CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206111Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

BIOPHARMACEUTICS REVIEW Office of New Drug Quality Assessment			
Application No.:	NDA 206111	**Primary Reviewer:** Kelly M. Kitchens, Ph.D.	
Submission Date:	August 4, 2014		
Division:	Division Metabolism and Endocrinology Products	**Secondary Reviewer:** Tapash Ghosh, Ph.D.	
Applicant:	Boehringer Ingelheim Pharmaceuticals, Inc.	**Acting Supervisor:** Paul Seo, Ph.D.	
Trade Name:	N/A	**Date Assigned:**	August 7, 2014
Established Name:	Empagliflozin/Metformin Hydrochloride Fixed Dose Combination Tablets	**Date of Review:**	April 13, 2015
Indication:	Type 2 Diabetes	**Type of Submission:** NDA 505(b)(2)	
Formulation/ Strengths	Tablets, 5+500/1000 mg and 12.5+500/1000 mg		
Route of Administration	Oral		
Type of Review:	Bioequivalence data and dissolution data		

SUMMARY:

Background: Empagliflozin is the subject of NDA 204629, resubmitted on June 2, 2014 and approved on August 1, 2014. Metformin was approved for patients with type 2 diabetes on March 3, 1995, subject of NDA 020357. The Applicant for the current NDA developed empagliflozin (BI 10773) and metformin hydrochloride (HCl) fixed dose combination (FDC) tablets to improve glycemic control in adults with type 2 diabetes mellitus (b) (4) The Applicant developed empagliflozin (BI 10773) and metformin HCl fixed dose combination (FDC) tablets to improve glycemic control in adults with type 2 diabetes mellitus (b) (4)

(b) (4)

Submission: The NDA includes data from bioequivalence studies for the proposed commercial FDC tablets and the corresponding doses of the free combination tablets, to support the bridging of the efficacy and safety results obtained with the free combination of empagliflozin and metformin. The results are summarized in the following tables:

BE Study 1276.6 Empagliflozin results from 5 mg Empagliflozin/500 mg Metformin HCl				
PK Parameter	**Mean T/R Ratio**	**90% CI Lower Limit (%)**	**90% CI Upper Limit (%)**	**Intra-individual %CV**
$AUC_{0-\infty}$ (nmol-h/L)	102.79	99.08	106.63	6.7
C_{max} (nmol/L)	102.96	97.95	108.26	9.2
AU_{0-t} (nmol-h/L)	102.77	99.15	106.52	6.5
BE Study 1276.6 Empagliflozin results from 12.5 mg Empagliflozin/500 mg Metformin HCl				
PK Parameter	**Mean T/R Ratio**	**90% CI Lower Limit (%)**	**90% CI Upper Limit (%)**	**Intra-individual %CV**
$AUC_{0-\infty}$ (nmol-h/L)	97.92	93.53	102.52	8.4
C_{max} (nmol/L)	104.61	99.88	109.56	8.4
AU_{0-t} (nmol-h/L)	98.00	93.53	102.69	8.5
BE Study 1276.6 Metformin results from 5 mg Empagliflozin/500 mg Metformin HCl				
PK Parameter	**Mean T/R Ratio**	**90% CI Lower Limit (%)**	**90% CI Upper Limit (%)**	**Intra-individual %CV**
$AUC_{0-\infty}$ (ng-h/L)	96.79	91.77	102.09	9.8
C_{max} (ng/L)	93.83	88.01	100.03	11.9
AU_{0-t} (ng-h/L)	95.94	91.20	100.93	9.3
BE Study 1276.6 Metformin results from 12.5 mg Empagliflozin/500 mg Metformin HCl				
PK Parameter	**Mean T/R Ratio**	**90% CI Lower Limit (%)**	**90% CI Upper Limit (%)**	**Intra-individual %CV**
$AUC_{0-\infty}$ (ng-h/L)	96.25	88.54	104.63	15.4
C_{max} (ng/L)	94.76	89.06	100.82	11.4
AU_{0-t} (ng-h/L)	95.78	88.00	104.26	15.7

BE Study 1276.8 Empagliflozin results from 5 mg Empagliflozin/1000 mg Metformin HCl Fed Conditions				
PK Parameter	**Mean T/R Ratio**	**90% CI Lower Limit (%)**	**90% CI Upper Limit (%)**	**Intra-individual %CV**
$AUC_{0-\infty}$ (nmol-h/L)	106.00	102.73	109.39	6.1
C_{max} (nmol/L)	104.54	99.15	110.22	10.3
AU_{0-t} (nmol-h/L)	105.98	102.73	109.33	6.0
BE Study 1276.8 Empagliflozin results from 12.5 mg Empagliflozin/1000 mg Metformin HCl Fasted Conditions				
PK Parameter	**Mean T/R Ratio**	**90% CI Lower Limit (%)**	**90% CI Upper Limit (%)**	**Intra-individual %CV**
$AUC_{0-\infty}$ (nmol-h/L)	102.55	99.53	105.65	5.9

C_{max} (nmol/L)	102.12	96.26	108.35	11.7
AU_{0-t} (nmol-h/L)	102.33	99.32	105.43	5.9
BE Study 1276.8 Empagliflozin results from 12.5 mg Empagliflozin/1000 mg Metformin HCl Fed Conditions				
PK Parameter	**Mean T/R Ratio**	**90% CI Lower Limit (%)**	**90% CI Upper Limit (%)**	**Intra-individual %CV**
$AUC_{0-\infty}$ (ng-h/L)	98.88	94.88	103.06	8.0
C_{max} (ng/L)	106.52	95.86	118.35	20.7
AU_{0-t} (ng-h/L)	98.82	94.78	103.04	8.0
BE Study 1276.8 Metformin results from 5 mg Empagliflozin/1000 mg Metformin HCl Fed Conditions				
PK Parameter	**Mean T/R Ratio**	**90% CI Lower Limit (%)**	**90% CI Upper Limit (%)**	**Intra-individual %CV**
$AUC_{0-\infty}$ (ng-h/L)	100.81	9.7	95.74	106.14
C_{max} (ng/L)	102.95	10.9	97.17	109.08
AU_{0-t} (ng-h/L)	100.74	9.5	95.77	105.96
BE Study 1276.8 Metformin results from 12.5 mg Empagliflozin/1000 mg Metformin HCl Fasted Conditions				
PK Parameter	**Mean T/R Ratio**	**90% CI Lower Limit (%)**	**90% CI Upper Limit (%)**	**Intra-individual %CV**
$AUC_{0-\infty}$ (ng-h/L)	96.13	91.25	101.26	10.3
C_{max} (ng/L)	94.87	88.93	101.21	12.8
AU_{0-t} (ng-h/L)	94.89	89.80	100.26	10.9
BE Study 1276.8 Metformin results from 12.5 mg Empagliflozin/1000 mg Metformin HCl Fed Conditions				
PK Parameter	**Mean T/R Ratio**	**90% CI Lower Limit (%)**	**90% CI Upper Limit (%)**	**Intra-individual %CV**
$AUC_{0-\infty}$ (ng-h/L)	99.34	92.56	106.62	13.7
C_{max} (ng/L)	97.97	92.34	103.94	11.5
AU_{0-t} (ng-h/L)	99.31	92.14	107.03	14.5

The NDA also includes data from dissolution testing conducted to support the empagliflozin/metformin FDC development program. The dissolution method and specifications as described below are acceptable.

Table 3 Dissolution conditions for the comparative dissolution tests

Parameter	Conditions
Instrument	Apparatus 2 (paddle)
Rotation speed	50 rpm
Volume	900 mL
Temperature	37 ± 0.5°C
Sampling time points	10, 15, 20, 30, and 45 minutes
Determination of empagliflozin	HPLC/UV at 224 nm
Determination of metformin hydrochloride	HPLC/UV at 218 nm or UV spectrophotometry at 233 nm[1]

1 Interchangeability of HPLC-UV and UV detection was demonstrated for all dissolution media

Q= (b) (4) % at 20 minutes for empagliflozin and metformin HCl

Review: The Biopharmaceutics review is focused on the evaluation and acceptability of the bioequivalence and dissolution data to support approvability of the proposed FDC tablets.

RECOMMENDATION:

The bioequivalence results and dissolution method are acceptable. From the Biopharmaceutics perspective, NDA 206111 for Empagliflozin/Metformin Hydrochloride Fixed Dose Combination Tablets is recommended for approval.

Signature

Kelly M. Kitchens -S

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DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000336574, cn=Kelly M. Kitchens -S
Date: 2015.04.15 15:55:42 -04'00'

Kelly M. Kitchens, Ph.D.
Acting Biopharmaceutics Lead
Office of New Drug Products

Signature

Tapash K. Ghosh -S

Digitally signed by Tapash K. Ghosh -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300148262, cn=Tapash K. Ghosh -S
Date: 2015.04.15 16:19:26 -04'00'

Tapash Ghosh, Ph.D.
Acting Biopharmaceutics Branch Chief
Office of New Drug Products

cc. PSeo.

BIOPHARMACEUTICS ASSESSMENT

Drug Product:

Empagliflozin is a reversible, highly potent (IC50 of 1.3 nmol) and selective competitive inhibitor of sodium-glucose transport protein 2 (SGLT2). Empagliflozin improves glycemic control in patients with type 2 diabetes by reducing renal glucose reabsorption. Empagliflozin improves both fasting and post-prandial plasma glucose levels. The mechanism of action of empagliflozin is independent of beta cell function and insulin pathway and this contributes to a low risk of hypoglycemia.

Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization.

Empagliflozin/metformin HCl FDC tablets are formulated for twice daily oral administration.
The tablets are film-coated and the available dose strengths are: 5/500 mg, 5/1000 mg, 12.5/500 mg, and 12.5/1000 mg. The qualitative and quantitative compositions of empagliflozin/metformin hydrochloride film-coated tablets are shown in the following tables.

Table 1 Qualitative and quantitative composition of empagliflozin / metformin hydrochloride film-coated tablets, 5 mg / 500 mg

Ingredient	[mg / tablet]	Function	Reference to Standards
Tablet core			
Empagliflozin	5.000	Drug substance	Company standard
Metformin hydrochloride	500.000	Drug substance	USP
Corn starch	(b) (4)		NF
Copovidone			NF
Colloidal silicon dioxide			NF
Magnesium stearate			NF
			(b) (4)
Film-coat			
			(b) (4)
Total mass of film-coated tablet	(b) (4)		
			(b) (4)

Table 1 Qualitative and quantitative composition of empagliflozin / metformin hydrochloride film-coated tablets, 5 mg / 1000 mg

Ingredient	[mg / tablet]	Function	Reference to Standards
Tablet core			
Empagliflozin	5.000	Drug substance	Company standard
Metformin hydrochloride	1000.000	Drug substance	USP
Corn starch	(b) (4)		NF
Copovidone			NF
Colloidal silicon dioxide			NF
Magnesium stearate			NF
(b) (4)			
Film-coat			
(b) (4)			
Total mass of film-coated tablet	(b) (4)		
(b) (4)			

Table 1 Qualitative and quantitative composition of empagliflozin / metformin hydrochloride film-coated tablets, 12.5 mg / 500 mg

Ingredient	[mg / tablet]	Function	Reference to Standards
Tablet core			
Empagliflozin	12.500	Drug substance	Company standard
Metformin hydrochloride	500.000	Drug substance	USP
Corn starch	(b) (4)		NF
Copovidone			NF
Colloidal silicon dioxide			NF
Magnesium stearate			NF
(b) (4)			
Film-coat			
(b) (4)			
Total mass of film-coated tablet	(b) (4)		
(b) (4)			

Table 1 Qualitative and quantitative composition of empagliflozin / metformin hydrochloride film-coated tablets, 12.5 mg / 1000 mg

Ingredient	[mg / tablet]	Function	Reference to Standards
Tablet core			
Empagliflozin	12.500	Drug substance	Company standard
Metformin hydrochloride	1000.000	Drug substance	USP
Corn starch	(b) (4)		NF
Copovidone			NF
Colloidal silicon dioxide			NF
Magnesium stearate			NF
(b) (4)			
Film-coat			
(b) (4)			
Total mass of film-coated tablet	(b) (4)		
(b) (4)			

On September 19 2014, an Office of Scientific Investigations (OSI) consult was submitted for the clinical and analytical sites of BE studies 1276.6, (b) (4) and 1276.8. On December 8, 2014, the OSI concluded that the BE study data are acceptable for review based on satisfactory inspections in the last 5 years, and the similarity of the methods and processes in the BE studies.[1]

[1] DARRTS: NDA-206111, SCHEIBNER, KARA A, Submit/Final Date: 12/09/2014, REV-DSI-05(Bioequivalence Establishment Inspection Report Review)

Bioequivalence Study No. 1276.6

Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Not applicable		**EudraCT No.:** 2012-000082-20	
Name of active ingredient: Empagliflozin (BI 10773), metformin		**Page:** 1 of 8	**Synopsis No.:**
Module:		**Volume:**	
Report date: 05 MAY 2014	**Trial No. / U No.:** 1276.6 / c01630240-02	**Date of trial:** 02 MAY 2013 – 04 NOV 2013	**Date of revision:** Not applicable

Title of trial:	Bioequivalence of empagliflozin/metformin (500 mg) fixed dose combination tablets compared to single tablets administered together in healthy male and female volunteers under fed conditions (an open-label, randomised, single-dose, four-way crossover study)
Principal Investigator:	Dr Peter Rose
Trial sites:	Boehringer Ingelheim Pharma GmbH & Co. KG Human Pharmacology Centre / Department of Translational Medicine Birkendorfer Str. 65, Biberach/Riss, Germany
Publication (reference):	Data from this trial have not been published.
Clinical phase:	I
Objective:	The objective of this trial was to demonstrate bioequivalence of a 12.5 mg empagliflozin/500 mg metformin fixed dose combination (FDC) tablet compared with the respective single tablets (10 mg empagliflozin + 2.5 mg empagliflozin + 500 mg metformin) as well as to establish bioequivalence of a 5 mg empagliflozin/ 500 mg metformin FDC tablet compared with the respective single tablets (5 mg empagliflozin + 500 mg metformin), following a high-fat, high-caloric meal.
Methodology:	This was an open-label, randomised, single-dose, 4-way crossover trial with 4 treatments (T1, R1, T2, and R2) and 4 treatment sequences (T1_R1_T2_R2, R1_T1_R2_T2, T2_R2_ T1_R1, and R2_T2_R1_T1). Drug administrations of the 4 individual single dose treatments were each separated by a washout period of at least 5 days.

No. of subjects:	
planned:	entered: 24 (at least 8 of each gender)
actual:	entered: 24 (9 male and 15 female subjects) Treatment T1 (12.5 mg empagliflozin/500 mg metformin FDC): treated and analysed (for primary endpoint): 21 Treatment R1 (12.5 mg empagliflozin and 500 mg metformin, single tablets): treated and analysed (for primary endpoint): 23 Treatment T2 (5 mg empagliflozin/500 mg metformin FDC): treated and analysed (for primary endpoint): 23 Treatment R2 (5 mg empagliflozin and 500 mg metformin, single tablets): treated and analysed (for primary endpoint): 20
Diagnosis and main criteria for inclusion:	Healthy male and female volunteers at the age of 18 to 50 years and with a body mass index (BMI) of 18.5 to 29.9 kg/m^2 were included.
Test product 1:	Empagliflozin/metformin FDC tablet
dose:	12.5 mg empagliflozin , 500 mg metformin
mode of admin.:	oral with 240 mL of water after intake of a high-fat, high-caloric meal
batch no.:	B121002208
Reference products 1:	Empagliflozin tablets + metformin (Glucophage®) tablet
dose:	10 mg empagliflozin, 2.5 mg empagliflozin, 500 mg metformin
mode of admin.:	oral with 240 mL of water after intake of a high-fat, high-caloric meal
batch no.:	B111003468 (2.5 mg empagliflozin) 107784 (10 mg empagliflozin) 11502 (500 mg metformin)
Test product 2:	Empagliflozin/metformin FDC tablet
dose:	5 mg empagliflozin , 500 mg metformin
mode of admin.:	oral with 240 mL of water after intake of a high-fat, high-caloric meal
batch no.:	B121002264

Reference products 2:	Empagliflozin tablet + metformin (Glucophage®) tablet
dose:	5 mg empagliflozin , 500 mg metformin
mode of admin.:	oral with 240 mL of water after intake of a high-fat, high-caloric meal
batch no.:	909478A (5 mg empagliflozin) 11502 (500 mg metformin)
Duration of treatment:	Single dose administrations in each of the 4 treatment periods separated by a washout phase of at least 5 days between drug administrations.
Criteria for evaluation:	
Clinical pharmacology:	The following pharmacokinetic parameters were analysed as primary endpoints: $AUC_{0-\infty}$ and C_{max} of empagliflozin and of metformin. The following pharmacokinetic parameters were analysed as secondary endpoints: AUC_{0-tz} of empagliflozin and of metformin. Other endpoints were calculated as appropriate.
Safety:	The evaluation of safety was based on monitoring of vital signs (blood pressure and pulse rate), 12-lead electrocardiogram (ECG), clinical laboratory tests, monitoring of adverse events, and physical examination.
Statistical methods:	The assessment of bioequivalence was based on 2-sided 90% confidence intervals (CIs) for the ratios (test to reference treatment) of the geometric means (gMeans) of the primary endpoints, using an acceptance range of 80.00 to 125.00%. This method is equivalent to two 1-sided t-tests, each at the 5% significance level. The statistical model used was an analysis of variance (ANOVA) on the logarithmic scale including effects for 'sequence', 'subjects within sequences', 'period', and 'treatment'. Two models, one with all effects being considered as fixed and one with 'subjects within sequences' being considered as random effect (instead of fixed effect) were fitted as co-primary analyses. CIs were calculated based on the residual error from ANOVA. Descriptive statistics were calculated for all endpoints.

Bioanalytical Results:

Analyte Name: Empagliflozin								
Parameter	**Standard Curve Samples**							
Concentration (nmol/mL)	1.11	2.22	111	55.4	222	665	998	1110
Inter day Precision (%CV)	7.5	5.2	2.8	2.3	2.2	2.2	2.6	1.7
Inter day Accuracy (%bias)	-0.8	0.6	1.0	0.3	-1.7	0.4	-0.2	0.1
Linearity (range of r^2 values)	0.994576 – 0.999437							
Linearity Range (nmol/mL)	1.11 – 1110 nmol/mL							
Sensitivity/LOQ (nmol/mL)	1.11 nmol/mL							

Analyte Name: Empagliflozin					
Parameter	**Quality Control Samples**				
Concentration (nmol/mL)	3.33	44.4	166	444	887
Inter day Precision (%CV)	8.0	2.5	2.2	1.9	3.0

Inter day Accuracy (%bias)	-0.2	-1.7	-2.6	-1.5	-0.5

Analyte Name: Metformin									
Parameter	**Standard Curve Samples**								
Concentration (ng/mL)	1.00	2.50	10.0	40.0	100	400	1500	2200	2500
Inter day Precision (%CV)	4.0	2.3	4.1	2.1	2.8	2.2	1.7	2.5	2.4
Inter day Accuracy (%bias)	-0.2	0.8	-1.2	-4.0	8.0	-2.5	-2.0	1.8	0.0
Linearity (range of r^2 values)	0.995305 – 0.998893								
Linearity Range (ng/mL)	1.00 – 2500 ng/mL								
Sensitivity/LOQ (ng/mL)	1.00 ng/mL								

Analyte Name: Metformin					
Parameter	**Quality Control Samples**				
Concentration (ng/mL)	3.00	125	400	1250	2000
Inter day Precision (%CV)	3.8	2.4	2.2	2.6	20.4
Inter day Accuracy (%bias)	-6.3	1.6	2.8	-3.2	-7.0

Comments on Bioanalytical Results:

- Subject samples were analyzed in 14 runs for empagliflozin, and 18 runs for metformin. One empagliflozin run was rejected, and 3 metformin runs were rejected due to analytical reasons as per the pre-established bioanalytical protocol.
- Incurred sample reproducibility (ISR) was determined with Cmax and elimination phase samples. Only one empagliflozin reassay sample was more than 20% different from the original assay value, and all the metformin reassay samples were within 20% of the original assay values. Therefore, the samples meet the ISR acceptance criteria: at least 2/3 of the samples were within ±20% of the original assay value.
- The bioanalytical results are **acceptable.**

Pharmacokinetic and Statistical Results:

The bioequivalence results are described in the following tables and figures.

Geometric Means, 90% Confidence Intervals and Plasma Concentration-Time Profiles

Empagliflozin

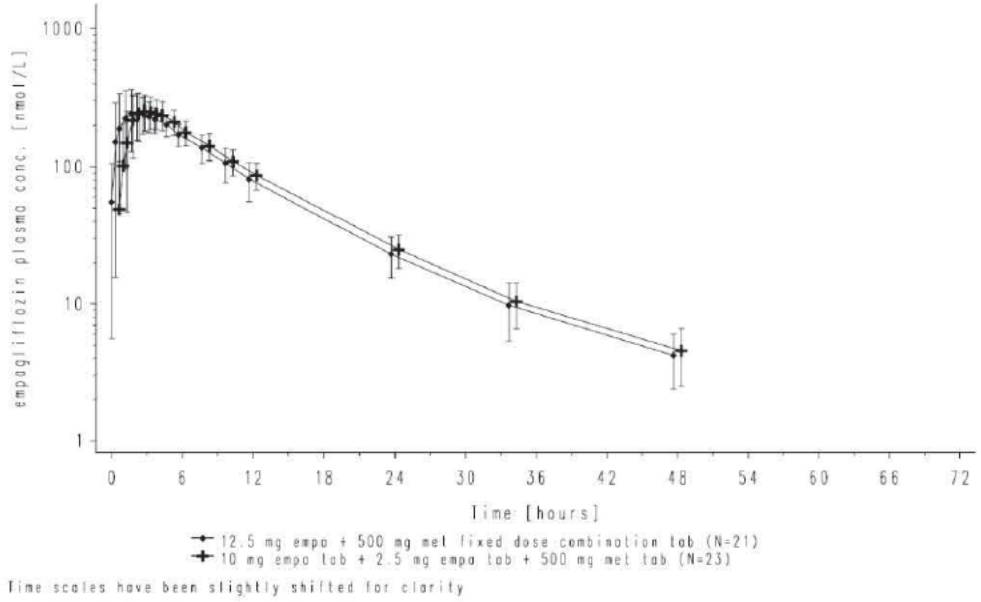


Table 11.5.2.3.1: 1 Analysis of bioequivalence of empagliflozin after oral administration of 12.5 mg empagliflozin and 500 mg metformin either as FDC (T1) or as single tablets (R1) - PKS

Pharmacokinetic parameter	Adjusted gMean for empagliflozin		Adjusted gMean ratio of treatment T1 to treatment R1 [%]	90% CI of gMean ratio		Intra-individual gCV [%]
	Treatment T1 (FDC tablet) N=21	Treatment R1 (single tablets) N=23		Lower limit [%]	Upper limit [%]	
$AUC_{0-\infty}$ [nmol·h/L]	2811	2870	97.92	93.53	102.52	8.4
C_{max} [nmol/L]	296.2	283.2	104.61	99.88	109.56	8.4
AUC_{0-tz} [nmol·h/L]	2770	2826	98.00	93.53	102.69	8.5

Source data: Tables 15.5.1: 1, 15.5.2: 1, and 15.5.3: 1

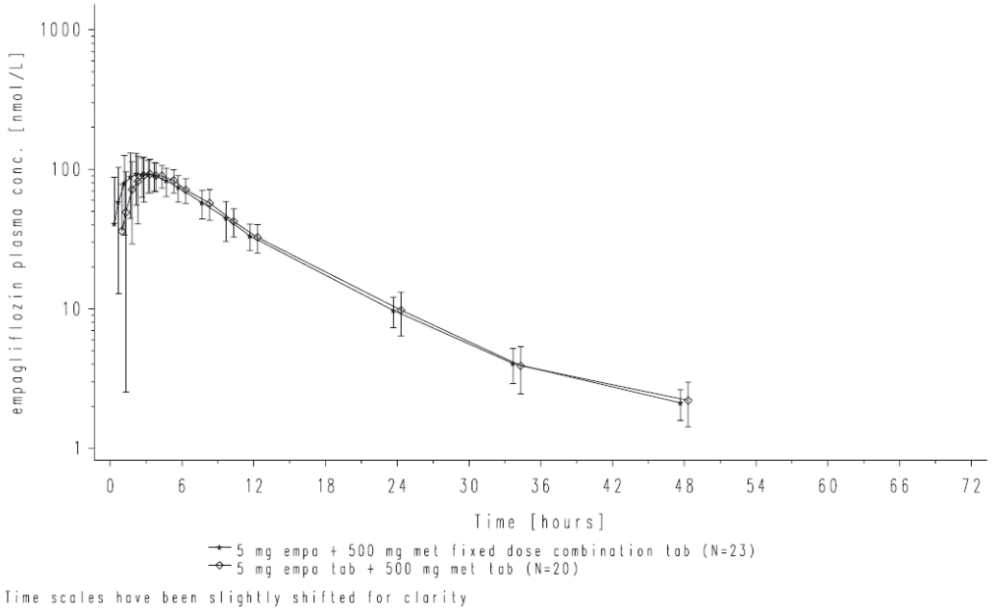


Table 11.5.2.3.2: 1 Analysis of bioequivalence of empagliflozin after oral administration of 5 mg empagliflozin and 500 mg metformin either as FDC (T2) or as single tablets (R2) - PKS

Pharmacokinetic parameter	Adjusted gMean for empagliflozin		Adjusted gMean ratio of treatment T2 to treatment R2 [%]	90% CI of gMean ratio		Intra-individual gCV [%]
	Treatment T2 (FDC tablet) N=23	Treatment R2 (single tablets) N=20		Lower limit [%]	Upper limit [%]	
$AUC_{0-\infty}$ [nmol·h/L]	1116	1085	102.79	99.08	106.63	6.7
C_{max} [nmol/L]	110.0	106.9	102.96	97.92	108.26	9.2
AUC_{0-tz} [nmol·h/L]	1086	1057	102.77	99.15	106.52	6.5

Source data: Tables 15.5.1: 3, 15.5.2: 3, and 15.5.3: 3

Metformin

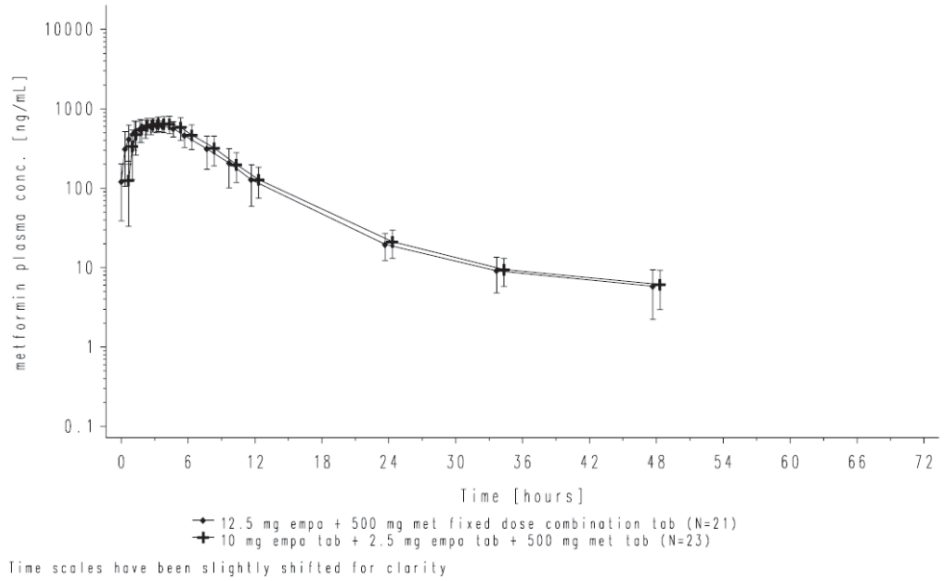
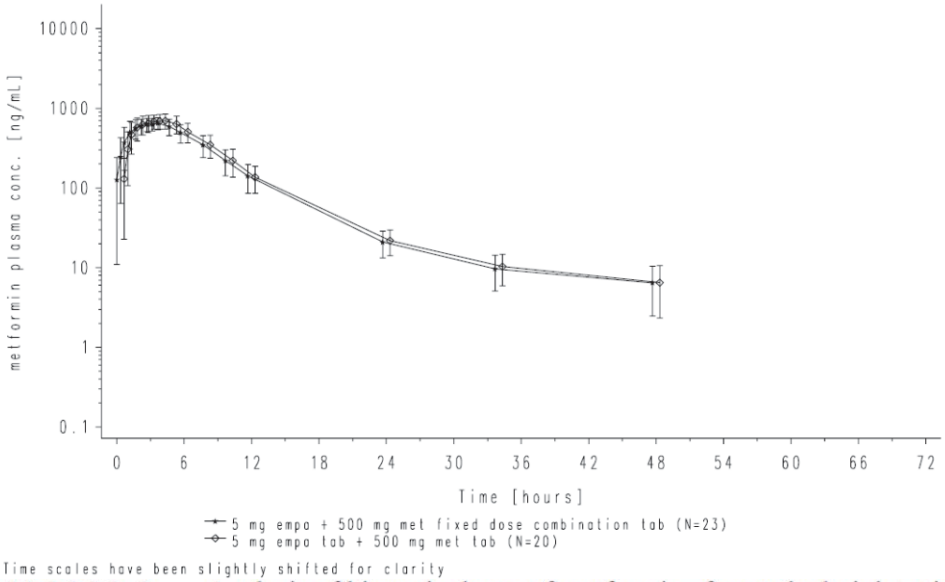


Table 11.5.2.3.1: 2 Analysis of bioequivalence of metformin after oral administration of 12.5 mg empagliflozin and 500 mg metformin either as FDC (T1) or as single tablets (R1) - PKS

Pharmacokinetic parameter	Adjusted gMean for metformin		Adjusted gMean ratio of treatment T1 to treatment R1 [%]	90% CI of gMean ratio		Intra-individual gCV [%]
	Treatment T1 (FDC tablet) N=21	Treatment R1 (single tablets) N=23		Lower limit [%]	Upper limit [%]	
$AUC_{0-\infty}$ [ng·h/mL]	5616	5835	96.25	88.54	104.63	15.4
C_{max} [ng/mL]	682.8	720.6	94.76	89.06	100.82	11.4
AUC_{0-tz} [ng·h/mL]	5501	5743	95.78	88.00	104.26	15.7

Source data: Tables 15.5.4: 1, 15.5.5: 1, and 15.5.6: 1



Time scales have been slightly shifted for clarity

Table 11.5.2.3.2: 2 Analysis of bioequivalence of metformin after oral administration of 5 mg empagliflozin and 500 mg metformin either as FDC (T2) or as single tablets (R2) - PKS

Pharmacokinetic parameter	Adjusted gMean for metformin		Adjusted gMean ratio of treatment T2 to treatment R2 [%]	90% CI of gMean ratio		Intra-individual gCV [%]
	Treatment T2 (FDC tablet) N=23	Treatment R2 (single tablets) N=20		Lower limit [%]	Upper limit [%]	
$AUC_{0-\infty}$ [ng·h/mL]	5960	6157	96.79	91.77	102.09	9.8
C_{max} [ng/mL]	693.5	739.1	93.83	88.01	100.03	11.9
AUC_{0-tz} [ng·h/mL]	5817	6063	95.94	91.20	100.93	9.3

Source data: Tables 15.5.4: 3, 15.5.5: 3, and 15.5.6: 3

Comments on Pharmacokinetic and Statistical Results for the Fasting Study:

- The 90% C.I. values for the least squares geometric means of AUC_{0-t}, AUC∞ and Cmax meet the criteria for bioequivalence (confidence intervals within 80.00% to 125.00%) for empagliflozin and metformin HCl.
- The bioequivalence study results demonstrate that the FDC products (5 mg empagliflozin /500 mg metformin HCl and 12.5 mg empagliflozin /500 mg

metformin HCl) are bioequivalent to the reference products (5 mg Empagliflozin + 500 mg Glucophage® and 2.5 mg Empagliflozin + 10 mg Empagliflozin + 500 mg Glucophage®).

Bioequivalence Study No. 1276.8

Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Not applicable		**EudraCT No.:** 2012-005156-42	**Synopsis No.:**
Name of active ingredient: Empagliflozin (BI 10773)/metformin		**Page:** 1 of 8	
Module:		**Volume:**	
Report date: 28 OCT 2013	**Trial No. / U No.:** 1276.8 / U13-2366-01	**Dates of trial:** 14 MAR 2013 – 31 MAY 2013	**Date of revision:** Not applicable

Title of trial:	Bioequivalence of empagliflozin/metformin fixed dose combination tablets compared to single tablets administered together in healthy male and female volunteers under fed and fasted conditions (an open-label, randomised, single-dose, crossover study)
Principal Investigator:	Dr Thomas Gießmann
Trial site:	Human Pharmacology Centre, Boehringer Ingelheim Pharma GmbH & Co. KG, Birkendorfer Str. 65, Biberach/Riss, Germany
Publication (reference):	Data from this trial have not been published
Clinical phase:	I

Objectives:	To establish the bioequivalence of an
	• empagliflozin 12.5 mg / metformin 1000 mg fixed dose combination (FDC) tablet (T1) compared with the free dose combination of empagliflozin 10 mg, empagliflozin 2.5 mg, and metformin 1000 mg (R1), Part I
	  ○ under fasted conditions
	  ○ under fed conditions
	• empagliflozin 5 mg / metformin 1000 mg FDC tablet (T2) compared with the free dose combination of empagliflozin 5 mg and metformin 1000 mg under fed conditions (R2), Part II

Methodology:	Randomised, open-label, single-dose, 4-way (Part I) or 2-way (Part II) crossover design. A single dose of test or reference treatment was administered in each treatment period.

No. of subjects:	
planned:	entered: 48 (24 in each part)
actual:	Treatment A (T1 fasted): FDC tablet of 12.5 mg empagliflozin / 1000 mg metformin under fasted conditions entered: 24 treated: 24 analysed (for primary endpoint): 23 Treatment B (T1 fed): FDC tablet of 12.5 mg empagliflozin / 1000 mg metformin under fed conditions entered: 24 treated: 24 analysed (for primary endpoint): 24 Treatment C (R1 fasted): Free dose combination of 12.5 mg empagliflozin and 1000 mg metformin under fasted conditions entered: 24 treated: 24 analysed (for primary endpoint): 24 Treatment D (R1 fed): Free dose combination of 12.5 mg empagliflozin and 1000 mg metformin under fed conditions entered: 24 treated: 24 analysed (for primary endpoint): 22 Treatment E (T2 fed): FDC tablet of 5 mg empagliflozin / 1000 mg metformin under fed conditions entered: 24 treated: 24 analysed (for primary endpoint): 22 Treatment F (R2 fed): Free dose combination of 5 mg empagliflozin and 1000 mg metformin under fed conditions entered: 24 treated: 24 analysed (for primary endpoint): 23
Diagnosis and main criteria for inclusion:	Healthy male and female volunteers aged 18 to 50 years, with body mass index (BMI) from 18.5 to 29.9 kg/m^2
Test product T1:	Empagliflozin/metformin FDC tablet
dose:	12.5 mg empagliflozin / 1000 mg metformin, single dose
mode of admin.:	Oral with 240 mL of water under fasted conditions (Treatment A) and after intake of a high-fat, high-calorie meal (Treatment B)
batch no.:	105936

Reference products R1:	Empagliflozin tablets and metformin tablet
dose:	10 mg empagliflozin, 2.5 mg empagliflozin, 1000 mg metformin, single dose
mode of admin.:	Oral with 240 mL of water under fasted conditions (Treatment C) and after intake of a high-fat, high-calorie meal (Treatment D)
batch nos.:	107784 (empagliflozin 10 mg), B111003468 (empagliflozin 2.5 mg), and X2076 (metformin 1000 mg)
Test product T2:	Empagliflozin/metformin FDC tablet
dose:	5 mg empagliflozin / 1000 mg metformin, single dose
mode of admin.:	Oral with 240 mL of water after intake of a high-fat, high-calorie meal (Treatment E)
batch no.:	202570
Reference products R2:	Empagliflozin tablets and metformin tablet
dose:	5 mg empagliflozin and 1000 mg metformin, single dose
mode of admin.:	Oral with 240 mL of water after intake of a high-fat, high-calorie meal (Treatment F)
batch nos.:	909478A (empagliflozin), X2076 (metformin)
Duration of treatment:	Single dose in each treatment period separated by a washout phase of at least 7 days between drug administrations
Criteria for evaluation:	
Clinical pharmacology:	Primary endpoints were $AUC_{0-\infty}$ and C_{max} for empagliflozin and metformin; the secondary endpoint was AUC_{0-tz} for empagliflozin and metformin. Other endpoints included t_{max}, λ_z, $t_{1/2}$, MRT_{po}, CL/F, and V_z/F for empagliflozin and metformin.
Safety:	Monitoring for adverse events (AEs), conducting clinical laboratory assessments, recording vital signs (blood pressure and pulse rate), performing 12-lead electrocardiograms, and physical examinations
Statistical methods:	The statistical model was an analysis of variance (ANOVA) on the logarithmic scale including effects for 'sequence', 'subjects within sequences', 'period' and 'treatment'. Two-sided 90% confidence intervals (CIs) were calculated for the ratios of the geometric means (test/reference) for the primary endpoints. Bioequivalence was assessed using an acceptance range of 80.00-125.00% for the 90% CI. This method is equivalent to two 1-sided t-tests procedures, each at the 5% significance level. Descriptive statistics were also calculated for all endpoints.

Bioanalytical Results:

Analyte Name: Empagliflozin								
Parameter	**Standard Curve Samples**							
Concentration (nmol/mL)	1.11	2.22	11.1	55.4	222	665	998	1110
Inter day Precision (%CV)	3.7	3.2	1.7	1.7	1.4	1.3	1.1	1.3
Inter day Accuracy (%bias)	1.0	-0.8	-2.6	2.1	1.0	0.7	0.0	-0.8
Linearity (range of r^2 values)	0.997811 – 0.999717							
Linearity Range (nmol/mL)	1.11 -1110 nmol/mL							

Sensitivity/LOQ (nmol/mL)	1.11 nmol/mL

Analyte Name: Empagliflozin					
Parameter	**Quality Control Samples**				
Concentration (nmol/mL)	3.33	44.4	166	444	887
Inter day Precision (%CV)	5.2	2.8	3.7	2.1	2.3
Inter day Accuracy (%bias)	2.8	2.4	-2.6	-1.7	2.9

Analyte Name: Metformin									
Parameter	**Standard Curve Samples**								
Concentration (ng/mL)	1.00	2.50	10.0	40.0	100	400	1500	2200	2500
Inter day Precision (%CV)	7.6	5.8	3.6	3.2	3.3	3.6	4.2	3.4	3.4
Inter day Accuracy (%bias)	-1.3	2.8	3.0	-2.0	0.0	-2.3	-2.7	0.5	2.4
Linearity (range of r^2 values)	0.992808 – 0.999674								
Linearity Range (ng/mL)	1.00 – 2500 ng/mL								
Sensitivity/LOQ (ng/mL)	1.00 ng/mL								

Analyte Name: Metformin					
Parameter	**Quality Control Samples**				
Concentration (ng/mL)	3.00	125	400	1250	2000
Inter day Precision (%CV)	5.5	3.8	3.5	3.5	4.3
Inter day Accuracy (%bias)	3.3	0.8	-1.5	-2.4	0.0

Comments on Bioanalytical Results:

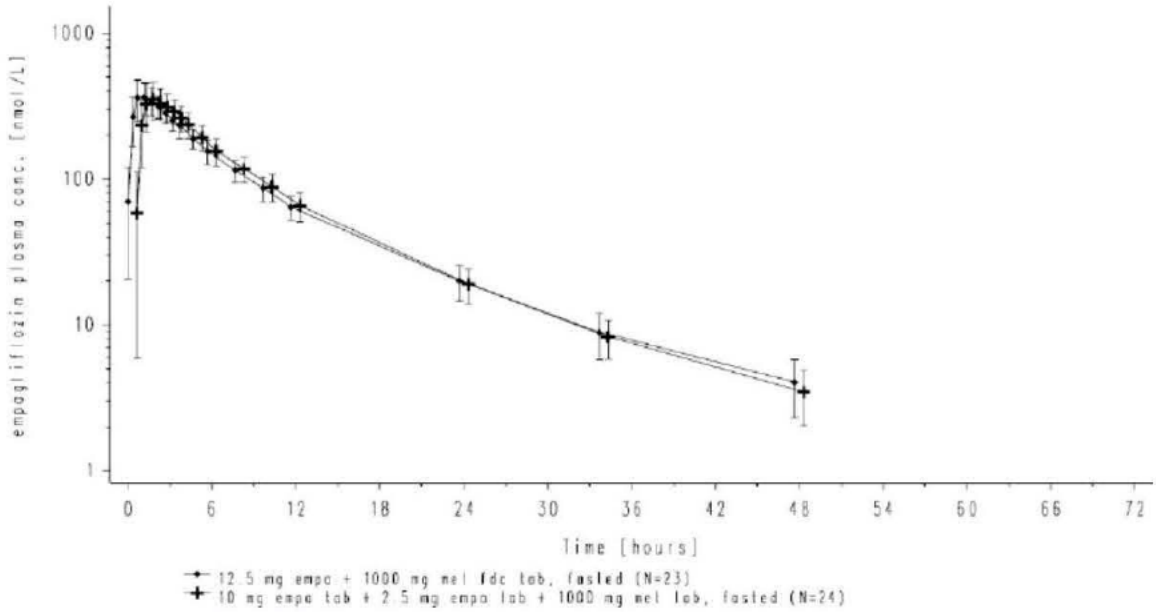
- Subject samples were analyzed in 24 runs for empagliflozin, and 21 runs for metformin. Two empagliflozin runs were rejected, and 1 metformin run was rejected due to analytical reasons as per the pre-established bioanalytical protocol.
- Incurred sample reproducibility (ISR) was determined with Cmax and elimination phase samples. Only two empagliflozin reassay samples were more than 20% different from the original assay value, and only one metformin reassay sample was more than 20% of the original assay values. Therefore, the samples meet the ISR acceptance criteria: at least 2/3 of the samples were within ±20% of the original assay value.
- The bioanalytical results are **acceptable.**

Pharmacokinetic and Statistical Results:

The bioequivalence results are described in the following tables and figures.

Geometric Means, 90% Confidence Intervals and Plasma Concentration-Time Profiles

Empagliflozin

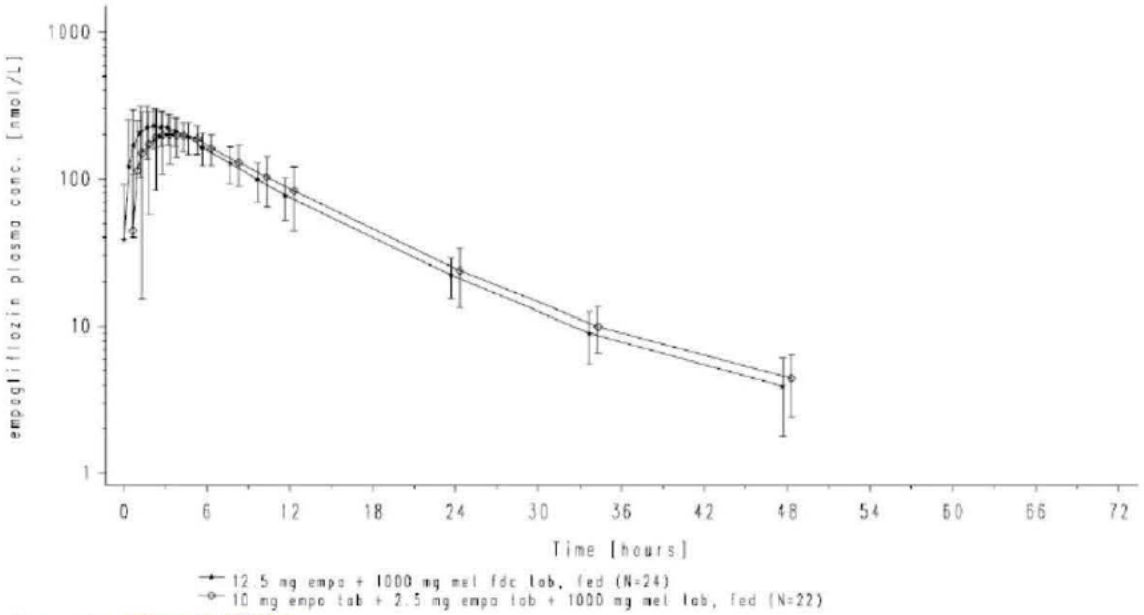


Source data: Figure 15.6.5.3: 2

Table 11.5.2.3.1: 1 Relative bioavailability comparison of empagliflozin after oral administration of 12.5 mg empagliflozin and 1000 mg metformin as either a fixed dose combination with 1000 mg metformin (T1 fasted) or in a free dose combination with 1000 mg metformin (R1 fasted)

PK Parameter	Units	gMean ratio T1/R1 [%]	Intra-indiv. gCV [%]	2-sided 90% CI [%]
$AUC_{0-\infty}$	[nmol·h/L]	102.55	5.9	99.53 to 105.65
C_{max}	[nmol/L]	102.12	11.7	96.26 to 108.35
AUC_{0-tz}	[nmol·h/L]	102.33	5.9	99.32 to 105.43

Source data: Tables 15.5.1.1: 1, 15.5.1.2: 1, and 15.5.1.3: 1

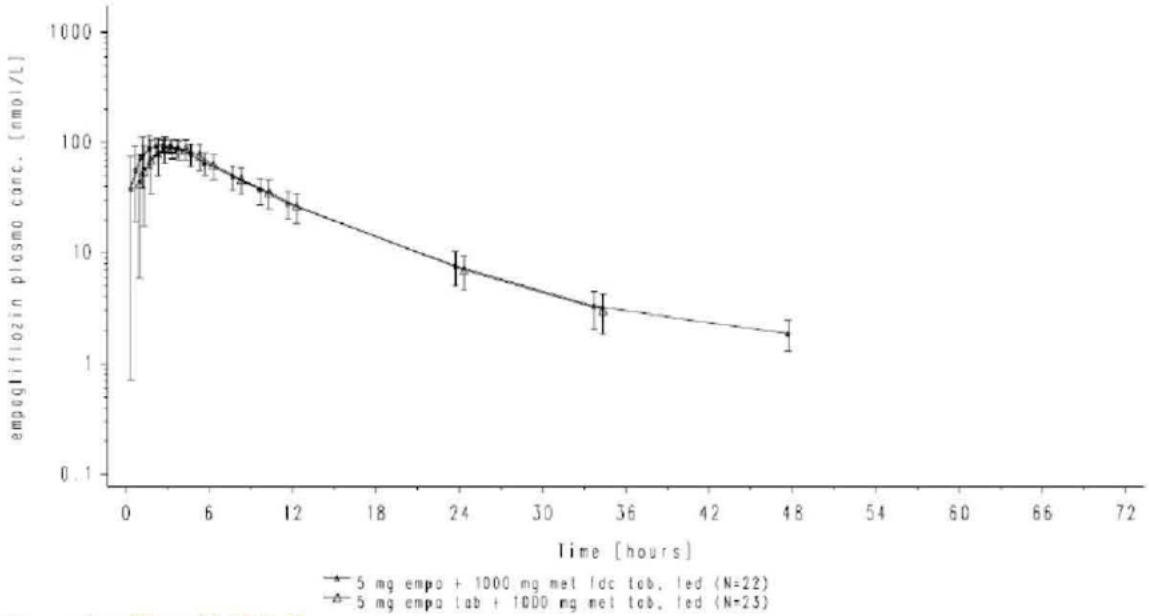


Source data: Figure 15.6.5.3: 6

Table 11.5.2.3.2: 1 Relative bioavailability comparison of empagliflozin after oral administration of 12.5 mg in either a fixed dose combination with 1000 mg metformin (T1 fed) or in a free dose combination with 1000 mg metformin (R1 fed)

PK Parameter	Units	gMean ratio T1/R1 [%]	Intra-indiv. gCV [%]	2-sided 90% CI [%]
$AUC_{0-\infty}$	[nmol·h/L]	98.88	8.0	94.88 to 103.06
C_{max}	[nmol/L]	106.52	20.7	95.86 to 118.35
AUC_{0-tz}	[nmol·h/L]	98.82	8.0	94.78 to 103.04

Source data: Tables 15.5.1.1: 3, 15.5.1.2: 3, and 15.5.1.3: 3



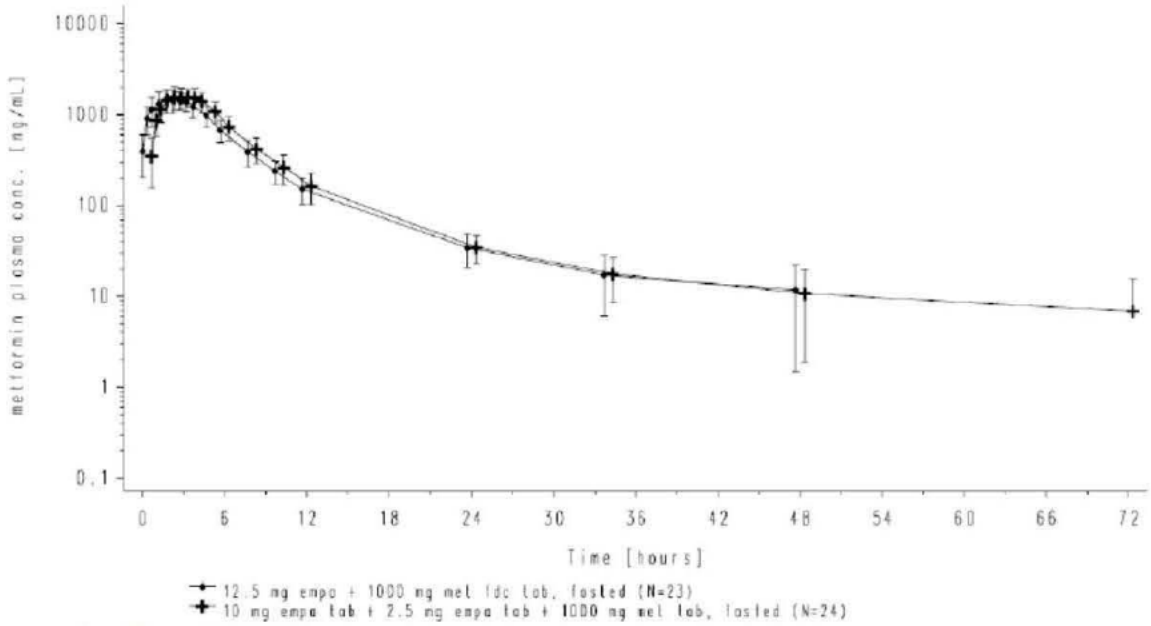
Source data: Figure 15.6.5.3: 18

Table 11.5.2.3.3: 1 Relative bioavailability comparison of empagliflozin after oral administration of 5 mg in either a fixed dose combination with 1000 mg metformin (T2 fed) or in a free dose combination with 1000 mg metformin (R2 fed)

PK Parameter	Units	gMean ratio T2/R2 [%]	Intra-indiv. gCV [%]	2-sided 90% CI [%]
$AUC_{0-\infty}$	[nmol·h/L]	106.00	6.1	102.73 to 109.39
C_{max}	[nmol/L]	104.54	10.3	99.15 to 110.22
AUC_{0-tz}	[nmol·h/L]	105.98	6.0	102.73 to 109.33

Source data: Tables 15.5.2.1: 1, 15.5.2.2: 1, and 15.5.2.3: 1

Metformin

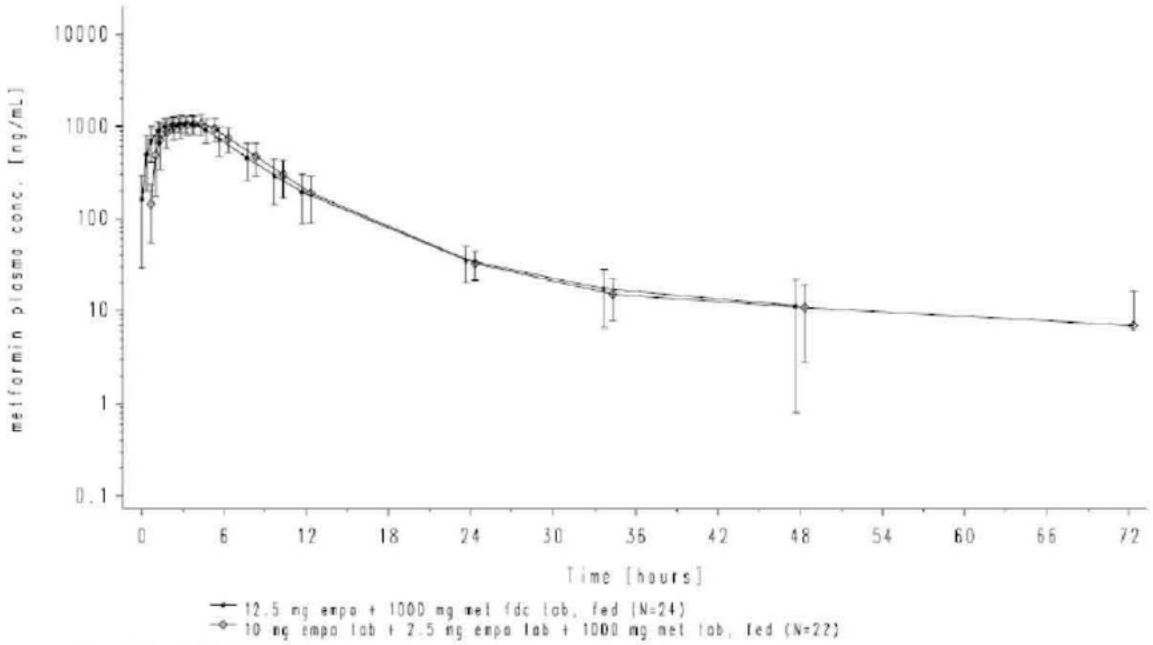


Source data: Figure 15.6.5.3: 22

Table 11.5.2.3.1: 2 Relative bioavailability of metformin after oral administration of 1000 mg in either a fixed dose combination with 12.5 mg empagliflozin (T1 fasted) or in a free dose combination with 12.5 mg empagliflozin (R1 fasted)

PK Parameter	Units	gMean ratio T1/R1 [%]	Intra-indiv. gCV [%]	2-sided 90% CI [%]
$AUC_{0-\infty}$	[ng·h/mL]	96.13	10.3	91.25 to 101.26
C_{max}	[ng/mL]	94.87	12.8	88.93 to 101.21
AUC_{0-tz}	[ng·h/mL]	94.89	10.9	89.80 to 100.26

Source data: Tables 15.5.1.4: 1, 15.5.1.5: 1, and 15.5.1.6: 1

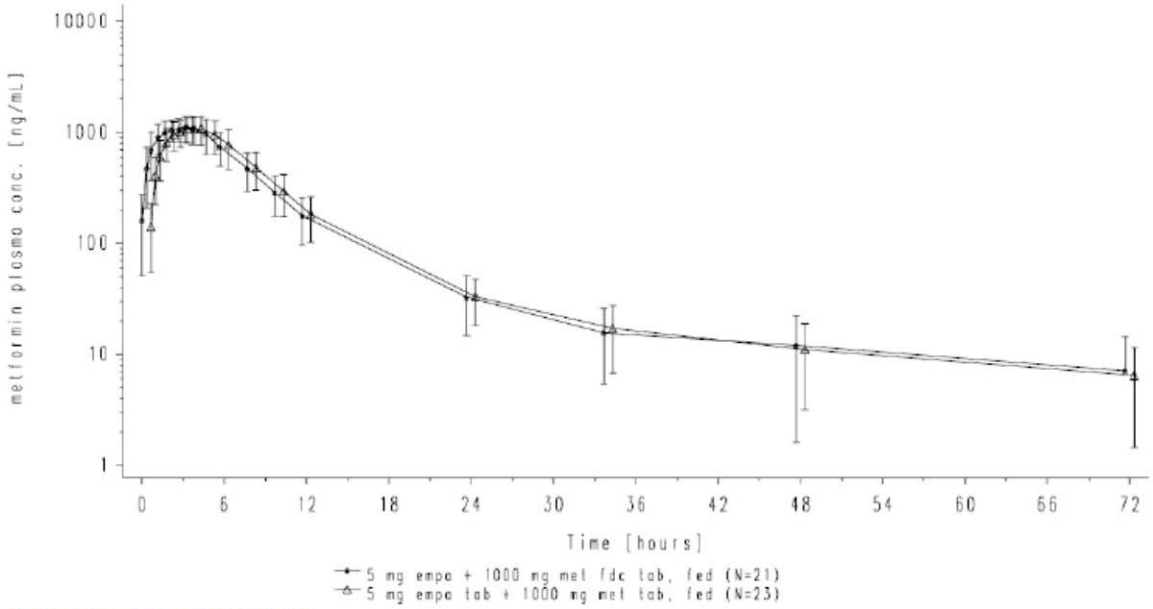


Source data: Figure 15.6.5.3: 26

Table 11.5.2.3.2: 2 Relative bioavailability comparison of metformin after oral administration of 1000 mg in either a fixed dose combination with 12.5 mg empagliflozin (T1 fed) or in a free dose combination with 12.5 mg empagliflozin (R1 fed)

PK Parameter	Units	gMean ratio T1/R1 [%]	Intra-indiv. gCV [%]	2-sided 90% CI [%]
$AUC_{0-\infty}$	[ng·h/mL]	99.34	13.7	92.56 to 106.62
C_{max}	[ng/mL]	97.97	11.5	92.34 to 103.94
AUC_{0-tz}	[ng·h/mL]	99.31	14.5	92.14 to 107.03

Source data: Tables 15.5.1.4: 3, 15.5.1.5: 3, and 15.5.1.6: 3



Source data: Figure 15.6.5.3: 38

Table 11.5.2.3.3: 2 Relative bioavailability comparison of metformin after oral administration of 1000 mg in either a fixed dose combination with 5 mg empagliflozin (T2 fed) or in a free dose combination with 5 mg empagliflozin (R2 fed)

PK Parameter	Units	gMean ratio T2/R2 [%]	Intra-indiv. gCV [%]	2-sided 90% CI [%]
$AUC_{0-\infty}$	[ng·h/mL]	100.81	9.7	95.74 to 106.14
C_{max}	[ng/mL]	102.95	10.9	97.17 to 109.08
AUC_{0-tz}	[ng·h/mL]	100.74	9.5	95.77 to 105.96

Source data: Tables 15.5.2.4: 1, 15.5.2.5: 1, and 15.5.2.6: 1

Comments on Pharmacokinetic and Statistical Results for the Fasting Study:

- The 90% C.I. values for the least squares geometric means of AUC_{0-t}, AUC∞ and Cmax meet the criteria for bioequivalence (confidence intervals within 80.00% to 125.00%) for empagliflozin and metformin HCl.
- The bioequivalence study results demonstrate that the FDC products (5 mg empagliflozin /1000 mg metformin HCl and 12.5 mg empagliflozin /1000 mg metformin HCl) are bioequivalent to the reference products (5 mg Empagliflozin + 1000 mg Glucophage® and 2.5 mg Empagliflozin + 10 mg Empagliflozin + 1000 mg Glucophage®) under fasting and fed conditions.

Dissolution Testing:

The approved dissolution methods for the metformin hydrochloride and empagliflozin components are described in the following tables:

Table 1 Dissolution conditions for metformin hydrochloride tablets

Parameter	Conditions
Instrument	Paddle (Apparatus 2, Ph. Eur., USP, JP)
Medium	Phosphate buffer pH 6.8
Rotation speed	50 rpm (500 mg) or 75 rpm ([redacted] (b) (4) 1000 mg)
Volume	1000 mL
Temperature	37 ± 0.5°C
Sampling time points	10, 15, 20, 30, and 45 minutes
Determination	UV spectrophotometry at 233 nm

Table 2 Dissolution conditions for empagliflozin film-coated tablets

Parameter	Conditions
Instrument	Paddle (Apparatus 2, Ph. Eur., USP, JP)
Medium	Phosphate buffer pH 6.8
Rotation speed	75 rpm
Volume	900 mL
Temperature	37 ± 0.5°C
Sampling time points	10, 15, 20, 30, and 45 minutes
Determination	HPLC/UV at 224 nm

Comparative dissolution testing was conducted on the biobatches using the following dissolution test conditions:

Table 3 Dissolution conditions for the comparative dissolution tests

Parameter	Conditions
Instrument	Apparatus 2 (paddle)
Rotation speed	50 rpm
Volume	900 mL
Temperature	37 ± 0.5°C
Sampling time points	10, 15, 20, 30, and 45 minutes
Determination of empagliflozin	HPLC/UV at 224 nm
Determination of metformin hydrochloride	HPLC/UV at 218 nm or UV spectrophotometry at 233 nm[1]

1 Interchangeability of HPLC-UV and UV detection was demonstrated for all dissolution media

Table 4 Dissolution media used for the comparative dissolution tests

Condition [pH]	Composition
(b) (4)	
6.8	Phosphate buffer

The Applicant provided the following justifications for the proposed dissolution method for the FDC product, which were verified by the Reviewer:

- The paddle apparatus 2 was selected (b) (4)
- Agitation speed of 50 rpm was selected (b) (4)
- (b) (4)
- Phosphate buffer pH 6.8 was selected as the dissolution medium (b) (4)
- (b) (4)
- The analytical assays for dissolution samples of empagliflozin and metformin HCl were adequately validated for specificity, robustness, accuracy and precision.
- Data supports the dissolution specification of Q= (b) (4)% at 20 minutes for all strengths of both drug substances.

The dissolution testing demonstrated that the dissolution profiles of the different dosage strengths are similar.

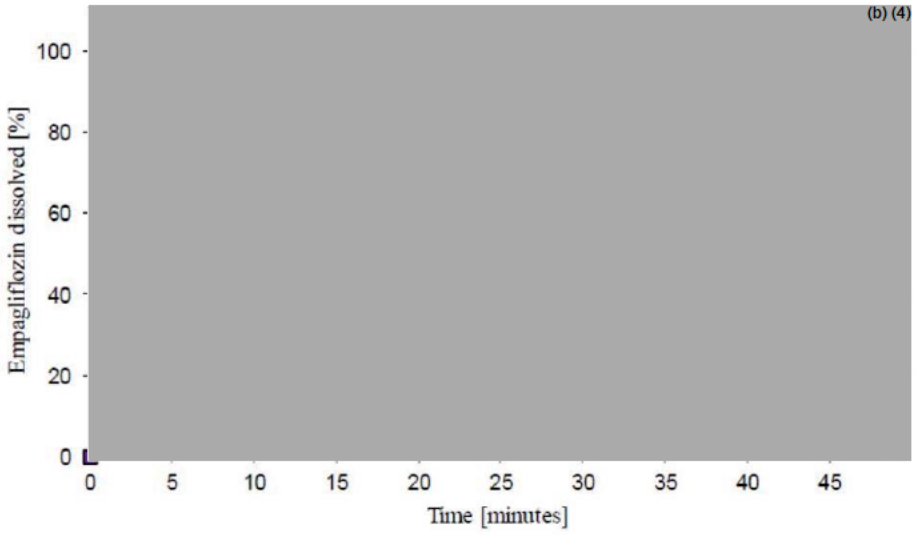


Figure 5 Dissolution profiles of empagliflozin from different dosage strengths of empagliflozin / metformin hydrochloride film-coated tablets

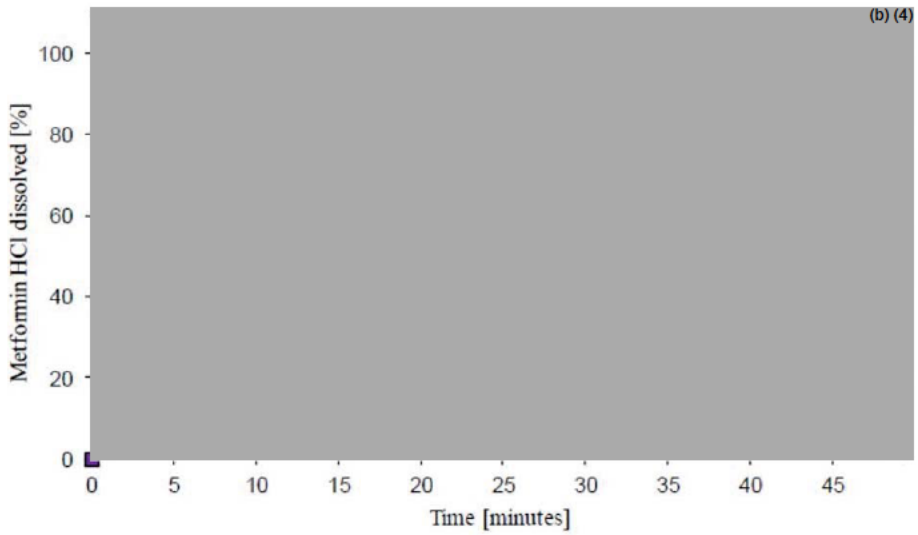
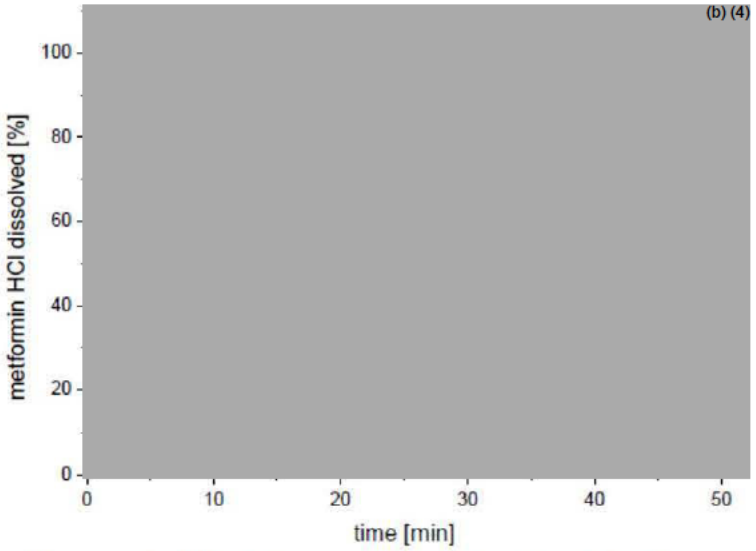


Figure 6 Dissolution profiles of metformin hydrochloride from different dosage strengths of empagliflozin / metformin hydrochloride film-coated tablets

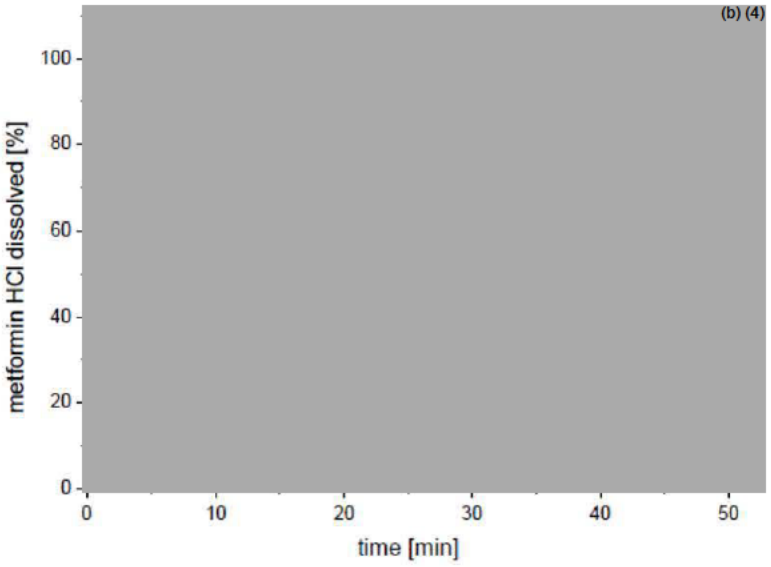
Comparative dissolution profiles of the proposed FDC product and reference mono-products (Glucophage® (metformin HCl) tablets, and Empagliflozin tablet manufactured by the Applicant) are described in the following figures (b) (4)

Metformin HCl

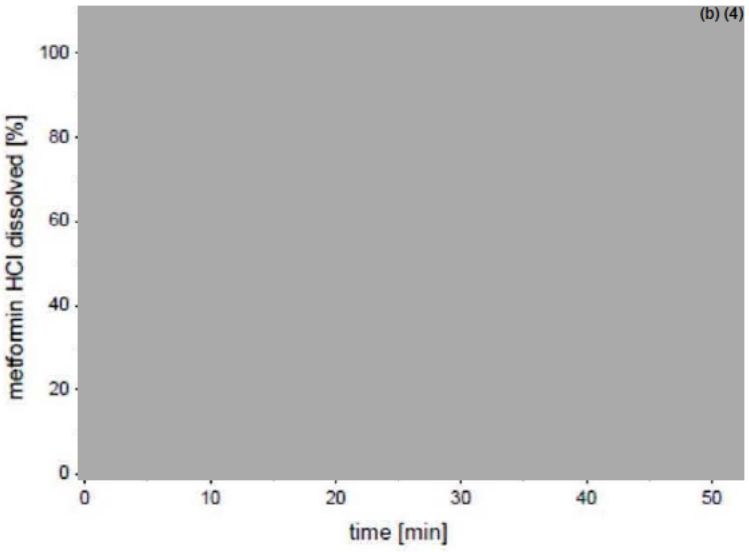
Test conditions: Paddle, 50 rpm, 900 mL (b) (4), n = 12



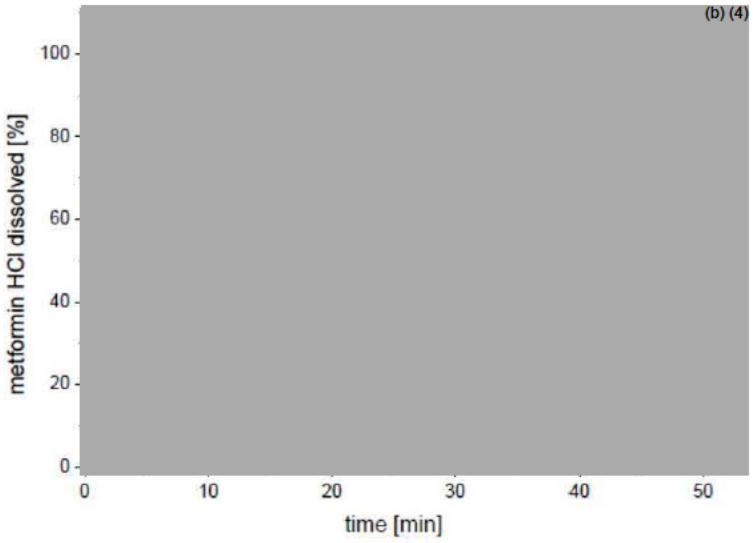
Test conditions: Paddle, 50 rpm, 900 mL (b) (4), n = 12



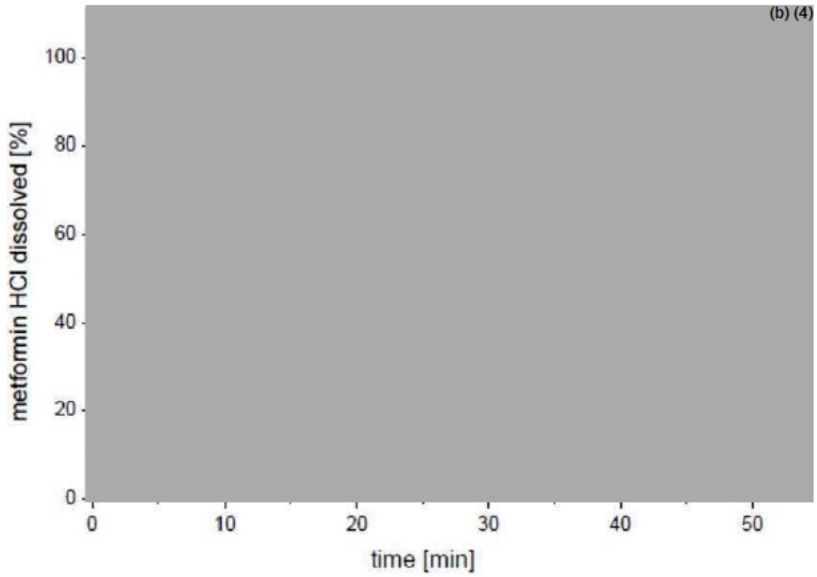
Test conditions: Paddle, 50 rpm, 900 mL buffer pH 6.8, n = 12



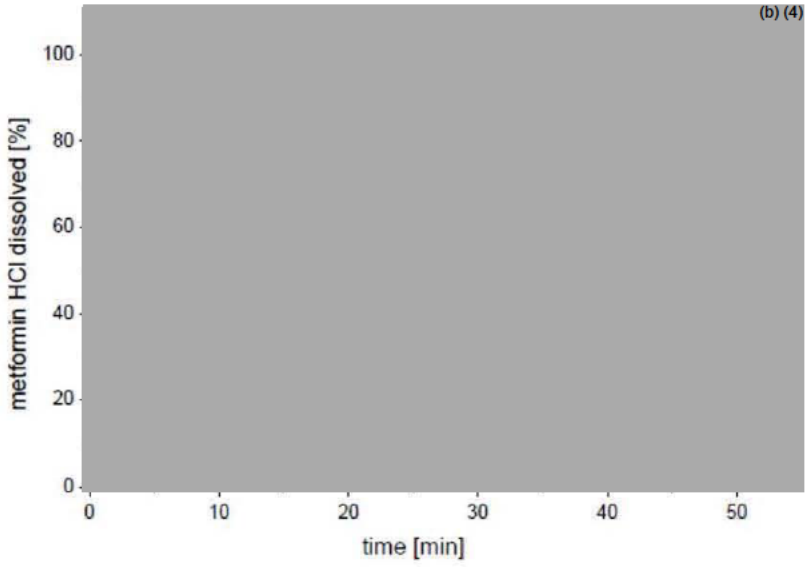
Test conditions: Paddle, 50 rpm, 900 mL (b) (4) n = 12 (



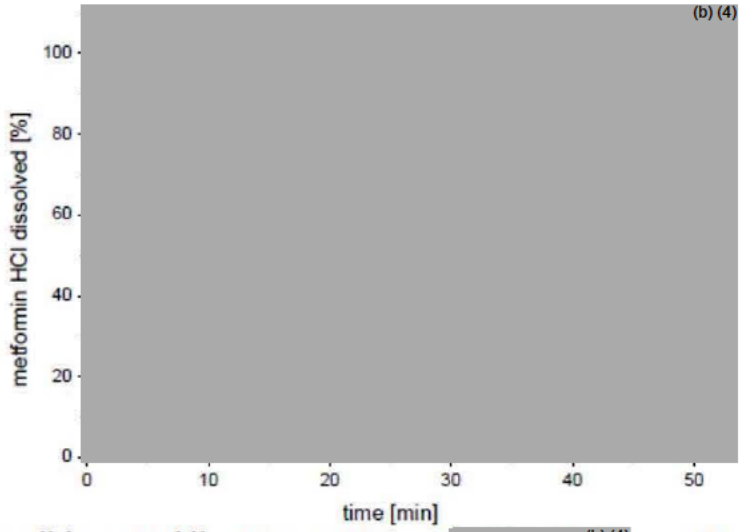
Test conditions: Paddle, 50 rpm, 900 mL [redacted] (b) (4) n = 12



Test conditions: Paddle, 50 rpm, 900 mL buffer pH 6.8, n = 12



Test conditions: Paddle, 50 rpm, 900 mL (b) (4) n = 12



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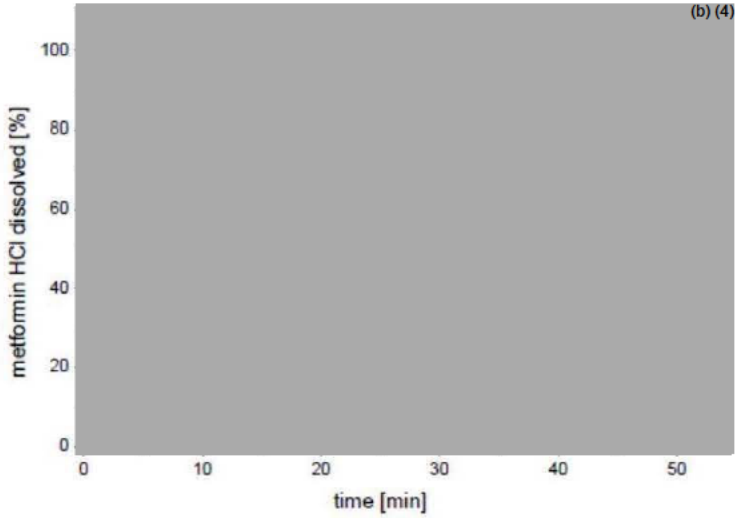
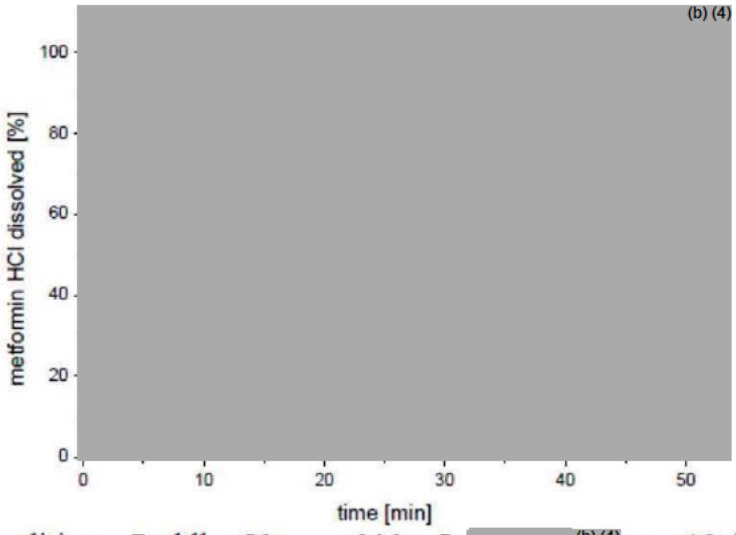
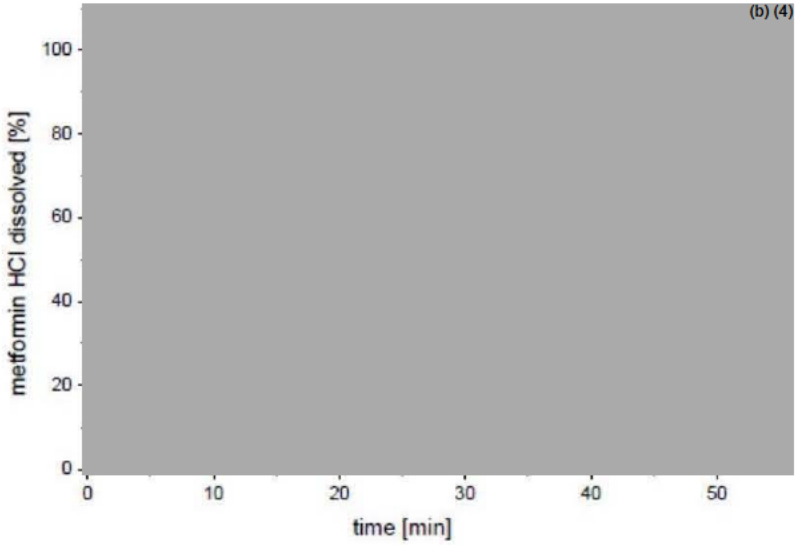


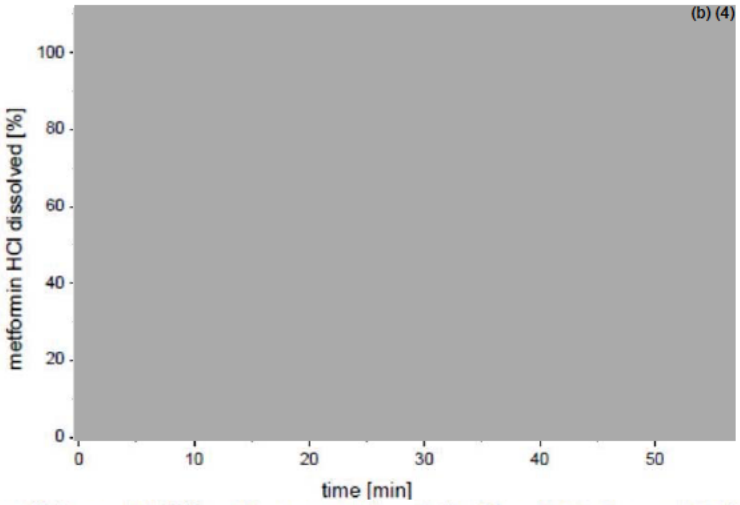
Test conditions: Paddle, 50 rpm, 900 mL buffer pH 6.8, n = 12



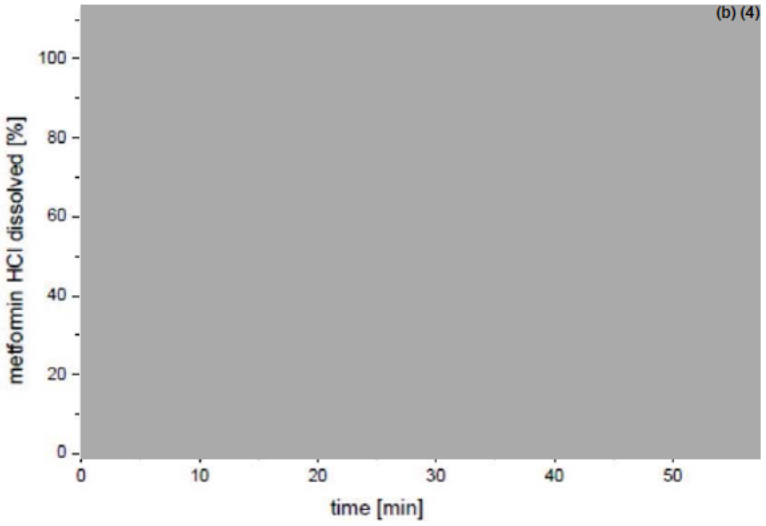
Test conditions: Paddle, 50 rpm, 900 mL [redacted] (b) (4) n = 12 (se



Test conditions: Paddle, 50 rpm, 900 mL (b) (4) n = 12 (s



Test conditions: Paddle, 50 rpm, 900 mL buffer pH 6.8, n = 12 (s



Reviewer's comments on metformin HCl dissolution:

- The dissolution profiles of 500 mg and 1000 mg metformin HCl from the FDC product were not similar to those of 500 mg and 1000 mg Glucophage® (b) (4) This is supported by the f2 similarity factor values calculated by the Applicant.

Table 17 f2 values for empagliflozin / metformin hydrochloride film-coated tablets with reference to metformin hydrochloride mono tablets

Test product: empagliflozin / metformin hydrochloride film-coated tablets (Batch No.)	Reference product: metformin hydrochloride film-coated tablets (Batch No.)	pH (medium)	f2 value
(b) (4)			

Table 18 f2 values for empagliflozin / metformin hydrochloride film-coated tablets with reference to metformin hydrochloride mono tablets

Test product: empagliflozin / metformin hydrochloride film-coated tablets (Batch No.)	Reference product: metformin hydrochloride film-coated tablets (Batch No.)	pH (medium)	f2 value
(b) (4)			

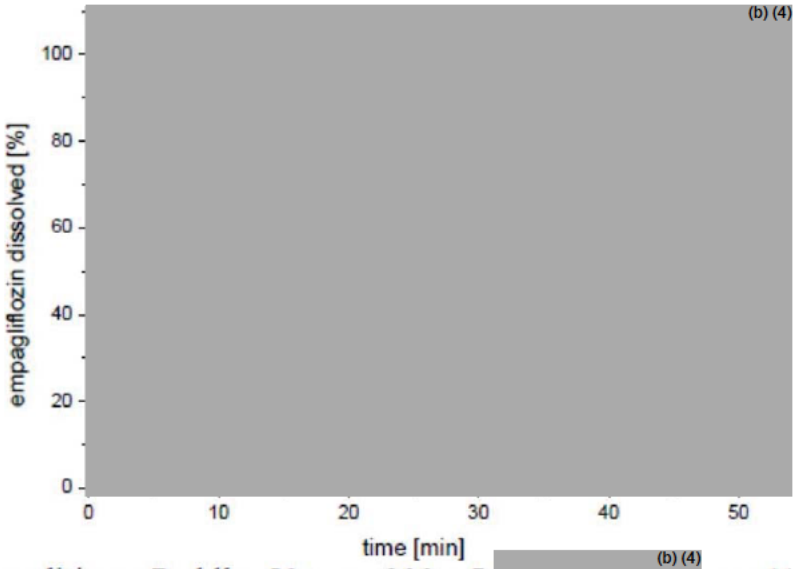
- (b) (4)

(b) (4)

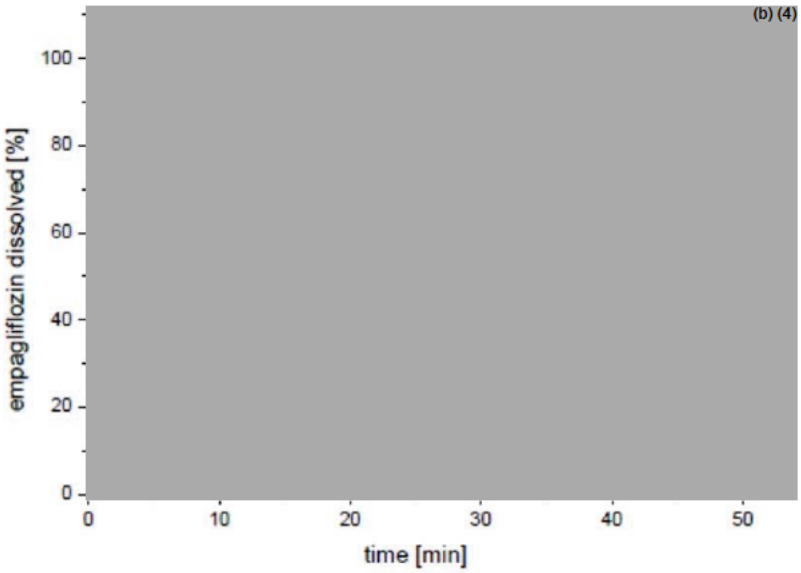
- Since the 500 mg and 1000 mg metformin HCl components of the FDC product are bioequivalent to 500 mg and 1000 mg Glucophage® tablets, and the dissolution method is adequate for the FDC product, the lack of dissolution similarity between the test and reference products does not affect the approvability of the proposed FDC product.

Empagliflozin

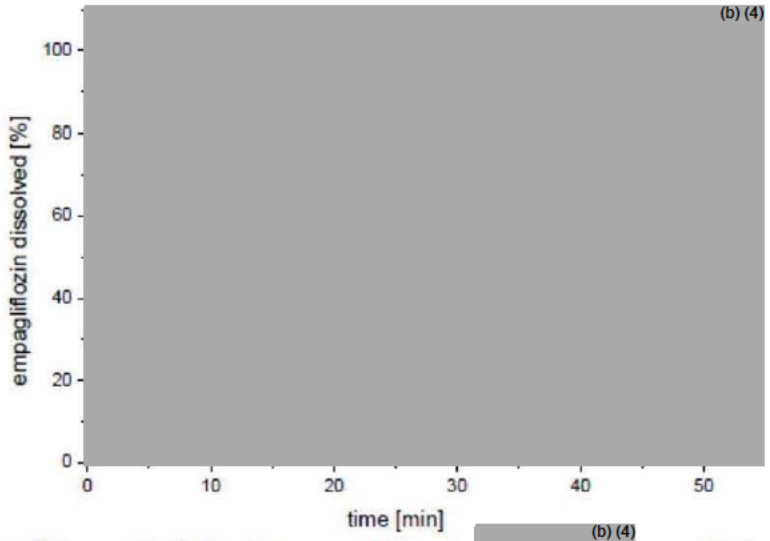
Test conditions: Paddle, 50 rpm, 900 mL (b) (4) n = 12 (s



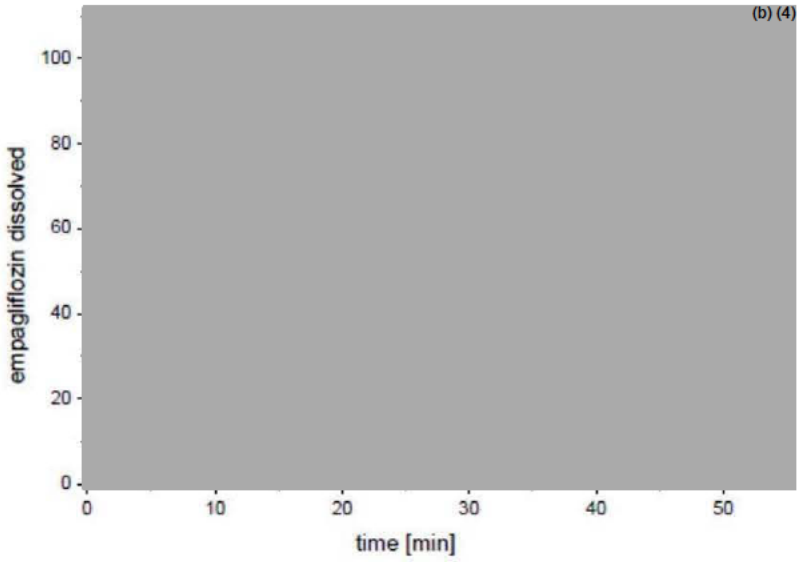
Test conditions: Paddle, 50 rpm, 900 mL (b) (4) n = 1



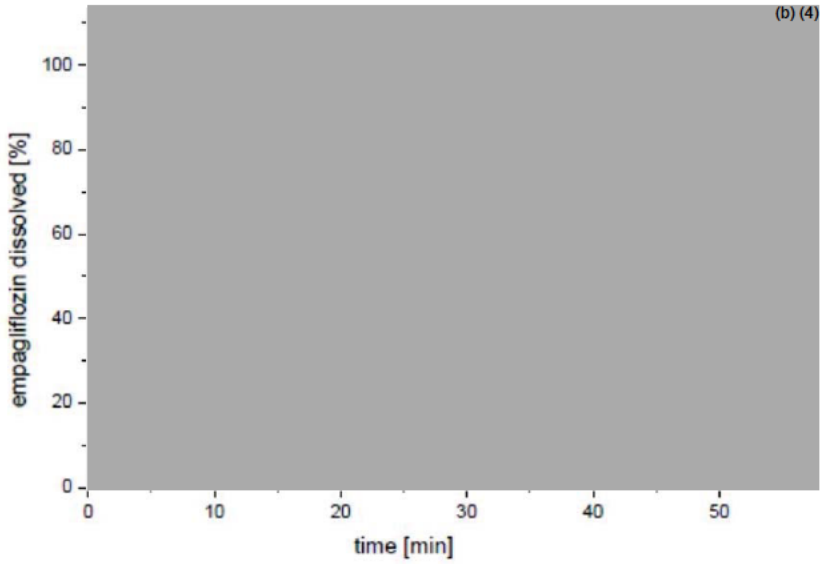
Test conditions: Paddle, 50 rpm, 900 mL buffer pH 6.8, n = 12



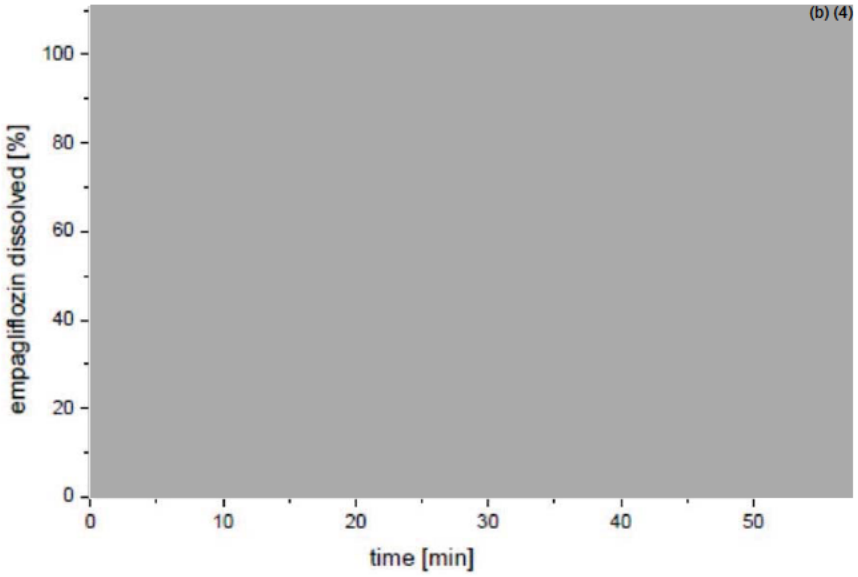
Test conditions: Paddle, 50 rpm, 900 mL (b) (4) n = 12 (see



Test conditions: Paddle, 50 rpm, 900 mL (b) (4) n = 12 (se



Test conditions: Paddle, 50 rpm, 900 mL buffer pH 6.8, n = 12 (s



Reviewer's comments on empagliflozin dissolution:

- The dissolution profiles of 5 mg empagliflozin from the FDC product were similar to those of 5 mg Empagliflozin (b) (4) This is supported by the f2 similarity factor values calculated by the Applicant (b) (4)

Table 18 f2 values for empagliflozin / metformin hydrochloride film-coated tablets with reference to empagliflozin mono tablets

Test product: empagliflozin / metformin hydrochloride film-coated tablets (Batch No.)	Reference product: empagliflozin film-coated tablets (Batch No.)	pH (medium)	f2 value
			(b) (4)

Table 19 f2 values for empagliflozin / metformin hydrochloride film-coated tablets with reference to empagliflozin mono tablets 2.5 mg and 10 mg

Test product: empagliflozin / metformin hydrochloride film-coated tablets (Batch No.)	Reference product: empagliflozin film-coated tablets (Batch No.)	pH (medium)	f2 value	
			2.5 mg	10 mg
				(b) (4)

- (b) (4)

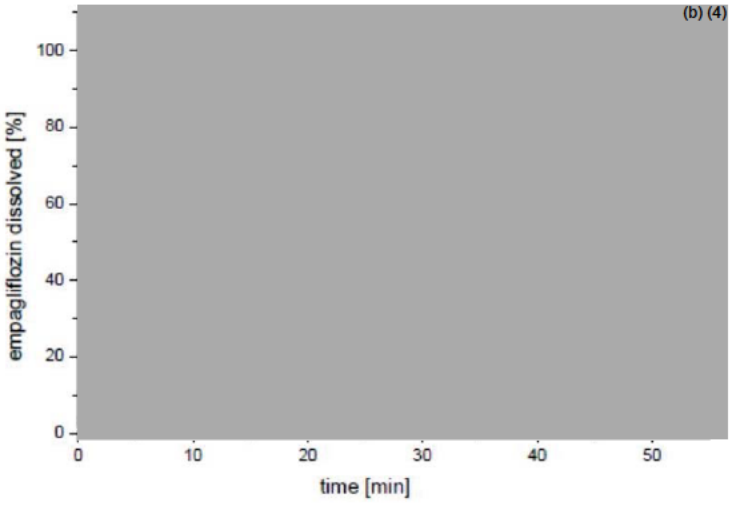
(b) (4)

- Since the 5 mg and 12.5 mg empagliflozin components of the FDC product are bioequivalent to 5 mg and 12.5 mg Empagliflozin tablets, and the dissolution method is adequate for the FDC product, the lack of dissolution similarity between the test and reference products does not affect the approvability of the proposed FDC product.

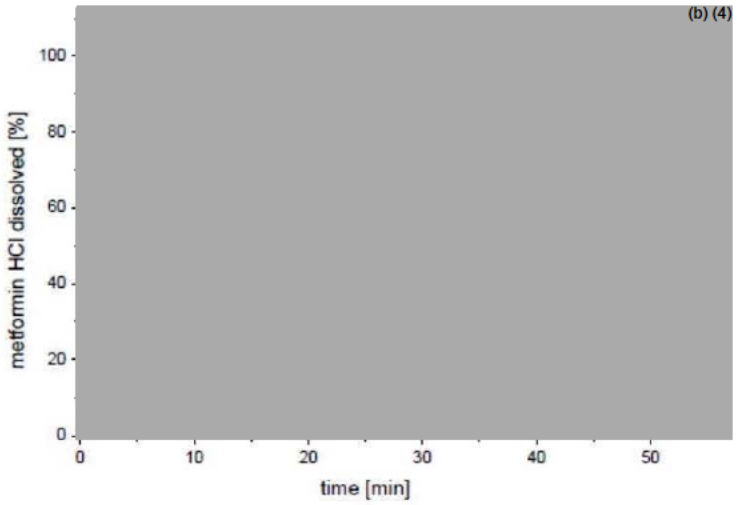
Production Scale Batches

- Comparative dissolution testing was performed on the first production scale batches of the FDC products to show similarity between these batches and the biobatches. (b) (4)
- Representative dissolution profiles are included to demonstrate that the dissolution profiles between the production scale batches and biobatches are similar:

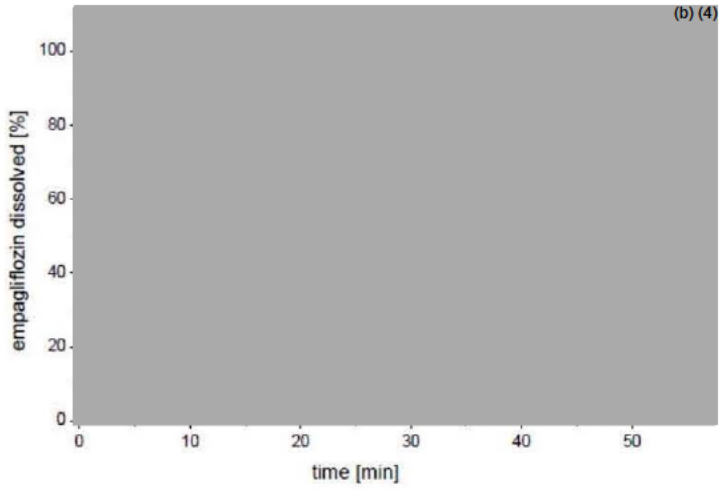
  Test conditions: Paddle, 50 rpm, 900 mL buffer pH 6.8, n = 12 (Table 61)



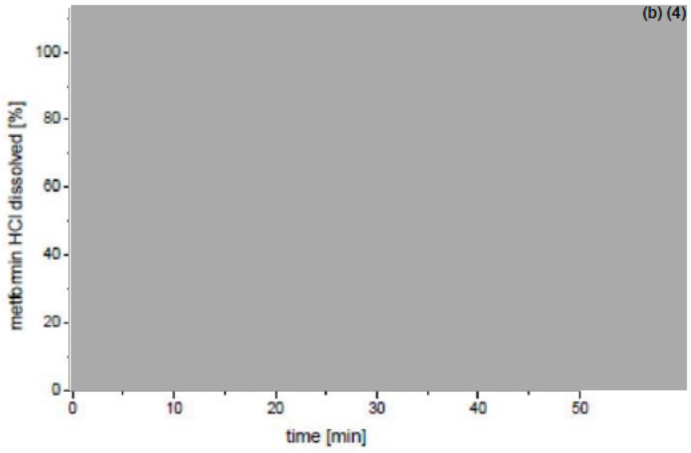
Test conditions: Paddle, 50 rpm, 900 mL buffer pH 6.8, n = 12 (Table 51)



Test conditions: Paddle, 50 rpm, 900 mL buffer pH 6.8, n = 12 (s Table 66)



Test conditions: Paddle, 50 rpm, 900 mL buffer pH 6.8, n = 12 (see Table 53)



Reviewer's Overall Assessment:

- The bioequivalence study results demonstrate that the FDC products are bioequivalent to the reference products under fasting and fed conditions. The demonstration of bioequivalence supports the bridging of the efficacy and safety results obtained with the free combination of Empagliflozin Tablets and Glucophage® (metformin) Tablets.
- The Applicant developed a suitable dissolution method for the proposed FDC product, and the dissolution acceptance criteria of Q= (b) (4) % at 20 minutes is acceptable.
- The comparative dissolution testing does not support the bridge of the FDC products to the reference products. However, the lack of dissolution similarity between the test and reference products does not affect the approvability of the proposed FDC product.

RECOMMENDATION:

The bioequivalence results and dissolution method are acceptable. From the Biopharmaceutics perspective, NDA 206111 for Empagliflozin/Metformin Hydrochloride Fixed Dose Combination Tablets is recommended for approval.

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA:	206111
Submission Date(s):	August 04, 2014
Brand Name	Synjardy
Generic Name	Empagliflozin / Metformin IR FDC
OCP Division	Clinical Pharmacology -2
OND division	Metabolism and Endocrinology Products
Sponsor	Boehringer Ingelheim Pharmaceuticals, Inc.
Submission Type; Code	NDA 505(b)(2); Standard
Formulation; Strength(s)	Tablets: • 5 mg empagliflozin/500 mg metformin • 5 mg empagliflozin/1000 mg metformin • 12.5 mg empagliflozin/500 mg metformin • 12.5 mg empagliflozin/1000 mg metformin
Proposed Indication	• Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (b) (4) [redacted]
Clinical Pharmacology Reviewer	Suryanarayana Sista, PhD
Clinical Pharmacology Team Leader (Acting)	Manoj Khurana, PhD

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1 Executive Summary

Boehringer Ingelheim Pharmaceuticals, Incorporated Inc. (BI) are seeking US marketing approval for Synjardy® tablets under the provisions of Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act. Synjardy is a fixed-dose combination (FDC) product of empagliflozin, a sodium-glucose co-transporter 2 (SGLT2) inhibitor, and metformin, a biguanide. Empagliflozin (Jardiance®, NDA 204629, BI) and metformin (Glucophage®, NDA 020357, Bristol-Myers Squibb) were approved by the Agency on 08/01/2014 and 03/03/1995, respectively. The proposed indication of Synjardy tablets is "adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (b) (4) .

If approved, Synjardy will be the third SGLT2/biguanide FDC to enter the market.

1.1 Recommendation

The Office of Clinical Pharmacology (OCP) has reviewed the clinical pharmacology data submitted under NDA 206111 and finds it acceptable to support the approval.

1.2 Phase IV Commitments

None.

1.3 Summary of Important Clinical Pharmacology Findings

Empagliflozin / metformin film-coated tablets, (Synjardy) are manufactured in empagliflozin/metformin strengths of 5/500, (b) (4) 5/1000, 12.5/500, (b) (4) and 12.5/1000 mg. (b) (4)

The sponsor has proposed the following dosing recommendation for Synjardy:

(b) (4)

This NDA is supported by data from five trials, which were conducted as part of the empagliflozin/metformin FDC development program. These include 3 phase I bioequivalence trials (1276.6, (b) (4) and 1276.8) and a phase I bioavailability study (1276.5). In addition, the sponsor conducted a phase IIb posology bridging study (1276.10) to fulfil the regulatory requirement by EMA to demonstrate comparable HbA_{1c} reduction for twice-daily versus once-daily dose regimens of empagliflozin as add-on therapy to metformin. In addition, the sponsor is referring to several Phase IIb and Phase III studies that were conducted as part of the Empagliflozin NDA (Jardiance®, NDA 204629) program, where empagliflozin was administered over a metformin background therapy. The studies that support empagliflozin/metformin FDC are listed in Table 1 below:

Table 1: Overview of studies conducted in support of empagliflozin/metformin FDC

Phase	Study	Description	Submitted to NDA #	Comment
I	1245.6	Drug-drug interaction empagliflozin with metformin	204629	Already Reviewed (Jardiance NDA)
	1276.5	**Relative bioavailability empagliflozin 12.5mg/metformin1000 mg FDC and food interaction**	**206111**	**Current NDA**
	1276.6	**Bioequivalence empagliflozin 12.5 mg or 5 mg/ metformin 500 mg FDCs**	**206111**	**Current NDA**
	(b) (4)			
	1276.8	**Bioequivalence empagliflozin 12.5 mg or 5 mg/ metformin 1000 mg FDCs**	**206111**	**Current NDA**
IIb	1245.10	12-week dose-finding; metformin background	204629	Already Reviewed (Jardiance NDA)
	1245.24	78-week extension of 1245.9 and 1245.10; ± metformin background	204629	Already Reviewed (Jardiance NDA)
	1245.33[1]	78-week; basal insulin ± metformin and/or Sulfonylurea background	204629	Already Reviewed (Jardiance NDA)
	1276.10	**16-week empagliflozin once daily vs. twice daily; metformin background**	**206111**	**Current NDA**
III	$1245.23_{(met)}$	24-week pivotal study, metformin background	204629	Already Reviewed (Jardiance NDA)
	$1245.23_{(met+SU)}$	24-week pivotal study, metformin + Sulfonylurea background	204629	Already Reviewed (Jardiance NDA)
	1245.19	24-week pivotal study, pioglitazone± metformin background	204629	Already Reviewed (Jardiance NDA)
	$1245.31_{(met)}$	Long-term extension of $1245.23_{(met)}$	204629	Already Reviewed (Jardiance NDA)
	$1245.31_{(met+SU)}$	Long-term extension of $1245.23_{(met+SU)}$	204629	Already Reviewed (Jardiance NDA)
	$1245.31_{(pio+met)}$	Long-term extension of $1245.19_{(pio+met)}$	204629	Already Reviewed (Jardiance NDA)
	1245.28 [2]	4-year; comparison with glimepiride; metformin background	204629	Already Reviewed (Jardiance NDA)
	1245.36	52-week; patients with renal impairment; various antidiabetic background	204629	Already Reviewed (Jardiance NDA)
	1245.48	12-week; ABPM in patients with T2DM and hypertension; various antidiabetic background	204629	Already Reviewed (Jardiance NDA)
	1245.49	52-week; MDI insulin± metformin background	204629	Already Reviewed (Jardiance NDA)
	$1275.1_{(met)}$	52-week; empagliflozin/linagliptin FDC vs. individual components; ± metformin background	204629	Already Reviewed (Jardiance NDA)

[1]Study 1245.33 was originally designated as a phase IIb study. Since it had confirmatory testing introduced via a protocol amendment, it is considered equivalent to a phase III study for the assessment of the efficacy and safety of empagliflozin.
[2]Study 1245.28: all safety data up to the study database lock of 27 September 2013 were included in the 104-week analyses
met = Metformin
SU = Sulfonylurea
pio = Pioglitazone

BE Study Results:
Evaluation of BE studies 1276.6, (b) (4) and 1276.8 were conducted by the ONDQA reviewer, Dr. Kelly Kitchens. The review has concluded that the proposed empagliflozin/metformin FDC tablets are bioequivalent to the individual tablets administered together (see review by Dr. Kelly Kitchens in DARRTS).

Empagliflozin-Metformin DDI Study Results:
The drug-drug interaction study (Study 1245.6) was already reviewed under NDA 204629 (see Clinical Pharmacology review by Dr. Manoj Khurana in DARRTS dated 11/08/2013). In brief, co-administration of multiple daily doses of empagliflozin 50 mg with metformin 2000 mg, an organic cationic transporter (OCT) substrate, demonstrated that there is no drug-drug interaction between empagliflozin and metformin.

Relative BA and Food Effect Study Results:
Study 1276.5 evaluated the relative bioavailability of empagliflozin and metformin when single doses of 12.5 mg empagliflozin and 1000 mg metformin were administered as the FDC tablet compared to individual components. Relative bioavailability of each moiety was estimated on the basis of $AUC_{0-\infty}$ and C_{max}. The least squares mean ratios for empagliflozin $AUC_{0-\infty}$ and C_{max} were 100.79% and 99.90%, respectively, and the corresponding 90% confidence intervals for $AUC_{0-\infty}$ and C_{max} were (95.70, 106.15), and (90.09, 110.77), respectively. The least squares mean ratios for metformin $AUC_{0-\infty}$ and C_{max} were 102.29% and 103.83%, respectively, and the corresponding 90% confidence intervals for $AUC_{0-\infty}$ and C_{max} were (93.28, 112.20), and (89.98, 119.79), respectively. Since the ratios of means and 90% CI for C_{max} and $AUC_{0-\infty}$ of both empagliflozin and metformin were within the pre-specified bioequivalence boundaries of 80-125%, it can be concluded that the rate and extent of absorption of both empagliflozin and metformin were equivalent when empagliflozin and metformin were administered as the FDC tablet compared to individual components under fasting conditions.

The clinical pharmacology review of the food effect portion of study 1276.5 showed that:

- Following administration of the 12.5/1000 FDC tablet, a food effect on Empagliflozin PK was observed. There was a 36% reduction in C_{max} and a 8% and 7% reduction in both $AUC_{(0-t)}$ and $AUC_{(0-\infty)}$, respectively.
- This effect of food on relative BA is consistent with previous findings with Empagliflozin (Jardiance, NDA 204629). In NDA 204629, the sponsor reported that reduction in C_{max} of empagliflozin did not influence the amounts of glucose excreted in the urine when empagliflozin was administered in the fed state.
- Following administration of the 12.5/1000 FDC tablet, a food effect on Metformin PK was observed. There was a 26% reduction in C_{max} and a 3% reduction in $AUC_{(0-t)}$, while $AUC_{(0-\infty)}$ was unchanged. The clinical relevance of these decreases in metformin exposure is unknown.

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

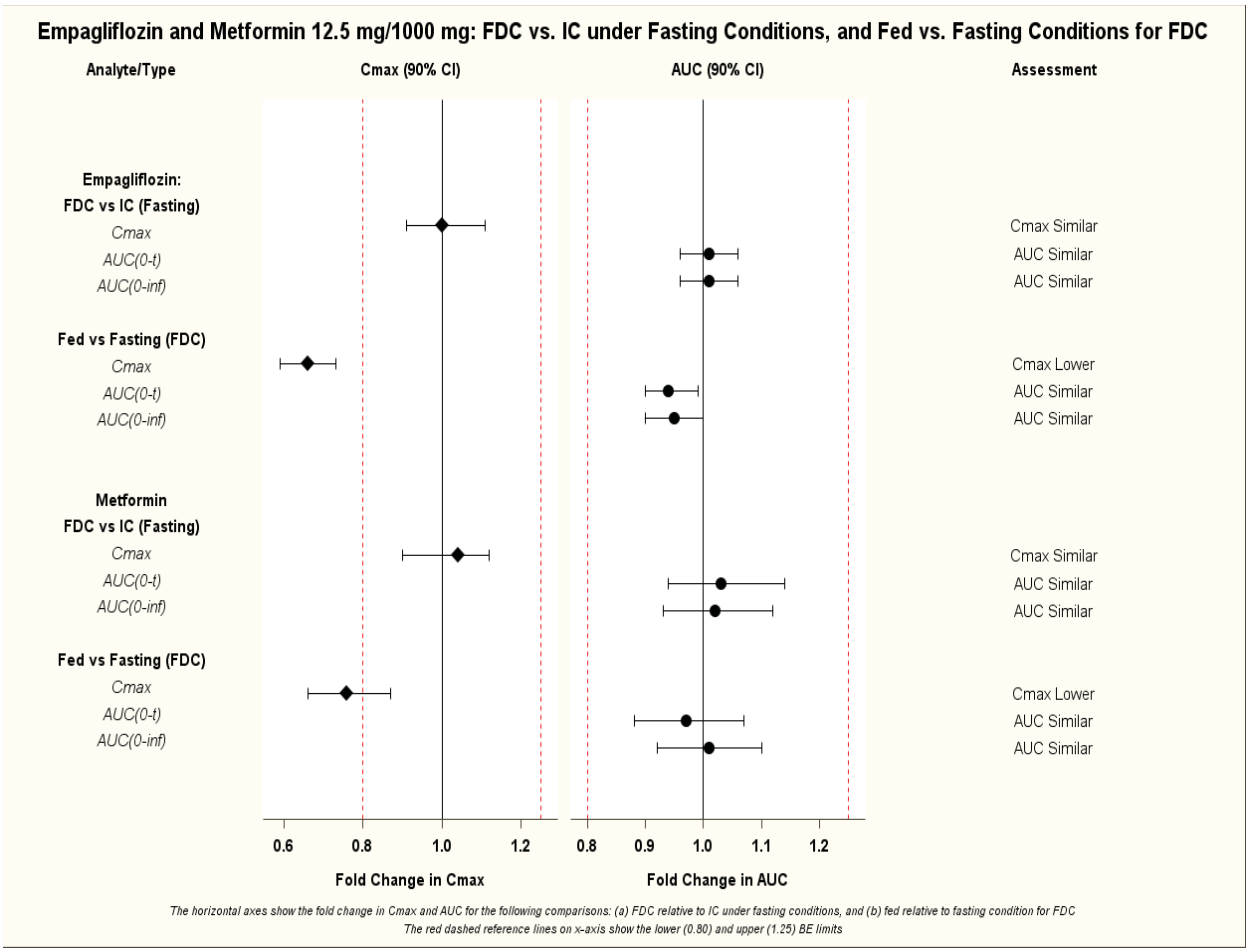


Figure 1: Food-effect Comparison for Empagliflozin and Metformin following 12.5 mg Empagliflozin/1000 mg Metformin FDC Formulation under Fasting and Fed Conditions

(Source Analysis performed by reviewer using SAS v9.3)

Phase IIb Bridging Trial Results:

The objective of the efficacy/safety trial (1276.10) was to investigate the efficacy and safety of different dosage regimens of empagliflozin (twice daily versus once daily) administered orally as add-on therapy to immediate release metformin in patients with type 2 diabetes mellitus and insufficient glycemic control. The study was designed to test the non-inferiority of treatment with empagliflozin 5 mg twice daily versus treatment with empagliflozin 10 mg once daily and of treatment with empagliflozin 12.5 mg twice daily versus treatment with empagliflozin 25 mg once daily. This trial also evaluated the superiority of all 4 empagliflozin dose regimens versus placebo.

As was noted with other empagliflozin applications (NDA 204629, Jardiance; NDA 206073, Glyxambi), there is lack of clear trend for dose dependent reduction in HbA_{1c} from baseline for the various dose and dosing regimen of empagliflozin (Figures 14). BID treatment, however, produced numerically greater reduction in HbA_{1c} compared to once-daily treatments for both the doses evaluated in this study. For further details on the analysis of non-inferiority of twice daily versus once daily administration, please refer to the statistical review of the findings from this study by Dr. Susie Sinks in DARRTS.

2 *Question-Based Review (QBR)*

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

The clinical pharmacology and Biopharmaceutics program performed to evaluate the bioequivalence and relative bioavailability of the Synjardy fixed-dose combination (FDC) compared to the mono components included four Phase 1 trials conducted in healthy volunteers (Table 2), and a Phase IIb study conducted in patients with type 2 diabetes mellitus and insufficient glycemic control. In addition, safety and efficacy data from Phase 2 and Phase 3 trials conducted as part of NDA 204629 with empagliflozin in presence of metformin background therapy are also included in the current NDA.

Table 2: Overview of studies with pharmacokinetic assessments relevant to the clinical pharmacology and biopharmaceutics of Synjardy

Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
Phase I Relative Bioavailability (1276.5)					
To determine the relative bioavailability of a 12.5 mg empagliflozin/1000 mg metformin fixed dose combination (FDC) tablet compared with its individual components administered together and to assess the effect of food on the relative bioavailability of the FDC tablet	Open-label, randomized, single-dose, 3-way crossover trial.	• Treatment A: Empagliflozin/metformin FDC tablet in fasted state • Treatment B: Empagliflozin and metformin single tablets (individual components) in fasted state • Treatment C: Empagliflozin/metformin FDC tablet after a high fat, high caloric meal	Treatment A (FDC tablet under fasted conditions): entered: 16 treated: 15 analyzed (for primary endpoint): 15 Treatment B (Empa+Met individual-component tablets under fasted conditions): entered: 16 treated: 16 analyzed (for primary endpoint): 16 Treatment C (FDC tablet under fed conditions): entered: 16 treated: 14 analyzed (for primary endpoint): 14	Healthy M or F, age 18-55 years, with a BMI of 18.5 to 29.9 kg/m^2	Treatments A, B, C and D: single-dose The subjects were to undergo 3 treatment periods and were to receive a single dose of trial medication in each treatment period. The 3 drug administrations were separated by washout phases of at least 7 days.
Phase I Bioequivalence (1276.6)					
To demonstrate bioequivalence of a 12.5 mg empagliflozin/500 mg metformin fixed dose combination (FDC) tablet compared with the respective single tablets (10 mg empagliflozin + 2.5 mg empagliflozin + 500 mg metformin) as well as to establish bioequivalence of a 5	Open-label, randomized, single-dose, 4-way crossover trial with 4 treatments (T1, R1, T2, and R2) and 4 treatment sequences (T1_R1_T2_R2, R1_T1_R2_T2, T2_R2_ T1_R1, and R2_T2_R1_T1).	• Test 1 (T1) single FDC tablet containing 12.5 mg empagliflozin and 500 mg metformin, 30 minutes after a high-fat, high-caloric breakfast • Reference 1 (R1) single 10 mg empagliflozin tablet, single 2.5 mg empagliflozin tablet, and single 500 mg metformin tablet, 30	Number of subjects entered: 24 (9 male and 15 female subjects) Treatment T1 (12.5 mg empagliflozin/500 mg metformin FDC): treated and analyzed (for primary endpoint): 21	Healthy male and female volunteers at the age of 18 to 50 years and with a body mass index (BMI) of 18.5 to 29.9 kg/m^2	Treatments T1, R1, T2 and R2: single-dose Drug administrations of the 4 individual single dose treatments were each separated by a washout period of at least 5 days.

Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
mg empagliflozin/ 500 mg metformin FDC tablet compared with the respective single tablets (5 mg empagliflozin + 500 mg metformin), following a high-fat, high-caloric meal.		minutes after a high-fat, high-caloric breakfast • Test 2 (T2) single FDC tablet containing 5 mg empagliflozin and 500 mg metformin, 30 minutes after a high-fat, high-caloric breakfast • Reference 2 (R2) single 5 mg empagliflozin tablet and single 500 mg metformin tablet, 30 minutes after a high-fat, high-caloric breakfast	Treatment R1 (12.5 mg empagliflozin and 500 mg metformin, single tablets): treated and analyzed (for primary endpoint): 23 Treatment T2 (5 mg empagliflozin/500 mg metformin FDC): treated and analyzed (for primary endpoint): 23 Treatment R2 (5 mg empagliflozin and 500 mg metformin, single tablets): treated and analyzed (for primary endpoint): 20		

(b) (4)

Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
			(b) (4)		
Phase I Bioequivalence (1276.8)					
To establish the bioequivalence of an • empagliflozin 12.5 mg / metformin 1000 mg fixed dose combination (FDC) tablet (T1) compared with the free dose combination of empagliflozin 10 mg, empagliflozin 2.5 mg, and metformin 1000 mg (R1), Part I o under fasted conditions o under fed conditions • empagliflozin 5 mg / metformin 1000 mg FDC tablet (T2) compared with the free dose combination of empagliflozin 5 mg and metformin 1000 mg under fed conditions (R2), Part II	Randomized, open-label, single-dose, 4-way (Part I) or 2-way (Part II) crossover design.	• Test 1 (T1) single FDC tablet containing 12.5 mg empagliflozin and 1000 mg metformin, (a) under fasting conditions (Treatment A), or (b) 30 minutes after a high-fat, high-caloric breakfast (Treatment B) • Reference 1 (R1) single 10 mg empagliflozin tablet, single 2.5 mg empagliflozin tablet, and single 1000 mg metformin tablet, (a) under fasting conditions (Treatment C), or (b) 30 minutes after a high-fat, high-caloric breakfast (Treatment D) • Test 2 (T2) single FDC tablet containing 5 mg empagliflozin and 1000 mg metformin, 30 minutes after a high-fat, high-caloric breakfast (Treatment E) • Reference 2 (R2) single 5 mg empagliflozin tablet and single 1000 mg metformin tablet, 30 minutes after a high-fat, high-caloric breakfast (Treatment F)	Treatment A (T1 fasted): FDC tablet of 12.5 mg empagliflozin / 1000 mg metformin under fasted conditions entered: 24 treated: 24 analyzed (for primary endpoint): 23 Treatment B (T1 fed): FDC tablet of 12.5 mg empagliflozin / 1000 mg metformin under fed conditions entered: 24 treated: 24 analyzed (for primary endpoint): 24 Treatment C (R1 fasted): Free dose combination of 12.5 mg empagliflozin and 1000 mg metformin under fasted conditions entered: 24 treated: 24 analyzed (for primary endpoint): 24 Treatment D (R1 fed): Free dose combination of 12.5 mg empagliflozin and 1000 mg metformin under fed conditions entered: 24 treated: 24 analyzed (for primary endpoint): 22 Treatment E (T2 fed): FDC tablet of 5 mg empagliflozin / 1000 mg metformin under fed conditions entered: 24	Healthy male and female volunteers aged 18 to 50 years, with BMI from 18.5 to 29.9 kg/m^2	A single dose of test or reference treatment was administered in each treatment period separated by a washout phase of at least 7 days between drug administrations

Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
			treated: 24 analyzed (for primary endpoint): 22 Treatment F (R2 fed): Free dose combination of 5 mg empagliflozin and 1000 mg metformin under fed conditions entered: 24 treated: 24 analyzed (for primary endpoint): 23		
Phase IIb Safety and Efficacy (1276.10)					
to investigate the efficacy and safety of different dosages of empagliflozin (twice daily versus once daily), administered orally as add-on therapy to immediate release metformin in patients with type 2 diabetes and insufficient glycemic control. The study was designed to test non-inferiority of treatment with empagliflozin 5 mg twice daily versus treatment with empagliflozin 10 mg once daily and of treatment with empagliflozin 12.5 mg twice daily versus treatment with empagliflozin 25 mg once daily. The superiority of all 4 empagliflozin dose regimens versus placebo was also tested.	Randomized, double-blind, placebo-controlled, parallel group comparison. Randomization was stratified by HbA_{1c}, renal function at screening, assessed based on eGFR values (according to MDRD staging criteria), and geographical region. A 2-week single-label placebo run-in period preceded randomization.	Patients who met the trial eligibility criteria at the end of the 2-week placebo run-in period were randomly assigned to 1 of the 5 treatment groups (empagliflozin 5 mg twice daily, empagliflozin 10 mg once daily, empagliflozin 12.5 mg twice daily, empagliflozin 25 mg once daily, or placebo) in a 2:2:2:2:1 ratio. To prevent unequal treatment allocation, blocks of 9 were used for randomization, and the blocks were assigned to strata. Randomization was performed at the randomization visit (Visit 3), and was stratified by HbA_{1c} at screening (8.5%; ≥8.5%), renal function at screening (eGFR ≤60-89 mL/min/1.73m^2; eGFR ≥ 90 mL/min/1.73m^2), and geographical region at run-in (Europe; North America; Latin America). Patients with an eGFR value <60 were also included in the strata eGFR value ≤60-89.	Enrolled: 1626 Entered: 983 Empagliflozin 12.5 mg twice daily: entered: 219 treated: 219 analyzed (for primary endpoint): 215 Empagliflozin 25 mg once daily: entered: 218 treated: 218 analyzed (for primary endpoint): 214 Empagliflozin 5 mg twice daily: entered: 219 treated: 219 analyzed (for primary endpoint): 215 Empagliflozin 10 mg once daily: entered: 220 treated: 220 analyzed (for primary endpoint): 213 Placebo: entered: 107 treated: 107 analyzed (for primary endpoint): 107	Patients with type 2 diabetes mellitus and insufficient glycemic control (HbA_{1c} ≥7.0 and ≤ 10.0%; in Germany: ≥7.0 to ≤8 5%) despite therapy with immediate release metformin (≥ 1500 mg/day, divided into twice daily doses); age ≥18 years; BMI ≤45 kg/m^2	2-week placebo run-in; 16-week treatment period; 1-week follow-up period. Metformin background medication (≥ 1500 mg/day, divided into twice daily doses) was to be taken during the entire trial duration (including placebo run-in period) at an unchanged dose.

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

Empagliflozin/Metformin 5 mg/500 mg:
Empagliflozin / metformin hydrochloride film-coated tablets, 5 mg / 500 mg are orange yellow, oval, biconvex film-coated tablets. One side is debossed with the Boehringer Ingelheim company symbol and "S5" the other side is debossed with "500".

(b) (4)

Empagliflozin/Metformin 5 mg/1000 mg:
Empagliflozin / metformin hydrochloride film-coated tablets, 5 mg / 1000 mg are brownish yellow, oval, biconvex film-coated tablets. One side is debossed with Boehringer Ingelheim company symbol and "S5", the other side is debossed with "1000".

Empagliflozin/Metformin 12.5 mg/500 mg:
Empagliflozin / metformin hydrochloride film-coated tablets, 12.5 mg / 500 mg are pale brownish purple, oval, biconvex film-coated tablets. One side is debossed with Boehringer Ingelheim company symbol and "S12", the other side is debossed with "500".

(b) (4)

Empagliflozin/Metformin 12.5 mg/1000 mg:
Empagliflozin / metformin hydrochloride film-coated tablets, 12.5 mg / 1000 mg are dark brownish purple, oval, biconvex film-coated tablets. One side is debossed with Boehringer Ingelheim company symbol and "S12", the other side is debossed with "1000".

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

The composition for the various strengths of empagliflozin/metformin tablet formulations are shown in Table 3.

Table 3Qualitative and quantitative composition of empagliflozin / metformin film-coated tablets

Ingredient	Empa/Met 5/500 (mg/tablet)	(b) (4)	Empa/Met 5/1000 (mg/tablet)	Empa/Met 12.5/500 (mg/tablet)	(b) (4)	Empa/Met 12.5/1000 (mg/tablet)	Function
Tablet Core							
Empagliflozin	5.000		5.000	12.500		12.500	Drug substance
Metformin hydrochloride	500.000		1000.000	500.000		1000.000	Drug substance
Corn starch							(b) (4)
Copovidone							
Colloidal silicon dioxide							
Magnesium stearate							
(b) (4)							
Film-coat							
							(b) (4)
Total mass of film-coated tablet							(b) (4)
*		(b) (4)					

(Source Synjardy NDA eCTD module 3.2.P.1; Description and Composition 5/500mg (A145633), Table 1, page 2; (b) (4) *Description and Composition 5/1000mg (A145641), Table 1, , page 2; Description and Composition 12.5/500mg (A145621), Table 1, , page 2,* (b) (4) *Description and Composition 12.5/1000mg (A145629), Table 1, , page 2)*

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

Empagliflozin:

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

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

Figure 2: Empagliflozin mechanism of action

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

Metformin:

Metformin is an anti-hyperglycemic agent which improves glucose tolerance in patients with type 2 diabetes, lowering both basal and postprandial plasma glucose. Its pharmacologic mechanisms of action are different from other classes of oral antihyperglycemic agents. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization (*source: product label for Glucophage at http://www.accessdata.fda.gov/drugsatfda_docs/label/2008/020357s031,021202s016lbl.pdf*).

A schematic of the mechanism of action of metformin is shown in Figure 3.

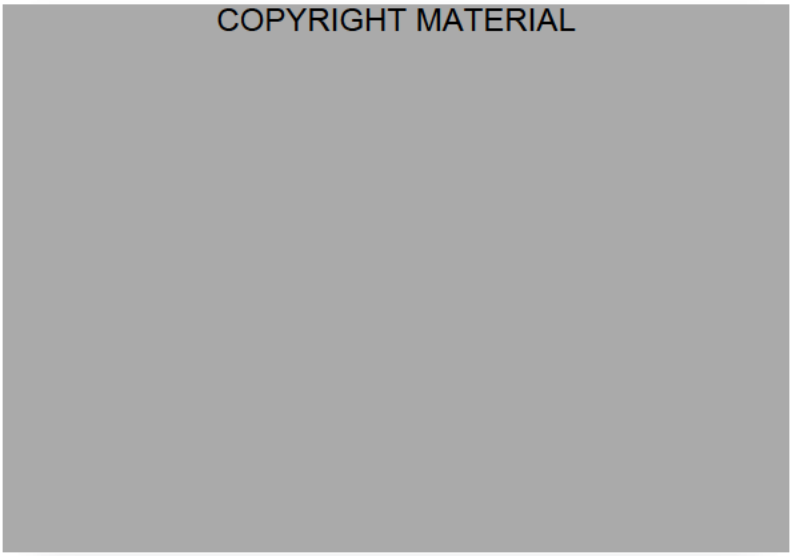


Figure 3: Metformin mechanism of action

(Source "Pernicova, I & Korbonits, M (2014) Metformin—mode of action and clinical implications for diabetes and cancer. Nature Reviews Endocrinology. 10, 143–156)

2.1.4 What are the proposed dosages and routes of administration?

The proposed doses of Synjardy are empagliflozin/metformin combinations of 5 mg/500 mg, (b) (4) 5 mg/1000 mg, 12.5 mg/500 mg, (b) (4) and 12.5 mg/1000 mg.

The sponsor has proposed the following dosing recommendation for Synjardy:

(b) (4)

2.2 General Clinical Pharmacology

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

Empagliflozin (Jardiance):

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

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

No major metabolites of empagliflozin were detected in human plasma and the most abundant metabolites were three glucuronide conjugates (2-O, 3-O, and 6-O glucuronide). Systemic exposure of each metabolite was less than 10% of total drug related material. O-dealkylation gave rise to metabolite M380/1 (EX 609), an active metabolite of empagliflozin, which was not detected in plasma after single oral doses of 0.5 to 50 mg empagliflozin; only partial profiles were obtained at doses of 100 to 800 mg empagliflozin. At the highest dose level, the EX 609 metabolite exposure (AUC and C_{max}) was approximately 0.12% of the parent drug. The total fraction of EX 609 excreted in urine ranged from 0.02

to 0.05% of the administered empagliflozin dose. *In vitro* studies suggested that the primary route of metabolism of empagliflozin in humans is glucuronidation by the uridine 5'-diphospho-glucuronosyltransferases UGT2B7, UGT1A3, UGT1A8, and UGT1A9.

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

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

In patients with mild (eGFR: 60 to less than 90 mL/min/1.73 m^2), moderate (eGFR: 30 to less than 60 mL/min/1.73 m^2), and severe (eGFR: less than 30 mL/min/1.73 m^2) renal impairment and subjects with kidney failure/end stage renal disease (ESRD) patients, AUC of empagliflozin increased by approximately 18%, 20%, 66%, and 48%, respectively, compared to subjects with normal renal function. Peak plasma levels of empagliflozin were similar in subjects with moderate renal impairment and kidney failure/ESRD compared to patients with normal renal function. Peak plasma levels of empagliflozin were roughly 20% higher in subjects with mild and severe renal impairment as compared to subjects with normal renal function. Population pharmacokinetic analysis showed that the apparent oral clearance of empagliflozin decreased, with a decrease in eGFR leading to an increase in drug exposure. However, the fraction of empagliflozin that was excreted unchanged in urine, and urinary glucose excretion, declined with decrease in eGFR. No dose adjustment is needed in patients with an eGFR greater than or equal to 45 mL/min/1.73 m^2. Empagliflozin should not be initiated in patients with an eGFR less than 45 mL/min/1.73 m^2.

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

Metformin (Glucophage):

Metformin pharmacokinetics as described in the product monograph for Glucophage (*http://www.accessdata.fda.gov/drugsatfda_docs/label/2008/020357s031,021202s016lbl.pdf*) is shown in the highlighted box below:

Metformin improves glucose tolerance in patients with type 2 diabetes, lowering both basal and postprandial plasma glucose. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization.

The absolute bioavailability of a Glucophage 500 mg tablet given under fasting conditions is approximately 50% to 60%. Studies using single oral doses of glucophage 500 mg to 1500 mg, and 850 mg to 2550 mg, indicate that there is a lack of dose proportionality with increasing doses, which is due to decreased absorption rather than an alteration in elimination. Food decreases the extent of and slightly delays the absorption of metformin, as shown by approximately a 40% lower mean peak plasma concentration (C_{max}), a 25% lower area under the plasma concentration versus time curve (AUC), and a 35-minute prolongation of time to peak plasma concentration (T_{max}) following administration of a single 850 mg tablet of metformin with food, compared to the same tablet strength administered fasting. The clinical relevance of these decreases is unknown.

The apparent volume of distribution (V/F) of metformin following single oral doses of glucophage 850 mg averaged 654 ± 358 L. Metformin is negligibly bound to plasma proteins, in contrast to sulfonylureas, which are more than

90% protein bound. Metformin partitions into erythrocytes, most likely as a function of time. At usual clinical doses and dosing schedules of glucophage, steady state plasma concentrations of metformin are reached within 24 to 48 hours and are generally <1 µg/mL. During controlled clinical trials of glucophage, maximum metformin plasma levels did not exceed 5 µg/mL, even at maximum doses.

Intravenous single-dose studies in normal subjects demonstrate that metformin is excreted unchanged in the urine and does not undergo hepatic metabolism (no metabolites have been identified in humans) nor biliary excretion. Renal clearance (see Table 1) is approximately 3.5 times greater than creatinine clearance, which indicates that tubular secretion is the major route of metformin elimination. Following oral administration, approximately 90% of the absorbed drug is eliminated via the renal route within the first 24 hours, with a plasma elimination half-life of approximately 6.2 hours. In blood, the elimination half-life is approximately 17.6 hours, suggesting that the erythrocyte mass may be a compartment of distribution.

In the presence of normal renal function, there are no differences between single- or multiple-dose pharmacokinetics of metformin between patients with type 2 diabetes and normal subjects, nor is there any accumulation of metformin in either group at usual clinical doses. In patients with decreased renal function (based on measured creatinine clearance), the plasma and blood half-life of metformin is prolonged and the renal clearance is decreased in proportion to the decrease in creatinine clearance.

Limited data from controlled pharmacokinetic studies of glucophage in healthy elderly subjects suggest that total plasma clearance of metformin is decreased, the half-life is prolonged, and C_{max} is increased, compared to healthy young subjects. From these data, it appears that the change in metformin pharmacokinetics with aging is primarily accounted for by a change in renal function.

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

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

2.3 Intrinsic Factors

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

No dedicated study was conducted with Synjardy to evaluate the pharmacokinetics in special populations such as geriatric, hepatic impaired and renal impaired patients. The Applicant referred to information regarding special population (geriatric and renal) and drug interaction from the NDAs for Jardiance® (Empagliflozin, NDA 204629) and Glucophage® (Metformin, NDA 020357).

2.4 Extrinsic Factors

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

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

2.5 General Biopharmaceutics

The sponsor conducted a relative bioavailability study to evaluate the pharmacokinetics of empagliflozin and metformin from the FDC tablet containing 12.5 mg empagliflozin and 1000 mg metformin compared to the individual tablets administered together under fasting conditions and also evaluated the effect of a high fat meal on the pharmacokinetics of empagliflozin and metformin from the FDC tablet.

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

The study was entitled "Relative bioavailability of a 12.5 mg BI 10773 / 1000 mg metformin fixed dose combination tablet compared with its mono components and administered with and without food (an open-label, randomized, single-dose, three-way crossover, Phase I trial in healthy volunteers).
Mean concentration-time plots of empagliflozin and metformin following administration of the FDC formulation under fasting and fed conditions, and the individual components under fasting conditions are presented in Figures 4 and 9, respectively.

The relative bioavailability of empagliflozin was similar when 12.5 mg empagliflozin and 1000 mg metformin were administered as the FDC tablet compared to individual components. The geometric mean ratios (GMR) of AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} were approximately 100% and their 90% confidence intervals (CI) were 96.14 – 106.37, 95.70 – 106.15 and 90.09-110.77%, respectively (Table 5).

The relative bioavailability of metformin was similar when 12.5 mg empagliflozin and 1000 mg metformin were administered as the FDC tablet compared to individual components. The GMR of AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} were approximately 103% and their 90% confidence intervals (CI) were 93.61-114.07, 93.28-112.20 and 89.98-119.79%, respectively (Table 7).

The pharmacokinetic data demonstrate that the proposed tablet containing a fixed-dose combination of 12.5 mg empagliflozin and 1000 mg metformin is bioequivalent to the co-administered individual components under fasting conditions.

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

Co-administration of Synjardy with high-fat high-calorie diet decreased the peak systemic exposure (C_{max}) for both empagliflozin (34% decrease) and metformin (24% decrease), however, the extent of exposure (AUC) of empagliflozin and metformin was unaffected. This effect of food on relative BA is consistent with previous findings with Empagliflozin (Jardiance, NDA 20-4629), and Metformin (Glucophage, NDA 020-357). In NDA 20-4629, the sponsor reported that reduction in C_{max} of empagliflozin did not influence the amounts of glucose excreted in the urine when empagliflozin was administered in the fed state. Therefore, the observed food effect for the empagliflozin and metformin components of the FDC tablet is unlikely to be of clinical importance. However, as metformin is recommended to be given with meals, the sponsor is proposing that Synjardy be administered with food.

The results of the food effect portion of study 1276.5 on the relative bioavailability of Empagliflozin and Metformin from the FDC formulation are summarized below.

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

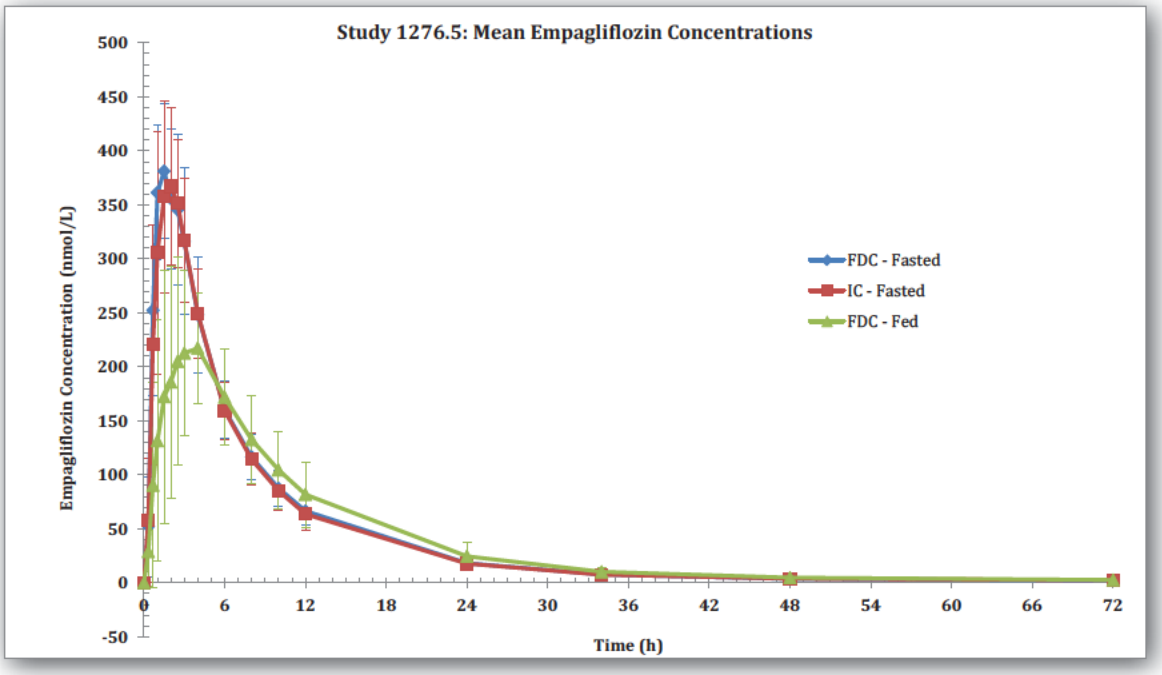


Figure 4: Mean plasma concentration time profile of empagliflozin following FDC formulation containing of 12.5 mg empagliflozin and 1000 mg metformin under fasting and fed conditions, and co-administration of individual tablets of 12.5 mg empagliflozin and 1000 mg metformin under fasting condition

Following administration of the 12.5/1000 FDC tablet, a food effect on Empagliflozin PK was observed. Based on the ratios of geometric means, there was a 36% reduction in C_{max} and a 8% and 7% reduction in both $AUC_{(0-t)}$ and $AUC_{(0-\infty)}$, respectively (Table 4). Though the 2 one-sided 90% confidence intervals for empagliflozin C_{max} were outside the standard bioequivalence boundaries of 80 to 125%, the corresponding 2 one-sided 90% confidence intervals for $AUC_{(0-t)}$ and $AUC_{(0-\infty)}$ were contained within the

standard bioequivalence boundaries of 80 to 125% (Table 5). Box-plot distribution for the pharmacokinetic parameters, C_{max}, $AUC_{(0-t)}$, $AUC_{(0-\infty)}$, and T_{max} are shown in Figures 5 - 8.

Table 4: Summary Statistics for Empagliflozin Pharmacokinetic Parameters following administration of FDC formulation containing of 12.5 mg empagliflozin and 1000 mg metformin under fasting and fed conditions, and co-administration of individual tablets of 12.5 mg empagliflozin and 1000 mg metformin under fasting condition to healthy subjects

Treatment	Empagliflozin Pharmacokinetic Parameters				
	C_{max} (ng/mL) GM [n] (CV%)	$AUC_{(0-t)}$ (ng h/mL) GM [n] (CV%)	$AUC_{(0-\infty)}$ (ng.h/mL) GM [n] (CV%)	T_{max} (h) Median [n] (Min-Max)	$t_{1/2}$ (h) Mean [n] (SD)
IC - Fasting	400 [16] (16.2)	2760 [16] (17.6)	2820 [16] (17.7)	1.75 [16] (1.00 – 2.50)	13.5 [16] (65.6)
FDC - Fasting	399 [15] (17.3)	2830 [15] (15.8)	2880 [15] (15.8)	1.50 [15] (0.667 – 2.50)	13.7 [15] (49.1)
FDC - Fed	253 [14] (22.8)	2610 [14] (14.2)	2680 [14] (14.2)	3.00 [14] (1.00 – 8.00)	15.3 [14] (47.0)

Abbreviations: GM = geometric mean; n = number of non-missing observations; CV% = coefficient of variation; SD = standard deviation

IC-Fasting: A single oral dose of one 12.5-mg empagliflozin tablet co-administered with a one 1000 mg metformin tablet in the fasting state.

FDC-Fasting: A single oral dose of FDC tablets (one 12.5-mg empagliflozin/1000 mg metformin) administered in the fasting state.

Fed: A single oral dose of FDC tablets (one 12.5-mg empagliflozin/1000 mg metformin) administered in the fed state.

(Source Report of Study 1276.5; Table 15.6.2.1 1, page 184; Table 15.6.2.1 2, page 185; Table 15.6.2.1 3, page 186)

Table 5: Bioequivalence and Food Effect Comparisons for Empagliflozin following administration of FDC formulation containing of 12.5 mg empagliflozin and 1000 mg metformin under fasting and fed conditions, and co-administration of individual tablets of 12.5 mg empagliflozin and 1000 mg metformin under fasting condition in healthy subjects

Treatment and Comparison	C_{max} (nmol/L) Least Squares Mean (n)	$AUC_{(0-t)}$ (ng.h/mL) Least Squares Mean (n)	$AUC_{(0-\infty)}$ (ng h/mL) Least Squares Mean (n)
IC - Fasting	382.2 (15)	2707 (15)	2560 (15)
FDC - Fasting	381.9 (15)	2737 (15)	2781 (15)
FDC - Fed	251.1 (15)	2584 (15)	2640 (15)
Ratio of Least Squares Means (90% CI) [intra-individual CV(%)]			
FDC-Fasting vs. IC-Fasting	99.9 (90.09, 110.77) (16.7)	101.12 (96.14 – 106.37) (8.2)	100.79 (95.70 – 106.15) (8.3)
FDC-Fed vs. FDC-Fasting	65.8 (59.29 – 72.93) (16.7)	94.38 (89.65 – 99.33) (8.2)	94.93 (90.20 – 99.99) (8.3)

n = number of non-missing observations

IC-Fasting: A single oral dose of one 12.5-mg empagliflozin tablet co-administered with a one 1000 mg metformin tablet in the fasting state.

FDC-Fasting: A single oral dose of FDC tablets (one 12.5-mg empagliflozin/1000 mg metformin) administered in the fasting state.

Fed: A single oral dose of FDC tablets (one 12.5-mg empagliflozin/1000 mg metformin) administered in the fed state.

(Source Analysis performed by reviewer using SAS v9.3)

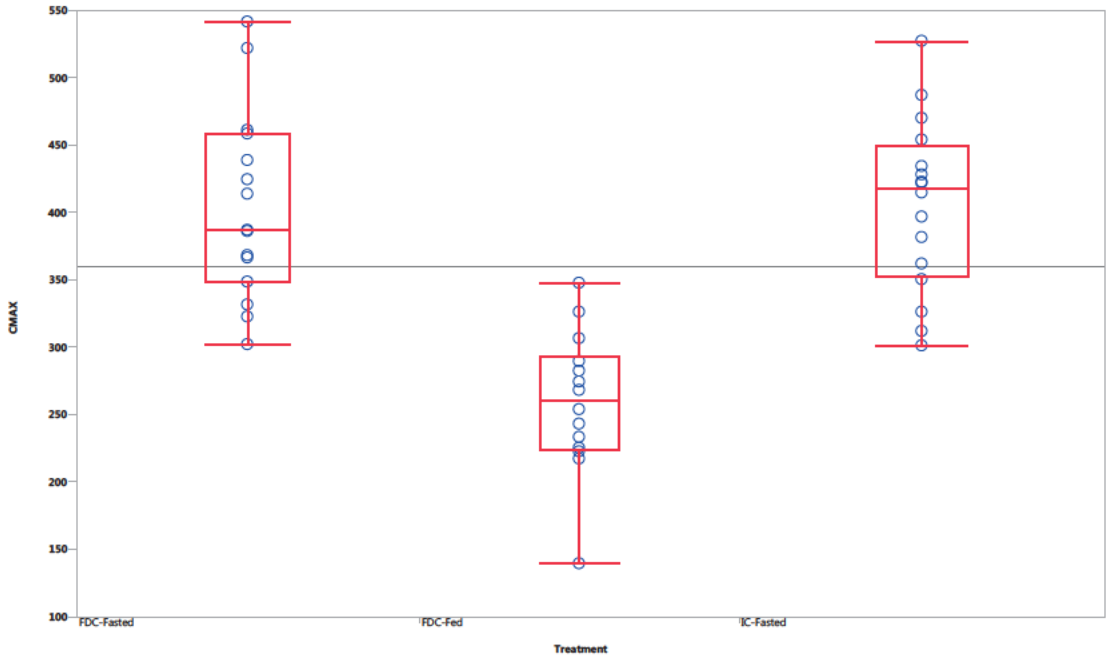


Figure 5: Boxplot of C_{max} vs. Treatment for Empagliflozin

(Source Analysis performed by reviewer using SAS JMP v11.1.1)

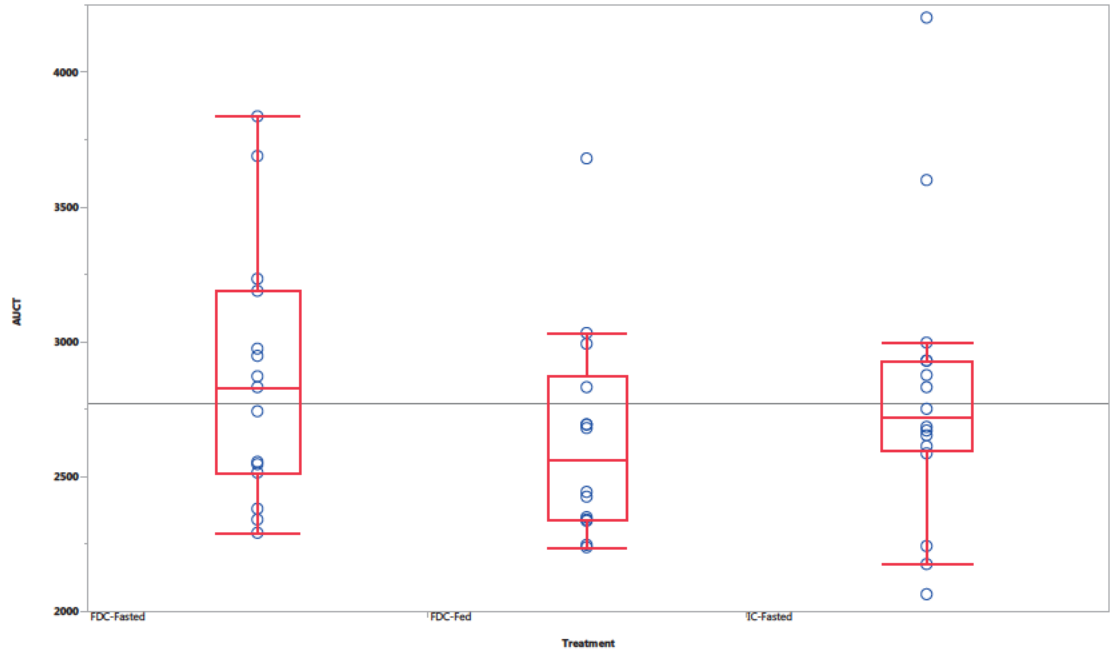


Figure 6: Boxplot of AUC_{0-t} vs. Treatment for Empagliflozin

(Source Analysis performed by reviewer using SAS JMP v11.1.1)

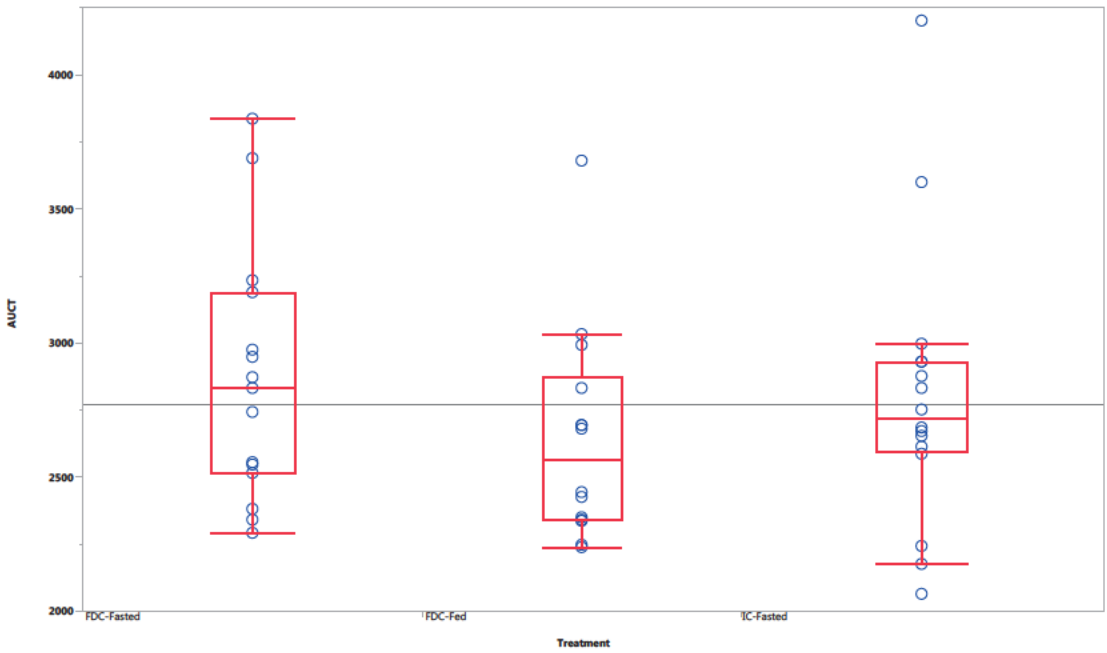


Figure 7: Boxplot of $AUC_{0-\infty}$ vs. Treatment for Empagliflozin

(Source Analysis performed by reviewer using SAS JMP v11.1.1)

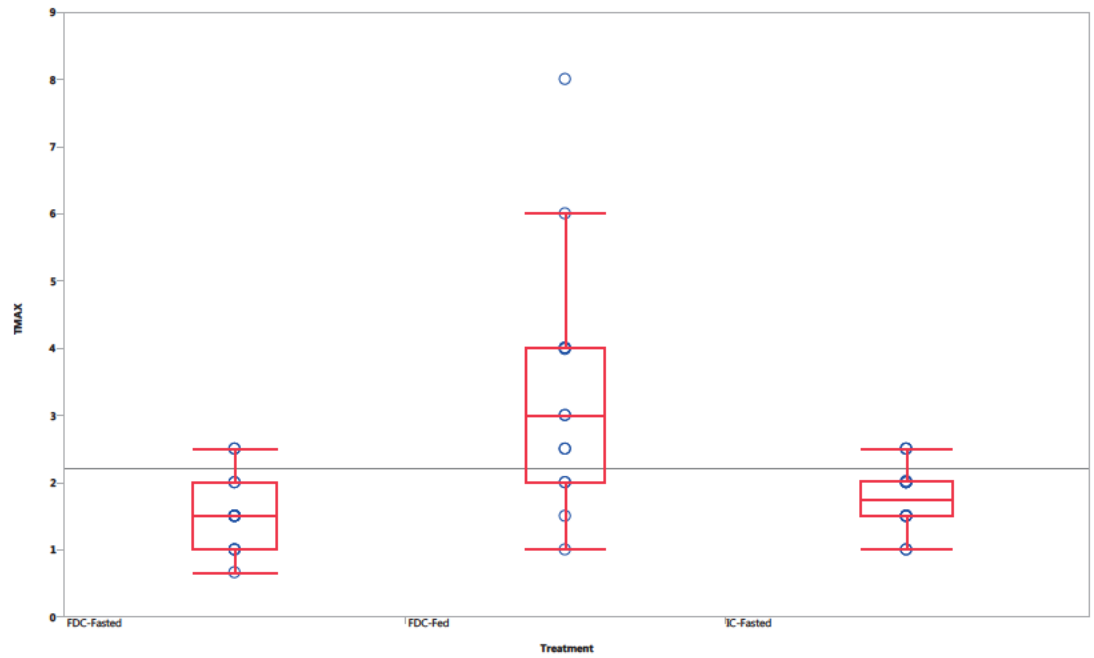


Figure 8: Boxplot of T_{max} vs. Treatment for Empagliflozin

(Source Analysis performed by reviewer using SAS JMP v11.1.1)

Metformin:

Mean concentration-time plot of metformin following administration of the FDC formulation under fasting and fed conditions is presented in Figure 9.

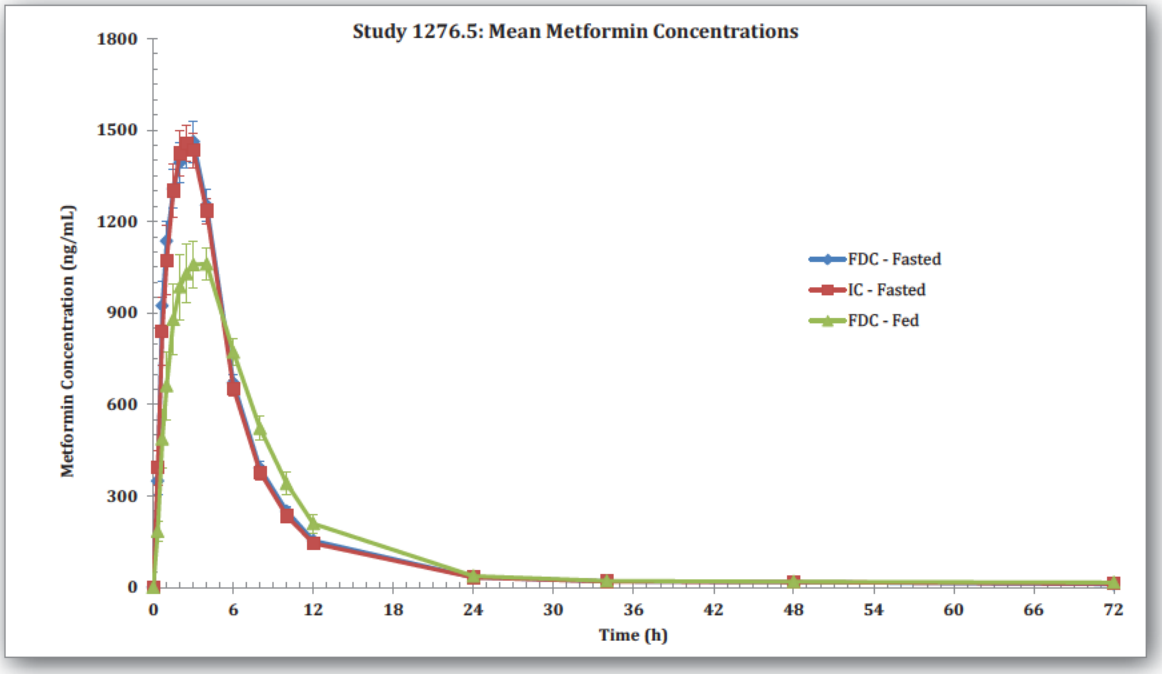


Figure 9: Mean plasma concentration time profile of metformin following FDC formulation containing of 12.5 mg empagliflozin and 1000 mg metformin under fasting and fed conditions, and co-administration of individual tablets of 12.5 mg empagliflozin and 1000 mg metformin under fasting condition

Following administration of the 12.5/1000 FDC tablet, a food effect on Metformin PK was observed. Based on the ratio of geometric means, there was a 26% reduction in C_{max} and a 3% reduction in $AUC_{(0-t)}$, while $AUC_{(0-\infty)}$ was unchanged (Table 6). The 2-one sided 90% confidence intervals for metformin C_{max} were outside the standard bioequivalence boundaries of 80 to 125%; the corresponding 2-one sided 90% confidence intervals for $AUC_{(0-t)}$ and $AUC_{(0-\infty)}$ were contained within the standard bioequivalence boundaries of 80 to 125% (Table 7). Box-plot distribution for the PK parameters, C_{max}, $AUC_{(0-t)}$, $AUC_{(0-\infty)}$, and T_{max} are shown in Figures 10 - 13.

Table 6: Summary Statistics for Metformin Pharmacokinetic Parameters following administration of FDC formulation containing of 12.5 mg empagliflozin and 1000 mg metformin under fasting and fed conditions, and co-administration of individual tablets of 12.5 mg empagliflozin and 1000 mg metformin under fasting condition to healthy subjects

Treatment	Metformin Pharmacokinetic Parameters				
	C_{max} (ng/mL) GM [n] (CV%)	$AUC_{(0-t)}$ (ng h/mL) GM [n] (CV%)	$AUC_{(0-\infty)}$ (ng.h/mL) GM [n] (CV%)	T_{max} (h) Median [n] (Min-Max)	$t_{1/2}$ (h) Mean [n] (SD)
IC - Fasting	1480 [16] (25.0)	9470 [16] (24.5)	9910 [16] (23.3)	2.50 [16] (1.50 – 4.00)	17.8 [16] (13.7)
FDC - Fasting	1520 [15] (19.8)	9740 [15] (19.2)	10100 [15] (18.5)	2.50 [15] (2.00 – 4.00)	16.6 [15] (15.7)
FDC - Fed	1120 [14] (44.5)	9330 [14] (24.6)	10100 [14] (17.1)	3.00 [14] (1.50 – 8.00)	19.4 [14] (19.6)

Abbreviations: GM = geometric mean; n = number of non-missing observations; CV% = coefficient of variation; SD = standard deviation

IC-Fasting: A single oral dose of one 12.5-mg empagliflozin tablet co-administered with a one 1000 mg metformin tablet in the fasting state.

FDC-Fasting: A single oral dose of FDC tablets (one 12.5-mg empagliflozin/1000 mg metformin) administered in the fasting state.

Fed: A single oral dose of FDC tablets (one 12.5-mg empagliflozin/1000 mg metformin) administered in the fed state.

(Source Report of Study 1276.5; Table 15.6.2.1 4, page 187; Table 15.6.2.1 5, page 188; Table 15.6.2.1 6, page 189)

Table 7: Bioequivalence and Food Effect Comparisons for Metformin following administration of FDC formulation containing of 12.5 mg empagliflozin and 1000 mg metformin under fasting and fed conditions, and co-administration of individual tablets of 12.5 mg empagliflozin and 1000 mg metformin under fasting condition in healthy subjects

Treatment and Comparison	C_{max} (nmol/L) Least Squares Mean (n)	$AUC_{(0-t)}$ (ng.h/mL) Least Squares Mean (n)	$AUC_{(0-\infty)}$ (ng h/mL) Least Squares Mean (n)
IC - Fasting	1457 (15)	9535 (15)	10230 (15)
FDC - Fasting	1513 (15)	9850 (15)	10465 (15)
FDC - Fed	1147 (15)	9579 (15)	10523 (15)
Ratio of Least Squares Means (90% CI) [intra-individual CV(%)]			
FDC-Fasting vs. IC-Fasting	103.8 (89.98, 119.79) (23.3)	103.3 (93.61 – 114.07) (16.0)	102.3 (93.28 – 112.20) (14.9)
FDC-Fed vs. FDC-Fasting	75.8 (65.67 – 87.45) (23.3)	97.3 (88.11 – 107.36) (16.0)	100.6 (91.63 – 110.33) (14.9)

n = number of non-missing observations

IC-Fasting: A single oral dose of one 12.5-mg empagliflozin tablet co-administered with a one 1000 mg metformin tablet in the fasting state.

FDC-Fasting: A single oral dose of FDC tablets (one 12.5-mg empagliflozin/1000 mg metformin) administered in the fasting state.

Fed: A single oral dose of FDC tablets (one 12.5-mg empagliflozin/1000 mg metformin) administered in the fed state.

(Source Analysis performed by reviewer using SAS v9.3)

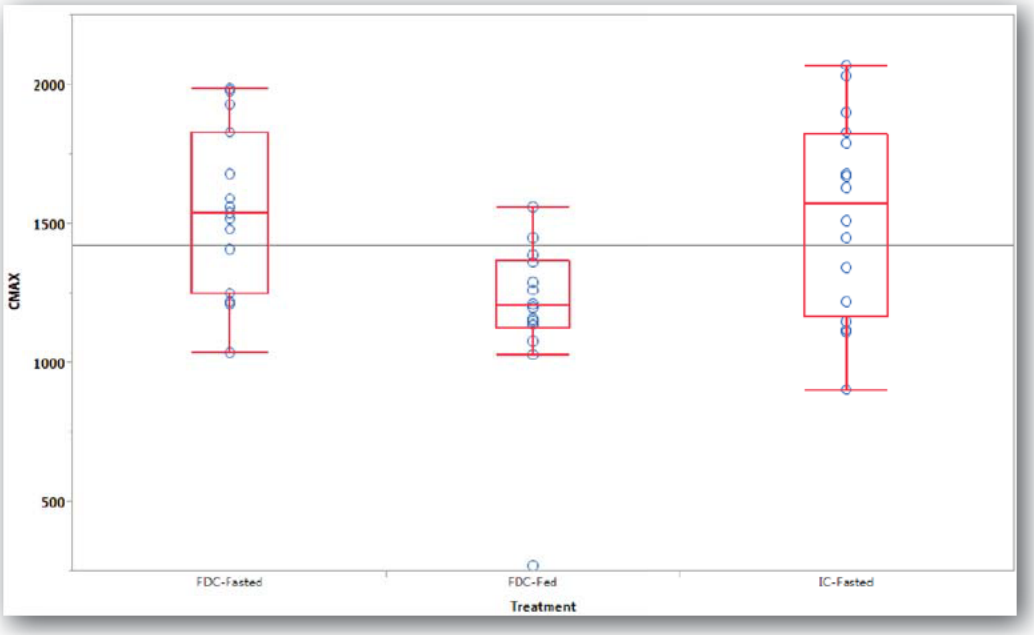


Figure 10: Boxplot of C_{max} vs. Treatment for Metformin

(Source Analysis performed by reviewer using SAS JMP v11.1.1)

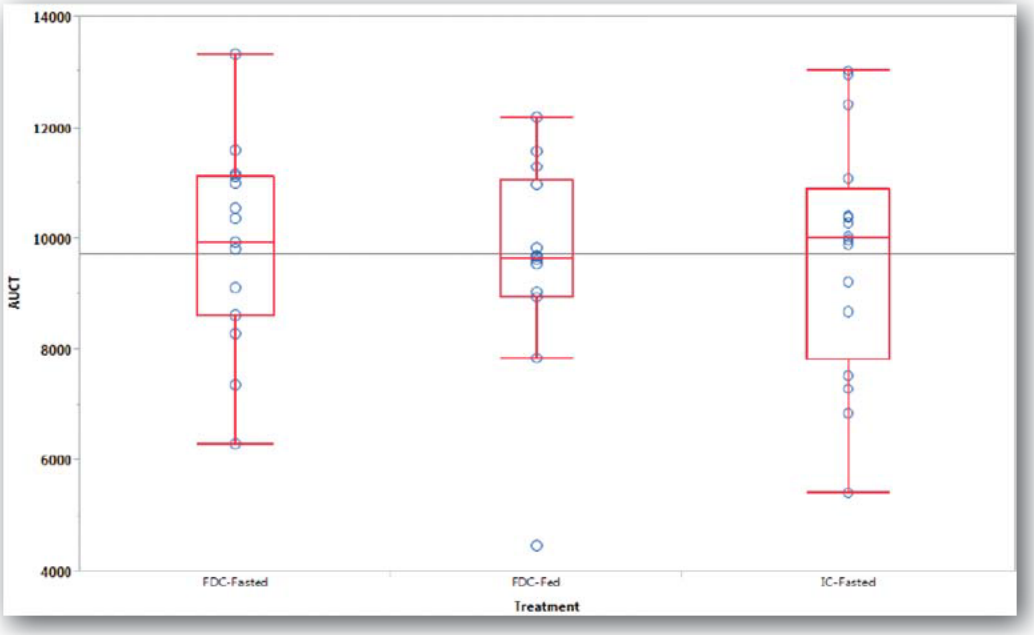


Figure 11: Boxplot of AUC_{0-t} vs. Treatment for Metformin

(Source Analysis performed by reviewer using SAS JMP v11.1.1)

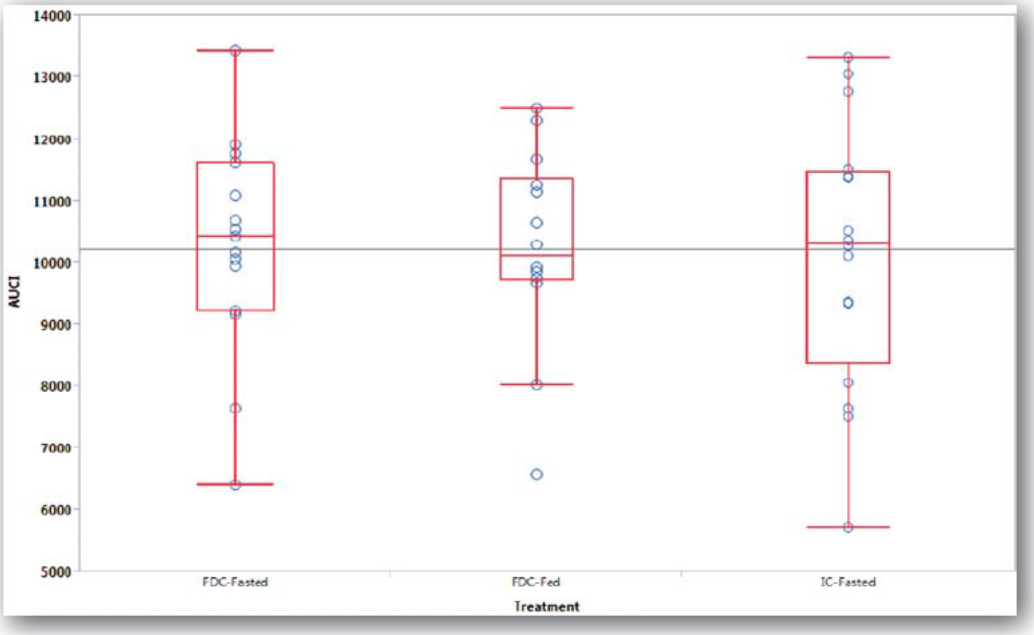


Figure 12: Boxplot of $AUC_{0-\infty}$ vs. Treatment for Metformin

(Source Analysis performed by reviewer using SAS JMP v11.1.1)

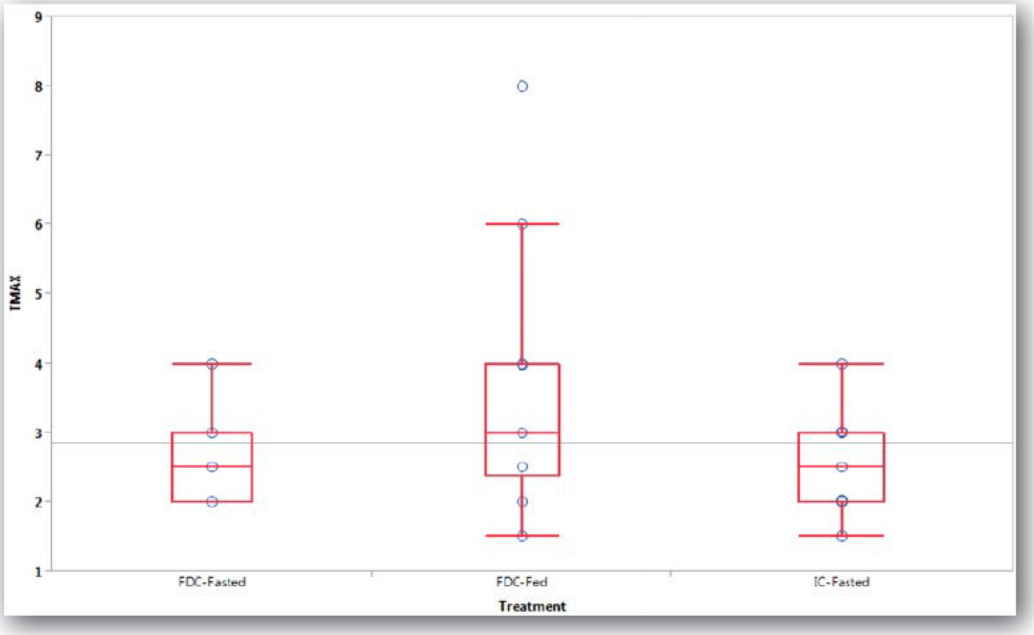


Figure 13: Boxplot of T_{max} vs. Treatment for Metformin

(Source Analysis performed by reviewer using SAS JMP v11.1.1)

2.6 Exposure Response

2.6.1 What are the characteristics of exposure-response (e.g. dose-response, concentration-response) relationship for effectiveness and safety for twice daily versus once daily empagliflozin when administered orally as add-on therapy to immediate release metformin in T2DM patients?

The objective of trial 1276.10 was to investigate the efficacy and safety of different dosage regimens of empagliflozin (twice daily versus once daily) administered orally as add-on therapy to immediate release metformin in patients with type 2 diabetes mellitus and insufficient glycemic control. The study was designed to test the non-inferiority of treatment with empagliflozin 5 mg twice daily versus treatment with empagliflozin 10 mg once daily and of treatment with empagliflozin 12.5 mg twice daily versus treatment with empagliflozin 25 mg once daily.

Empagliflozin trough concentrations were similar within each dose group on Days 28 and 112 indicating that steady-state concentrations of empagliflozin were maintained during the course of the study. The increase in empagliflozin exposure with dose was roughly proportional with an increase in dose from 5 mg twice daily to 12.5 mg twice daily and 10 mg once daily to 25 mg once daily.

The primary endpoint was the change of HbA_{1c} from baseline at Week 16. The primary analysis showed non-inferiority of each dose of twice daily (12.5 and 5 mg) empagliflozin compared to the respective empagliflozin once daily (25 and 10 mg) dose. In all treatment groups, HbA_{1c} reductions following empagliflozin treatments compared to placebo was significant (Figure 14). The adjusted mean difference in change in HbA_{1c} from baseline after 16 weeks of treatment for empagliflozin 12.5 mg twice daily vs. empagliflozin 25 mg once daily was -0.11% (95% CI: -0.26, 0.03); the adjusted mean difference in change in HbA_{1c} from baseline after 16 weeks of treatment for empagliflozin 5 mg twice daily vs. empagliflozin 10 mg once daily was -0.02 (95% CI: -0.16, 0.13) (Table 8).

The treatments were well tolerated across treatment groups, with an overall safety profile comparable between the empagliflozin treatment groups and placebo; the frequency of patients reported with urinary tract infections and genital infections was higher with empagliflozin treatment than with placebo. There were no clinically meaningful differences between the safety profiles of the once daily and twice daily administration regimes of empagliflozin.

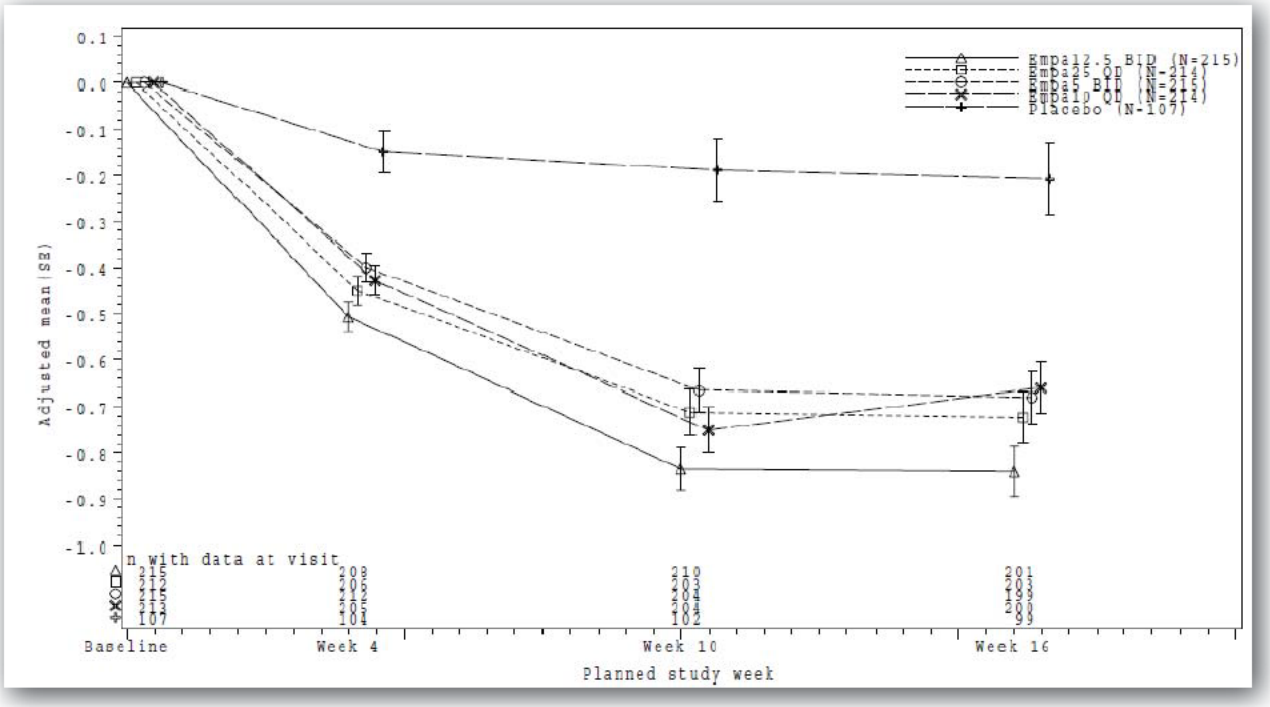


Figure 14: Adjusted mean change in HbA_{1c} (%) over time up to Week 16based on mixed-model repeated measures (MMRM) of the full analysis dataset (FAS) observed case (OC) (add-on therapy to metformin background)

(Source Study Report 1276.10 Figure 11.4.1.1.2 1 Adjusted mean change in HbA1c (%) over time up to Week 16 –MMRM FAS (OC)[1] (Page 91)

[1] Model includes treatment, eGFR (MDRD) at screening, region, visit, and visit by treatment interaction as fixed effects and baseline HbA1c as a linear covariate. Unstructured covariance matrix is used)

Table 8: Adjusted mean change in HbA1c (%) at Week 16 – FAS (LOCF) (add-on therapy to metformin background)

Visit Description Statistic	Empa12.5 BID	Empa25 QD	Empa5 BID	Empa10 QD	Placebo
Number of patients in analysis set	215	214	215	214	107
Number of analysed patients	215	214	215	213	107
Baseline mean (SE)	7.78 (0.05)	7.73 (0.05)	7.79 (0.06)	7.83 (0.05)	7.69 (0.07)
Week 16					
Values at visit					
Mean (SE)	6.94 (0.06)	7.03 (0.06)	7.12 (0.06)	7.17 (0.06)	7.50 (0.10)
Adjusted* mean (SE)	6.94 (0.05)	7.05 (0.05)	7.11 (0.05)	7.13 (0.05)	7.55 (0.07)
Change from baseline					
Mean (SE)	-0.84 (0.06)	-0.70 (0.05)	-0.67 (0.06)	-0.66 (0.06)	-0.19 (0.08)
Adjusted* mean (SE)	-0.83 (0.05)	-0.72 (0.05)	-0.66 (0.05)	-0.64 (0.05)	-0.22 (0.07)
Comparison vs Empa10 QD					
Adjusted* mean (SE)			-0.02 (0.07)		
95.0% confidence interval			(-0.16, 0.13)		
97.5% confidence interval			(-0.19, 0.15)		
p-value non-inferiority**			<0.0001		
Comparison vs Empa25 QD					
Adjusted* mean (SE)	-0.11 (0.07)				
95.0% confidence interval	(-0.26, 0.03)				
97.5% confidence interval	(-0.28, 0.05)				
p-value non-inferiority**	<0.0001				

* Model for Week 16 includes baseline HbA1c (p<0.0001) as linear covariate(s) and screening eGFR (MDRD) (p=0.2244), geographical region (p=0.8591), treatment (p<0.0001) as fixed effect(s).

** One-sided test relative to 0.35

(Source: Report of Study 1276.10; Table 15.2.1.1: 1, page 342)

As was noted with other empagliflozin applications (NDA 204629, Jardiance; NDA 206073, Glyxambi), there is lack of clear trend for dose dependent reduction in HbA_{1c} from baseline for the various dose and dosing regimen of empagliflozin (Figures 14). BID treatment, however, produced numerically greater reduction in HbA_{1c} compared to once-daily treatments for both the doses evaluated in this study. For further details on the analysis of non-inferiority of twice daily versus once daily administration, please refer to the statistical review of the findings from this study by Dr. Susie Sinks in DARRTS.

2.7 Analytical

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

Empagliflozin:

Empagliflozin in human plasma was measured using a LC-MS/MS assay. The method was validated for a range of 1.11-1110 nmol/L (0.500 – 500 ng/mL), based on the analysis of 0.150 mL of plasma. Briefly, empagliflozin is extracted from EDTA human plasma by solid phase supported liquid extraction (SLE+). (b) (4)

(b) (4)

Metformin:
Metformin is extracted (b) (4)

Detection is by MS-MS (b) (4)

A summary of key descriptive parameters for the bioanalytical assays used in clinical studies is listed in Table 9.

Table 9 Summary of key descriptive parameters for Empagliflozin and Metformin bioanalytical assays in plasma used in clinical studies

Study Number/Report Number	Study Title	Analytical Laboratory	Assay Range	LLOQ	Accuracy	Precision
Protocol 1276.5/Part: Analytical Final report – BI (b) (4) - Plasma	Quantification of Metformin in K3EDTA Human Plasma by LC-MS/MS	(b) (4)	Metformin 10.0 – 3500 ng/mL	Metformin 10 ng/mL	Metformin 96% - 104% at 30.0 – 3000 ng/mL	Metformin -4% - 4% at 30.0 – 3000 ng/mL
Protocol 1276.5 / (b) (4) Report #0016- 10251-1.01	Quantification of BI 10773 in EDTA Human Plasma by LC-MS/MS		Empagliflozin 1.11-1110 nmol/L	Empagliflozin 1.11 nmol/L	Empagliflozin 99.4% - 103.7% at 3.33 - 887 nmol/L	Empagliflozin -0.6% to 3.7% at 3.33 - 887 nmol/L

3 Labeling Comments (Preliminary)

The following are the labeling recommendations relevant to clinical pharmacology for NDA 204961. The ~~red strikeout font~~ is used to show the proposed text to be deleted and underline blue font to show text to be included or comments communicated to the sponsor.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

[redacted] *SYNJARDY*
[redacted] SYNJARDY combines 2 antihyperglycemic agents with [redacted] ~~complementary~~ mechanisms of action to improve glycemic control in patients with type 2 diabetes: empagliflozin, a sodium- glucose co-transporter 2 (SGLT2) inhibitor, and metformin, a member of the biguanide class.

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

Metformin hydrochloride
Metformin is an antihyperglycemic agent which improves glucose tolerance in patients with type 2 diabetes mellitus, lowering both basal and postprandial plasma glucose. [redacted] Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. Unlike SUs, metformin does not produce hypoglycemia in either patients with type 2 diabetes mellitus or normal subjects (except in special circumstances) [see Warnings and Precautions (5.5)] and does not cause hyperinsulinemia. With metformin therapy, insulin secretion remains unchanged while fasting insulin levels and day-long plasma insulin response may actually decrease.

12.2 Pharmacodynamics

Empagliflozin
Urinary Glucose Excretion
In patients with type 2 diabetes, urinary glucose excretion increased immediately following a dose of empagliflozin and was maintained at the end of a 4-week treatment period averaging at approximately 64 grams per day with 10 mg empagliflozin and 78 grams per day with 25 mg empagliflozin once daily [see Clinical Studies (14)].

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

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

12.3 Pharmacokinetics

[redacted] *SYNJARDY*
The results of a bioequivalence study in healthy subjects demonstrated that [redacted] SYNJARDY (empagliflozin/metformin hydrochloride) 5 mg/500 mg, [redacted] 5 mg/1000 mg, 12.5 mg/500 mg, [redacted], and 12.5 mg/1000 mg combination tablets are bioequivalent to coadministration of corresponding doses of empagliflozin and metformin as individual tablets.

Administration of 12.5 mg empagliflozin/1000 mg metformin under fed conditions resulted in a 9% decrease in AUC and a 28% decrease in C_{max} for empagliflozin, when compared to fasted conditions. For metformin, AUC decreased by 12% and C_{max} decreased by 26% compared to fasting conditions. The observed effect of food on empagliflozin and metformin is not considered to be clinically relevant. [redacted]

Empagliflozin

Absorption

The pharmacokinetics of empagliflozin has been characterized in healthy volunteers and patients with type 2 diabetes and no clinically relevant differences were noted between the two populations. After oral administration, peak plasma concentrations of empagliflozin were reached at 1.5 hours post-dose. Thereafter, plasma concentrations declined in a biphasic manner with a rapid distribution phase and a relatively slow terminal phase. The steady state mean plasma AUC and C_{max} were 1870 nmol•h/L and 259 nmol/L, respectively, with 10 mg empagliflozin once daily treatment, and 4740 nmol•h/L and 687 nmol/L, respectively, with 25 mg empagliflozin once daily treatment. Systemic exposure of empagliflozin increased in a dose-proportional manner in the therapeutic dose range. The single-dose and steady-state pharmacokinetic parameters of empagliflozin were similar, suggesting linear pharmacokinetics with respect to time.

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

Distribution

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

Metabolism

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

Elimination

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

Metformin hydrochloride

Absorption

The absolute bioavailability of a metformin hydrochloride 500-mg tablet given under fasting conditions is approximately 50% to 60%. Studies using single oral doses of metformin tablets 500 mg to 1500 mg, and 850 mg to 2550 mg, indicate that there is a lack of dose proportionality with increasing doses, which is due to decreased absorption rather than an alteration in elimination.

Food decreases the extent of and slightly delays the absorption of metformin, as shown by approximately a 40% lower C_{max}, a 25% lower AUC, and a 35 minute prolongation of time to peak plasma concentration (T_{max}) following administration of a single 850 mg tablet of metformin with food, compared to the same tablet strength administered fasting. The clinical relevance of these decreases is unknown.

Distribution

The apparent volume of distribution (V/F) of metformin following single oral doses of immediate-release metformin hydrochloride tablets 850 mg averaged 654±358 L. Metformin is negligibly bound to plasma proteins, in contrast to SUs, which are more than 90% protein bound. Metformin partitions into erythrocytes, most likely as a function of time. At usual clinical doses and dosing schedules of metformin tablets, steady-state plasma concentrations of

metformin are reached within 24 to 48 hours and are generally <1 mcg/mL. During controlled clinical trials of metformin, maximum metformin plasma levels did not exceed 5 mcg/mL, even at maximum doses.

Metabolism
Intravenous single-dose studies in normal subjects demonstrate that metformin is excreted unchanged in the urine and does not undergo hepatic metabolism (no metabolites have been identified in humans) nor biliary excretion.

(b) (4)
Renal clearance is approximately 3.5 times greater than creatinine clearance, which indicates that tubular secretion is the major route of metformin elimination. Following oral administration, approximately 90% of the absorbed drug is eliminated via the renal route within the first 24 hours, with a plasma elimination half-life of approximately 6.2 hours. In blood, the elimination half-life is approximately 17.6 hours, suggesting that the erythrocyte mass may be a compartment of distribution.

Specific Populations
Renal Impairment
(b) (4) *SYNJARDY*: Studies characterizing the pharmacokinetics of empagliflozin and metformin after administration of (b) (4) in renally impaired patients have not been performed. Since metformin is contraindicated in patients with renal impairment, use of (b) (4)-SYNJARDY is also contraindicated in patients with renal impairment (e.g., (b) (4)) [see Contraindications (4) and Warnings and Precautions (5.3)].

Empagliflozin: In patients with mild (eGFR: 60 to less than 90 mL/min/1.73 m2), moderate (eGFR: 30 to less than 60 mL/min/1.73 m^2), and severe (eGFR: less than 30 mL/min/1.73 m^2) renal impairment and subjects with kidney failure/end stage renal disease (ESRD) patients, AUC of empagliflozin increased by approximately 18%, 20%, 66%, and 48%, respectively, compared to subjects with normal renal function. Peak plasma levels of empagliflozin were similar in subjects with moderate renal impairment and kidney failure/ESRD compared to patients with normal renal function. Peak plasma levels of empagliflozin were roughly 20% higher in subjects with mild and severe renal impairment as compared to subjects with normal renal function. Population pharmacokinetic analysis showed that the apparent oral clearance of empagliflozin decreased with a decrease in eGFR leading to an increase in drug exposure. However, the fraction of empagliflozin that was excreted unchanged in urine, and urinary glucose excretion, declined with decrease in eGFR.

Metformin hydrochloride: In patients with decreased renal function (based on measured creatinine clearance), the plasma and blood half-life of metformin is prolonged and the renal clearance is decreased in proportion to the decrease in creatinine clearance [see Contraindications (4) and Warnings and Precautions (5.3)].

Hepatic Impairment
(b) (4)-*SYNJARDY*: Studies characterizing the pharmacokinetics of empagliflozin and metformin after administration of T-(b) (4)-SYNJARDY in hepatically impaired patients have not been performed. However, use of metformin alone in patients with hepatic impairment has been associated with some cases of lactic acidosis. Therefore, use of (b) (4)-SYNJARDY is not recommended in patients with hepatic impairment [see Warnings and Precautions (5.4)].

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

Metformin hydrochloride: No pharmacokinetic studies of metformin have been conducted in patients with hepatic impairment.

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

Metformin hydrochloride: Metformin pharmacokinetic parameters did not differ significantly between normal subjects and patients with type 2 diabetes mellitus when analyzed according to gender. Similarly, in controlled clinical studies in patients with type 2 diabetes mellitus, the antihyperglycemic effect of metformin was comparable in males and females.

No studies of metformin pharmacokinetic parameters according to race have been performed. In controlled clinical studies of metformin in patients with type 2 diabetes mellitus, the antihyperglycemic effect was comparable in Caucasians (n=249), Blacks (n=51), and Hispanics (n=24).

Geriatric

(b) (4) *SYNJARDY*: Studies charactering the pharmacokinetics of empagliflozin and metformin after administration of (b) (4)-SYNJARDY in geriatric patients have not been performed [see Warnings and Precautions (5.1), (5.3) and Use in Specific Populations (8.5)

Empagliflozin: Age did not have a clinically meaningful impact on the pharmacokinetics of empagliflozin based on a population pharmacokinetic analysis [see Use in Specific Populations (8.5)].

Metformin hydrochloride: Limited data from controlled pharmacokinetic studies of metformin in healthy elderly subjects suggest that total plasma clearance of metformin is decreased, the half-life is prolonged, and C_{max} is increased, compared with healthy young subjects. From these data, it appears that the change in metformin pharmacokinetics with aging is primarily accounted for by a change in renal function.

Pediatric

Studies characterizing the pharmacokinetics of empagliflozin or metformin after administration of (b) (4) SYNJARDY in pediatric patients have not been performed.

Drug Interactions

Pharmacokinetic drug interaction studies with (b) (4)-SYNJARDY have not been performed; however, such studies have been conducted with the individual components empagliflozin and metformin.

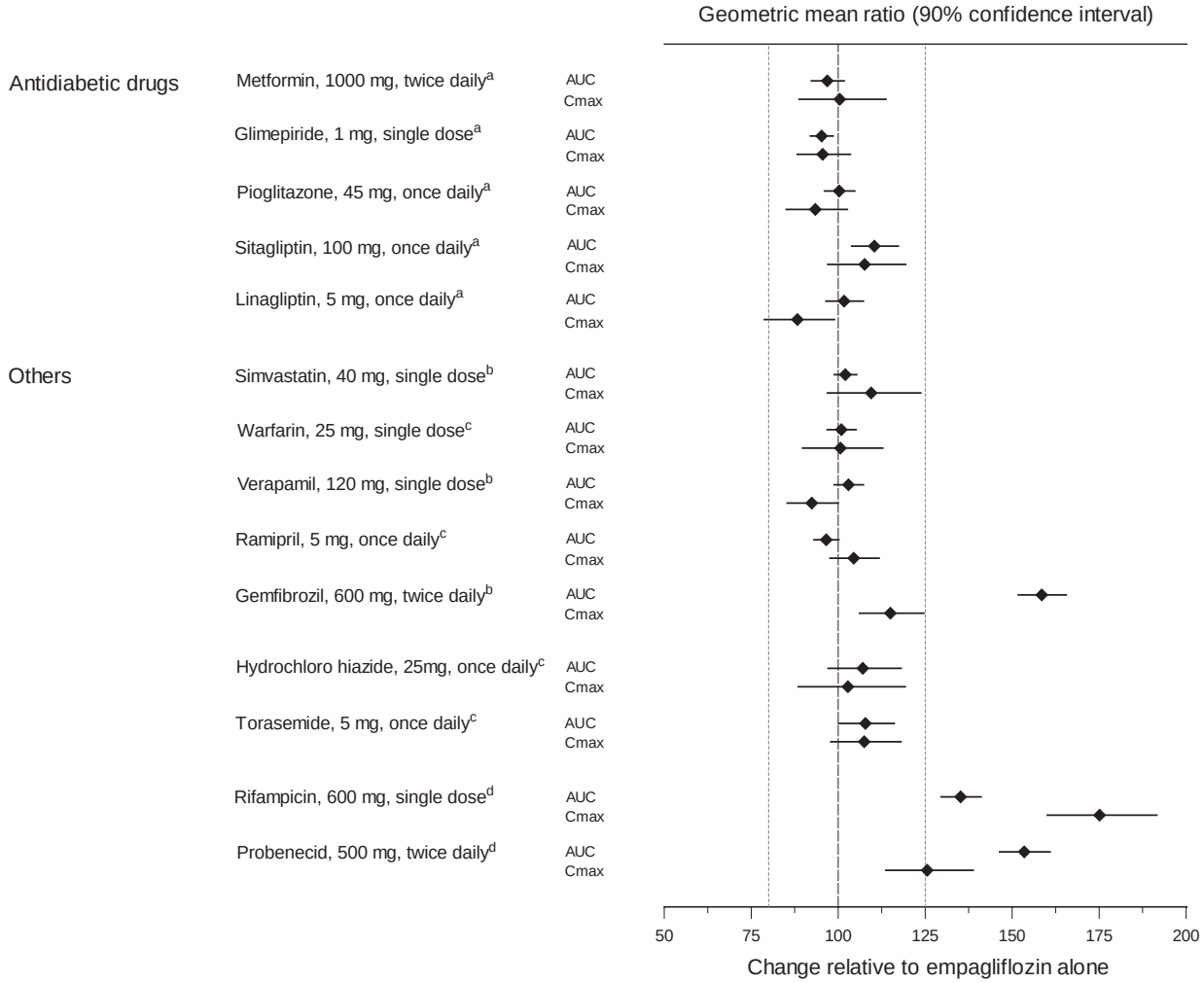
Empagliflozin

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

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

In vivo Assessment of Drug Interactions: No dose adjustment of empagliflozin is recommended when coadministered with commonly prescribed medicinal products based on results of the described pharmacokinetic studies. Empagliflozin pharmacokinetics were similar with and without coadministration of metformin, glimepiride, pioglitazone, sitagliptin, linagliptin, warfarin, verapamil, ramipril, simvastatin, hydrochlorothiazide, and torasemide in healthy volunteers (see Figure 1). The observed increases in overall exposure (AUC) of empagliflozin following co-administration with gemfibrozil, rifampicin, or probenecid are not clinically relevant. In subjects with normal renal function, coadministration of empagliflozin with probenecid resulted in a 30% decrease in the fraction of empagliflozin excreted in urine without any effect on 24-hour urinary glucose excretion. The relevance of this observation to patients with renal impairment is unknown.

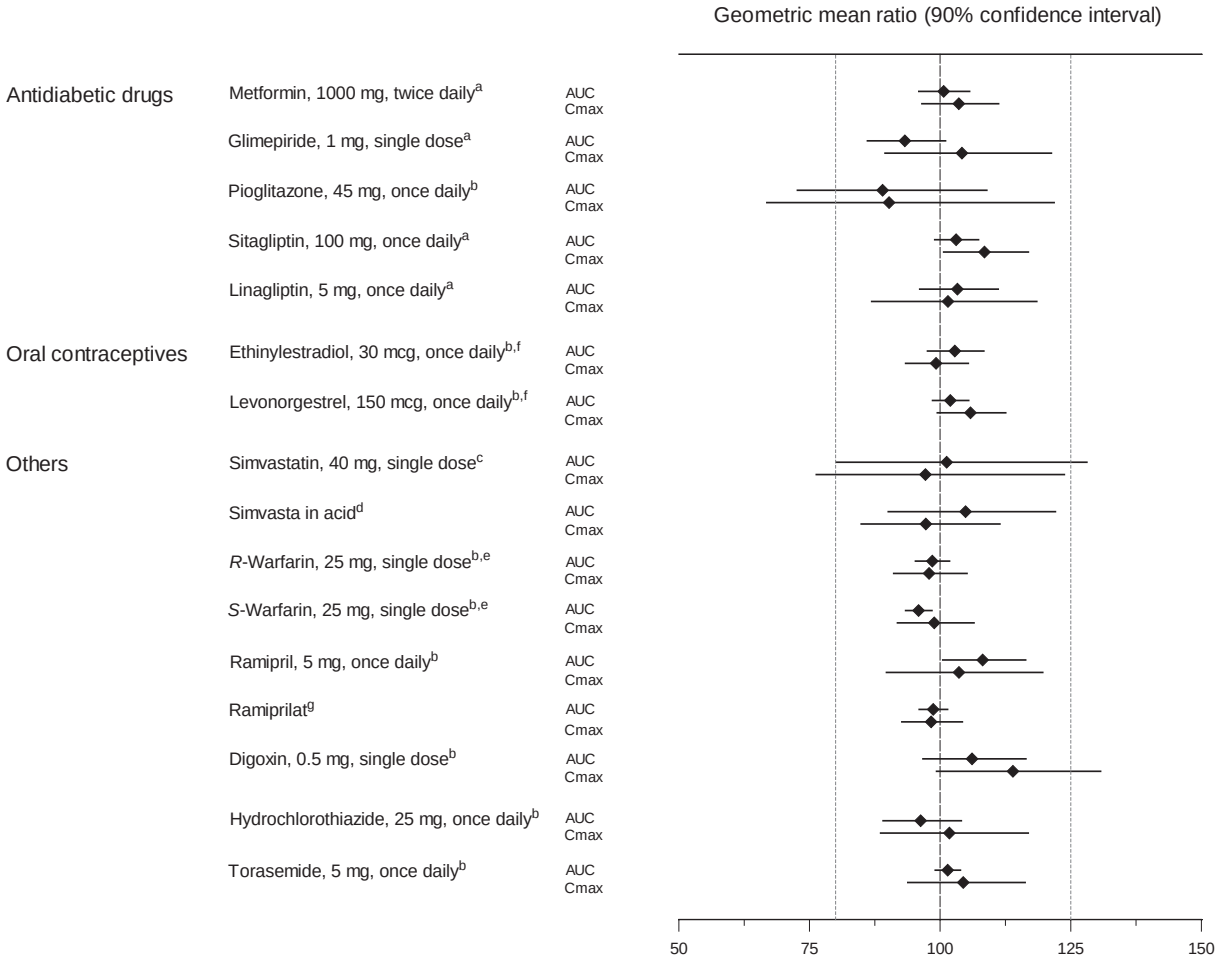
Figure 1Effect of Various Medications on the Pharmacokinetics of Empagliflozin as Displayed as 90% Confidence Interval of Geometric Mean AUC and C_{max} Ratios [reference lines indicate 100% (80% - 125%)]



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

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

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



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

Metformin hydrochloride

Table 5 Effect of Coadministered Drug on Plasma Metformin Systemic Exposure

Coadministered Drug	Dosing of Coadministered Drug*	Dose of Metformin*	Geometric Mean Ratio (ratio with/without coadministered drug) No effect=1.0		
				AUC†	C_{max}
No dosing adjustments required for the following coadministered drugs:					
Furosemide	40 mg	850 mg	metformin	1.09‡	1.22‡
Nifedipine	10 mg	850 mg	metformin	1.16	1.21
Propranolol	40 mg	850 mg	metformin	0.90	0.94
Ibuprofen	400 mg	850 mg	metformin	1.05‡	1.07‡
Cationic drugs eliminated by renal tubular secretion may reduce metformin elimination: use with caution *[see Warnings and Precautions (5.3) and Drug Interactions (7.1)]*.					
Cimetidine	400 mg	850 mg	metformin	1.40	1.61
Carbonic anhydrase inhibitors may cause metabolic acidosis: use with caution *[see Warnings and Precautions (5.1) and Drug Interactions (7.1)]*.					

Topiramate**	100 mg	500 mg	metformin	1.25	1.17

* All metformin and coadministered drugs were given as single doses
† AUC = AUC(INF)
‡ Ratio of arithmetic means
**At steady state with topiramate 100 mg every 12 hours and metformin 500 mg every 12 hours; AUC = AUC0-12h

Table 6 Effect of Metformin on Coadministered Drug Systemic Exposure

Coadministered Drug	**Dosing of Coadministered Drug***	**Dose of Metformin***	**Geometric Mean Ratio (ratio with/without metformin) No effect=1.0**		
				AUC†	C_{max}
No dosing adjustments required for the following coadministered drugs:					
Glyburide	5 mg	500 mg§	glyburide	0.78‡	0.63‡
Furosemide	40 mg	850 mg	furosemide	0.87‡	0.69‡
Nifedipine	10 mg	850 mg	nifedipine	1.10§	1.08
Propranolol	40 mg	850 mg	propranolol	1.01§	0.94
Ibuprofen	400 mg	850 mg	ibuprofen	0.97¶	1.01¶

* All metformin and coadministered drugs were given as single doses
† AUC = AUC(INF) unless otherwise noted
‡ Ratio of arithmetic means, p-value of difference <0.05
§ AUC(0-24 hr) reported
¶ Ratio of arithmetic means

4 APPENDIX

OCP Filing Memo

12 Pages have been withheld in full as repeat pages of September 15, 2014 Other Review immediately following this page

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

/s/

SURYANARAYANA M SISTA
04/15/2015

MANOJ KHURANA
04/15/2015

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information about the Submission

	Information		Information
NDA/BLA Number	206111	Brand Name (Proposed)	SYNJARDY
OCP Division (I, II, III, IV, V)	II	Generic Name	Empagliflozin + Metformin IR FDC
Medical Division	DMEP	Drug Class	SGLT-2 inhibitor and biguanide combination product
OCP Reviewer	Suryanarayana Sista, Ph.D.	Indication(s)	Treatment of Type 2 diabetes
OCP Team Leader	Lokesh Jain, Ph.D.	Dosage Form	oral tablet
Pharmacometrics Reviewer		Dosing Regimen	see below[a]
Date of Submission	08/04/2014	Route of Administration	oral
Estimated Due Date of OCP Review	04/04/2015	Sponsor	Boehringer Ingelheim Pharmaceuticals, Inc.
Medical Division Due Date		Priority Classification	505 (b)(2) Standard
PDUFA Due Date	06/04/2015		

[a] Labeling proposed by the sponsor:

(b) (4)

[redacted]

Clinical Pharmacology and Biopharmaceutics Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Study Nos./Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X	42 (4new studies; 38 studies were previously submitted to other NDAs, see list below)	4	1276.5, 1276.6, (b) (4) 1276.8
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X	10		1000-071216-1, u12-3090-01, u12-3444-02, u12-3445-01, 1813_070, 1813_071, u12-3414-01, u12-3415-01, DM-07-1032, DM-07-1033
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Human Biomaterials:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I)				
Healthy Volunteers-				

Clinical Pharmacology and Biopharmaceutics Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Study Nos./Critical Comments If any
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
in-vivo effects on primary drug:				
in-vivo effects of primary drug:				
in-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 1:				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	**X**	**1**		1276.5
Bioequivalence studies -				
traditional design; single / multi dose:	**X**	**3**		1276.6, (b) (4), 1276.8
replicate design; single / multi dose:				
Food-drug interaction studies		**2[a]**		1276.5, 1276.8
Bio-waiver request based on BCS				Not Applicable
BCS class				Not Applicable
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan	**X**			A proposed PSP requests waiver of requirements under CFR 314.55 for patients 0 to less than 10 years and a deferral for patients 10 to less than 18 years
Literature References	**X**	**16**		
Total Number of Studies		**4**		

[a]These studies have been counted earlier under alternate formulation as reference and traditional design; single / multi dose

List of Studies referenced in this NDA from previous NDAs:

No.	Study No.	Referenced NDA	Objective
1	1245.79	Empagliflozin (Jardiance)- NDA 204629	To investigate the effect of food on the bioavailability of empagliflozin and to assess the dose proportionality of empagliflozin 10 mg and 25 mg (tablets) under fasting conditions
2	1218.57	Linagliptin + Metformin IR (Jentadueto) – NDA 201281	To establish the bioequivalence of Bristol-Myers Squibb (BMS) Glucophage® tablets (reference treatment R) and Merck Glucophage® (test treatment T) tablets in the strengths of 1000 mg and 500 mg
3	1275.3	Empagliflozin + Linagliptin – NDA 206073	a. To determine the relative bioavailability of 2 formulations of empagliflozin 25mg / linagliptin 5 mg fixed dose combination (FDC) tablets ('FDC A1' and 'FDC A3') compared with the co-administered individual tablets b. To assess the effect of food on the relative bioavailability of the FDC A1 tablet
4	1276.9	Empagliflozin (Jardiance)- NDA 204629	To investigate the influence of different dosage regimens on the steady state pharmacokinetics and pharmacodynamics of empagliflozin administered orally
5	1245.1	Empagliflozin (Jardiance)- NDA 204629	To investigate the safety, tolerability, pharmacokinetics and pharmacodynamics of empagliflozin
6	1245.8	Empagliflozin (Jardiance)- NDA 204629	To determine the pharmacokinetics and total radioactivity of empagliflozin, including excretion mass balance, excretion pathways, and metabolism after oral administration of a [^{14}C] empagliflozin solution
7	1245.2	Empagliflozin (Jardiance)- NDA 204629	To investigate the safety, tolerability, pharmacokinetics, and pharmacodynamics of empagliflozin after multiple doses
8	1245.12	Empagliflozin (Jardiance)- NDA 204629	To assess the effect of kidney function in patients with type 2 diabetes on pharmacokinetics, pharmacodynamics and safety of empagliflozin
9	1245.13	Empagliflozin (Jardiance)- NDA 204629	To assess the effect of liver function in patients with type 2 diabetes on the pharmacokinetics, pharmacodynamics, safety, and tolerability of empagliflozin
10	1245.6	Empagliflozin (Jardiance)- NDA 204629	To investigate a possible drug-drug interaction between empagliflozin and metformin after co-administration as multiple oral doses
11	1245.7	Empagliflozin (Jardiance)- NDA 204629	To investigate a possible drug-drug interaction between empagliflozin and glimepiride after co-administration as multiple oral doses
12	1245.17	Empagliflozin (Jardiance)- NDA 204629	To investigate a possible drug-drug interaction between empagliflozin and pioglitazone when co-administered as multiple oral doses
13	1245.18	Empagliflozin (Jardiance)- NDA 204629	To investigate a possible drug-drug interaction between empagliflozin and warfarin when co-administered
14	1245.27	Empagliflozin (Jardiance)- NDA 204629	To investigate a possible drug-drug interaction between empagliflozin and sitagliptin when co-administered as multiple oral doses
15	1245.30	Empagliflozin (Jardiance)- NDA 204629	To investigate a possible drug-drug interaction between empagliflozin and linagliptin when co-administered as multiple oral doses
16	1245.40	Empagliflozin (Jardiance)- NDA 204629	To evaluate the effect of multiple doses of empagliflozin on the single dose pharmacokinetics of digoxin (model P-gp substrate)
17	1245.41	Empagliflozin (Jardiance)- NDA 204629	To investigate the possible effect of multiple oral doses of empagliflozin on the steady state pharmacokinetics of ethinylestradiol and levonorgestrel (Microgynon®)
18	1245.42	Empagliflozin (Jardiance)- NDA 204629	a. The effect of empagliflozin, given alone and with hydrochlorothiazide (HCT) or torasemide (TOR) on electrolytes, water balance, activation of the renin-angiotensin-aldosterone system, acid-base balance, glucose metabolism, bone metabolism, and body weight b. The effect of empagliflozin on micturition frequency and muscle sympathetic nerve activity
19	1245.43	Empagliflozin (Jardiance)- NDA 204629	To investigate a possible drug-drug interaction between empagliflozin and the model P-gp inhibitor verapamil when co-administered as single oral dose
20	1245.45	Empagliflozin (Jardiance)- NDA 204629	To investigate a possible drug-drug interaction between empagliflozin and ramipril when co-administered as multiple oral doses
21	1245.50	Empagliflozin (Jardiance)- NDA 204629	To investigate the effect of different doses of empagliflozin on the bioavailability of pioglitazone after multiple oral doses of both drugs
22	1245.58	Empagliflozin (Jardiance)- NDA 204629	To investigate a possible drug-drug interaction between empagliflozin and gemfibrozil when co-administered
23	1245.63	Empagliflozin (Jardiance)- NDA 204629	To investigate a possible drug-drug interaction between empagliflozin and simvastatin
24	1245.83	Empagliflozin (Jardiance)- NDA 204629	To investigate a possible drug-drug interaction between single dose of empagliflozin and single dose of rifampicin and multiple doses of probenecid

No.	Study No.	Referenced NDA	Objective
25	1245.16	Empagliflozin (Jardiance)- NDA 204629	To demonstrate that empagliflozin does not prolong the QT_c interval compared with placebo
26	1245.4	Empagliflozin (Jardiance)- NDA 204629	To investigate safety, tolerability, pharmacokinetics and pharmacodynamics of empagliflozin for 28 days
27	1276.10	Empagliflozin (Jardiance)- NDA 204629	To investigate the efficacy and safety of several empagliflozin doses (twice daily vs. once daily); to test non-inferiority of empagliflozin 5 mg bid vs. 10 mg qd and of empagliflozin 12.5 mg bid vs. 25 mg qd, as add-on therapy to metformin in patients with type 2 diabetes and insufficient glycemic control. Superiority of all 4 empagliflozin doses vs. placebo was also tested.
28	1245.10	Empagliflozin (Jardiance)- NDA 204629	To evaluate the efficacy, safety, and pharmacokinetics of 5 different doses of empagliflozin in patients with type 2 diabetes, insufficient glycemic control, and metformin background medication
29	1245.19	Empagliflozin (Jardiance)- NDA 204629	To investigate the efficacy, safety, and tolerability of empagliflozin given for 24 weeks as add-on therapy to pioglitazone alone or pioglitazone in combination with metformin in patients with type 2 diabetes with insufficient glycemic control
30	1245.23	Empagliflozin (Jardiance)- NDA 204629	A. Metformin background therapy To investigate the efficacy, safety, and tolerability of empagliflozin compared with placebo given for 24 weeks as add-on therapy with metformin in patients with type 2 diabetes with insufficient glycemic control Open-label arm: to assess the efficacy and safety of empagliflozin in patients with type 2 diabetes and very poor glycemic control open-label (HbA1c >10%) B. Metformin + sulphonylurea background therapy To investigate the efficacy, safety, and tolerability of empagliflozin compared with placebo given for 24 weeks as add-on therapy with metformin plus sulphonylurea in patients with type 2 diabetes with insufficient glycemic control Open-label arm: to assess the efficacy and safety of empagliflozin in patients with type 2 diabetes and very poor glycemic control (HbA1c >10%)
31	1245.31	Empagliflozin (Jardiance)- NDA 204629	Extension study to investigate the long-term safety and tolerability and the long-term efficacy of empagliflozin in patients with type 2 diabetes compared with placebo on a background of pioglitazone (study $1245.19_{(pio±met)}$), with placebo on a metformin background (study $1245.23_{(met)}$) and with placebo met+SU background (study $1245.23_{(met+SU)}$)
32	1245.33	Empagliflozin (Jardiance)- NDA 204629	To investigate the safety, efficacy, tolerability, and pharmacokinetics of empagliflozin given for 78 weeks in combination with background basal insulin therapy
33	1245.36	Empagliflozin (Jardiance)- NDA 204629	To investigate the efficacy, safety and tolerability of empagliflozin as add-on to preexisting antidiabetic therapy compared with placebo in patients with type 2 diabetes, insufficient glycemic controlled, and different degrees of renal impairment over 52 weeks
34	1245.48	Empagliflozin (Jardiance)- NDA 204629	To investigate the efficacy, safety and tolerability of empagliflozin compared with placebo in patients with type 2 diabetes and hypertension over 12 weeks
35	1245.49	Empagliflozin (Jardiance)- NDA 204629	To investigate the safety and efficacy of empagliflozin (10 mg and 25 mg once daily) compared with placebo, added to MDI insulin± metformin in patients with type 2 diabetes and insufficient glycemic control
36	1275.1	Empagliflozin + Linagliptin – NDA 206073	To investigate the efficacy, safety, and tolerability of the FDCs empagliflozin 25 mg/linagliptin 5 mg and empagliflozin 10 mg/ linagliptin 5 mg compared with the individual components (empagliflozin 25 mg or 10 mg, and linagliptin 5 mg) given once daily for 52 weeks in metformin-treated patients with type 2 diabetes and insufficient glycemic control.
37	1245.28	Empagliflozin (Jardiance)- NDA 204629	To investigate the efficacy, safety and tolerability of empagliflozin compared with glimepiride administered over 52 and 104 weeks as add-on therapy to immediate release metformin with a 104-week extension period in patients with type 2 diabetes and insufficient glycemic control despite treatment with metformin
38	1245.24	Empagliflozin (Jardiance)- NDA 204629	To investigate the safety of empagliflozin during open-label long-term treatment and the efficacy of empagliflozin as monotherapy and as add-on therapy to metformin

Brief summary about the submission:

Boehringer Ingelheim Pharmaceuticals, Inc. are seeking US marketing approval for empagliflozin/metformin hydrochloride fixed dose combination (FDC) tablets (Proposed Trade Name: Synjardy) under the provisions of Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act. The proposed indication of Synjardy tablets is "an ove ntrol in adults with type 2 diabetes mellitus [redacted] (b) (4) .

This NDA is supported by data from four biopharmaceutic studies (1 relative bioavailability/food-effect study, and 3 pivotal fed bioequivalence studies):

Type of Study / Study Identifier Location of Study Report (eCTD)	Objective(s) of the Study	Study Design
Phase I Relative Bioavailability Study *Study 1276.5* *Module 5.3.1.2*	1. To determine the relative bioavailability of empagliflozin 12.5 mg/metformin 1000 mg FDC tablets compared with the co-administered individual tablets 2. To assess the effect of food on the relative bioavailability of the FDC tablet	Randomized, open-label, single dose, 3-way cross-over design • Treatment A: FDC empagliflozin 12.5 mg/ metformin 1000 mg, fasted • Treatment B: empagliflozin 12.5 mg and metformin 1000 mg, co-administered, fasted • Treatment C: FDC, after a high-fat, high-caloric meal All treatments: tablets, oral, single dose
Phase I Bioequivalence Study *Study 1276.6* *Module 5.3.1.2*	To establish the bioequivalence of an FDC tablet of empagliflozin 12.5 mg/ metformin 500 mg (T1) and the co-administered tablets (R1); to establish the bioequivalence of an FDC tablet of empagliflozin 5 mg/ metformin 500 mg (T2) and the co-administered individual	Randomized, open-label, single dose, 4-way cross-over design • Treatment T1: FDC empagliflozin 12.5 mg/metformin 500 mg • Treatment R1: free dose combination, co-administered empagliflozin 12.5 mg and metformin 500 mg • Treatment T2: FDC empagliflozin 5 mg/metformin 500 mg • Treatment R1: co-administered empagliflozin 5 mg and metformin 500 mg All treatments: tablets, oral, after a high-fat, high caloric meal,
[redacted]		(b) (4)
Study 1276.8 *Module 5.3.1.2*	**Part I:** To establish the bioequivalence of an FDC tablet empagliflozin 12.5 mg/ metformin 1000 mg (T1) and the co-administered individual tablets (R1), either under fasted conditions or after a high-fat, high-caloric meal **Part II:** To establish the bioequivalence of an FDC tablet empagliflozin5 mg/ metformin 1000 mg (T2) and the co-administered individual tablets (R2) after a high fat, high-caloric meal	(part II) crossover design **Part I** • Treatment T1 without food: FDC empagliflozin 12.5 mg/metformin 1000 mg • Treatment T1 with food: FDC empagliflozin 12.5 mg/metformin 1000 mg • Treatment R1 without food: co-administered empagliflozin 12.5 mg and metformin 1000 mg • Treatment R1 with food: co-administered empagliflozin 12.5 mg and metformin 1000 mg **Part II** • Treatment T2 with food: FDC empagliflozin 5 mg/metformin 1000 mg • Treatment R2 with food: co-administered empagliflozin 5 mg and metformin 1000 mg All treatments: tablets, oral, single dose

U.S. Food and Drug Administration
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NDA 206111 Filing Meeting

Empagliflozin + Metformin IR (Synjardi)

Sponsor: Boehringer Ingelheim Pharmaceuticals, Inc.

Submitted: 08/04/2014

Clinical Pharmacology Review Team:

Sury Sista

Lokesh Jain (TL)

U.S. Food and Drug Administration
Protecting and Promoting Public Health
www.fda.gov

Overview

- **Type of Submission:** 505 (b)(2)
- **Proposed Indication:**
  - adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
    (b) (4)
- **Formulation:** Oral Tablets
  - 5 mg empagliflozin/500 mg metformin
  - (b) (4)
  - 5 mg empagliflozin/1000 mg metformin
  - 12.5 mg empagliflozin/500 mg metformin
  - (b) (4)
  - 12.5 mg empagliflozin/1000 mg metformin
- **Clinical Pharmacology/Biopharmaceutics Program**
  - Pivotal Studies - 4 Phase 1 (Studies 1276 5, 1276.6, (b) (4) and 1276.8) studies
- **Cross reference to other NDAs:**
  - Empagliflozin (Jardiance; NDA 204629, approved August 1, 2014)
  - Empagliflozin + Linagliptin (NDA 206073, under review)
  - Linagliptin + Metformin (Jentadueto; NDA 201281, approved January 30, 2012)

U.S. Food and Drug Administration
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Overview: Recommended Dose

- **Recommended Dose (Proposed):**
  (b) (4)

U.S. Food and Drug Administration
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Results

Study 1276.5

- **Relative Bioavailability and Food-Effect:**
  - Median empagliflozin t_{max} in the fed state delayed approximately 1.25 h relative to the fasted state (3.00 h (min – max, 1.00 – 8.00 h) *vs.* 1.75 h (min – max, 1.00 – 2.50 h)).
  - Median metformin t_{max} in the fed state delayed 0.5 h relative to the fasted state (3.00 h (min – max, 1.50 – 8.00 h) *vs.* 2.50 h (min – max, 1.50 – 4.00 h))

Relative bioavailability of the 12.5 mg empagliflozin / 1000 mg metformin hydrochloride FDC tablet (T) vs. individual tablets of empagliflozin and metformin hydrochloride in the fasted state (R)

Empagliflozin		
PK Parameter	gMean ratio T/R [%]	2-sided 90% CI [%]
$AUC_{0-\infty}$	100.59	95.75 – 105.67
C_{max}	99.31	91.76 – 107.49
AUC_{0-tz}	100.94	96.03 – 106.11
Metformin		
$AUC_{0-\infty}$	102.15	93.87 – 111.15
C_{max}	103.49	95.30 – 112.39
AUC_{0-tz}	103.13	95.59 – 111.25

Relative bioavailability of the 12.5 mg empagliflozin /1000 mg metformin hydrochloride fixed dose combination (FDC) tablet in the fed (T) vs. fasted state (R)

Empagliflozin		
PK Parameter	gMean ratio T/R [%]	2-sided 90% CI [%]
$AUC_{0-\infty}$	94.94	89.85 – 100.33
C_{max}	64.30	55.97 – 73.87
AUC_{0-tz}	94.39	89.22 – 99.87
Metformin		
$AUC_{0-\infty}$	100.67	91.70 – 110.51
C_{max}	75.13	63.68 – 88.64
AUC_{0-tz}	96.96	87.23 – 107.78

Results

Study 1276.6

- **Relative Bioavailability of 5/500, 12.5/500 Empagliflozin/Metformin FDC compared to IC:**

Relative bioavailability of empagliflozin for 12.5 mg or 5 mg empagliflozin / 500 mg metformin hydrochloride fixed-dose combination tablets vs. individual tablets of empagliflozin and metformin hydrochloride

12.5 mg empagliflozin+500 mg metformin hydrochloride fixed dose tablet (T1) vs. individual 10 mg + 2.5 mg empagliflozin and 500 mg metformin hydrochloride tablets (R1)

PK Parameter	gMean ratio T1/R1 [%]	2-sided 90% CI [%]
$AUC_{0-\infty}$	97.92	93.529 – 102.52
C_{max}	104.61	99.882 – 109.56
AUC_{0-tz}	98.00	93.530 – 102.69

5 mg empagliflozin+500 mg metformin hydrochloride fixed dose tablet (T2) vs. individual 5 mg empagliflozin and 500 mg metformin hydrochloride tablets (R2)

	gMean ratio T2/R2 [%]	2-sided 90% CI [%]
$AUC_{0-\infty}$	102.79	99.077 – 106.63
C_{max}	102.96	97.917 – 108.26
AUC_{0-tz}	102.77	99.146 – 106.52

Relative bioavailability of metformin hydrochloride for 12.5 mg or 5 mg empagliflozin / 500 mg metformin hydrochloride fixed-dose combination tablets vs. individual tablets of empagliflozin and metformin hydrochloride

12.5 mg empagliflozin+500 mg metformin hydrochloride fixed dose tablet (T1) vs. individual 10 mg + 2.5 mg empagliflozin and 500 mg metformin hydrochloride tablets (R1)

PK Parameter	gMean ratio T1/R1 [%]	2-sided 90% CI [%]
$AUC_{0-\infty}$	96.25	88.542 – 104.63
C_{max}	94.76	89.056 – 100.82
AUC_{0-tz}	95.78	88.000 – 104.26

5 mg empagliflozin+500 mg metformin hydrochloride fixed dose tablet (T2) vs. individual 5 mg empagliflozin and 500 mg metformin hydrochloride tablets (R2)

	gMean ratio T2/R2 [%]	2-sided 90% CI [%]
$AUC_{0-\infty}$	96.79	91.772 – 102.09
C_{max}	93.83	88.006 – 100.03
AUC_{0-tz}	95.94	91.199 – 100.93

Results

(b) (4)

Results

Study 1276.8

- **Relative Bioavailability Under Fed Conditions**

Relative bioavailability of empagliflozin and metformin after oral administration of 12.5 mg empagliflozin / 1000 mg metformin hydrochloride fixed dose combination tablet (T1) or individual tablets administered together (R1) in the fed state (Part I)

T1 fed / R1 fed

Empagliflozin PK Parameter	gMean ratio T1/R1 [%]	2-sided 90% CI [%]
$AUC_{0-\infty}$	98.88	94.88 – 103.06
C_{max}	106.52	95.86 – 118.35
AUC_{0-tz}	98.82	94.78 – 103.04
Metformin		
$AUC_{0-\infty}$	99.34	92.56 – 106.62
C_{max}	97.97	92.34 – 103.94
AUC_{0-tz}	99.31	92.14 – 107.03

Relative bioavailability of empagliflozin and metformin after oral administration of 5 mg empagliflozin / 1000 mg metformin hydrochloride fixed dose combination tablet (T2) or individual tablets administered together (R2) in the fed state (Part II)

T2 fed / R2 fed

Empagliflozin PK Parameter	gMean ratio T2/R2 [%]	2-sided 90% CI [%]
$AUC_{0-\infty}$	106.00	102.73 – 109.39
C_{max}	104.54	99.15 – 110.22
AUC_{0-tz}	105.98	102.73 – 109.33
Metformin		
$AUC_{0-\infty}$	100.81	95.74 – 106.14
C_{max}	102.95	97.17 – 109.08
AUC_{0-tz}	100.74	95.77 – 105.96

Results

Study 1276.8

- **Relative Bioavailability Under Fasting Conditions**

Relative bioavailability of empagliflozin and metformin after oral administration of 12.5 mg empagliflozin / 1000 mg metformin hydrochloride fixed dose combination tablet (T1) or individual tablets administered together (R1) in the fasted states (Part I)

T1 fasted / R1 fasted

Empagliflozin PK Parameter	gMean ratio T1/R1 [%]	2-sided 90% CI [%]
$AUC_{0-\infty}$	102.55	99.53 – 105.65
C_{max}	102.12	96.26 – 108.35
AUC_{0-tz}	102.33	99.32 – 105.43
Metformin		
$AUC_{0-\infty}$	96.13	91.25 – 101.26
C_{max}	94.87	88.93 – 101.21
AUC_{0-tz}	94.89	89.80 – 100.26

Results

Study 1276.8

- **Relative Bioavailability Under Fasting and Fed Conditions**

Relative bioavailability of empagliflozin and metformin after oral administration of individual tablets of 12.5 mg empagliflozin /1000 mg metformin hydrochloride (R1) in the fed and fasted states (Part I)

R1 fed/R1 fasted Empagliflozin PK Parameter	gMean ratio [%]	2-sided 90% CI [%]
$AUC_{0-\infty}$	93.38	89.94 – 96.96
C_{max}	68.65	61.18 – 77.03
AUC_{0-tz}	92.73	89.41 – 96.18
Metformin		
$AUC_{0-\infty}$	82.39	74.91 – 90.63
C_{max}	70.05	64.32 – 76.28
AUC_{0-tz}	82.52	75.17 – 90.60

Relative bioavailability of empagliflozin and metformin after oral administration of fixed-dose combination tablets of 12.5 mg empagliflozin / 1000 mg metformin hydrochloride (T1) in the fed and fasted states (Part I)

T1 fed/T1 fasted Empagliflozin PK Parameter	gMean ratio [%]	2-sided 90% CI [%]
$AUC_{0-\infty}$	91.33	86.88 – 96.02
C_{max}	72.06	65.58 – 79.20
AUC_{0-tz}	91.21	86.80 – 95.85
Metformin		
$AUC_{0-\infty}$	87.91	80.54 – 95.95
C_{max}	73.55	67.00 – 80.75
AUC_{0-tz}	88.60	80.91 – 97.01

Pediatric Plan

- **Sponsor Request**
  - The sponsor is requesting a waiver of requirements outlined in CFR 314.55 for the empagliflozin/metformin FDC product for pediatric population from birth to less than 10 years of age on the grounds that a trial using the FDC product would not be feasible and that the FDC product would not represent a significant therapeutic benefit over existing treatments.
  - The sponsor is planning a PK/PD study with empagliflozin (study 1245.87) in adolescents aged 10 to <18 years, and has requested a partial deferral.
  - The sponsor submitted a double blind, placebo controlled, add-on to metformin, safety and efficacy study of empagliflozin in adolescents aged 10 to <18 years (study 1245.56.)

Key Questions: Mid Cycle Deliverables

- Was bioequivalence between the individual components and the FDC established?

Application Filability and Consults

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

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

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?		X		The empagliflozin/metformin FDC tablet formulation was not used in any phase II/III clinical studies included in the evaluation of efficacy and safety in the current application. The evaluation of efficacy and safety of the combination of empagliflozin and metformin was based on phase II/III clinical studies that investigated empagliflozin in patients taking ongoing metformin background medication. Bioequivalence studies were performed for the FDCs against the respective individual components.
2	Has the applicant provided metabolism and drug-drug interaction information?			X	Data in original NDA for empagliflozin (Jardiance, NDA 20-4629)
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?			X	Data in original NDA for empagliflozin (Jardiance, NDA 20-4629)
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?			X	Rationale for empagliflozin dose selection in NDA 20-4629. Rationale for available FDC strengths submitted with current application.
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?			X	Data in original empagliflozin NDA (Jardiance, 20-4629).
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			X	Data in original empagliflozin NDA (Jardiance, 20-4629).
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			X	Data in original empagliflozin NDA (Jardiance, 20-4629).
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			X	Data in original empagliflozin NDA (Jardiance, 20-4629).
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			

	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? Yes

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

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

Comment to Sponsor:
None

Suryanarayana M. Sista	09 Sep, 2014
Reviewing Clinical Pharmacologist	Date
Lokesh Jain	09 Sep, 2014
Team Leader	Date

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

/s/

SURYANARAYANA M SISTA
09/15/2014

LOKESH JAIN
09/15/2014