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APPLICATION NUMBER:

212614Orig1s000

NON-CLINICAL REVIEW(S)

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:	NDA 212614
Supporting document/s:	SDN-1
Applicant's letter date (CDER Stamp Date):	March 27, 2019
Product:	Empagliflozin/linagliptin/metformin XR FDC
Indication:	Type 2 diabetes mellitus
Applicant:	Boehringer Ingelheim Pharmaceuticals, Inc.
Review Division:	Metabolism and Endocrinology Products
Reviewer:	David B. Carlson, Ph.D.
Supervisor/Team Leader:	Todd Bourcier, Ph.D.
Division Director (Acting):	Lisa Yanoff, M.D.
Project Manager:	Michael White, Ph.D.
Review Completion Date:	4 December, 2019

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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 in relation to concurrent vehicle control groups in each study unless otherwise noted.

Key: Linagliptin (LINA); empagliflozin (EMPA); metformin HCl (MET) extended release (metformin XR, aka metformin ER); fixed-dose combination (FDC), once daily dosing (QD); MRHD (maximum recommended human dose); IR (immediate release), XR (extended release); mg/kg (mg/kg/day); polyethylene oxide (PEO), polyethylene glycol (PEG); molecular weight (MW); body weight (BW); type 2 diabetes mellitus (T2D); low dose (LD), mid dose (MD), high dose (HD), no observed adverse effect level (NOAEL), lowest observed adverse effect level (LOAEL), maximum tolerated dose (MTD); pharmacokinetic (PK), toxicokinetic (TK); sodium-glucose co-transporter 2 (SGLT2); dipeptidyl peptidase 4 (DPP4)

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1 Executive Summary

1.1 Introduction

The proposed drug product is a once daily triple fixed dose combination (FDC) tablet containing three listed drugs which the Sponsor owns or has licensed and indicated as an adjunct to diet and exercise to (b) (4) type 2 diabetes mellitus (T2D). The proposed tablet formulation is nearly (b) (4) . The Sponsor cross-refenced NDA data from the existing listed drugs and conducted a triple combination (empagliflozin/linagliptin/metformin) 13-week rat toxicity study to support the proposed drug product. The three drug substances have different mechanisms of action to treat T2D and the triple combination FDC tablet was developed to simultaneously target the three metabolic mechanisms with once daily dosing. Empagliflozin/linagliptin FDC tablets are listed in the US and the prior clinical development program assessed safety on background metformin treatment, consistent with current clinical practice with first line metformin therapy for T2D, thus proposed FDC use as empagliflozin/linagliptin/metformin XR tablets has a history of clinical use.

1.2 Brief Discussion of Nonclinical Findings

The drug substances in the proposed empagliflozin/linagliptin/metformin XR FDC tablet formulation have been studied extensively nonclinically and there is a history of clinical use in various FDC tablets on a background of metformin therapy. The primary objective of the current nonclinical development program was to identify or rule out any potentially adverse interactions from coadministration.

A 13-week rat empagliflozin/linagliptin/metformin combination toxicity study was conducted to bridge to previous pharmacology and toxicology assessments of individual and combined drug substances. Drug substance ratios in the toxicity study were similar to those in the proposed FDC tablets and doses were chosen to provide approximately 1-time, 5-times, and 10-times clinical exposures at the maximum recommended human dose (MRHD).

There was no evidence of supra-additive or synergistic drug interactions relative to toxicities observed from the individual drug substances. A no observed adverse effect level (NOAEL) was established in the rat study at approximately 1-time empagliflozin and 3-times linagliptin and metformin compared to clinical exposures at the MRHD. There was increased incidence and severity of toxicity in target organs at the mid dose and high dose combination groups at approximately 5-times/8-times/6-times and 11-times/14-times/15-times clinical exposures at the MRHD (empagliflozin/linagliptin/metformin, respectively). The exacerbated toxicity findings in

combination treatment groups could be evidence of additive toxicity or simply attributed to slightly higher metformin exposures due to toxicokinetic interactions.

Target organs in the triple combination rat study were consistent with known nonclinical toxicity trends from individual drugs and dual combination treatments. Tolerability in rats was generally driven by metformin-related toxicity. Primary target organs were kidney, heart, and liver with additional drug-related findings in stomach, GI tract, salivary glands, lymphoreticular tissues, and ovaries.

Formulation of the proposed drug products is nearly [redacted] (b) (4)

No new or novel excipients were used and no concerns were identified from potential impurities, degradants, or [redacted] (b) (4).

Proposed maximum clinical doses of 25 mg empagliflozin, 5 mg linagliptin, and 2000 mg metformin XR FDC are consistent with daily MRHDs for individual drug substances and existing dual FDCs. Exposure estimates from the 13-week rat combination toxicity study are summarized below, with clinical MRHD exposure estimates consistent with clinical exposures from listed drugs and cross-refenced nonclinical data and reviews.

Rat Exposure Summary – 13-Week Combination Toxicity Study				
Drug (monotherapy exposure)	Empagliflozin/linagliptin/metformin			
	Exposure (Day 88)	MRHD[a]		
		LD[b]	MD	HD
Empagliflozin (1X)	0.6X	1X	5X	11X
Linagliptin (1X)	0.3X	3X	8X	14X
Metformin (1X)	1.6X	3X	6X	15X

[a] Maximum recommended human dose (MRHD) estimates based on:
Empagliflozin (25 mg) $AUC_{0\text{-}24\ h}$ = 4740 nM*h
Linagliptin (5 mg) $AUC_{0\text{-}24\ h}$ = 158 nM*h
Metformin (2000 mg) $AUC_{0\text{-}24\ h}$ = 159 µM*h
[b] NOAEL dose in 13-week rat combination toxicity study

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

In general, the label is consistent with existing labels for the listed monotherapy and FDC drugs and it does not contain new nonclinical information. Editorial changes will be made during label negotiations.

2 Drug Information

2.1 Drug

Summaries of individual drug substance information provided by the Sponsor are shown below.

Table 1 – Empagliflozin Drug Information (CAS RN – 864070-44-0)

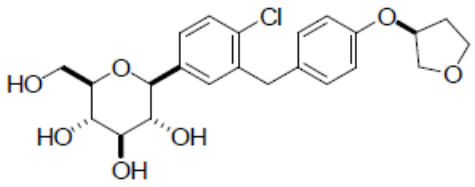
Chemical Name:	D-Glucitol,1,5-anhydro-1-C-[4-chloro-3-[[4-[[(3S)-tetrahydro-3-furanyl]oxy]phenyl] methyl]phenyl]-,(1S)
International non-proprietary name (INN):	Empagliflozin
Pharmacological class:	SGLT2 inhibitor
Boehringer Ingelheim code:	BI 10773 XX
Molecular Formula:	C23H27ClO7
Molecular Weight:	450.91 g/mol
Chemical Structure:	

Table 2 – Linagliptin Drug Information (CAS RN – 668270-12-0)

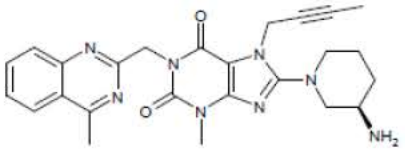
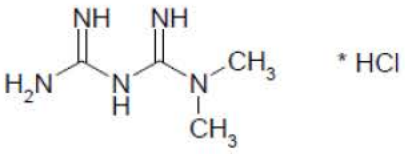
Chemical Name:	1H-Purine-2,6-dione, 8-[(3R)-3-amino-1-piperidinyl]-7-(2-butyn-1-yl)-3,7-dihydro-3-methyl-1-[(4-methyl-2-quinazolinyl)methyl]
International non-proprietary name (INN):	Linagliptin
Pharmacological class:	DPP-4 inhibitor
Boehringer Ingelheim code:	BI 1356 BS
Molecular Formula:	C25H28N8O2
Molecular Weight:	472.54 g/mol
Chemical Structure:	

Table 3 – Metformin HCl Drug Information (CAS RN – 1115-70-4)

Chemical Name:	N,N-dimethylimidodicarbonimidic diamide hydrochloride
International non-proprietary name (INN):	Metformin HCl
Pharmacological class:	Biguanide
Molecular Formula:	$C_4H_{11}N_5$*HCl
Molecular Weight:	165.6 (b) (4) g/mol
Chemical Structure:	

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

NDA 204629 (empagliflozin; JARDIANCE®) – owned and referenced by the Sponsor for the empagliflozin drug substance and nonclinical data
NDA 201280 (linagliptin; TRADJENTA®) – owned and referenced by the Sponsor for the linagliptin drug substance and nonclinical data
NDA 201281 (linagliptin plus metformin FDC; JENTADUETO®) and DMF (b) (4) (metformin) – owned and/or written 'right of reference' materials referenced by the Sponsor for the metformin drug substance and nonclinical data
NDA 206073 (empagliflozin plus linagliptin FDC; GLYXAMBI®) – owned and referenced by the Sponsor for nonclinical data
NDA 206111 (empagliflozin plus metformin HCl FDC; SYNJARDY®) – owned and referenced by the Sponsor for nonclinical data
NDA 208026 (linagliptin plus metformin XR; JENTADUETO XR®) and NDA 208658 (empagliflozin plus metformin XR; SYNJARDY XR®) – owned by the Sponsor and includes drug product information on extended release formulations which were used to guide drug product development
NDA 021748 (extended release metformin HCl; GLUMETZA®) – referenced by the Sponsor with a written 'right of reference' provided for full access to all information

2.2 Drug Formulation

The triple combination tablets were designed to allow immediate release of empagliflozin and linagliptin and extended release of metformin HCl to allow once daily dosing. The layered tablet is qualitatively similar to the tablets used for U.S. listed empagliflozin plus metformin XR FDC tablets and linagliptin plus metformin XR FDC tablets (Figure 1).

Figure 1 – Empagliflozin, Linagliptin, Metformin HCl ER Coated Tablet

Cross Section of an Empagliflozin/Linagliptin/Metformin HCl ER Coated Tablet

Tablets for the triple drug combination contain qualitatively and quantitatively similar components as those in the listed FDC tablets for empagliflozin plus metformin XR and linagliptin plus metformin XR (Table 4 and Table 5). The proposed drug product tablet core, (b) (4) There are slight differences in the (b) (4) film-coat, and printing ink formulations of the drug product compared to the previously approved FDC tablets. The (b) (4) coating agents and printing inks are proprietary products and are not published as reference standards. Components of the (b) (4) products were provided to the Sponsor and are shown in Table 5. All of the individual excipients and colors in the (b) (4) products are compendial and have been previously used in similar or higher quantities in U.S. listed drugs as shown in the Agency's Inactive Ingredient Database.[3]

[1] Carlson DB, NDA 208026, Pharmacology/Toxicology Review and Evaluation, 5/4/16
[2] Carlson DB, NDA 208658, Pharmacology/Toxicology Review and Evaluation, 11/7/16
[3] FDA Inactive Ingredient Database, accessed 11/18/19 at http://intranetapps.dev.fda.gov/scripts/cder/iig/index.cfm

Table 4 – Drug Product Composition

Qualitative and Quantitative Composition of Empagliflozin/ Linagliptin/Metformin HCl ER Coated Tablets

Ingredient	5 mg / 2.5 mg / 1000 mg	10 mg / 5 mg/ 1000 mg	12.5 mg / 5 mg / 1000 mg	25 mg / 5 mg / 1000 mg	Function	Reference to Standards
	[mg / tablet]					
Tablet Core						
Metformin HCl1	1000.0	1000.0	1000.0	1000.0	Drug substance	USP
Polyethylene Oxide (b) (4)	(b) (4)					NF2
Hypromellose (b) (4) (b) (4)						USP
Magnesium Stearate						NF
						(b) (4)
Empagliflozin	5.0	10.0	12.5	25.0	Drug substance	Company Standard
Linagliptin	2.5	5.0	2.5	5.0	Drug substance	Company Standard
						(b) (4)
Arginine	(b) (4)					USP
Polyethylene Glycol (b) (4)						NF
Talc						USP
						(b) (4)

(b) (4)					
Carnauba Wax					(b) (4) NF
Purified Water					(b) (4) USP
					(b) (4)
Isopropyl Alcohol					(b) (4) USP
Propylene Glycol					USP
Total mass	1633.2	1650.7	1640.7	1665.7	

[1] The strength for the core tablet (1000 mg) represents the amount of the metformin HCl salt. It is equivalent to 779.86 mg free base of metformin.

(b) (4)

Table 5 – Tablet Coatings and Ink Composition

Qualitative and Quantitative Composition of (b) (4) Coating Agents and Printing Ink

Ingredient	[mg / tablet]	Reference to Standards
(b) (4)		
Hydroxypropyl Cellulose	(b) (4)	NF
Hypromellose (b) (4)		USP
Talc		USP
Titanium Dioxide		USP
(b) (4)		
Polyethylene Glycol (b) (4)	(b) (4)	NF
(b) (4)		
Ferrosoferric Oxide	(b) (4)	NF
(b) (4)		
Ferric Oxide Yellow	(b) (4)	NF
(b) (4)		
Ferric Oxide Red	(b) (4)	NF
(b) (4)		

Ingredient	[mg / tablet]	Reference to Standards
(b) (4)		

Ingredient	[%wt/wt]	Reference to Standards
(b) (4)		
Shellac Glaze (b) (4) (b) (4)	(b) (4)	NF (b) (4) (b) (4)
(b) (4)		
N-Butyl Alcohol		NF
Isopropyl Alcohol		USP
Propylene Glycol		USP
Ammonium Hydroxide, (b) (4)		NF

2.4 Comments on Novel Excipients

The Sponsor reported that all of the excipients are compendial grade, no novel excipients are used in the drug product formulation, and all excipients are used in U.S. listed drug products (see Table 4 and Table 5). This Pharmacology/Toxicology Reviewer confirmed the status of the drug product excipients, including the individual components of the proprietary (b) (4) coating agents and printing inks that do not have reference standards (see Table 5).

2.5 Comments on Impurities/Degradants of Concern

No impurities, degradants, or (b) (4) were identified that raise new concerns or were not previously reviewed under cross-referenced drug product NDAs. The linagliptin drug substance degradation product (b) (4) observed above the 0.1% reporting threshold has been previously identified and discussed under cross-referenced linagliptin listed product NDAs. A slight increase in unidentified empagliflozin degradation products were observed under long term storage and high temperature and humidity only in the lowest combination dose tablet formulation.

Manufacturing controls limit levels of (b) (4). Inorganic impurities in the drug substances and drug product are controlled to compendial and ICH limits. Low levels of elemental (b) (4) impurities from (b) (4) in the coating agents are possible. The manufacturer limits elemental (b) (4) impurities in their manufacturing specifications and the (b) (4) have been previously used in U.S. listed drug products as noted above. The Sponsor's Elemental Impurities Risk Assessment concluded "no additional controls are needed to ensure that empagliflozin/linagliptin/metformin HCl ER coated tablets meet the requirements of ICH Q3D".

2.6 Proposed Clinical Population and Dosing Regimen

The proposed indication for empagliflozin, linagliptin, and metformin HCl extended-release tablets is to improve glycemic control as an adjunct to diet and exercise in adults with type 2 diabetes mellitus (b) (4). The tablet formulation allows once daily dosing of empagliflozin and linagliptin drug substances for immediate release with an extended release of metformin to allow once daily dosing.

The maximum recommended human dose (MRHD) with the proposed triple combination is 25 mg empagliflozin, 5 mg linagliptin, 2000 mg metformin. The proposed triple combination FDC tablets are formulated for once daily (QD) oral administration are shown here and in Table 6:

- Empagliflozin 10 mg/Linagliptin 5 mg/Metformin HCl 1000 mg (1 tablet QD)
- Empagliflozin 25 mg/Linagliptin 5 mg/Metformin HCl 1000 mg (1 tablet QD)
- Empagliflozin 5 mg/Linagliptin 2.5 mg/Metformin HCl 1000 mg (2 tablets QD)
- Empagliflozin 12.5 mg/Linagliptin 2.5 mg/Metformin HCl 1000 mg (2 tablets QD)

Table 6 – Dose regimen and daily dose

Tablet strength	Posology	Daily dose		
		Empagliflozin	Linagliptin	Metformin HCl
5 mg /2.5 mg/1000 mg	2 tablets once daily	10 mg	5 mg	2000 mg
10 mg/5 mg/1000 mg	1 tablet once daily	10 mg	5 mg	1000 mg
12.5 mg/2.5 mg/1000 mg	2 tablets once daily	25 mg	5 mg	2000 mg
25 mg/5 mg/1000 mg	1 tablet once daily	25 mg	5 mg	1000 mg

2.7 Regulatory Background

The Sponsor owns the listed drugs empagliflozin and linagliptin in the proposed triple combination tablets. The Sponsor also owns fixed-dose combination (FDC) tablets of empagliflozin plus metformin XR, linagliptin plus metformin XR, and they have provided written 'right of reference' to GLUMETZA® (extended-release metformin tablets) which are the basis for the existing and proposed metformin XR formulations in the referenced and proposed FDC tablets.

Pre-IND meeting (12/12/14; FDA Written Responses 2/26/15) – no nonclinical questions or responses.

Type C meeting (FDA Written Responses 6/14/16) – nonclinical concurrence that a triple combination rat study and cross-references to existing nonclinical data should be sufficient to support NDA submission. General agreement and advice on the proposed 13-week rat triple combination toxicity study were provided by the DMEP nonclinical reviewer.

Pre-NDA meeting (FDA Written Responses 1/25/18) – nonclinical plan to submit a Nonclinical Overview and triple combination rat toxicity study report with appropriate cross-reference to existing nonclinical materials acceptable for filing NDA.

Agreed iPSP (1/8/18) – no juvenile animal or other specific additional nonclinical studies necessary prior to clinical trials in children or adolescents.

3 Studies Submitted

3.1 Studies Reviewed

Empagliflozin (BI 10773)/Linagliptin (BI 1356)/Metformin: 13-Week oral (gavage) combination toxicity study in rats (Study No. 17B039; Doc. No. N00256132)

3.2 Studies Not Reviewed

None

3.3 Previous Reviews Referenced

The Sponsor cross-referenced nonclinical data used to support the approval of their linagliptin and empagliflozin monotherapy drugs and their various fixed-dose combination drugs for linagliptin and empagliflozin with immediate release or extended release metformin which were previously reviewed in the Division (listed in Section 2.2 Relevant IND/s, NDA/s, and DMF/s). Sponsor's data and Division reviews for the various cross-referenced NDAs were consulted and used to support this Pharmacology/Toxicology review, as necessary.

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 GLP1 expression, leading to enhanced insulin response and glucose tolerance.

Metformin pharmacology is still not entirely understood but it seems to improve insulin sensitivity at peripheral target tissues including liver, muscle, and adipose. Metformin does not seem to directly affect insulin production or metabolism, but treatment increases glucose uptake and utilization in peripheral tissues, decreases hepatic glucose production, and decreases intestinal glucose absorption.

The three drugs lower blood glucose by separate mechanisms and combined treatment is expected to additively increase total glucose lowering activity. None of the three drugs independently increase the risk of hypoglycemia and combination treatment is not expected to increase the risk of hypoglycemia compared to any individual drug or combination of two drugs. Efficacy of the triple drug combination was not assessed in any diabetic animal model but neither the Division nor ICH guidance considered an additional efficacy study with the triple drug combination necessary to support clinical testing.

5 Pharmacokinetics/ADME/Toxicokinetics

5.2 Toxicokinetics

Toxicokinetic interactions have been previously observed in combination toxicity studies with empagliflozin and linagliptin. The rat TK trends were not predictive of clinical pharmacokinetics of empagliflozin and linagliptin coadministration. Toxicokinetic interactions were modest in the triple combination rat study with slightly lower empagliflozin exposure, lower linagliptin exposure, and slightly higher metformin exposure observed after three months of combination treatment compared to individual drug groups. Toxicokinetic trends from the 13-week rat triple combination toxicity study are summarized below.

Rat Exposure Summary – 13-Week Combination Toxicity Study

Drug (monotherapy exposure)	Empagliflozin/linagliptin/metformin			
	Exposure (Day 88)	MRHD[a]		
		LD[b]	MD	HD
Empagliflozin (1X)	0.6X	1.2X	4.6X	11X
Linagliptin (1X)	0.3X	3.2X	8.5X	13.7X
Metformin (1X)	1.6X	2.7X	5.9X	15.4X

[a] Maximum recommended human dose (MRHD) estimates based on:
Empagliflozin (25 mg) $AUC_{0\text{-}24\ h}$ = 4740 nM*h
Linagliptin (5 mg) $AUC_{0\text{-}24\ h}$ = 158 nM*h
Metformin (2000 mg) $AUC_{0\text{-}24\ h}$ = 159 µM*h
[b] NOAEL dose in 13-week rat combination toxicity study

6 General Toxicology

6.2 Repeat-Dose Toxicity

Empagliflozin (BI 10773)/Linagliptin (BI 1356)/Metformin: 13-week oral (gavage) combination toxicity study in rats

Study no.:	17B039 (Doc. No. N00256132)
Study report location:	eCTD 4.3.2. 17b039
Conducting laboratory and location:	Boehringer Ingelheim Pharma GmbH & Co. KG, Birkendorfer Str. 65, 88397 Biberach an der Riss, Germany
Date of study initiation:	4/24/17
GLP compliance:	Yes
QA statement:	Yes, finalized 11/5/18
Drug, lot #, and % purity:	**Empagliflozin –** BI 10773 XX (Batch 1085991, 99.9% purity) **Linagliptin –** BI 1356 BS (Batch 1086801, 98.7% purity) **Metformin HCl –** metformin HCl ((b) (4) (BI Internal Batch 608477), 99.6% purity)

Key Study Findings:

- Triple combination empagliflozin/linagliptin/metformin doses based on clinical drug ratios provided approximately 1X to 10X estimated MRHD exposures
- No unexpected or synergistic toxicity was identified with triple empagliflozin/linagliptin/metformin treatment
    - Additive toxicity was evident in triple combination groups by increased incidence and severity of toxicity compared to individual drug groups
- Major target organs in the study were kidney, heart, liver, and salivary glands, consistent with known metformin and empagliflozin toxicity
- The high dose triple combination exceeded the MTD based on mortality and severity of target organ toxicity
- **NOAEL = 10/5/90 mg/kg/d empagliflozin/linagliptin/metformin (approximately 1X/2X/3X MRHD)**

Methods

Doses:	Empagliflozin/linagliptin/metformin (mg/kg/d) 0/0/0 (Vehicle) 100/0/0 (empagliflozin only) 0/20/0 (linagliptin only) 0/0/500 (metformin only) 10/5/90 (low dose combination) 30/10/200 (mid dose combination) 100/20/500 (high dose combination)
Frequency of dosing:	Once daily (QD)
Route of administration:	Oral gavage
Dose volume:	10 ml/kg
Formulation/Vehicle:	0.5% aqueous hydroxyethyl cellulose (Natrosol® 250 HX) in demineralized water
Species/Strain:	Wistar Han rat / Crl:WI(Han) (Charles River Laboratories, Sulzfeld, Germany)
Number/Sex/Group:	10 (main) + 10 recovery (vehicle control, monotherapy drug controls, HD combination)
Age:	8-9 weeks
Weight:	Males – 223 to 290 g / Females – 153 to 203 g
Satellite groups:	4/sex/group for toxicokinetics
Unique study design:	Group housed (up to 4/cage of same sex) and enrichment provided (gnawing sticks, raised seating platform)
Deviation from study protocol:	None identified that affected the integrity of the study

<table>
<tr><th colspan="2">13-Week Combination Repeat Dose Toxicity in Rat — Summary</th></tr>
<tr><td>SPECIES
DOSES AND ADMINISTRATION
ANIMALS
FOLLOW-UP</td><td>NOAEL = 10/5/90 MG/KG/DAY
(EMPAGLIFLOZIN/LINAGLIPTIN/METFORMIN)
1X / 3X / 3X MRHD</td></tr>
<tr><td>Wistar Han (Crl:WI(Han))
QD Oral gavage
13-wk + 6-wk recovery
(10/sex/group + recovery)

Empa/lina/met (mg/kg/d)
0/0/0 (Vehicle)
100/0/0 (empagliflozin only)
0/20/0 (linagliptin only)
0/0/500 (metformin only)
10/5/90 (LD combo)
30/10/200 (MD combo)
100/20/500 (HD combo)</td><td>
<table>
<tr><th colspan="5">Exposure Summary</th></tr>
<tr><td rowspan="3">Drug (monotherapy)</td><td colspan="4">Empagliflozin/linagliptin/metformin</td></tr>
<tr><td rowspan="2">Exposure (Day 88)</td><td colspan="3">MRHD</td></tr>
<tr><td>LD</td><td>MD</td><td>HD</td></tr>
<tr><td>Empa (1X)</td><td>0.6X</td><td>1X</td><td>5X</td><td>11X</td></tr>
<tr><td>Lina (1X)</td><td>0.3X</td><td>3X</td><td>8X</td><td>14X</td></tr>
<tr><td>Met (1X)</td><td>1.6X</td><td>2X</td><td>6X</td><td>15X</td></tr>
</table>
MRHD estimates based on:
Empa (25 mg) $AUC_{0\text{-}24}$ = 4740 nM*h
Lina (5 mg) $AUC_{0\text{-}24}$ = 158 nM*h
Met (25 mg) $AUC_{0\text{-}24}$ = 159 µM*h
</td></tr>
<tr><td colspan="2"><u>Mortality:</u> Empa/lina/met HD – 1 female found dead on day 61, 1 female euthanized on day 82 for humane reasons (abnormal clinical signs) considered treatment-related; target organ toxicity consistent with the study findings were observed (kidney, heart, liver, glands (salivary, parotid, sublingual)) and severity of kidney findings suggest contribution to mortality and moribund condition</td></tr>
<tr><td colspan="2"><u>Clinical Signs</u>: Metformin – soft feces (all animals, occasionally starting day 22); empa/lina/met HD – soft feces (all animals, occasionally starting day 22), distended abdomen (5/20 ♀, 1/19 ♂; partially reversible, 3/10 recovery ♀)</td></tr>
<tr><td colspan="2"><u>Body Weight</u>: Findings in males only (no BW effects observed in females) Empagliflozin – slight -10% ♂ BW gain (reversible); metformin – slight -10% ♂ BW gain (reversible); empa/lina/met MD – slight -10% ♂ BW gain; empa/lina/met HD – moderate -20% ♂ BW gain (reversible but remained slight -10% reduced compared to recovery controls)</td></tr>
<tr><td colspan="2"><u>Hematology / Clinical Chemistry / Urinalysis</u>: Various findings were seen in monotherapy and triple combination groups and treatment-related findings increased with increasing dose. All findings were reversible (nearly or completely) after the drug-free recovery period. Trends were consistent with those seen in previous toxicity studies and with known mechanisms of toxicity and exaggerated pharmacology. Empagliflozin-related trends consistent with SGLT2 inhibition included glucosuria, decreased plasma glucose and metabolism-related changes (hepatic gluconeogenesis, lipid and protein changes), and various serum electrolyte (K, Cl, Ca, Mg, P) and urine (↑</td></tr>
</table>

volume, ↑ specific gravity, ↓ pH) changes. Metformin-related trends in RBC (↓ MCH, ↓ MCHC), WBC (↑ neutrophils), plasma (↓ glucose, creatinine, urea), urine ↑ bilirubin.
Organ Weights: Reversible changes in absolute and relative organ weights were observed in some groups; due to treatment-related reductions in body weight the Sponsor highlighted changes relative to brain weight (shown here). ***Empagliflozin* – kidney** ↑ weight (+20% ♂, +30% ♀ with no histopathologic correlates); ***Metformin* – heart** (minimal ↑ weight, +10% ♂, +20% ♀, no histopathologic correlates); **liver** (minimal ↑ weight, +20%, no histopathologic correlates), **ovaries** (+20% ↑ weight attributable to ↑ # of corpora lutea); ***Empa/Lina/Met combination groups –*** **LD:** no organ weight findings; **MD: kidney** ↑ weight +20% ♂ to +30% ♀, **liver** slight ↑ weight +10% ♀ (only), **thymus** ↓ weight -20% ♀ (only) (no histopathologic correlates in any MD organ) **HD: heart** ↑ weight + 30% ♂ to + 40% ♀ (histopathologic correlate of cardiac hypertrophy and vacuolation of septal and left ventricular myocardiocytes), **kidney** ↑ weight +30% ♂ to +70% ♀ (histopathologic correlate of tubular epithelium degeneration/regeneration), **liver** ↑ weight +30% ♂ to +70% ♂ (histopathologic correlate of panlobular hepatocellular hypertrophy in ♀ only), **ovary** ↑ weight +50% ♀ (correlative gross increased ovary size, histopathologic increased corpora lutea number), **thymus** ↓ weights -50% ♂ and -30% ♀ (histopathologic correlate of minimal lymphocyte decrease in the cortex)
Gross Pathology: Findings only in empa/lina/met HD animals at terminal sacrifice in kidneys (abnormal surface 4/10 ♀), heart (right ventricle dilated 1/10 ♀), liver (hypertrophy 2/10 ♀), ovaries (hypertrophy 3/10 ♀), stomach (impaction, gastric wall thickening 1/10 ♂), thymus (decreased size 3/10 ♂). Gross findings were correlated with histopathological findings in every instance.
Histopathology: Detailed histopathology findings are shown in Table 7 and Table 8. Findings in the triple combination group were unremarkable in the LD, with combination treatment generally increasing incidence and severity of metformin-related findings in the MD (kidney only) and HD. HD combination target organs included **kidney** (degeneration/regeneration)**, heart** (myocardial hypertrophy)**, liver** (hypertrophy)**, salivary glands, ovaries,** and **thymus.**
Toxicokinetics: TK trends in combination treatments compared to monotherapy exposures were limited to: empagliflozin C_{max} increased slightly in males while mean (combined male and female) AUC_{0-24} was 40% lower (day 88) in the HD combination group; linagliptin C_{max} and AUC_{0-24} were approximately 70% lower in the triple combination (day 88); metformin exposures in the triple combination group increased 90% (C_{max}) and 60% (AUC_{0-24}) compared to monotherapy and exposures increased after repeated dosing.

Summary: There was no evidence of unexpected or synergistic toxicity in the triple combination groups compared to concurrent monotherapy drug groups or cross-referenced combination rat toxicity studies. Major target organs in the study were kidney, heart, liver, and salivary glands, consistent with known toxicity from the individual drugs. Incidence and severity of toxicity was slightly higher in the HD triple combination group compared to monotherapies, consistent with an additive effect of drugs on general animal disposition and target organ toxicity. Toxicity in the triple combination was generally driven by metformin and the NOAEL at the LD combination (10/5/90 mg/kg/d empa/lina/met) is consistent with prior metformin monotherapy and combination rat toxicity study NOAELs of approximately 100 mg/kg/d. Kidney findings in the MD triple combination identified the LOAEL dose. The HD combination treatment exceeded the MTD due to mortality/euthanasia in 2/20 females and extensive gross and histopathologic changes seen in target organs of kidney, heart, liver, salivary glands, thymus, and ovaries. Recovery animals showed complete or partial reversibility of all findings after a 6-week drug-free period. **NOAEL = 10/5/90 mg/kg/d empagliflozin/linagliptin/metformin (approximately 1X/2X/3X MRHD)**

Dose Selection Summary

Doses of each compound for the triple combination toxicity study were chosen based on drug ratios in the proposed clinical drug product and results from prior rat combination toxicity studies (see Sponsor summary tables below). The doses in the high dose triple combination were expected to provide approximately 10-times clinical exposures at the MRHD and to cause target organ toxicity and adverse effects in the rats. The low dose triple combination was expected to result in approximately 1-times clinical drug exposures at the MRHD and to be below the toxic rat doses (i.e., NOAEL). The mid dose triple combination was the approximate geometric mean between HD and LD and was expected to cause minimal signs of toxicity at approximately 4-times exposures to the MRHD. The high dose levels of each drug in the HD triple combination were used in monotherapy groups to assess individual compound toxicity and for evaluation of potential additive, supra-additive, or synergistic toxicity when rats were exposed to the triple combination.

Study Design Summary

Daily Dose [mg/kg]	Control	Mono			Combination		
	Group 1	Group 2	Group 3	Group 4	Group 5 Low-Dose	Group 6 Mid-Dose	Group 7 High-Dose
Empagliflozin (BI 10773)	0	100	0	0	10	30	100
Linagliptin (BI 1356)	0	0	20	0	5	10	20
Metformin	0	0	0	500	90	200	500

Summary of prior combination toxicity studies and Sponsor's NOAELs

Study	Doses [mg/kg] Empagliflozin	Linagliptin	Metformin	NOAEL [mg/kg]
Empagliflozin/Linagliptin: 13-wk oral toxicity study in rats (U11-1622)	30	6	--	100/20
	30	15	--	
	100	20	--	
	300	60	--	
	300	0	--	
	0	60	--	
Empagliflozin/Metformin: 13-wk oral toxicity study in rats (U11-3632)	200	--	0	50/100
	0	--	400	
	50	--	100	
	100	--	200	
	200	--	400	
Linagliptin/Metformin: 13-wk oral toxicity study in rats (U10-1492)	--	0.5	100	0.5/100
	--	2.0	400	
	--	4.0	800	
	--	2.0	800	
	--	4.0	0	
	--	0	800	

Table 7 – Sponsor's 13-Week Rat EMPA/LINA/MET Toxicity Study Summary

Duration of Dosing	Dose [mg/kg/day]	Findings	NOAEL [mg/kg/day]
13-weeks with 6-weeks recovery	**Empagliflozin /linagliptin/ metformin**	**100 mg/kg/day Empagliflozin:** Kidneys: ↑organ weight	**Empagliflozin /linagliptin/ metformin:**
	0/0	**20 mg/kg/day Linagliptin:** No findings	
	100/0/0	**500 mg/kg/day Metformin:**	**10/5/90**
	0/20/0	Heart: organ weight ↑	
	0/0/500	Liver: organ weight ↑	
	10/5/90	Kidneys: degeneration and regeneration, basophilic tubules	1.2/3.2/2.7
	30/10/200	hyaline droplets proximal tubules	times the
	100/20/500	Salivary glands: ductal hypertrophy, degeneration	clinical AUC
		Ovaries: number of corpora lutea ↑	exposure
		10/5/90 mg/kg/day Empagliflozin/linagliptin/metformin: No findings	
		≥30/10/200 mg/kg Empagliflozin/linagliptin/metformin: Kidneys: Cellular swelling distal nephron, PAS-positive granules and hyaline droplets proximal tubules	
		100/20/500 mg/kg Empagliflozin/linagliptin/metformin: Body weight gain ↓, mortality	
		Heart: organ weight ↑, myocardial hypertrophy	
		Liver: organ weight ↑, hepatocellular hypertrophy	
		Kidneys: organ weight ↑, degeneration and regeneration, basophilic tubules single cell necrosis, karyomegaly, vacuolation proximal tubules	
		Mineralization of pelvis	
		Thymus: size ↓, cellularity cortex↓	
		Salivary glands: ductal hypertrophy, degeneration	
		Ovaries: number of corpora lutea ↑	
		Recovery: Kidneys: signs of regeneration	
		Other changes: ameliorated or fully reversible	

NOAEL: No observed adverse effect level. ↑: increased, ↓: decreased.

Observations and Results *(Additional details not summarized above)*

Mortality

Empagliflozin – 1 female in the recovery group was euthanized on Day 129 due to a large 'multilocular' mass on the left thoracic wall which correlated with a histopathological designation of a malignant mammary gland adenocarcinoma. The tumor type was not seen previously in the cross-referenced empagliflozin carcinogenicity study and was considered incidental in this 13-week study.

Empa/lina/met HD – 1 male died on day 3 under anesthesia during blood collection considered procedure related (not treatment-related)

Feed/Water Consumption –reversible, transient decreased food consumption on day 4 (all groups, more pronounced in males), food consumption slightly increased starting day 11 (all groups, more pronounced in males); reversible, dose-related increased water consumption, typically more pronounced in males (1.4X/1.3X, 1.7X/1.4X, 1.8X/1.9X in LD, MD, HD combination treatment males/females, respectively)

Ophthalmoscopy – unremarkable

Urinalysis – dose-related urinalysis findings consistent with SGLT2 inhibition by empagliflozin, seen in empagliflozin only and triple combination groups; no apparently supra-additive or synergistic effects of combination treatment

Organ Weights *(additional findings not summarized above)*

Prostate weights (absolute and relative to brain weight) were decreased in empagliflozin only (0.8X relative to brain weight) and HD combination (0.7X relative to brain weight) males. The pathologist considered the prostate findings to be unremarkable and not pathologically significant due to an absence of histopathologic correlates and absence of prostate weight change relative to body weights (which were reduced). There were no prostate findings after the drug-free recovery period.

There were slight changes (absolute and relative) in HD combination female adrenal gland weight (+20%) and pituitary gland weight (-10%). The modest changes and absence of histopathologic findings in the tissues suggest the findings were unremarkable. The absence of organ weights or histopathologic findings in adrenal gland or pituitary gland after the drug-free recovery period provide further evidence that any findings were reversible and unlikely to be toxicologically meaningful. The pathologist considered the absence of adrenal and pituitary findings in males to be further evidence of the incidental nature of the female findings, however, females seemed to have modestly increased toxicity in various organs, so reversibility and slight severity are more important factors to reduce toxicity concerns about the adrenal gland and pituitary gland weight changes.

Histopathology (Adequate Battery and Peer Review confirmed; analyzed in vehicle and monotherapy control groups plus HD combo, all groups when target organs identified, all organs with relevant macroscopic findings)

Histopathology summary tables

Incidence and severity of histopathologic lesions in target organs are shown in the Sponsor's summary tables, below.

Table 8 – Target organ histopathology summaries

Incidence of test item-related microscopic findings in the kidneys at the end of the treatment period

	Main phase									
Group	1		4		5		6		7	
Daily dose of Metformin (G4) and Empagliflozin/Linagliptin/Metformin (G5 – 7) [mg/kg]	0		500		10/5/90		30/10/200		100/20/500	
Gender	M	F	M	F	M	F	M	F	M	F
Kidneys: No. examined	10	10	10	10	10	10	10	10	9	10
Degeneration/regeneration	0	0	0	3	0	0	0	0	7	5
minimal	0	0	0	1	0	0	0	0	5	1
slight	0	0	0	2	0	0	0	0	2	2
moderate	0	0	0	0	0	0	0	0	0	2
PAS+ granules proximal tubules	0	0	0	0	0	0	6	0	8	0
Hyaline droplet tubules	0	0	8	0	0	0	2	0	0	0
Cellular swelling tubules distal nephron	0	0	0	0	0	0	4	1	4	5
Vacuolation tubular epithelium	0	0	0	0	0	0	0	1	1	10
Karyomegaly	0	0	0	0	0	0	0	0	4	4
Dilatation tubulus cortex	0	0	0	0	0	0	0	0	1	4
Hypertrophy tubular epithelium	0	0	0	0	0	0	0	0	0	3
Necrosis single cell	0	0	0	0	0	0	0	0	1	2
Deposition mineral pelvis	0	0	0	0	0	0	0	0	1	3
Hyperplasia transitional epithelium pelvis	0	0	0	0	0	0	0	0	0	2
Inflammation papilla	0	0	0	0	0	0	0	0	0	2

Incidence of test item-related microscopic findings in the heart at the end of the treatment period

	Treatment period								Recovery period			
Group	1		5		6		7		1		7	
Daily dose of Empagliflozin/Linagliptin/ Metformin [mg/kg]	0		10/5/90		30/10/200		100/20/500		0		100/20/500	
Gender	M	F	M	F	M	F	M	F	M	F	M	F
Heart: No. examined	10	10	10	10	10	10	9	10	10	10	10	9
Vacuolation myofiber	0	0	0	0	0	0	9	9	1	1	0	1
minimal	0	0	0	0	0	0	4	3	1	1	0	1
slight	0	0	0	0	0	0	5	6	0	0	0	0
Hypertrophy myofiber	0	0	0	0	0	0	4	4	0	0	0	0
Dilation right ventricle	0	0	0	0	0	0	0	1	0	0	0	0

Incidence of test item-related microscopic findings in the salivary glands (gl.) at the end of the treatment period

	Main phase											
Group	1		2		4		5		6		7	
Daily dose in mg/kg	0		100		500		10/5/90		30/10/200		100/20/500	
Test item	Control		Empagli-flozin		Met-formin		Empagliflozin/Linagliptin/Metformin					
Gender	M	F	M	F	M	F	M	F	M	F	M	F
Parotid gl.: No. examined	10	10	10	10	10	10	10	10	10	10	9	10
Hypertrophy duct	0	0	0	0	10	10	0	0	8	8	9	10
minimal	0	0	0	0	0	0	0	0	8	8	0	0
slight	0	0	0	0	10	10	0	0	0	0	9	9
moderate	0	0	0	0	0	0	0	0	0	0	0	1
Atrophy acinus	0	0	0	0	1	6	1	1	0	2	6	9
minimal	0	0	0	0	1	4	1	1	0	2	2	7
slight	0	0	0	0	0	2	0	0	0	0	4	1
moderate	0	0	0	0	0	0	0	0	0	0	0	1
Deposition mineral increased	0	0	0	0	4	3	1	0	0	0	8	5
minimal	0	0	0	0	4	3	1	0	0	0	8	4
slight	0	0	0	0	0	0	0	0	0	0	0	1
Vacuolation increased	2	0	3	0	2	0	2	0	3	0	6	8
minimal	2	0	2	0	2	0	2	0	3	0	6	7
slight	0	0	1	0	0	0	0	0	0	0	0	0
moderate	0	0	0	0	0	0	0	0	0	0	0	1
Inflammation interstitium	0	0	0	0	1	3	0	1	0	0	2	3
minimal	0	0	0	0	1	3	0	1	0	0	2	2
slight	0	0	0	0	0	0	0	0	0	0	0	1
Sublingual gl.: No. examined	10	10	10	10	10	10	10	10	10	10	9	10
Hypertrophy duct	0	0	0	0	10	9	0	0	7	0	8	9
minimal	0	0	0	0	0	0	0	0	7	0	1	0
slight	0	0	0	0	10	9	0	0	0	0	7	8
moderate	0	0	0	0	0	0	0	0	0	0	0	1
Mandibular gl.: No. examined	10	10	10	10	10	10	10	10	10	10	9	10
Depletion zymogen	0	0	0	0	10	9	0	0	0	0	9	10
minimal	0	0	0	0	1	1	0	0	0	0	0	0
slight	0	0	0	0	9	8	0	0	0	0	0	0
moderate	0	0	0	0	0	0	0	0	0	0	9	10

Incidence of test item-related microscopic findings in the tongue at the end of the treatment period

	Main phase									
Group	1		4		5		6		7	
Daily dose of Metformin (G4) and Empagliflozin/Linagliptin/Metformin (G5 – 7) [mg/kg]	0		500		10/5/90		30/10/200		100/20/500	
Gender	M	F	M	F	M	F	M	F	M	F
Tongue: No. examined	10	10	10	10	10	10	10	10	9	10
Vacuolation serous gland	0	0	2	3	0	0	1	5	9	10
minimal	0	0	2	2	0	0	1	5	2	4
slight	0	0	0	1	0	0	0	0	5	2
moderate	0	0	0	0	0	0	0	0	1	4
severe	0	0	0	0	0	0	0	0	1	0

Incidence of test item-related microscopic findings in the adrenal glands at the end of the treatment period

	Main phase													
Group	1		2		3		4		5		6		7	
Daily dose in mg/kg	0		100		20		500		10/5/90		30/10/200		100/20/500	
Test item	Control		Empa-gliflozin		Lina-gliptin		Met-formin		Empagliflozin/Linagliptin/Metformin					
Gender	M	F	M	F	M	F	M	F	M	F	M	F	M	F
Adrenal glands: No. examined	10	10	10	10	10	10	10	10	10	10	10	10	9	10
Vacuolation zona glomerulosa	1	1	10	6	2	0	1	0	4	4	6	4	2	1
minimal	0	1	0	2	2	0	1	0	2	4	6	4	2	1
slight	1	0	10	4	0	0	0	0	2	0	0	0	0	0
Vacuolation zona reticularis	0	0	0	0	0	0	0	0	0	0	0	0	3	2

Incidence of test item-related microscopic findings in the ovaries at the end of the treatment period

	Main phase						
Group	1	2	3	4	5	6	7
Daily dose in mg/kg	0	100	20	500	10/5/90	30/10/200	100/20/500
Test item	Control	Empa-gliflozin	Lina-gliptin	Met-formin	Empagliflozin/Linagliptin/Metformin		
Sex	F	F	F	F	F	F	F
Ovaries: No. examined	10	10	10	10	10	10	10
Increased number of corpora lutea	0	0	0	3	0	2	6

Incidence of test item-related microscopic findings in the lymphoid organs at the end of the treatment period

	Main phase									
Group	1		4		5		6		7	
Daily dose of Metformin (G4) and Empagliflozin/Linagliptin/ Metformin (G5 – 7) in mg/kg	0		500		10/5/90		30/10/200		100/20/500	
Gender	M	F	M	F	M	F	M	F	M	F
Mesenteric lymph nodes: No. examined	10	10	10	10	10	10	10	10	9	10
Decreased cellularity lymphocytes paracortex	0	0	1	0	0	0	3	3	6	8
minimal	0	0	1	0	0	0	3	3	1	4
slight	0	0	0	0	0	0	0	0	5	2
moderate	0	0	0	0	0	0	0	0	0	2
Thymus: No. examined	10	10	10	10	10	10	9	10	9	10
Decreased cellularity lymphocytes cortex	1	0	1	1	0	0	1	0	5	4

Recovery animals (6-week drug free period)

Empagliflozin only animals had increased vacuolation in adrenal gland zona glomerulosa (5/10 ♂ minimal, 4/10 ♂ slight, 1/10 ♀ minimal) and cardiomyocyte vacuolation, right ventricle (2/10 ♀) which weren't observed in the main study animals.

Kidney lesions showed partial recovery and continued evidence of regeneration in the metformin only and triple combination recovery groups (Sponsor's table below). Incidence and severity of tongue (3/10 ♀), adrenal gland (2/10 ♂), and mesenteric lymph node (2/10 ♂) were reduced but still evident in some triple combination recovery animals supporting partial but ongoing recovery.

Incidence of test item-related microscopic findings in the kidneys at the end of the recovery period

	Recovery period					
Group	1		4		7	
Daily dose of Metformin (G4) and Empagliflozin/Linagliptin/Metformin (G5 – 7) in mg/kg	0		500		100/20/500	
Gender	M	F	M	F	M	F
Kidneys: No. examined	10	10	10	10	10	9
Basophilic tubules	2	3	0	1	2	7
minimal	2	3	0	1	2	3
slight	0	0	0	0	0	4
Infiltrate mononuclear interstitium	1	1	1	1	1	6
PAS+ granules proximal tubules	0	0	0	0	1	0
Karyomegaly	0	0	0	0	4	0

Stability and Homogeneity

Stability and homogeneity of individual compounds in dosing formulations were planned on blood sampling days for toxicokinetics on Days 1, 24, and 88. Additional formulation analyses were added after inconsistencies in some dosing solutions were noted on Day 1. Analyses confirmed the validity of the dosing solutions, the absence of drug contamination in single drug group formulations, and the general validity of the study treatments. A few exceptions were identified in isolated dose group formulations which were 'out of target' from pre-specified homogeneity ranges and solutions were further scrutinized with additional testing which identified improper preparation for analyses (e.g., Group 5 dose formulations on Days 1 and 15). The overall integrity of the study was confirmed.

Toxicokinetics

The spectrum of toxicokinetic analyses was extensive based on the complex triple combination study design (see exposure summary in Table 9). Exposure comparisons included potential dose effects, sex effects, repeated dose effects, and combination effects for individual drugs. Drug exposures increased with increasing dose for all drugs. There were limited apparent sex differences in exposure, with the exceptions of slightly lower male exposure to empagliflozin (monotherapy group only, approximately 30% to 50% lower than females), approximately 50% lower male linagliptin exposure at the high dose only (monotherapy group), and increased metformin C_{max} (↑ 3-fold) and AUC_{0-24} (+60%) in females only on day 1. Metformin increased slightly with repeated dosing (+38% on day 88).

Combination treatment affected drug exposures compared to monotherapy exposures in some instances. Empagliflozin C_{max} increased slightly in males while mean (combined male and female) AUC_{0-24} was 40% lower on day 88 in the HD combination group. Linagliptin C_{max} and AUC_{0-24} were approximately 70% lower in the triple combination on day 88. Metformin exposures in the triple combination group increased 90% (C_{max}) and 60% (AUC_{0-24}) compared to monotherapy and exposures increased after repeated dosing.

Table 9 – Toxicokinetic summary

Mean toxicokinetic parameters of Empagliflozin

Parameter	Day	Sex	Mono	Combination		
			Group 2 100 mg/kg	Group 5 10 mg/kg	Group 6 30 mg/kg	Group 7 100 mg/kg
			---	+ 5 mg/kg Linagliptin	+ 10 mg/kg Linagliptin	+ 20 mg/kg Linagliptin
			---	+ 90 mg/kg Metformin	+ 200 mg/kg Metformin	+ 500 mg/kg Metformin
C(max) [nmol/L]	Day 88	m	13700	1280	9800	19800
		f	27400	1540	12800	26800
		m & f	20500	1410	11300	23300
AUC(0-24h) [nmol·h/L]	Day 88	m	58600	5050	18600	50600
		f	105000	5920	25400	53400
		m & f	81600	5490	22000	52000

Mean toxicokinetic parameters of Linagliptin

Parameter	Day	Sex	Mono	Combination		
			Group 3 20 mg/kg	Group 5 5 mg/kg	Group 6 10 mg/kg	Group 7 20 mg/kg
			---	+ 10 mg/kg Empagliflozin	+ 30 mg/kg Empagliflozin	+ 100 mg/kg Empagliflozin
			---	+ 90 mg/kg Metformin	+ 200 mg/kg Metformin	+ 500 mg/kg Metformin
C(max) [nmol/L]	Day 88	m	1250	63.3	260	292
		f	1650	68.2	322	524
		m & f	1450	65.7	291	408
AUC(0-24h) [nmol·h/L]	Day 88	m	6580	492	1200	1920
		f	9070	517	1490	2410
		m & f	7820	504	1350	2160

Mean toxicokinetic parameters of Metformin

Parameter	Day	Sex	Mono	Combination		
			Group 4 500 mg/kg	Group 5 90 mg/kg	Group 6 200 mg/kg	Group 7 500 mg/kg
			---	+ 10 mg/kg Empagliflozin	+ 30 mg/kg Empagliflozin	+ 100 mg/kg Empagliflozin
			---	+ 5 mg/kg Linagliptin	+ 10 mg/kg Linagliptin	+ 20 mg/kg Linagliptin
C(max) [nmol/L]	Day 88	m	118000	48100	76400	303000
		f	181000	54100	124000	251000
		m & f	150000	51100	100000	277000
AUC(0-24h) [nmol·h/L]	Day 88	m	1330000	369000	845000	2410000
		f	1660000	481000	1040000	2480000
		m & f	1490000	425000	943000	2450000

7 Genetic Toxicology

Genotoxicity was not assessed with combined empagliflozin/linagliptin/metformin. None of the individual drug substances were found to be genotoxic in cross-referenced NDA reviews. No impurities were identified in the triple combination drug product that warranted genotoxic assessment.

8 Carcinogenicity

Carcinogenicity has been assessed for the individual drug substances and findings are noted in listed drug labels. Cross-referenced data did not provide evidence that additional carcinogenicity assessment was needed for combined empagliflozin/linagliptin/metformin exposure.

9 Reproductive and Developmental Toxicology

Reproductive and developmental toxicity has been assessed for the individual drug substances as well as combined empagliflozin/linagliptin, empagliflozin/metformin, and linagliptin/metformin and findings are noted in listed drug labels. Cross-referenced data did not provide evidence that additional developmental or reproductive toxicity assessment was needed for combined empagliflozin/linagliptin/metformin exposure.

11 Integrated Summary and Safety Evaluation

Toxicology

The primary nonclinical toxicologic assessment for the proposed triple combination drug comes from the 13-week rat combination empagliflozin/linagliptin/metformin toxicity study. Toxicity of individual drugs and double combinations of each component of the proposed triple combination were previously assessed in animal models and reviewed under the cross-referenced NDAs for listed drug products. Prior toxicology assessments included empagliflozin/metformin, linagliptin/metformin, and empagliflozin/linagliptin. The extended release metformin drug product formulations were not assessed directly in animal models, but excipients and impurities were assessed in cross-referenced NDAs for listed empagliflozin/metformin XR and linagliptin/metformin XR drug products.

The 13-week rat empagliflozin/linagliptin/metformin combination was designed to identify any potential supra-additive or synergistic effects of combined treatment. Rat combination doses were chosen to approximate clinical drug ratios in the triple combination tablet at three different combination dose levels (i.e., low, medium, high doses) and compared to vehicle and individual drug controls at the highest individual drug doses. The triple combination rat study identified limited toxicokinetic drug interactions and there was no evidence of supra-additive or synergistic toxicity. Toxicities that identified the maximum tolerable and no observable adverse effect levels were consistent with known toxicity of individual drugs on kidney (empagliflozin) and heart and liver (metformin). Metformin exposure in the high dose triple combination was approximately 60% higher (1.6X) than in the equivalent metformin only dose group. Increased incidence and severity of heart and liver toxicity in the combination treatment group was consistent with the higher metformin exposures compared to the metformin only group. Apparent additive effects of empagliflozin and metformin on kidney toxicity resulted in increased kidney toxicity in the triple combination groups. As expected from clinical exposure margins and cross-referenced prior toxicity studies, linagliptin did not appear to contribute to any of the toxicity findings in the triple combination rat study. The absence of toxicity in the lowest empagliflozin/linagliptin/metformin supported a NOAEL determination at approximate exposures of 1X/3X/3X MRHD, respectively. Findings from the triple combination rat toxicity study are summarized in the Reviewer's table, below.

Reviewer's 13-Week Rat Empa/Lina/Met Overall Toxicity Summary

Group	Empa	Lina	Met	Target Organ Toxicity Summary	Notes
1	0	0	0	None	Vehicle
2	**100**	0	0	**Kidney** (↑ kidney weight)	NOAEL
3	0	**20**	0	None	NOAEL
4	0	0	**500**	**Kidney** (proximal tubule) **Heart** (↑ heart wt., hypertrophy) **Salivary glands** *Additional toxicity: l*iver, tongue, ovaries, mesenteric lymph nodes, mandibular gland	LOAEL
5	**10**	**5**	**90**	Adrenal gland (non-adverse)	NOAEL
6	**30**	**10**	**200**	**Kidney** (proximal tubule, distal nephron); *Additional toxicity: p*arotid gland, sublingual glands, mesenteric lymph nodes, adrenal gland	LOAEL
7	**100**	**20**	**500**	**Mortality**; **Kidney** (↑ weight, proximal tubular, distal nephron, pelvis, papilla); **Heart** (↑ wt., myocardial hypertrophy, cardiomyocyte vacuolation); **Liver** (↑ weight/size, hepatocellular hypertrophy); **Parotid gland** (ductal hypertrophy, acinar atrophy, interstitial inflammation); **Sublingual gland** (ductal hypertrophy); *Additional toxicity:* tongue, ovaries, adrenal glands, mesenteric lymph nodes, thymus, mandibular gland	> MTD; (6-week recovery near complete reversibility)

Empagliflozin (empa) – SGLT2 inhibitor; Linagliptin (lina) – DPP4 inhibitor; Metformin (met) – biguanide

Pediatrics

Pediatric studies are not planned for the combination. Nonclinical data do not support the need to study the combination in juvenile animals to inform risks to a pediatric population.

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/s/

DAVID B CARLSON
12/06/2019 03:32:18 PM
Nonclinical - recommend approval

TODD M BOURCIER
12/09/2019 11:32:34 AM
I concur