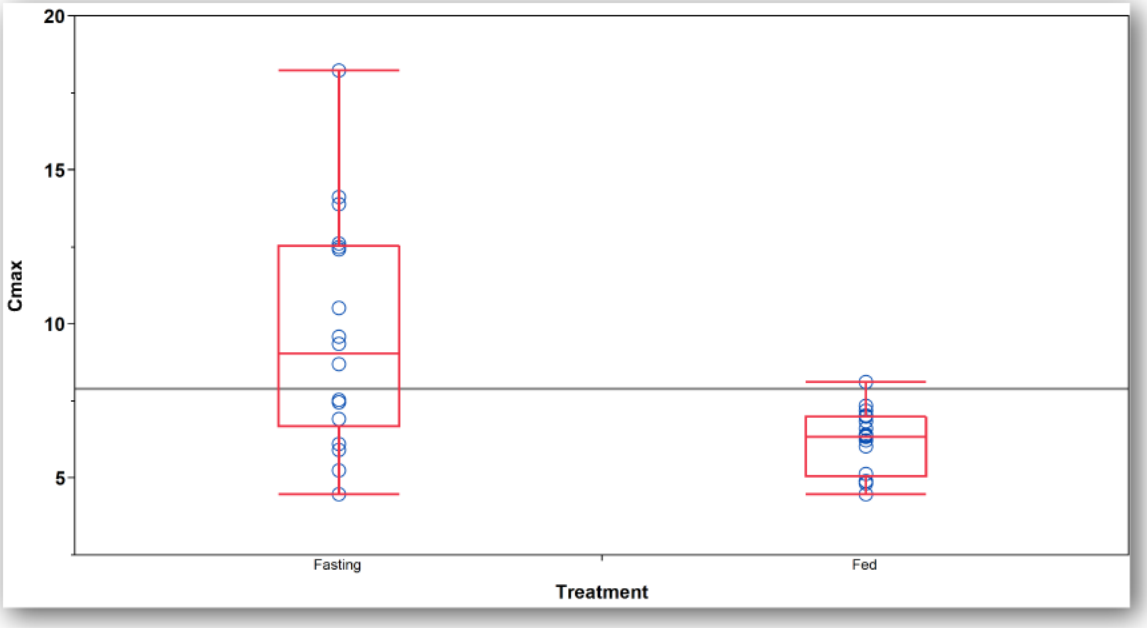

Figure 9: Boxplot of C_{max} vs. Treatment for Linagliptin

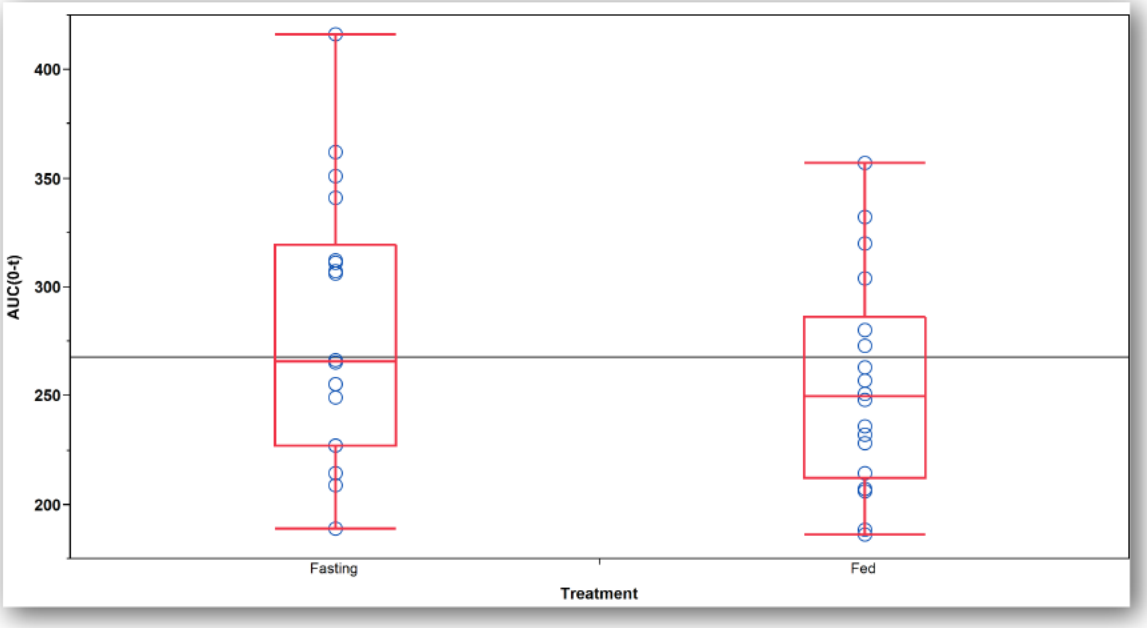

Figure 10: Boxplot of AUC_{0-t} vs. Treatment for Linagliptin

Reference ID: 3640237

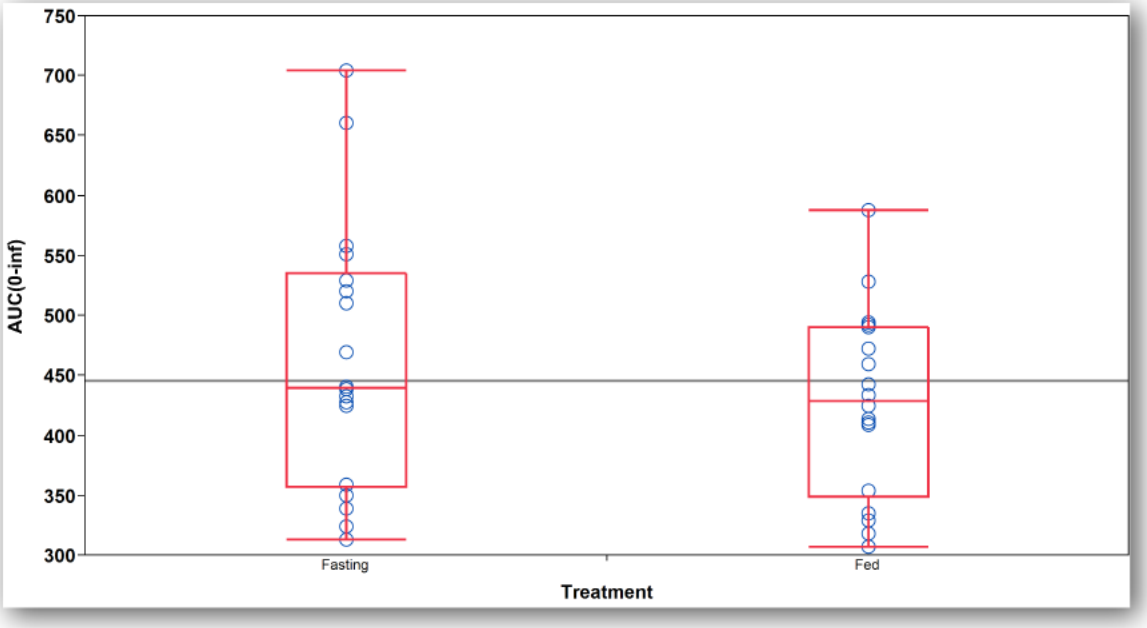

Figure 11: Boxplot of $AUC_{0-\infty}$ vs. Treatment for Linagliptin

2.5.3 How did the systemic exposure of empagliflozin and linagliptin from FDA compare to the individual treatment in the Phase III program?

Blood samples of patients who were on metformin background therapy, and treatment naïve patients were taken at Visits 4 (Day 43), 5 (Day 85), and 7 (Day 169) for analysis of trough plasma concentrations of empagliflozin and linagliptin.

Empagliflozin:

No trends in empagliflozin exposure over time between visits 4 and 7 were observed in patients who were on metformin background therapy or treatment naïve patients (Table 7):

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Table 7: Empagliflozin plasma trough concentrations (geometric mean, CV) in patients who were on metformin background therapy and treatment naïve patients from Study 1275.1

Patients on metformin background therapy									
	Visit 4			Visit 5			Visit 7		
Treatment	N	gMean (nmol/L)	gCV (%)	N	gMean (nmol/L)	gCV (%)	N	gMean (nmol/L)	gCV (%)
Empa 25 mg/Lina 5 mg	119	82.1	103	118	74.9	92.3	115	68.7	94.9
Empa 10 mg/Lina 5 mg	114	28.7	94.1	118	25.9	87.3	116	25.6	95.9
Empa 25 mg	114	58.6	107	115	58.3	96.5	107	64.8	102
Empa 10 mg	118	29.2	111	110	24.4	97.9	104	25.8	87.9
Treatment naïve patients									
	Visit 4			Visit 5			Visit 7		
Treatment	N	gMean (nmol/L)	gCV (%)	N	gMean (nmol/L)	gCV (%)	N	gMean (nmol/L)	gCV (%)
Empa 25 mg/Lina 5 mg	113	66.6	128	113	67.3	116	109	56.7	120
Empa 10 mg/Lina 5 mg	114	34.6	113	118	30.8	127	114	29.0	96.8
Empa 25 mg	117	72.5	126	119	57.6	127	108	67.1	99.0
Empa 10 mg	115	27.7	96.3	111	29.1	122	107	27.6	118

(Source: Study Report 1275.1: Table 11.A.5.2: 1 (Page 197); Table 11.B.5.2: 1 (Page 259))

The sponsor graphically summarized the plasma concentrations of empagliflozin by demographics such as age, weight, gender, race/ethnicity, geographical region, eGFR (MDRD) and eCLcr (Cockcroft-Gault). The empagliflozin trough plasma concentrations - covariate relationship was comparable among patients who were on metformin background therapy, and treatment naïve patients. No particular trends were apparent between empagliflozin trough concentrations and the tested covariates.

Linagliptin:

No trends in linagliptin exposure over time between visits 4 and 7 were observed in patients who were on metformin background therapy or treatment naïve patients (Table 8):

Table 8: Linagliptin plasma trough concentrations (geometric mean, CV) in patients who were on metformin background therapy and treatment naïve patients from Study 1275.1

Patients on metformin background therapy									
	Visit 4			Visit 5			Visit 7		
Treatment	N	gMean (nmol/L)	gCV (%)	N	gMean (nmol/L)	gCV (%)	N	gMean (nmol/L)	gCV (%)
Empa 25 mg/Lina 5 mg	121	5.71	57.8	120	5.14	60.6	116	5.45	31.5
Empa 10 mg/Lina 5 mg	118	5.02	74.2	124	4.89	59.6	118	5.25	48.2
Lina 5 mg	114	5.57	56.6	111	5.42	52.5	106	5.50	55.7
Treatment naïve patients									
	Visit 4			Visit 5			Visit 7		
Treatment	N	gMean (nmol/L)	gCV (%)	N	gMean (nmol/L)	gCV (%)	N	gMean (nmol/L)	gCV (%)
Empa 25 mg/Lina 5 mg	116	5.08	71.6	114	5.50	41.1	112	5.24	50.8
Empa 10 mg/Lina 5 mg	121	5.49	75.9	120	5.68	49.6	117	5.23	58.2
Lina 5 mg	119	5.51	57.1	118	5.47	54.3	111	5.24	68.1

(Source: Study Report 1275.1: Table 11.A.5.2: 2 (Page 198); Table 11.B.5.2: 2 (Page 260))

Similar to empagliflozin, the sponsor conducted graphical evaluation of plasma concentrations of linagliptin by demographics such as age, weight, gender, race/ethnicity, geographical region, eGFR (MDRD) and eCLcr (Cockcroft-Gault). Linagliptin trough plasma concentrations-covariate

Reference ID: 3640237

relationships were comparable among patients who were on metformin background therapy, and treatment naïve patients. No particular trends were apparent between linagliptin trough concentrations and the tested covariates.

2.6 Exposure Response

2.6.1 Is there an exposure-response (e.g. dose-response, concentration-response) relationship for effectiveness and safety for empagliflozin/linagliptin FDC in T2DM patients?

There was a trend for dose dependent reduction in HbA_{1c} from baseline for the FDC treatment, when data from add on therapy (metformin) was examined (Figure 12). (For details on the statistical analysis on dose-response, please refer to the Statistical Review by Dr. Jennifer Clark in DAARTS). As seen from data described in Tables 9 and 10, from efficacy perspective, the use of 25 mg empagliflozin/5 mg linagliptin FDC once daily produced slightly higher reduction in HbA_{1c} than the 10 mg empagliflozin/5 mg linagliptin FDC (change from baseline of -1.20 for 25/5 FDC compared to -1.07 for 10/5 FDC at 24 weeks (primary end-point); change from baseline of -1.21 for 25/5 FDC compared to -1.04 for 10/5 FDC at 52 weeks).

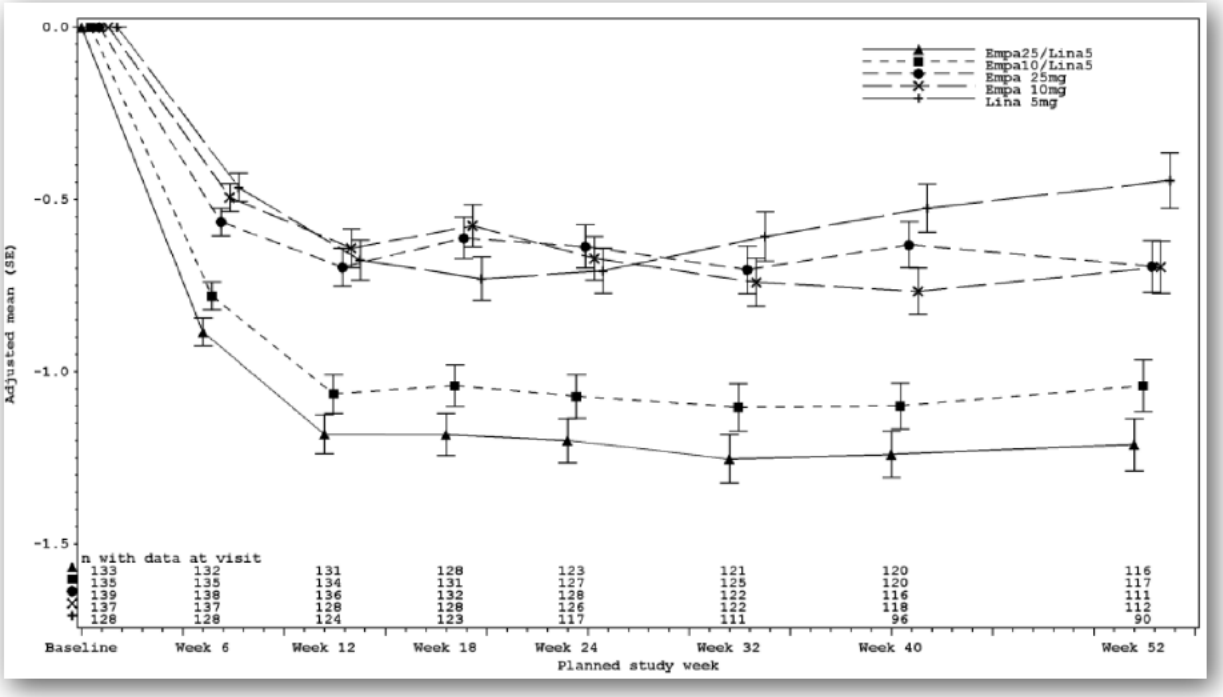

Figure 12: Adjusted mean change in HbA_{1c} (%) over time from baseline based on mixed-model repeated measures (MMRM) of the full analysis dataset (FAS) observed case (OC) (add-on therapy to metformin background)

(Source: Study Report 1275.1: Figure 11.A.4.1.1.2: 1 Adjusted mean change in HbA1c (%) over time from baseline based on MMRM– FAS (OC) (metformin) (Page 162))

Reference ID: 3640237

Table 9: HbA_{1c} (%) change from baseline MMRM results at week 24 – FAS(OC) (add-on therapy to metformin background)

Visit Description Statistic	Empa25/Lina5	Empa10/Lina5	Empa 25mg	Empa 10mg	Lina 5mg
Week 24					
Values at visit					
Number of analysed patients	123	127	128	126	117
Mean (SE)	6.67 (0.05)	6.81 (0.06)	7.28 (0.08)	7.28 (0.07)	7.26 (0.09)
Adjusted* mean (SE)	6.75 (0.06)	6.88 (0.06)	7.32 (0.06)	7.28 (0.06)	7.25 (0.07)
Change from baseline					
Mean (SE)	-1.19 (0.06)	-1.11 (0.07)	-0.73 (0.09)	-0.70 (0.07)	-0.76 (0.07)
Adjusted* mean (SE)	-1.20 (0.06)	-1.07 (0.06)	-0.64 (0.06)	-0.67 (0.06)	-0.71 (0.07)
Comparison vs Empa 25mg					
Adjusted* mean (SE)	-0.56 (0.09)				
95.0% confidence interval	(-0.74,-0.39)				
p-value	<0.0001				
Comparison vs Empa 10mg					
Adjusted* mean (SE)		-0.40 (0.09)			
95.0% confidence interval		(-0.58,-0.22)			
p-value		<0.0001			
Comparison vs Lina 5mg					
Adjusted* mean (SE)	-0.49 (0.09)	-0.36 (0.09)			
95.0% confidence interval	(-0.67,-0.31)	(-0.54,-0.19)			
p-value	<0.0001	<0.0001			

* Model includes baseline HbA1c (p<0.0001) as linear covariate(s), baseline eGFR (MDRD) (p=0.0050), geographical region (p<0.0001), treatment (p<0.0001), visit (p<0.0001) and visit by treatment interaction (p<0.0001) as fixed effect(s).

(Source: Report of Study 1275.1; Table 15.5.2.1.2:1, page 5927)

Table 10: HbA_{1c} (%) change from baseline MMRM results at week 52 – FAS(OC) (add-on therapy to metformin background)

Visit Description Statistic	Empa25/Lina5	Empa10/Lina5	Empa 25mg	Empa 10mg	Lina 5mg
Week 52					
Values at visit					
Number of analysed patients	116	117	111	112	90
Mean (SE)	6.63 (0.06)	6.82 (0.08)	7.07 (0.07)	7.14 (0.08)	7.21 (0.09)
Adjusted* mean (SE)	6.74 (0.08)	6.91 (0.07)	7.26 (0.07)	7.26 (0.08)	7.51 (0.08)
Change from baseline					
Mean (SE)	-1.22 (0.07)	-1.10 (0.09)	-0.94 (0.08)	-0.79 (0.09)	-0.62 (0.08)
Adjusted* mean (SE)	-1.21 (0.08)	-1.04 (0.07)	-0.69 (0.07)	-0.70 (0.08)	-0.45 (0.08)
Comparison vs Empa 25mg					
Adjusted* mean (SE)	-0.52 (0.11)				
95.0% confidence interval	(-0.73,-0.31)				
p-value	<0.0001				
Comparison vs Empa 10mg					
Adjusted* mean (SE)		-0.34 (0.11)			
95.0% confidence interval		(-0.55,-0.14)			
p-value		0.0013			
Comparison vs Lina 5mg					
Adjusted* mean (SE)	-0.77 (0.11)	-0.60 (0.11)			
95.0% confidence interval	(-0.98,-0.55)	(-0.81,-0.38)			
p-value	<0.0001	<0.0001			

* Model includes baseline HbA1c (p<0.0001) as linear covariate(s), baseline eGFR (MDRD) (p=0.0050), geographical region (p<0.0001), treatment (p<0.0001), visit (p<0.0001) and visit by treatment interaction (p<0.0001) as fixed effect(s).

(Source: Report of Study 1275.1; Table 15.5.2.1.2:1, page 5930)

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There is, however, lack of clear trend for dose dependent reduction in HbA_{1c} from baseline for the FDC treatment, when data from patients without background therapy (treatment naïve) was examined (Figure 13). As seen from data described in Tables 11 and 12, from efficacy perspective, the use of 25 mg empagliflozin/5 mg linagliptin FDC once daily produced slightly lower reduction in HbA_{1c} than the 10 mg empagliflozin/5 mg linagliptin FDC (change from baseline of -1.07 for 25/5 FDC compared to -1.25 for 10/5 FDC at 24 weeks (primary end-point); change from baseline of -1.18 for 25/5 FDC compared to -1.25 for 10/5 FDC at 52 weeks).

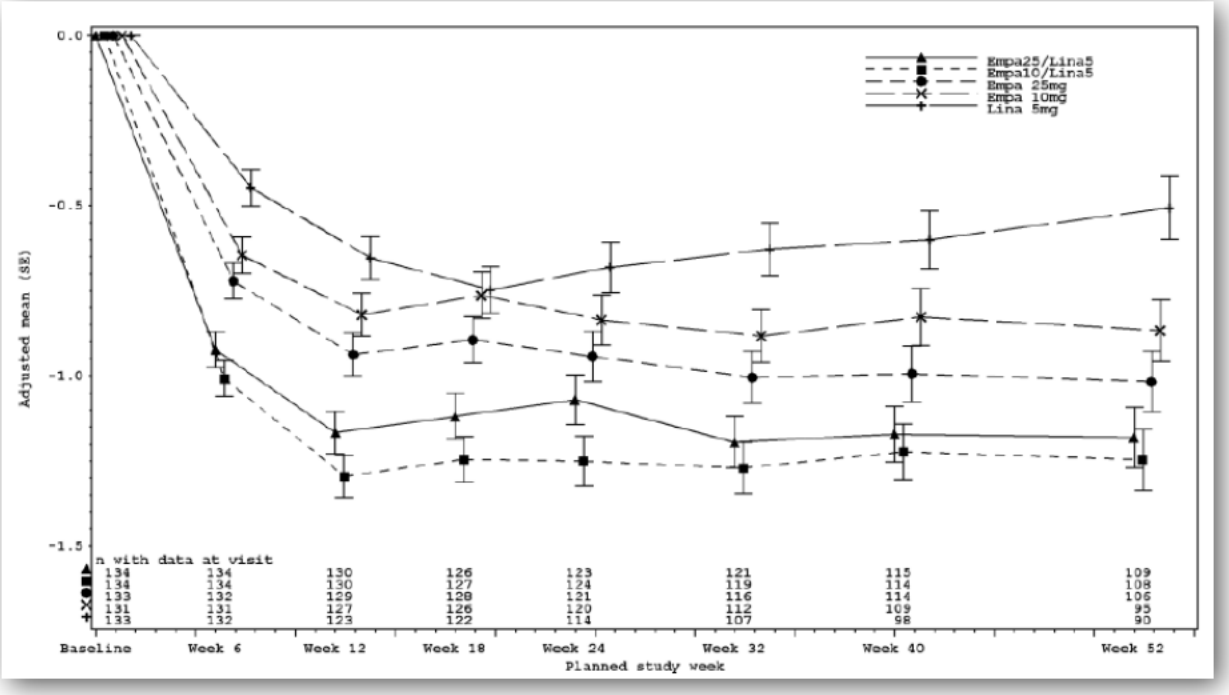

Figure 13: Adjusted mean change in HbA_{1c} (%) over time from baseline based on mixed-model repeated measures (MMRM) of the full analysis dataset (FAS) observed case (OC) (treatment naïve)

(Source: Study Report 1275.1: Figure 11.B.4.1.1.2: 1 Adjusted mean change in HbA1c (%) over time from baseline based on MMRM– FAS (OC) (treatment naïve) (page 227))

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Table 11: HbA_{1c} (%) change from baseline MMRM results at week 24 – FAS (OC) (treatment naïve)

Visit Description Statistic	Empa25/Lina5	Empa10/Lina5	Empa 25mg	Empa 10mg	Lina 5mg
Week 24					
Values at visit					
Number of analysed patients	123	124	121	120	114
Mean (SE)	6.85 (0.07)	6.74 (0.07)	6.93 (0.07)	7.08 (0.08)	7.23 (0.09)
Adjusted* mean (SE)	6.90 (0.07)	6.72 (0.07)	7.03 (0.07)	7.13 (0.07)	7.29 (0.07)
Change from baseline					
Mean (SE)	-1.09 (0.09)	-1.29 (0.08)	-0.97 (0.09)	-0.93 (0.08)	-0.78 (0.08)
Adjusted* mean (SE)	-1.07 (0.07)	-1.25 (0.07)	-0.94 (0.07)	-0.84 (0.07)	-0.68 (0.07)
Comparison vs Empa 25mg					
Adjusted* mean (SE)	-0.13 (0.10)				
95.0% confidence interval	(-0.33, 0.08)				
p-value	0.2187				
Comparison vs Empa 10mg					
Adjusted* mean (SE)		-0.41 (0.10)			
95.0% confidence interval		(-0.62,-0.21)			
p-value		<0.0001			
Comparison vs Lina 5mg					
Adjusted* mean (SE)	-0.39 (0.10)	-0.57 (0.10)			
95.0% confidence interval	(-0.59,-0.18)	(-0.77,-0.37)			
p-value	0.0002	<0.0001			

* Model includes baseline HbA1c (p<0.0001) as linear covariate(s), baseline eGFR (MDRD) (p=0.0144), geographical region (p=0.0094), treatment (p<0.0001), visit (p<0.0001) and visit by treatment interaction (p=0.0013) as fixed effect(s).

(Source: Report of Study 1275.1; Table 15.4.2.1.2:1, page 4272)

Table 12: HbA_{1c} (%) change from baseline MMRM results at week 52 – FAS (OC) (treatment naïve)

Visit Description Statistic	Empa25/Lina5	Empa10/Lina5	Empa 25mg	Empa 10mg	Lina 5mg
Week 52					
Values at visit					
Number of analysed patients	109	108	106	95	90
Mean (SE)	6.64 (0.07)	6.66 (0.09)	6.78 (0.08)	6.92 (0.10)	7.08 (0.09)
Adjusted* mean (SE)	6.79 (0.09)	6.72 (0.09)	6.95 (0.09)	7.10 (0.09)	7.46 (0.09)
Change from baseline					
Mean (SE)	-1.28 (0.09)	-1.33 (0.11)	-1.05 (0.09)	-1.03 (0.09)	-0.80 (0.11)
Adjusted* mean (SE)	-1.18 (0.09)	-1.25 (0.09)	-1.02 (0.09)	-0.87 (0.09)	-0.51 (0.09)
Comparison vs Empa 25mg					
Adjusted* mean (SE)	-0.16 (0.13)				
95.0% confidence interval	(-0.41, 0.08)				
p-value	0.1923				
Comparison vs Empa 10mg					
Adjusted* mean (SE)		-0.38 (0.13)			
95.0% confidence interval		(-0.63,-0.13)			
p-value		0.0030			
Comparison vs Lina 5mg					
Adjusted* mean (SE)	-0.67 (0.13)	-0.74 (0.13)			
95.0% confidence interval	(-0.93,-0.42)	(-0.99,-0.49)			
p-value	<0.0001	<0.0001			

* Model includes baseline HbA1c (p<0.0001) as linear covariate(s), baseline eGFR (MDRD) (p=0.0144), geographical region (p=0.0094), treatment (p<0.0001), visit (p<0.0001) and visit by treatment interaction (p=0.0013) as fixed effect(s).

(Source: Report of Study 1275.1; Table 15.4.2.1.2:1, page 4275)

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The sponsor has proposed that the recommended starting dose of Glyxambi be 10 mg empagliflozin/5 mg linagliptin once daily. In patients who require additional glycemic control, the dose can be increased to 25 mg empagliflozin/5 mg linagliptin once daily. However, the additional benefit from 25 mg empagliflozin/5 mg linagliptin once daily appears to be available only in select treatment settings (add-on to metformin in this case) as demonstrated by the data.

2.7 Analytical

2.7.1 Is the analytical method for Empagliflozin and Linagliptin appropriately validated?

Empagliflozin:

Empagliflozin in human plasma was measured using a LC-MS/MS assay. The method was validated for a range of 1.11-1110 nmol/L, based on the analysis of 0.150 mL of plasma. Briefly, empagliflozin is extracted from EDTA human plasma by solid phase supported liquid extraction (SLE+). Before the extraction, isotope-labeled drug is added as an internal standard. The sample is transferred to a 96-well diatomaceous earth extraction plate (SLE+) and allowed to absorb. The analytes are eluted with isopropyl acetate. The eluate is evaporated to dryness and the samples reconstituted with acetonitrile/water. The reconstituted samples are injected into an LC-MS/MS system using a C6-phenyl column with an ammonium acetate/acetonitrile/water mobile phase.

Linagliptin:

Linagliptin in human plasma was measured using a HPLC-MS/MS assay by (b) (4) (b) (4). The method was validated for a range of 0.100 – 20.0 ng/mL, based on the analysis of 0.150 mL of plasma. . The samples were extracted by solid phase extraction (SPE), transferred to 96-well SPE plate and washed with acetic acid and methanol. The samples were then eluted from the packing material into fresh 96 –well plates with ammonia in methanol and formic acid. The plates were capped, vortex mixed, centrifuged and submitted for HPLC-MS/MS analysis. Linagliptin was detected and quantified using a tandem mass spectrometer in the positive ionization mode and an injection volume of approximately 30 µL. The ion masses monitored were 473.1/420.2 (± 0.5 Da) for Linagliptin and 476.2/423.2 (± 0.5 Da) for [$^{13}C_3$] Linagliptin. Additionally, the ion masses for the metabolite CD 1750 XX (474.2/421.3 (± 0.5 Da)) and [$^{13}C_3$]CD 1750 XX (477.2/424.2 (± 0.5 Da)) were monitored in this study, however they were not quantified.

A summary of key descriptive parameters for the bioanalytical assays used in clinical studies is listed in Table 13.

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Table 13 Summary of key descriptive parameters for Empagliflozin and Linagliptin bioanalytical assays used in clinical studies

Study Number/Report Number	Study Title	Analytical Laboratory	Sample Matrix	Assay Range	LLOQ	Accuracy	Precision
Protocol 1275.3/Part: Analytical Final report – BI 1356 BS - Plasma	Determination of BI 1356 (Linagliptin) in Human Plasma Samples from an open-Label, Randomized, Single Dose, Crossover, Phase I Study (Sponsor Reference Number 1275.3) using Liquid Chromatography with Tandem Mass Spectrometric Detection (LC-MS/MS)	(b) (4)	Plasma	Linagliptin 0.100 – 20.0 nmol/L ng/mL	Linagliptin 0.1 nmol/L	Linagliptin 95.3% - 105.2% at 0.25 – 15.0 nmol/L	Linagliptin 4.2% - 35.1% at 0.25 – 15.0 nmol/L 4.2% - 18.8% at 0.25 – 15.0 nmol/L after excluding a statistical outlier
Protocol 1275.3 / (b) (4) Report #0016-10327-1	Quantification of BI 10773 in K3EDTA Human Plasma by LC-MS/MS		Plasma	Empagliflozin 1.11-1110 nmol/L	Empagliflozin 1.11 nmol/L	Empagliflozin 95.1% - 104.2% at 3.33 - 887 nmol/L	Empagliflozin -4.9% to 4.2% at 3.33 - 887 nmol/L

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3 Labeling Comments (Preliminary)

The following are the labeling recommendations relevant to clinical pharmacology for NDA (b) (4). The ~~red strikeout font~~ is used to show the proposed text to be deleted and underline blue font to show text to be included or comments communicated to the sponsor.

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12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.1 Mechanism of Action

~~*TRADENAME*~~*GLYXAMBI*

~~TRADENAME~~ GLYXAMBI combines 2 antihyperglycemic agents with different ~~complementary~~ mechanisms of action to improve glycemic control in patients with type 2 diabetes: empagliflozin, a sodium-glucose co-transporter (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 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

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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

~~*TRADENAME*~~ *GLYXAMBI*

The results of the bioequivalence study in healthy subjects demonstrated that ~~TRADENAME~~ 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 by 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%-89% at $\geq$ 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.

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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

~~*TRADENAME*~~*GLYXAMBI:* Studies characterizing the pharmacokinetics of empagliflozin and linagliptin after administration of ~~TRADENAME~~ GLYXAMBI in renally impaired patients have not been performed *[see Dosage and Administration (2.3)]*.

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.

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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

~~*TRADENAME*~~ *GLYXAMBI:* Studies characterizing the pharmacokinetics of empagliflozin and linagliptin after administration of ~~TRADENAME~~ 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 (b) (4) linagliptin *[see Use in Specific Populations (8.5)]*.

Pediatric

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

Drug Interactions

Pharmacokinetic drug interaction studies with ~~TRADENAME~~ GLYXAMBI have not been performed; however, such studies have been conducted with the individual components of ~~TRADENAME~~ 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

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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, simvastatin, hydrochlorothiazide, and torasemide in healthy volunteers (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.

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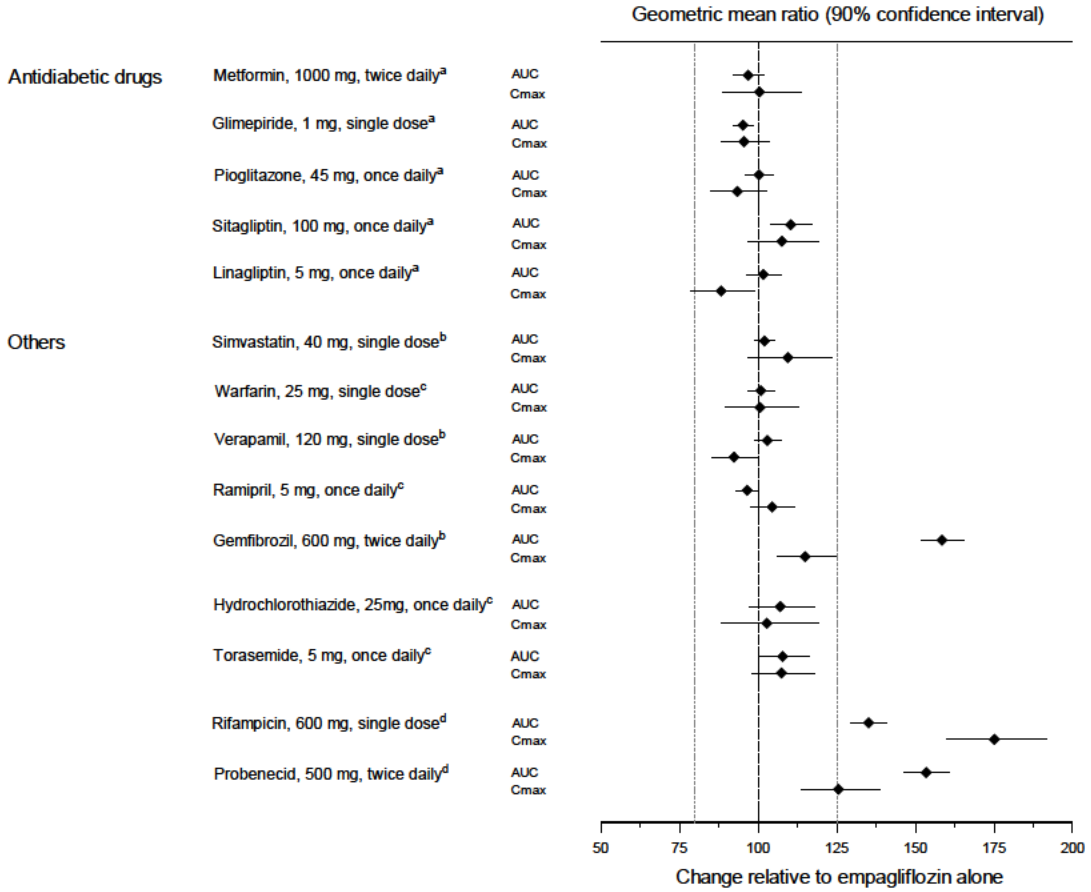
Figure 1 **Effect of Various Medications on the Pharmacokinetics of Empagliflozin as Displayed as 90% Confidence Interval of Geometric Mean AUC and C_{max} Ratios [reference lines indicate 100% (80% - 125%)]**



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

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

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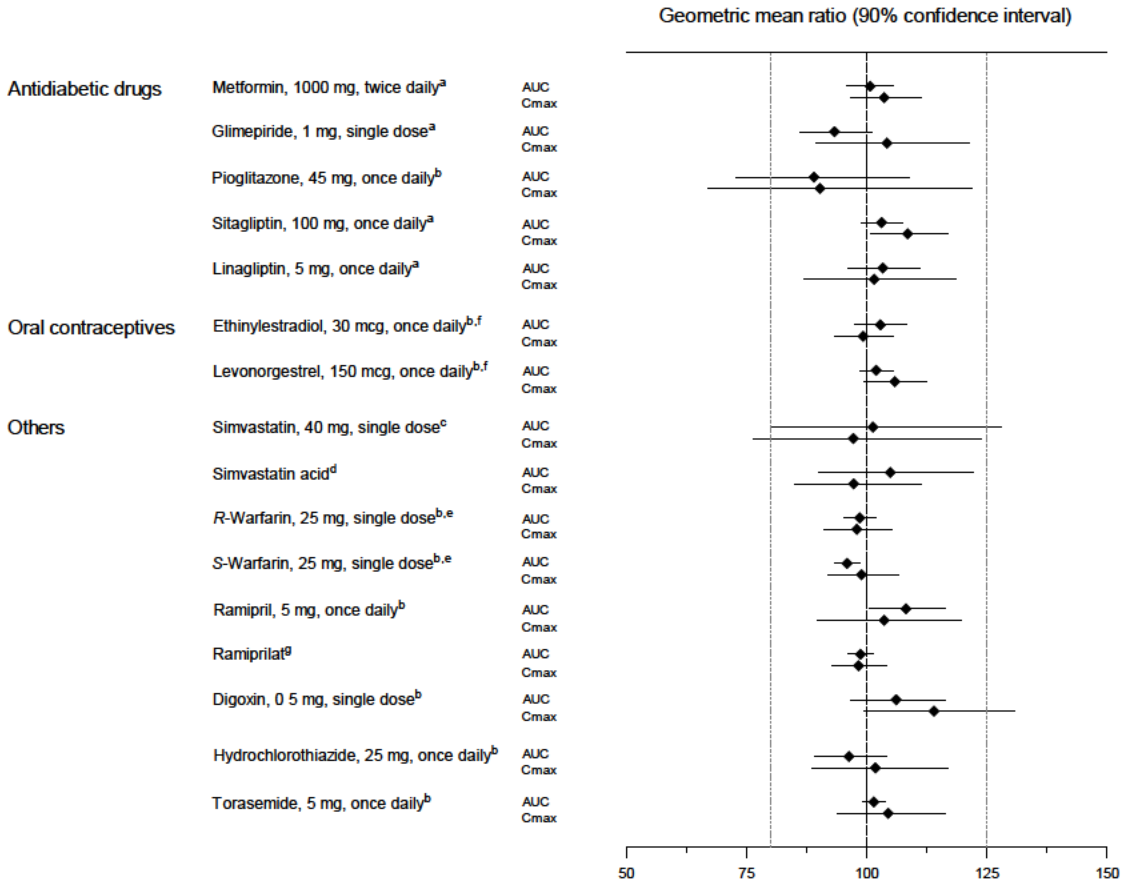
Figure 2 **Effect of Empagliflozin on the Pharmacokinetics of Various Medications as Displayed as 90% Confidence Interval of Geometric Mean AUC and C_{max} Ratios [reference lines indicate 100% (80% - 125%)]**



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

Linagliptin

In vitro Assessment of Drug Interactions

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

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

In vivo Assessment of Drug Interactions

Strong inducers of CYP3A4 or P-gp (e.g., rifampin) decrease exposure to linagliptin to subtherapeutic and likely ineffective concentrations. 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.

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Table 3 Effect of Coadministered Drugs on Systemic Exposure of Linagliptin

Coadministered Drug	Dosing of Coadministered Drug*	Dosing of Linagliptin*	Geometric Mean Ratio (ratio with/without coadministered drug) No effect = 1.0	
			AUC†	Cmax
No dosing adjustments required for linagliptin when given with the following coadministered drugs:				
Metformin	850 mg TID	10 mg QD	1.20	1.03
Glyburide	1.75 mg#	5 mg QD	1.02	1.01
Pioglitazone	45 mg QD	10 mg QD	1.13	1.07
Ritonavir	200 mg BID	5 mg#	2.01	2.96
The efficacy of linagliptin may be reduced when administered in combination with strong inducers of CYP3A4 or P-gp (e.g., rifampin). Use of alternative treatments is strongly recommended [see Drug Interactions (7.2)].				
Rifampin	600 mg QD	5 mg QD	0.60	0.56

*Multiple dose (steady state) unless otherwise noted
#Single dose
†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*	Dosing of Linagliptin*	Geometric Mean Ratio (ratio with/without coadministered drug) No effect = 1.0		
				AUC†	Cmax
No dosing adjustments required for the following coadministered drugs:					
Metformin	850 mg TID	10 mg QD	metformin	1.01	0.89
Glyburide	1.75 mg#	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#	5 mg QD	R-warfarin S-warfarin INR PT	0.99 1.03 0.93** 1.03**	1.00 1.01 1.04** 1.15**
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

*Multiple dose (steady state) unless otherwise noted
#Single dose
†AUC = AUC(INF) for single dose treatments and AUC = AUC(TAU) for multiple dose treatments
**AUC=AUC(0-168) and Cmax=Emax for pharmacodynamic end points
INR = International Normalized Ratio
PT = Prothrombin Time
QD = once daily
TID = three times daily

Reference ID: 3640237

4 APPENDIX

OCP Filing Memo

Reference ID: 3640237

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	**206073**	**Brand Name**	**Glyxambi**
OCP Division (I, II, III, IV, V)	**II**	**Generic Name**	**Empagliflozin + Linagliptin FDC**
Medical Division	**DMEP**	**Drug Class**	**SGLT2 inhibitor and DPP-4 inhibitor combination product**
OCP Reviewer	**Suryanarayana Sista, Ph.D.**	**Indication(s)**	**Treatment of Type 2 diabetes**
OCP Team Leader	**Lokesh Jain, Ph.D.**	**Dosage Form**	**oral tablet**
Pharmacometrics Reviewer		**Dosing Regimen**	**see below[a]**
Date of Submission	**01/30/2014**	**Route of Administration**	**oral**
Estimated Due Date of OCP Review		**Sponsor**	**Boehringer Ingelheim Pharmaceuticals, Inc.**
Medical Division Due Date		**Priority Classification**	**505 (b)(1) Standard**
PDUFA Due Date	**01/30/2015**		

[a]
- The recommended starting dose of Glyxambi is 10 mg empagliflozin/5 mg linagliptin once daily In patients who require additional glycemic control, the dose can be increased to 25 mg empagliflozin/5 mg linagliptin once daily
- Glyxambi can be taken with or without food

Clinical Pharmacology and Biopharmaceutics Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Study Nos./Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**	**3**		1275.3, 1245.30, 1275.1
HPK Summary				
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Human Biomaterials:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I)	**X**	**2**		1275.3, 1245.30
Healthy Volunteers-				
single dose:				
multiple dose:	**X**	**1[a]**		1245.30
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
in-vivo effects on primary drug:				
in-vivo effects of primary drug:				
in-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				

Reference ID: 3640237

Clinical Pharmacology and Biopharmaceutics Information				
	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Study Nos./Critical Comments If any
hepatic impairment:				
PD -				
Phase 1:				
Phase 2:				
Phase 3:	X	1		1275.1
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:	X	1[a]		1275.3
replicate design; single / multi dose:				
Food-drug interaction studies	X	1[a]		1275.3
Bio-waiver request based on BCS				Not Applicable
BCS class				Not Applicable
Dissolution study to evaluate alcohol induced dose-dumping				Not Applicable
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		3		

[a]Study counted more than once

Brief summary about the submission:

Boehringer Ingelheim Pharmaceuticals, Incorporated Inc. are seeking US marketing approval for Empagliflozin+Linagliptin FDC tablets (Trade Name: Glyxambi) under the provisions of Section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act. The proposed indication of Glyxambi tablets is "adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both empagliflozin and linagliptin is appropriate". This NDA is supported by data from one bioequivalence and food-effect trial, one multiple-dose relative bioavailability study and one efficacy trial.

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Type of Study / Study Identifier Location of Study Report	Objective(s) of the Study	Study Design
Phase I BE study */ 1275.3* *Section 5.3.1.2*	To evaluate the relative BA of 25 mg empagliflozin + 5 mg linagliptin FDC (formulation A1), including the comparison with the monocomponents, a second FDC (formulation A3), and the effect of food	Open-label, randomized, single-dose, crossover, Phase I study • Treatment A: FDC formulation A1 tablets/fasted-oral once daily • Treatment B: BI 10773 + linagliptin as individual tablets/fasted –oral once daily • Treatment C: FDC A1 tablets/fed condition-oral once daily • Treatment D: FDC A3 tablets (b) (4) formulation)/fasted oral once daily
Phase I PK study */ 1245.30* *Section 5.3.3.4*	To evaluate the relative BA of multiple doses of BI 10773 50 mg and linagliptin 5 mg after concomitant administration compared to multiple doses of BI 10773 50 mg and linalgiptin 5 mg administered alone	Open-label, randomized, cross-over, Phase I study • Empagliflozin 25 mg (2 tablets of 25 mg)-oral once daily • Linagliptin 5 mg tablets-oral once daily
Phase III Efficacy and Safety study */ 1275.1* *Section 5.3.5.1*	To evaluate the efficacy and safety of empagliflozin (10 mg or 25 mg) + linagliptin fixed dose combination (FDC) compared to the individual components in treatment naïve and metformin treated patients	Randomized, double-blind, active controlled, parallel group, Phase III study • Empagliflozin 25 mg + linagliptin 5 mg (E25+L5) FDC tablets-oral once daily • Empagliflozin 10 mg + linagliptin 5 mg (E10+L5) FDC tablets-oral once daily • Empagliflozin 10 mg (E10) tablets oral once daily • Empagliflozin 25 mg (E25) tablets oral once daily • Linagliptin 5 mg (L5) tablets-oral once daily

Reference ID: 3640237

NDA 206073 Filing Meeting

Empagliflozin + Linagliptin FDC (Glyxambi)

Sponsor: Boehringer Ingelheim Pharmaceuticals, Inc.

Submitted: 01/30/2014

Clinical Pharmacology Review Team:

Sury Sista

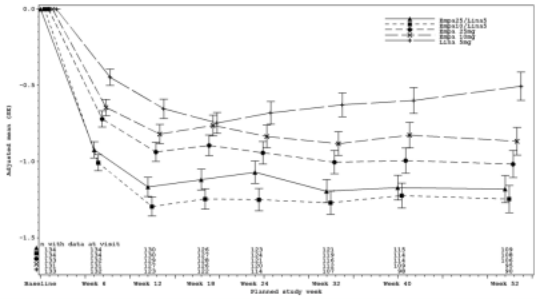
Lokesh Jain (TL)

Overview

- **Type of Submission:** 505 (b)(1)
- **Proposed Indication:**
  - adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both linagliptin and metformin is appropriate
- **Formulation:** Oral Tablets
  - 10 mg empagliflozin/5 mg linagliptin
  - 25 mg empagliflozin/5 mg linagliptin
- **Clinical Pharmacology Program**
  - Pivotal Studies - 2 Phase 1 (Studies 1275.3, 1245 30), and 1 Phase 3 (Study 1275.1) studies
- **Cross reference to other NDAs:**
  - Empagliflozin (NDA 204629, CR letter issued 04 March, 2014)
  - Linagliptin (NDA 201280, approved 02 May, 2011)
- **Pivotal BE studies:**
  - Study 1275.3 evaluated the bioavailability of 25 mg empagliflozin+ 5 mg linagliptin FDC relative to the mono components. This study also evaluated the effect of food on the FDC. ONDQA is responsible for the evaluation of the BE component of this study and request an OSI inspection.

Overview: Recommended Dose

- **Recommended Dose (Proposed):**
  - *"The recommended starting dose of Glyxambi is 10 mg empagliflozin/5 mg linagliptin once daily. In patients who require additional glycemic control, the dose can be increased to 25 mg empagliflozin/5 mg linagliptin once daily".* – **However, dosing recommendation needs to be aligned with Empagliflozin label**
  - Glyxambi can be taken with or without food.



Results

Study 1275.3

- **Bioequivalence:**
  - Per MOU with ONDQA, the bioequivalence component of this study will be reviewed by ONDQA.
- **Food-Effect:**
  - Following a high-fat, high-calorie meal, there was a 15% reduction in the AUC for empagliflozin and a 9% reduction in the AUC for linagliptin. However, the 90% confidence intervals for the comparison were contained within the 80% - 125% limits. There was a 39% reduction in the C_{max} for empagliflozin and a 31% reduction in linagliptin C_{max}. However, AUC is regarded as the more relevant parameter for chronically administered drugs. Therefore, the 25 mg empagliflozin / 5 mg linagliptin FDC tablet may be administered without regard to food.

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Results

Study 1245.30

	Geometric Mean Ratio	90% Confidence Intervals Lower Limit (%)	Upper Limit (%)
Empagliflozin			
$AUC_{\tau,ss}$ (nmol·h/L)	101.7	96.5	107.2
$C_{max,ss}$ (nmol/L)	88.3	78.8	98.9
Linagliptin			
$AUC_{\tau,ss}$ (nmol·h/L)	103.3	96.1	111.1
$C_{max,ss}$ (nmol/L)	101.5	86.9	118.5

- Administration of empagliflozin had no effect on the relative bioavailability of linagliptin. Exposure of empagliflozin was similar with regard to $AUC_{\tau,ss}$, however, $C_{max,ss}$ was reduced by 12%.
- Urinary excretion of both empagliflozin and linagliptin was not affected when the drugs were administered concomitantly.
- Trough DPP-4 inhibition was similar when linagliptin was given alone and in combination with empagliflozin.
- The mean cumulative amount of glucose excreted in urine over 24 h was lower when empagliflozin was administered with linagliptin than when empagliflozin was given alone.

Application Filability and Consults

- NDA is filable from Clinical Pharmacology perspective
- OSI consults – Deferred to ONDQA
- Request for Sponsor - None

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On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			X	Pivotal clinical trial used the to be marketed formulation
2	Has the applicant provided metabolism and drug-drug interaction information?			X	Data in original approved NDA for linagliptin and NDA under review for Empagliflozin
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	X			Data also in original approved NDA for linagliptin and NDA under review for Empagliflozin
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?			X	Data in original approved NDA for linagliptin and NDA under review for Empagliflozin
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	X			Data also in original approved NDA for linagliptin and NDA under review for Empagliflozin
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			X	Data in original approved NDA for linagliptin and NDA under review for Empagliflozin
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	X			
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			X	Data in original approved NDA for linagliptin and NDA under review for Empagliflozin
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? Yes

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Comment to Sponsor:
None.

Suryanarayana M. Sista — 14 Mar, 2014

Reviewing Clinical Pharmacologist — Date

Reference ID: 3640237

Lokesh Jain	14 Mar, 2014
Team Leader	Date

Reference ID: 3640237

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

/s/

SURYANARAYANA M SISTA
10/07/2014

MANOJ KHURANA
10/07/2014

BIOPHARMACEUTICS REVIEW Office of New Drug Quality Assessment			
Application No.:	NDA 206-073	**Reviewer:** Kareen Riviere, Ph.D.	
Submission Date(s):	1/30/14; 6/3/14		
Division:	DMEP	**Secondary Signature:** Tapash Ghosh, Ph.D.	
Applicant:	Boehringer Ingelheim Pharmaceuticals, Inc.	**Supervisor:** Paul Seo, Ph.D.	
Trade Name:	Glyxambi	**Date Assigned:**	1/30/14
Generic Name:	empagliflozin/linagliptin fixed-dose combination tablets	**Date of Review:**	9/16/14
Indication:	adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus	**Type of Submission:** 505(b)(1) New Drug Application	
Formulation/strengths:	IR Tablet; 10 mg/5 mg and 25 mg/5mg		
Route of Administration:	Oral		

SUMMARY:

This submission is a 505(b)(1) New Drug Application for 10 mg/5 mg and 25 mg/5mg of Glyxambi (empagliflozin/linagliptin) fixed-dose combination tablets. The proposed indication is for adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both empagliflozin and linagliptin is appropriate.

The Biopharmaceutics review for this NDA is focused on the evaluation and acceptability of 1) using the disintegration testing in lieu of dissolution testing, 2) the proposed dissolution method and acceptance criterion for supporting post-approval changes, and 3) the relative bioavailability data of the FDC tablet containing 25 mg BI 10773 and 5 mg linagliptin compared to the individual tablets administered together.

A. Relative Bioavailability Study

The main purpose of Study 1275.3 was to investigate the relative bioavailability of the FDC tablet containing 25 mg empagliflozin and 5 mg linagliptin compared to the individual tablets administered together. The study title is "Relative bioavailability investigations of a 25 mg empagliflozin / 5 mg linagliptin fixed dose combination (FDC) tablet (formulation A1) including the comparison with its mono-components, the comparison with a second FDC tablet (formulation A3), and the investigation of food (an open-label, randomized, single dose, crossover, Phase I trial in healthy male and female volunteers)".

The BE data demonstrate that the proposed tablet containing 25 mg empagliflozin and 5 mg linagliptin is bioequivalent to the individual tablets administered together.

B. Dissolution Method

The proposed dissolution acceptance method (for supporting post-approval changes) is:

USP Apparatus	Rotation Speed	Media Volume	Temp	Medium
2	50 rpm	900 ml	37 °C	pH 6.8 phosphate buffer

The proposed dissolution method is deemed acceptable for supporting post-approval changes.

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C. Dissolution Acceptance Criterion

The proposed acceptance criterion (for supporting post-approval changes) is:

Acceptance Criterion
Q = (b) (4)% at 30 min

The proposed dissolution acceptance criterion is deemed acceptable for supporting post-approval changes.

D. Disintegration in lieu of Dissolution

The Applicant requested disintegration testing in lieu of dissolution testing for routine quality control testing. A disintegration apparatus with disc is used, and water is used as immersion fluid. The proposed disintegration acceptance crietrion is shown below.

Test Parameter	Method Type	Acceptance Criterion
Disintegration	Physical test	≤ (b) (4) minutes

The proposed disintegration acceptance crietrion is adequate and the Applicant's proposal to use disintegration testing in lieu of dissolution testing for routine quality control testing is deemed acceptable.

RECOMMENDATION:

1. Glyxambi (empagliflozin/linagliptin) 10 mg/5 mg and 25 mg/5mg immediate release tablets are recommended for approval from a Biopharmaceutics standpoint, pending the OSI inspection results for the pivotal BE Study 1275.3.
2. Disintegration testing in lieu of dissolution testing is acceptable. A disintegration acceptance criterion of ≤ (b) (4) minutes is recommended.
3. The following dissolution method and acceptance criterion are recommended for both strengths for supporting post-approval changes.
   i. Dissolution Method: Apparatus 2, 100 rpm agitation rate, 500 mL media volume, 37 °C, 50 mM potassium phosphate buffer, pH 6.8.
   ii. Dissolution acceptance criterion (b) (4)% at 30 minutes.

Kareen Riviere, Ph.D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Tapash Ghosh, Ph.D.
Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

cc: Dr. Paul Seo

Reference ID: 3628597

ASSESSMENT OF BIOPHARMACEUTICS INFORMATION

1. Background

Drug Substance

The chemical structures of both substances are shown in Figures 1 and 2.

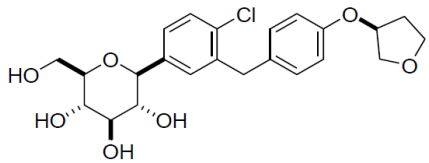

Figure 1. Chemical Structure of empagliflozin

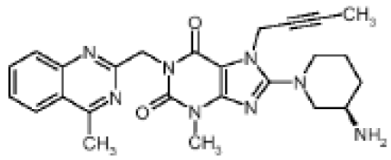

Figure 2. Chemical Structure of linagliptin

The Applicant claims that both APIs are BCS Class 3 drugs substances. The solubility profile and intrinsic dissolution profile of empagliflozin are shown in Tables 1 and 2, respectively.

Table 1. Solubility of Empagliflozin at 37 °C in Different Medium pH

Medium pH	Solubility after 2h (mg/ mL)	Solubility (mg/ 900 mL)	pH after 2 h
water	0.5	450	6.3
pH 1 0.1 M HCl	0.5	450	1.2
pH 3.0 McIlvaine buffer	0.5	450	3.0
pH 4.5 acetate buffer 0.2 M	0.5	450	4.5
pH 6.8 phosphate buffer 0.2 M	0.4	360	6.8
pH 7.5 phosphate buffer 0.2 M	0.4	360	7.5

Table 2. Intrinsic Dissolution Rates of Empagliflozin at 37 °C in Aqueous Media

Medium pH	Dissolution rate [µg/cm^2/min]
1.1	38
4.1	37
7.4	26

The solubility profile and intrinsic dissolution profile of linagliptin are shown in Tables 3 and 4, respectively.

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Table 3. Solubility of Linagliptin at 37 °C in Different Medium pH

Medium pH	Solubility after 2h (mg/ mL)	Solubility (mg/ 900 mL)	pH after 2 h
pH 1 0.1 M HCl	> 10	> 9000	1.5
pH 2 0.01 M HCl	6.6	5940	7.7
pH 3.0 McIlvaine buffer	> 10	> 9000	3.7
pH 4.0 McIlvaine buffer	> 10	> 9000	4.9
pH 4.5 acetate buffer 0.2 M	> 10	> 9000	5.0
pH 6.8 phosphate buffer 0.2 M	2.8	2520	7.2
pH 7.5 phosphate buffer 0.2 M	2.9	2610	7.8

The pH of the medium after 2 h increases due to the addition of linagliptin.

Table 4. Intrinsic Dissolution Rates of Linagliptin at 37 °C in Aqueous Media

Medium pH	Dissolution rate [µg/cm^2/min]
0.1 N HCl	8700
McIlvaine buffer pH 2.2	3500
McIlvaine buffer pH 3.0	2600
McIlvaine buffer pH 4.0	1600
McIlvaine buffer pH 5.0	650
McIlvaine buffer pH 6.0	410

Reviewer's Assessment:
Table 1 shows that empagliflozin solubility ranges from 0.4 – 0.5 mg/mL from pH 1 to 7.5 at 37 °C. For the high strength tablet, the dose to solubility volume range is 25mg/0.5 mg/mL to 25mg/0.4 mg/mL which correspond to 50 mL to 62.5 mL. Hence, empagliflozin is considered highly soluble within the physiological pH range. Also, this table shows that sink conditions are achieved for empagliflozin in the proposed medium (900 mL of pH 6.8 buffer) since a solubility of 360 mg/900 ml is achieved which is more than three times the solubility needed (i.e., 3 x 25 mg/900 mL).

Table 3 shows that linagliptin solubility ranges from 2.8 to at least 10 mg/mL from pH 1 to 7.5 at 37 °C. For the high strength of 5 mg, the dose to solubility volume range is 5mg/10 mg/mL to 5mg/2.9mg/mL which corresponds to 0.5mL to 1.79 mL. Hence, linagliptin is considered highly soluble within the physiological pH range. Also this table shows that sink conditions are achieved for linagliptin in the proposed medium (900 mL of pH 6.8 buffer) since a solubility of 2520 mg/900 ml is achieved, which is more than 3 times the solubility needed (i.e., 5 mg/900 mL).

Drug Product

Boehringer Ingelheim has developed two strength of empagliflozin + linagliptin fixed-dose combination (FDC) tablets (25 mg empagliflozin + 5 mg linagliptin and 10 mg empagliflozin + 5 mg linagliptin) for once daily administration. The Applicant conducted two phase 1 trials and one phase 3 trial. The Phase 3

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study evaluated the two strengths of the empagliflozin/linagliptin tablets for 52 weeks. The final commercial formulation was used in the phase 3 study. The composition of both strengths of the proposed drug product is displayed in Tables 5 and 6.

Table 5. Qualitative and quantitative composition of empagliflozin / linagliptin film-coated tablets, 10 mg / 5 mg

Ingredient	[mg / tablet]	Function	Reference to Standards
Tablet core			
Empagliflozin	10.00	Drug substance	Company standard
Linagliptin	5.00	Drug substance	Company standard
Mannitol	(b) (4)		USP
Pregelatinized starch			NF
Corn starch			NF
Copovidone			NF
Crospovidone			NF
Talc			USP
Magnesium stearate			NF
(b) (4)			USP
Film-coat			
(b) (4)			Company standard
			USP
Total mass of film-coated tablet	**185.0**		

Table 6. Qualitative and quantitative composition of empagliflozin / linagliptin film-coated tablets, 25 mg / 5 mg

Ingredient	[mg / tablet]	Function	Reference to Standards
Tablet core			
Empagliflozin	25.00	Drug substance	Company standard
Linagliptin	5.00	Drug substance	Company standard
Mannitol	(b) (4)		USP
Pregelatinized starch			NF
Corn starch			NF
Copovidone			NF
Crospovidone			NF
Talc			USP
Magnesium stearate			NF
(b) (4)			USP
Film-coat			
(b) (4)			Company standard
			USP
Total mass of film-coated tablet	**185.0**		

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Reviewer's Assessment:

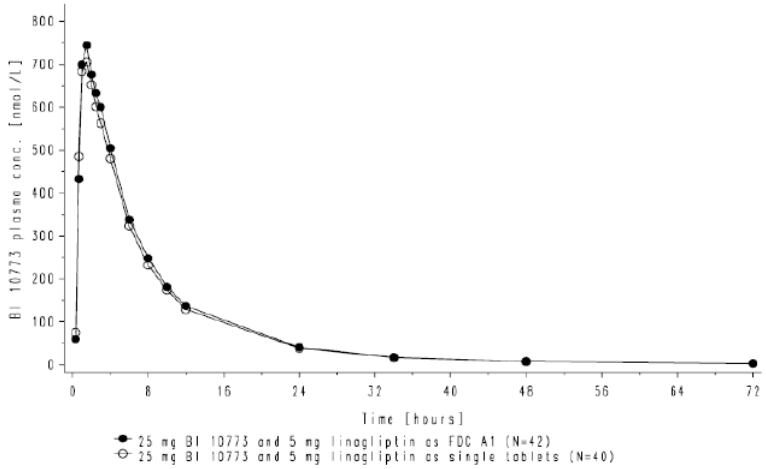
(b) (4)

2. BE Studies

The main purpose of Study 1275.3 was to investigate the relative bioavailability of the FDC tablet containing 25 mg empagliflozin and 5 mg linagliptin compared to the individual tablets administered together. The study title is "Relative bioavailability investigations of a 25 mg empagliflozin / 5 mg linagliptin fixed dose combination (FDC) tablet (formulation A1) including the comparison with its mono-components, the comparison with a second FDC tablet (formulation A3), and the investigation of food (an open-label, randomized, single dose, crossover, Phase I trial in healthy male and female volunteers)".

The mean plasma concentration-time profiles of empagliflozin are shown in Figure 3.

Figure 3. Geometric Mean Plasma Concentration-Time Profiles of Empagliflozin after Single Oral Administration of 25 mg Empagliflozin and 5 mg Linagliptin as FDC A1 Tablet (N=42) or Individual Tablets (N=40)



The mean pharmacokinetic parameters for empagliflozin are displayed in Table 7.

Table 7. Mean Pharmacokinetic Parameters for Empagliflozin by Treatment

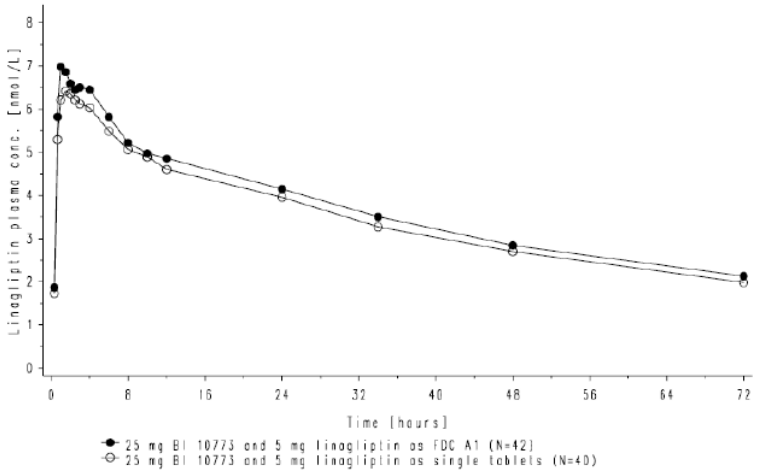
BI 10773		FDC A1 (N=42)		Individual tablets (N=40)	
		gMean	gCV [%]	gMean	gCV [%]
AUC_{0-tz}	[nmol·h/L]	5990	21.0	5720	20.8
C_{max}	[nmol/L]	862	26.8	803	24.9
$AUC_{0-\infty,pred}$	[nmol·h/L]	6060	20.7	5790	20.9
t_{max}[1]	[h]	1.50	0.667-4.00	1.25	0.667-3.98
$t_{1/2}$	[h]	13.3	32.7	12.9	36.4
CL/F	[mL/min]	153	20.7	159	20.9
V_z/F	[L]	175	38.3	178	35.5

[1]For t_{max}, the median and range (minimum to maximum) are given.

The mean plasma concentration-time profiles of linagliptin are shown in Figure 4.

Reference ID: 3628597

Figure 4. Geometric Mean Plasma Concentration-Time Profiles of Linagliptin after Single Oral Administration of 25 mg Empagliflozin and 5 mg Linagliptin as FDC A1 Tablet (N=42) or Individual Tablets (N=40)



The mean pharmacokinetic parameters for linagliptin are displayed in Table 8.

Table 8. Mean Pharmacokinetic Parameters for Linagliptin by Treatment

Linagliptin		FDC A1 (N=42)		Individual tablets (N=40)	
		gMean	gCV [%]	gMean	gCV [%]
AUC_{0-72}	[nmol·h/L]	264	22.1	250	22.1
C_{max}	[nmol/L]	8.19	36.4	7.49	31.0
$AUC_{0-\infty,pred}$	[nmol·h/L]	434	26.3	410	29.9
AUC_{0-tz}	[nmol·h/L]	264	22.1	250	22.1
t_{max}[1]	[h]	1.50	0.333-6.03	1.75	0.667-10.0
$t_{1/2}$	[h]	54.4	18.9	54.3	24.6
CL/F	[mL/min]	406	26.3	430	29.9
V_z/F	[L]	1910	22.1	2020	21.6

[1]For t_{max}, the median and range (minimum to maximum) are given.

The bioequivalence data for Study 1275.3 is presented in Table 9.

Table 9. gMeans and 90% Confidence Interval of the gMean Ratio for the Primary Pharmacokinetic Parameters of Empagliflozin and Linagliptin after Administration of 25 mg Empagliflozin and 5 mg Linagliptin as FDC A1 Tablet and Individual Tablets

Analyte Parameter	FDC A1 (Test) gMean (N=42)	Individual tablets (Reference) gMean (N=40)	Adjusted gMean ratio (Test/Reference) [%]	Two-sided 90% confidence interval Lower limit [%]	Two-sided 90% confidence interval Upper limit [%]	Intra-individual gCV [%]
BI 10773						
AUC_{0-tz} [nmol·h/L]	6025.1	5743.7	104.9	102.1	107.8	7.2
C_{max} [nmol/L]	868.7	806.7	107.7	101.7	114.0	15.3
Linagliptin						
AUC_{0-72} [nmol·h/L]	265.2	252.8	104.9	100.0	110.1	12.8
C_{max} [nmol/L]	8.3	7.5	109.7	99.6	120.8	26.2

Source data: Tables 15.5.1.1.1: 2, 15.5.1.1.2: 2, 15.5.1.2.1: 2, 15.5.1.2.2: 2

Reviewer's Assessment:
The BE study design as well as the bioanalytical method development and validation report are adequate.

Reference ID: 3628597

The data in Table 9 show that the point estimates of geometric mean ratios for AUCinf and Cmax were greater than 90% and that 90% confidence intervals for Cmax and AUC for both empagliflozin and linagliptin fell within FDA's bioequivalence criterion of 80-125%. This reviewer re-analayzed the bioequivalence data using Pheonix software version 6.2.1.51. The analysis is summarized in Reviewer's Tables 1 and 2.

Reviewer's Table 1. Re-Analysis of Empagliflozin BE Data

Parameter	Geometric Mean of Test	Geometric Mean of Reference	Ratio of Means	Lower Limit of 90% CI	Upper Limit of 90% CI
Cmax (nmol/L)	868.38	810.76	107.11	100.70	113.92
AUC (nmol*h/L)	6203.44	5937.25	104.48	101.28	107.79

Reviewer's Table 2. Re-Analysis of Linagliptin BE Data

Parameter	Geometric Mean of Test	Geometric Mean of Reference	Ratio of Means	Lower Limit of 90% CI	Upper Limit of 90% CI
Cmax (nmol/L)	8.27	7.53	109.94	100.87	119.82
AUC (nmol*h/L)	266.12	254.42	104.60	99.94	109.47
AUCinf (nmol*h/L)	422.90	407.53	103.77	97.52	110.43

This reviewer's BE data analysis confirms the Applicant's BE data analysis. Thus, the tablet containing 25 mg empagliflozin and 5 mg linagliptin are bioequivalent to the individual tablets administered together.

3. Dissolution Method

The proposed dissolution method is shown below.

USP Apparatus	Rotation Speed	Media Volume	Temp	Medium
2	50 rpm	900 ml	37 °C	pH 6.8 phosphate buffer

Selection of Rotation Speed and Apparatus

The Applicant evaluated the dissolution profile of the proposed empagliflozin / linagliptin film-coated tablets using the paddle method at rotation speeds of (b) (4) [redacted] For all the above reasons, the Applicant decided to use the paddle apparatus at 50 rpm agitation speed for the dissolution method.

Reference ID: 3628597

Figure 5. Influence of Rotation Speed Using the Paddle Apparatus (900 mL, pH 6.8)

Linagliptin ***Empagliflozin***

(b) (4)

Reviewer's Assessment:

The Applicant's selection of the paddle apparatus and paddle speed are adequately justified.

Selection of the Dissolution Medium

The Applicant examined the dissolution profiles of empagliflozin / linagliptin film-coated tablets, 10 mg/5 mg and 25 mg/5 mg in the pH range (b) (4) in order to select the most suitable dissolution medium (see Figures 6 and 7). These dissolution tests were carried out using the paddle apparatus with an agitation speed of 50 rpm and a volume of 900 mL of various dissolution media (b) (4).

Figure 6. Linagliptin Dissolution Profile Comparison in Different Media (Paddle, 50 rpm, 900 mL, n = 12)

(b) (4)

Figure 7. Empagliflozin Dissolution Profile Comparison in Different Media (Paddle, 50 rpm, 900 mL, n = 12)

(b) (4)

Reference ID: 3628597

The Applicant selected phosphate buffer pH 6.8 as the appropriate dissolution medium for empagliflozin/ linagliptin film-coated tablets (b) (4).

Reviewer's Assessment:
Both strengths of the drug product have rapid dissolution (dissolution > (b) (4) % in 15 minutes) at pH 1.2, 4.0, and 6.8) for both drug substances. Thus, the selection of dissolution medium is justified.

Discriminating Ability of the Dissolution Method

The Applicant selected several variables that might affect tablet dissolution to investigate the discriminating ability of the proposed method. These variables include different types of formulations, different compression forces resulting in different tablet hardness, and different particle sizes of both active ingredients.

Influence of Magnesium Stearate Content

Figures 8 and 9 show the effect of different amounts of magnesium stearate on the dissolution profiles for both strength products.

(b) (4)

Reference ID: 3628597

Influence of (b) (4) Content

(b) (4)

Influence of Film Coat

Figure 11 shows the influence of the film-coat on dissolution.

(b) (4)

(b) (4)

Reference ID: 3628597

(b) (4)

Influence of Drug Substance Particle Size

The Applicant evaluated the influence of the particle size of empagliflozin on dissolution (see Figure 14 and 15).

(b) (4)

Reference ID: 3628597

Figure 14. Dissolution Comparison of 25 mg/5 mg Film-Coated Tablets with Different Empagliflozin Particle Sizes (Paddle, 50 rpm, 900 mL, n = 12)

(b) (4)

Figure 15. Dissolution Comparison of 10 mg/5 mg Film-Coated Tablets with Different Linagliptin Particle Sizes (Paddle, 50 rpm, 900 mL, n = 12)

Linagliptin ***Empagliflozin***

(b) (4)

Reviewer's Assessment:
The data in Figures 8 to 15 show that the dissolution method does not discriminate changes (b) (4) ***Thus, it can be concluded that the proposed method has some discriminating ability.***

Overall, the proposed dissolution method is acceptable since the testing conditions have been adequately justified.

4. Dissolution Acceptance Criterion

The proposed dissolution acceptance criterion is shown below.

Acceptance Criterion
Q = (b) (4)% at 30 min

Reference ID: 3628597

Table 10 and 11 provide the dissolution release data of representative clinical and stability batches of the 10 mg/5 mg and 25 mg/5 mg strengths of the empagliflozin / linagliptin film-coated tablets.

Table10. Dissolution Release Data of Clinical Batches, 10 mg/5 mg Strength

Batch	Dissolution of empagliflozin at 30 minutes (min – max/average)	Dissolution of linagliptin at 30 minutes (min – max/average)
B101005412	(b) (4)	
B101005413		
104286		

Table 11. Dissolution Release Data of Clinical Batches, 25 mg/5 mg Strength

Batch	Dissolution of empagliflozin at 30 minutes (min – max/average)	Dissolution of linagliptin at 30 minutes (min – max/average)
B101003271	(b) (4)	
B101003361		
B101005414		
B101005415		
104287		

In the relative bioavailability study 1275.3, empagliflozin / linagliptin film-coated tablets 25 mg/5 mg with different dissolution behaviors were also tested (see Figure 16). One of the batches tested exhibits a dissolution profile which is similar to that of the intended market batches whereas the second batch tested exhibits a slower dissolution profile. The Applicant stated that the amount of (b) (4) for the side batch formulation compared to the production scale formulation.

Table 12. Adjusted by Treatment gMeans and 90% Confidence Interval of the gMean Ratio for the Primary Pharmacokinetic Parameters of Empagliflozin and Linagliptin after Administration of 25 mg Empagliflozin And 5 mg Linagliptin as FDC A1 Tablet and FDC A3 Tablet

Analyte Parameter	N	FDC A3 (Test) gMean	FDC A1 (Reference) gMean	Adjusted gMean ratio (Test/Reference) [%]	Two-sided 90% confidence interval Lower limit [%]	Two-sided 90% confidence interval Upper limit [%]	Intra-individual gCV [%]
BI 10773							
AUC_{0-tz} [nmol·h/L]	24	5489.5	5736.7	95.7	91.2	100.4	9.8
C_{max} [nmol/L]	24	786.6	802.3	98.0	92.0	104.5	13.0
Linagliptin							
AUC_{0-72} [nmol·h/L]	24	247.1	256.4	96.4	89.8	103.4	14.3
C_{max} [nmol/L]	24	7.9	7.7	103.7	92.9	115.7	22.4

Source data: Tables 15.5.3.1.1: 2, 15.5.3.1.2: 2, 15.5.3.2.1: 2, 15.5.3.2.2: 2

Reference ID: 3628597

Figure 16. Comparison of Different Formulations Tested in Study 1275.3 (Paddle, 50 rpm, 900 mL pH 6.8, n = 12)

Linagliptin ***Empagliflozin***

(b) (4)

Reviewer's Assessment:

The data in Figure 16 and Table 12 demonstrate that although slow and fast releasing batches indicate no dissolution profile similarity, both batches can be considered bioequivalent based on the results of study 1275.3. Hence, an appropriate dissolution acceptance criterion would be one that allows both of these bathes to pass the specification. Therefore, the proposed acceptance criterion seems adequate. Furthermore, the dissolution data in Tables 10 and 11 for representative clinical and stability batches of the 10 mg/5 mg and 25 mg/5 mg strengths further demonstrate the suitability of the proposed acceptance criterion. Thus, the proposed dissolution acceptance criterion is deemed acceptable.

5. Evaluating the Acceptability of Disintegration Testing in Lieu of Dissolution Testing

The Applicant is requesting disintegration testing in lieu of dissolution testing for routine quality control testing. They claim that the test method used for determination of disintegration time is in compliance with the current harmonized compendial requirements for disintegration as described in USP general chapter <701>. A disintegration apparatus with disc is used, and water is used as immersion fluid.

The propose disintegration acceptance crietrion is shown below.

Test Parameter	Method Type	Acceptance Criterion
Disintegration	Physical test	≤ (b) (4) minutes

To demonstrate that the disintegration process is the rate-determining step for the release of both active ingredients, the Applicant determined the disintegration time of the film-coated tablets in the dissolution vessel by applying the proposed dissolution method parameters. The results are shown in Tables 13 and 14.

Reference ID: 3628597

Table 13. Influence of the Disintegration Process on Linagliptin Dissolution

10 mg/5 mg Strength

Test conditions: Paddle 50 rpm, 900 mL buffer pH 6.8			
Batch No.	**Sample No.**	**% Dissolved at time in minutes** (b) (4)	**Disintegration time vessel* [minutes:seconds]** (b) (4)
108244	1		
	2		
	3		
	4		
	5		
	6		
	Mean		
	RSD		

* Disintegration times in the dissolution vessel were determined visually by the same analyst.

25 mg/5 mg Strength

Test conditions: Paddle 50 rpm, 900 mL buffer pH 6.8			
Batch No.	**Sample No.**	**% Dissolved at time in minutes** (b) (4)	**Disintegration time vessel* [minutes:seconds]** (b) (4)
108247	1		
	2		
	3		
	4		
	5		
	6		
	Mean		
	RSD		

* Disintegration times in the dissolution vessel were determined visually by the same analyst.

Table 14. Influence of the Disintegration Process on Empagliflozin Dissolution

10 mg/5 mg Strength

Test conditions: Paddle 50 rpm, 900 mL buffer pH 6.8			
Batch No.	**Sample No.**	**% Dissolved at time in minutes** (b) (4)	**Disintegration time vessel* [minutes:seconds]** (b) (4)
108244	1		
	2		
	3		
	4		
	5		
	6		
	Mean		
	RSD		

* Disintegration times in the dissolution vessel were determined visually by the same analyst.

Reference ID: 3628597

25 mg/5 mg Strength

Test conditions: Paddle 50 rpm, 900 mL buffer pH 6.8			
Batch No.	**Sample No.**	**% Dissolved at time in minutes** (b) (4)	**Disintegration time vessel* [minutes:seconds]** (b) (4)
108247	1		
	2		
	3		
	4		
	5		
	6		
	Mean		
	RSD		

* Disintegration times in the dissolution vessel were determined visually by the same analyst.

The Applicant examined the correlation between the mean disintegration times of empagliflozin / linagliptin film-coated tablets in a disintegration tester with the mean dissolution rates at the 10 minute time point. They chose this time point based on the mean disintegration time range in the dissolution vessel of approximately 9 - 15 minutes.

Figures 17 and 18 are plots of the correlation between the mean dissolution rate at 10 minutes and the disintegration time for the proposed product.

(b) (4)

Reference ID: 3628597

(b) (4)

To assess the discriminating ability of disintegration testing according to ICH 6QA, the Applicant tested the influence of compression force, (b) (4) content and different formulations on disintegration. They also evaluated the differences in disintegration time by statistical evaluation.

Influence of Tablet Hardness

The influence of tablet hardness on the disintegration time was evaluated by measuring tablet cores and film-coated tablets manufactured with different compression forces. The results are shown in Figures 19-21.

Figure 19. Impact of Compression Force / Tablet Hardness on Disintegration Time, Tablet Cores, 25 mg/5 mg

(b) (4)

Reference ID: 3628597

Figure 20. Impact of Compression Force / Tablet Hardness on Disintegration Time, Tablet Cores, 10 mg/5 mg

(b) (4)

Figure 21. Impact of Compression Force/Tablet Hardness on Disintegration Time, Film-Coated Tablets, 10 mg/5mg

(b) (4)

Influence of Film Coat

The influence of the film-coat on disintegration time was evaluated using primary stability batches (see Figures 22-23).

Figure 22. Impact of Film-Coat on Disintegration Time, Cores and Film-Coated Tablets, 10 mg/5 mg

(b) (4)

Reference ID: 3628597

Figure 23. Impact of Film-Coat on Disintegration Time, Cores and Film-Coated Tablets, 25 mg/5 mg

(b) (4)

Influence of (b) (4) Content

Figure 24 shows the effect of 0 %, 1 %, and 2 % of crospovidone on the disintegration behavior of empagliflozin / linagliptin tablet cores.

Figure 24. Impact of (b) (4) Content (Crospovidone) on Disintegration Time, Tablet Cores, 25 mg/5 mg

(b) (4)

Influence of Formulation and Manufacturing Variables

In the relative bioavailability study 1275.3 empagliflozin / linagliptin film-coated tablets 25 mg/5 mg with different disintegration behavior were tested. One of the batches exhibits a mean disintegration time of (b) (4) minutes whereas the other tested batch exhibits a mean disintegration time of (b) (4) minutes (see Figure 25).

Reference ID: 3628597

Figure 25. Impact of Different Formulation Types on Disintegration Time, Clinical Batches Study 1275.3, Film-

(b) (4)

To derive the specification for disintegration, the Applicant used release results of clinical, stability and primary stability batches as well as results obtained during long-term and accelerated stability study for the statistical evaluation under consideration of the following prerequisites:

• The stage testing concept according to USP is included in the statistical evaluation

• Confidence level of 0.95 is applied based on the statistical evaluation a specification limit of (b) (4) min:sec was calculated under above mentioned conditions.

Figure 26 shows the mean disintegration times of all considered release and stability data and their standard deviation.

Figure 26. Impact of a proposed specification limit based on the tolerance interval approach for the objectives 'Acceptance at Stage 1 or 2 and the confidence level 0.95'.

(b) (4)

Reference ID: 3628597

Reviewer's Assessment:

According to ICH Q6A, disintegration testing in lieu of dissolution testing is appropriate if the following conditions are met:

a. ***The drug(s) has high solubility (dose/solubility ≤ 250 mL) throughout the physiological pH range (pH 1.2-6.8),***
b. ***The drug product has rapid dissolution (dissolution > (b) (4) % in 15 minutes at pH 1.2, 4.0, and 6.8), and***
c. ***A relationship has been determined between disintegration and dissolution, or disintegration is shown to be more discriminating than dissolution.***

The Applicant has shown that both drugs have high solubility throughout the physiological pH range (pH 1.2-6.8). Refer to discussion in section 1 above. Additionally, the dissolution data in Figures 6 and 7 demonstrate that the drug product has rapid dissolution (dissolution > (b) (4) % in 15 minutes at pH 1.2, 4.0, and 6.8). Thus, the proposed product could meet a dissolution acceptance criterion of Q= (b) (4) % at 15 minutes.

Furthermore, the dissolution rate correlates with the disintegration time of the empagliflozin / linagliptin film-coated tablets. The results show that in the time range of complete disintegration in the vessel (about (b) (4) minutes) approximately (b) (4) % of both active ingredients are dissolved (see Tables13 and 14). Therefore, it can be seen that the dissolution process is mainly influenced by the disintegration process. Figures 17 and 18 also demonstrate a relationship between dissolution and disintegration.

Lastly, the disintegration and dissolution method seems to have similar discriminating ability. Figures 19 to 23 shows that changes in some formulation and manudactuing variables led to changes in the disinigertation time. Also the data in Figure 25 and Table 12 demonstrate that although slow and fast releasing batches have markedly different disintegration times, both batches can be considered bioequivalent based on the results of Study 1275.3. This same phenomenon was obtained with the proposed dissolution method. These data suggest that the disintegration and dissolution method can be somewhat over discriminating.

Thus, the Applicant's proposal to use disintegration testing in lieu of dissolution testing is acceptable. Additionally, the proposed disintegration acceptance crietrion is adequate.

Reference ID: 3628597

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/s/

KAREEN RIVIERE
09/16/2014

TAPASH K GHOSH
09/16/2014

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	**206073**	**Brand Name**	**Glyxambi**
OCP Division (I, II, III, IV, V)	**II**	**Generic Name**	**Empagliflozin + Linagliptin FDC**
Medical Division	**DMEP**	**Drug Class**	**SGLT2 inhibitor and DPP-4 inhibitor combination product**
OCP Reviewer	**Suryanarayana Sista, Ph.D.**	**Indication(s)**	**Treatment of Type 2 diabetes**
OCP Team Leader	**Lokesh Jain, Ph.D.**	**Dosage Form**	**oral tablet**
Pharmacometrics Reviewer		**Dosing Regimen**	**see below[a]**
Date of Submission	**01/30/2014**	**Route of Administration**	**oral**
Estimated Due Date of OCP Review		**Sponsor**	**Boehringer Ingelheim Pharmaceuticals, Inc.**
Medical Division Due Date		**Priority Classification**	**505 (b)(1) Standard**
PDUFA Due Date	**01/30/2015**		

[a]
- The recommended starting dose of Glyxambi is 10 mg empagliflozin/5 mg linagliptin once daily. In patients who require additional glycemic control, the dose can be increased to 25 mg empagliflozin/5 mg linagliptin once daily.
- Glyxambi can be taken with or without food.

Clinical Pharmacology and Biopharmaceutics Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Study Nos./Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**	**3**		1275.3, 1245.30, 1275.1
HPK Summary				
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Human Biomaterials:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I)	**X**	**2**		1275.3, 1245.30
Healthy Volunteers-				
single dose:				
multiple dose:	**X**	**1[a]**		1245.30
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
in-vivo effects on primary drug:				
in-vivo effects of primary drug:				
in-vitro:				
Subpopulation studies -				

Reference ID: 3480814

Clinical Pharmacology and Biopharmaceutics Information				
	"X" if included at filing	**Number of studies submitted**	**Number of studies reviewed**	**Study Nos./Critical Comments If any**
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 1:				
Phase 2:				
Phase 3:	**X**	**1**		1275.1
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:	**X**	**1[a]**		1275.3
replicate design; single / multi dose:				
Food-drug interaction studies	**X**	**1[a]**		1275.3
Bio-waiver request based on BCS				Not Applicable
BCS class				Not Applicable
Dissolution study to evaluate alcohol induced dose-dumping				Not Applicable
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		**3**		

[a]Study counted more than once

Brief summary about the submission:

Boehringer Ingelheim Pharmaceuticals, Incorporated Inc. are seeking US marketing approval for Empagliflozin+Linagliptin FDC tablets (Trade Name: Glyxambi) under the provisions of Section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act. The proposed indication of Glyxambi tablets is "adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both empagliflozin and linagliptin is appropriate". This NDA is supported by data from one bioequivalence and food-effect trial, one multiple-dose relative bioavailability study and one efficacy trial.

Reference ID: 3480814

Type of Study / Study Identifier Location of Study Report	Objective(s) of the Study	Study Design
Phase I BE study */ 1275.3* *Section 5.3.1.2*	To evaluate the relative BA of 25 mg empagliflozin + 5 mg linagliptin FDC (formulation A1), including the comparison with the monocomponents, a second FDC (formulation A3), and the effect of food	Open-label, randomized, single-dose, crossover, Phase I study • Treatment A: FDC formulation A1 tablets/fasted-oral once daily • Treatment B: BI 10773 + linagliptin as individual tablets/fasted –oral once daily • Treatment C: FDC A1 tablets/fed condition-oral once daily • Treatment D: FDC A3 tablets ((b) (4) formulation)/fasted oral once daily
Phase I PK study */ 1245.30* *Section 5.3.3.4*	To evaluate the relative BA of multiple doses of BI 10773 50 mg and linagliptin 5 mg after concomitant administration compared to multiple doses of BI 10773 50 mg and linalgiptin 5 mg administered alone	Open-label, randomized, cross-over, Phase I study • Empagliflozin 25 mg (2 tablets of 25 mg)-oral once daily • Linagliptin 5 mg tablets-oral once daily
Phase III Efficacy and Safety study */ 1275.1* *Section 5.3.5.1*	To evaluate the efficacy and safety of empagliflozin (10 mg or 25 mg) + linagliptin fixeddose combination (FDC) compared to the individual components in treatment naïve and metformin treated patients	Randomized, double-blind, active controlled, parallel group, Phase III study • Empagliflozin 25 mg + linagliptin 5 mg (E25+L5) FDC tablets-oral once daily • Empagliflozin 10 mg + linagliptin 5 mg (E10+L5) FDC tablets-oral once daily • Empagliflozin 10 mg (E10) tablets oral once daily • Empagliflozin 25 mg (E25) tablets oral once daily • Linagliptin 5 mg (L5) tablets-oral once daily

Reference ID: 3480814

NDA 206073 Filing Meeting

Empagliflozin + Linagliptin FDC (Glyxambi)

Sponsor: Boehringer Ingelheim Pharmaceuticals, Inc.

Submitted: 01/30/2014

Clinical Pharmacology Review Team:

Sury Sista

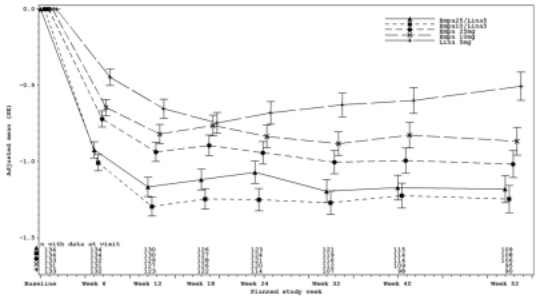
Lokesh Jain (TL)

Overview

- **Type of Submission:** 505 (b)(1)
- **Proposed Indication:**
  - adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both linagliptin and metformin is appropriate
- **Formulation:** Oral Tablets
  - 10 mg empagliflozin/5 mg linagliptin
  - 25 mg empagliflozin/5 mg linagliptin
- **Clinical Pharmacology Program**
  - Pivotal Studies - 2 Phase 1 (Studies 1275.3, 1245.30), and 1 Phase 3 (Study 1275.1) studies
- **Cross reference to other NDAs:**
  - Empagliflozin (NDA 204629, CR letter issued 04 March, 2014)
  - Linagliptin (NDA 201280, approved 02 May, 2011)
- **Pivotal BE studies:**
  - Study 1275.3 evaluated the bioavailability of 25 mg empagliflozin+ 5 mg linagliptin FDC relative to the mono components. This study also evaluated the effect of food on the FDC. ONDQA is responsible for the evaluation of the BE component of this study and request an OSI inspection.

Overview: Recommended Dose

- **Recommended Dose (Proposed):**
  - *"The recommended starting dose of Glyxambi is 10 mg empagliflozin/5 mg linagliptin once daily. In patients who require additional glycemic control, the dose can be increased to 25 mg empagliflozin/5 mg linagliptin once daily".* – **However, dosing recommendation needs to be aligned with Empagliflozin label**
  - Glyxambi can be taken with or without food.



Results

Study 1275.3

- **Bioequivalence:**
  - Per MOU with ONDQA, the bioequivalence component of this study will be reviewed by ONDQA.
- **Food-Effect:**
  - Following a high-fat, high-calorie meal, there was a 15% reduction in the AUC for empagliflozin and a 9% reduction in the AUC for linagliptin. However, the 90% confidence intervals for the comparison were contained within the 80% - 125% limits. There was a 39% reduction in the C_{max} for empagliflozin and a 31% reduction in linagliptin C_{max}. However, AUC is regarded as the more relevant parameter for chronically administered drugs. Therefore, the 25 mg empagliflozin / 5 mg linagliptin FDC tablet may be administered without regard to food.

Results

Study 1245.30

	Geometric Mean Ratio	90% Confidence Intervals Lower Limit (%)	Upper Limit (%)
Empagliflozin			
$AUC_{\tau,ss}$ (nmol·h/L)	101.7	96.5	107.2
$C_{max,ss}$ (nmol/L)	88.3	78.8	98.9
Linagliptin			
$AUC_{\tau,ss}$ (nmol·h/L)	103.3	96.1	111.1
$C_{max,ss}$ (nmol/L)	101.5	86.9	118.5

- Administration of empagliflozin had no effect on the relative bioavailability of linagliptin. Exposure of empagliflozin was similar with regard to $AUC_{\tau,ss}$, however, $C_{max,ss}$ was reduced by 12%.
- Urinary excretion of both empagliflozin and linagliptin was not affected when the drugs were administered concomitantly.
- Trough DPP-4 inhibition was similar when linagliptin was given alone and in combination with empagliflozin.
- The mean cumulative amount of glucose excreted in urine over 24 h was lower when empagliflozin was administered with linagliptin than when empagliflozin was given alone.

Application Filability and Consults

- NDA is filable from Clinical Pharmacology perspective
- OSI consults – Deferred to ONDQA
- Request for Sponsor - None

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			X	Pivotal clinical trial used the to be marketed formulation
2	Has the applicant provided metabolism and drug-drug interaction information?			X	Data in original approved NDA for linagliptin and NDA under review for Empagliflozin
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	X			Data also in original approved NDA for linagliptin and NDA under review for Empagliflozin
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?			X	Data in original approved NDA for linagliptin and NDA under review for Empagliflozin
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	X			Data also in original approved NDA for linagliptin and NDA under review for Empagliflozin
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			X	Data in original approved NDA for linagliptin and NDA under review for Empagliflozin
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	X			
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			X	Data in original approved NDA for linagliptin and NDA under review for Empagliflozin
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? **Yes**

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Reference ID: 3480814

Comment to Sponsor:
None.

Suryanarayana M. Sista	14 Mar, 2014
Reviewing Clinical Pharmacologist	Date
Lokesh Jain	14 Mar, 2014
Team Leader	Date

Reference ID: 3480814

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

/s/

SURYANARAYANA M SISTA
03/31/2014

LOKESH JAIN
04/08/2014

PRODUCT QUALITY - BIOPHARMACEUTICS
FILING REVIEW

NDA Number	206-073
Submission Date	1/30/2014
Product name, generic name of the active	Glyxambi (empagliflozin/linagliptin fixed-dose combination tablets)
Dosage form and strength	IR Tablet; 10 mg/5 mg and 25 mg/5 mg
Applicant	Boehringer Ingelheim Pharmaceuticals, Inc.
Clinical Division	DMEP
Indication	adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both empagliflozin and linagliptin is appropriate
Type of Submission	505 (b)(1) New Drug Application
Biopharmaceutics Reviewer	Kareen Riviere, Ph.D.
Biopharmaceutics Team Leader	Tapash Ghosh, Ph.D.
Biopharmaceutics Supervisor (acting)	Richard Lostritto, Ph.D.

The following parameters for the ONDQA's Product Quality-Biopharmaceutics filing checklist are necessary in order to initiate a full biopharmaceutics review (i.e., complete enough to review but may have deficiencies).

ONDQA-BIOPHARMACEUTICS **A. INITIAL** OVERVIEW OF THE NDA APPLICATION FOR FILING				
	Parameter	**Yes**	**No**	**Comment**
1.	Does the application contain dissolution data?	x		
2.	Is the dissolution test part of the DP specifications?		x	The Applicant is requesting disintegration testing in lieu of dissolution testing for routine quality control testing. They have also developed a dissolution method to support future post-approval changes.
3.	Does the application contain the dissolution method development report?	x		
4.	Is there a validation package for the analytical method and dissolution methodology?		x	See the Initial Assessment section for the IR comment that will be conveyed to the Applicant.
5.	Does the application include a biowaiver request?		x	Not Applicable. Both strengths were tested in Phase 3 clinical studies.
6.	Is there information provided to support the biowaiver request?	-	-	
7.	Does the application include a IVIVC model?		x	
8.	Is information such as BCS classification mentioned, and supportive data provided?	x		The Applicant claims that both APIs are BCS Class 3 drugs substances.

Reference ID: 3473575

9.	Is information on mixing the product with foods or liquids included?		x	Not Applicable.
10.	Is there any in *vivo* BA or BE information in the submission?	x		BE component of Study 1275.3 will be reviewed by ONDQA Biopharmaceutics. The food effect component of Study 1275.3 and PK Study 1245.30 will be reviewed by OCP.
11.	Is there a complete bio-analytical method development and validation report?	x		

B. FILING CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
12.	**IS THE BIOPHARMACEUTICS SECTIONS OF THE APPLICATION FILEABLE?**	x		
13.	If the NDA is not fileable from the biopharmaceutics perspective, state the reasons and provide **filing** comments to be sent to the Applicant.	-	-	
14.	Are there any **potential review** issues to be forwarded to the Applicant for the 74-day letter?	x		IR comments will be sent to the Applicant in the 74 day letter. The comments are outlined in the Initial Assessment.

{See appended electronic signature page}
Kareen Riviere, Ph.D. 03/19/14
Biopharmaceutics Reviewer Date
Office of New Drug Quality Assessment

{See appended electronic signature page}
Tapash Ghosh, Ph.D. 03/19/14
Biopharmaceutics Team Leader Date
Office of New Drug Quality Assessment

Reference ID: 3473575

PRODUCT QUALITY - BIOPHARMACEUTICS
FILING REVIEW

INITIAL BIOPHARMACEUTICS ASSESSMENT

Boehringer Ingelheim has developed two strength of empagliflozin + linagliptin fixed-dose combination tablets (25 mg empagliflozin + 5 mg linagliptin and 10 mg empagliflozin + 5 mg linagliptin) for once daily administration. The Applicant conducted two phase 1 trials and one phase 3 trial. The Phase 3 study evaluated two doses of the empagliflozin/linagliptin tablets (25 mg empagliflozin/5 mg linagliptin and 10 mg empagliflozin/5 mg linagliptin) for 52 weeks. The final commercial formulation was used in the phase 3 study.

BE Study

The main purpose of Study 1275.3 was to investigate the relative bioavailability of the FDC tablet containing 25 mg BI 10773 and 5 mg linagliptin compared to the individual tablets administered together. The study title is "Relative bioavailability investigations of a 25 mg BI 10773 / 5 mg linagliptin fixed dose combination (FDC) tablet (formulation A1) including the comparison with its mono-components, the comparison with a second FDC tablet (formulation A3), and the investigation of food (an open-label, randomised, single dose, crossover, Phase I trial in healthy male and female volunteers)".

Figure 1. Geometric mean plasma concentration-time profiles of BI 10773 after single oral administration of 25 mg BI 10773 and 5 mg linagliptin as FDC A1 tablet (N=42) or individual tablets (N=40)

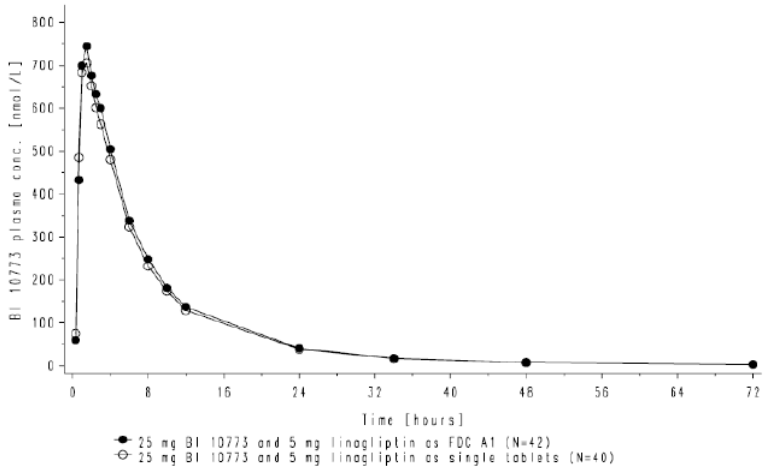


Table 1. Mean Pharmacokinetic Parameters of BI 10773 by Treatment

BI 10773		FDC A1 (N=42)		Individual tablets (N=40)	
		gMean	gCV [%]	gMean	gCV [%]
AUC_{0-tz}	[nmol·h/L]	5990	21.0	5720	20.8
C_{max}	[nmol/L]	862	26.8	803	24.9
$AUC_{0-\infty,pred}$	[nmol·h/L]	6060	20.7	5790	20.9
t_{max}[1]	[h]	1.50	0.667-4.00	1.25	0.667-3.98
$t_{1/2}$	[h]	13.3	32.7	12.9	36.4
CL/F	[mL/min]	153	20.7	159	20.9
V_z/F	[L]	175	38.3	178	35.5

[1]For t_{max}, the median and range (minimum to maximum) are given.

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Figure 2. Geometric mean plasma concentration-time profiles of linagliptin after single oral administration of 25 mg BI 10773 and 5 mg linagliptin as FDC A1 tablet (N=42) or individual tablets (N=40)

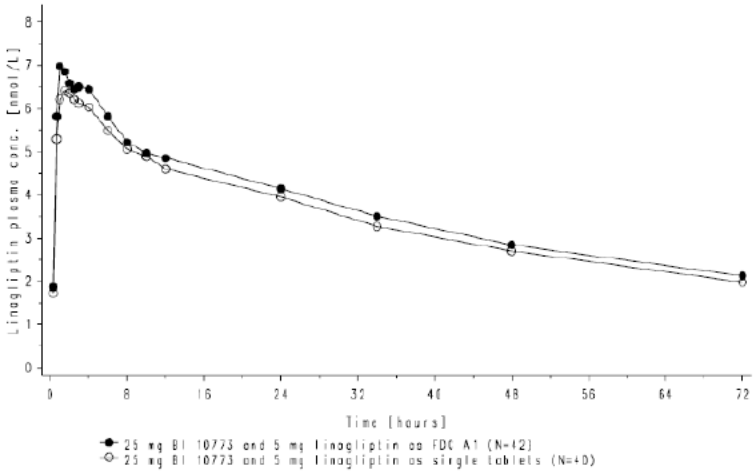

Table 2. Mean Pharmacokinetic Parameters of Linagliptin by Treatment

Linagliptin		FDC A1 (N=42)		Individual tablets (N=40)	
		gMean	gCV [%]	gMean	gCV [%]
AUC_{0-72}	[nmol·h/L]	264	22.1	250	22.1
C_{max}	[nmol/L]	8.19	36.4	7.49	31.0
$AUC_{0-\infty,pred}$	[nmol·h/L]	434	26.3	410	29.9
AUC_{0-tz}	[nmol·h/L]	264	22.1	250	22.1
t_{max}[1]	[h]	1.50	0.333-6.03	1.75	0.667-10.0
$t_{1/2}$	[h]	54.4	18.9	54.3	24.6
CL/F	[mL/min]	406	26.3	430	29.9
V_z/F	[L]	1910	22.1	2020	21.6

[1]For t_{max}, the median and range (minimum to maximum) are given.

Dissolution and Disintegration

The Applicant is requesting disintegration testing in lieu of dissolution testing for routine quality control testing. They claim that the test method used for determination of disintegration time is in compliance with the current harmonized compendial requirements for disintegration as described in USP general chapter <701>. A disintegration apparatus with disc is used, and water is used as immersion fluid.

The proposed disintegration acceptance criterion is:

Test Parameter	Method Type	Acceptance Criterion
Disintegration	Physical test	≤ (b) (4) minutes

Since dissolution testing may be needed to support future post-approval changes, the Applicant has also proposed a dissolution method and acceptance criterion.

The proposed dissolution method is:

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USP Apparatus	Rotation Speed	Media Volume	Temp	Medium
2	50 rpm	900 ml	37 °C	pH 6.8 phosphate buffer

The proposed dissolution acceptance criterion is:

Acceptance Criterion
Q = (b) (4) % at 30 min

The Biopharmaceutics review for this NDA will be focused on the evaluation and acceptability of 1) using the disintegration testing in lieu of dissolution testing, 2) the proposed dissolution method and acceptance criterion for supporting post-approval changes, and 3) the relative bioavailability data of the FDC tablet containing 25 mg BI 10773 and 5 mg linagliptin compared to the individual tablets administered together.

To aid the review of the Applicant's submission, the following comment should be conveyed to the Applicant:

1. Provide supportive validation data for the dissolution method (i.e., method robustness, etc.) and analytical method (precision, accuracy, linearity, stability, etc.).
2. Submit SAS Transport files of the pharmacokinetic data from the BE study. The data should include AUC0-t, AUC0-inf, Cmax, Tmax, Kel, and T1/2 as shown. Please submit the data in the following format:

   SUBJ SEQ PER TRT AUCT AUCI CMAX TMAX KE Thalf

RECOMMENDATION:
The ONDQA Biopharmaceutics team has reviewed NDA 206-037 for filing purposes. We found this NDA **fileable** from a Biopharmaceutics perspective. The Applicant has submitted a reviewable submission.

Reference ID: 3473575

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/s/

KAREEN RIVIERE
03/19/2014

TAPASH K GHOSH
03/19/2014