

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

206073Orig1s000

PHARMACOLOGY REVIEW(S)



Pharmacology/Toxicology
Center for Drug Evaluation and Research
Division of Metabolic & Endocrine Products

Date	13 October 2014
NDA #	206073
Sponsor	Boehringer Ingelheim
Drug	Empagliflozin/linagliptin FDC tablet
Primary Reviewer	David B. Carlson, PhD
Secondary Reviewer	Patricia Brundage, PhD

Boehringer Ingelheim is seeking approval for the fixed-dose combination product of linagliptin and empagliflozin as a treatment for type 2 diabetes. Both pharmaceutical components are currently approved for the chronic treatment of type 2. Linagliptin is a dipeptidylpeptidase-4 (DPP4) inhibitor approved in 2011 (NDA 201280) and empagliflozin is a sodium-glucose co-transporter 2 (SGLT2) inhibitor (NDA 204629) approved during the review cycle. The mechanisms of action of the two different drug classes are distinct but complementary on glucose control. Boehringer Ingelheim is the primary NDA holder for both linagliptin and empagliflozin.

Dr. David Carlson, the primary nonclinical reviewer, recommends approval of NDA 206073. *I concur with Dr. Carlson's recommendation.* The recommendation is based on the information for linagliptin and empagliflozin as monotherapies, and on the toxicology studies conducted with the drugs in combination to assess general toxicity and embryofetal development.

The toxicology of linagliptin and empagliflozin in combination was evaluated in a 3-month study in rats. Each drug was evaluated separately and in combination for comparison. No additive or unique toxicity was observed with the drugs in combination. Toxicity associated with the co-administration of the two drugs at exposures ≥ 14 -times the clinical exposure was attributable to the SGLT2 inhibitor empagliflozin and is consistent with the established toxicology profile of empagliflozin.

Co-administration of the drugs in rats caused an increase in empagliflozin exposure (2- to 3-fold), which was associated with an increase in renal and hepatic toxicity at the highest dose combination ($>50X$ clinical exposure) compared to that of empagliflozin alone. There was also a less consistent decrease in linagliptin exposure (up to 3-fold) with co-administration of the drugs. Similar changes in the pharmacokinetic profiles of the two drugs when co-administered were not observed in humans in the bioequivalence and pharmacokinetic trials with the linagliptin/empagliflozin FDC. Clinical drug-drug interactions between empagliflozin and linagliptin at clinical doses is unlikely based on in vitro metabolic enzyme induction and inhibition assays with the individual drugs, and on co-incubation assays of the two drugs in human hepatocytes. Although there is presently no mechanistic explanation for the systemic drug exposure changes in the rats, the clinical relevance is considered negligible.

An embryofetal development study in rats was conducted by the applicant. The administration of linagliptin and empagliflozin alone and in combination was not teratogenic, which is concordant with the previous findings with the individual drugs in rats and rabbits.

As both drugs target the kidney, the embryofetal development study included histopathological examination of fetal kidneys. Linagliptin accumulates in kidney tubules due to high DPP4 expression and DPP4-specific binding. Empagliflozin, which targets SGLT2 in the renal proximal tubules, causes changes in renal histology with chronic exposure and may affect fetal renal development and maturation, as determined from prior juvenile rat toxicology studies in this drug class. There was no evidence of kidney toxicity with linagliptin and empagliflozin administered alone or in combination at very high multiples of clinical exposure in the embryofetal development study, suggesting a low likelihood of an overt toxicological interaction between the two drugs on renal development.

The combination linagliptin and empagliflozin toxicity studies in rats did not identify any potential interactions between the drugs to suggest an elevated clinical risk with FDC treatment. Labeling for the combination product will be consistent with the labeling for the individual monotherapies of linagliptin and empagliflozin.

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/s/

PATRICIA M BRUNDAGE
10/13/2014

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number: 206-073

Supporting document/s: SDN-1

Applicant's letter date
(CDER Stamp Date): 30 January, 2014

Product: Empagliflozin / linagliptin FDC tablets

Indication: Type 2 Diabetes Mellitus treatment

Applicant: Boehringer Ingelheim Pharmaceuticals (BI)

Review Division: Metabolism and Endocrinology Products

Reviewer: David B. Carlson, Ph.D.

Supervisor/Team Leader: Todd Bourcier, Ph.D.

Division Director / Jean-Marc Guettier, M.D.
Deputy Director: Eric Colman, M.D.

Project Manager: Raymond Chiang, M.S.

Review Completion Date: 05 October, 2014

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 206073 are owned by BI or are data for which BI has obtained a written right of reference. Any information or data necessary for approval of NDA 206073 that BI does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as described in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 206073.

Review Notes and Abbreviations/Key

Some of the sponsor's tables and figures from the electronic NDA submission have been included and cited in this review. All drug-related trends are discussed with respect to combination empagliflozin and linagliptin coadministration in relation to concurrent vehicle control groups and individual drug substances unless otherwise noted. Vehicle for oral gavage administration was water for phentermine and 0.5% hydroxyethylcellulose unless otherwise noted. Common animal strains were used and abbreviated by common animal name, unless noted, as follows: Wistar Han rat, CD-1 mouse, Beagle dog, New Zealand White rabbit.

Key: Empagliflozin (empa), linagliptin (lina); fixed-dose combination (FDC), once daily dosing (QD); dosing groups – LD (low dose), MD (mid dose), LMD (low mid dose), HMD (high mid dose), HD (high dose); mg/kg (mg/kg/day); MRHD (maximum recommended human dose); NOAEL (no observed adverse effect level); LOAEL (lowest observed adverse effect level); statistically significant (ss); not statistically significant (nss); PD (pharmacodynamic), PK (pharmacokinetic), TK (toxicokinetic); BW (body weight); GD (gestation day)

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1 Executive Summary

1.1 Introduction

Boehringer Ingelheim (BI) has developed a Fixed Dose Combination (FDC) formulation of two of its drugs, linagliptin and empagliflozin. Linagliptin is a dipeptidyl peptidase 4 (DPP4) inhibitor approved under NDA 201280 for treatment of type 2 diabetes mellitus (T2DM). Empagliflozin is a sodium-glucose co-transporter 2 inhibitor (SGLT2 inhibitor) that was approved under NDA 204629 during this review cycle for treatment of T2DM. The nonclinical recommendation will rely in part on FDA's prior determination of safety and effectiveness for the individual drugs and the focus of this review is potential interactions between empagliflozin and linagliptin in a FDC tablet based on nonclinical data submitted in support of the FDC drug product.

1.2 Brief Discussion of Nonclinical Findings

Linagliptin and empagliflozin have distinct, complementary mechanisms of action on glucose metabolism and coadministration in a FDC tablet is expected to provide robust glucose control in diabetic patients. Estimated clinical exposures to individual drugs were originally established in monotherapy trials and the same clinical exposures were used in this review – 4750 nM*h empagliflozin at the maximum approved 25 mg dose and 158 nM*h linagliptin at the approved 5 mg dose.

There were no clear signals of increased toxicity when empagliflozin and linagliptin were coadministered to rats in subchronic (13-week) and embryofetal development toxicity studies. Toxicity in rats was driven by the SGLT2 inhibitor, empagliflozin, with empagliflozin-mediated toxicity responsible for the lowest observed adverse effect levels (LOAELs) determined in the bridging toxicity studies. Toxicity in the combination empagliflozin and linagliptin groups was consistently more severe (higher incidence, higher severity) than similar individual drug groups which was consistent with increased empagliflozin exposure in rats due to an unknown pharmacokinetic/toxicokinetic (PK/TK) interaction.

Toxicokinetic interactions were not predicted from *in vitro* metabolism based on metabolizing enzyme inhibition or induction or from hepatocyte cocultures. However, TK interactions were consistently evident in combination toxicity studies in rats. Linagliptin coadministration caused 2- to 3-fold increased plasma empagliflozin maximum (C_{max}) and total ($AUC_{0-24 h}$) exposure in rats. Empagliflozin effects on linagliptin were less consistent, but coadministration reduced linagliptin total plasma exposure (AUC) up to 3-fold, often without any change in C_{max} .

There were no apparent drug-drug interactions on plasma exposure in humans based on bioequivalence and pharmacokinetic trials with the FDC formulation. It is not clear if there are species differences between rat and human responses to coadministration or if findings in rats may simply be due to different responses to excessive dosing compared to clinical dosing. Drug interactions on rat exposure were not assessed at

lower dose combinations and the large effects on plasma exposure occurred at exposures 100-fold or greater than maximum clinical exposures. Because drug interactions have not been observed in controlled clinical trials the applicability of drug interactions on rat exposures seem limited.

Nonclinical issues relevant to clinical use are consistent with the known individual drug risks and with known risks for DPP4 inhibitor and SGLT2 inhibitor drug classes. Potential linagliptin clinical concerns include hypersensitivity/pseudoallergy, DPP4-specific targets distinct from incretin metabolism (e.g., immune system), and pancreatitis. Potential empagliflozin clinical concerns include glucosuria, urinary tract infections, and kidney toxicity (in adults or from exposure during fetal development). No new risks were clearly identified at clinical exposures of coadministered drugs, however, kidney toxicity risks may be increased due to combined empagliflozin and linagliptin exposure. Linagliptin accumulates in kidney tubules due to high DPP4 expression and DPP4-specific binding, while proximal tubules are also the empagliflozin site of action. Rat kidney toxicity was also increased with combination treatment, albeit at very high multiples of clinical exposure (> 100X MRHD) and at increased empagliflozin exposures compared to individual drug treatment. However, a search of the publically available literature did not uncover any evidence of increased nonclinical kidney toxicity with DPP4 inhibitor and SGLT2 inhibitor coadministration. Thus, potential increased clinical renal toxicity with empagliflozin and linagliptin FDC treatment exists but is largely theoretical in nature.

1.3 Recommendations

1.3.1 Approvability

Approval is recommended from a nonclinical perspective.

1.3.2 Additional Non Clinical Recommendations

None.

1.3.3 Labeling

Nonclinical labeling recommendations were included on the proposed label in the Division's shared document system (i.e., 'Sharepoint' file). Labeling recommendations were limited to combination empagliflozin and linagliptin toxicity studies relevant to the proposed FDC drug product. Current labels for monotherapy empagliflozin and linagliptin were relied on for prior findings of safety and effectiveness.

2 Drug Information

2.1 Drug

Glyxambi™ (proposed); Empagliflozin + linagliptin FDC tablets

2.1.1 CAS Registry Number

Empagliflozin – 864070-44-0
Linagliptin – 668270-12-0

2.1.2 Generic Name

Empagliflozin + linagliptin FDC

2.1.3 Code Name

Empagliflozin – BI 10773; BI 10773 XX
Linagliptin – BI 1356 BS; BI 1356

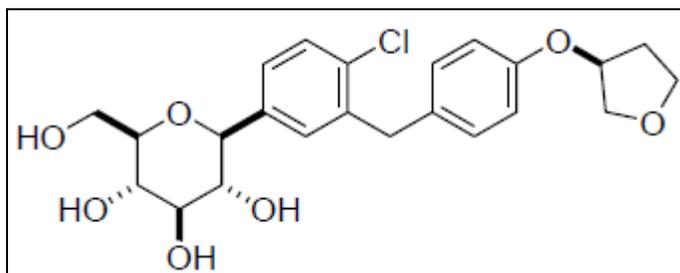
2.1.4 Chemical Name

Empagliflozin – (1S)-1,5-anhydro-1-(4-chloro-3-{4-[(3S)-tetrahydrofuran-3-yloxy]benzyl}phenyl)-D-glucitol
Linagliptin – 1H-purine-2,6-dione, 8-[(3R)-3-amino-1-piperidiny]-7-(2-butynyl)-3,7-dihydro-3-methyl-1-[(4-methyl-2-quinazoliny)methyl]-

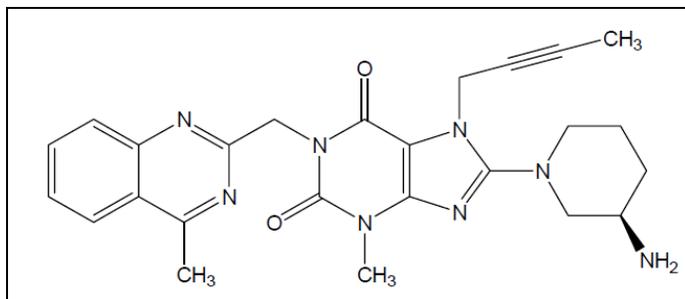
2.1.5 Molecular Formula/Molecular Weight

Empagliflozin – C₂₃H₂₇ClO₇ / 450.91 g/mol
Linagliptin – C₂₅H₂₈N₈O₂ / 472.54 g/mol

2.1.6 Structure (or Biochemical Description)



Empagliflozin



Linagliptin

2.1.7 Pharmacologic class

Sodium-glucose co-transporter 2 inhibitor (SGLT2 inhibitor) and dipeptidyl peptidase 4 inhibitor (DPP4 inhibitor)

2.2 Relevant IND/s, NDA/s, and DMF/s

Empagliflozin – NDA 204629, Jardiance® (IND 102145)

Linagliptin – NDA 201280, Tradjenta® (IND 70963); NDA 201281, Jentaducto® (b) (4)
(b) (4) – linagliptin + metformin HCl FDC)

Linagliptin / Empagliflozin FDC – IND 108,388

2.2 Drug Formulation

Two dosage strength FDC film-coated tablets for once daily oral dosing:

25 mg empagliflozin / 5 mg linagliptin

10 mg empagliflozin / 5 mg linagliptin

Both drug substances are approved for use in the United States and only the manufacturing of the two strengths of FDC tablet drug products is unique to this application. There are no novel excipients in the drug product formulation. All excipients are compendial and are similar to those used in linagliptin and empagliflozin drug products. All of the ingredients in the tablet core and in the (b) (4) coatings have been previously used in oral drugs at similar or higher concentrations and printing inks are food grade.

Table 1 – Drug product composition

Composition of empagliflozin / linagliptin film-coated tablets,
10 mg/5 mg and 25 mg/5 mg

Ingredient	Dosage strength		Function	Reference to Standards
	10 mg/5 mg	25 mg/5 mg		
Tablet core	[mg/tablet]		--	
Empagliflozin	10.00	25.00	Drug substance	Company standard
Linagliptin	5.00	5.00	Drug substance	Company standard
Mannitol	(b) (4)		(b) (4)	USP
Pregelatinized starch			NF	
Corn starch			NF	
Copovidone			NF	
Crospovidone			NF	
Talc			USP	
Magnesium stearate			NF	
(b) (4)			USP	
Film coat			[mg/tablet]	
(b) (4)	(b) (4)		(b) (4)	Company standard
(b) (4)			Company standard	
(b) (4)			USP	
Total film-coated tablet	185.0	185.0	--	--
(b) (4)	(b) (4)		(b) (4)	(b) (4)

Table 2 – Film coating excipients List

Composition of (b) (4) (b) (4) film coat

Ingredient	(b) (4)		Function	Reference to Standards
	[mg/tablet]	[mg/tablet]		
--	[mg/tablet]	[mg/tablet]	--	
Hypromellose (b) (4)	(b) (4)		(b) (4)	USP
Mannitol			USP	
Talc			USP	
Titanium dioxide			USP	
Polyethylene glycol (b) (4)			NF	
Ferric oxide, yellow			NF	
Ferric oxide, red			NF	
Total			5.00	5.00

2.4 Comments on Novel Excipients

There are no novel excipients in the proposed tablet formulations.

2.5 Comments on Impurities/Degradants of Concern

No new degradants or impurities that have not been previously qualified in the drug substances were identified by the FDA chemistry (CMC) reviewer.

2.6 Proposed Clinical Population and Dosing Regimen

The proposed clinical population of type 2 diabetes mellitus patients are similar to those indicated for use of the individual drugs. The FDC tablets are intended for patients with inadequate glucose control on individual drugs or background therapies and for whom a single combination tablet is desired. Results of pivotal clinical trials to support bioequivalence, pharmacokinetics and relative bioavailability, and safety and efficacy are summarized briefly below.

Empagliflozin and Linagliptin FDC Clinical studies 1275.3 – Bioequivalence Trial (U11-1690-01)

- Single dose bioequivalence in healthy adults
 - Cross-over design (each patient received 3 of 4 treatments)
 - Oral Dosing, QD (empagliflozin/linagliptin)
 - FDC formulation A1 (25 mg / 5 mg)
 - Fasted (n=42)
 - Coadministration 25 mg empagliflozin tablet + 5 mg linagliptin tablet
 - Fasted (n=41)
 - FDC formulation A1 (25 mg / 5 mg)
 - Fed (n=18)
 - FDC formulation A3 (25 mg / 5 mg) – slow dissolving tablet
 - Fasted (n=24)
 - Summary results
 - Bioequivalence between FDC A1 and individual tablets
 - 90% CI met acceptance of 80-125%
 - No difference in AUC or C_{max} between A1 and slow dissolving tablet FDC A3
 - FDC A1 C_{max} was lower but AUC was equivalent for both drugs in fed state compared to fasted

1245.30 – Pharmacokinetics Trial (U10-2248-01)

- 1-Week PK and relative bioavailability in healthy adults (n=16)
 - Crossover design
 - Oral Dosing, QD
 - 50 mg empagliflozin (5 days)

- 5 mg linagliptin (7 days)
- 50 mg / 5 mg empagliflozin/linagliptin (7 days)
 - Total 12 days empagliflozin (\pm linagliptin) and 14 days linagliptin (\pm empagliflozin) treatment in crossover design
- Summary results
 - Linagliptin steady state bioavailability was not affected by concomitant empagliflozin treatment
 - 90% CI met acceptance of 80-125%
 - Empagliflozin total exposure (AUC) was unaffected by linagliptin coadministration but maximum plasma exposure was decreased
 - Empagliflozin C_{max} was reduced 12% with linagliptin coadministration

1275.1 – Efficacy and Safety Trial (U13-2755-01)

- 52-Week efficacy and safety in T2DM (n=2504)
 - Treatment naïve or metformin background
 - Oral Dosing, QD (empagliflozin/linagliptin)
 - 25 mg / 5 mg or
 - 10 mg / 5 mg
 - Summary results
 - FDC treatment lowered plasma glucose (HbA_{1c} and FPG) compared to either monotherapy \pm metformin background
 - Overall safety profile similar in FDC compared to known profiles for monotherapies
 - No new safety issues identified

2.7 Regulatory Background

Both linagliptin and empagliflozin have been approved for treatment of T2DM as monotherapy. Linagliptin has also been approved for treatment of T2DM as a fixed-dose combination with metformin HCl. Empagliflozin was under review in NDA 204629 after an initial review cycle “Complete Response” letter (3/4/2014) for manufacturing deficiencies and it was approved for monotherapy use on (8/1/2014) during the review cycle for this FDC NDA.

3 Studies Submitted

3.1 Studies Reviewed

See Table of Contents.

3.2 Studies Not Reviewed

None.

3.3 Previous Reviews Referenced

Carlson, DB. NDA 201280, Pharmacology/Toxicology Review and Evaluation. March 7, 2011.

Carlson, DB. IND 108388, Pharmacology/Toxicology Review and Evaluation. July 22, 2011.

Summan, M. NDA 206429, Pharmacology/Toxicology Review and Evaluation. November 4, 2013.

4 Pharmacology

4.1 Primary Pharmacology

Empagliflozin is a reversible, competitive inhibitor of sodium-glucose co-transporter 2 (SGLT2); $IC_{50} = 1.3$ nM in vitro. Empagliflozin shows approximately 5000-fold selectivity for SGLT2 inhibition compared to SGLT1 inhibition ($IC_{50} = 6278$ nM). SGLT2 is localized to kidney proximal tubules where it facilitates reuptake of glucose prior to excretion in urine. Inhibition of SGLT2 prevents glucose reuptake in proximal tubules and results in increased glucose excretion, or glucosuria.

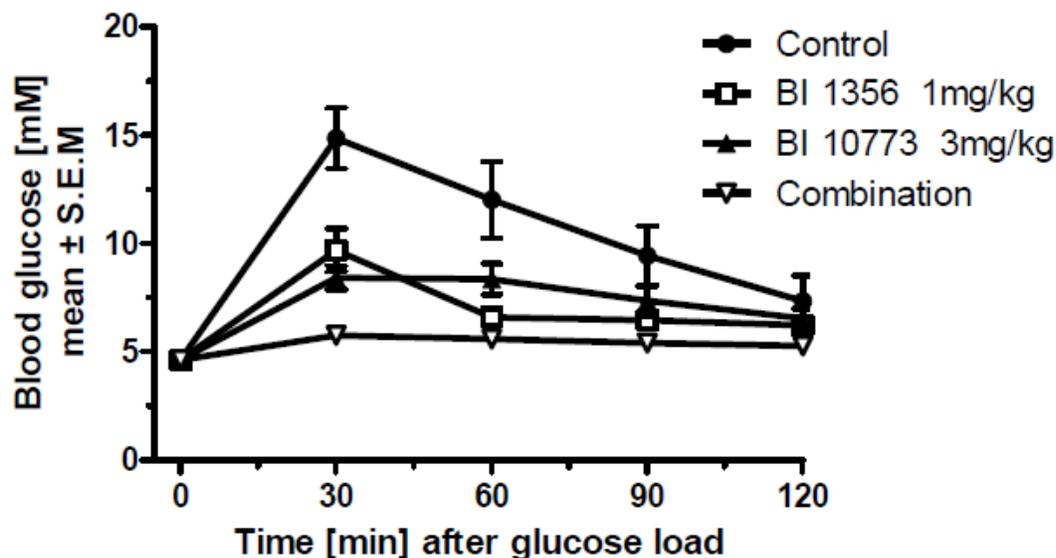
Linagliptin is a potent, selective inhibitor of dipeptidyl peptidase 4 (DPP4). DPP4 is a protease that metabolizes gut incretin hormones glucagon-like peptide 1 (GLP1) and gastric inhibitory peptide (GIP), among other substrates. Inhibition of DPP4 prolongs postprandial, glucose-dependent GLP-1 expression, leading to enhanced insulin response and glucose tolerance.

Combination of BI 10773 and linagliptin (BI 1356) in a diabetic rat model (ZDF): Effect on glucose tolerance (Study # MD2012-16-ppss, Doc. No. U12-1784-01)

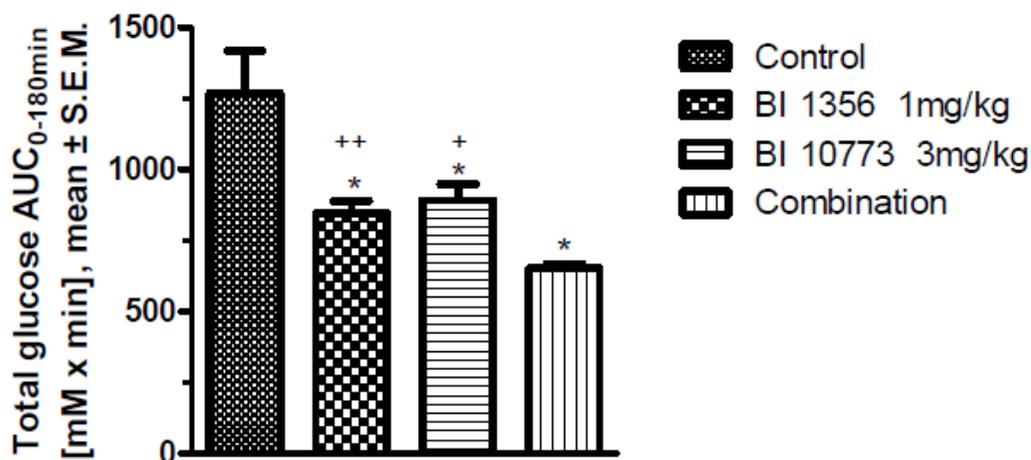
Non-GLP

Summary: Empagliflozin, linagliptin, and combined empagliflozin + linagliptin treatment were investigated for glucose lowering efficacy in 8-9 week old male Zucker Diabetic Fatty rats (ZDF-*Lep^{fa}/Crl*). Response to an oral glucose tolerance test (OGTT) of a single oral gavage dose of empagliflozin (3 mg/kg) ± linagliptin (1 mg/kg) was compared to vehicle (0.015% Tween 80, 5% hydroxyethylcellulose (Natrosol 250 HX)) and linagliptin alone. Rats were fasted overnight for 12 h, treated by gavage, and given 2 g/kg glucose orally (5 ml/kg) 30 min post-dose. Blood glucose was assessed at pre-dose, 30, 60, 90, and 120 min post-dose by tail bleed. $AUC_{0-180 \text{ min}}$ for glucose excursion was reduced 30%, 33%, or 49% by empagliflozin, linagliptin, or combined empagliflozin plus linagliptin, respectively. Results showed improved efficacy for glycemic control with approximate additive effect of combination treatment of the two drugs with distinct mechanisms. A single combination treatment resulted in virtually no blood glucose elevation 30 min or more after bolus oral glucose challenge. It is possible there was a blood glucose spike within the first 30 min after glucose challenge, as was seen at 15 min post-dose sampling in other empagliflozin studies. Results imply a robust insulin response in diabetic rats after combined empagliflozin plus linagliptin treatment.

Figure 1 – Empagliflozin + linagliptin improves glucose response in ZDF rats



Effect of single oral dosing of BI 10773, BI1356, or a combination thereof, on oral glucose tolerance in overnight fasted ZDF rats. For combination, the same doses as for monotherapy were used. Compound administration was 30 min before the test.



Total area under the blood glucose-time curves in an oral glucose tolerance test in ZDF rats after single oral dosing of BI 10773, BI 1356, or a combination thereof. The glucose-time curves are shown in [Figure 1](#); source data are given in [Table 1](#). Asterisks indicate *p* values versus control, crosses indicate *p* values versus the combination (one symbol, *p*<0.05; two symbols, *p*<0.01; three symbols, *p*<0.001).

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

Analytical Methods and Validation

Analytical methods were validated previously for individual drugs for all relevant species. Additional analytical methods reports are briefly summarized here.

BI 1356 BS 96-well method for rat, dog, and minipig plasma (Study # V203_03BE; Doc. No. U04-1551-02)

No GLP compliance statement; signed, 6/29/09

Summary: Validation of 96-well plate method for BI 1356 BS quantification in rat, dog, and minipig plasma from 0.5 to 500 nmol/L (from 50 µl plasma). Stability was confirmed in plasma for long term storage up to 14 months for rat and dog plasma. Long term minipig plasma storage was not evaluated because the species was not continued for toxicity assessment.

BI 1356 BS and CD 1750 XX 96-well method for rat plasma (Study # M217_06MI; Doc. No. U07-1768-02)

No GLP compliance statement; signed 1/14/10

Summary: Validation of 96-well plate method for BI 1356 BS and CD 1750 XX quantification in rat plasma from 2.5 to 2500 nmol/L for BI 1356 BS and 1.0 to 1000 nmol/l for metabolite CD 1750 XX (from 50 µl plasma). Stability was confirmed in plasma for long term storage up to 6 months.

Assay method validation for the quantitation of BI 10773 in EDTA Wistar rat plasma (Study # DM-06-1016; Doc. No. U08-3272-01)

GLP compliant; QA statement, signed 4/28/08

Summary: Empagliflozin quantification from Wistar rat plasma with EDTA coagulant was validated using a protein precipitation method and HPLC/MS/MS analysis. Empagliflozin was quantifiable from 50 µl rat plasma across a range of 50 to 50,000 ng/ml. Stability was confirmed in plasma for long term storage up to 6 months.

Metabolism

Effect of BI 10773 XX on the in vitro metabolism of [¹⁴C]BI 1356 BS by human hepatocytes (Study # A252-08LU; Doc. No. U09-2263-01)

Non-GLP; signed 11/2/09

Summary: Linagliptin turnover by human hepatocytes was very low in vitro. Effects of 10 µM empagliflozin on hepatocyte metabolism of 10 and 50 µM linagliptin were assessed. There were no apparent differences in linagliptin metabolism profile in the presence or absence of empagliflozin. Data suggest limited potential drug-drug

interactions on hepatic metabolism of linagliptin at estimated empagliflozin clinical plasma exposures below 1 μ M.

Effect of BI 1356 BS on the in vitro metabolism of [14 C]BI 10773 by human hepatocytes (Study # A253-08LU; Doc. No. U10-1340-01)

Non-GLP; signed 6/15/10

Summary: Empagliflozin turnover by human hepatocytes was very low in vitro. Effects of up to 50 μ M linagliptin on hepatocyte metabolism of 10 μ M empagliflozin were assessed. Two prominent metabolites, M482/1, an oxidation product, and M626/3, a glucuronic acid conjugate, were identified. Low levels of additional glucuronic acid conjugates (M626/1, M626/2) were also formed. Similar metabolites have been seen in vivo in human plasma.

Weak inhibition of empagliflozin metabolism was seen with linagliptin co-incubation. Calculated K_i of 8.8 to 69 μ M by linagliptin on empagliflozin metabolism. Estimated linagliptin plasma C_{max} were in the 10 to 20 nM range in healthy human volunteers, or approximately 3 orders of magnitude lower than estimated in vitro K_i values that may affect empagliflozin metabolism. Based on the very low ratios of estimated drug concentration to estimated K_i (1/500 or less) the in vivo risk for drug-drug interactions is remote.

5.2 Toxicokinetics

Pharmacokinetics of BI 1356 (linagliptin) with concomitant administration of BI 10773 in rats (Study # A229-10RB; Doc. No. U10-2636-01)

No GLP compliance statement; signed 10/24/10

Summary¹: Linagliptin (BI 1356) and BI 10773 (empagliflozin) were administered in single oral gavage doses (10 ml/kg in 0.5% hydroxyethyl cellulose (Natrosol® 250X) vehicle) alone or concomitantly to Wistar Han rats. BI 10773 (75 or 250 mg/kg) was dosed at a 5-fold excess compared to linagliptin (15 or 50 mg/kg). Dose ratios were based on a planned maximum 5-fold excess BI 10773 in clinical FDC tablets. Blood was collected for analysis at 0.25, 0.5, 1, 2, 4, 8, 24 h postdose (100 μ l, potassium-EDTA anticoagulant). Only linagliptin concentrations were analyzed, so no potential effect of linagliptin on BI 10773 pharmacokinetics could be determined.

Linagliptin mean C_{max} was similar when dosed alone or in combination, but total exposure (AUC_{0-24}) decreased modestly (\downarrow 33-39%) when dosed in combination. Plasma T_{max} and $t_{1/2}$ trends from combination dosing suggested faster clearance or a potential effect on linagliptin plasma protein distribution, as T_{max} curves were shifted from a clear biphasic peak plasma distribution with peaks at 0.25 h and 4 h and $t_{1/2}$ decreased 35-37% in combination (see Sponsor's summary table and figures below).

¹ Carlson, DB. IND 108388, Pharmacology/Toxicology Review and Evaluation. July 22, 2011.

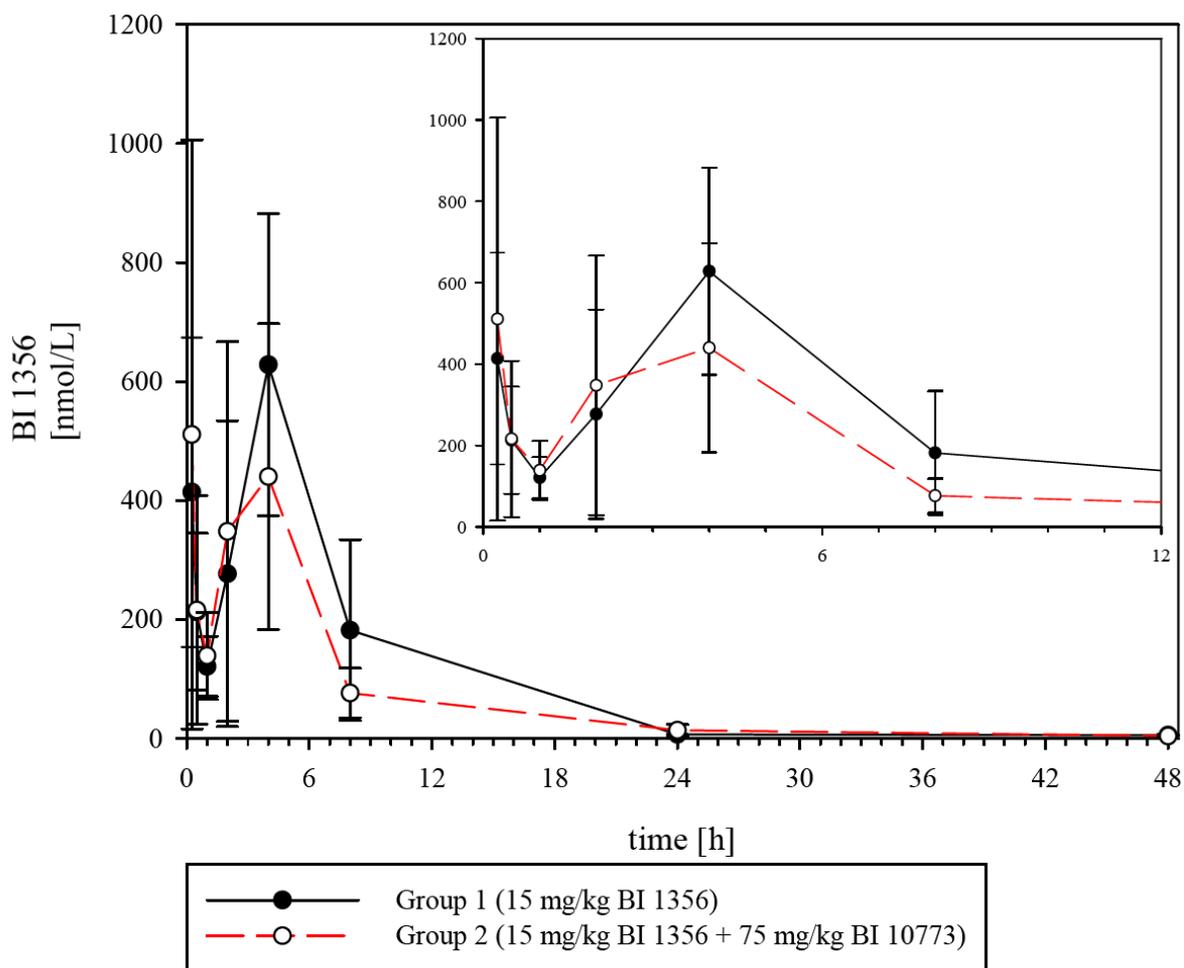
Table 3 – Linagliptin + BI 10773 PK summary (Sponsor table)

Summary Table: PK parameters of BI 1356 in rats dosed with BI 1356 alone or concomitantly with BI 10773

		Group 1 15 mg/kg BI 1356			Group 2 15 mg/kg BI 1356 + 75 mg/kg BI 10773		
Parameter	Unit	mean	SD	CV	mean	SD	CV
C(max)	nmol/L	630	252	40.0	757	348	45.9
C(max)/dose	(nmol/L)/(mg/kg)	42.1	16.8	40.0	50.6	23.2	45.9
t(max)*	h	4	2-4		1.13	0.25-4	
t(1/2)	h	46.0	12.5	27.1	19.1	7.26	38.0
MRT(tot)	h	13.8	3.34	24.2	9.00	2.30	25.5
AUC(0-24h)	nmol·h/L	4450	1450	32.5	3030	1230	40.7
AUC(0-48h)	nmol·h/L	4600	1460	31.8	3250	1170	35.9
AUC(0-inf)	nmol·h/L	4590	1670	36.4	3370	1190	35.2
AUC(0-inf)/dose	(nmol·h/L)/(mg/kg)	306	111	36.4	225	79.2	35.2
		Group 3 50 mg/kg BI 1356			Group 4 50 mg/kg BI 1356 + 250 mg/kg BI 10773		
Parameter	Unit	mean	SD	CV	mean	SD	CV
C(max)	nmol/L	3680	1250	34.0	3920	634	16.2
C(max)/dose	(nmol/L)/(mg/kg)	73.6	25.0	34.0	78.3	12.7	16.2
t(max)*	h	4	2-4		3	0.25-4	
t(1/2)	h	18.4	3.97	21.6	11.5	2.08	18.1
MRT(tot)	h	6.29	0.616	9.8	5.03	0.443	8.8
AUC(0-24h)	nmol·h/L	35900	17300	48.3	22000	4680	21.3
AUC(0-48h)	nmol·h/L	36200	17300	47.7	22500	4700	20.9
AUC(0-inf)	nmol·h/L	36400	17300	47.6	22600	4720	20.9
AUC(0-inf)/dose	(nmol·h/L)/(mg/kg)	728	346	47.6	452	94.2	20.9

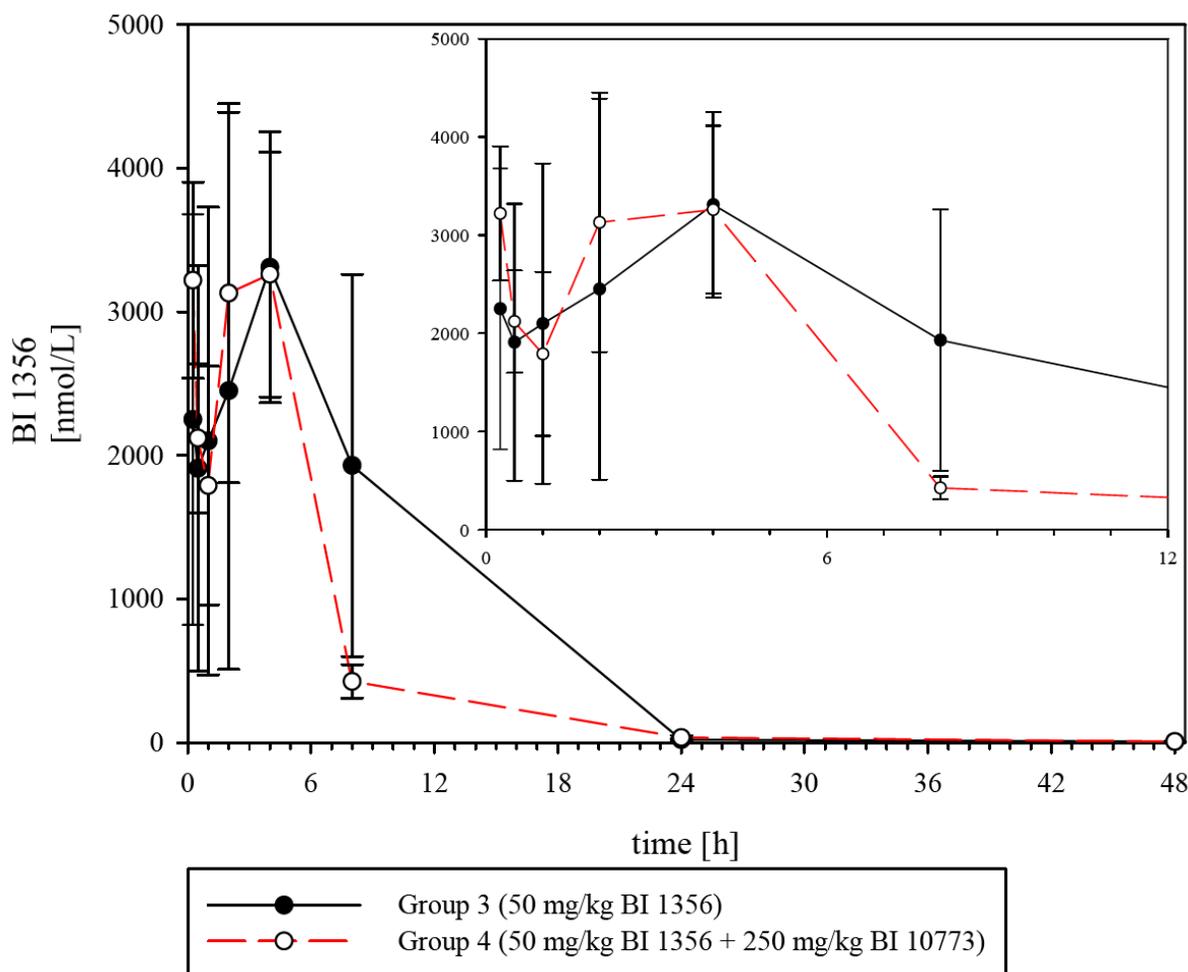
* median and range

Figure 2 – Linagliptin in rat plasma (LD oral coadministration with empagliflozin)



Mean (\pm SD) of BI 1356 in plasma after single oral (gavage) administration of 15 mg/kg (31.7 μ mol/kg) BI 1356 with or without concomitant BI 10773 to rats (Groups 1 and 2).

Figure 3 – Linagliptin in rat plasma (HD oral coadministration with empagliflozin)



Mean (\pm SD) of BI 1356 in plasma after single oral (gavage) administration of 50 mg/kg (106 μ mol/kg) BI 1356 with or without concomitant BI 10773 to rats (Groups 3 and 4)

6 General Toxicology

Pivotal toxicology studies to support the FDC application were limited to bridging studies for subchronic toxicity and embryofetal development in rats with coadministration of approved drug substances empagliflozin and linagliptin. All other toxicity studies to support individual drugs have been reviewed under prior NDAs.

6.2 Repeat-Dose Toxicity

2-Week rat combination empagliflozin + linagliptin toxicity

GLP statement, signed 4/27/2011 (Study No. 09R180; Doc. No. U11-3125-01)

*0/0, 30/15, 100/50, 500/250, 500/0 mg/kg/d empagliflozin/linagliptin
NOAEL = 30/15 mg/kg empagliflozin/linagliptin (3X/5X MRHD)*

Summary and Key Study Findings²: Toxicity was mostly limited to the HD BI 10773 groups, alone or in combination with linagliptin, with toxicity slightly increased in the combination group. There was no apparent additive toxicity of linagliptin and BI 10773, but higher exposure to BI 10773 in the HD combination group likely contributed to slightly higher toxicity in the combination. Data showed HD combination treatment stressed the animals and many findings were secondary to decreased body weight (due to exaggerated pharmacology). Male reproductive tissue atrophy was seen in the HD combination but not HD BI 10773, consistent with toxicity at high linagliptin exposures (and consistent with other DPP4 inhibitors). No kidney mineralization was seen (which was seen in the 6-month BI 10773 rat study at all doses).

- NOAEL = 30/15 mg/kg/d empagliflozin / linagliptin based on modest dose-related toxicity in MD combination and more pronounced effects in animals treated with HD BI 10773 (empagliflozin) alone or in combination. Dose-related findings at MD combination (100/50) were consistent with HD findings but MD toxicity was generally minimal and reversible.
- No apparent effect of combination treatment on toxicity in rats
 - Toxicity was generally attributed to BI 10773 (alone or in combination), although slightly greater toxicity in combination with linagliptin which was likely due to increased exposure to BI 10773 in combination
- Decreased BW and BW gain at the HD combination and HD BI 10773 alone, consistent with SGLT2 inhibitor class and glucosuria. BW effects likely contributed to stress and depletion of fat stores seen in various tissues.
- HD BI 10773 treatment (alone or in combination) identified target organs of liver, kidney, GI tract organs, pancreas, male reproductive tissues (prostate, seminal

² Carlson, DB. IND 108388, Pharmacology/Toxicology Review and Evaluation. July 22, 2011.

vesicles), bone, and thymus and spleen depletion consistent with response to stress.

Empagliflozin – AUC_{0-24h} (µg*h/ml)				
Dose (mg/kg)	Males		Females	
	Day 1	Day 14	Day 1	Day 14
30/15	13	14	25	17
100/50	67	56	77	58
500/250	140	533	258	604
500/0	124	259	129	428

Linagliptin – AUC_{0-24h} (µg*h/ml)				
Dose (mg/kg)	Males		Females	
	Day 1	Day 14	Day 1	Day 14
15/30	0.4	0.5	1	1
50/100	4	3	3.5	2
250/500	28	40	41	82

13-Week rat combination empagliflozin + linagliptin toxicity

GLP statement, signed 10/24/2011

*0/0, 6/30, 15/30, 20/100, 60/300, 60/0, 0/300 mg/kg/d linagliptin/empagliflozin
NOAEL = 15/30 mg/kg linagliptin/empagliflozin (9X/3X MRHD)*

BI 1356 (linagliptin) and BI 10773: 13-Week oral (gavage) combination toxicity study in rats Amendment No. 1 (Study No. 10B060-AM1; Doc. No. U11-1622-01-AM1)

Summary and Key Study Findings³: Liver was identified as the major target organ based on increased LFTs, although histopathological lesions (low incidence of necrosis) could not explain the biomarker increases. LFT increases were fully or partially reversed after the recovery period and they are routinely monitored in clinical trials. Kidney toxicity was also evident as increased kidney weight and tubular dilatation, consistent with SGLT2 inhibitor effects secondary to exaggerated pharmacology. BI 10773 toxicity in a chronic rat study included dose-related adrenal vacuolation and hypertrophy, liver hepatocellular vacuolation (lipid accumulation), and kidney tubular and cortical

³ Carlson, DB. IND 108388, Pharmacology/Toxicology Review and Evaluation. July 22, 2011.

mineralization which were not clearly seen in this study. There was no apparent additive toxicity in the combination groups, although toxicity in the HD combination was often slightly greater than in the HD BI 10773 group, likely due to higher exposure to BI 10773 when given in combination. NOAEL = 15/30 mg/kg linagliptin/BI 10773 based on the absence of kidney tubule dilatation and other modest signs of toxicity at 20/100; nevertheless, major conclusions of the study were (1) there were no remarkable signs of additive toxicity when combining linagliptin and BI 10773 treatment, and (2) toxicity was generally driven by BI 10773 and consistent with the SGLT2 inhibitor class.

- Kidney toxicity evident based on increased kidney weights and tubular dilatation, consistent with SGLT2 inhibitor class effects secondary to exaggerated pharmacology.
 - Kidney toxicity was partially reversed after a 6-week recovery period.
- Liver toxicity was suggested from elevated serum biomarkers (ALT, AST, ALP, GGT, GLDH) and modest relative liver weight increases, although there were no clear gross or histological correlative lesions.
 - Liver toxicity was largely reversible with the exception of GGT and GLDH
- Toxicity was driven by BI 10773. Combination treatment with linagliptin did not produce any clearly additive toxicity of the DPP4 and SGLT2 inhibitors.
- Toxicity was slightly worse in the high dose combination treatment compared to BI 10773 treatment alone, however co-administration with linagliptin resulted in increased plasma BI 10773 which likely accounted for increased toxicity.
- Co-administration in rats resulted in approximately 50-100% increased maximum (C_{max}) and total (AUC) exposure to BI 10773 and approximately 3-fold decreased linagliptin C_{max} and AUC compared to treatment with individual drugs. No drug-drug interactions were predicted from *in vitro* metabolism data and the mechanisms by which exposure varies with combination treatment are not known.
- NOAEL = 15 mg/kg linagliptin / 30 mg/kg BI 10773 (9X linagliptin / 3X BI 10773 MRHD), based on reversible, modest dose-related kidney and liver toxicity in the 20/100 mg/kg combination group and more pronounced toxicity and decreased BW gain in the 50/300 mg/kg combination group.

Rat AUC_{0-24h} (µM*h)				
Linagliptin/ empagliflozin (mg/kg)	Males		Females	
	Day 1	Day 80	Day 1	Day 80
6/ 30	0.33/ 18	0.36/ 19	0.39/ 19	0.46/ 26
15/ 30	1.7/ 18	1.2/ 18	1.7/ 18	1.7/ 22
20/ 100	2.0/ 73	1.6/ 79	3.1/ 59	2.7/ 65
60/ 300	12/ 276	10/ 240	17/ 196	9/ 314
60/ 0	20/ --	32/ --	25/ --	21/ --
0/ 300	--/ 153	--/ 130	--/ 187	--/ 163

8 Carcinogenicity

Carcinogenicity of individual drugs empagliflozin and linagliptin are listed in the approved drug labels. Carcinogenic potential of combined empagliflozin and linagliptin treatment has not been investigated. A brief discussion of carcinogenicity findings in individual drug studies and potential clinical carcinogenicity risks are provided here.

Empagliflozin treatment did not cause drug-related tumors in female rats or mice at exposures up to 72-times and 62-times clinical exposures, respectively. Male rats had Leydig cell tumors at 42X MRHD or greater, consistent with findings in the SGLT2 inhibitor class, which are not thought to predict significant human risk due to species differences in physiology and Leydig cell tumor induction. Whole body/cavity hemangioma from the mesenteric lymph node were seen at 42-times clinical exposures, which have not been observed in other SGLT2 inhibitor drugs.

Renal tubular adenoma and carcinoma (combined) were seen in male rats treated chronically with approximately 45-times greater empagliflozin than expected maximum clinical exposures. Male rats with renal tumors also showed renal atypical hyperplasia and renal cystic tubular hyperplasia was seen at all doses in male rats. Based on the presence of renal tubular injury preceding or concomitant with renal tumors, it was considered "likely that renal tumors were the culmination of chronic renal injury over the two year dosing period".⁴

NOAELs for tumor induction were identified in both sexes of mice and rats. Male NOAELs in rats (17- to 21-times MRHD) and mice (4- to 7-times MRHD) were seen at 2- to 10-fold lower exposures than LOAELs for tumor induction in males. NOAELs in females were higher than males in rats (72X MRHD) and mice (62X MRHD).

During the original review of empagliflozin the Sponsor submitted several mechanistic studies and a 'Nonclinical Expert Statement' characterizing the male mouse specific renal tumors. The expert statement was submitted to support the review of the empagliflozin and linagliptin FDC under this NDA. A full review of the purported mechanisms of male mouse renal tumors is beyond the scope of this review based on the FDA's prior findings of safety and effectiveness for empagliflozin (and linagliptin). The Sponsor's analysis suggests a multi-step process including species dependent metabolism that are unlikely in humans. In short, the events in male mice were reported to include: (1) a diminished oxidative stress response and sensitivity to renal cystogenesis in male mice compared to female mice or other species; (2) pharmacology related renal stress associated with processing excess urine volume and urine glucose; (3) drug-specific renal metabolic stress associated with oxidative stress from a 4-OH crotonaldehyde (4-OH CTA) in male mice compared to predominantly Phase 2 conjugative O-glucuronidation in humans; (4) exhaustion of stress handling 'reserve'

⁴ Summan, M. NDA 206429, Pharmacology/Toxicology Review and Evaluation. November 4, 2013.

capacity in chronic exposure to 4-OH CTA and chronic oxidative and pharmacologic renal stress; and, (5) conversion to constitutive cell growth and a 'proliferative phenotype' resulting in tumor progression.

Linagliptin did not cause any treatment-related tumors in rat (418X MRHD) or male mouse (271X male) in lifetime carcinogenicity studies. Malignant lymphoma was induced at very high exposure multiple in female mice, 271X MRHD, but not at 34X clinical exposures.

Neither empagliflozin nor linagliptin have significant genotoxic potential based on absence of genotoxicity *in vitro* or in rodents. The absence of exacerbated toxicity in the 13-week combination study or predicted interactions on tumor response suggest limited potential for drug interactions that would increase carcinogenic risk. Regardless of the exact mechanism of action in male mice, renal tumors and other tumors in male rats occur at high exposure margins and human renal tumor risk is considered minimal or remote at clinical exposures. Limited clinical carcinogenic risk is predicted from either individual drugs alone or in combination.

9 Reproductive and Developmental Toxicology

Fertility and early embryonic development, embryofetal development, and pre-/post-natal development were investigated in individual drugs. Embryofetal development in rats coadministered linagliptin and empagliflozin was investigated to bridge to the existing reproductive and developmental toxicology data for the individual drug substances.

9.2 Embryonic Fetal Development

Embryofetal rat development range-finding (Seg 2 combination empa + lina)

Non-GLP ('GLP 'principles'), signed 11/6/13

BI 1356 and BI 10773: Dose-range finding study for effects on embryo-fetal development in rats (oral administration by gavage) (Doc. No. U13-2536-01, Study No. 11B226)

Doses 0/0 (vehicle control)
(mg/kg/d) 15/30, 60/300, 140/700 (Linagliptin / Empagliflozin)

NOAEL (maternal) = 15/30 (Linagliptin / Empagliflozin)

NOAEL (fetal) = 60/300 (Linagliptin / Empagliflozin)

NOAEL determination – Maternal toxicity was evident at $\geq 60/300$ mg/kg linagliptin/empagliflozin due to reduced body weight gain and reduced food consumption during treatment. Fetal body weights were reduced at the high dose of 140/700 mg/kg linagliptin/empagliflozin.

Key study findings:

- Dose range finding study for definitive combination oral empagliflozin/linagliptin rat embryofetal development study
 - Doses chosen from general combination toxicity study in rats to cover range from no adverse effect to moderate toxicity
- Dose-related decreased maternal body weight gain, including body weight loss during treatment in HD combination (140/700 mg/kg)
 - Body weight gain recovered after treatment ended, commensurate with increased food consumption (dose-related), but MD and HD maternal body weight remained below controls
- Food consumption was reduced during treatment, supporting dose-related maternal toxicity
- Maternal plasma glucose trended lower with increasing dose at the end of the treatment period (no statistical analysis was performed)

- Maternal hypoglycemia would increase the risk of adverse effects on fetal development
- Doses proposed for definitive study – 15/30, 60/300, 140/700 mg/kg linagliptin/empagliflozin
 - Dose groups expected to be NOAEL (LD), no or slight maternal toxicity (MD), and distinct signs of toxicity (HD)

Study no: Doc. U13-2536-01, Study 11B226
Study report location: eCTD N-0001/4.2.3.5
Conducting laboratory and location: BI Nonclinical Drug Safety Germany (NDS GER)
Biberach, Germany
Date of study initiation: 1/5/12 (animal arrival and acclimatization)
GLP compliance: No
QA statement: None
Drug, lot #, and % purity: BI 1356 BS, Batch 1050530, 99.8% purity;
BI 10773 XX, Batch 1045396, 99.6% purity

Methods

Doses: 0/0, 15/30, 60/300, 140/700 mg/kg
linagliptin/empagliflozin
Frequency of dosing: Daily – GD 7 to GD 16
Dose volume: 10 ml/kg
Route of administration: Oral
Formulation/Vehicle: 0.5% hydroxyethylcellulose (Natrosol® 250 HX)
Species/Strain: Female rat (presumed pregnant) / CrI:WI(Han)
Number/Sex/Group: 10
Satellite groups: 3/group/timepoint (TK and blood glucose on GD 7 and GD 16)
Study design: In life (maternal mortality, clinical observations, BW, food consumption) and Caesarean section GD 22 (corpora lutea, implantation sites, fetuses (live, dead, resorptions), fetal weight, sex, external abnormalities); maternal blood (main study) at necropsy for fructosamine determination.
Deviation from study protocol: None that affected integrity or outcome of the study.

Study Design Summary

BI 1356 and BI 10773: Dose-range finding study for effects on embryo-fetal development in rats – Study design, groups and animal numbers

Group	Females/group	Daily dose [mg/kg]			Animal numbers [†]	
		BI 1356 BS	BI 10773 XX		Main study	Toxicokinetics/ Clinical chemistry
1	16	0	0		107-116	101-106
2	16	15	30		203, 208-216	201, 202, 204-206
3	16	60	300		307-316	301-306
4	16	140	700		407-416	401-406

[†] non-pregnant main study animals: 107, 111, 113, 314; non-pregnant satellite animals: 303
Animal 203 died during anaesthesia before treatment (1st blood sample) on GD7 and was excluded from the study.

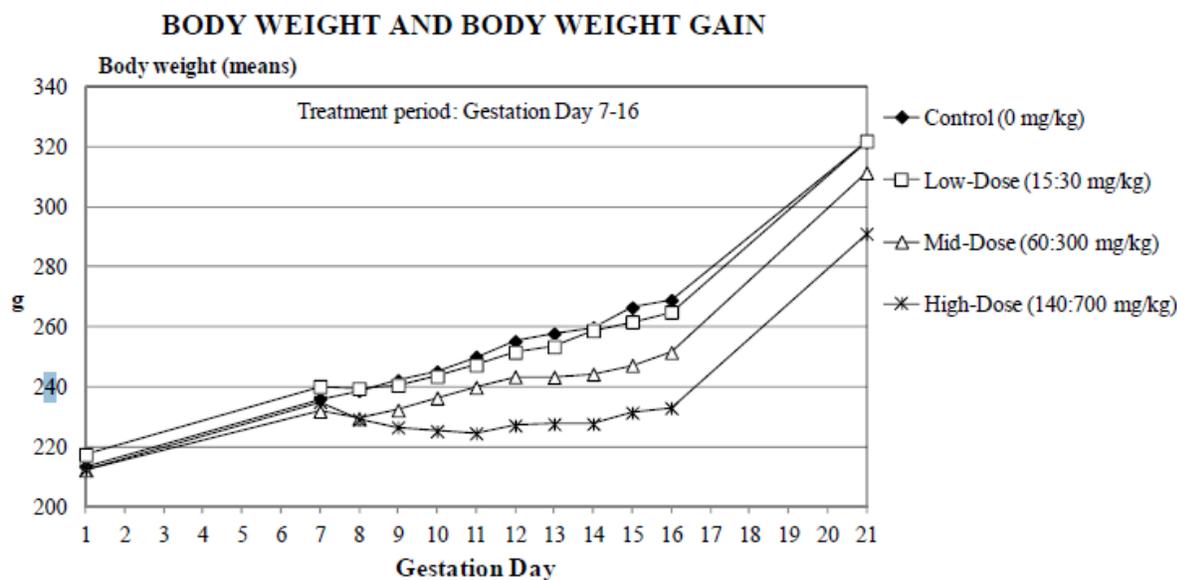
Observations and Results:

Mortality – None.

Clinical Signs – Unremarkable.

Body Weight (GD 1, 7-16, 21) – Dose-related effects on maternal body weight gain and body weight, consistent with exaggerated pharmacologic effect of SGLT2 inhibition by empagliflozin (glucosuria). Low dose effects were unremarkable, with slightly reduced BW gain at the beginning of dosing (GD 9-13; ss) but maternal BW was unaffected. Mid dose BW gain was reduced during treatment (GD 8-9 and GD 11-16, ss), concomitant with reduced food consumption; maternal BW was reduced during treatment (GD 15, ss) but was not statistically different from control at study termination after post-treatment BW gain. High dose combination treatment resulted in reduced BW gain from GD 8 (GD 8 – GD 21, ss) with reduced food consumption, resulting in reduced maternal BW (GD 8 – 16, ss; ↓ 10% study termination, ss) with body weight loss compared to GD 7 from GD 8 – 16. BW gain increased in MD and HD dams from GD 17 through study termination after treatment ended.

Figure 4 – Body weight effects (embryofetal rat rangefinding)



Feed Consumption (GD 7, 14, 21) – Food consumption measurements were limited and did not correspond directly with the treatment period (GD 7 – 16), limiting the power of the data. Reduced maternal food consumption was seen in MD (↓ 10%, nss) and HD (↓ 33%, ss) during treatment (GD 14 measurement), showing evidence of maternal toxicity. Food consumption increased in HD during week 3 (↑ 11%, ss; GD 21 measurement), suggesting compensatory increased food consumption post-treatment. Water consumption increased in MD and HD from GD 7 until necropsy (estimated by visual examination). Reduced body weight gain due to exaggerated pharmacology with SGLT2 inhibitors ordinarily results in increased food consumption, presumably compensatory to consistently reduced blood sugar due to glucosuria, in rats and other animals. The dose-related decreased maternal food consumption suggests drug-related maternal toxicity.

Toxicokinetics (GD 7, GD 16 @ 0, 0.5, 1, 3, 8, 24 h postdose; non-fasted animals) –

Drugs were readily absorbed and exposure in dams increased with increasing dose. No control drug monotherapy groups were included in the study so exposure from combination treatment could not be compared to monotherapy trends.

Empagliflozin (dams)

Parameter	Dosing Day	Gestation Day	15 mg/kg	60 mg/kg	140 mg/kg
			BI 1356	BI 1356	BI 1356
			+30 mg/kg	+300 mg/kg	+700 mg/kg
			BI 10773	BI 10773	BI 10773
C(max)	1	7	308	1470	8160
[(nmol/L)]	10	16	224	2710	9120
AUC(0-24h)	1	7	1270	7810	50200
[(nmol·h/L)]	10	16	2150	25700	92800

Empagliflozin (dams)

Parameter	Dosing Day	Gestation Day	15 mg/kg	60 mg/kg	140 mg/kg
			BI 1356	BI 1356	BI 1356
			+30 mg/kg	+300 mg/kg	+700 mg/kg
			BI 10773	BI 10773	BI 10773
C(max)	1	7	8170	29000	51000
[(nmol/L)]	10	16	2720	44400	98100
AUC(0-24h)	1	7	16500	231000	320000
[(nmol·h/L)]	10	16	17800	490000	839000

Plasma glucose was assessed in non-fasted animals from TK blood samples. Trends suggested blood glucose was trending lower after treatment, with glucose lowering effect increased with dose. No statistical analysis was done.

Plasma glucose – Rat embryofetal development rangefinding

Daily dose of BI 1356 BS:BI 10773 XX [mg/kg]	Group	Gestation Day	Sample time point					
			Pre-Dose	0.5 h	1 h	3 h	8 h	24 h
0:0	1	7	9.84	14.00	13.71	12.10	12.31	11.99
		16	7.40	8.78	8.44	10.03	9.48	8.54
15:30	2	7	9.68	10.03	9.62	10.17	10.40	10.82
		16	8.56	9.08	9.17	9.02	8.05	8.35
60:300	3	7	10.28	9.61	8.56	8.45	5.93	9.58
		16	7.79	7.74	8.17	8.57	7.61	7.61
140:700	4	7	9.91	9.95	9.28	8.74	6.25	8.90
		16	8.05	7.20	6.73	6.86	7.08	6.43

Further details are described in the raw data of laboratory for Clinical Pathology.

Fructosamines were determined from 0.3 ml blood drawn at necropsy (potassium-EDTA anticoagulant, non-fasted animals). Fructosamines were used as a marker of average plasma glucose over a longer preceding time period than glucose. No clear drug-related trends were evident. HD fructosamine was approximately 7% lower than controls and other treatment groups at necropsy but variability was high and relationship to drug was not clear.

Necropsy –

Cesarean Section Data (Implantation Sites, Pre- and Post-Implantation Loss, etc.)

Pregnancy was confirmed in 7, 9, 9, and 10 females in control, LD, MD, and HD groups, respectively. Any pregnancy differences (or early resorptions) were unrelated to treatment because presumed pregnant rats were started on study GD 1 prior to treatment beginning GD 6. One control female had only resorptions at c-section, while all other dams had viable fetuses at necropsy.

No apparent treatment-related effects on number of corpora lutea, implantations, viable fetuses, pre-implantation loss (prior to dosing), or resorption rate. Fetuses in combination HD (140/700 mg/kg) had slightly lower mean body weight compared to controls but differences were not statistically significant.

Offspring (Malformations, Variations, etc.) – None. No external variations or malformations seen in any group. No visceral or skeletal examinations performed.

Embryofetal development in rat (Seg 2 rat combination empa + lina)

GLP compliant, signed 11/13/13

BI 1356 and BI 10773: Study for effects on embryo-fetal development in rats (oral administration by gavage) (Document No. U13-2287-01, Study 12B124)

Doses 0/0 (vehicle control)
(mg/kg/d) 15/30, 60/300, 140/700, 140/0, 0/700 (Linagliptin / Empagliflozin)
9X/5X, 227X/199X, 353X/253X, 483X/0, 0/94X MRHD

NOAEL (maternal) = 15/30 mg/kg (Linagliptin / Empagliflozin) (9X / 15X MRHD)

NOAEL (fetal) = 60/300 mg/kg (Linagliptin / Empagliflozin) (227X / 199X MRHD)

NOAEL determination – Slight, transient decreased maternal body weight gain in LD (15/30 mg/kg linagliptin/empagliflozin) was likely due to exaggerated pharmacology and not considered adverse in the absence of reduced food consumption or BW effects at study termination. Decreased fetal weight in the HD (140/700 mg/kg) was the only treatment-related fetal finding.

Key study findings:

- Dose-related reduced maternal body weight gain and body weight loss (HD only) during treatment
 - BW gain recovered slightly after the initial dose (except HD) and BW gain recovered during the post-dosing period
 - Maternal body weight remained lower (↓ 12%) in the HD at study termination compared to controls
 - Concomitant dose-related reduced food consumption during treatment consistent with maternal toxicity (≥ 60 mg/kg linagliptin, ≥ 300 mg/kg empagliflozin) rather than exaggerated pharmacology
- Dose-related decreased plasma glucose during treatment (absent in LD dams)
- Fetal body weight mean was reduced 5% in the HD, consistent with reduced maternal BW gain and lower BW at study termination
- No clear drug-related increase in malformations
- Numerous skeletal ossification delays (variations) in various bones were increased in the HD combination (140/700)
 - Consistent with reduced fetal BW (i.e., delayed fetal growth), typically corrected during post-natal bone growth and remodeling
 - Consistent with maternal toxicity during organogenesis (the treatment period)
- No effects of treatment on kidney development, including histopathology
- Linagliptin exposure decreased 30% to 60% with empagliflozin coadministration.
- Empagliflozin exposure markedly increased nearly 3-fold with linagliptin coadministration.

Study no:	Doc. No. U13-2287-01, Study No. 12B124
Study report location:	eCTD N-0001/4.2.3.5
Conducting laboratory and location:	BI Nonclinical Drug Safety Germany (NDS GER) Biberach, Germany
Date of study initiation:	Not noted (original protocol not provided); in-life study initiated 9/6/12 (animal arrival)
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	BI 1356 BS, Batch 1059019, 99.5% purity; BI 10773 XX, Batch 1045396, 99.6% purity

Methods	
Doses:	0/0, 15/30, 60/300, 140/700, 140/0, 0/700 mg/kg linagliptin/empagliflozin; Dose ratios of 1:2 (LD) and 1:5 (MD, HD) cover intended clinical FDC dose ratios
Frequency of dosing:	Daily – GD 7 to GD 16
Dose volume:	10 ml/kg
Route of administration:	Oral
Formulation/Vehicle:	0.5% hydroxyethylcellulose (Natrosol® 250 HX); concentration, homogeneity, and stability were confirmed within $\pm 5\%$ throughout the study
Species/Strain:	Female rat (presumed pregnant) / CrI:WI(Han)
Number/Sex/Group:	24
Satellite groups:	12 (3/group/timepoint) (maternal TK and blood glucose on GD 7 and GD 16)
Study design:	In life (maternal mortality, clinical observations, BW, food/water consumption) and Caesarean section GD 22 (corpora lutea, implantation sites, fetuses (live, dead, resorptions early/late), fetal weight, sex, external abnormalities); fetal exams for external, visceral, skeletal variations and malformations; fetal kidney histopathology at terminal necropsy; histopathology of other “selected organs” from gross morphological findings and “on decision of the Study Director”
Deviation from study protocol:	Unremarkable. No deviations affected study outcome.

Study Design Summary

BI 1356 and BI 10773: Study for effects on embryo-fetal development in rats – Study design, groups and animal numbers

Group	Females/group	Daily dose [mg/kg]		Animal numbers [†]	
		BI 1356 BS	BI 10773 XX	Main study	Toxicokinetics/ Clinical chemistry
1	36	0	0	107-116, 120-122, 126-136	101-106, 117-119, 123-125
2	36	15	30	207-216, 220-222, 226-236	201-206, 217-219, 223-225
3	36	60	300	307-316, 320-322, 326-336	301-306, 317-319, 323-325
4	36	140	700	407-416, 420-422, 426-436	401-406, 417-419, 423-425
5	36	140	0	507-516, 520-522, 526-536	501-506, 517-519, 523-525
6	36	0	700	607-616, 620-622, 626-636	601-606, 617-619, 623-625

[†] non-pregnant main study animals: 113, 116, 209, 222, 231, 233, 235, 310, 312, 409, 413, 427, 520; non-pregnant satellite animals: 223, 501

The volume administered was adjusted daily according to the actual body weight of the animals. The Control group received the vehicle, 0.5% hydroxyethylcellulose (Natrosol[®] 250 HX), dissolved in demineralised water. The dose volume was 10 mL/kg body weight in each group. The females were treated (orally, gavage) from early to late organogenesis (GD 7-16).

Observations and Results:

Mortality – None.

Clinical Signs – Unremarkable.

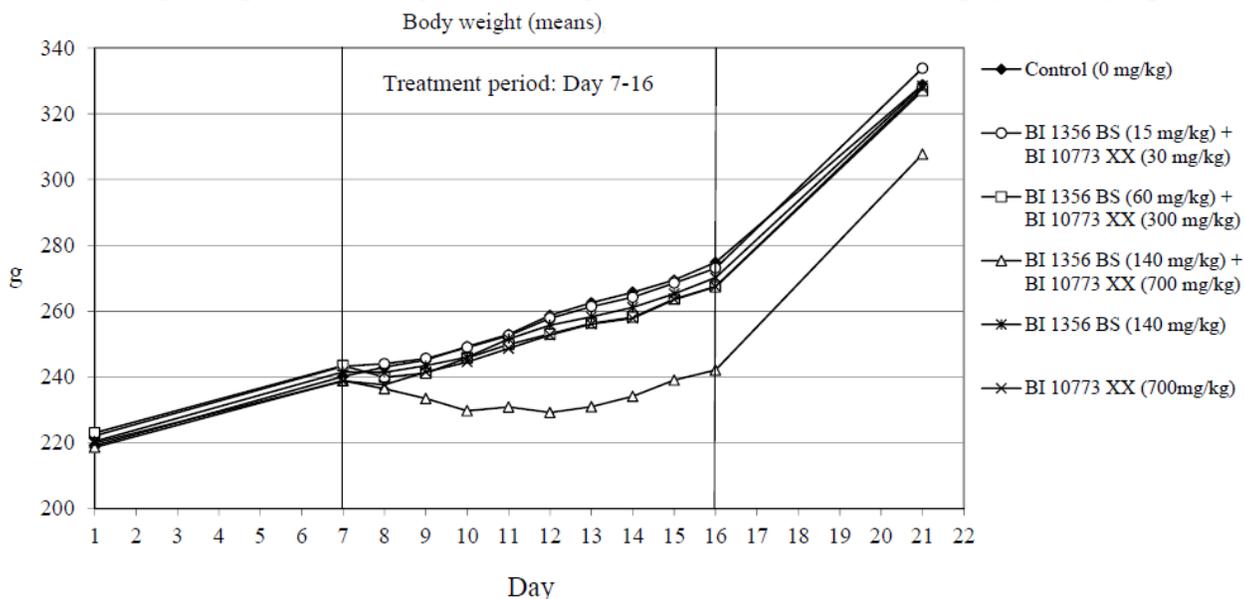
Body Weight (GDs 1, 7–16, 21) – Dose-related decreased body weight gain was seen in all treatment groups compared to controls during the treatment period. The LD combination (15/30 mg/kg) was considered a NOAEL for BW effects because after markedly reduced BW gain (↓ 53%, ss) after the initial dose, BW gain was similar to controls and remained reduced for the treatment period (↓ 14%, ss) but rebounded post-treatment with maternal BW recovered to similar levels as controls at study termination.

Body weight gain reductions were -14%, -31%, -91%, -17%, -17% (LD, MD, HD, linagliptin, empagliflozin, respectively) at treatment cessation (GD 16). Body weight gain rebounded after treatment ended, but remained reduced in MD (-6%, nss) and HD (-22%, ss) combination groups at study termination.

Body weight loss was evident during treatment (compared to GD 7 pre-treatment) in the HD combination group resulting in 12% lower BW after GD 16. Body weight gain rebounded in all treatment groups after treatment termination (concomitant with increased food consumption), but HD body weight remained decreased compared to

controls at study termination after GD 21 (-6%, ss). Although there was a slight trend of reduced BW in the MD combination at the end of treatment GD 16 (-3%, nss), mean BW was not significantly different from controls at study termination in any other group, including individual drug groups.

Body weight summary (rat embryofetal development linagliptin/empagliflozin)



Feed Consumption (GDs 7, 14, 21; water consumption by daily visual analysis) –

Food consumption measurements were limited to weekly analysis which did not correspond directly with the treatment period (GD 7 – 16), limiting the power of the data. Food consumption was reduced during treatment in MD (-9%, ss) and HD (-32%, ss) combination groups and linagliptin (-8%, ss) and empagliflozin (-4% trend, nss) only groups. After treatment termination, food consumption increased in MD and HD combination and empagliflozin only groups. Increased food consumption was likely a compensatory effect to decreased food consumption, glucosuria, and decreased BW gain during the treatment period.

Qualitative visual inspection of water consumption noted increased water consumption in all animals in groups treated with ≥ 300 mg/kg empagliflozin \pm linagliptin.

Toxicokinetics (GD 7, GD 16 @ 0, 0.5, 1, 3, 8, 24 h postdose; non-fasted animals) –

Both linagliptin and empagliflozin were readily absorbed and detected in maternal plasma during treatment. Linagliptin t_{max} was 0.5 to 1 h and both maximum (C_{max}) and total ($AUC_{0-24 h}$) exposure increased greater than dose-proportionally. There was no evidence of linagliptin accumulation from repeated dosing.

Empagliflozin exposure increased with dose but dose-proportionality was not clear because of interactions with linagliptin coadministration (discussed below).

Empagliflozin t_{max} was 0.5 h in when coadministered with linagliptin but t_{max} was later, at 3 h postdose, in the empagliflozin only group. Total empagliflozin exposure seemed to be higher after repeated dosing (GD 16 compared to GD 7), particularly in MD and HD combination groups, but C_{max} trends were not clear as there was no consistent increase in empagliflozin C_{max} after repeated dosing. Summary TK data are shown in the Sponsor's tables, below.

Drug exposures were affected by combination treatment. Linagliptin exposure was lower when coadministered with empagliflozin, with total exposure ($AUC_{0-24 h}$) approximately decreased 30% (repeated dosing, GD 16) to 60% (initial dose, GD 7) in the HD combination group compared to high dose linagliptin treatment alone. There was no clear effect of coadministration on linagliptin C_{max} .

In contrast, empagliflozin exposure was markedly increased in dams coadministered linagliptin. Empagliflozin C_{max} and AUC were increased approximately 2-fold after initial dosing (GD 7) and nearly 3-fold after repeated dosing (GD 16) in the HD combination group compared to HD empagliflozin treatment alone.

Figure 5 – TK summary of empagliflozin and linagliptin in pregnant rats

Mean toxicokinetic parameters of BI 1356

Parameter	Dosing Day	GD	15 mg/kg	60 mg/kg	140 mg/kg	140 mg/kg
			BI 1356 BS +30 mg/kg BI 10773 XX	BI 1356 BS +300 mg/kg BI 10773 XX	BI 1356 BS +700 mg/kg BI 10773 XX	BI 1356 BS +0 mg/kg BI 10773 XX
			Group 2	Group 3	Group 4	Group 5
C(max)	1	7	104	3020	9900	16700
[nmol/L]	10	16	168	3670	10000	8130
AUC(0-24h)	1	7	910	9480	60800	149000
[nmol·h/L]	10	16	1430	35800	55800	76400

Mean toxicokinetic parameters of BI 10773

Parameter	Dosing Day	GD	15 mg/kg	60 mg/kg	140 mg/kg	0 mg/kg
			BI 1356 BS +30 mg/kg BI 10773 XX	BI 1356 BS +300 mg/kg BI 10773 XX	BI 1356 BS +700 mg/kg BI 10773 XX	BI 1356 BS +700 mg/kg BI 10773 XX
			Group 2	Group 3	Group 4	Group 6
C(max)	1	7	5620	54700	58100	28500
[nmol/L]	10	16	5160	49000	105000	39400
AUC(0-24h)	1	7	17200	205000	494000	288000
[nmol·h/L]	10	16	22300	469000	1200000	445000

There was a trend of dose-related decreased plasma glucose in dams during the treatment period. Glucose decreased from baseline from 3 h (HD) to 8 h (MD, HD) postdose after a single dose (GD 7) and glucose decreased from baseline by 3 h (HD) to 8 h (MD, HD). After repeated dosing plasma glucose seemed decreased from predose (\downarrow 5% to 17% vs. control) in MD and HD combination and both linagliptin and

empagliflozin alone groups, with glucose remaining decreased through 3 h (MD combination) to 24 h postdose (HD combination and individual drug groups). In general, glucose trends in linagliptin and empagliflozin groups seemed similar to trends in MD and HD combinations, with the lowest glucose levels seen in the HD combination group. Because no low dose monotherapy drug groups were tested, the magnitude of drug interactions was not clear in LD and MD combination groups. Summary data are shown in the Sponsor's table, below.

Plasma glucose – Rat embryofetal development

BI 1356 and BI 10773: Study for effects on embryo-fetal development in rats – glucose mean values [mmol/L]

Daily dose of BI 1356 BS: BI 10773 XX [mg/kg]	Group	GD	Sample time point					
			Pre-Dose	0.5 h	1 h	3 h	8 h	24 h
			Pre-Treatment					
0:0	1	7	9.91	9.41	12.11	10.90	10.80	11.62
		16	8.67	8.88	9.20	10.92	8.72	9.00
15:30	2	7	10.28	9.31	9.73	10.87	10.95	10.90
		16	8.21	8.68	9.65	9.39	10.03	9.69
60:300	3	7	9.59	8.59	8.75	9.27	7.56	8.28
		16	7.22	7.78	7.74	8.03	8.73	9.03
140:700	4	7	11.53	10.10	8.19	10.29	6.18	7.64
		16	7.31	6.63	6.87	6.44	6.03	7.66
140:0	5	7	10.09	11.80	11.48	10.43	10.59	11.63
		16	8.23	8.45	7.40	7.68	8.19	8.37
0:700	6	7	11.18	10.60	11.21	9.53	6.66	10.00
		16	7.86	8.16	8.27	8.06	9.89	8.39

Necropsy –

Cesarean Section Data (Implantation Sites, Pre- and Post-Implantation Loss, etc.)

There were 22, 19, 22, 21, 23, and 24 pregnancies in each group, respectively, determined at necropsy. Pregnancy status was unrelated to treatment because mating occurred prior to study initiation. All pregnant females had viable fetuses at necropsy and no dead fetuses were found in any group. No gross morphological findings were seen in any pregnant female.

There were no drug-related effects on litter (i.e., pregnancy) parameters including corpora lutea, implantations, number of viable fetuses, resorptions, or fetal sex. Fetal weights were reduced (- 5%, ss) in the HD combination group, consistent with reduced BW gain and reduced BW in dams. Single runts ($\leq 65\%$ fetal weight of control mean) were found in HD combination and empagliflozin alone groups, which were considered unremarkable because of the low incidence.

Offspring (Malformations, Variations, etc.)

Histopathology of fetal kidneys found no treatment-related findings. Minimal tubular dilatation of immature and mature proximal convoluted tubules were found in a subset of animals from each group, including controls, which was attributed to immature status of fetal kidneys.

Malformations and variations were seen in all groups, including controls, and no treatment-related effect on total malformations or variations was evident (Table 4).

Table 4 – Embryofetal rat fetal abnormalities summary

Hysterectomy, parameters of viable fetuses										
Group		Examined			Malformations			Variations		
		external	skeleton	viscera	external	skeleton	viscera	external	skeleton	viscera
Control 0 [mg/kg]	f	239	126	113	0	18	0	0	123	17
	f%		52.72	47.28	0.00	14.29	0.00	0.00	97.62	15.04
	p									
15:30 <multi comp.>	f	225	118	107	1	14	0	0	117	21
	f%		52.44	47.56	0.44	11.86	0.00	0.00	99.15	19.63
	p				0.4849	0.7048	1.0000	1.0000	0.6227	0.3793
60:300 <multi comp.>	f	244	126	118	0	28	0	0	125	23
	f%		51.64	48.36	0.00	22.22	0.00	0.00	99.21	19.49
	p				1.0000	0.1416	1.0000	1.0000	0.6220	0.3902
140:700 <multi comp.>	f	243	125	118	1	4	3	0	125	22
	f%		51.44	48.56	0.41	3.20	2.54	0.00	100.00	18.64
	p				1.0000	*0.0029	0.2471	1.0000	0.2470	0.4875
BI 1356 BS 140 [mg/kg]	f	270	138	132	1	22	0	0	137	22
	f%		51.11	48.89	0.37	15.94	0.00	0.00	99.28	16.67
	p				1.0000	0.7342	1.0000	1.0000	0.3508	0.8612
BI 10773 XX 700 [mg/kg]	f	275	145	130	0	14	1	0	144	26
	f%		52.73	47.27	0.00	9.66	0.77	0.00	99.31	20.00
	p				1.0000	0.2617	1.0000	1.0000	0.3407	0.3997

No external variations were seen.

Various individual visceral and skeletal variations and individual malformations (external, skeletal, and visceral) occurred in treatment groups that were absent or at lower incidence in the concurrent control group. None of the variations or malformations were clearly exacerbated in combination treatment groups compared to individual drug groups. No malformations were clearly related to treatment. Variation and malformation data are discussed below.

There were no dose-related increases in visceral variations (Table 5). Shortened truncus brachiocephalicus was elevated in all treatment groups but the absence of a

dose-response and absence of a contribution of an individual drug or an increase in combination groups suggest findings were incidental. Displaced vena cava caudalis and adrenal gland were observed only in two HD combination fetuses from different litters. The two fetuses had other rare variations and malformations and may represent incidental findings but since the findings were not seen in individual drug treatments a contribution of combination treatment cannot be rule out. Nevertheless, the findings were limited to two fetuses at maternally toxic exposures at 353-times and 253-times expected maximum clinical exposures.

Table 5 – Embryofetal rat fetal visceral variations summary

BI 1356 and BI 10773: Study for effects on embryo-fetal development in rats - visceral variations with increased incidences above the Control group and spontaneous incidences from evaluation study U03-1549

Findings	Daily dose of BI 1356 BS:BI 10773 XX [mg/kg]						Spontaneous incidences from evaluation study [U03-1549]
	G 1	G 2	G3	G4	G5	G6	
	Control	15:30	60:300	140:700	140:0	0:700	
n fetuses / incidences (%)							
Decimals rounded						Decimals rounded	
Total number of litters	22	19	22	21	23	24	85
Total number of fetuses	239	225	244	242 [@]	270	275	889
Runts	0	0	0	1/0.41	0	1/0.36	2/0.22
Variations							
Visceral Variations	Decimals truncated						Decimals rounded
Number of litters	22	19	22	21	23	24	85
Number of fetuses	113	107	118	118	132	130	424
Subcutaneous edema cranium	0	0	<u>1/0.84</u>	0	0	<u>1/0.76</u>	0
Shortened truncus brachiocephalicus	1/0.88	<u>4/3.73</u>	<u>7/5.93</u>	<u>6/5.08</u>	<u>7/5.30</u>	<u>5/3.84</u>	1/0.24 3/2.75 ⁺
Small distance between the carotids	0	5/4.67	6/5.08	0	5/3.78	3/2.30	5/1.18 6/5.50 ⁺
No distance between the carotids	3/2.65	1/0.93	2/1.69	0	4/3.03	5/3.84	4/0.94 6/5.26 ⁺
No distance between left A. carotis and left A. subclavia	2/1.76	4/3.73	6/5.08	5/4.23	2/1.51	1/0.76	5/1.18 7/6.14 ⁺ 7/6.42 ⁺
Vena cava caudalis displaced	0	0	0	<u>2/1.69</u> 433L04/40 7L04	0	0	0
Adrenal gland displaced	uni	0	0	<u>2/1.69</u> 433L04/40 7L04	0	0	0
Dilated ureter	bil	0	2/1.86	0	0	0	1/0.24 5/4.38*
Bowed ureter	uni	3/2.65	5/4.67	6/5.08	5/4.23	3/2.27	4/3.07 3/0.71 6/5.26*

Findings at incidences above the actual Control group and above spontaneous incidences from evaluation study U03-1549 or Control groups from other embryo-fetal development studies underlined and in bold letters

uni = unilateral

bil = bilateral

⁺ = data from Control group of U10-2386-01, 21 litters, 109 fetuses

* = data from Control group of U09-1990-01, 22 litters, 114 fetuses

[@]Body weight of fetus 407R02 was excluded from the calculation because it was accidentally injected during anesthesia of its mother

Skeletal variations were prevalent in all groups, including controls. No clear dose-related trends were evident. Many of the findings in treatment groups, particularly some increased variations in HD combination fetuses, indicate delayed or incomplete ossification, consistent with delayed development and observed reductions in fetal weight (i.e., reduced fetal growth).

Malformations (external, visceral, skeletal) were seen in all groups, including controls, but at single incidence for most observations (Table 6). One HD combination fetus accounted for several unique malformations. Vena cava caudalis without connection to liver was seen in two HD combination fetuses. Flat and thickened rib, unilateral or bilateral, were elevated in LD, MD, or linagliptin only groups, but not in HD fetuses. Similar rib findings were seen in the same strain of rat in linagliptin embryofetal development studies and historical data suggests Wistar(Han) rats may be susceptible to the rib malformations ('Wistar Chondroplasty Syndrome'). None of the malformations were considered to be drug-related.

Table 6 – Embryofetal rat fetal malformations summary

BI 1356 – BI 10773: Study for effects on embryo-fetal development in rats - malformations

Findings	Daily dose of BI 1356 BS:BI 10773 XX [mg/kg]						Spontaneous incidences from evaluation study [U03-1549]	
	G 1	G 2	G3	G4	G5	G6		
	Control	15:30	60:300	140:700	140:0	0:700		
n fetuses / incidences (%)								
Malformations								
External Malformations	Decimals truncated						Decimals rounded	
Number of litters	22	19	22	21	23	24	85	
Number of fetuses	239	225	244	243	270	275	889	
Cleft palate	0	1/0.44 214R06	0	0	0	0	0 6/0.48 [§] 1/0.60 [§]	
Microglossia	0	<u>1/0.44</u> 214R06	0	0	<u>1/0.37</u> 528L04	0	0	
Micrognathia	0	0	0	0	<u>1/0.37</u> 528L04	0	0	
Anasarca	0	0	0	<u>1/0.41</u> 433L04	0	0	0	
Visceral malformations	Decimals truncated						Decimals rounded	
Number of litters	22	19	22	21	23	24	85	
Number of fetuses	113	107	118	118	132	130	424	
Situs inversus	0	0	0	<u>1/0.84</u> 433L04	0	0	0	
Ventricular septal defect (VSD)	0	0	0	<u>1/0.84</u> 433L04	0	0	0	
Aortic arch rotated to the right	0	0	0	<u>1/0.84</u>	0	<u>1/0.76</u>	0	
Vena cava caudalis without connection to liver	0	0	0	<u>2/1.69</u> 433L04/4 07L04	0	0	0	
Skeletal malformations	Decimals truncated						Decimals rounded	
Number of litters	22	19	22	21	23	24	85	
Number of fetuses	126	118	126	125	138	145	465	
Cleft cervical vertebral body	4/3.17	1/0.84	0	1/0.80	0	3/2.06	5/1.08	
Cervical vertebral body unilaterally ossified	1/0.79	0	2/1.58	1/0.80	0	0	1/0.22 3/2.88 [#] 4/3.27 [*]	
Flat and thickened rib	bil	11/ 8.73	4/ 3.38	<u>21/</u> <u>16.66</u>	1/ 0.80	15/ 10.86	9/ 6.20	45/9.68 (bil + uni) 7/15.55 ^{§§}
	uni	2/1.58	<u>9/7.62</u>	5/3.96	1/0.80	<u>7/5.07</u>	2/1.37	45/9.68 (bil + uni) 2/4.44 ^{§§}
Rib z-shaped	bil	0	0	2/1.58	0	0	0	2/0.43 (bil + uni) 1/2.22 ^{§§}
Fetal findings without classification								
Skeletal	Decimals truncated						Decimals rounded	
Number of litters	22	19	22	21	23	24	85	
Number of fetuses	126	118	126	125	138	145	465	
Scapula bent inwardly	uni	0	0	<u>2/1.58</u>	0	0	0	0 1/0.87 ⁺⁺

Findings at incidences above the actual Control group and above the spontaneous incidences from evaluation study U03-1549 or Control groups from other embryo-fetal development studies underlined and in bold letters

uni = unilateral

bil = bilateral

* = data from Control group of U10-2386-01, 21 litters, 122 fetuses

§ = data from Control group of U07-2330, 122 litters, 1256 fetuses. Cleft palate occurred in 6 fetuses from one litter

= data from Control group of U07-1325, 20 litters, 104 fetuses

§ = data from Control group of U04-2101, 17 litters, 164 fetuses

§§ = data from Control group of U11-1221-01, 8 litters, 45 fetuses, vehicle of Control group: PEG 400

++ = data from Control group of U06-1637, 21 litters, 114 fetuses

11 Integrated Summary and Safety Evaluation

The proposed empagliflozin and linagliptin FDC tablet(s) was submitted in accordance with 21 USC 505(b)(1) for treatment of type 2 diabetes mellitus.

Nonclinical studies to support combination empagliflozin and linagliptin treatment in the FDC tablets were submitted to bridge safety and efficacy data of the individual drugs for T2DM. The pivotal toxicology studies included subchronic toxicity and embryofetal development combination empagliflozin and linagliptin in rats. All pivotal studies were conducted in compliance with current GLP standards.

Pharmacology

Empagliflozin, an SGLT2 inhibitor, and linagliptin, a DPP4 inhibitor, lower blood glucose by distinct mechanisms. Coadministration is expected to provide superior blood glucose control in diabetics compared to individual drugs. A study in Zucker Diabetic Fatty rats showed superior improved glycemic control with combination treatment compared to either drug alone.

PK/ADME

No drug-drug interactions were predicted from coadministration of empagliflozin and linagliptin based on inhibition or induction of metabolizing enzymes. Empagliflozin had no effect on linagliptin metabolism by human hepatocytes *in vitro*. Linagliptin weakly inhibited empagliflozin metabolism in human hepatocytes but at linagliptin concentrations approximately 500-times higher than maximum clinical exposures. Findings in human hepatocyte incubations and metabolizing enzyme profiles suggest limited potential interactions that would affect metabolism of either drug clinically.

Toxicokinetic data from standard toxicity and embryofetal development studies consistently showed empagliflozin and linagliptin coadministration do alter exposure *in vivo* in rats. Empagliflozin effects on linagliptin exposure were variable, with coadministration reducing plasma linagliptin total AUC exposures from 40% to up to 3-fold, with or without effects on C_{max} in healthy rats. Linagliptin total exposures were reduced up to 60% in pregnant rats with no effect on C_{max} with empagliflozin coadministration. Linagliptin effects on rat empagliflozin exposures were more consistent, causing up to 2- to 3-fold increased empagliflozin C_{max} and AUC. It is not clear why the rat *in vivo* drug exposures were altered by coadministration when no interactions were predicted from *in vitro* data. Rat exposure interactions did seem to affect toxicity in combination toxicity studies.

Toxicology

Pivotal combination toxicology studies in rats were conducted to investigate potential interactions between empagliflozin and linagliptin. Ratios of 2:1 and 5:1 empagliflozin:linagliptin were used based on ratios in the proposed clinical FDC

combinations. Linagliptin was well tolerated in the rat studies used to support initial approval for T2DM with irreversible or non-monitorable toxicity typically occurring at greater than 90-times clinical exposures. Consistent with empagliflozin and SGLT2 inhibitor class toxicity and the 2- to 5-fold lower linagliptin concentrations, toxicity in combination rat studies was driven by empagliflozin.

There were no apparent drug interactions on toxicity endpoints in the subchronic, 13-week toxicity study in rats. No unexpected toxicity was seen. However, incidence and severity of toxicity increased in the combination groups compared to empagliflozin only groups. Consistent with empagliflozin toxicity, target organ toxicity in the high dose combination group was characterized by increased liver enzymes (ALT, AST, ALP, GGT, GLDH) and kidney toxicity (increased kidney weight and tubular dilatation). The higher toxicity in the combination group was likely due to increased empagliflozin exposure.

Similarly, there were no apparent drug interactions on maternal or embryofetal toxicity. There were no drug-related malformations in fetuses at any dose. Compared to individual drug groups, the highest combination group had increased maternal toxicity as evidenced by reduced body weight gain, weight loss during treatment, reduced body weight compare to controls at study termination, and lower plasma glucose during treatment. Fetal weights were also reduced in the high dose combination. The increased toxicity was considered to be due to increased empagliflozin exposure in the combination group.

While incidence and severity of toxicity was increased slightly with coadministration of empagliflozin and linagliptin, NOAELs were established for all toxicity and there were exposure margins compared to clinical exposures. A summary of NOAELs compared to the lowest doses that caused toxicity (LOAELs) with clinical exposure margins is shown in Table 7.

Table 7 – Human Exposure Summary

Human Equivalent Doses †				
Species	NOAEL (mg/kg) (lina/empa)	LOAEL (mg/kg) (lina/empa)	MRHD (AUC _{0-24 h}) (lina/empa)	
			NOAEL	LOAEL
Rat (3-month)	15 / 30	20 / 100	9X / 3X	14X / 15X
Rat (Embryofetal development)	15/30 (maternal) 60/300 (fetal)	60/300 (maternal) 140/700 (fetal)	9X / 15X 227X / 199X	227X / 199X 353X / 253X

† Clinical exposure multiples based on proposed maximum human dose 5 mg linagliptin (158 nM*h) and 25 mg empagliflozin (4750 nM*h) FDC

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/s/

DAVID B CARLSON

10/10/2014

Nonclinical approval recommendation

PATRICIA M BRUNDAGE

10/12/2014

Signing as acting pharm/tox supervisor.

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: 206073

Applicant: Boehringer Ingelheim
Pharmaceuticals, Inc.

Stamp Date: 30 January, 2014

Drug Name: Empagliflozin/
Linagliptin FDC tablets

NDA/BLA Type: 505(b)(1)

(Proposed: Glyxambi®)

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	X		
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	X		
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	X		
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	X		NDA's for individual components empagliflozin (NDA 204629) and linagliptin (NDA 201280) were previously submitted and cross-referenced from this NDA. Requested studies to support the proposed FDC tablets have been completed and submitted.
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).	X		FDC tablets (i.e., drug product) to be marketed were not tested in nonclinical studies but coadministration of drug substances was consistent with individual NDA's. Safety of FDC drug product excipients and impurities will be evaluated.
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant <u>submitted</u> a rationale to justify the alternative route?	X		
7	Has the applicant <u>submitted</u> a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) <u>or</u> an explanation for any significant deviations?	X		

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR A NEW NDA/BLA

	Content Parameter	Yes	No	Comment
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X		
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?	X		Proposed labeling in relevant pharmacology/toxicology sections accurately conveys information from the proposed (empagliflozin) and listed (linagliptin) individual drug labels.
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)	X		No unresolved impurity issues were identified for either individual drug substance prior to NDA submission. Any impurities unique to the FDC tablet formulation will be reviewed.
11	Has the applicant addressed any abuse potential issues in the submission?			No abuse liability issues were identified for either individual drug substance.
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			Not applicable.

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? Yes _____

If the NDA/BLA is not fileable from the pharmacology/toxicology 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.

Reviewing Pharmacologist

Date

Team Leader/Supervisor

Date

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

/s/

DAVID B CARLSON

03/24/2014

Nonclinical -- Suitable for filing

TODD M BOURCIER

03/27/2014

I concur