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APPLICATION NUMBER:

208658Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

NDA	208658
Link to EDR	\\CDSESUB1\evsprod\NDA208658\0000
Submission Date(s)	February 02, 2016
Submission Type	505(b)(1)
OND Division	Division of Metabolism and Endocrinology Products
Brand Name	Synjardy® XR
Generic Name	Empagliflozin and metformin HCl extended-release fixed dose combination tablets
Dosage Form and Strength	Tablets; 5 mg empagliflozin/1000 mg metformin; 10 mg empagliflozin/1000 mg metformin; 12.5 mg empagliflozin/1000 mg metformin; 25 mg empagliflozin/1000 mg metformin;
Route of Administration	Oral
Proposed Indication	Indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (b) (4) [redacted]
Applicant	Boehringer Ingelheim
Associated INDs	111919
OCP Review Team	Ritesh Jain, Ph.D., Manoj Khurana, Ph.D.

TABLE OF CONTENTS

CLINICAL PHARMACOLOGY REVIEW 1
1 Executive Summary 3
1.1 Recommendation 3
1.2 Post-Market Requirements and Commitments 3
2 Summary of Clinical Pharmacology Assessment 4
2.1 Pharmacology and Clinical Pharmacokinetics 4
2.2 Summary of Labeling Recommendations 6
3 Comprehensive Clinical Pharmacology Review 8
3.1 Overview of the Product and Regulatory Background 8
3.2 Clinical Pharmacology Review Questions 10
3.2.1 Does the available clinical pharmacology information provide the pivotal bridging? 10
4 Appendix 15

4.1 Summary of Bioanalytical Method Validation and Performance 15
4.1.1 How are the active moieties identified and measured in the clinical pharmacology and Summary of Bioanalytical Method Validation and Performance 15
4.2 Qualitative and Quantitative Composition of Empagliflozin/Metformin HCl XR Coated Tablets 16
4.3 Individual Study Synopsis 18
Trial 1276.15 Study Synopsis 18
Trial 1276.28 Study Synopsis 24

List of Tables

Table 1: Overview of pivotal bridging studies for empagliflozin/metformin FDC XR 4
Table 2: Summary of Pharmacokinetic Parameters of Empagliflozin and Metformin Following Single Dose oral administration of 25 mg empagliflozin and 1000 mg metformin XR either as FDC (T) or Co-administration of Empagliflozin and Metformin Tablets (R) Administration in Fed Condition (Study 1276.15) 12
Table 3: Summary of Pharmacokinetic Parameters of Empagliflozin and Metformin Following Single Dose oral administration of 25 mg empagliflozin and 1000 mg metformin XR either as FDC (T) or Co-administration of Empagliflozin and Metformin Tablets (R) Administration in Fed Condition (Study 1276.15) 14
Table 4: Summary of key descriptive parameters for Empagliflozin and Metformin bioanalytical assays in plasma used in clinical studies 15

List of Figures

Figure 1: A) Ratios of Geometric Means and the 90% Confidence Intervals for the Pharmacokinetic Parameter of Empagliflozin and Metformin Following Co-administration of Empagliflozin 25 mg and Metformin 1000 mg and FDC XR Product (Empa 25/met XR 1000). B) Ratios of Geometric Means and the 90% Confidence Intervals for the Pharmacokinetic Parameter of Empagliflozin and Metformin Following Co-administration of Empagliflozin 10 mg and Metformin 1000 mg and FDC XR Product (Empa 10/met XR 1000). 5
Figure 2: Schematic of the Cross Section of an Empagliflozin/Metformin HCl ER Coated Tablet 8
Figure 3: Schematic of the tablet and photographs of Synjardy® XR 8
Figure 4: Schematic Summary of Pivotal Bridging Information Supporting Synjardy® XR 10
Figure 5: Plasma concentration time profile following oral administration of 25 mg empagliflozin and 1000 mg metformin XR either as FDC (T) or co-administration of empagliflozin and metformin Tablets (R) under fed condition in Study 1276.15. A) Plasma Concentration Time Profile of Empagliflozin (upper graph) B) Plasma Concentration Time Profile of Metformin (lower graph) 11
Figure 6: Plasma concentration time profile following oral administration of 10 mg empagliflozin and 1000 mg metformin XR either as FDC (T) or co-administration of empagliflozin and metformin Tablets (R) under fed condition in Study 1276.28. A) Plasma Concentration Time Profile of Empagliflozin (upper graph) B) Plasma Concentration Time Profile of Metformin (lower graph) 13

1 Executive Summary

The applicant "Boehringer Ingelheim Pharmaceuticals" has submitted NDA 208658 for Synjardy® XR, the fixed dose combination (FDC XR) of empagliflozin and metformin extended-release tablets. The applicant is seeking marketing application of Synjardy XR® under the provisions of the section 505(b) (1) of the Federal Food, Drug, and Cosmetic Act. The proposed indication is an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both empagliflozin and metformin is appropriate.

Synjardy®, a fixed dose combination product of empagliflozin and metformin hydrochloride immediate release (IR) (NDA 206111), was approved in August 2015. In the current application, sponsor has developed a fixed dose combination of empagliflozin and metformin hydrochloride (HCl) XR tablets for once-daily use in patients with type 2 diabetes mellitus. The proposed dose strengths for empagliflozin and metformin HCl extended release fixed dose combination tablets are 5mg/1000mg, 10mg/1000mg, 12.5mg/1000mg, and 25mg/1000mg. The proposed trade name is Synjardy® XR. All 4 tablet strengths have an identical core containing 1000 mg metformin hydrochloride in an XR formulation. The core is surrounded with an empagliflozin IR coating of 4 different strengths.

In this application sponsor is seeking approval based on the 2 pivotal bioequivalence (BE) of FDC XR (empagliflozin/metformin XR FDC tablet strengths 25mg/1000 mg in study 1276.15 and 10/1000 mg in study 1276.28) to co-administration of empagliflozin and metformin hydrochloride (HCl) extended-release in healthy volunteers. For the 2 lower empagliflozin/metformin XR FDC tablet strengths (12.5mg/1000 mg and 5mg/1000 mg), no bioequivalence studies were performed, and sponsor has requested a bio waiver to conduct clinical studies at these strengths.

The applicant is the sponsor of empagliflozin (Jardiance®, NDA 204629) and Synjardy® (FDC of empagliflozin and metformin HCl twice daily, NDA 206111), and also provided a Letter of Authorization from the sponsor of metformin extended-release product (Glumetza®, NDA 021748). The applicant refers pertinent labeling information of Glumetza® and Synjardy® for Synjardy XR®.

1.1 Recommendation

The Office of Clinical Pharmacology has reviewed NDA 208026 for Synjardy XR® and recommends approval.

1.2 Post-Market Requirements and Commitments

None

2 Summary of Clinical Pharmacology Assessment

2.1 Pharmacology and Clinical Pharmacokinetics

To bridge the existing clinical safety and efficacy data sponsor in this NDA conducted two pivotal bioequivalence studies to demonstrate bioequivalence between the empagliflozin/metformin XR FDC tablets (Synjardy® XR) to the co-administration of the individual components (Jardiance® and Glumetza®). The applicant conducted the following two pivotal BE studies to support the approval of Synjardy® XR under fed conditions (Table 1).

Table 1: Overview of pivotal bridging studies for empagliflozin/metformin FDC XR

Study No. Report No.	Objective and description	Study part, meal status	Test (FDC dose tested (mg))	Reference (co-administration dose tested (mg))
1276.15 c02998110	Bioequivalence, single-dose, Pivotal Study	Fed	Empa 25/Met XR 1000	Empa 25 + 2x Met XR 500
1276.28 c03125719	Bioequivalence, single-dose, Pivotal	Fed	Empa 10/Met XR 1000	Empa 10 + 2x Met XR 500

BE Study Results:

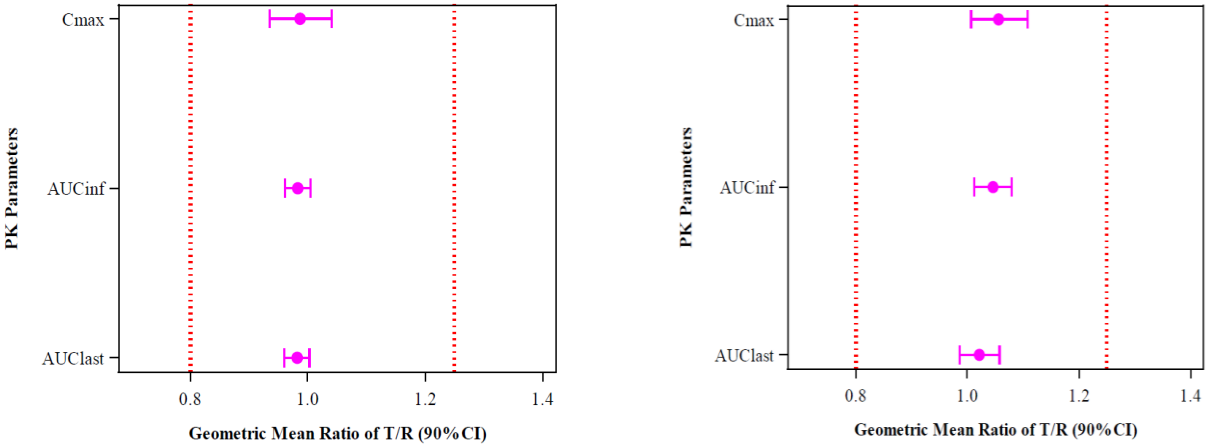
As shown in Figure 1, BE was demonstrated for both strengths of Synjardy® XR referencing corresponding co-administration of Jardiance® and Glumetza® under both fed conditions. For the 2 lower empagliflozin/metformin XR FDC tablet strengths (12.5mg/1000 mg and 5mg/1000 mg), no bioequivalence studies were performed, and sponsor has requested a bio waiver to conduct clinical studies at these strengths.

Empagliflozin-Metformin DDI Study Results:

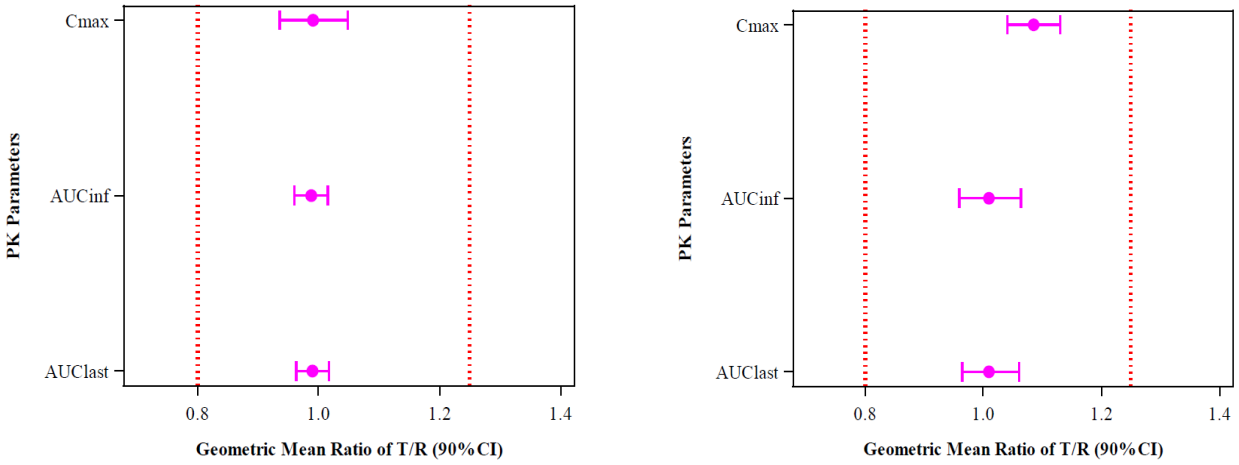
No DDI studies were conducted under this NDA. The drug-drug interaction study were conducted NDA 204629 (see Clinical Pharmacology review by Dr. Manoj Khurana in DARRTS dated 11/08/2013). In brief, co-administration of multiple daily doses of empagliflozin 50 mg with metformin 2000 mg, an organic cationic transporter (OCT) substrate, demonstrated that there is no drug-drug interaction between empagliflozin and metformin.

Figure 1: A) Ratios of Geometric Means and the 90% Confidence Intervals for the Pharmacokinetic Parameter of Empagliflozin and Metformin Following Co-administration of Empagliflozin 25 mg and Metformin 1000 mg and FDC XR Product (Empa 25/met XR 1000). B) Ratios of Geometric Means and the 90% Confidence Intervals for the Pharmacokinetic Parameter of Empagliflozin and Metformin Following Co-administration of Empagliflozin 10 mg and Metformin 1000 mg and FDC XR Product (Empa 10/met XR 1000).

A) **BE Study 1276.15**



B) **BE Study 1276.28**



In conclusion, the clinical pharmacology information of Synjardy® XR supports the recommendation of approval based on:

- The pivotal BE study results are acceptable from the clinical pharmacology perspective.
- The clinical comparability between metformin twice daily (Glucophage®) and once daily (Glumetza®) was shown in the original NDA for Glumetza®, the metformin XR reference product for Synjardy® XR.

- The efficacy and safety of co-administration between empagliflozin and metformin twice daily (Glucophage®) has been adequately demonstrated as add-on (Jardiance®) and initial (Synjardy®) therapy.

2.2 Summary of Labeling Recommendations

The following are the labeling recommendations relevant to clinical pharmacology for NDA 208658. 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.

Section 2.2 Recommended Dosages in Patients with Renal Impairment

- Assess renal function prior to initiation of TRADENAME and periodically, thereafter.

(b) (4)

[redacted]

- TRADENAME is contraindicated in patients with an eGFR less than 45 mL/min/1.73 m^2 *[see Contraindications (4) and Warnings and Precautions (5.1, 5.4)]*.

Section 2.3 Discontinuation for Iodinated Contrast Imaging Procedures

- Discontinue SYNJARDY at the time of, or prior to, an iodinated contrast imaging procedure in patients with an eGFR between 45 and 60 mL/min/1.73 m2; in patients with a history of liver disease, alcoholism or heart failure; or in patients who will be administered intra-arterial iodinated contrast. Re-evaluate eGFR 48 hours after the imaging procedure; restart SYNJARDY if renal function is stable [see Warnings and Precautions (5.1)].

Reviewer's Comment: The proposed changes above were done to make the current label consistent with the SYNJARDY label and the class labeling changes that are ongoing for metformin. All other sections of the label also needs to be updated with regards to dosing in patients with eGFR less than 45 mL/min/1.73 m2

Section 4 Contraindications

TRADENAME is contraindicated in patients with:

(b) (4)

[redacted]

- Moderate to severe renal impairment (eGFR less than 45 mL/min/1.73 m^2), end stage renal disease, or dialysis *[see Warnings and Precautions (5.1, 5.4) and Use in Specific Populations (8.6)].*

Section 7.2 Drug Interactions with Metformin Hydrochloride

(b) (4)

Drugs that Reduce Metformin Clearance
Concomitant use of drugs that interfere with common renal tubular transport systems involved in the renal elimination of metformin (e.g., organic cationic transporter-2 [OCT2] / multidrug and toxin extrusion [MATE] inhibitors such as ranolazine, vandetanib, dolutegravir, and cimetidine) could increase systemic exposure to metformin and may increase the risk for lactic acidosis [see Clinical Pharmacology (12.3)]. Consider dose adjustment and increased patient monitoring with concomitant use.

Alcohol
Alcohol is known to potentiate the effect of metformin on lactate metabolism. Warn patients against excessive alcohol intake while receiving TRADENAME.

Reviewers Comments: The proposed changes above were done to make the current label consistent with the SYNJARDY label.

Section 12.6 Pharmacokinetics

(b) (4)

Administration of TRADE NAME with food resulted in no change in overall exposure of empagliflozin. For metformin extended-release high-fat meals increased systemic exposure (as measured by area-under-the-curve [AUC]) by approximately 70% relative to fasting, while Cmax is not affected. Meals prolonged Tmax by approximately 3 hours. (b) (4)

Reviewer's Comment: Not according to current Clinical Pharmacology labeling guidance. Comparative claims should be avoided in the label. Sponsor can describe the results of the BE study.

3 Comprehensive Clinical Pharmacology Review

3.1 Overview of the Product and Regulatory Background

The Synjardy® XR consists of a metformin HCl extended release tablet core that (b) (4) contains the immediate-release drug substance empagliflozin (Figure 2). Components and composition of formulations are summarized in Appendix 1. The tablets are oval shaped (b) (4) color of the film coat and by imprint as shown in Figure 3.

(b) (4)

Figure 3: Schematic of the tablet and photographs of Synjardy® XR

- The 5 mg/1000 mg tablets are olive green coated. One side is printed with the BI company logo and "S5" on the top line and "1000 M" on the bottom line.
- The 10 mg/1000 mg tablets are orange coated. One side is printed with the BI company logo and "S10" on the top line and "1000 M" on the bottom line.
- The 12.5 mg/1000 mg tablets are blue coated. One side is printed with the BI company logo and "S12" on the top line and "1000 M" on the bottom line.
- The 25 mg/1000 mg tablets are light-green coated. One side is printed with the BI company logo and "S25" on the top line and "1000 M" on the bottom line

Product specific regulatory background

Sponsor had a pre-IND meeting (May 2011) and Type C meeting (December 2013) and pre NDA meeting (July 2015) for the development of this FDC product. In the Type C meeting dated December 2013 Agency agreed upon:

- Sponsor's proposal to conduct two bioequivalence (BE) studies for the empagliflozin + extended-release metformin FDC tablets
- Sponsor was advised to conduct the two planned BE studies under the more clinically relevant fed conditions instead of fasting conditions. Agency in its response noted that the bioequivalence studies conducted under fed conditions will generate useful information for the product label, negating the need for a separate food effect study.

In addition no Phase 3 clinical studies investigating the efficacy of empagliflozin/metformin XR FDC were conducted in this NDA. The sponsor is relying on existing clinical safety and efficacy data from clinical studies under following NDA:

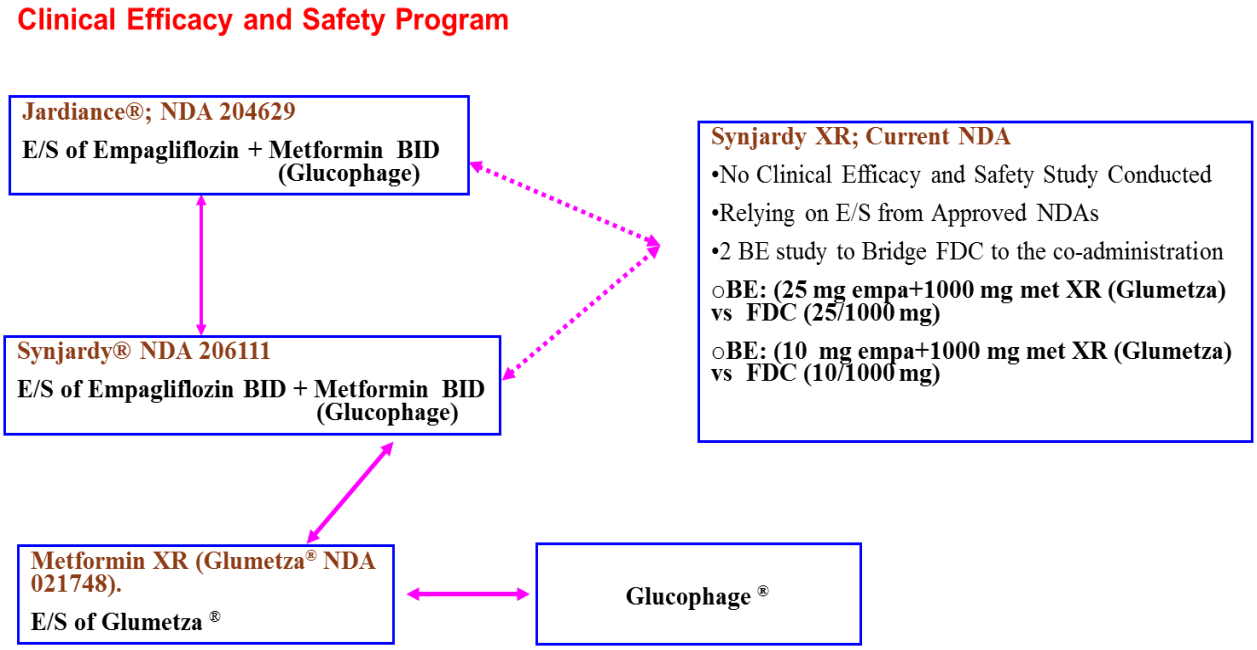
- Empagliflozin (Jardiance®; NDA 204629),
- Empagliflozin/metformin IR (Synjardy® NDA 206111),
- Metformin XR (Glumetza® NDA 021748).

As shown in Figure 4, the efficacy and safety of empagliflozin given once daily as add-on to metformin IR given twice daily was adequately demonstrated in several Phase 3 studies under the original NDA for Jardiance® (empagliflozin) and Synjardy® NDA 206111 (Empagliflozin/metformin IR). In addition under the original NDA for Glumetza® (NDA 021748) safety and efficacy between the metformin XR and IR product have been established. Readers are referred to Clinical Pharmacology review of empagliflozin by Dr. Manoj Khurana dated 11/08/2013 and Clinical Pharmacology review of empagliflozin and metformin IR FDC by Dr. Sury Sista dated 04/15/2015 for further details on the safety and efficacy of empagliflozin and metformin when administered together.

To bridge the existing clinical safety and efficacy data sponsor in this NDA conducted two pivotal bioequivalence studies to demonstrate bioequivalence between the empagliflozin/metformin XR FDC tablets (Synjardy® XR) to the co-administration of the individual components (Jardiance® and Glumetza®).

Both pivotal studies were randomized, open-label, 2-way crossover design with a wash-out period of at least 7-days between the 2 treatments - empagliflozin/metformin XR FDC tablets (Synjardy® XR) or the co-administration of the individual components (Jardiance® and Glumetza®) administered orally as single dose in healthy men and women under fed conditions.

Figure 4: Schematic Summary of Pivotal Bridging Information Supporting Synjardy® XR



3.2 Clinical Pharmacology Review Questions

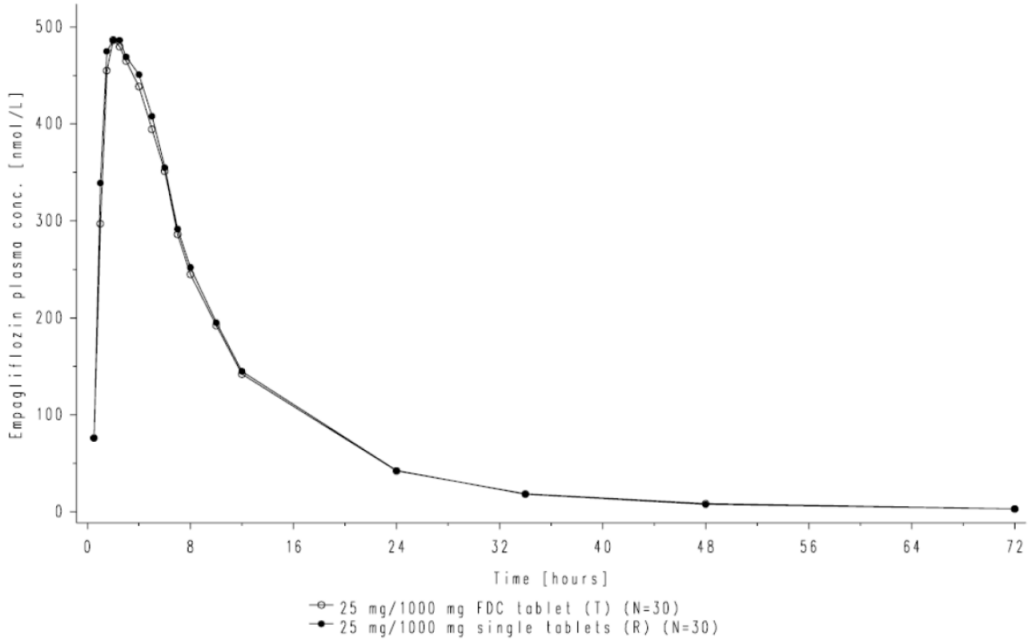
3.2.1 Does the available clinical pharmacology information provide the pivotal bridging?

Yes. Results of the two pivotal studies demonstrated the bioequivalence between empagliflozin/ metformin XR FDC tablet strengths 25 mg/1000 mg (study 1276.15) and 10 mg/1000 mg (study 1276.28) to the free combination of the individual components administered orally as single dose in healthy subjects under fed conditions.

Figure 5 shows the plasma concentration-time profile of empagliflozin and metformin following FDC-XR administration and co-administration of individual components at the highest dose strength of empagliflozin/metformin XR 25 mg/1000 mg. Pharmacokinetic parameters are also summarized in Table 2. Study results clearly demonstrates that the FDC-XR product in the pivotal BE study is bioequivalent to the individual metformin and empagliflozin tablets given concurrently. Table 2 shows 90% confidence intervals (CIs) of the ratios of geometric least square (LS) means for AUC_{0-t}, AUC_{0-inf}, and C_{max} were entirely contained within 0.80 to 1.25 for both empagliflozin and metformin at highest empagliflozin/metformin XR 25 mg/1000 mg dose strengths.

Figure 5: Plasma concentration time profile following oral administration of 25 mg empagliflozin and 1000 mg metformin XR either as FDC (T) or co-administration of empagliflozin and metformin Tablets (R) under fed condition in Study 1276.15. A) Plasma Concentration Time Profile of Empagliflozin (upper graph) B) Plasma Concentration Time Profile of Metformin (lower graph)

A)



B)

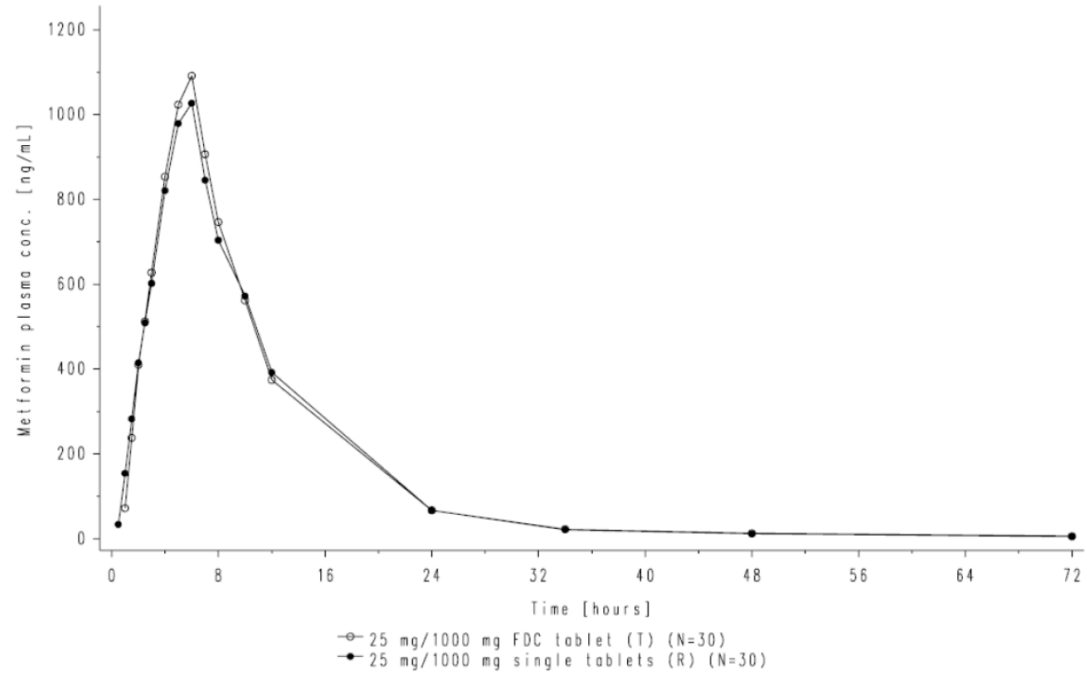


Table 2: Summary of Pharmacokinetic Parameters of Empagliflozin and Metformin Following Single Dose oral administration of 25 mg empagliflozin and 1000 mg metformin XR either as FDC (T) or Co-administration of Empagliflozin and Metformin Tablets (R) Administration in Fed Condition (Study 1276.15)

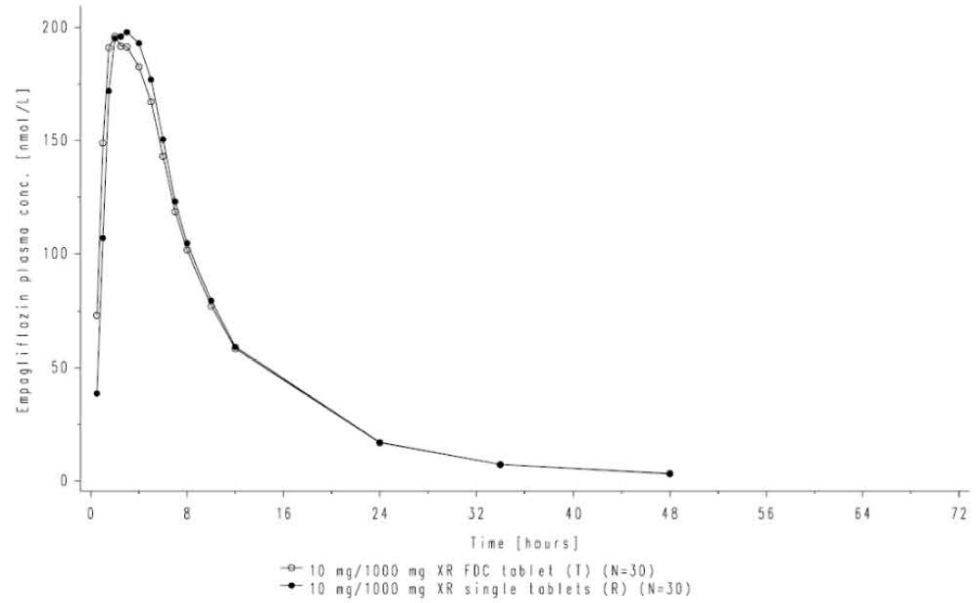
PK parameters	Geometric Least Squares Mean		Ratio T/R*100 (90% CI)
	Empagliflozin/Metformin 25 mg/100 mg FDC tablets (Fed) (T)	Co-administration of Empagliflozin 25 mg + Metformin 1000 mg (Fed) (R)	
Empagliflozin			
C_{max} (ng/mL)	589.5	597.3	98.70 (93.51-104.17)
$AUC_{0\text{-last}}$ (ng.hr/mL)	5373.6	5470.8	98.22 (96.11-100.39)
$AUC_{0\text{-inf}}$ (ng.hr/mL)	5455.9	5549.1	98.32 (96.16 100.53)
Median T_{max} (hr) (Range min, max)	1.8 (0.5-6.0)	1.5 (1.0-6.0)	
Metformin			
C_{max} (ng/mL)	1118.9	1058.7	105.69 (100.78-110.84)
$AUC_{0\text{-last}}$ (ng.hr/mL)	11008.1	10777	102.14 (98.65 105.76)
$AUC_{0\text{-inf}}$ (ng.hr/mL)	11517.7	11005.1	104.66 (101.36-108.07)
Median T_{max} (hr) (Range min, max)	6.00 (5.0-7.0)	6.00 (4.0-7.0)	

Figure 6 shows the plasma concentration-time profile of empagliflozin and metformin following FDC-XR administration and co-administration of individual components of empagliflozin/metformin XR 10/1000 mg. Pharmacokinetic parameters are also summarized in Table 3. Study results clearly demonstrates that the FDC-XR product in the pivotal BE study is bioequivalent to the individual metformin and empagliflozin tablets given concurrently. Table 3 shows 90% confidence intervals (CIs) of the ratios of geometric least square (LS) means for $AUC_{0\text{-t}}$, $AUC_{0\text{-inf}}$, and C_{max} were entirely contained within 0.80 to 1.25 for both empagliflozin and metformin at empagliflozin/metformin XR 10/1000 mg dose strengths.

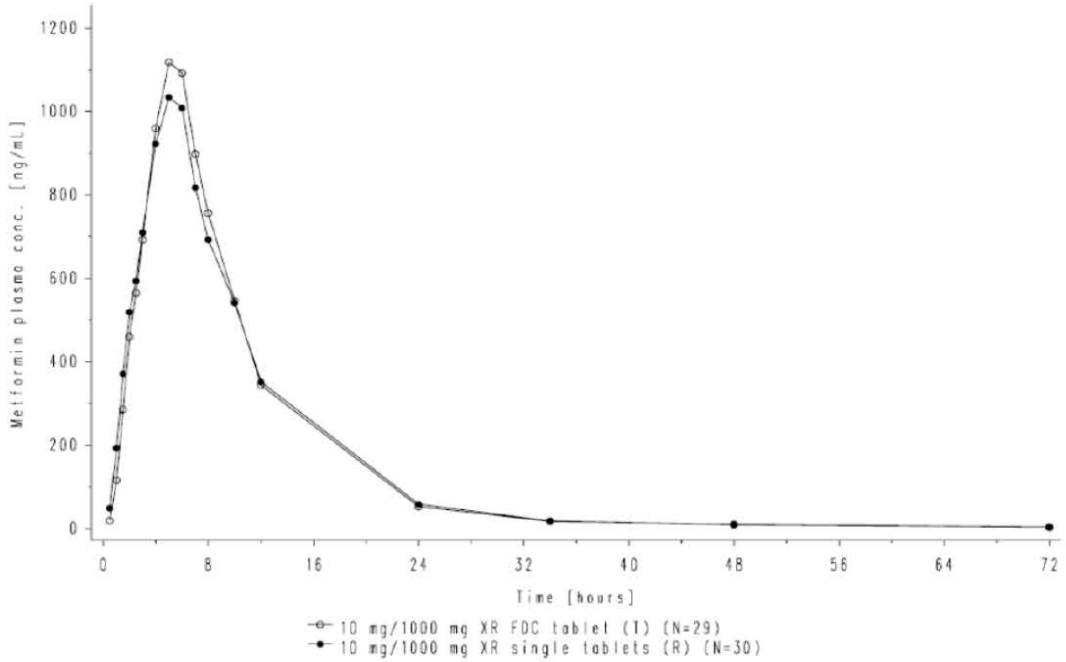
There were no notable protocol deviations in study 1276.15 and study 1276.28. Office of Study Integrity and Surveillance (OSIS) completed the inspection of the clinical portion of bioequivalence study 1276.28 and recommended that the data from the study 1276.28 be accepted for further agency review (See OSI memo by Dr. Mohsen Rajabi in DAARTS dated 10/17/2016).

Figure 6: Plasma concentration time profile following oral administration of 10 mg empagliflozin and 1000 mg metformin XR either as FDC (T) or co-administration of empagliflozin and metformin Tablets (R) under fed condition in Study 1276.28. A) Plasma Concentration Time Profile of Empagliflozin (upper graph) B) Plasma Concentration Time Profile of Metformin (lower graph)

A)



B)



Empagliflozin and metformin in human plasma was measured using a validated LC-MS/MS assay. Empagliflozin method was validated for a range of 1.11-1110 nmol/L (0.500 – 500 ng/mL). Metformin method was validated for a range of 1 ng/mL to 2500 ng/mL. A summary of key descriptive parameters for the bioanalytical assays used in clinical studies is listed in Appendix 4.1. Sponsor's analytical method met the FDA guidance "Bioanalytical Method Validation" recommendations, and was therefore acceptable. The accuracy and precision of the assay was with in the guidance acceptance limits. In addition, Office of Study Integrity and Surveillance (OSIS) completed the inspection of the analytical portion of bioequivalence studies 1276.28 and 1276.15 and recommended that the data analytical is reliable and recommends accepting the data for further Agency review (See OSIS memo by Dr. Sripal R. Mada in DAARTS dated 07/08/2016).

Table 3: Summary of Pharmacokinetic Parameters of Empagliflozin and Metformin Following Single Dose oral administration of 25 mg empagliflozin and 1000 mg metformin XR either as FDC (T) or Co-administration of Empagliflozin and Metformin Tablets (R) Administration in Fed Condition (Study 1276.15)

PK parameters	Geometric Least Squares Mean		Ratio T/R*100 (90% CI)
	Empagliflozin/Metformin 25 mg/100 mg FDC tablets (Fed) (T)	Co-administration of Empagliflozin 25 mg + Metformin 1000 mg(R)	
Empagliflozin			
C_{max} (ng/mL)	242.9	249.4	99.12 (93.69-104.87)
$AUC_{0\text{-last}}$ (ng.hr/mL)	2192.6	2212.4	99.11 (96.4-101.89)
$AUC_{0\text{-inf}}$ (ng.hr/mL)	2232.9	2258.0	98.89 (96.18- 101.67)
Median T_{max} (hr) (Range min, max)	1.5 (0.5-6.0)	1.5 (0.5-5.0)	
Metformin			
C_{max} (ng/mL)	1169.6	1077.9	108.58 (104.17-113.17)
$AUC_{0\text{-last}}$ (ng.hr/mL)	10830.9	10697.3	101.25 (96.54-106.19)
$AUC_{0\text{-inf}}$ (ng.hr/mL)	10975.4	10827.2	101.3 (96.54-106.45)
Median T_{max} (hr) (Range min, max)	5.02 (4.0-7.1)	5.02 (4.0-7.0)	

4 Appendix

4.1 Summary of Bioanalytical Method Validation and Performance

4.1.1 How are the active moieties identified and measured in the clinical pharmacology and Summary of Bioanalytical Method Validation and Performance

Empagliflozin:

Empagliflozin in human plasma was measured using a validated 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 sample. Briefly, empagliflozin and the internal standard [$^{13}C_6$]-empagliflozin were extracted from human plasma by supported liquid extraction. After evaporation under nitrogen, the residue was reconstituted and analyzed by HPLC-MS/MS.

Metformin:

Metformin in human plasma was measured using a validated LC-MS/MS assay. The method was validated for a range of 1 ng/mL to 2500 ng/mL, based on the analysis of 0.05 mL of sample. Briefly, Metformin and the internal standard [D_6]-metformin were extracted from human plasma by protein precipitation method. A summary of key descriptive parameters for the bioanalytical assays used in clinical studies is listed in Table 4. Sponsor's analytical method met the FDA guidance "Bioanalytical Method Validation" recommendations, and was therefore acceptable. The accuracy and precision of the assay was with in the guidance acceptance limits

Table 4: 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
BE study 1276.15/Analytical Report #0016-14301-1	Quantification of Empagliflozin and Metformin in K3EDTA Human Plasma By LC-MS/MS	(b) (4)	Metformin 1 – 2500 ng/mL	Metformin 1 ng/mL	Metformin 97% - 104% at 3– 2000 ng/mL	Metformin 1.9% -8.1% at 3 – 2000 g/mL
BE study 1276.15/Analytical Report #0016-14301-1	Quantification of Empagliflozin and Metformin in K3EDTA Human Plasma By LC-MS/MS		Empagliflozin 0.5-500 ng/mL	Empagliflozin 0.5 ng/mL	Empagliflozin 99.8% - 107% at 1.5-2000 ng/mL	Empagliflozin 1.4% - 6.6% at 1.5-2000 ng/mL
BE study 1276.28/Analytical Report #0016-14249-1	Quantification of Empagliflozin and Metformin in K3EDTA Human Plasma By LC-MS/MS		Metformin 1 – 2500 ng/mL	Metformin 1 ng/mL	Metformin 99.8% - 103% at 3– 2000 ng/mL	Metformin 2.2-% -7.3% at 3 – 2000 g/mL
BE study 1276.28/Analytical Report #0016-14249-1	Quantification of Empagliflozin and Metformin in K3EDTA Human Plasma By LC-MS/MS		Empagliflozin 0.5-500 ng/mL	Empagliflozin 0.5 ng/mL	Empagliflozin 101% - 110% at 1.5-400 ng/mL	Empagliflozin 1.7% - 6% at 1.5-400 ng/mL

4.2 Qualitative and Quantitative Composition of Empagliflozin/Metformin HCl XR Coated Tablets

Ingredient	5 mg / 1000 mg	10 mg / 1000 mg	12.5 mg / 1000 mg	25 mg / 1000 mg	Function	Reference to Standards
	[mg / tablet]					
Tablet Core						
Metformin HCl[1]	1000.0	1000.0	1000.0	1000.0	Drug substance	USP
Polyethylene Oxide (b) (4)	(b) (4)				(b) (4)	NF[2]
Hypromellose (b) (4) (b) (4)						USP
Magnesium Stearate						NF
Purified Water						USP
(b) (4)						
Empagliflozin	(b) (4)				(b) (4)	Company Standard
(b) (4)						Company Standard
Polyethylene Glycol (b) (4)						NF
Talc						USP
Purified Water						USP


(b) (4)
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4.3 Individual Study Synopsis

Trial 1276.15 Study Synopsis

Boehringer Ingelheim

Clinical Trial Report

BI Trial Number:	1276.15
EudraCT Number:	2014-002016-17
BI Investigational Products:	Jardiance® (empagliflozin, BI 10773) and empagliflozin/metformin extended release (XR) fixed dose combination (FDC)
Title:	Bioequivalence of a fixed dose combination tablet of empagliflozin/metformin extended release (25 mg/1000 mg) compared with the free combination of empagliflozin and metformin extended release tablets in healthy subjects following a high-fat, high-caloric meal (an open-label, randomised, single dose, crossover trial)
Clinical Phase:	I
GCP Compliance:	Yes **USA 21 CFR 312.120:** Yes
Authors:	Regina Sennewald[1], Dr Dagmar Hobson[1], Dr Caroline Lippert[1], Ulrich Elsasser[1] [1] Boehringer Ingelheim Pharma GmbH & Co. KG, Birkendorfer Str. 65, Biberach/Riß, Germany
Principal Investigator:	Dr Fabian Müller
Institute/ Department:	Boehringer Ingelheim Pharma GmbH & Co. KG Department of Translational Medicine & Clinical Pharmacology Human Pharmacology Centre Birkendorfer Straße 65, Biberach/Riß, Germany
Date of Report:	02 June 2015
Dates of Trial:	From 18 September 2014 To 28 October 2014
Additional Reports:	None

Name of Company: Boehringer Ingelheim		**Synopsis**	Boehringer Ingelheim
BI Proprietary Name: Jardiance®		**EudraCT No.:** 2014-002016-17	
BI Investigational Products: Jardiance® (empagliflozin, BI 10773) and empagliflozin/metformin extended release (XR) fixed dose combination		**Page:** 1 of 5	
Report Date: 02 Jun 2015	**Trial No. / Doc. No.:** 1276.15 / c02998110-01	**Dates of Trial:** 18 Sep 2014 - 28 Oct 2014	**Date of Revision:** Not applicable

Title of Trial:	Bioequivalence of a fixed dose combination tablet of empagliflozin/metformin extended release (25 mg/1000 mg) compared with the free combination of empagliflozin and metformin extended release tablets in healthy subjects following a high-fat, high-caloric meal (an open-label, randomised, single dose, crossover trial)
Principal Investigator:	Dr Fabian Müller
Trial Site:	Boehringer Ingelheim Pharma GmbH & Co. KG Department of Translational Medicine & Clinical Pharmacology Human Pharmacology Centre Birkendorfer Straße 65, Biberach/Riß, Germany
Publications:	Data from this trial have not been published at the time of this clinical trial report.
Clinical Phase:	I
Objective:	The objective of this trial was to investigate bioequivalence under fed conditions of 1 fixed dose combination (FDC) tablet of 25 mg empagliflozin/1000 mg metformin extended release (XR) compared with the free combination of one 25 mg empagliflozin and two 500 mg metformin XR tablets administered as single dose.
Methodology:	This was an open-label, randomised, 2-way crossover trial with 2 treatments (T and R) and 2 treatment sequences (T_R and R_T). Trial drug administrations of the 2 single dose treatments were separated by a washout period of at least 7 days.
No. of Subjects:	
Planned:	Entered: 30 subjects
Actual:	Entered: 30 subjects (15 subjects in each of the 2 treatment sequences) Treatment T (25 mg empagliflozin/1000 mg metformin XR FDC): Treated and analysed (for primary endpoints): 30 Treatment R (25 mg empagliflozin + 2 x 500 mg metformin XR, single tablets): Treated and analysed (for primary endpoints): 30
Diagnosis:	Not applicable

Name of Company: Boehringer Ingelheim		**Synopsis**	Boehringer Ingelheim
BI Proprietary Name: Jardiance®		**EudraCT No.:** 2014-002016-17	
BI Investigational Products: Jardiance® (empagliflozin, BI 10773) and empagliflozin/metformin extended release (XR) fixed dose combination		**Page:** 2 of 5	
Report Date: 02 Jun 2015	**Trial No. / Doc. No.:** 1276.15 / c02998110-01	**Dates of Trial:** 18 Sep 2014 - 28 Oct 2014	**Date of Revision:** Not applicable

Main Criteria for Inclusion:	Healthy male and female subjects at the age of 18 to 55 years and with a body mass index (BMI) of 18.5 to 29.9 kg/m^2 were included.
Test Product:	Empagliflozin/Metformin hydrochloride (HCl) XR, 25 mg/1000 mg film-coated FDC tablet
Dose:	Single dose of 25 mg empagliflozin/1000 mg metformin HCl XR (1 tablet) in treatment period T
Mode of Admin.:	Oral with 240 mL of water after intake of a high-fat, high-caloric meal
Batch No.:	B141002025
Comparator Product 1:	Empagliflozin, 25 mg film-coated tablet
Dose:	Single dose of 25 mg empagliflozin (1 tablet) together with comparator product 2 in treatment period R
Mode of Admin.:	Oral with 240 mL of water after intake of a high-fat, high-caloric meal
Batch No.:	107785
Comparator Product 2:	Metformin HCl XR (Glumetza®), 500 mg film-coated tablet
Dose:	Single dose of 1000 mg metformin HCl XR (2 tablets) together with comparator product 1 in treatment period R
Mode of Admin.:	Oral with 240 mL of water after intake of a high-fat, high-caloric meal
Batch No.:	B141001813
Duration of Treatment:	Single dose administrations in each of the treatments, with trial drug administrations in the 2 treatments separated by a wash-out period of at least 7 days

Name of Company: Boehringer Ingelheim		**Synopsis**	Boehringer Ingelheim
BI Proprietary Name: Jardiance®		**EudraCT No.:** 2014-002016-17	
BI Investigational Products: Jardiance® (empagliflozin, BI 10773) and empagliflozin/metformin extended release (XR) fixed dose combination		**Page:** 3 of 5	
Report Date: 02 Jun 2015	**Trial No. / Doc. No.:** 1276.15 / c02998110-01	**Dates of Trial:** 18 Sep 2014 - 28 Oct 2014	**Date of Revision:** Not applicable

Criteria for Evaluation:

Clinical Pharmacology:	The following pharmacokinetic parameters were analysed as primary endpoints: AUC_{0-tz} and C_{max} for empagliflozin and metformin The following pharmacokinetic parameter was assessed as secondary endpoint: $AUC_{0-\infty}$ for empagliflozin and metformin Other endpoints are described in the clinical trial report body.
Safety:	The evaluation of safety was based on monitoring of adverse events including clinically relevant findings from the physical examination, conducting safety laboratory tests, performing 12-lead electrocardiogram (ECG), and recording vital signs (blood pressure, pulse rate)
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 the two 1-sided t-tests procedure, each at the 5% significance level. The statistical model was an analysis of variance (ANOVA) on the logarithmic scale including effects for 'sequence', 'subjects within sequences', 'period', and 'treatment'. The CIs were calculated based on the residual error from ANOVA. Descriptive statistics were calculated for all endpoints.

SUMMARY - CONCLUSIONS:

Trial Subjects and Compliance with Trial Protocol:	A total of 30 subjects were entered into this trial and treated at a single centre (Human Pharmacology Centre, Biberach/Riß, Germany). All 30 subjects completed the trial observation time according to the clinical trial protocol. The treated subjects in this trial were 15 male and 15 female healthy white subjects. The mean age was 34.3 years, ranging from 22 to 52 years, and the mean BMI was 24.4 kg/m^2, ranging from 18.8 to 29.4 kg/m^2. Each of the 30 entered subjects received a total dose of 50 mg empagliflozin (corresponding to two 25 mg doses) and of 2000 mg metformin XR (corresponding to two 1000 mg doses) over the entire course of the trial.

Name of Company: Boehringer Ingelheim		**Synopsis**	Boehringer Ingelheim
BI Proprietary Name: Jardiance®		**EudraCT No.:** 2014-002016-17	
BI Investigational Products: Jardiance® (empagliflozin, BI 10773) and empagliflozin/metformin extended release (XR) fixed dose combination		**Page:** 5 of 5	
Report Date: 02 Jun 2015	**Trial No. / Doc. No.:** 1276.15 / c02998110-01	**Dates of Trial:** 18 Sep 2014 - 28 Oct 2014	**Date of Revision:** Not applicable

Safety Results:	Out of 30 treated subjects, a total of 12 treated subjects (40.0%) reported at least 1 adverse event during the on-treatment periods (residual effect periods + post-treatment phases) of the trial. The most frequently reported adverse events overall at the SOC level were nervous system disorders (5 subjects, 16.7%), followed by gastrointestinal disorders, infections/infestations, and respiratory/thoracic/mediastinal disorders (2 subjects, 6.7%, each). On the preferred term level, the most frequent adverse events were headache (5 subjects, 16.7%) as well as nasopharyngitis, cough, and diarrhoea (2 subjects, 6.7% each). All other adverse events were reported by only 1 subject (3.3%) each. No adverse events leading to discontinuation of trial medication were reported in this trial. The investigator judged the adverse events (1 episode of 'decreased appetite' and 3 episodes of 'diarrhoea') of 3 subjects as related to the trial medication. One subject experienced a severe adverse event ('pain in extremity') during treatment period R (single tablets). All other reported adverse events were of mild or moderate intensity. No deaths, no serious adverse events, no other 'significant' adverse event according to ICH E3, and no adverse events of special interest (AESIs) were reported by any of the treated subjects during the on-treatment periods of the trial. Two subjects reported 1 episode each of project-defined AESI ('presyncope' in both cases due to insertion of the canula) during screening and therefore prior to the first trial drug administration. No clinically relevant findings regarding safety laboratory measurements, ECG recordings, physical examinations, and vital sign measurements were reported.
Conclusions:	Bioequivalence in healthy male and female subjects under fed conditions was established between a newly developed FDC tablet, containing 25 mg empagliflozin and 1000 mg metformin XR and the free combination of 1 tablet containing 25 mg empagliflozin and 2 tablets containing 500 mg metformin XR each. For both empagliflozin and metformin, gMean ratios of FDC to single tablets for AUC_{0-tz} and C_{max} were close to 100% and the corresponding 90% CIs were within the bioequivalence acceptance criteria of 80.00 to 125.00%. Single-dose administration of 25 mg empagliflozin together with 1000 mg metformin XR, either as FDC tablet or as single tablets, was safe and well tolerated by the healthy male and female subjects in this trial.

Name of Company: Boehringer Ingelheim		**Synopsis**	Boehringer Ingelheim
BI Proprietary Name: Jardiance®		**EudraCT No.:** 2014-002016-17	
BI Investigational Products: Jardiance® (empagliflozin, BI 10773) and empagliflozin/metformin extended release (XR) fixed dose combination		**Page:** 4 of 5	
Report Date: 02 Jun 2015	**Trial No. / Doc. No.:** 1276.15 / c02998110-01	**Dates of Trial:** 18 Sep 2014 - 28 Oct 2014	**Date of Revision:** Not applicable

Clinical Pharmacology Results:

Following administration of 25 mg empagliflozin and 1000 mg metformin XR under fed conditions, geometric mean (gMean) plasma concentration-time profiles and pharmacokinetic parameters of empagliflozin and metformin were similar for the FDC (treatment T) and the free combination (treatment R). Adjusted gMean ratios of treatment T to treatment R (FDC to single tablets) for AUC_{0-tz}, C_{max}, and $AUC_{0-\infty}$ were close to 100% for both empagliflozin and metformin. The corresponding 90% CIs were all within the bioequivalence acceptance criteria of 80.00 to 125.00%. Therefore, bioequivalence (which was to be based on the primary endpoints AUC_{0-tz} and C_{max}) of both empagliflozin and metformin was demonstrated for the FDC tablet containing 25 mg empagliflozin and 1000 mg metformin XR compared with the free combination of the single tablets when administered under fed conditions. The results of the inferential analysis of the primary and secondary endpoints are given in Table 1.

Table 1: Analysis of relative bioavailability following administration under fed conditions of 25 mg empagliflozin and 1000 mg metformin XR either as FDC tablet or as single tablets

Analyte/ pharmaco-kinetic parameter	Adjusted gMean		Adjusted gMean ratio of FDC to single tablets [%]	90% CI of gMean ratio		Intra-individual gCV [%]
	FDC N=30	Single tablets N=30		Lower limit [%]	Upper limit [%]	
Empagliflozin						
AUC_{0-tz} [nmol·h/L]	5373.67	5470.86	98.22	96.11	100.39	5.0
C_{max} [nmol/L]	589.57	597.36	98.70	93.51	104.17	12.3
$AUC_{0-\infty}$ [nmol·h/L]	5455.92	5549.14	98.32	96.16	100.53	5.1
Metformin						
AUC_{0-tz} [ng·h/mL]	11 008.11	10 777.06	102.14	98.65	105.76	7.9
C_{max} [ng/mL]	1118.95	1058.72	105.69	100.78	110.84	10.9
$AUC_{0-\infty}$ [ng·h/mL]	11 517.77	11 005.13	104.66	101.36	108.07	7.3

Trial 1276.28 Study Synopsis

Boehringer Ingelheim

Clinical Trial Report

BI Trial Number:	1276.28
EudraCT Number:	2014-002360-32
BI Investigational Products:	Jardiance® (empagliflozin, BI 10773) and empagliflozin/metformin extended release (XR) fixed dose combination (FDC)
Title:	Bioequivalence of a fixed dose combination tablet of empagliflozin/metformin extended release (10 mg/1000 mg) compared with the free combination of empagliflozin and metformin extended release tablets in healthy subjects following a high-fat, high-caloric meal (an open-label, randomised, single dose, crossover trial)
Clinical Phase:	I
GCP Compliance:	Yes **USA 21 CFR 312.120:** Yes
Authors:	Regina Sennewald[1], Dr Dagmar Hobson[1], Dr Caroline Lippert[1], Ulrich Elsasser[1] [1] Boehringer Ingelheim Pharma GmbH & Co. KG, Birkendorfer Str. 65, Biberach/Riß, Germany
Principal Investigator:	Dr Klaus Kammerer
Institute/ Department:	Boehringer Ingelheim Pharma GmbH & Co. KG Department of Translational Medicine & Clinical Pharmacology Human Pharmacology Centre Binger Straße 173, Ingelheim am Rhein, Germany
Date of Report:	13 July 2015
Dates of Trial:	From 07 November 2014 To 15 December 2014
Additional Reports:	None

Name of Company: Boehringer Ingelheim		**Synopsis**	Boehringer Ingelheim
BI Proprietary Name: Jardiance®		**EudraCT No.:** 2014-002360-32	
BI Investigational Products: Jardiance® (empagliflozin, BI 10773) and empagliflozin/metformin extended release (XR) fixed dose combination (FDC)		**Page:** 1 of 5	
Report Date: 13 July 2015	**Trial No. / Doc. No.:** 1276.28/ c03125719-01	**Dates of Trial:** 07 Nov 2014 – 15 Dec 2014	**Date of Revision:** Not applicable

Title of Trial:	Bioequivalence of a fixed dose combination tablet of empagliflozin/metformin extended release (10 mg/1000 mg) compared with the free combination of empagliflozin and metformin extended release tablets in healthy subjects following a high-fat, high-caloric meal (an open-label, randomised, single dose, crossover trial)
Principal Investigator:	Dr Klaus Kammerer
Trial Site:	Boehringer Ingelheim Pharma GmbH & Co. KG Department of Translational Medicine & Clinical Pharmacology Human Pharmacology Centre Binger Straße 173, Ingelheim am Rhein, Germany
Publications:	Data from this trial have not been published at the time of this clinical trial report.
Clinical Phase:	I
Objectives:	The objective of this trial was to investigate the bioequivalence under fed conditions of 1 fixed dose combination (FDC) tablet of 10 mg empagliflozin/ 1000 mg metformin extended release (XR) compared with the free combination of one 10 mg empagliflozin and two 500 mg metformin XR tablets administered as single dose.
Methodology:	This was an open-label, randomised, 2-way crossover trial with 2 treatments (T and R) and 2 treatment sequences (T_R and R_T). Trial drug administrations of the 2 single dose treatments were separated by a washout period of at least 7 days.
No. of Subjects:	
Planned:	Entered: 30 subjects
Actual:	Entered: 30 subjects (15 subjects in each of the treatment sequences) <u>Treatment T (10 mg empagliflozin/1000 mg metformin XR FDC):</u> Treated: 30 Analysed (for primary endpoint): 30 for empagliflozin, 29 for metformin <u>Treatment R (10 mg empagliflozin + 2 x 500 mg metformin XR, single tablets):</u> Treated: 30 Analysed (for primary endpoint): 30 for empagliflozin, 30 for metformin
Diagnosis:	Not applicable

Name of Company: Boehringer Ingelheim		**Synopsis**	Boehringer Ingelheim
BI Proprietary Name: Jardiance®		**EudraCT No.:** 2014-002360-32	
BI Investigational Products: Jardiance® (empagliflozin, BI 10773) and empagliflozin/metformin extended release (XR) fixed dose combination (FDC)		**Page:** 2 of 5	
Report Date: 13 July 2015	**Trial No. / Doc. No.:** 1276.28/ c03125719-01	**Dates of Trial:** 07 Nov 2014 – 15 Dec 2014	**Date of Revision:** Not applicable

Main Criteria for Inclusion:	Healthy male and female subjects at the age of 18 to 55 years and with a body mass index (BMI) of 18.5 to 29.9 kg/m^2 were included.
Test Product:	Empagliflozin/Metformin hydrochloride (HCl) XR, 10 mg/1000 mg film-coated FDC tablet
Dose:	Single dose of 10 mg empagliflozin/1000 mg metformin HCl XR (1 tablet) in treatment period T
Mode of Admin.:	Oral with 240 mL of water after intake of a high-fat, high-caloric meal
Batch No.:	B141002925
Comparator Product 1:	Empagliflozin, 10 mg film-coated tablet
Dose:	Single dose of 10 mg empagliflozin (1 tablet) together with comparator product 2 in treatment period R
Mode of Admin.:	Oral with 240 mL of water after intake of a high-fat, high-caloric meal
Batch No.:	B141002726
Comparator Product 2:	Metformin HCl XR (Glumetza®), 500 mg film-coated tablet
Dose:	Single dose of 1000 mg metformin HCl XR (2 tablets) together with comparator product 1 in treatment period R
Mode of Admin.:	Oral with 240 mL of water after intake of a high-fat, high-caloric meal
Batch No.:	B141002731
Duration of Treatment:	Single dose administrations in each of the treatments, with the trial drug administrations in the 2 treatments being separated by a washout period of at least 7 days.

Name of Company: Boehringer Ingelheim		**Synopsis**	Boehringer Ingelheim
BI Proprietary Name: Jardiance®		**EudraCT No.:** 2014-002360-32	
BI Investigational Products: Jardiance® (empagliflozin, BI 10773) and empagliflozin/metformin extended release (XR) fixed dose combination (FDC)		**Page:** 3 of 5	
Report Date: 13 July 2015	**Trial No. / Doc. No.:** 1276.28/ c03125719-01	**Dates of Trial:** 07 Nov 2014 – 15 Dec 2014	**Date of Revision:** Not applicable

Criteria for Evaluation:

Clinical Pharmacology:

The following pharmacokinetic parameters were analysed as primary endpoints: AUC_{0-tz} and C_{max} for empagliflozin and metformin

The following pharmacokinetic parameter was assessed as secondary endpoint: $AUC_{0-\infty}$ for empagliflozin and metformin

Other endpoints were calculated as appropriate.

Safety:

The evaluation of safety was based on monitoring of adverse events including clinically relevant findings from the physical examination, conducting safety laboratory tests, performing 12-lead electrocardiogram (ECG), and recording vital signs (blood pressure, pulse rate)

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 the two 1-sided t-tests procedure, each at the 5% significance level. The statistical model was an analysis of variance (ANOVA) on the logarithmic scale including effects for 'sequence', 'subjects within sequences', 'period', and 'treatment'. The CIs were calculated based on the residual error from ANOVA.

Descriptive statistics were calculated for all endpoints.

SUMMARY - CONCLUSIONS:

Trial Subjects and Compliance with Trial Protocol:

A total of 30 subjects were entered into this trial and treated at a single centre (Human Pharmacology Centre, Ingelheim, Germany). All 30 subjects completed the trial observation time according to the clinical trial protocol. The treated subjects in this trial were 16 male and 14 female healthy white subjects. The mean age was 33.6 years, ranging from 18 to 53 years, and the mean BMI was 24.6 kg/m^2, ranging from 18.8 to 29.4 kg/m^2. Each of the 30 entered subjects received a total dose of 20 mg empagliflozin (corresponding to two 10 mg doses) and of 2000 mg metformin XR (corresponding to two 1000 mg doses) over the entire course of the trial.

Name of Company: Boehringer Ingelheim		**Synopsis**	Boehringer Ingelheim
BI Proprietary Name: Jardiance®		**EudraCT No.:** 2014-002360-32	
BI Investigational Products: Jardiance® (empagliflozin, BI 10773) and empagliflozin/metformin extended release (XR) fixed dose combination (FDC)		**Page:** 4 of 5	
Report Date: 13 July 2015	**Trial No. / Doc. No.:** 1276.28/ c03125719-01	**Dates of Trial:** 07 Nov 2014 – 15 Dec 2014	**Date of Revision:** Not applicable

Clinical Pharmacology Results:

Following administration of 10 mg empagliflozin and 1000 mg metformin XR under fed conditions, geometric mean (gMean) plasma concentration-time profiles and pharmacokinetic parameters of empagliflozin and metformin were similar for the FDC (treatment T) and the free combination (treatment R). Adjusted gMean ratios of treatment T to treatment R (FDC to single tablets) for AUC_{0-tz}, C_{max}, and $AUC_{0-\infty}$ were close to 100% for both empagliflozin and metformin. The corresponding 90% CIs were all within the bioequivalence acceptance criteria of 80.00 to 125.00%. Therefore, bioequivalence (which was to be based on the primary endpoints AUC_{0-tz} and C_{max}) of both empagliflozin and metformin was demonstrated for the FDC tablet containing 10 mg empagliflozin and 1000 mg metformin compared with the free combination of the single tablets when administered under fed conditions. The results of the inferential analysis of the primary and secondary endpoints are given in Table 1.

Table 1: Analysis of relative bioavailability following administration under fed conditions of 10 mg empagliflozin and 1000 mg metformin XR either as FDC tablet or as single tablets

Analyte/ pharmaco-kinetic parameter	Adjusted gMean[1]		Adjusted gMean ratio of FDC to single tablets [%]	90% CI of gMean ratio		Intra-individual gCV [%]
	FDC	Single tablets		Lower limit [%]	Upper limit [%]	
Empagliflozin (N=30 for FDC and single tablets)						
AUC_{0-tz} [nmol·h/L]	2192.66	2212.43	99.11	96.40	101.89	6.3
C_{max} [nmol/L]	242.98	245.13	99.12	93.69	104.87	12.9
$AUC_{0-\infty}$ [nmol·h/L]	2232.92	2258.07	98.89	96.18	101.67	6.3
Metformin (N=29 for FDC and N=30 for single tablets)						
AUC_{0-tz} [ng·h/mL]	10 830.90	10 697.31	101.25	96.54	106.19	10.7
C_{max} [ng/mL]	1169.60	1077.19	108.58	104.17	113.17	9.3
$AUC_{0-\infty}$ [ng·h/mL]	10 975.41	10 827.29	101.37	96.53	106.45	11.0

Name of Company: Boehringer Ingelheim		**Synopsis**	Boehringer Ingelheim
BI Proprietary Name: Jardiance®		**EudraCT No.:** 2014-002360-32	
BI Investigational Products: Jardiance® (empagliflozin, BI 10773) and empagliflozin/metformin extended release (XR) fixed dose combination (FDC)		**Page:** 5 of 5	
Report Date: 13 July 2015	**Trial No. / Doc. No.:** 1276.28/ c03125719-01	**Dates of Trial:** 07 Nov 2014 – 15 Dec 2014	**Date of Revision:** Not applicable

Safety Results:	Out of 30 treated subjects, a total of 14 treated subjects (46.7%) reported at least 1 adverse event during the on-treatment periods (residual effect periods + post-treatments phases) of the trial. The most frequently reported adverse events overall at the SOC level were nervous system disorders (7 subjects, 23.3%), followed by gastrointestinal disorders (5 subjects, 16.7%) and infections/infestations (2 subjects, 6.7%). On the preferred term level, the most frequent adverse events were headache (7 subjects, 23.3%) as well as diarrhoea, nausea, and nasopharyngitis (2 subjects, 6.7% each). All other adverse events were reported by only 1 subject (3.3%) each. No adverse events leading to discontinuation of trial medication were reported in this trial. The investigator judged the adverse events (headache, diarrhoea, dizziness, abdominal distension, nausea, and pollakiuria) of 10 subjects as related to the trial medication. All reported adverse events were of mild or moderate intensity. No deaths, no serious adverse events, and no other 'significant' adverse event according to ICH E3 were reported by any of the treated subjects during the on-treatment periods of the trial. One subject reported 1 episode (pollakiuria) of project-defined adverse events of special interest (AESI) during his first treatment period (FDC). No clinically relevant findings regarding safety laboratory measurements, ECG recordings, physical examinations, and vital sign measurements were reported.
Conclusions:	Bioequivalence in healthy male and female subjects under fed conditions was established between a newly developed FDC tablet, containing 10 mg empagliflozin and 1000 mg metformin XR and the free combination of 1 tablet containing 10 mg empagliflozin and 2 tablets containing 500 mg metformin XR each. For both empagliflozin and metformin, gMean ratios of FDC to single tablets for AUC_{0-tz} and C_{max} were close to 100% and the corresponding 90% CIs were within the bioequivalence acceptance criteria of 80.00 to 125.00%. Single-dose administration of 10 mg empagliflozin together with 1000 mg metformin XR, either as FDC tablet or as single tablets, was safe and well tolerated by the healthy male and female subjects in this trial.

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/s/

RITESH JAIN
11/03/2016

MANOJ KHURANA
11/03/2016

CLINICAL PHARMACOLOGY FILING FORM

Application Information			
NDA/BLA Number	208658	**SDN**	0000
Applicant	Boehringer Ingelheim Pharmaceuticals, Inc.	**Submission Date**	02/10/2015
Generic Name	Empagliflozin and metformin hydrochloride extended-release tablets	**Brand Name**	Synjardy® XR.
Drug Class	Fixed Dose Combination of SGLT-2 inhibitor and Metformin		
Indication	Indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus [redacted (b) (4)].		
Dosage Regimen	Individualize the starting dose of TRADENAME based on the patient's current regimen: • In patients on metformin, switch to TRADENAME containing empagliflozin 10 mg with a similar total daily dose of metformin [redacted (b) (4)] once daily. • In patients on empagliflozin, switch to TRADENAME containing metformin extended release 1000 mg with [redacted (b) (4)] total daily dose of empagliflozin. • In patients already treated with empagliflozin and metformin, switch to TRADENAME containing [redacted (b) (4)]		
Dosage Form	• 5 mg empagliflozin/1000 mg metformin hydrochloride extended-release tablets • 10 mg empagliflozin/1000 mg metformin hydrochloride extended-release tablets • 12.5 mg empagliflozin/1000 mg metformin hydrochloride extended-re lease tablets • 25 mg empagliflozin/1000 mg metformin hydrochloride extended-release tablets	**Route of Administration**	Oral
OCP Division	DCPII	**OND Division**	DMEP

OCP Review Team	Primary Reviewer(s)	Secondary Reviewer/ Team Leader
Division	Ritesh Jain	Manoj Khurana (Acting)
Pharmacometrics		
Genomics		

Review Classification	☑ Standard ☐ Priority ☐ Expedited		
Filing Date	4/10/2015	**74-Day Letter Date**	4/22/2016
Review Due Date	11/4/2016	**PDUFA Goal Date**	12/9/2016

Application Fileability

Is the Clinical Pharmacology section of the application fileable?

☑ Yes
☐ No
If no list reason(s)

Are there any potential review issues/ comments to be forwarded to the Applicant in the 74-day letter?
☐ Yes
☑ No
If yes list comment(s)

Is there a need for clinical trial(s) inspection?
☑ Yes
☐ No
If yes explain: **OSI inspection is needed for the pivotal BE studies 1276.15 and 1276.28. Since both studies are conducted at same clinical and bioanalytical site, the OSI consult will have a note reflecting this fact.**

Clinical Pharmacology Package

Tabular Listing of All Human Studies	☑ Yes ☐ No	Clinical Pharmacology Summary	☑ Yes ☐ No
Bioanalytical and Analytical Methods	☑ Yes ☐ No	Labeling	☑ Yes ☐ No

Clinical Pharmacology Studies

Study Type		Count	Comment(s)
In Vitro Studies			
☐ Metabolism Characterization			
☐ Transporter Characterization			
☐ Distribution			
☐ Drug-Drug Interaction			
In Vivo Studies			
Biopharmaceutics			
☐ Absolute Bioavailability			
☑ Relative Bioavailability		2	Studies 1276.13 and 1276.14 (Pilot Studies)
☑ Bioequivalence		2	• Pivotal BE Study 1276.15: BE of 1 FDC tablet of 25 mg empagliflozin/ 1000 mg metformin XR versus co-administration of one 25 mg empagliflozin and two 500 mg metformin XR tablets administered as single dose under fed condition. • Pivotal BE Study 1276.28: BE of 1 FDC tablet of 10 mg empagliflozin/ 1000 mg metformin XR versus co-administration of one 10 mg empagliflozin and two 500 mg metformin XR tablets administered as single dose under fed condition.
☐ Food Effect			
☐ Other			
Human Pharmacokinetics			
Healthy Subjects	☐ Single Dose		
	☐ Multiple Dose		
Patients	☐ Single Dose		

	☐ Multiple Dose		
☐ Mass Balance Study			
☐ Other (e.g. dose proportionality)			
Intrinsic Factors			
☐ Race			
☐ Sex			
☐ Geriatrics			
☐ Pediatrics			
☐ Hepatic Impairment			
☐ Renal Impairment			
☐ Genetics			
Extrinsic Factors			
☐ Effects on Primary Drug			
☐ Effects of Primary Drug			
Pharmacodynamics			
☐ Healthy Subjects			
☐ Patients			
Pharmacokinetics/Pharmacodynamics			
☐ Healthy Subjects			
☐ Patients			
☐ QT			
Pharmacometrics			
☐ Population Pharmacokinetics			
☐ Exposure-Efficacy			
☐ Exposure-Safety			

Total Number of Studies	**In Vitro**		**In Vivo**	4
Total Number of Studies to be Reviewed				4

Criteria for Refusal to File (RTF)		
RTF Parameter	**Assessment**	**Comments**
1. Did the applicant submit bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	☑Yes ☐No ☐N/A	
2. Did the applicant provide metabolism and drug-drug interaction information? (Note: RTF only if there is complete lack of information)	☐Yes ☐No ☑N/A	Metabolism and drug-drug interaction studies are not conducted in this NDA. Sponsor is relying upon the approved NDA's for Glumetza and Synjardy for the metabolism and drug-drug interaction information.
3. Did the applicant submit pharmacokinetic studies to characterize the drug product, or submit a waiver request?	☑Yes ☐No ☐N/A	
4. Did the applicant submit comparative bioavailability data between proposed drug	☐Yes ☐No ☑N/A	

product and reference product for a 505(b)(2) application?		
5. Did the applicant submit data to allow the evaluation of the validity of the analytical assay for the moieties of interest?	☑Yes ☐No ☐N/A	
6. Did the applicant submit study reports/rationale to support dose/dosing interval and dose adjustment?	☐Yes ☐No ☑N/A	
7. Does the submission contain PK and PD analysis datasets and PK and PD parameter datasets for each primary study that supports items 1 to 6 above (in .xpt format if data are submitted electronically)?	☑Yes ☐No ☐N/A	
8. Did the applicant submit the module 2 summaries (e.g. summary-clin-pharm, summary-biopharm, pharmkin-written-summary)?	☑Yes ☐No ☐N/A	
9. Is the clinical pharmacology and biopharmaceutics section of the submission legible, organized, indexed and paginated in a manner to allow substantive review to begin? If provided as an electronic submission, is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work leading to appropriate sections, reports, and appendices?	☑Yes ☐No ☐N/A	
Complete Application **10.** Did the applicant submit studies including study reports, analysis datasets, source code, input files and key analysis output, or justification for not conducting studies, as agreed to at the pre-NDA or pre-BLA meeting? If the answer is 'No', has the sponsor submitted a justification that was previously agreed to before the NDA submission?	☑Yes ☐No ☐N/A	
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality) Checklist		
Data		
1. Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	☑Yes ☐No ☐N/A	
2. If applicable, are the pharmacogenomic data sets submitted in the appropriate format?	☐Yes ☐No ☑N/A	
Studies and Analysis		
3. Is the appropriate pharmacokinetic information submitted?	☑Yes ☐No ☐N/A	
4. 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)?	☐Yes ☐No ☑N/A	

5. Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	☐Yes ☐No ☑N/A	
6. 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?	☐Yes ☐No ☑N/A	
7. Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?	☐Yes ☐No ☑N/A	
General		
8. Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	☑Yes ☐No ☐N/A	
9. Was the translation (of study reports or other study information) from another language needed and provided in this submission?	☑Yes ☐No ☐N/A	

Filing Memo

Indication and Dosage Administration: Boehringer Ingelheim (BI) is submitting this application for the fixed-dose combination (FDC) of empagliflozin and metformin hydrochloride extended-release (XR) for the treatment of adults with type 2 diabetes mellitus. The proposed indication is:

- As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus

(b) (4)

[redacted]

Drug Molecule and Its Mechanism of Action: Empagliflozin is an approved (NDA204629) sodium dependent glucose co-transporter-2 (SGLT-2) inhibitor indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. Metformin has been available for over 50 years as the first-line therapy for type 2 diabetes. Synjardy®, a fixed dose combination product of **empagliflozin and metformin hydrochloride IR** (NDA 206111), was approved in August 2015.In the current application, sponsor has developed a fixed dose combination of **empagliflozin and metformin hydrochloride (HCl) XR** tablets for once-daily use in patients with type 2 diabetes mellitus. The proposed dose strengths for empagliflozin and metformin HCl extended release fixed dose combination (FDC) tablets are 5mg / 1000mg, 10mg / 1000mg, 12.5mg / 1000mg, and 25mg / 1000mg. The proposed trade name is Synjardy® XR.

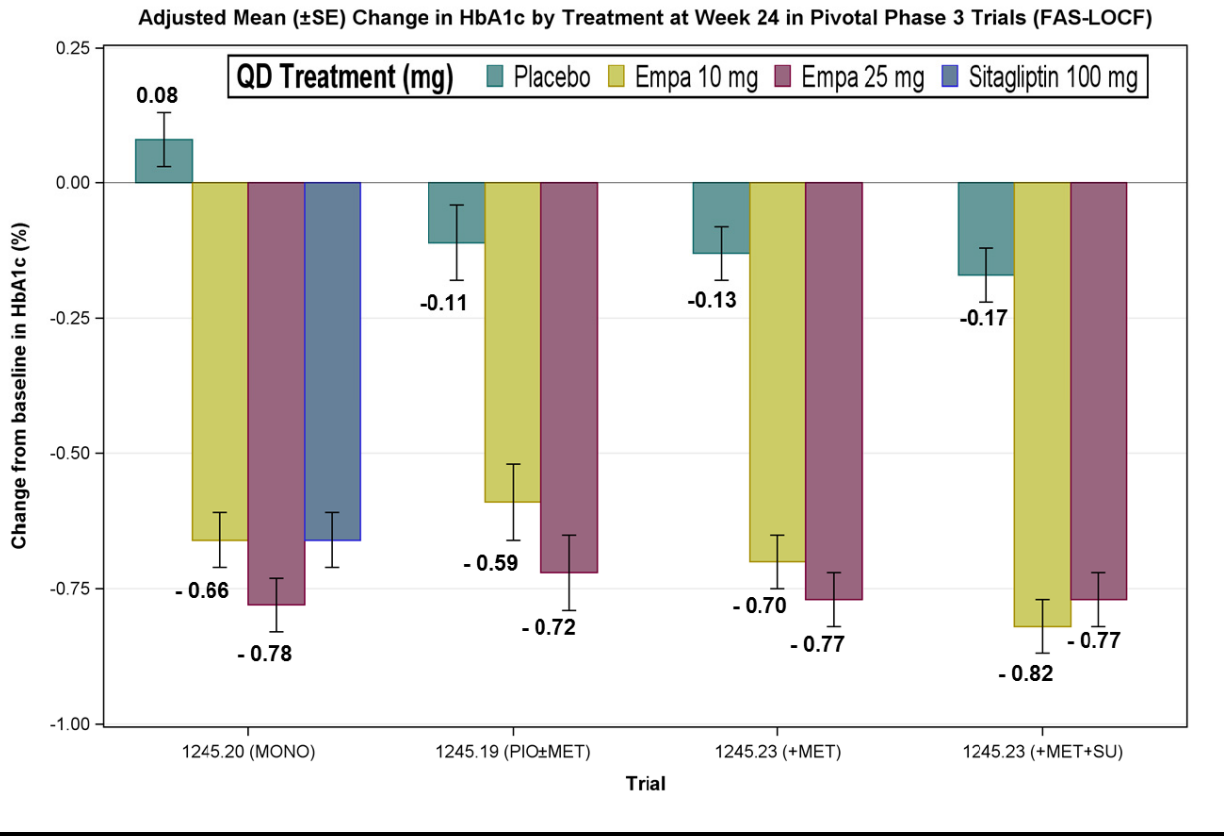
Regulatory History: Sponsor had a pre-IND meeting (May 2011) and Type C meeting (December 2013) and pre NDA meeting (July 2015) for the development of this FDC product. In the Type C meeting dated December 2013 Agency agreed upon:

- Sponsor's proposal to conduct two bioequivalence (BE) studies for the empagliflozin + extended-release metformin FDC tablets
- Sponsor was advised to conduct the two planned BE studies under the more clinically relevant fed conditions instead of fasting conditions. Agency in its response noted that the bioequivalence studies conducted under fed conditions will generate useful information for the product label monograph, negating the need for a separate food effect study.

Clinical Program: No Phase 3 clinical trials were conducted in this NDA. The sponsor is relying on existing clinical safety and efficacy data from:

- Empagliflozin (Jardiance®; NDA 204629),
- Empagliflozin/metformin IR (Synjardy® NDA 206111),
- Metformin XR (Glumetza® NDA 021748).

As seen in figure below, mean change from baseline in HbA1c is greater when empagliflozin is co-administered with background metformin therapy.



Source: Figure Adopted from Clinical Pharmacology Review for NDA 204629

Clinical Pharmacology Program: The clinical development program for the empagliflozin/metformin XR FDC was designed to bridge the existing clinical efficacy and safety data by demonstrating bioequivalence of the empagliflozin/metformin XR FDC tablets to the free combinations of the individual components co-administered in healthy men and women in Phase I studies. To support registration, the application provides data demonstrating bioequivalence of empagliflozin and metformin hydrochloride extended release fixed dose combination tablets to the single entity components in healthy volunteers. Based on the intended posology,

these 4 empagliflozin strengths reflect a daily dose of either 10 mg or 25 mg empagliflozin, taken as 1 tablet per day (10/1000 mg or 25/1000 mg) to account for 1000 mg metformin XR daily or 2 tablets taken at the same time each day (5/1000 mg or 12.5/1000 mg) to account for 2000 mg metformin XR daily. Table below shows the overview of studies in the clinical program for empagliflozin/ metformin XR FDC.

BI study no. Report no.	Objective and description	Study part, Meal status	FDC dose tested (mg)	Free combination dose tested (mg)
(b) (4)				
1276.15 c02998110	Bioequivalence, single-dose, pivotal study	1, fed	Empa 25/met XR 1000	Empa 25 + 2x met XR 500
1276.28 c03125719	Bioequivalence, single-dose, pivotal study	1, fed	Empa 10/met XR 1000	Empa 10 + 2x met XR 500
(b) (4)				

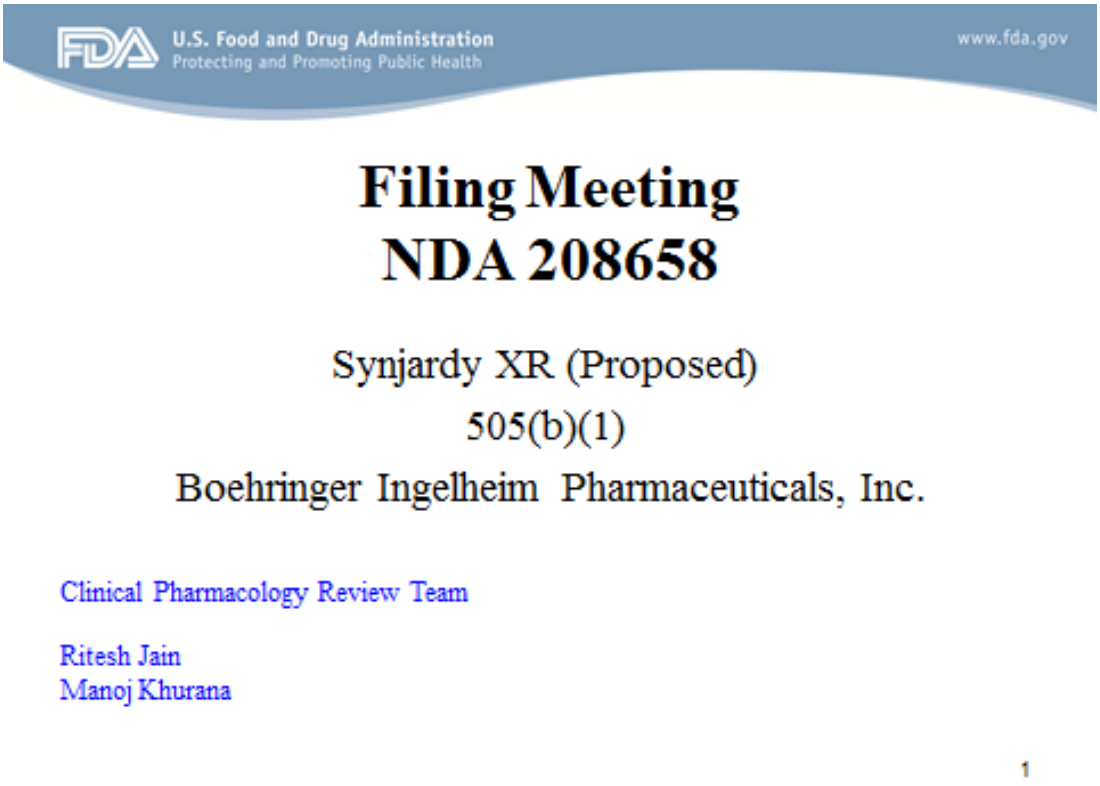
Empa = empagliflozin; met = metformin

In this NDA, the empagliflozin/metformin XR FDC tablet strengths 25/1000 mg (1276.15) and 10/1000 mg (1276.28) were tested for bioequivalence in 2 pivotal studies. These pivotal studies were performed under fed conditions only with the highest XR FDC tablet strength formulation. For the 2 lower empagliflozin/metformin XR FDC tablet strengths (12.5/1000 mg and 5/1000 mg), no bioequivalence studies were performed, and sponsor is seeking a bio-waiver for these two formulation strengths.

Summary: This NDA is file able from Office of Clinical Pharmacology standpoint. OSI inspection is needed for the pivotal BE Studies. The Clinical Pharmacology Review for this NDA will focus on the following key review question:

1. Is co-administration of individual empagliflozin and metformin XR tablets bioequivalent to the FDC of empagliflozin and metformin XR?

Filing Meeting Slides:



Background: Synjardy XR

Indication:

- Indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (b) (4) (b) (4)

Dosage and Administration:

- Individualize the starting dose of TRADENAME based on the patient's current regimen:
  - In patients on metformin, switch to TRADENAME containing empagliflozin 10 mg with a similar total daily dose of metformin (b) (4) once daily.
  - In patients on empagliflozin, switch to TRADENAME containing metformin extended release 1000 mg with (b) (4) total daily dose of empagliflozin.
  - In patients already treated with empagliflozin and metformin, switch to TRADENAME containing (b) (4)

2

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Background: Synjardy XR

Dosage Form and Strengths:

- 5 mg empagliflozin/1000 mg metformin hydrochloride extended-release tablets
- 10 mg empagliflozin/1000 mg metformin hydrochloride extended-release tablets
- 12.5 mg empagliflozin/1000 mg metformin hydrochloride extended-release tablets
- 25 mg empagliflozin/1000 mg metformin hydrochloride extended-release tablets

3

Overview: Clinical Program

- **The sponsor is relying on existing clinical safety and efficacy data from:**
  - Empagliflozin (Jardiance®; NDA 204629),
  - Empagliflozin/metformin IR (Synjardy® NDA 206111),
  - Metformin XR (Glumetza® NDA 021748).

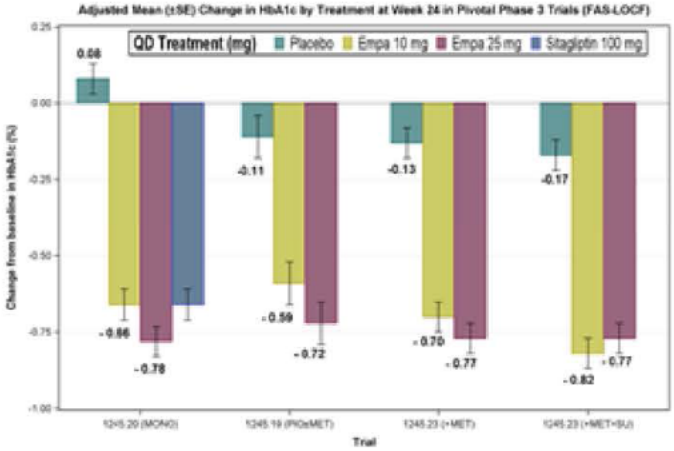

Figure Adopted from Clinical Pharmacology Review for NDA 204629

Overview: Clinical Pharmacology Program

- Program consists of 2 pilot and 2 pivotal BE studies:
  - **Pivotal BE Study 1276.15:** BE of 1 FDC tablet of 25 mg empagliflozin/ 1000 mg metformin XR versus co-administration of one 25 mg empagliflozin and two 500 mg metformin XR tablets administered as single dose under fed condition.
  - **Pivotal BE Study 1276.28:** BE of 1 FDC tablet of 10 mg empagliflozin/ 1000 mg metformin XR versus co-administration of one 10 mg empagliflozin and two 500 mg metformin XR tablets administered as single dose under fed condition.

- **Biowaiver requested for:**
  - 12.5 empa /1000 mg met XR FDC
  - 5 empa /1000 mg met XR FDC

5

BE Established Between FDC and Free Combination at 25/1000 mg and 10/1000 mg Strength

Table 2.1.1: 2 Statistical evaluations for bioequivalence in Study 1276.15 (tablet strength investigated: 25/1000 mg)

	Adjusted gMean ratio of FDC/free combination (90% CI) [%]	gCV [%]
Empagliflozin		
AUC_{0-tz}	98.22 (96.11, 100.39)	5.0
C_{max}	98.70 (93.51, 104.17)	12.3
Metformin		
AUC_{0-tz}	102.14 (98.65, 105.76)	7.9
C_{max}	105.69 (100.78, 110.84)	10.9

gCV = geometric coefficient of variation within subjects

Table 2.1.2: 2 Statistical evaluations for bioequivalence in study 1276.28 (tablet strength investigated: 10/1000 mg)

	Adjusted gMean ratio of FDC/free combination (90% CI) [%]	gCV [%]
Empagliflozin		
AUC_{0-tz}	99.11 (96.40, 101.89)%	6.3
C_{max}	99.12 (93.69, 104.87)%	12.9
Metformin		
AUC_{0-tz}	101.25 (96.54, 106.19)%	10.7
C_{max}	108.58 (104.17, 113.17)%	9.3

gCV = geometric coefficient of variation within subjects

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Filability

- NDA is filable.
- OSI inspection for the 2 pivotal BE studies.

Filing Memo

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?	☑Yes ☐No

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.

Comments to Sponsor:	None

Ritesh Jain
Clinical Pharmacology Reviewer

11 April, 2016
Date

Manoj Khurana
Team Leader(Acting)

11 April, 2016
Date

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

/s/

RITESH JAIN
04/12/2016

MANOJ KHURANA
04/12/2016