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APPLICATION NUMBER:

204629Orig1s000

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

BIOPHARMACEUTICS REVIEW			
Office of New Drug Quality Assessment			
Application No.:	NDA 204-629	Reviewer: Houda Mahayni, Ph.D.	
Division:	DMEP		
Applicant:	Boehringer Ingelheim Pharmaceuticals, Inc.	Team Leader: Angelica Dorantes, Ph.D.	
Trade Name:	Jardiance	Acting Supervisor: Richard T. Lostritto, Ph.D.	
Generic Name:	Empagliflozin (BI 10733)	Date Assigned:	June 6, 2014
Indication:	An adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus	Date of Review:	July 18, 2014
Formulation/strength	Film-coated immediate-release tablets/10 mg and 25 mg		
Route of Administration	Oral		
SUBMISSIONS REVIEWED IN THIS DOCUMENT			
NDA Resubmission Date June 3, 2014		Date of Consult	PDUFA DATE
		June 6, 2014	August 1, 2014
Type of Submission:	Class 1 Resubmission		

I) SUMMARY

Original NDA 204-629 for Empagliflozin (BI 10773) was submitted on March 5, 2013 in accordance with the regulations set forth in section 505 (b) (1) of the FDC Act. This NDA received a Complete Response (CR) action on March 4, 2014.

On June 3, 2014, the Applicant Resubmitted NDA 204-629 addressing the deficiency identified in the action letter dated March 4, 2014. The deficiencies identified in the CR letter are not related to Biopharmaceutics. It is noted that during the first review cycle, Biopharmaceutics recommended approval for this NDA. For details refer to the Biopharmaceutics review by Dr. Houda dated November 4, 2013 in DARRTS.

II) RECOMMENDATION

The Resubmission of NDA 204-629 dated June 3, 2014, does not include any additional Biopharmaceutics data for review and from the Biopharmaceutics perspective APPROVAL is recommended for the Class 1 Resubmission of NDA 204-629 for Jardiance (empagliflozin) Tablets.

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/s/

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07/20/2014

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07/20/2014

CLINICAL PHARMACOLOGY REVIEW

NDA: 204629	Submission Date(s): 03/05/2013
Brand Name (PROPOSED)	JARDIANCE™
Generic Name	Empagliflozin
Clinical Pharmacology Reviewer	Manoj Khurana, Ph.D.
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Pharmacometrics Team Leader	Nitin Mehrotra, Ph.D.
OCP Division	Clinical Pharmacology 2
OND division	Metabolism and Endocrinology Products
Sponsor	Boehringer Ingelheim
Submission Type; Code	NDA 505(b)(1); Standard
Formulation; Strength(s)	Film-coated Immediate-release Tablets; 10 mg and 25 mg
Proposed Indication	An adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

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1 Executive Summary

The sponsor, Boehringer Ingelheim Pharmaceuticals, Inc. (hereafter BI) is seeking approval for JARDIANCE® (Empagliflozin) as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. Empagliflozin is a new molecular entity that belongs to the sodium-glucose cotransporter-2 (SGLT2) inhibitor class of anti-diabetic agents. Among two other NDAs for SGLT2 inhibitors, Canagliflozin (NDA 204042) was approved on March 29, 2013 and Dapagliflozin (NDA 202293) received a Complete Response (CR) action from the Agency. If approved, Empagliflozin will be the second drug in the class of SGLT2 inhibitors. Empagliflozin is available as a film coated immediate release tablet formulation in two dosage strengths: 10 and 25 mg.

1.1 Recommendation

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 2 (OCP/DCP-2) and Division of Pharmacometrics (OCP/DPM) have reviewed the clinical pharmacology data submitted in support of NDA 204629 for JARDIANCE® (Empagliflozin) and recommend approval of this application. A Required Office Level OCP briefing was held on 10/31/2013 to discuss the review team's recommendations. OCP recommends the following regulatory and labeling actions:

Regulatory:

- **Recommend approval of both 10 mg and 25 mg once daily doses.**

Dosage and Administration:

1. **Dosing in type 2 diabetic patients with $eGFR \geq 45$ mL/min/1.73m² [Includes patients with Normal Renal Function ($eGFR \geq 90$ mL/min/1.73m²), Mild Renal Impairment ($90 > eGFR \geq 60$ mL/min/1.73m²), and Moderate Renal Impairment-A ($60 > eGFR \geq 45$ mL/min/1.73m²)]:**
 - The recommended dose for empagliflozin is 10 mg once daily, which can be increased to 25 mg once daily. 25 mg once daily dose provides additional benefit only in select settings (see Section 14, Clinical Trials); therefore, not all patients may get additional benefit by increasing the dose to 25 mg once daily dose. Patient tolerability should also be considered while increasing the dose to 25 mg once daily.
2. **Dosing in type 2 diabetic patients with $eGFR < 45$ mL/min/1.73m² (Includes patients with Moderate Renal Impairment–B, Severe Renal Impairment and End-stage Renal Disease):**
 - Do not use empagliflozin because of lack of benefit.
3. **Renal function and volume status should be closely monitored in elderly patients and patients with high risk of volume depletion (e.g., on loop diuretics, renal impairment).**

4. **No dose adjustment is recommended for patients with hepatic impairment or based on pharmacokinetic drug-drug interaction studies with metformin, glimepiride, sitagliptin, linagliptin, simvastatin, warfarin, ramipril, digoxin, hydrochlorothiazide, torasemide, and oral contraceptives. Even though pharmacokinetic drug-drug interactions were not significant, possible impact on safety (e.g., incidences of hypoglycemia) following concomitant administration of medications need to be considered. For example dose adjustments may be needed when empagliflozin is coadministered with insulin secretagogues (e.g., sulfonylurea) or insulin to reduce the risk of hypoglycemia.**
5. **Monitoring of HbA1c levels are recommended when empagliflozin is co-administered with inhibitors of OAT3 transporter, such as probenecid, and UGT enzyme inducers, such as rifampicin.**

1.2 Phase IV Commitments

None.

1.3 Summary of Important Clinical Pharmacology Findings

The clinical development program for empagliflozin was composed of 30 Phase I trials and 13 Phase IIb/III trials. Overall, 13767 subjects were treated in these clinical trials, 6808 patients were treated with empagliflozin for at least 24 weeks, 4415 patients for at least 52 weeks, and 1486 patients for at least 76 weeks. In clinical studies, empagliflozin was evaluated as mono-therapy and in combination with metformin, metformin plus a sulphonylurea, pioglitazone (\pm metformin), and basal insulin. In addition, sponsor conducted a dedicated efficacy/safety trial in type 2 diabetic subjects with renal impairment. At the time of NDA submission, the cardiovascular safety trial was ongoing. The sponsor assessed the cardiovascular (CV) risk associated with empagliflozin therapy by conducting a prospective, pre-specified meta-analysis of independently adjudicated cardiovascular events including the interim data from this trial.

Clinical Pharmacology review of the information submitted by the sponsor, in support of their application, revealed the following important findings:

Dose/Exposure-Response for Efficacy:

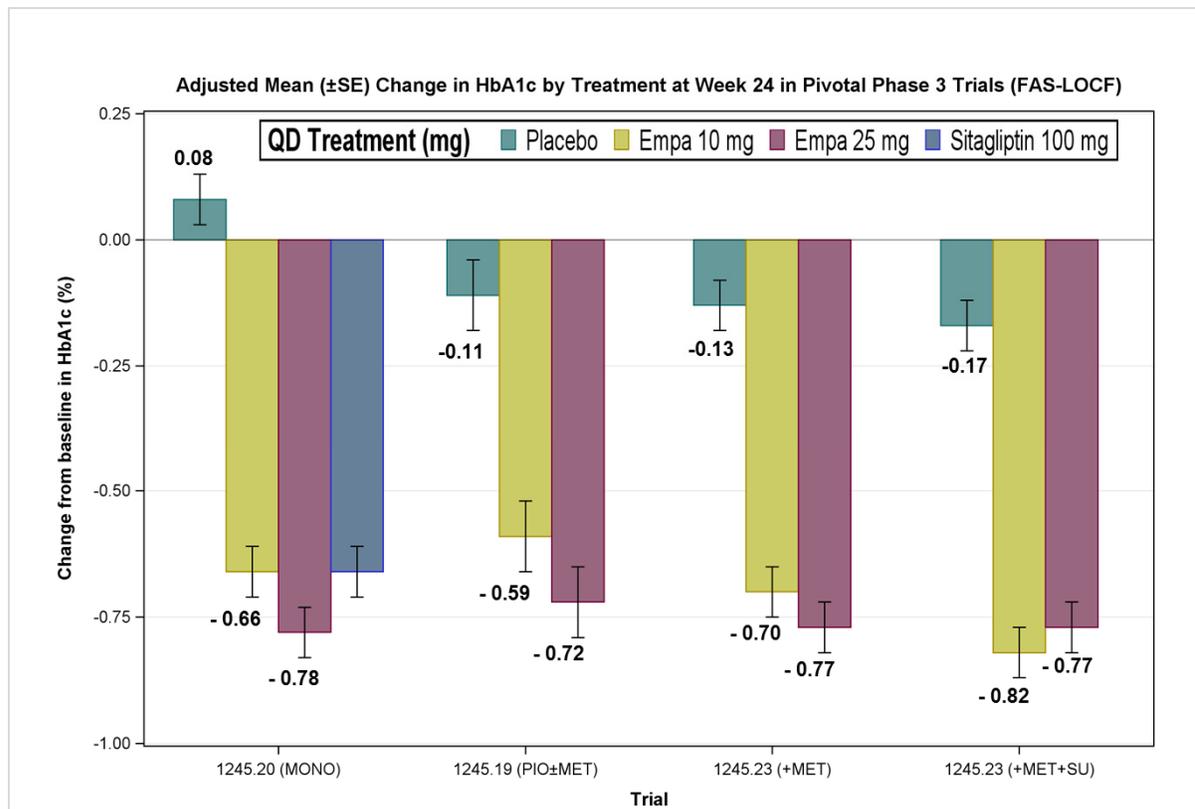
Sponsor proposed *a starting dose of 10 mg once daily, which can be increased to 25 mg once daily for additional glycemetic control.* The adequacy of the proposed dosage regimen was evaluated from the dose-response relationship.

Evaluation of longitudinal (over time) and cross-sectional (across treatments) HbA1c data from the placebo-controlled Phase 3 trials showed the following:

- The HbA1c reduction appeared to reach plateau by Week 24 in the Phase 3 trials, thus allowing for a reasonable dose-response evaluation at Week 24.
- There was lack of evidence of clear dose-response when primary end-point data from monotherapy and add on therapy trials was examined (See Figure 1). From efficacy perspective, the dose-response data suggests that the use of 25 mg once daily dose of empagliflozin does not always produce higher reduction in HbA1c than 10 mg once daily.

- In case of add on therapy to metformin or add on to metformin+sulfonylurea, the responses seen with 10 and 25 mg were similar.
- In some specific treatment settings, such as when administered as monotherapy, as add-on therapy to patients on pioglitazone with or without metformin or as add-on to insulin, 25 mg once daily dose offers an additional HbA1c reduction of up to 0.14% units at population level.
- There was however, a dose-dependent increase in proportion of patients who achieved <7% HbA1c by the time of primary end-point measurement in most of the efficacy evaluations.
- This suggests that in certain treatment settings, the 25 mg dose could provide additional benefit for some patients in certain treatment settings.

The mean (95%CI) change from baseline in HbA1c by treatment from the confirmatory Phase 3 trials is shown in Figure 1 below.



EMPA = empagliflozin, CI = confidence interval, LOCF = last observation carried forward, FAS = Full Analysis Set, MONO= Monotherapy, MET= Metformin, SU = sulfonylurea, PIO = Pioglitazone.

Figure 1 Mean (95%CI) Changes from Baseline in HbA1c (%) at Primary Assessment Time-point-LOCF: Study-by-Study Comparison (Phase 3 Studies: Full Analysis Set).

Results from the Monotherapy Trial (1245.20):

At week 24, the adjusted mean change (SE) in HbA1c from baseline at Week 24 was -0.08 (0.05)%, -0.66 (0.05)%, and -0.78 (0.05)% for placebo, empagliflozin 10 mg once daily, and empagliflozin 25 mg once daily, respectively. Accordingly, the difference versus placebo for the adjusted mean change (95%CI) in HbA1c from baseline at Week 24 was -0.74 (-0.88, -0.59) % for the empagliflozin 10 mg once daily group and -0.85 (-0.99, -0.71)% for the empagliflozin 25 mg once daily group, showing numerically higher HbA1c reduction with the latter. The proportion of subjects who achieved target HbA1c levels of <7.0% by Week 24 was higher for the 25 mg once daily dose group (43.6%) than the 10 mg once daily dose group (35.3%), while both being higher than placebo (12.0%).

Results from the Add-on therapy Trials:

Add-on to (pioglitazone ± metformin): In the dual/triple therapy setting in trial 1245.19 (~25% Add on to pioglitazone and ~75% Add on to pioglitazone plus metformin), the adjusted mean change (SE) in HbA1c from baseline at Week 24 was -0.11 (0.07)%, -0.59 (0.07)%, and -0.72 (0.07)% for placebo, empagliflozin 10 mg once daily, and empagliflozin 25 mg once daily, respectively. Accordingly, the difference versus placebo for the adjusted mean change (95%CI) in HbA1c from baseline at Week 24 was -0.48 (-0.66, -0.29) % for the empagliflozin 10 mg once daily group and -0.61 (-0.79, -0.42)% for the empagliflozin 25 mg once daily group, showing numerical advantage of the latter. The proportion of subjects who achieved target HbA1c levels of <7.0% by Week 24 was also slightly higher for the 25 mg once daily dose group (30.0%) than the 10 mg once daily dose group (23.8%), while both doses being higher than placebo (7.7%).

Add-on to metformin: In the dual therapy setting in trial 1245.23 (Add-on to metformin), the adjusted mean change (SE) in HbA1c from baseline at Week 24 was -0.13 (0.05)%, -0.70 (0.05)%, and -0.77 (0.05)% for placebo, empagliflozin 10 mg once daily, and empagliflozin 25 mg once daily, respectively. Accordingly, the difference versus placebo for the adjusted mean change (95%CI) in HbA1c from baseline at Week 24 was -0.57 (-0.70, -0.43) % for the empagliflozin 10 mg once daily group and -0.64 (-0.77, -0.50)% for the empagliflozin 25 mg once daily group, showing only slight numerical advantage of the latter. The proportion of subjects who achieved target HbA1c levels of <7.0% by Week 24 was comparable for the 25 mg once daily dose group (38.7%) and the 10 mg once daily dose group (37.7%), while both doses being higher than placebo (12.5%).

Add-on to (metformin + sulphonylurea): In trial 1245.23 (Add-on to metformin plus sulphonylurea), the adjusted mean change (SE) in HbA1c from baseline at Week 24 was -0.18 (0.05)%, -0.80 (0.05)%, and -0.77 (0.05)% for placebo, empagliflozin 10 mg once daily, and empagliflozin 25 mg once daily, respectively. Accordingly, the difference versus placebo for the adjusted mean change (95%CI) in HbA1c from baseline at Week 24 was -0.64 (-0.77, -0.51) % for the empagliflozin 10 mg once daily group and -0.59 (-0.73, -0.46)% for the empagliflozin 25 mg once daily group, showing a lack of dose response between the two doses. The proportion of subjects who achieved target HbA1c levels of <7.0% by Week 24 however, was slightly higher numerically for the 25 mg once daily dose group (32.2%) than the 10 mg once daily dose group (26.3%), while both doses being higher than placebo (9.3%).

Add-on to basal insulin (1245.33, Phase 2b): In add-on to basal insulin trial (Phase 2b, 1245.33), the adjusted mean differences versus placebo were -0.56% in the empagliflozin 10 mg group (97.5% CI: -0.78, -0.33) and -0.70% in the empagliflozin 25 mg group (97.5% CI: -0.93, -0.47) showing a dose response between the two doses for HbA1c reduction. For the key secondary endpoint of basal insulin dose, the adjusted mean differences from placebo at Week 78 were -6.66 IU in the empagliflozin 10 mg group (97.5% CI: -11.56, -1.77) and -5.92 IU in the empagliflozin 25 mg group (97.5% CI: -11.00, -0.85). At Week 18, among patients with a baseline HbA1c of 7.0% or greater, 18.0% of the patients in the empagliflozin 10 mg group and 19.5% of the patients in the empagliflozin 25 mg group had attained HbA1c values of less than 7.0% compared with 5.5% of patients in the placebo group.

Impact of Renal Impairment on Efficacy

Results from the Phase 3 Trial in Patients with Renal Impairment (1245.36):

Consistent with the known mechanism of action of empagliflozin, there is a lower reduction in HbA1c levels with increasing degree of renal impairment in subjects with type 2 diabetes. The reduction in HbA1c from baseline in subjects with moderate renal impairment (1245.36) was of lower magnitude (approximately half) when compared to the magnitude observed in type 2 diabetic subjects in trial 1245.20 or add-on therapy trials 1245.19 and 1245.23 (majority of subjects were with normal renal function or with mild renal impairment) (see Figure 2).

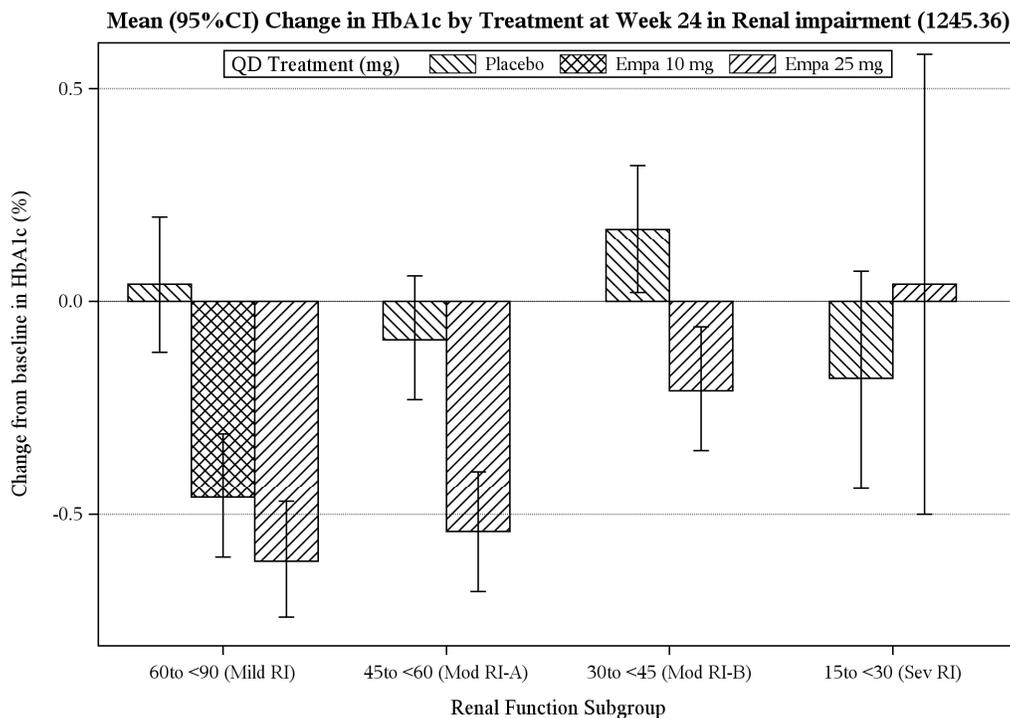


Figure 2 Mean (95%CI) change from baseline in HbA1c by treatment and renal impairment subgroup in phase 3 trial 1245.36).

Even though the mean response is lower in type 2 diabetic subjects with mild renal impairment compared to those with normal renal function, efficacy of Empagliflozin is preserved in these subjects for both 10 mg and 25 mg once daily doses.

In type 2 diabetic subjects with moderate renal impairment only 25 mg dose was evaluated, limiting any dose-response assessment. However, decrease in HbA1c was observed following 24 weeks treatment with empagliflozin. Post-hoc evaluation based on baseline renal function showed that this response was primarily driven by subjects with eGFR 45 to <60 mL/min/1.73m² (Figure 2). Based on absolute response, empagliflozin showed modest efficacy in patients with eGFR 30 to <45 mL/min/1.73 m² *per se* [absolute mean (SE) change from baseline in HbA1c of -0.21 (0.07)]. However, placebo adjusted response for empagliflozin 25 mg once daily dose (Mean reduction in HbA1c of -0.39% unit) seems to be inflated by worsening of HbA1c response in placebo group [absolute mean (SE) change from baseline in HbA1c of 0.17 (0.07)] in eGFR 30 to <45 ml/min/1.73 m² subgroup.

Empagliflozin was not efficacious in type 2 diabetic subjects with severe renal impairment.

Dose/Exposure-Response for Safety:

Empagliflozin causes only modest decreases in eGFR from baseline in a dose-dependent manner in patients with normal renal function or mild renal impairment. Overall, among patients with mild, moderate (3A and 3B), and severe renal impairment there were more patients with decline in eGFR from baseline at week 12 in comparison to placebo. On average, the decline in eGFR appeared to regress over time towards baseline.

In all empagliflozin treated subjects, the adverse event profile of 10 mg once daily and 25 mg once daily dose was similar except for hypoglycemia incidences being higher with 25 mg once daily dose.

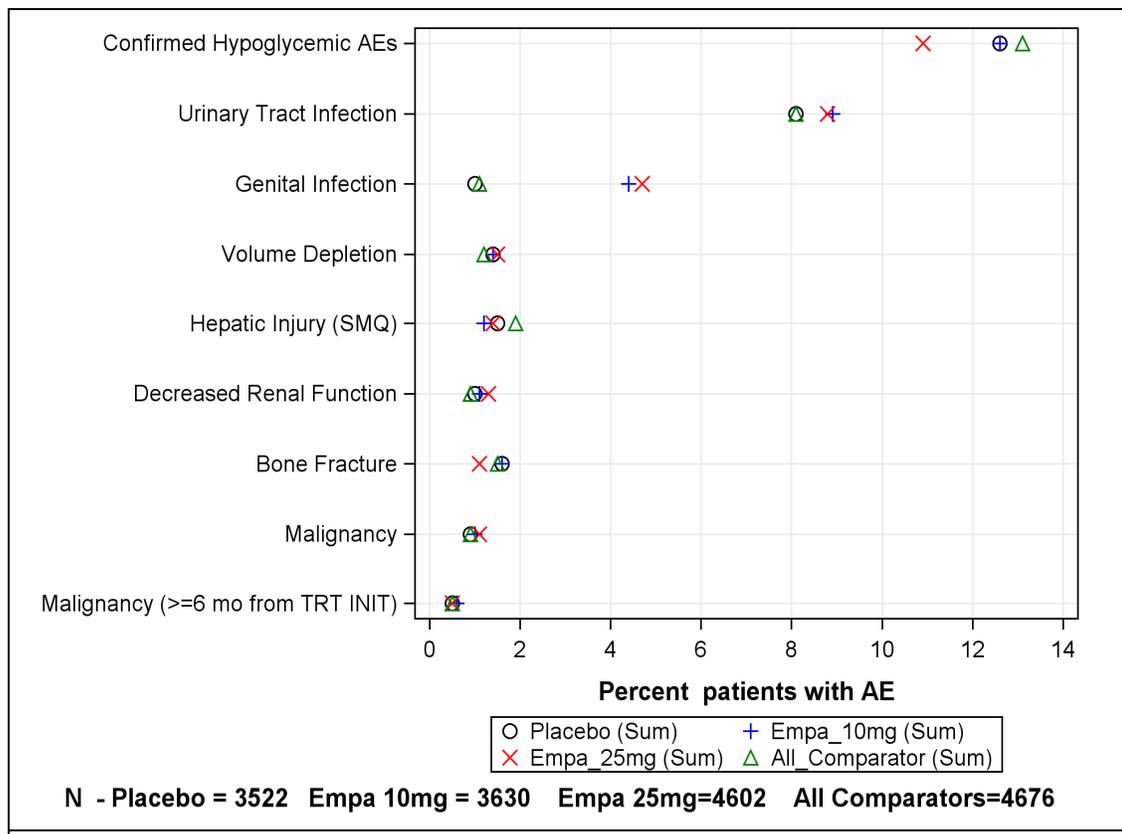


Figure 3 Dose-response for adverse events in pooled clinical data (SAF-5)

- Elderly patients (> 65 year age), patients with moderate or severe renal impairment (See Figure 4 below) showed higher susceptibility for hypoglycemia, volume depletion, and urinary tract infection AEs for both doses.

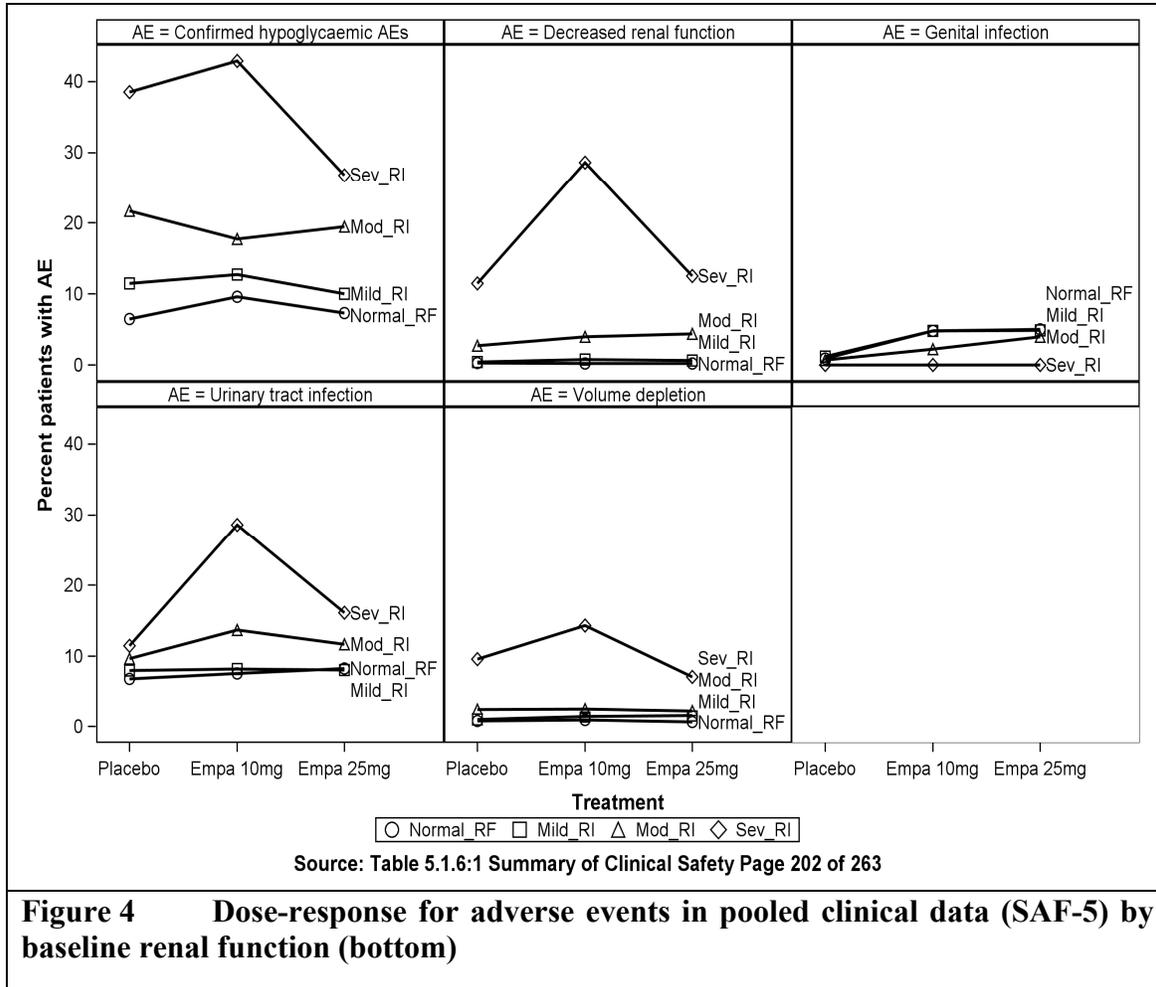


Figure 4 Dose-response for adverse events in pooled clinical data (SAF-5) by baseline renal function (bottom)

Acceptability of the proposed dose based on Dose-Efficacy/Safety relationship:

Type 2 diabetic patients with normal renal function (eGFR ≥90 mL/min/1.73m²) and mild renal impairment (90>eGFR ≥60 mL/min/1.73m²): From a benefit perspective, there is lack of evidence of clear dose-response when data from monotherapy and add on therapy trials was examined. From efficacy perspective, the dose-response data suggests that the use of 25 mg once daily dose of empagliflozin does not always produce numerically higher reduction in HbA1c than 10 mg once daily, which does not support the sponsor’s original proposal of 25 mg once daily dose. However, in some specific treatment settings, such as when administered as monotherapy, as add-on therapy to patients on pioglitazone with or without metformin or as add on to insulin, 25 mg once daily dose offers an additional HbA1c reduction of up to 0.14% units. In addition, there was a dose-dependent increase in proportion of patients who achieved <7% HbA1c by

the time of primary end-point measurement. Therefore, there is merit in having both doses available for use. Placebo adjusted mean reductions in HbA1c (% units) for monotherapy/dual therapy/triple therapy Phase 3 trials ranged from -0.48 to -0.74 % units and -0.59 to -0.85 % units for 10 mg once daily and 25 mg once daily dose, respectively.

Notably, most of the diabetic patients need combination therapies in order to get an optimal glycemic control and empagliflozin is also likely to be used in background of metformin or other antidiabetic therapies. The combination therapy trials that sponsor conducted for empagliflozin showed a modest incremental benefit (up to 0.14% unit additional reductions in HbA1c) of using 25 mg once daily as compared to the 10 mg once daily. Even with lower mean response in comparison to subjects with normal renal function, efficacy of empagliflozin was preserved in type 2 diabetes mellitus subjects with mild renal impairment with both 10 mg once daily and 25 mg once daily doses.

On the safety side, there are slight dose-dependent changes in eGFR, whereas both doses were essentially similar in their adverse event profiles.

Therefore, given that dose related benefit is present in select treatment settings along with no increase in risk of adverse events for 25 mg once daily dose, compared to the 10 mg once daily dose, approval of both 10 mg and 25 mg once daily doses is recommended. The recommended dose for empagliflozin is 10 mg once daily, which can be increased to 25 mg once daily. Although, it has not been established if 25 mg once daily dose provides additional benefit in patients who show less than optimal response at 10 mg once daily dose, there is a general trend for greater benefit with 25 mg once daily dose in select treatment settings. Therefore, some patients may benefit from 25 mg once daily dose and for some patients, a lower dose of 10 mg once daily may be sufficient. The dose increases above 10 mg once daily should be made only after clinical reassessment including assessment of tolerability, and generally should occur at intervals of more than 3 months. When dose increase is indicated, the maximum recommended dose is 25 mg once daily.

Type 2 diabetic patients with moderate renal impairment ($60 > \text{eGFR} \geq 30 \text{ mL/min/1.73m}^2$): From a benefit perspective, consistent with the known dependence of empagliflozin mechanism of action on integrity of the renal function, the 25 mg once daily dose showed only a modest efficacy in subjects with moderate renal impairment (Figure 2 1245.36 results) when compared to type 2 diabetes mellitus subjects with normal renal function or mild renal impairment. The magnitude of response is markedly attenuated in the presence of moderate renal impairment. Further, reduction in HbA1c (week 24 end-point) from baseline are dependent on dose and baseline eGFR in patients with RI (1245.36).

A post-hoc evaluation of the data from Trial 1245.36, evaluating efficacy in moderate RI subgroups using an eGFR cut-off of $45 \text{ mL/min/1.73m}^2$, demonstrated that the efficacy in patients with moderate renal impairment was primarily driven by the subjects with baseline $\text{eGFR} \geq 45 \text{ mL/min/1.73m}^2$ where, mean (SE) HbA1c reduction with 25 mg once daily empagliflozin dose $[-0.54 (0.07)]$ was well separated from placebo $[-0.08 (0.07)]$, showing that efficacy was preserved in these patients although attenuated compared to patients with normal renal function. Although 10 mg dose was not directly evaluated in this subgroup, based on the dose response observed in other studies the 10 mg dose is also likely to be efficacious.

On the safety side, there was a trend for decrease in eGFR in patients with moderate renal impairment following treatment with empagliflozin. In addition, the susceptibility to several adverse events was notably increased with worsening degree of renal impairment.

In the eGFR 30 to <45 mL/min/1.73m² subgroup, based on absolute response a modest efficacy was observed for the empagliflozin 25 mg once daily dose ; however, placebo adjusted response appeared to be inflated by worsening of HbA1c response in the placebo group. It is anticipated that the response for the 10 mg once daily dose will be further reduced in this subgroup. In addition, it is not certain what factors were responsible for the trend of worsening placebo response in eGFR 30 to <45 mL/min/1.73m² subgroup. Note that a similar post-hoc analysis for two other SGLT-2 inhibitors (canagliflozin and dapagliflozin) showed that HbA1c response for patients with eGFR 30 to <45 mL/min/1.73m² didn't worsen on placebo treatment. With respect to safety comparison between eGFR 45 to <60 mL/min/1.73m² (generally regarded as Moderate RI-A) and eGFR 30 to <45 mL/min/1.73m² (generally regarded as Moderate RI-B), the latter group is likely to experience more adverse events because these patients have relatively poor renal function and further reduction in eGFR could bring them closer to severe renal impairment group. Patients with severe renal impairment appeared to be more susceptible to adverse events, such as confirmed hypoglycemia and volume depletion, even on placebo treatment, compared to mild/moderate renal impairment. Therefore, given the lack of certainty in efficacy and higher susceptibility towards adverse events, the benefit-risk does not seem to favor the use of empagliflozin in patients with eGFR 30 to <45 mL/min/1.73m².

Therefore, it is recommended that empagliflozin be only used in patients with eGFR 45 to <60 mL/min/1.73m² in a dosage regimen similar to that recommended for patients with normal renal function.

Type 2 diabetes mellitus patients, eGFR<30 mL/min/1.73m² (Severe Renal Impairment and End-stage Renal Disease): For patients with eGFR<30 mL/min/1.73m² empagliflozin 25 mg did not show any efficacy. There was a trend for decrease in eGFR and higher susceptibility for adverse events in patients with severe renal impairment following treatment with empagliflozin. Therefore, empagliflozin use is not recommended in patients with eGFR<30 mL/min/1.73m².

QT/QTc: Empagliflozin does not prolong QTc interval. A thorough QT study was conducted for Empagliflozin. According to the review by Inter-disciplinary Review Team (IRT), the trial was sufficient to rule out significant changes in QTc interval (i.e., upper bound of 90% confidence interval excludes 10 ms), as defined by ICH E14 guidance.

General ADME:

Absorption: 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-∞} 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.

Distribution: The apparent steady-state volume of distribution ranged from 180-230 L. Following administration of an oral [¹⁴C]-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%.

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. 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.

Elimination: 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.

Intrinsic Factors (Body weight, Age, BMI, Gender, Race, and Genetics etc.) Affecting Exposure:

The population pharmacokinetic/pharmacodynamic analyses were conducted for empagliflozin. The effects of various covariates e.g. eGFR, body weight, age, BMI, race, and gender on empagliflozin PK parameters were evaluated in this analysis. Overall, the findings do not warrant for any dose-adjustments of Empagliflozin based on any of these covariates.

Elderly patients: Empagliflozin clinical program provided safety and efficacy information on patients above 65 years of age. Although age was a significant covariate for clearance of empagliflozin, the finding could be confounded by the known decrease in renal function with age. Nevertheless, empagliflozin is expected to accumulate to a greater extent in elderly than young adults. However, the elderly population is susceptible to adverse events that are related to mode of action of the drug rather than the systemic exposure of drug. This susceptibility is increased if renal impairment is present in the elderly population. With the dosing recommendation of limiting the use of empagliflozin in eGFR \geq 45 ml/min/1.73m², empagliflozin will not be used in elderly patients with

relatively poor renal function (eGFR < 45 mL/min/1.73m²), which will likely reduce the occurrence of adverse events in these patients. In addition, the recommended dose for treatment initiation being 10 mg once daily should also minimize the risk for adverse events in this population.

Renal Impairment: In patients with mild (eGFR: 60 to <90 mL/min/1.73m²), moderate (eGFR: 30 to <60 mL/min/1.73m²), and severe (eGFR: <30 mL/min/1.73m²) renal impairment and patients with kidney failure/ESRD patients, AUC of empagliflozin increased by approximately 18%, 20%, 66%, and 48%, respectively, compared to patients with normal renal function (eGFR: ≥90 mL/min/1.73m²). Peak plasma levels of empagliflozin (i.e., C_{max}) were approximately 20% higher in subjects with mild and severe renal impairment and were similar in subjects with moderate renal impairment and kidney failure/ESRD compared to patients with normal renal function. The pharmacodynamic effect assessed from urinary glucose excretion decreased in parallel with the decrease in empagliflozin renal clearance and glomerular filtration rate (see Figure 19). The systemic exposure increase did not result in increase in effect, as expected, because the primary mechanism of action of empagliflozin is dependent on the functional integrity of renal filtration/reabsorption. Dosing recommendations in patients with renal impairment are discussed above.

Hepatic Impairment: In subjects with mild, moderate, and severe hepatic impairment, categorized according to the Child-Pugh classification, AUC_{0-inf} of empagliflozin increased approximately by 23%, 47%, and 75% and C_{max} by approximately 4%, 23%, and 48%, respectively, compared to subjects with normal hepatic function. There was an increase in the fraction of drug excreted in urine without any effect on amount/rate of urinary glucose excretion. Therefore, no dose adjustments are warranted in patients with hepatic impairment.

Extrinsic Factors:

Food Effect: On average the extent of absorption (AUC_{0-∞}/AUC_{0-tlast}) was 16% lower and peak exposure (C_{max}) was 27% lower under fed conditions. In the phase 3 trials, patients were instructed to take their trial medication once daily in morning with water. Further, to ensure a dosing interval of about 24 hour, patients were asked to take the trial medication at about the same time every day, taken with or without food. Therefore, empagliflozin can be administered with or without food similar to the way it was tested in Phase 3 trials.

Effect of Co-administered Drugs on Empagliflozin (Drug-drug Interactions):

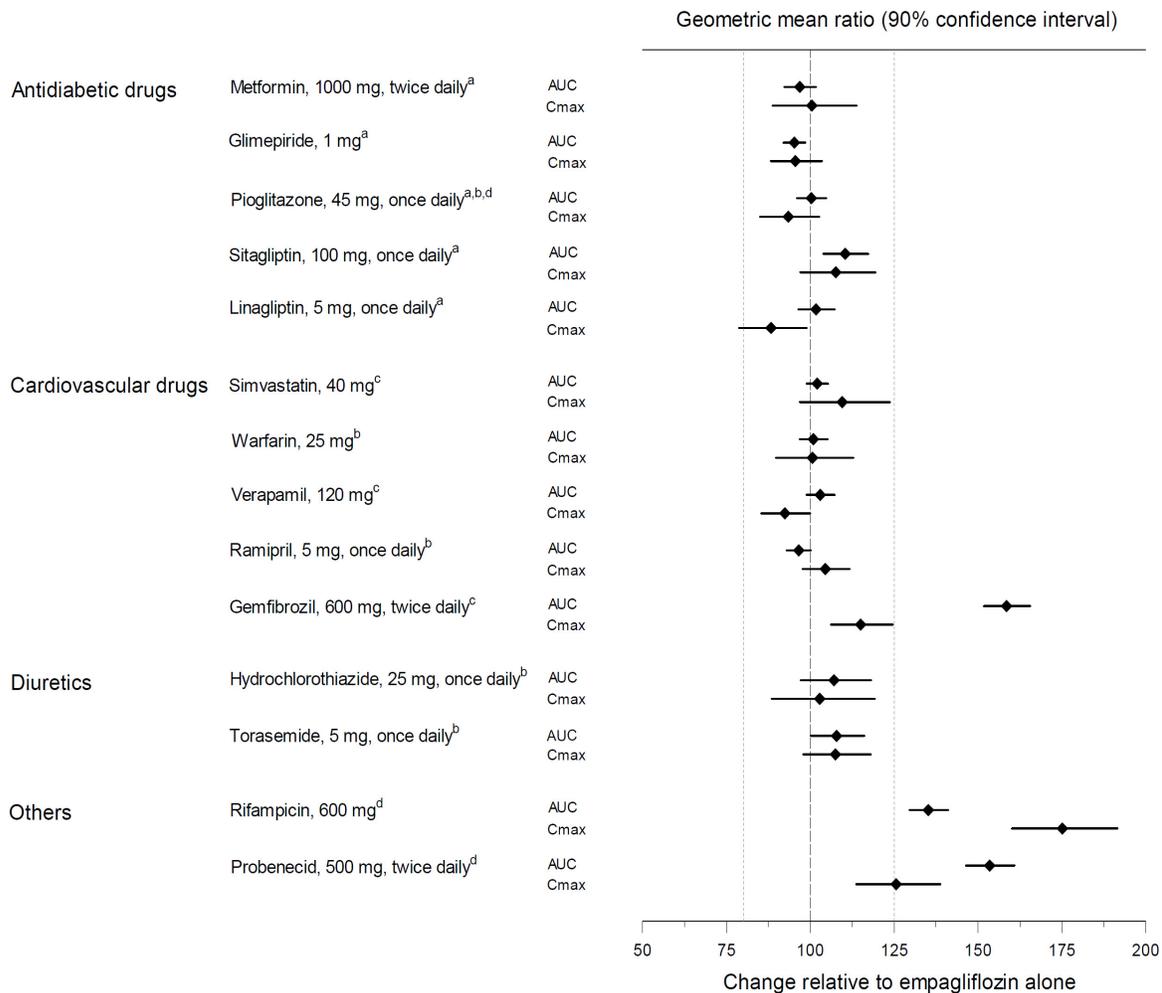
Clinical DDI investigations were conducted at the 25 to 50 mg dose (except as noted) with representative medications from anti-hypertensive, anti-diabetic and lipid-lowering classes.

Co-administration of various representative drugs did not affect the exposure of empagliflozin in a clinically meaningful way (see Figure 5 below).

Co-administration with probenecid resulted in about 30% decrease in fraction of unchanged empagliflozin excreted in urine (20% to 14%) without any effect on UGE0-24h. Notably, 14% Fe was still in maximal region of Fe0-24h – UGE0-24h relationship seen in PKPD studies (see Figures 12 and 13). However, similar reductions in Fe (%) in patients with renal impairment could further jeopardize the pharmacodynamic response. Therefore, even if the PK change is not clinically relevant, the relevance of PD effect cannot be disregarded for patients with renal impairment. Therefore, we recommend that HbA1c levels are monitored when using empagliflozin in type 2 diabetic patients with renal impairment who are taking OAT3 inhibitors such as probenecid (as monotherapy or its combination products).

DDI evaluation with rifampicin was conducted in a single-dose setting, which was sensitive for detecting the inhibition of OATP1B1 mediated uptake in liver and consequent increase in C_{max} and AUC of empagliflozin. However, in absence of a multiple-dose DDI study with rifampicin, the effect of UGT enzyme induction by rifampicin on empagliflozin exposure is not evaluated. Therefore, we recommend that HbA1c levels should be monitored when using empagliflozin in type 2 diabetic patients who are taking rifampicin or other inducers of UGT2B7, UGT1A3, UGT1A8, and UGT1A9.

When co-administered with diuretics (hydrochlorothiazide or torasemide) the urine osmolality and urine volume were increased after treatment with empagliflozin alone and with a diuretic, while diuretics alone had no apparent effect. Mean urine volume was higher (341 mL/day) than baseline after single doses of empagliflozin and tended to be higher (135 mL/day) than baseline after multiple doses of empagliflozin. At baseline, mean micturition frequencies were 4 to 5 voids in the day and 3 voids at night. On the first and fifth days of empagliflozin treatment, daytime micturition increased to about 6 voids per day while night-time micturition frequency was similar to baseline. The mean increase in total micturition frequency was about 1 to 2 voids per day. Treatment with hydrochlorothiazide or torasemide tended to increase both urinary glucose excretion and fasting serum glucose levels. When empagliflozin was added to either diuretic, the effects on urinary glucose excretion were maintained while the reductions in the fasting serum glucose concentration were less pronounced than when empagliflozin was given alone.

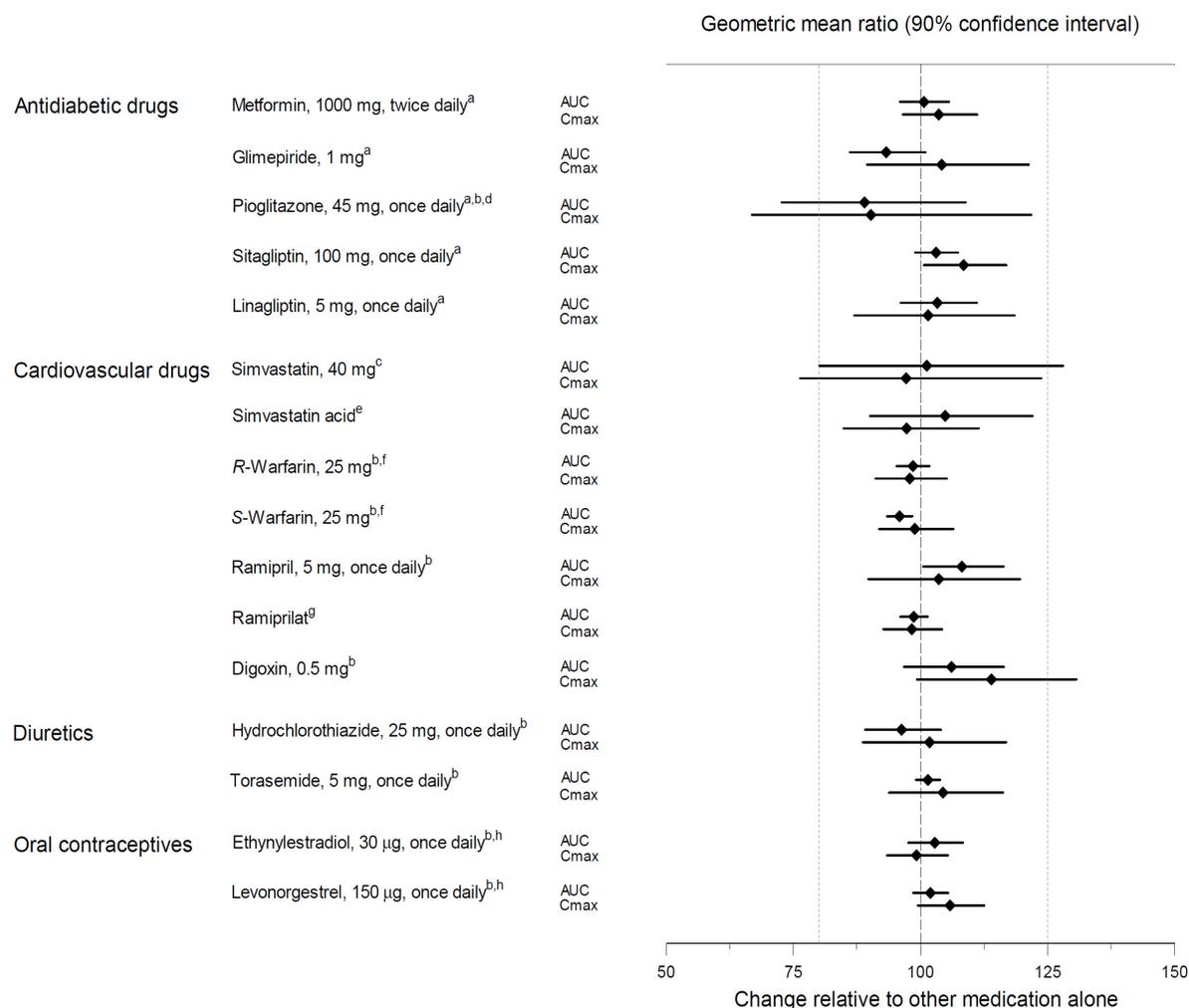


^a empagliflozin, 50 mg, once daily; ^b empagliflozin, 25 mg, once daily; ^c empagliflozin, 25 mg, single dose; ^d empagliflozin, 10 mg, single dose

Figure 5 Effect of co-administered drugs on empagliflozin pharmacokinetics.

Effect of Empagliflozin on Co-administered Drugs:

Empagliflozin had no clinically relevant effect on the PK of metformin, glimepiride, sitagliptin, linagliptin, simvastatin, warfarin, ramipril, digoxin, hydrochlorothiazide, torasemide, and oral contraceptives when co-administered with empagliflozin (see Figure 6 below). No dose adjustments are warranted for these drugs when co-administered with empagliflozin based on PK drug interaction studies or change in systemic exposure. However, concomitant use of certain drugs with empagliflozin may increase the risk for hypoglycemia (e.g. insulin secretagogue or insulin) or volume depletion (e.g. diuretics) and may require dose adjustments or use with caution (see Clinical Review by Dr. William Chong for further details).



^a empagliflozin, 50 mg, once daily; ^b empagliflozin, 25 mg, once daily; ^c empagliflozin, 25 mg, single dose; ^d empagliflozin, 10 mg, single dose; ^e administered as simvastatin; ^f administered as warfarin recemic mixture; ^g administered as ramipril; ^h administered as Microgynon[®]

Figure 6 Effect of empagliflozin on pharmacokinetics of co-administered drugs

Bioanalytical Methodology:

For the clinical pharmacology assessments, empagliflozin concentrations in plasma and urine were determined using validated LC-MS/MS assay. The assays were adequately validated for recovery, range, accuracy, precision and sensitivity. The changes to the analytical sites or procedures were adequately supported by partial validation of methods whenever necessary. The DDI assessments were also supported by validated analytical methods.

2 Question Based Review

2.1 General Attributes

2.1.1 What are the physicochemical properties of the drug substance and the intended commercial formulation of the drug product as they relate to clinical pharmacology review?

Empagliflozin is a small molecule drug (Figure 7).

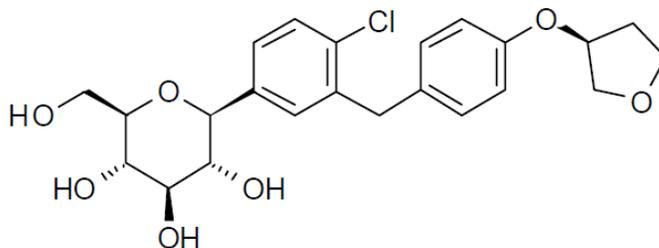


Figure 7 Chemical Structure of Empagliflozin

The highlights of the physicochemical characteristics are presented in Table 1 below.

Table 1 Chemistry and Physicochemical Properties of Empagliflozin

Chemical Name (IUPAC)	D-Glucitol,1,5-anhydro-1-C-[4-chloro-3-[[4-[[[(3S)-tetrahydro-3-furanyl]oxy]phenyl] methyl]phenyl]-,(1S)
Molecular Formula/Weight	C ₂₃ H ₂₇ ClO ₇ / 450.91 g/mol
Molecular Weight	450.91 g/mol
Appearance	White to yellowish powder
Solubility	Very slightly soluble in aqueous media at all pH
Melting Point:	150 ° C
Log P	1.7
Chiral Inversion	(b) (4)

The proposed commercial presentations of empagliflozin are film coated immediate release tablet containing 10 or 25 mg empagliflozin (See Table 2 below). Sponsor mentioned that empagliflozin drug substance (b) (4)

(b) (4). The particle size for empagliflozin drug substance is tightly controlled to (b) (4) μm (b) (4)

Table 2 Quantitative Composition of the Empagliflozin Tablets

Ingredient	[mg / tablet] 10 mg	[mg / tablet] 25 mg	Function	Reference to Standards
(b) (4)				
Empagliflozin	10.000	25.000	Drug substance	Company standard
Lactose monohydrate	(b) (4)			NF
Microcrystalline cellulose				NF
Hydroxypropylcellulose				NF
Croscarmellose sodium				NF
Colloidal silicon dioxide				NF
Magnesium stearate				NF
(b) (4)				USP
			Company standard	
			USP	
Total mass of film-coated tablet	257.0	206.0		

*) Removed during processing; does not appear in the final drug product

2.2 General Clinical Pharmacology

2.2.1 What are the features of the clinical pharmacology studies and the efficacy and safety trials used to support dosing or claims?

The clinical pharmacology and biopharmaceutics program for empagliflozin is supported by studies that compare different developmental and intended commercial drug product formulations, food effect, effect of co-administered drugs, and population pharmacokinetic/pharmacodynamics analysis (See Table 3).

Table 3 Overview of Clinical Pharmacology and Biopharmaceutics for Empagliflozin

Pharmacokinetic (PK) and pharmacodynamics (PD) evaluation in healthy volunteers			
Trial 1245.1	Single rising dose study in Caucasian healthy volunteers		
Trial 1276.9	Once daily vs. twice daily regimen in healthy volunteers		
Trial 1245.8	Human ADME study		
Trial 1245.16	Thorough QT study		
Trial 1245.79	Food-effect and dose-proportionality with final formulation		
Trial 1245.51	Relative BA, final formulation <i>versus</i> trial formulation II		
PK and PD evaluation in patients with T2DM			
Trial 1245	28-day multiple rising dose study in Caucasian patients		
Trial 1245.4	4-week repeated dose study in Caucasian patients		
PK and PD evaluation in other populations including Special Populations			
Trial 1245.5	Single rising dose study in Japanese healthy volunteers		
Trial 1245.44	8-day multiple dosing study in Chinese patients		
Trial 1245.15	4-week repeated dose study in Japanese patients		
Trial 1245.12	Renal impairment study in Caucasians subjects		
Trial 1245.13	Hepatic impairment study in Caucasians subjects		
Drug-drug interaction studies			
Trial 1245.6	With metformin	Trial 1245.40	With digoxin
Trial 1245.7	With glimepiride	Trial 1245.43	With verapamil
Trial 1245.17	With pioglitazone	Trial 1245.45	With ramipril
Trial 1245.50	With pioglitazone	Trial 1245.58	With gemfibrozil
Trial 1245.18	DDI with warfarin	Trial 1245.83	With rifampicin and probenecid
Trial 1245.27	DDI with sitagliptin	Trial 1245.42	With hydrochlorothiazide and torasemide (diuretics)
Trial 1245.30	DDI with linagliptin		
Trial 1245.63	With simvastatin	Trial 1245.41	With OCs (ethinylestradiol and levonorgestrel)
Population pharmacokinetic/pharmacodynamics analysis was performed using data from Phase 1 and Phase 3 studies			

The clinical program for empagliflozin comprised of 30 Phase 1 trials and 13 Phase 2b/3 trials. Overall, 13767 subjects were treated in these clinical trials, 6808 patients were treated with empagliflozin for at least 24 weeks, 4415 patients for at least 52 weeks, and 1486 patients for at least 76 weeks. In clinical studies, empagliflozin was evaluated as monotherapy, and in combination with metformin, glimepiride, pioglitazone, insulin, and DPP-4 inhibitors (See Table 4).

During the clinical development program, the sponsor also assessed the cardiovascular (CV) risk associated with empagliflozin therapy by conducting a prospective, pre-specified meta-analysis of independently adjudicated cardiovascular events.

Table 4 Overview of Clinical Trials for Empagliflozin

Trial characteristics	Trial number	Reference	Geographical regions	Duration analysed
Pivotal double-blind phase III trials	1245.19	[U12-1516]	Europe, Asia, North America	24 weeks
	1245.20	[U12-1517]	Europe, Asia, North America	24 weeks
	1245.23 _(met)	[U12-1518]	Europe, Asia, North America, Latin America	24 weeks
	1245.23 _(met+SU)	[U12-1518]	Europe, Asia, North America, Latin America	24 weeks
Double-blind phase III extension trials	1245.31	[U12-1521]	Europe, Asia, North America, Latin America	52 weeks ¹
Additional phase IIb/III double-blind individual trials	1245.28	[U12-1520]	Europe, Asia, North America, Latin America, Africa/Middle East	52 weeks ²
	1245.33 ³	[U12-3817]	Europe, Asia, North America,	78 weeks
	1245.48	[U12-1526]	Europe, North America, Africa/Middle East	12 weeks
	1245.36	[U12-1522]	Europe, Asia, North America, Africa/Middle East	52 weeks
	1245.25	No clinical trial report available	Europe, Asia, North America, Latin America, Africa/Middle East	12 weeks ⁴
Open label phase IIb extension trial	1245.24	[U12-1213]	Europe, Asia, North America, Latin America	90 weeks ⁵

¹ Including the 24-week treatment duration in the preceding trials; 52-week efficacy data from a prespecified interim analysis are included in this submission. The overall planned duration (initial trials + extensions) is 76 weeks

² Minimum duration at time of interim analysis; overall planned duration is 208 weeks

³ Trial 1245.33 was conducted in patients with basal insulin as background therapy. This trial was originally designated as a phase IIb trial. Since it had confirmatory testing introduced via a protocol amendment, it is considered to be equivalent to a confirmatory phase III trial for the assessment of the efficacy and safety of empagliflozin

⁴ Minimum duration at time of interim analysis; overall anticipated duration is between 6 and 8 years

⁵ Data from a combined analysis with the preceding double-blind preceding trials 1245.9 and 1245.10 are presented

2.2.2 Are active moieties and response endpoints measured in pivotal clinical trials and clinical pharmacology studies appropriate to assess PK/PD parameters and exposure response relationships?

Empagliflozin: Plasma empagliflozin the major circulating active moiety, and its metabolites (minor) were appropriately measured in clinical pharmacology studies and Phase 2/3 trials. See Section 3.3 for details.

Hemoglobin A1c (HbA1c): The primary efficacy endpoint in the pivotal Phase 3 trials was the change in HbA1c from baseline at week 24. In addition to HbA1c, other secondary efficacy endpoints such as fasting plasma glucose (FPG), post prandial glucose (PPG) were also evaluated.

Urinary glucose excretion (UGE): Primary mechanism of action Urinary glucose excretion was measured to characterize the pharmacodynamics (PD) activity of empagliflozin in clinical pharmacology trials. Urine samples were generally collected over several time intervals during the day in these trials. In most of the studies, UGE analyses used 24-hour cumulative UGE.

2.2.3 What are the ADME characteristics of empagliflozin after oral administration?

Absorption: 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 (see Figure 8).

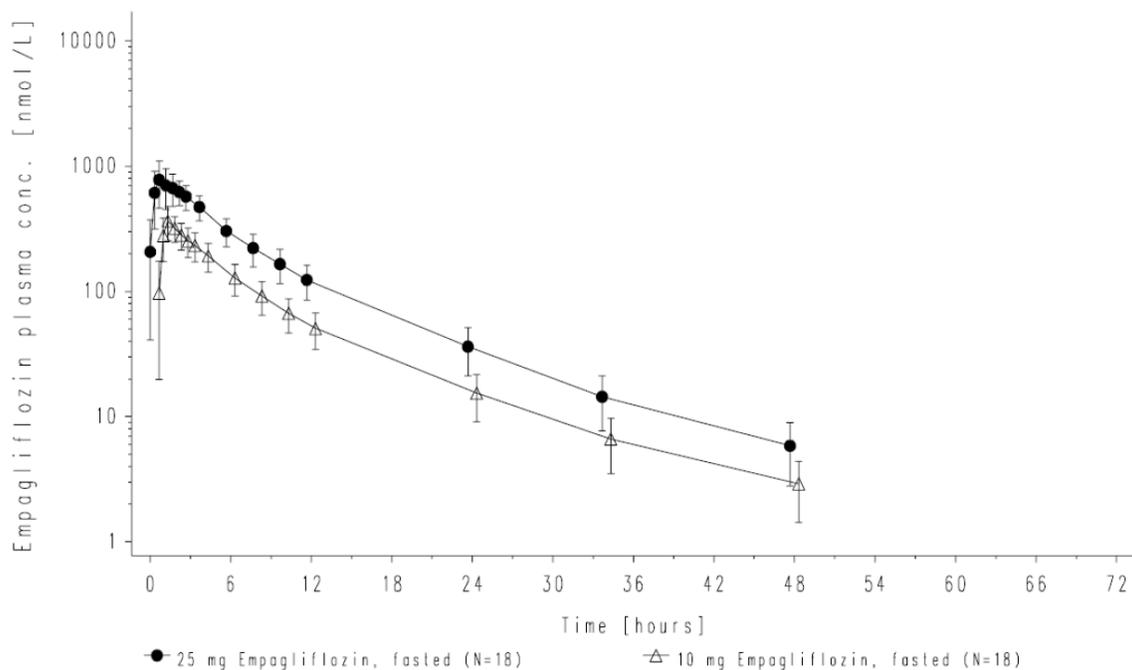


Figure 8 Mean plasma concentration time profile of empagliflozin after single oral dose of 10 mg and 25 mg under fasted condition (1245.79)

Empagliflozin exposure increased in proportion to the dose. Mean (%CV) AUC_{0-∞} 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 (see Table 5).

Table 5 Pharmacokinetic parameters of empagliflozin after single oral dose of 10 mg and 25 mg tablets under fasted condition (1245.79)

Parameter	10 mg empagliflozin fasted (treatment C) N=18	25 mg empagliflozin fasted (treatment A) N=18
AUC _{0-tz} [nmol·h/L]	2330 (26.7)	5490 (25.9)
AUC _{0-∞} [nmol·h/L]	2360 (26.7)	5550 (26.0)
C _{max} [nmol/L]	377 (26.2)	867 (26.8)
t _{max} [h]	1.09 (27.3)	1.38 (60.6)
t _{1/2} [h]	11.9 (40.7)	11.5 (35.9)
λ _z [1/h]	0.0658 (31.8)	0.0678 (33.9)
MRT _{po} [h]	9.56 (16.8)	9.36 (17.2)
CL/F [mL/min]	167 (26.2)	177 (25.1)
V _z /F [L]	168 (41.4)	172 (38.5)

Distribution

The apparent steady-state volume of distribution ranged from 180-230 L. Following administration of an oral [¹⁴C]-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%.

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 (Table 6).

O-dealkylation giving rise to metabolite M380/1 (EX 609), an active metabolite of empagliflozin, was monitored in this trial. It 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 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 (Figure 9).

Table 6 Metabolite profile of parent empagliflozin and its metabolites in the humans following oral dosing of 50 mg [¹⁴C]empagliflozin

Compounds	Human Male Plasma						Feces + Urine (95.6% of dose) ^a				
	2 hr		6 hr		12 hr		Feces (41.1% dose) ^a		Urine (54.5% dose) ^a		Total
	% [¹⁴ C] _b	nM	% [¹⁴ C] _b	nM	% [¹⁴ C] _b	nM	% [¹⁴ C] _b	% dose _a	% [¹⁴ C] _b	% dose _a	% dose _a
M482/1	1.2	24.3	1.8	17.1	3.1	11.5	4.6	1.9	5.2	2.8	4.7
M626/1 ^c	6.2	109	5.0	42.2	5.2	19.3	-- ^f	--	14.4	7.8	7.8
M626/2 ^d	3.7	62.8	6.0	49.4	3.3	12.3	--	--	3.9	2.1	2.1
M468/1	0.4	5.6	0.2	1.5	--	--	1.4	0.6	--	--	0.6
M626/3 ^e	7.4	127	6.3	53.4	5.4	20.1	--	--	24.1	13.2	13.2
M464/1	0.5	8.5	0.4	3.1	1.1	4.1	2.6	1.1	1.5	0.9	2.0
Empagliflozin	77.4	1320	75.5	638	76.2	283	82.9	34.2	43.5	23.7	57.9
Total	96.8	1660	95.0	805	94.3	351	91.5	37.8	92.6	50.5	88.3

^a % of dosed radioactivity.

^b % of sample radioactivity.

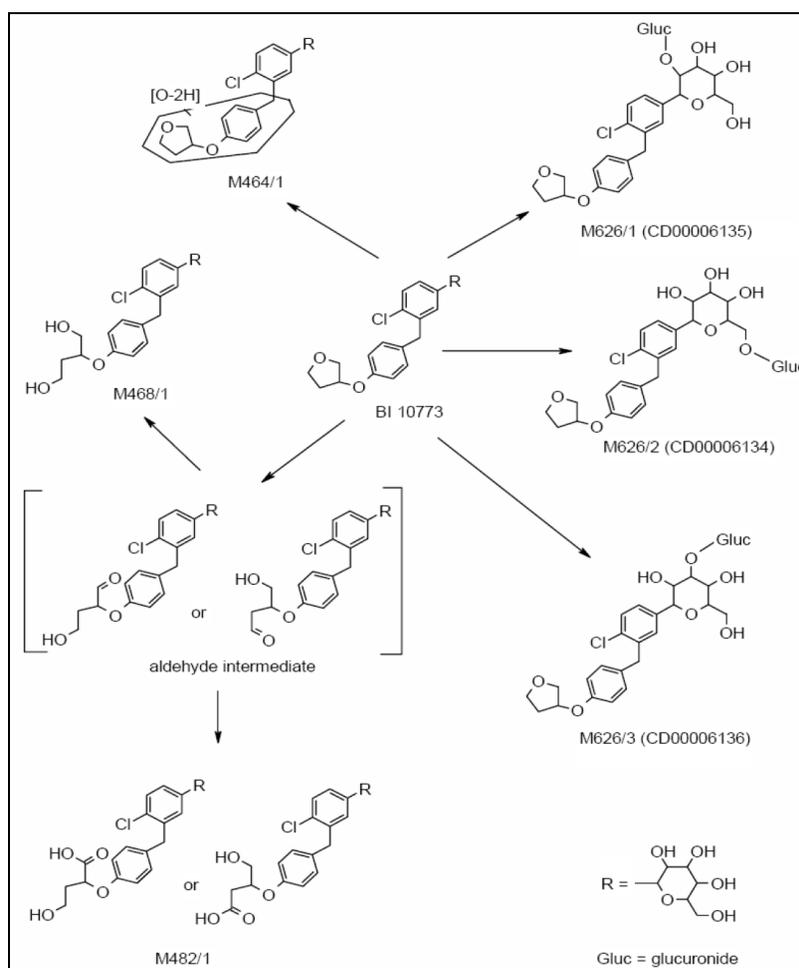


Figure 9 Metabolism pathways of [¹⁴C]-empagliflozin in humans

Elimination

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%) and approximately 83% of the drug related radioactivity excreted in feces was unchanged parent (~34%). 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.

2.2.4 What are the pharmacokinetic and pharmacodynamic characteristics of empagliflozin after oral administration and how do they relate to the dose?

Single Rising Dose PK/PD in Healthy Subjects (adult white males, n=6/dose group):

In a single rising oral dose (0.5 to 800 mg) study empagliflozin plasma exposure (AUC and C_{max}) were approximately proportional over the dose range of 0.5 to 800 mg, though dose-proportionality for exposure was only observed for the dose range of 2.5 mg to 200 mg as the apparent oral clearance was 221 to 245 mL/min (or ~13.5 L/h) for this dose range.

The mean plasma concentration-time and urinary glucose excretion rate-time profiles of empagliflozin from single oral doses of 0.5 to 800 mg and exclusively for 10 and 25 mg doses in study 1245.001 are illustrated in Figures 10 and 11 below, respectively.

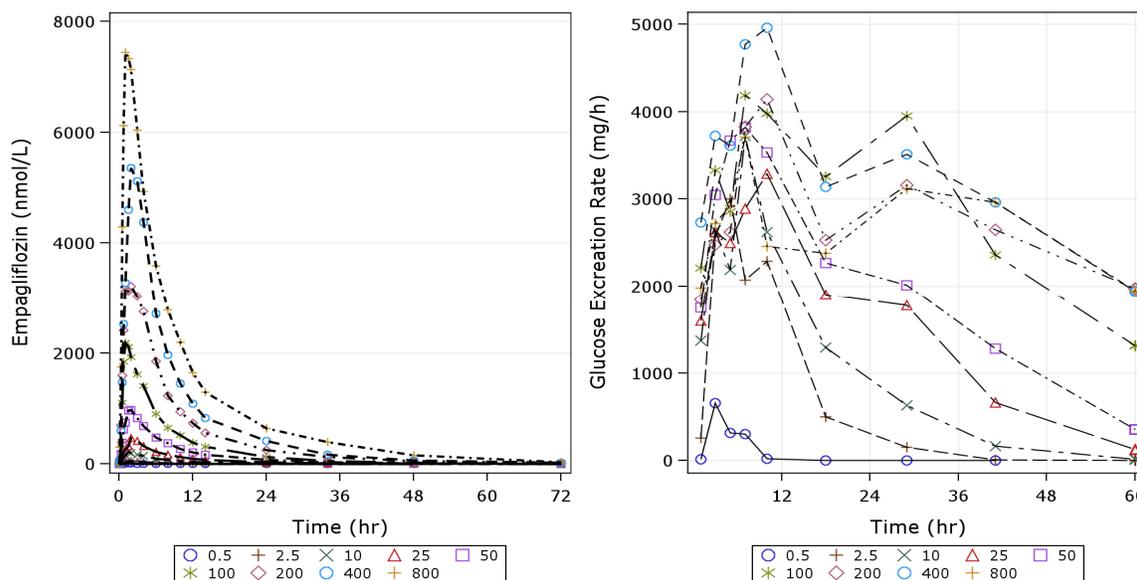


Figure 10 Mean plasma concentration (left) and urinary glucose excretion rate (right) versus time profile of empagliflozin (0.5 to 50 mg single oral dose)

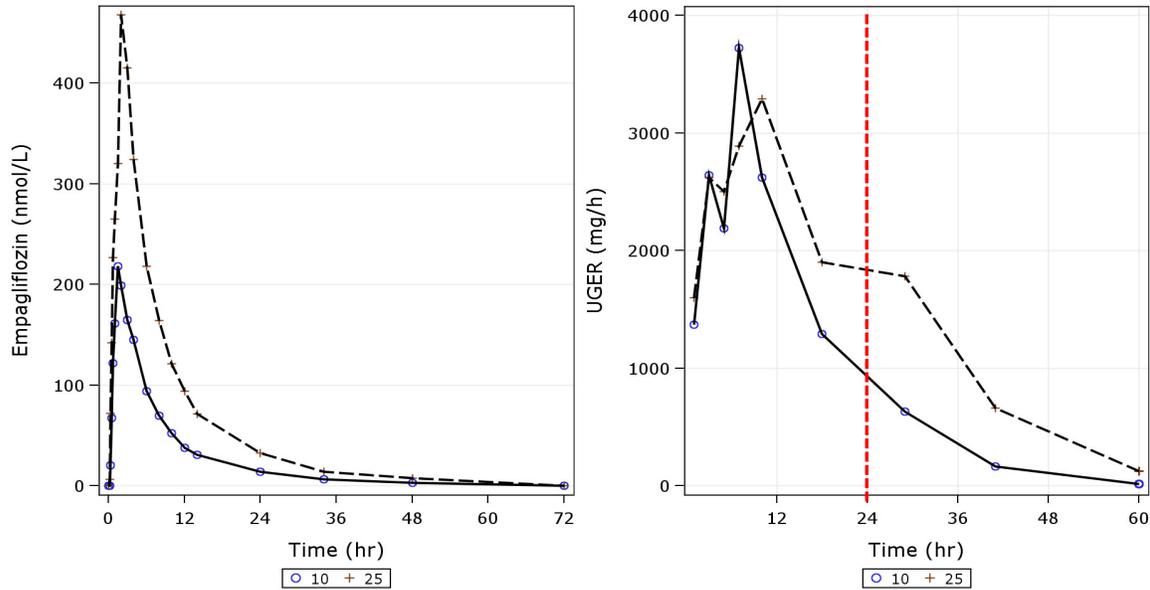


Figure 11 Mean plasma concentration (left) and urinary glucose excretion rate (right) versus time profile of empagliflozin (Only for 10 and 25 mg single oral doses)

The amount of unchanged empagliflozin in urine was increased almost in proportion over the dose range of 0.5 to 800 mg (fraction of drug excreted being fairly constant, 11.0% to 18.7% of the administered dose of empagliflozin). The amount of glucose excreted during first 24 hours exhibited a log-linear relationship with amount of empagliflozin excreted during the first 24h interval post-dose (Figure 12).

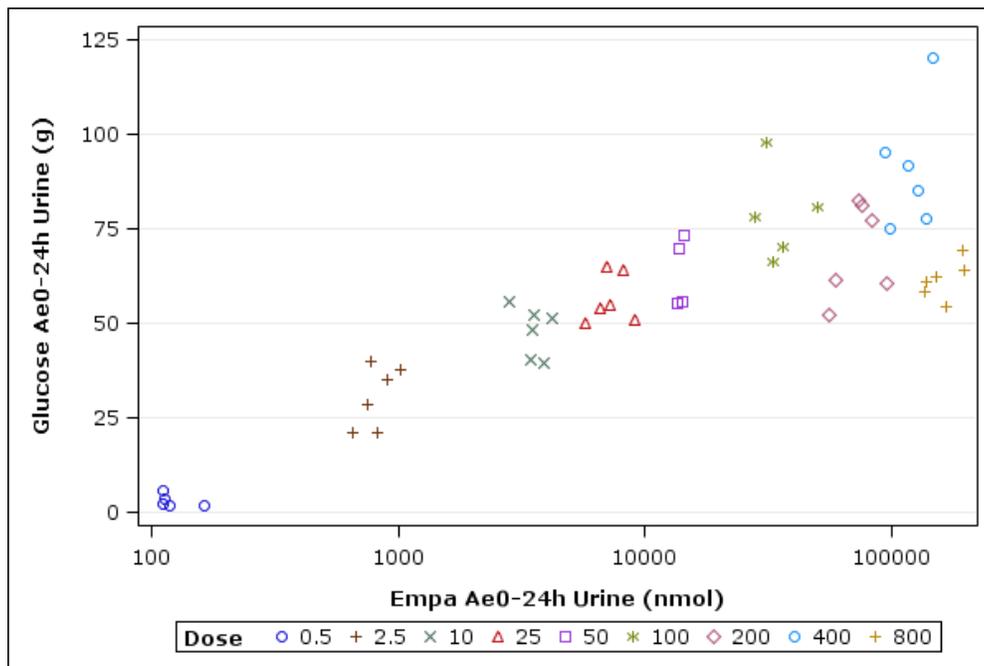


Figure 12 Observed Ae0-24h glucose in urine versus Ae0-24h empagliflozin in urine during first 24h of 72h collection over 0.5 to 800 mg single oral doses

An exploratory analysis of PK and PD data, using solver option in excel and a sigmoidal emax model suggested an EC50 value of ~1500 nmol, which along with graphical evaluation suggest that the UGE0-24h reached a plateau at or above 10 mg dose (Figure 13).

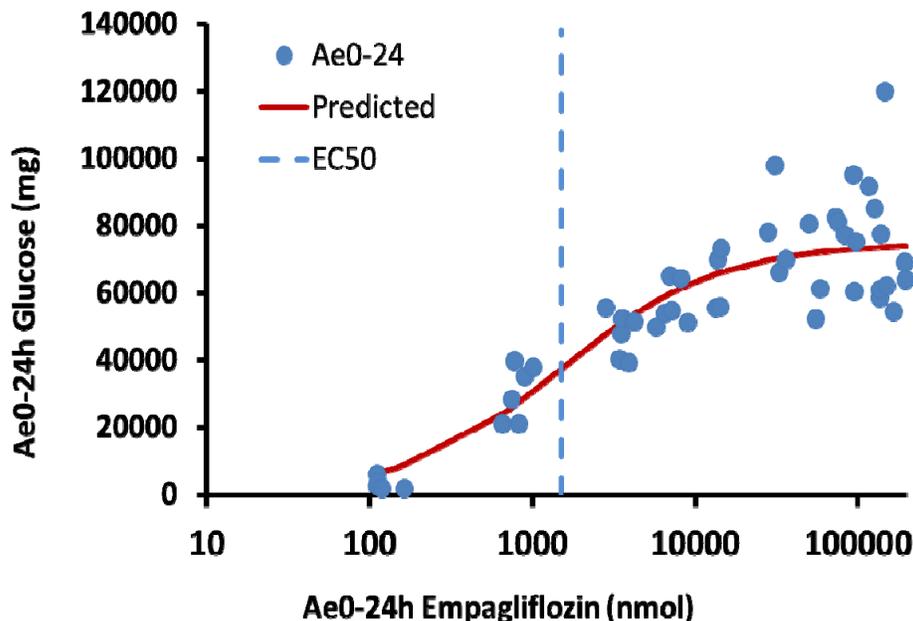


Figure 13 Observed and predicted Ae0-24 glucose in urine versus Ae empagliflozin in urine during first 24h of 72h collection over 0.5 to 800 mg single oral doses in healthy subjects

[Exploratory analysis based on mean data in Excel using solver and a Sigmoidal Emax Model: $E_{max} \times \frac{C^{\gamma}}{EC50^{\gamma} + C^{\gamma}}$]

The pharmacodynamic effect of empagliflozin as assessed by urinary glucose excretion revealed the following:

- In a single dose setting, on average the increase in dose resulted in greater magnitude of increase in duration of effect in comparison to the increase in magnitude of urinary glucose excretion rate, which ranged from 3000 to 5000 mg/h at maximum above the 0.5 mg dose (Figure 10)
- Comparison of PK and PD profiles of 10 and 25 mg dose from this study (Figure 8) indicate numerical, albeit small, difference in Ae0-24h [mean(%CV) 47.9 g (13.9) versus 56.5 g (11.6), respectively] in patients with normal renal function
- PD effect measured as amount of empagliflozin excreted in urine during first 24h was correlated to the amount of glucose excreted in urine during first 24h and appeared to plateau at dose ≥ 10 mg in patients with normal renal function.

Multiple Rising Dose PKPD in Type 2 Diabetic Patients:

The pharmacokinetics of empagliflozin was similar after administration of a single dose (10, 25, or 100 mg) on Day 1 and multiple doses at steady-state on Day 28. Following oral administration, peak levels reached at approximately 1.5 h after dosing. Plasma concentration-time profiles showed a biphasic decline with mean terminal elimination half-life of 13.2 to 16.5 h. Consistent with the half-life, up to 22% accumulation was observed at steady-state.

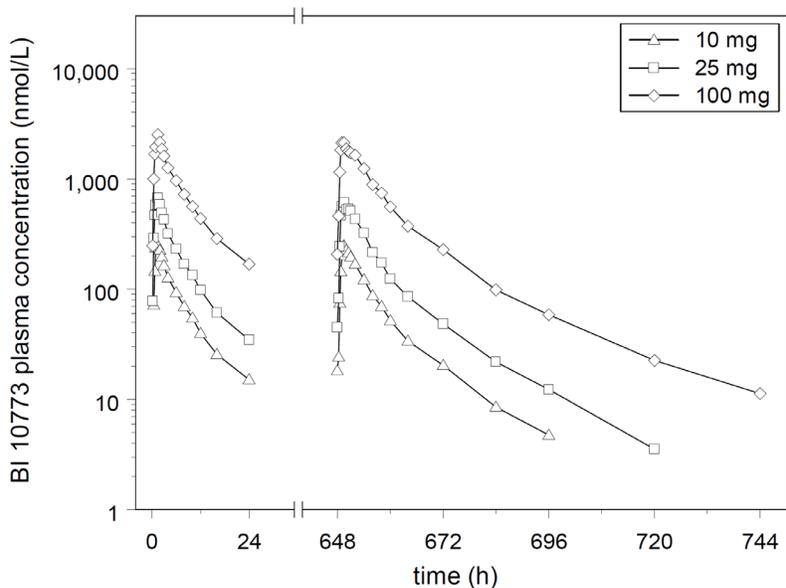


Figure 14 Mean plasma concentration-time profile of empagliflozin after single oral multiple once daily oral (steady state assessed on Day 27)

Apparent oral clearance on Day 1 (215 to 223 mL/min or ~13.4 L/h) was consistent to that observed on Day 28 (202 to 208 mL/min or ~12.5 L/h), which was also similar to the apparent clearance observed in healthy subjects.

The amount of empagliflozin excreted unchanged in the urine ranged from 17.5% to 18.3% of the administered dose at steady-state. Renal clearance of empagliflozin was similar in all dose groups on both Day 1 ($CL_{R,0-24h}$; 30.1 to 33.0 mL/min) and Day 9 ($CL_{R,\tau,ss}$; 36.2 to 37.0 mL/min).

The summary statistics of pharmacokinetic parameters for empagliflozin are presented in Table 7 below.

Table 7 Pharmacokinetic parameters of empagliflozin on (a) Day1 and (b) Day 2 after multiple once daily oral doses of 10, 25, 100 mg

(a): Day 1

Parameter	Unit	10 mg		25 mg		100 mg	
		Mean	% CV	Mean	% CV	Mean	% CV
AUC ₀₋₂₄	[nmol·h/L]	1550	16.2	3930	22.9	15900	21.2
AUC _{0-inf}	[nmol·h/L]	1740	16.4	4340	23.1	18000	24.3
AUC _{0-inf,norm}	[nmol·h/L/mg]	181	22.2	184	19.9	171	23.3
%AUC _{tz-inf}	[%]	10.9	26.7	9.36	28.8	11.4	34.8
C _{max}	[nmol/L]	309	45.2	722	20.0	2630	25.8
C _{max,norm}	[nmol/L/mg]	30.9	45.2	28.9	20.0	26.3	25.8
C _{24,1}	[nmol/L]	15.1	24.4	34.8	30.0	169	42.5
t _{max}	[h]	1.50	29.8	1.39	28.7	1.60	30.9
t _{1/2}	[h]	8.76	13.0	8.24	14.9	8.67	18.7
MRT _{po}	[h]	10.1	14.2	9.34	13.3	10.5	18.2
CL/F	[mL/min]	218	15.3	223	21.2	215	20.8
V _z /F	[L]	165	20.1	158	22.2	159	22.8
Ae ₀₋₂₄	[nmol]	2780	24.0	7360	24.5	30300	34.1
fe ₀₋₂₄	[%]	12.5	24.0	13.3	24.5	13.7	34.1
CL _{R,0-24}	[mL/min]	30.1	25.1	32.4	28.1	33.0	39.3

(b): Day 28

Parameter	Unit	10 mg		25 mg		100 mg	
		Mean	% CV	Mean	% CV	Mean	% CV
AUC _{τ,ss}	[nmol·h/L]	1870	15.9	4740	21.2	18700	25.2
AUC _{τ,ss,norm}	[nmol·h/L/mg]	187	15.9	189	21.2	187	25.2
C _{max,ss}	[nmol/L]	259	24.8	687	18.4	2390	28.1
C _{max,ss,norm}	[nmol/L/mg]	25.9	24.8	27.5	18.4	23.9	28.1
C _{min,ss}	[nmol/L]	17.9	29.6	39.9	48.3	204	47.9
C _{24,28}	[nmol/L]	20.4	25.5	48.2	36.8	228	45.2
C _{avg}	[nmol/L]	78.0	15.9	197	21.2	781	25.2
t _{max,ss}	[h]	1.72	42.5	1.55	49.9	1.87	72.2
t _{1/2,ss}	[h]	13.2	44.7	13.3	32.6	16.5	47.9
MRT _{po,ss}	[h]	11.6	16.2	11.4	17.8	13.0	20.6
CL/F _{ss}	[mL/min]	202	15.9	203	21.4	208	22
V _z /F _{ss}	[L]	225	41.3	237	40.7	293	51.1
PTF	[%]	307	15.6	335	19.3	285	25.9
Linearity index	[%]	1.09	11.1	1.10	12.5	1.04	9.21
R _{A,AUC}	[%]	1.22	13.1	1.22	12.5	1.18	11.2
R _{A,Cmax}	[%]	0.916	27.7	0.973	21.2	0.933	25.4
Ae _{0-24,ss}	[nmol]	4060	25.0	9890	17.8	38800	28.3
fe _{0-24,ss}	[%]	18.3	25.0	17.8	17.8	17.5	28.3
CL _{R,τ,ss}	[mL/min]	37.0	31.1	36.2	26.3	36.5	35.2

The dose-proportionality assessment, based on statistical analysis of empagliflozin PK parameters is presented in Table 8 below. Dose-proportionality was evident for empagliflozin peak and total exposure over the dose range of 10 to 100 mg once daily.

Table 8 Dose-proportionality assessment of empagliflozin PK parameters (a) on Day 1 and (b) after multiple doses

(a) After single dose on Day 1

Parameter	Unit	Exponent	95% confidence interval for exponent	
			lower	upper
C _{max}	[nmol/L]	0.9382	0.8691	1.0073
AUC ₀₋₂₄	[nmol·h/L]	1.0081	0.9581	1.0582

(b) After multiple doses:

Parameter	Unit	Exponent	95% confidence interval for exponent	
			lower	upper
C _{max,ss}	[nmol/L]	0.9489	0.8839	1.0140
AUC _{τ,ss}	[nmol·h/L]	0.9923	0.9384	1.0461

The pharmacodynamic effect of three empagliflozin doses on urinary glucose excretion (amount and rate) in subjects with type 2 diabetes is summarized below in Figure 15 and Figure 16, respectively.

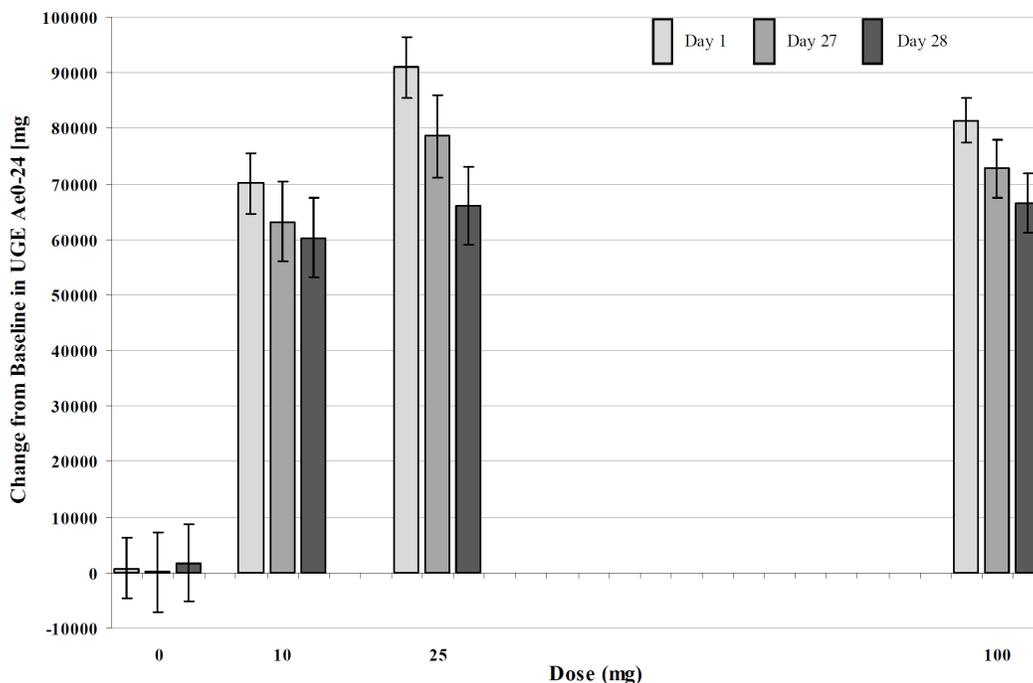


Figure 15 LS Mean (±SE) change in cumulative amount of UGE (UGE0-24 [mg]) from baseline after single (Day 1) and multiple (Days 27 and 28) oral doses of empagliflozin or placebo in patients with type 2 diabetes

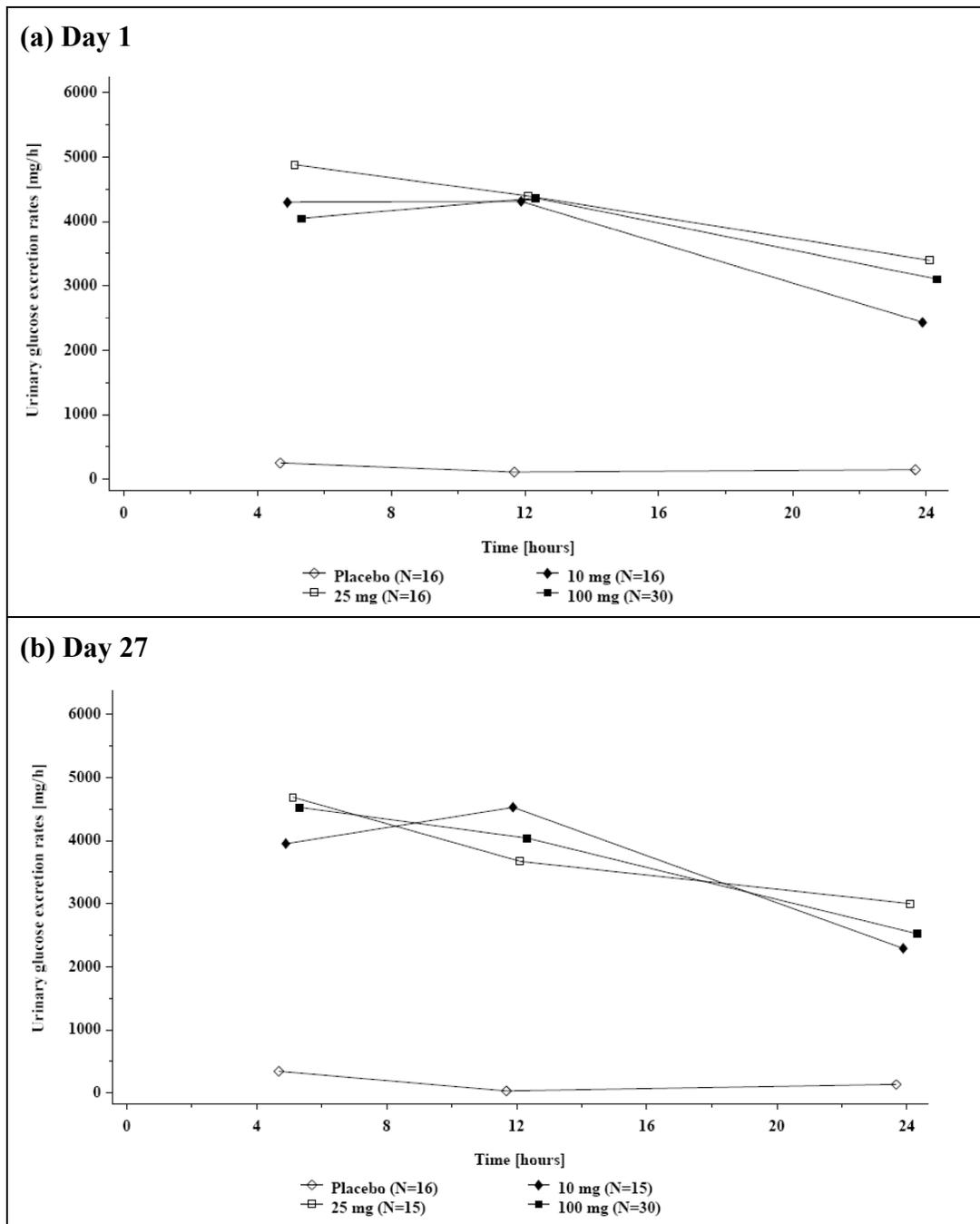


Figure 16 Mean rate of UGE (Ue0-5, Ue5-12, Ue12-24 [mg/h]) after single (Day 1) and multiple (Days 27) oral doses of empagliflozin or placebo in patients with type 2 diabetes

There was significant increase in urinary glucose excretion (both rate and amount) from baseline in comparison to placebo for all three dose levels. However, there was no clear dose-response for urinary glucose excretion rate at all observation days. The doses seems to be comparable for amount of glucose excreted in urine over 24 hour duration (UGE0-24h) observed after multiple doses, although observations from Day 1 showed a dose-

dependent increase in UGE0-24h between 10 and 25 mg dose groups. Notably, there was no correlation between the amount of empagliflozin excreted and amount of glucose excreted in urine over 24-hour duration on Day 27 (Figure 17). These patients were mostly with normal renal function (creatinine clearance ranged from 80-230 mL/min) and the fraction of empagliflozin excreted in urine was ~18% with mean empagliflozin Ae0-24h of 4060 nmol for the 10 mg dose on Day 27. Therefore, these doses appear to be at the plateau of the exposure-response for the primary pharmacodynamic effect, and may suggest that there is no added pharmacodynamic benefit by increasing the dose from 10 to 25 mg.

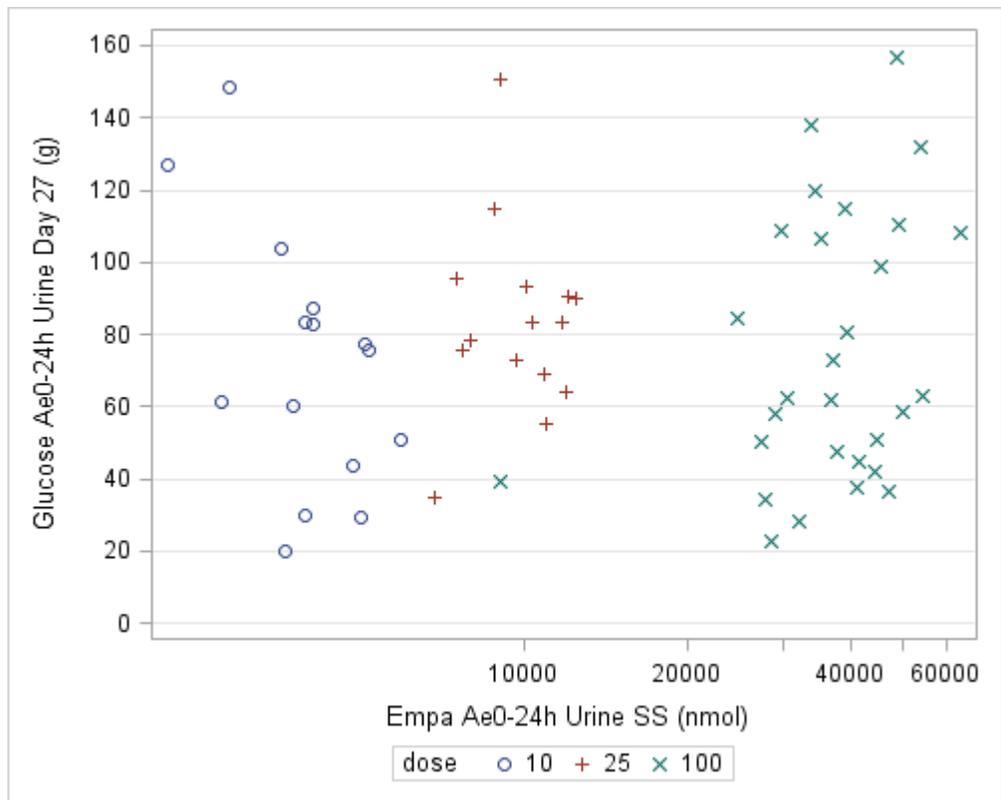


Figure 17 LS Mean (\pm SE) change in cumulative amount of UGE (Ae0-24 [mg]) from baseline after single (Day 1) and multiple (Days 27 and 28) oral doses of empagliflozin or placebo in patients with type 2 diabetes

2.3 Exposure Response

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

There is lack of evidence of clear dose-response when data from monotherapy and add on therapy trials was examined. From efficacy perspective, the dose-response data suggests that the use of 25 mg once daily dose of empagliflozin does not always produce higher reduction in HbA1c than 10 mg once daily.

The HbA1c reduction appeared to reach plateau by Week 24 in the Phase 3 monotherapy trial 1245.20, thus allowing for a reasonable dose-response evaluation at Week 24 (See Appendix 4.2 Pharmacometric Review).

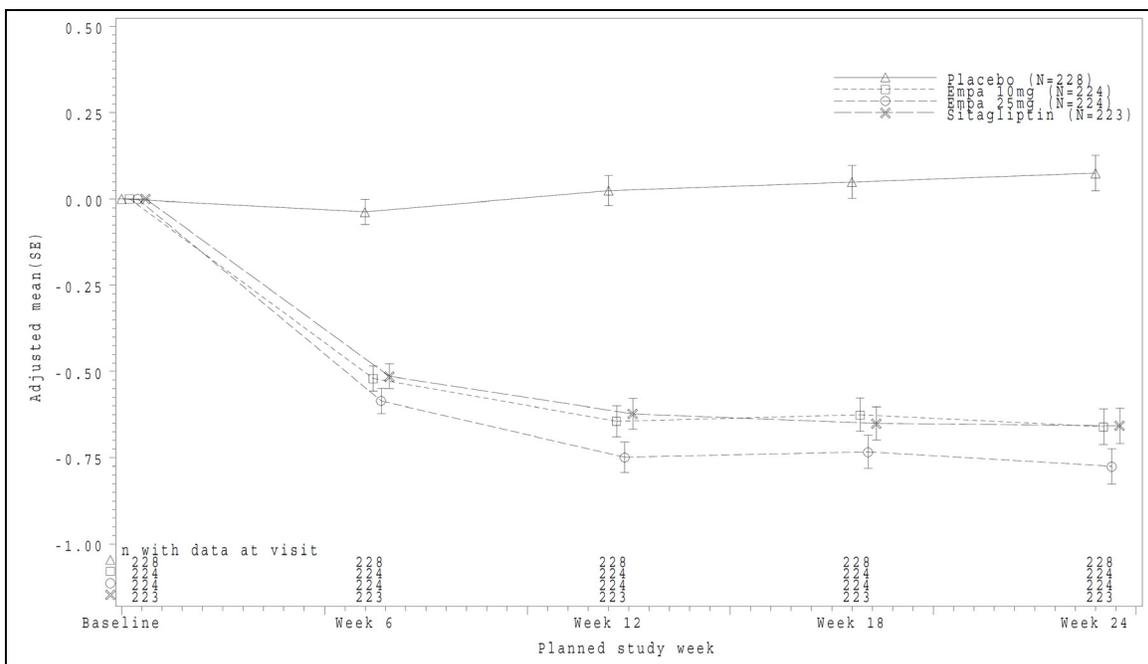


Figure 18 Time-profiles for adjusted mean (SE) change from baseline in HbA1c in Phase 3 monotherapy trial 1245.20

[Source: Sponsor's Figure 15.2.1.2.2:5 - HbA1c (%) ANCOVA results over time - FAS(LOCF) in Report U12-1517-01 Page 388. Model included treatment, baseline eGFR (MDRD), background medication and region as fixed effects and baseline HbA1c as a linear covariate.]

The dose-response evaluation showed that in add on to metformin and add on to metformin plus sulfonylurea trials, both 10 mg and 25 mg once daily treatments showed almost similar response against the placebo group (Figure 1) with modest to no separation in mean HbA1c reduction from baseline between the two active treatment arms. In some specific treatment settings, such as when administered as monotherapy, as add-on therapy to patients on pioglitazone with or without metformin or as add on to insulin, 25 mg once daily dose provided an additional HbA1c reduction of up to 0.14% units. There was however, a dose-dependent increase in proportion of patients who achieved <7% HbA1c by the time of primary end-point measurement (Figure 19).

This suggests that in certain treatment settings, the 25 mg dose could provide additional benefit for some patients.

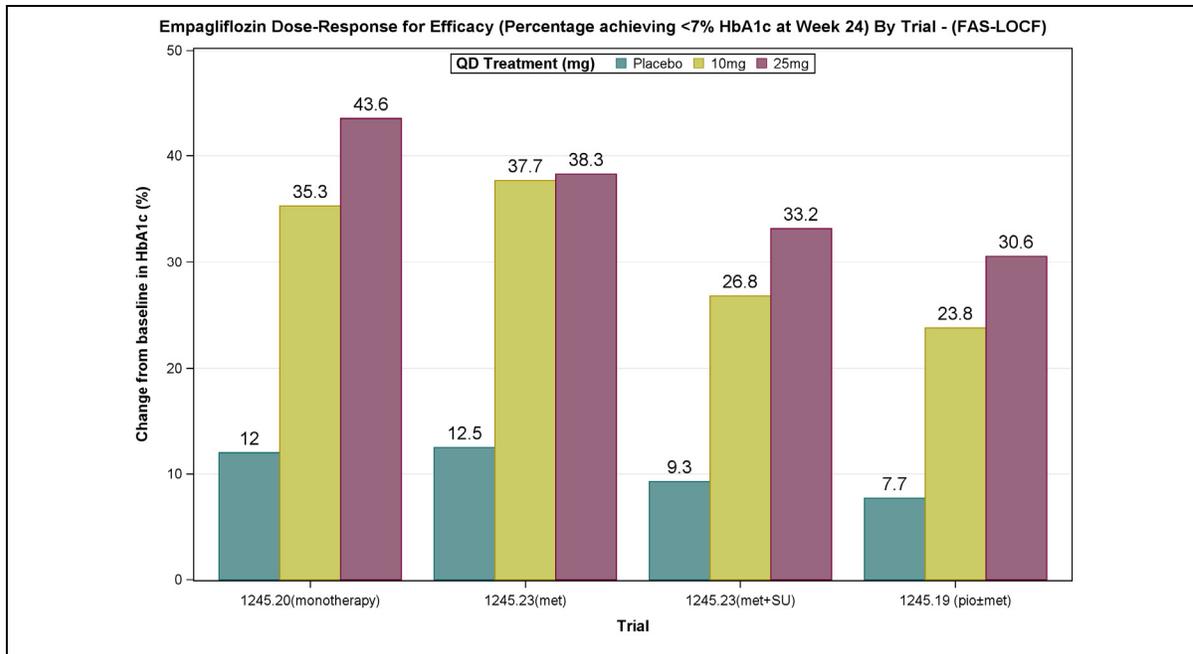


Figure 19 Proportion of Patients who Achieve <7% HbA1c by End of Trial: Study-by-Study Comparison (Phase 3 Studies: Full Analysis Set)

Efficacy results for Individual trials are summarized in Pharmacometric Review Section 1.1.1 and Executive Summary.

Impact of Renal Impairment on Efficacy

Consistent with the known mechanism of action of empagliflozin, there is a lower reduction in HbA1c levels with increasing degree of renal impairment in subjects with type 2 diabetes. The reduction in HbA1c from baseline in patients with moderate renal impairment (1245.36) was of lower magnitude (approximately half) when compared to the magnitude observed in type 2 diabetic subjects majority with normal renal function or with mild renal impairment in trial 1245.20 or add-on therapy trials 1245.19 and 1245.23.

Even though the mean response is lower in subjects with mild renal impairment compared to subjects with normal renal function, efficacy of Empagliflozin is preserved in these patients.

In subjects with moderate renal impairment only 25 mg dose was evaluated, limiting any dose-response assessment. However, decrease in HbA1c was observed following 24 weeks treatment with empagliflozin (Figure 2). Overall, in patients with mild renal impairment a trend of modest, dose-dependant decrease in HbA1c is observed following 24 weeks treatment with empagliflozin. In moderate RI, however, this trend is primarily driven by changes in HbA1c from baseline in subjects with eGFR 45 to <60 mL/min/1.73m² [Adjusted mean (SE) HbA1c change from baseline of -0.54 (0.07) for empagliflozin and -0.08 (0.07) for placebo].

Based on absolute response, empagliflozin showed modest efficacy in patients with eGFR 30 to <45 mL/min/1.73 m² *per se* [absolute mean (SE) change from baseline in HbA1c of -0.21 (0.07)]. However, placebo adjusted response for empagliflozin 25 mg once daily dose (Mean reduction in HbA1c of -0.39% unit) seems to be inflated by

worsening of HbA1c response in placebo group [absolute mean (SE) change from baseline in HbA1c of 0.17 (0.07)] in eGFR 30 to < 45 ml/min/1.73 m² subgroup. At week 24, magnitude of change in HbA1c from baseline in subjects with eGFR < 30 mL/min/1.73m² appears similar between placebo and treatment groups.

In summary, from efficacy perspective, the dose-response data suggests that the use of 25 mg once daily dose of empagliflozin, does not always produce numerically higher reduction in HbA1c than 10 mg once daily. In some specific treatment settings, such as when administered as monotherapy, as add-on therapy to patients on pioglitazone with or without metformin or as add on to insulin, 25 mg once daily dose provides an additional HbA1c reduction of up to 0.14% units. The efficacy is lower in presence of renal impairment however, preserved in patients with mild renal impairment, and in patients with eGFR 45 to <60 mL/min/1.73m² among moderate renal impairment for the 25 mg once daily dose. Further, the efficacy decreases with worsening of renal function.

Dose/Exposure-Response for Safety (See PM Review for details):

- Empagliflozin causes only modest decreases in eGFR from baseline in a dose-dependent manner. On average, the decline in eGFR appeared to regress over time towards baseline.
- In all empagliflozin treated subjects, the adverse event profile of 10 mg once daily and 25 mg once daily dose was similar except for hypoglycemia incidences being higher with 25 mg once daily dose.
- Elderly population (> 65 year age) and patients with moderate renal impairment showed higher susceptibility for hypoglycemia, volume depletion, and urinary tract infection AEs for both doses.

2.2.6 Does empagliflozin prolong the QT or QTc Interval?

Based on the Interdisciplinary Review Team review of the thorough QT study, no significant QTc prolongation effect of empagliflozin (25 mg and 200 mg) was detected in the TQT study. The largest upper bounds of the 2-sided 90% CI for the mean difference between empagliflozin (25 mg and 200 mg) and placebo were below 10 milliseconds (ms), the threshold for regulatory concern as described in ICH E14 guidelines. The largest lower bound of the two-sided 90% CI for the $\Delta\Delta\text{QTcF}$ for moxifloxacin was greater than 5 ms.

Table 9 The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for BI10773 (25 mg and 200 mg) and the Largest Lower Bound for Moxifloxacin (FDA Analysis)

Treatment	Time (hour)	$\Delta\Delta\text{QTcF}$ (ms)	90% CI (ms)
BI10773 25 mg	12	1.6	(-0.7, 3.9)
BI10773 200 mg	2.5	2.0	(-0.1, 4.2)
Moxifloxacin 400 mg*	2.5	14.4	(11.6, 17.1)

* Multiple endpoint adjustment of 3 time points was not applied. The largest lower bound without Bonferroni adjustment is 12.2 ms.

2.4 Intrinsic Factors

2.4.1 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?

The effect of various covariates e.g. Ideal body weight, Weight, Age, BMI, Gender and Race was assessed in the population pharmacokinetic analysis. The details are mentioned in the Pharmacometric review under **Appendix 4.2**. Highlights of the results for empagliflozin are described below:

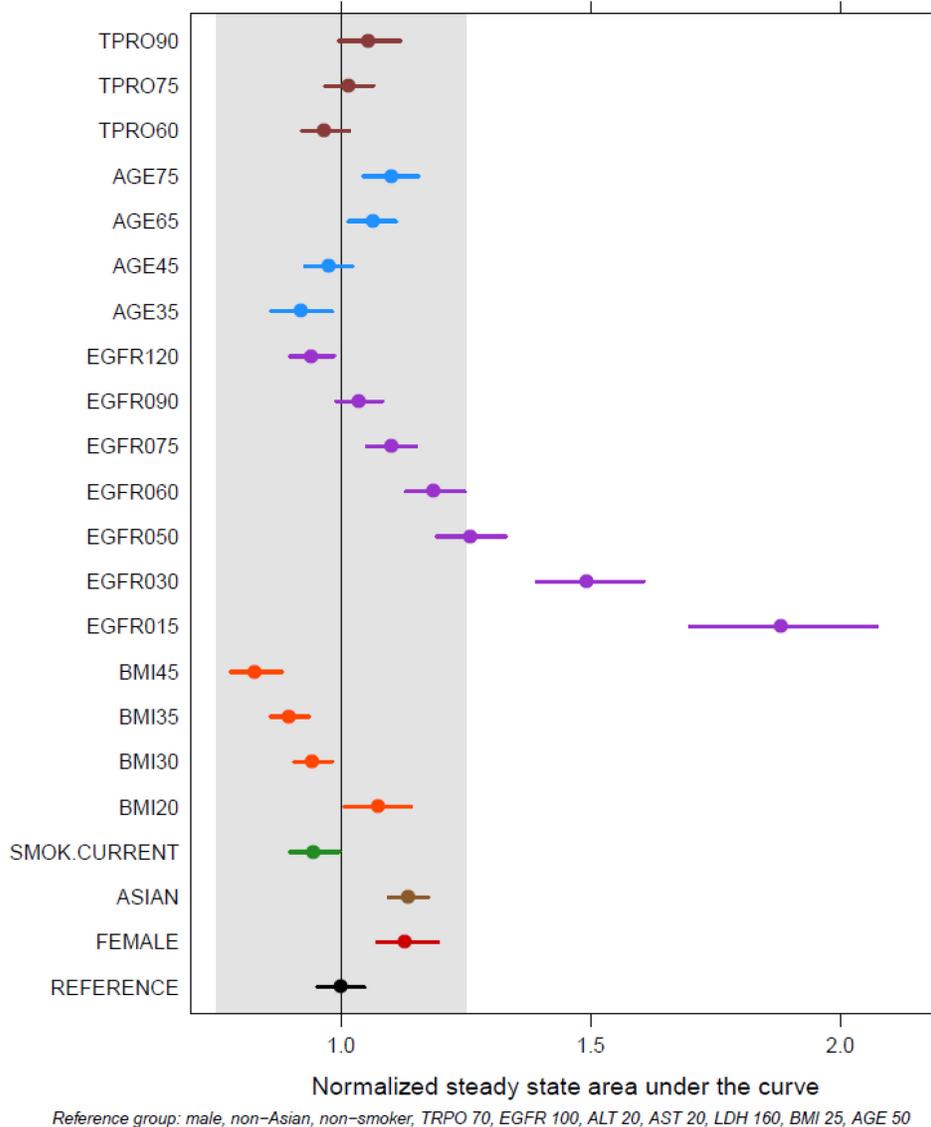


Figure 20 Effect of various covariates on relative empagliflozin exposure (AUC_{τ,ss}/ reference AUC_{τ,ss}) from the population pharmacokinetic model

According to the sponsor’s analysis, a clinically relevant effect of age, gender or BMI or race (Asians versus primarily Whites) on empagliflozin clearance was not evident from the data.

2.4.2 Does the hepatic function affect empagliflozin pharmacokinetics and pharmacodynamics?

In subjects with mild, moderate, and severe hepatic impairment, categorized according to the Child-Pugh classification, AUC_{0-∞} of empagliflozin increased approximately by 23%, 47%, and 75% and C_{max} by approximately 4%, 23%, and 48%, respectively, compared to subjects with normal hepatic function.

Table 10 Relative bioavailability of empagliflozin after oral administration of single 50 mg dose in subjects with impaired hepatic function vs. normal hepatic function

Group	Parameter	gMean ratio		
		hepatic impaired /normal group [%]	Lower limit [%]	Upper limit [%]
Mild liver impairment (N=8)	AUC _{0-∞}	123.15	98.89	153.36
	C _{max}	103.81	82.29	130.95
Moderate liver impairment (N=8)	AUC _{0-∞}	146.97	118.02	183.02
	C _{max}	123.31	97.74	155.55
Severe liver impairment (N=8)	AUC _{0-∞}	174.70	140.29	217.55
	C _{max}	148.41	117.65	187.23

The subjects in each liver impairment group were compared with 12 healthy subjects.

The extent of exposure (AUC_{0-∞}) of all three glucuronide conjugates of empagliflozin ranged from ~10% to 11% compared to unchanged parent in subjects with normal liver function. Within subjects with hepatic impairment, empagliflozin-2-O- and empagliflozin-6-O-glucuronide exposures (AUC_{0-∞} and C_{max}) decreased with the degree of hepatic impairment. On the contrary, empagliflozin-3-O-glucuronide exposure increased with the degree of hepatic impairment. In subjects with severe liver impairment, empagliflozin AUC_{0-∞} increased by ~75%; whereas, AUC_{0-∞} of empagliflozin-2-O- and empagliflozin-6-O-glucuronides was decreased by ~9% and 32%, respectively, and empagliflozin-3-O-glucuronide AUC_{0-∞} increased by roughly 2.8-fold.

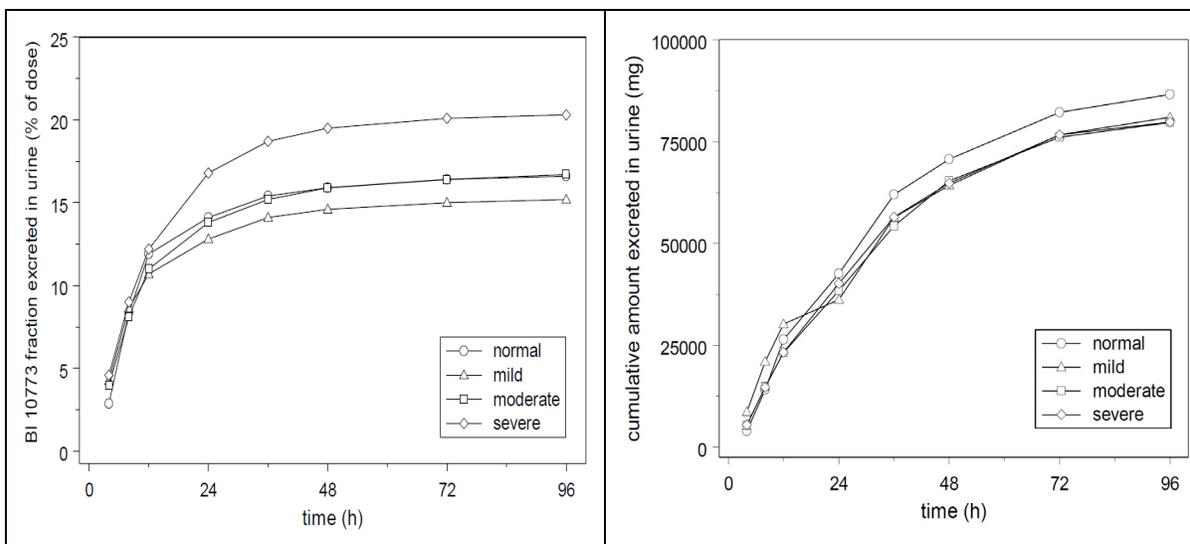


Figure 21 Mean cumulative amounts of empagliflozin (left) and glucose (right) excreted in urine after oral administration of 50 mg BI 10773 in subjects with normal and impaired hepatic functions

In this study fraction of empagliflozin excreted in urine was also measured. On average, there was an increase in the fraction of empagliflozin dose excreted unchanged in urine with degree of hepatic impairment; however, at 24 hour post dose the increase ranged from 10-18% of the administered dose. Consistent to the PK/PD profile seen in the patient PKPD studies, the observed increase in urinary excretion of empagliflozin is not expected to increase the urinary glucose excretion (based on Figures 13 and 17). Therefore, no dose adjustment is recommended despite of PK changes observed in patients with hepatic impairment.

2.4.3 Does the renal function affect empagliflozin pharmacokinetics and pharmacodynamics?

In patients with mild (eGFR: 60 to <90 mL/min/1.73m²), moderate (eGFR: 30 to <60 mL/min/1.73m²), severe (eGFR: <30 mL/min/1.73m²) renal impairment and patients with kidney failure/ESRD patients, AUC of empagliflozin increased by approximately 18%, 20%, 66%, and 48%, respectively, compared to patients with normal renal function (eGFR: > 90 mL/min/1.73 m²). Plasma C_{max} of empagliflozin were similar in subjects with moderate renal impairment and kidney failure/ESRD compared to patients with normal renal function. Plasma C_{max} of empagliflozin was roughly 20% higher in subjects with mild, moderate and severe renal impairment as compared to patients with normal renal function. Plasma AUC_{0-inf} of empagliflozin was roughly 66% higher in subjects with severe renal impairment as compared to patients with normal renal function. The changes are not considered clinically relevant and solely based on PK, no dosage adjustment would be required in patients with renal insufficiency.

Table 11 Relative bioavailability of empagliflozin after oral administration of single 50 mg dose in subjects with impaired renal function vs. normal renal function

Group	Parameter	gMean ratio renal impaired /normal group [%]	90% CI for gMean ratio	
			Lower limit [%]	Upper limit [%]
Mild renal impairment	AUC _{0-∞}	118.24	96.17	145.38
	C _{max}	118.83	93.62	150.84
Moderate renal impairment	AUC _{0-∞}	119.94	96.25	149.47
	C _{max}	102.27	79.33	131.85
Severe renal impairment	AUC _{0-∞}	166.29	134.44	205.68
	C _{max}	120.68	94.42	154.25
Kidney failure/ ESRD	AUC _{0-∞}	148.29	119.89	183.42
	C _{max}	103.75	81.18	132.61

ESRD: end stage renal disease

In type 2 diabetes patients with normal renal function, following administration of 50 mg dose, mean amount of empagliflozin excreted in urine over 24 hour was 15600 nmol, which decreased to 11100, 6910, 2970, 304 nmol in mild RI, moderate, severe RI, and ESRD subjects, respectively.

Similarly, the cumulative amount of glucose recovered in urine decreased with renal impairment. The total amount of glucose excreted in urine (change from baseline) over 24 h in type 2 diabetes patients with normal renal function was approximately 97.6 g, which decreased to 61.6, 55.7, 18.3, and 0.8 g in patients with mild, moderate, severe renal impairment and kidney failure/ESRD patients, respectively roughly 37%, 53%, 81%, and 99% lowering of pharmacodynamic response from normal renal function. The decrease in glucose excretion matched with the decrease in empagliflozin renal clearance and decrease in renal function (as measured by glomerular filtration rate) (see Figure 22).

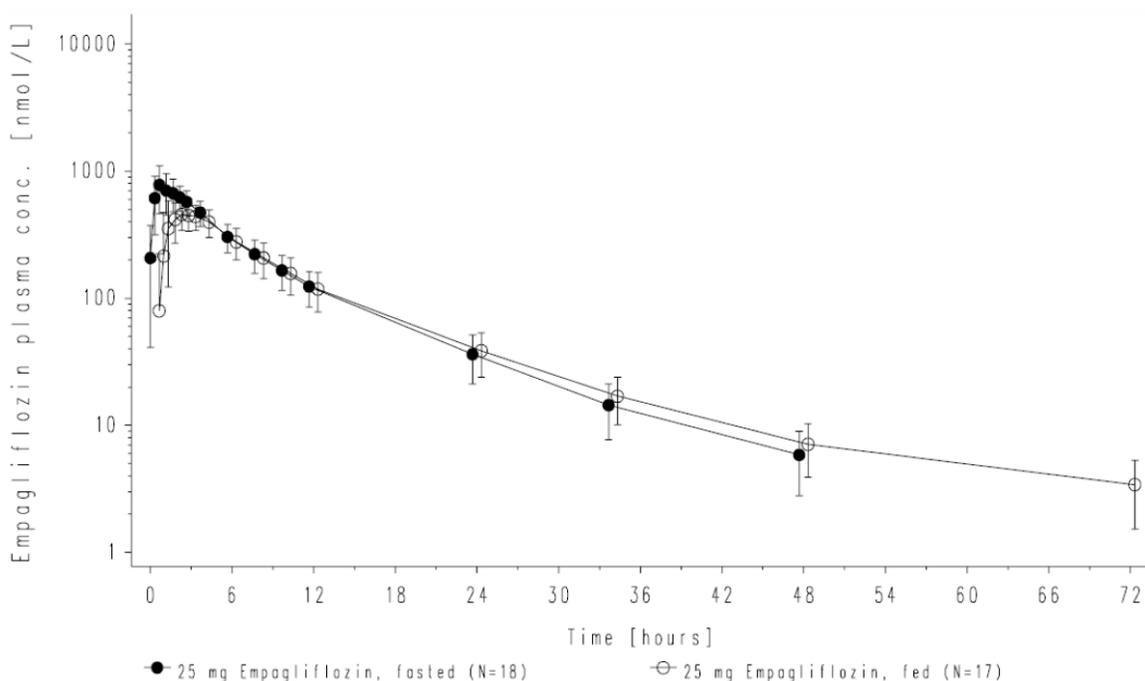


Figure 23 Mean plasma concentration-time profiles of empagliflozin after administration of a single oral 25 mg empagliflozin dose under fasted and fed conditions (semi-log scale)

The results of single dose food effect study are summarized in Table 12 below.

Table 12 Relative bioavailability (intra-individual comparison) of empagliflozin after single oral administration of 25 mg empagliflozin under fed versus fasted conditions

Parameter	gMean ratio (fed versus fasted conditions) [%] ¹	95% CI for gMean ratio	
		Lower limit [%]	Upper limit [%]
AUC _{0-∞}	84.04	80.86	87.34
C _{max}	63.22	56.74	70.44
AUC _{0-tz}	83.53	80.46	86.72

In the phase 3 trials, patients were instructed to take their trial medication once daily in the morning with water. Further, to ensure a dosing interval of about 24 hour, patients were asked to take the trial medication at about the same time every day. Also it was specified that empagliflozin can be taken with or without food. Therefore, empagliflozin can be administered with or without food similar to the way it was tested in Phase 3 trials.

2.5.2 Drug-Drug Interactions

2.5.2.1 What is the CYP inhibition/induction potential of empagliflozin?

The *in vitro* enzyme inhibition studies conducted with empagliflozin using human liver microsomes demonstrate that:

- Empagliflozin IC₅₀ values for inhibition of the major drug metabolizing CYP450 isoforms (CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4) were in excess

of 150 μM . The glucuronide metabolites also possessed IC_{50} s in excess of 100 μM for inhibition of these enzymes.

- Empagliflozin did not inactivate CYP2C9, CYP2D6 and CYP3A4 when incubated up to 40 minutes and in concentrations up to 100 μM .

In Vitro Assessment of CYP1A2, CYP2B6, and CYP3A4 Induction Potential of empagliflozin in primary cultures of human hepatocytes demonstrated that:

- Empagliflozin, up to concentrations of 30 μM , produced little change (<5%) in the activity of CYP1A2, CYP2B6, and CYP3A4 in comparison to that observed with positive controls (3-MC, phenobarbital, and rifampin, respectively). This change in the activity of CYP1A2, CYP2B6, or CYP3A4 was only evident at the highest concentration tested (30 μM) and therefore have little potential for inducing these drug metabolizing enzymes.

Thus, empagliflozin is not expected to cause any drug-drug interactions related to inhibition/induction of cytochrome P450s.

2.5.2.2 What is the inhibition potential of empagliflozin at human efflux transporters (P-gp and BCRP) and Organic Anion Transporters (OATs)?

In vitro transport studies demonstrated that:

- In MDCK-MDR1 cells, empagliflozin was a P-gp substrate as demonstrated by a rate of secretory transport exceeding its rate of absorptive transport. The secretory transport of empagliflozin was completely inhibited by co-incubation with the selective P-gp inhibitor, LY335979. The apparent secretory permeability of empagliflozin was generally constant at concentrations between 1 μM and 2 mM, indicating that the P-gp-mediated efflux of empagliflozin could not be saturated in this system.
- Empagliflozin did not inhibit P-gp as determined in MDCK-MDR1 cells using two P-gp probe substrates, taxol and digoxin, which have been shown to interact with distinct binding sites on P-gp.
- Efflux of empagliflozin was only partially inhibited by the P-gp specific inhibitor LY335979 in Caco-2 cells, indicating that empagliflozin is a substrate for multiple efflux transporters. Additional transport studies conducted in Caco-2 cells using the BCRP selective inhibitor prazosin indicate that empagliflozin is a substrate of BCRP. Thus, empagliflozin is dual substrate of human P-gp and BCRP.
- HEK293 cells transfected with human SLC transporters were used to evaluate the potential for empagliflozin to inhibit renal uptake transporters, OAT1, OAT3, and OCT2, and other uptake transporters OATP1B1, OATP1B3, and OATP2B1.
- Results for interaction of empagliflozin with OAT1, OAT3, OCT2, OATP1B1, OATP1B3, MRP2 and BCRP are summarized in the table below.

Table 13 Interaction of empagliflozin with OAT1, OAT3, OCT2, OATP1B1, OATP1B3, MRP2 and BCRP

Transporter	IC ₅₀ (μM)	[I]/IC ₅₀	[I ₂]/IC ₅₀	<i>In vivo</i> DDI prediction
OAT1	>1000	<0.001	not relevant	unlikely
OAT3	295	0.0023	not relevant	unlikely
OCT2	>1000	<0.001	not relevant	unlikely
OATP1B1	71.8	0.009	not relevant	unlikely
OATP1B3	58.6	0.012	not relevant	unlikely
OATP2B1	45.2	0.015	not relevant	unlikely
BCRP	114.1	0.006	1.9	unlikely
MRP2	1399	0.0005	0.16	unlikely

- Empagliflozin is a substrate of 3 of the 5 major human solute carrier (SLC) transporters, including OAT3 (uptake was inhibited by probenecid), OATP1B1 and OATP1B3 (uptake was inhibited by rifampicin), but was not a substrate of OAT1 and OCT2.
- Empagliflozin uptake was dependent on incubation time and concentration, and was saturable in OAT3-, OATP1B1- and OATP1B3-injected oocytes at 300 μM

2.5.2.3 What is the effect of co-administered drugs on the pharmacokinetics of empagliflozin?

Clinical DDI investigations were conducted at the 25 to 50 mg dose (except as noted) with representative medications from anti-hypertensive, anti-diabetic and lipid-lowering classes. Co-administration of various representative drugs did not affect the exposure of empagliflozin in a clinically meaningful way (See Figure 24 below). The geometric mean ratios were close to one and 90% confidence intervals were contained within the 0.8 to 1.25 interval. However, overall exposure (AUC) of empagliflozin increased by 1.59-fold following co-administration with gemfibrozil, 1.75-fold with rifampicin (OATP1B1 inhibition), and 1.53-fold with probenecid (OAT3 inhibition). Co-administration with probenecid also resulted in about 30% decrease in fraction of unchanged empagliflozin excretion in urine [20% (4280 nmol) to 14% (3060 nmol)] without any effect on UGE0-24h. Notably, this study was conducted in subjects with normal renal function and 14% Fe (3060 nmol) was still in maximal region of Ae0-24h – UGE0-24h relationship seen in PKPD studies (Figures 12 and 17). However, any such reduction of Fe(%) in patients with renal impairment could further jeopardize the pharmacodynamic response. Therefore, even if the PK change is not clinically relevant, the relevance of PD effect cannot be disregarded.

Co-administration with probenecid resulted in about 30% decrease in fraction of unchanged empagliflozin excreted in urine (20% to 14%) without any effect on UGE0-24h. Notably, 14% Fe was still in maximal region of Fe0-24h – UGE0-24h relationship seen in PKPD studies (see Figures 12 and 13). However, any such reduction of Fe (%) in patients with renal impairment could further jeopardize the pharmacodynamic response. Therefore, even if the PK change is not clinically relevant, the relevance of PD effect cannot be disregarded for patients with renal impairment. Therefore, we recommend that HbA1c levels are monitored when using empagliflozin in type 2 diabetic patients with renal impairment who are taking probenecid (Monotherapy/Combination products) or other OAT3 inhibitors.

While the single dose DDI evaluation with rifampicin was sensitive in detecting the inhibition of OATP1B1 mediated uptake in liver and consequent increase in C_{max} and AUC of empagliflozin, in absence of a multiple-dose DDI study with rifampicin, the effect of UGT induction by rifampicin on empagliflozin exposure is not evaluated. Therefore, we recommend that HbA1c levels should be monitored when using empagliflozin in type 2 diabetic patients who are taking rifampicin or other inducers of UGT2B7, UGT1A3, UGT1A8, and UGT1A9.

When co-administered with diuretics (hydrochlorothiazide or torasemide) the urine osmolality and urine volume were increased after treatment with empagliflozin alone and with a diuretic, while diuretics alone had no apparent effect. Mean urine volume was higher (341 mL/day) than baseline after single doses of empagliflozin and tended to be higher (135 mL/day) than baseline after multiple doses of empagliflozin. At baseline, mean micturition frequencies were 4 to 5 voids in the day and 3 voids at night. On the first and fifth days of empagliflozin treatment, daytime micturition increased to about 6 voids per day while night-time micturition frequency was similar to baseline. The mean increase in total micturition frequency was about 1 to 2 voids per day. Treatment with hydrochlorothiazide or torasemide tended to increase both urinary glucose excretion and fasting serum glucose levels. When empagliflozin was added to either diuretic, the effects on urinary glucose excretion were maintained while the reductions in the fasting serum glucose concentration were less pronounced than when empagliflozin was given alone.

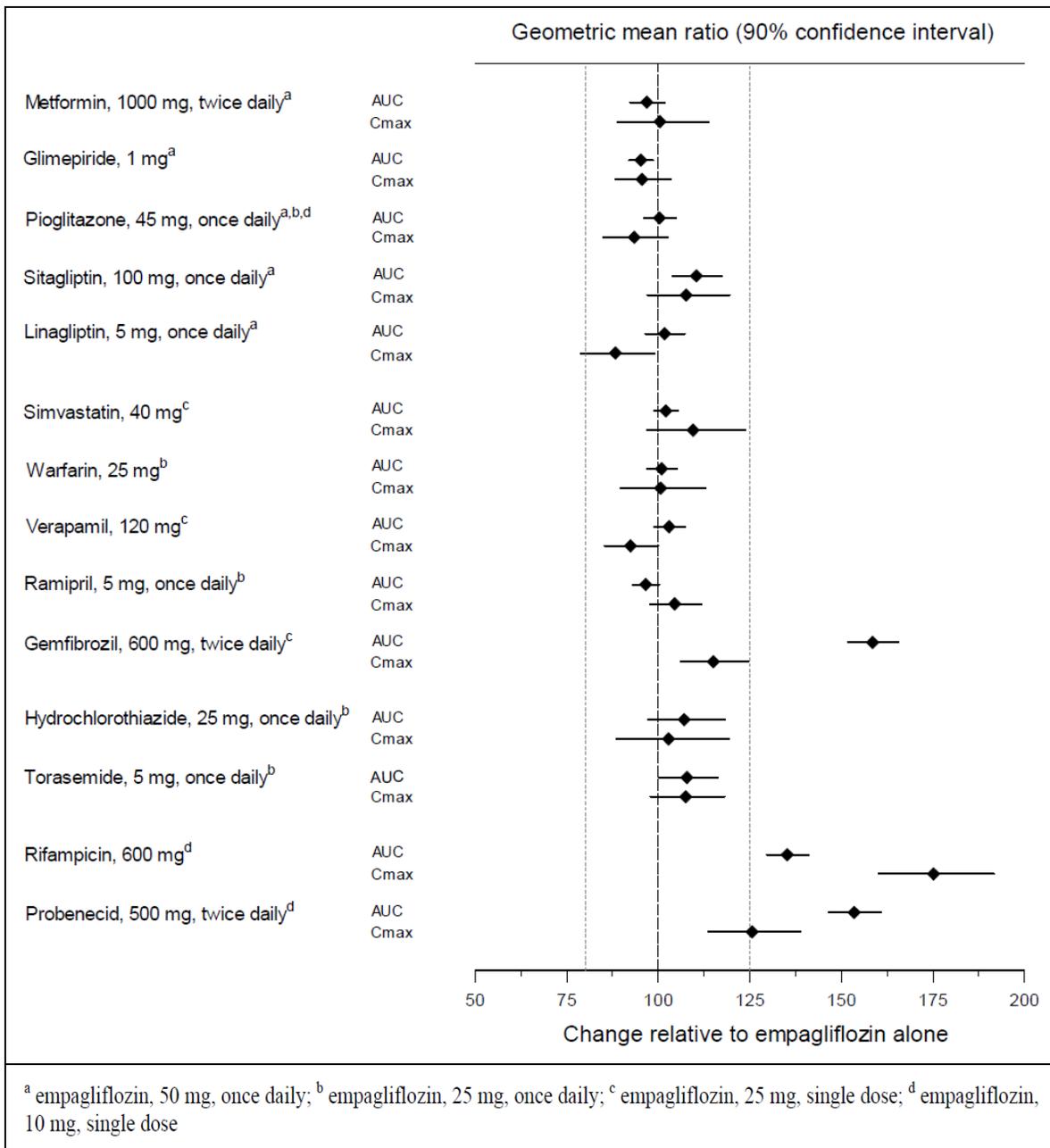


Figure 24 Effect of co-administered drugs on empagliflozin pharmacokinetics

2.5.2.4 What is the effect of empagliflozin co-administration on the pharmacokinetics of other drugs?

Empagliflozin had no clinically relevant effect on the PK of metformin, glimepiride, sitagliptin, linagliptin, simvastatin, warfarin, ramipril, digoxin, hydrochlorothiazide, torasemide, and oral contraceptives when co-administered (see Figure 25). A moderate increase in pioglitazone exposure (approximately 36% increase in the overall exposure of pioglitazone and its two active metabolites, M-III and M-IV, combined) was observed in one of two trials when pioglitazone was co-administered with 50 mg empagliflozin. In

the second more robust drug-drug interaction study with pioglitazone, only a slight decrease in exposures of pioglitazone and its two active metabolites were observed with three different doses of empagliflozin (10, 25, and 50 mg) .

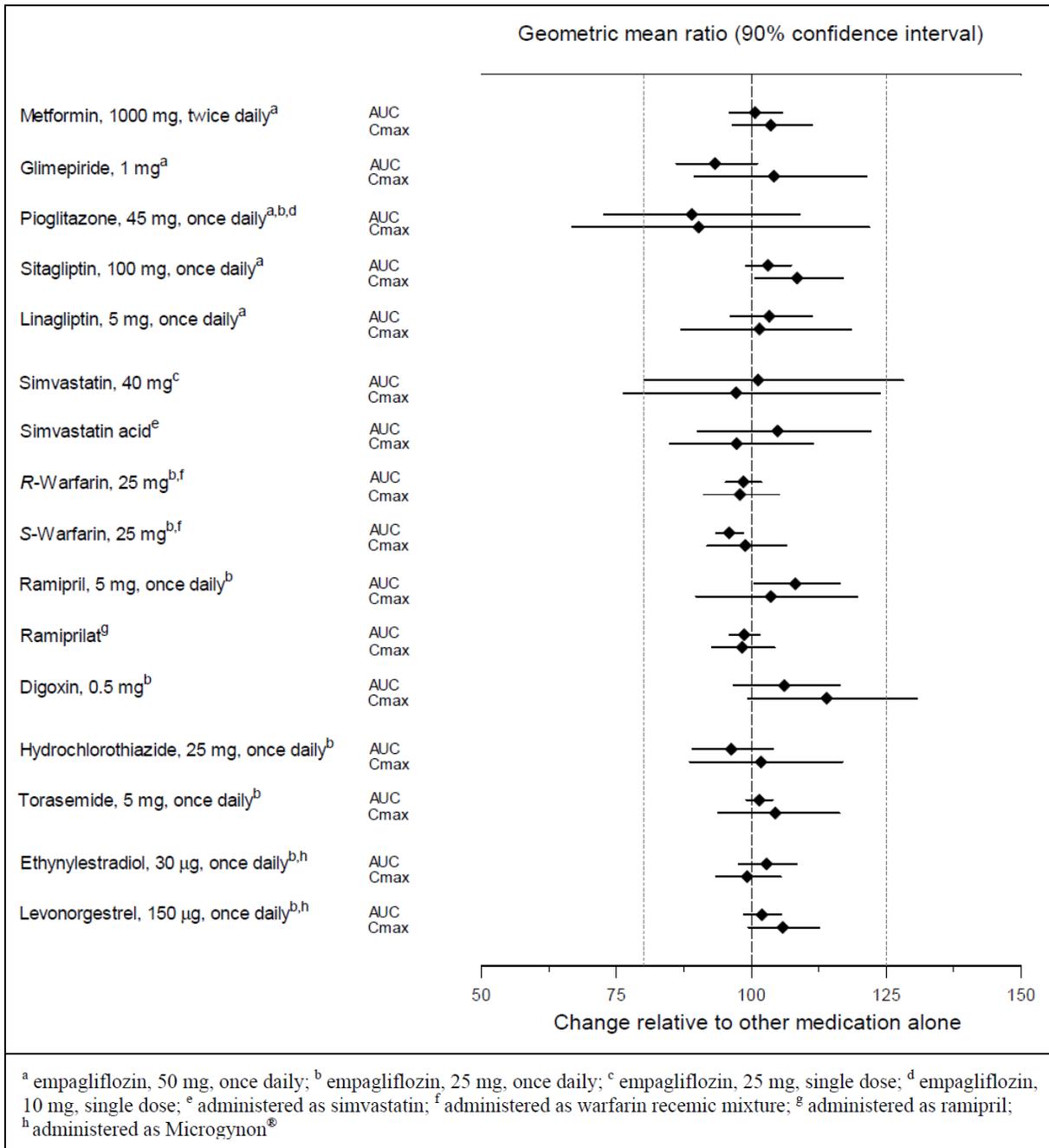


Figure 25 Effect of empagliflozin on pharmacokinetics of co-administered drugs

2.6 General Biopharmaceutics

2.6.1 Is bioequivalence established between the to-be-marketed formulation and the Phase 2/3 trial formulation and how does it relate to the overall product development?

The final to be marketed formulation was evaluated in Phase 3 trials (see Table 14 below). The Trial formulation II and Final Formulation FF, intended for commercial supply, were compared in a relative bioavailability study.

The final formulation was used in the pivotal Phase 3 trials. Therefore, no pivotal bioequivalence study was conducted. Office of Scientific Investigation inspection was not requested for any clinical pharmacology study in this application.

Table 14 Details of formulations utilized in various clinical trials

Formulation type	General manufacturing principle	Clinical studies *
(b) (4) tablets (TF I)	(b) (4)	Phase I: 1245.1, 2, 3, 4
tablets (TF II)		Phase I: 1245.5, 6, 7, 12, 13, 17, 27, 30, 51 Phase II: 1245.9, 10, 15, 24, 33
Film-coated tablets (FF)		Phase I: 1245.16, 18, 40, 41, 43, 44, 45, 50, 51, 53, 58, 63, 79, 83 Phase II: 1245.38 Phase III: 1245.19, 20, 23, 25, 28, 31, 36, 48

* numbers in bold indicate pivotal clinical studies

Mean empagliflozin concentrations from the Trial formulation II and Final Formulation FF are presented in Figure 26 below.

The results of statistical analyses showed that the GMR (90% CI) for empagliflozin AUC_{0-∞} and C_{max} were 101.67% (98.10 to 105.37%) and 99.46% (90.18 to 109.68%), respectively, with the FF compared to TF-II. The 90% CIs for the GMR of both AUC_{0-∞} and C_{max} were within the standard bioequivalence criteria of 80 to 125%, indicating that empagliflozin exposure was bioequivalent when empagliflozin was administered as the FF or as TF-II.

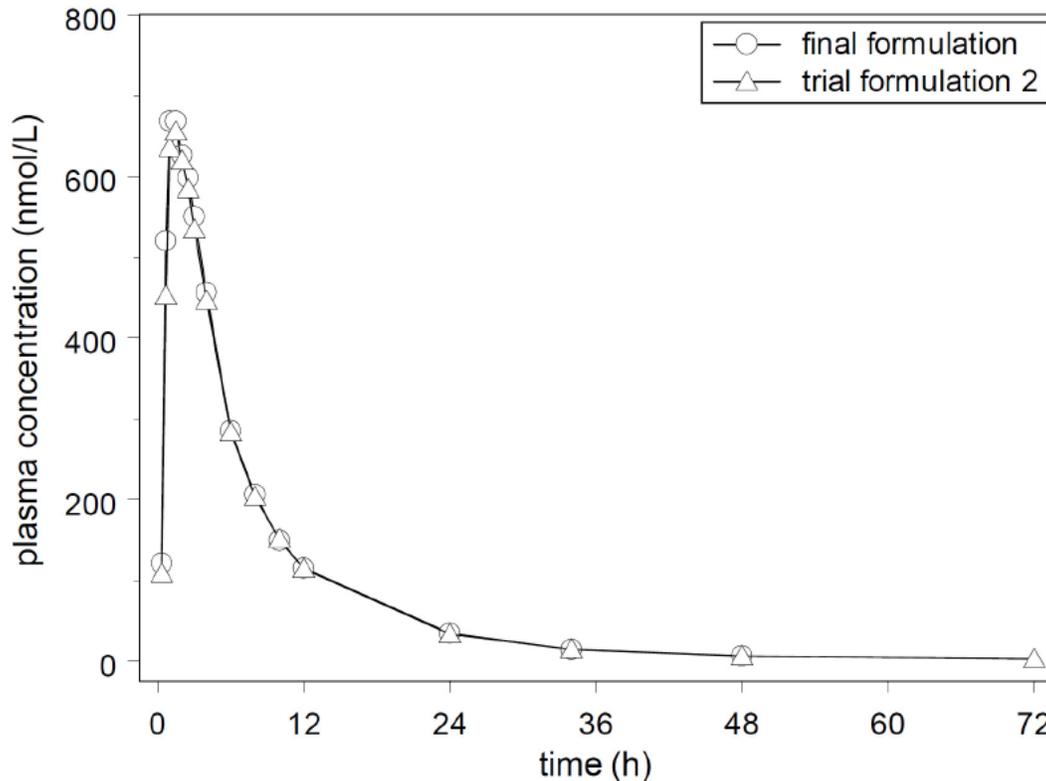


Figure 26 Mean plasma concentration-time profiles of empagliflozin after oral administration of 25 mg empagliflozin final formulation tablet or empagliflozin trial formulation II tablet

2.7 Analytical

2.7.1 Are the analytical methods for empagliflozin appropriately validated?

Tandem method for the Analysis of empagliflozin in Human Plasma and urine: Specific and highly sensitive high performance liquid chromatography tandem mass spectrometry (HPLC-MS/MS) methods for the quantification of empagliflozin and its metabolite, EX 609, were developed and validated for human urine and plasma to support the clinical empagliflozin development program. Assays were validated at Boehringer Ingelheim Pharmaceuticals, Inc. Bioanalytical Systems, Inc., (b) (4)

All samples were extracted by solid phase supported liquid extraction. Before the extraction, stable isotope-labeled drug was added as the internal standard. Samples were transferred to 96-well diatomaceous earth extraction plates and allowed to absorb. The analytes were eluted with isopropyl acetate, evaporated to dryness, and reconstituted with acetonitrile/water. The reconstituted samples were injected into an HPLC-MS/MS system using a C6-phenyl column with a pre-column filter and an isocratic elution.

Summary of all major assay validations is presented by site below in Tables 15, 16, and 17.

Table 15 Summary of validation results of bioanalytical assays for the quantitation of empagliflozin and EX 609 in human plasma (Assay validation performed at Boehringer Ingelheim Pharmaceuticals, Inc.)

Analytes:	empagliflozin EX 609	Internal Standards:	¹³ C ₆ -empagliflozin ¹³ C ₆ -EX 609			
Matrix:	Human Plasma	Detection Method:	LC/MS/MS			
Standard Curve Range:	0.500 -500 ng/mL (1.11 - 1110 nM)	Assay Volume:	150 µL			
Extraction Method:	solid phase supported liquid-liquid	Regression Type:	Quadratic 1/x ² weighting			
Room Temperature Plasma Stability:	18.5 h	Processed Sample Stability:	7 days			
Freeze/Thaw Stability, (-30°C):	3 cycles	Long-term Freezer Stability, (-30°C):	106 days			
Matrix	QC name	Concentration	Inaccuracy [%]		Imprecision [%]	
			Empagliflozin	EX 609	Empagliflozin	EX 609
Plasma	LLOQ	0.500 ng/mL (1.11 nM)	1.4	2.4	9.7	5.0
	QC_low	1.50 ng/mL (3.33 nM)	1.3	0.7	3.3	3.3
	QC_mid	20.0 ng/mL (44.4 nM)	0.5	0.5	2.2	2.4
	QC_high	400 ng/mL (888 nM)	1.0	-0.5	2.5	2.9
	ULOQ	500 ng/mL (1110 nM)	2.4	0.6	1.9	2.3
	QC_dil (df=10)	2500 ng/mL (5550 nM)	6.4	6.0	1.2	3.2

Table 16 Summary of validation results of bioanalytical assays for the quantitation of empagliflozin and EX 609 in human urine (Assay validation performed at Boehringer Ingelheim Pharmaceuticals, Inc.)

Analytes:	empagliflozin EX 609	Internal Standards:	¹³ C ₆ -empagliflozin ¹³ C ₆ -EX 609			
Matrix:	Human Urine	Detection Method:	LC/MS/MS			
Standard Curve Range:	2-2000 ng/mL (4.44 - 4440 nM)	Assay Volume:	50 µL			
Extraction Method:	solid phase supported liquid-liquid	Regression Type:	Quadratic 1/x ² weighting			
Room Temperature Plasma Stability:	17.5 h	Processed Sample Stability:	70.5 h			
Freeze/Thaw Stability, (-30°C):	3 cycles	Long-term Freezer Stability, (-30°C):	84 days			
Matrix	QC name	Concentration	Inaccuracy [%]		Imprecision [%]	
			Empagliflozin	EX 609	Empagliflozin	EX 609
Urine	LLOQ	2.00 ng/mL (4.44 nM)	-8.0	-1.5	7.4	6.2
	QC_low	6.00 ng/mL (13.3 nM)	1.3	3.0	3.5	6.7
	QC_mid	80.0 ng/mL (178 nM)	1.3	0.9	3.9	3.0
	QC_high	1600 ng/mL (3552 nM)	0.0	0.6	4.2	2.2
	ULOQ	2000 ng/mL (4440 nM)	-1.5	1.0	3.9	1.6
	QC_dil (df = 10)	10000 ng/mL (22200 nM)	-1.8	3.0	4.8	2.0

Table 17 Summary of validation results of bioanalytical assays for the quantitation of empagliflozin in human plasma (Assay validation performed at

(b) (4)

Analyte:	empagliflozin	Internal Standard:	¹³ C ₆ -empagliflozin
Matrix:	Human Plasma	Detection Method:	LC/MS/MS
Standard Curve Range:	0.500 – 500 ng/mL	Assay Volume:	150 µL
Extraction Method:	Solid phase supported liquid-liquid	Regression Type:	Quadratic, 1/x ² weighting
Room Temperature Plasma Stability:	18.5 h	Processed Sample Stability:	7 days at 12.5°C
Freeze/Thaw Stability, (-20°C):	6 cycles	Long-term Freezer Stability, (-20°C):	484 days

Matrix	QC name	Concentration	Inaccuracy [%]	Imprecision [%]
Plasma	LLOQ	0.5 ng/mL (1.11 nM)	-1.6	8.1
	QC_low	1.5 ng/mL (3.33 nM)	0.0	7.9
	QC_mid	20 ng/mL (44.4 nM)	-1.0	5.5
	QC_high	400 ng/mL (888 nM)	0.8	7.5
	QC_dil (df = 50)	2500 ng/mL (5550 nM)	0.4	1.6

Table 18 Summary of validation results of bioanalytical assays for the quantitation of empagliflozin in human urine (Assay validation performed at

(b) (4)

Analyte:	empagliflozin	Internal Standard:	¹³ C ₆ -empagliflozin
Matrix:	Human urine	Detection Method:	LC/MS/MS
Standard Curve Range:	2.00 – 2000 ng/mL	Assay Volume:	50 µL
Extraction Method:	Solid phase supported liquid-liquid	Regression Type:	Quadratic, 1/x ² weighting
Room Temperature Plasma Stability:	17.5 h	Processed Sample Stability:	70.5 h at 12.5°C
Freeze/Thaw Stability, (-20°C):	4 cycles	Long-term Freezer Stability, (-20°C):	493 days

Matrix	QC name	Concentration	Inaccuracy [%]	Imprecision [%]
Urine	LLOQ	2 ng/mL (4.44 nM)	1.5	7.5
	QC_low	6 ng/mL (13.3 nM)	7.2	6.2
	QC_mid	80 ng/mL (178 nM)	3.0	4.4
	QC_high	1600 ng/mL (3552 nM)	0.0	3.7
	QC_dil (df = 100)	10000 ng/mL (22200 nM)	-6.7	2.7

Table 19 Summary of validation results of bioanalytical assays for the quantitation of empagliflozin in human plasma (Assay validation performed at

(b) (4)

Analyte:	empagliflozin	Internal Standard:	¹³ C ₆ -empagliflozin	
Matrix:	Human plasma	Detection Method:	LC/MS/MS	
Standard Curve Range:	0.500 – 500 ng/mL	Assay Volume:	75 µL	
Extraction Method:	Supported liquid	Regression Type:	Quadratic, 1/x ² weighting	
Room Temperature Plasma Stability:	46 h	Processed Sample Stability:	82 h, refrigerated	
Freeze/Thaw Stability, (-10 to -30°C):	3 cycles	Long-term Freezer Stability, (-10 to -30°C):	42 days	
Matrix	QC name	Concentration	Inaccuracy [%]	Imprecision [%]
Plasma	LLOQ	0.5 ng/mL (1.11 nM)	0.0	6.4
	QC_low	1.5 ng/mL (3.33 nM)	-6.0	4.0
	QC_mid	20 ng/mL (44.4 nM)	-2.5	3.2
	QC_high	400 ng/mL (888 nM)	-4.2	2.1
	QC_dil (df = 10)	2500 ng/mL (5550 nM)	-5.2	2.0

Table 20 Summary of validation results of bioanalytical assays for the quantitation of empagliflozin in human urine (Assay validation performed at

(b) (4)

Analyte:	empagliflozin	Internal Standard:	¹³ C ₆ -empagliflozin	
Matrix:	Human urine	Detection Method:	LC/MS/MS	
Standard Curve Range:	2.00 – 2000 ng/mL	Assay Volume:	75 µL	
Extraction Method:	Supported liquid extraction	Regression Type:	Quadratic, 1/x ² weighting	
Room Temperature Plasma Stability:	27 h	Processed Sample Stability:	95 h, refrigerated	
Freeze/Thaw Stability, (-10 to -30°C):	3 cycles	Long-term Freezer Stability, (-10 to -30°C):	42 days	
Matrix	QC name	Concentration	Inaccuracy [%]	Imprecision [%]
Urine	LLOQ	2 ng/mL (4.44 nM)	-1.5	6.3
	QC_low	6 ng/mL (13.3 nM)	-2.0	4.3
	QC_mid	80 ng/mL (178 nM)	-0.9	3.8
	QC_high	1600 ng/mL (3552 nM)	0.6	1.5
	QC_dil (df = 10)	10000 ng/mL (22200 nM)	-12.6	2.0

Table 21 Summary of cross validation results of bioanalytical assays for the quantitation of empagliflozin in human plasma (Assay validation performed at (b) (4) and cross validated with (b) (4).)

Analyte:	empagliflozin	Internal Standard:	¹³ C ₆ -empagliflozin
Matrix:	Human plasma	Detection Method:	LC/MS/MS
Standard Curve Range:	0.500 – 500 ng/mL	Assay Volume:	150 µL
Extraction Method:	Supported liquid extraction	Regression Type:	Quadratic, 1/x ² weighting
Unknown A (75.0 ng/mL):	Within 10.4%	Unknown C (400 ng/mL):	Within 6.8%
Unknown B (200 ng/mL):	Within 7.0%		

Matrix	QC name	Concentration	Inaccuracy [%]	Imprecision [%]
Plasma	LLOQ	0.500 ng/mL	-5.8	3.5
	QC_low	1.50 ng/mL	-7.3	3.7
	QC_mid	20.0 ng/mL	-5.5	2.8
	QC_high	400 ng/mL	-2.0	3.6
	ULOQ	500 ng/mL	-1.6	3.6
	QC_dil	2500 ng/mL	-1.6	2.1
		(df = 10)		

Table 22 Summary of non-GLP assay results for the quantitation of empagliflozin glucuronides in human plasma (Assay performed at Boehringer-Ingelheim Pharmaceuticals, Inc.)

Analytes:	empa-2-O-gluc empa-3-O-gluc empa-6-O-gluc	Internal Standard:	¹³ C ₆ -empagliflozin ^a
Matrix:	Human plasma	Detection Method:	LC/MS/MS
Standard Curve Range:	2.5 – 2500 ng/mL ^a	Assay Volume:	100 µL
Extraction Method:	Protein precipitation	Regression Type:	Quadratic, 1/x ² weighting

Matrix	QC name	Conc ^a	Inaccuracy [%]			Imprecision [%]		
			empa-2-O-gluc	empa-3-O-gluc	empa-6-O-gluc	empa-2-O-gluc	empa-O-gluc	empa-6-O-gluc
Plasma	QC_low	7.50 nM	-0.4	-0.7	-1.3	10.6	7.1	7.1
	QC_mid	125 nM	1.3	3.2	4.6	7.0	3.3	5.2
	QC_high	2000 nM	1.4	-0.7	2.3	8.7	4.5	6.6

Assays utilized for quantitation of co-administered drugs in the DDI studies (plasma and urine, as applicable) were also appropriately validated.

3 Labeling Comments (Preliminary)

Note: Labeling statements to be removed are shown in ~~red strikethrough font~~ and suggested labeling to be included is shown in underline blue font.

Proposed Text:

The following are the labeling recommendations relevant to clinical pharmacology for NDA 204629 that were based on population PK analysis. The ~~red strikethrough 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.

Highlights of Prescribing Information



2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosing

The recommended starting dose of ~~(b) (4)~~ JARDIANCE is 10 mg once daily. ~~(b) (4)~~

which can be increased to 25 mg once daily. The recommended dose for empagliflozin is 10 mg once daily, which can be increased to 25 mg once daily. 25 mg once daily dose provides additional benefit only in select settings (see Section 14, Clinical Trials); therefore, not all patients may get additional benefit by increasing the dose to 25 mg once daily dose. Patient tolerability should also be considered while increasing the dose to 25 mg once daily.



2.3 Renal Impairment



8.6 Renal Impairment

8.7 Hepatic Impairment

(b) (4) may be used in patients with (b) (4) hepatic impairment [see (b) (4) Clinical Pharmacology (12.3)].

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Sodium glucose co-transporter (SGLT2) is the predominant transporter responsible for reabsorption of (b) (4) glucose from the glomerular filtrate back into (b) (4) circulation. (b) (4)

Empagliflozin is an (b) (4) inhibitor of SGLT2 ([IC₅₀: 1.3 nM for human renal SGLT2 transporter *in vitro*](#)) (b) (4) ([IC₅₀: 6278 nM](#)), (b) (4)

12.2 Pharmacodynamics

Urinary Glucose Excretion

In patients with type 2 diabetes, urinary glucose excretion increased immediately following (b) (4) dose of (b) (4) and was maintained at the end of a 4-week treatment period averaging at approximately 64 g/day (b) (4) with 10 mg empagliflozin and 78 g/day (b) (4) with 25 mg (b) (4) once daily. (b) (4)

Urinary Volume

In a 5-day study, mean 24-hour urine volume increased 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 (b) (4) 25 mg, (b) (4) 200 mg (8 times the maximum dose), moxifloxacin, and placebo. No increase in QTc was observed with either (b) (4) 25 mg or 200 mg empagliflozin.

(b) (4)

(b) (4)

12.3 Pharmacokinetics

Specific Populations

Renal Impairment

In patients with mild (eGFR: 60 - <90 mL/min/1.73 m²), moderate (eGFR: 30 - <60 mL/min/1.73 m²), severe (eGFR: <30 mL/min/1.73 m²) 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. (b) (4) population pharmacokinetic analysis showed that the apparent oral clearance of empagliflozin decreased with a decrease in eGFR leading to an increase in drug exposure (see [Dosage and Administration \(2\)](#); [Warnings and Precautions \(5.2\)](#); [Adverse Reactions \(6.1\)](#); [Specific Populations \(8.5\)](#)).

Effects of Age, Body weight, and Gender

Based on the population PK analysis with data collected from 1526 subjects, age, BMI, gender, and race (Asians versus primarily Whites) do not have a clinically meaningful effect on pharmacokinetics of empagliflozin [see [Dosage and Administration \(2\)](#); [Warnings and Precautions \(5.2\)](#); [Adverse Reactions \(6.1\)](#); [Specific Populations \(8.5\)](#)].

(b) (4)

Drug Interactions

In vivo Assessment of Drug Interactions

No dose adjustment of (b) (4) is recommended when coadministered with commonly prescribed medicinal products based on results of the described pharmacokinetic studies. Empagliflozin pharmacokinetics were similar with and without co-administration of metformin, glimepiride, pioglitazone, sitagliptin, linagliptin, warfarin, verapamil, ramipril, simvastatin, hydrochlorothiazide, and torasemide in healthy volunteers (Figure 2). The observed increases in overall exposure (AUC) of

empagliflozin following co-administration with gemfibrozil, rifampicin, or probenecid are not clinically relevant. However, coadministration with probenecid resulted in 30% decrease in fraction of empagliflozin excreted in urine. This decrease could be clinically relevant for patients with renal impairment, where there is reduction in fraction of drug excreted in urine. Impact of UGT induction with rifampicin or any other UGT enzyme inducer has not been studied. Monitoring of HbA1c in patients is recommended in patients who are concomitantly taking OAT3 inhibitors, such as probenecid and UGT inducers, such as rifampicin.

4 Appendix

4.1 Summary of Individual Studies

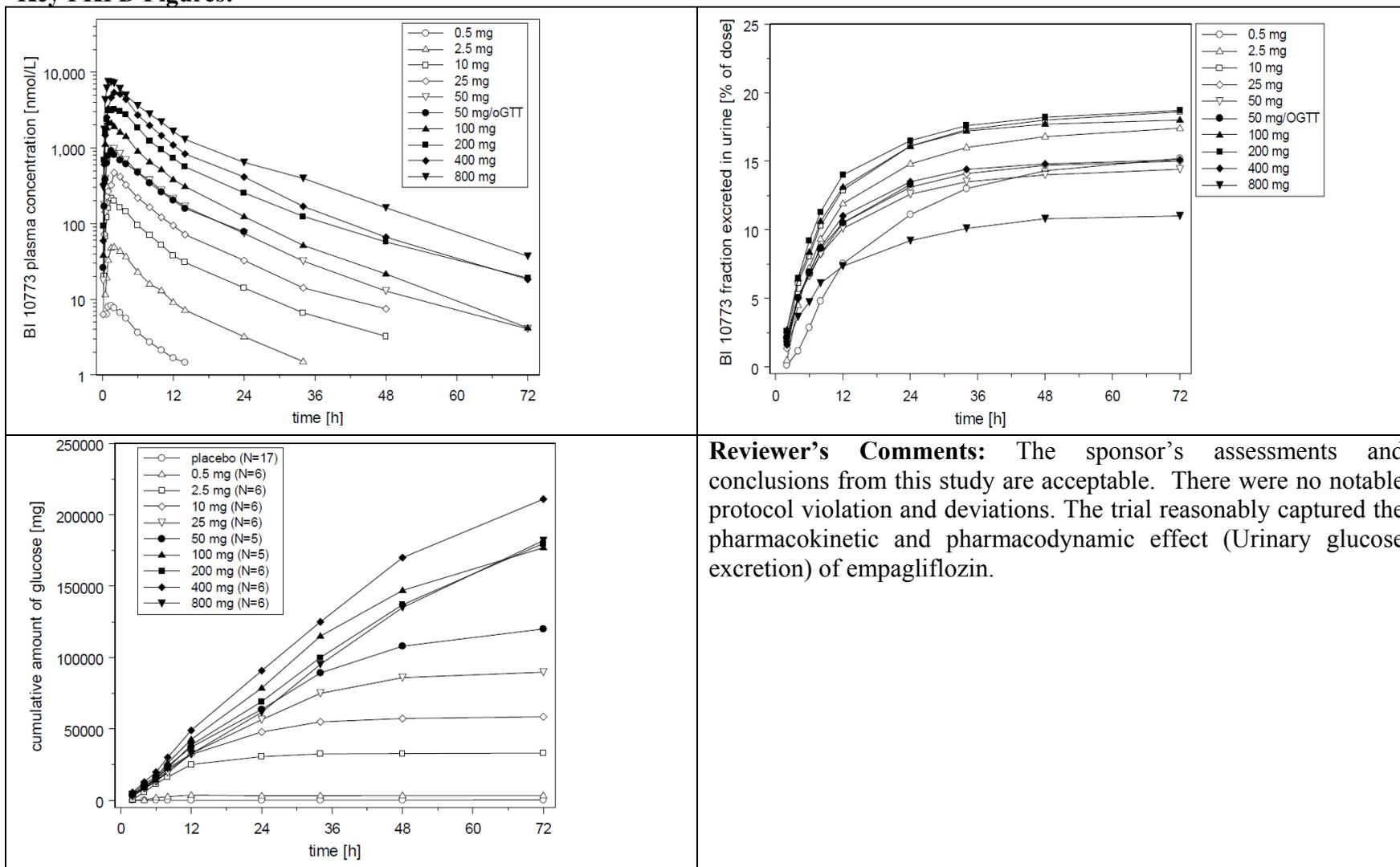
(Based on sponsor's Summary of Clinical Pharmacology, Summary of Biopharmaceutics and Associated Bioanalytical Methods, and Review of Individual Study Reports)

4.1.1 Single Rising Dose PK and PD in Healthy (1245.1)

Study Objective	Study Design and Type of Control	Healthy Subjects or patients Age: (median, range)	# Subjects Entered/ Completed (M/F)	Treatment (Dose, dosage Form, Route) [Batch no.]	Mean Pharmacokinetic Parameters (%CV)						Mean Pharmacodynamic parameters (%CV)	
					AUC _{0-∞} [nmol.h/L] AUC _{0-∞, norm} [nmol.h/L/mg]	C _{max} [nmol/L] C _{max, norm} [nmol/L/mg]	t _{max} ¹ [h]	t _{1/2} [h]	fe _{0.72} [%]	CL _{R,0.72} [mL/min]	UGE ² [g/day]	FPG [mg/dL]
Single rising dose study in Caucasian healthy volunteers	Randomised, double-blind, placebo controlled	HV (34.0, 23 - 46)	16/16 (M)	placebo, tablet, p.o. B061002444 B061002445 B061002446	--	--	--	--	--	--	0.058 (34.4)	--
		HV (41.0, 24 - 45)	6/6 (M)	0.5 mg, tablet, p.o. B061002447	61.2 (28.1) 122 (28.1)	9.33 (40.0) 18.7 (40.0)	1.51 (0.983 - 3.02)	5.57 (12.4)	15.2 (28.9)	51.3 (22.4)	3.12 (58.0)	--
		HV (36.5, 36 - 45)	6/6 (M)	2.5 mg, tablet, p.o. B061002447	396 (11.0) 158 (11.0)	53.2 (11.7) 21.3 (11.7)	1.75 (0.983 - 2.98)	8.57 (6.86)	17.4 (14.8)	41.3 (22.2)	30.6 (27.2)	--
		HV (35.0, 23 - 46)	6/6 (M)	10 mg, tablet, p.o. B061002448	1730 (21.8) 173 (21.8)	226 (20.4) 22.6 (20.4)	1.50 (0.983 - 2.03)	13.1 (30.9)	18.6 (13.2)	41.1 (10.1)	47.9 (13.9)	--
		HV (41.0, 26 - 49)	6/6 (M)	25 mg, tablet, p.o. B061002449	3830 (21.5) 153 (21.5)	505 (25.9) 20.2 (25.9)	2.05 (1.00 - 3.02)	10.2 (20.9)	15.0 (16.0)	37.7 (24.9)	56.5 (11.6)	--
		HV (40.0, 40 - 44)	5/5 (M)	50 mg, tablet, p.o. B061002449	8580 (19.6) 172 (19.6)	1110 (24.6) 22.2 (24.6)	1.50 (0.750 - 3.00)	10.3 (18.0)	14.4 (3.99)	32.1 (22.7)	63.6 (14.6)	--

Study Objective	Study Design and Type of Control	Healthy Subjects or patients Age: (median, range)	# Subjects Entered/ Completed (M/F)	Treatment (Dose, dosage Form Route) [Batch no.]	Mean Pharmacokinetic Parameters (%CV)						Mean Pharmacodynamic parameters (%CV)	
					AUC _{0-∞} [nmol.h/L] AUC _{0-∞, norm} [nmol.h/L/mg]	C _{max} [nmol/L] C _{max, norm} [nmol/L/mg]	t _{max} ³ [h]	t _{1/2} [h]	fe ₀₋₇₂ [%]	CL _{R,0-72} [mL/min]	UGE ⁴ [g/day]	FPG [mg/dL]
Single rising dose study in Caucasian healthy volunteers	Randomised, double-blind, placebo controlled	HV (40.0, 40 – 44)	5/5 (M)	50 mg/ OGTT, tablet, p.o. B061002449	8090 (15.3) 162 (15.3)	951 (31.5) 19.0 (31.5)	1.50 (1.47 – 5.98)	8.83 (20.9)	13.3 (20.1)	35.5 (25.1)	66.1 (11.3)	--
		HV (39.0, 32 – 46)	5/5 (M)	100 mg, tablet, p.o. B061002450	16500 (14.5) 165 (14.5)	2500 (26.7) 25.0 (26.7)	1.00 (0.750 – 3.00)	10.6 (23.5)	18.0 (23.5)	40.7 (22.3)	78.6 (15.6)	--
		HV (35.5, 28 – 47)	6/6 (M)	200 mg, tablet, p.o. B061002450	31200 (20.1) 156 (20.1)	3490 (23.4) 17.5 (23.4)	1.76 (1.00 – 2.98)	11.1 (23.7)	18.7 (18.5)	45.6 (20.0)	69.1 (18.4)	--
		HV (36.0, 26 – 48)	6/6 (M)	400 mg, tablet, p.o. B061002450	46600 (21.8) 117 (21.8)	6060 (28.4) 15.2 (28.4)	2.03 (0.750 – 4.00)	11.2 (32.4)	15.1 (15.2)	49.5 (19.8)	90.8 (18.0)	--
		HV (36.0, 24 – 40)	6/6 (M)	800 mg, tablet, p.o. B061002450	70200 (13.6) 87.8 (13.6)	7950 (22.8) 9.94 (22.8)	1.52 (0.733 – 2.02)	11.2 (14.5)	11.0 (21.8)	47.3 (21.2)	61.6 (8.03)	--

Key PKPD Figures:



Reviewer's Comments: The sponsor's assessments and conclusions from this study are acceptable. There were no notable protocol violation and deviations. The trial reasonably captured the pharmacokinetic and pharmacodynamic effect (Urinary glucose excretion) of empagliflozin.

4.1.2 Multiple dose PKPD in Patients (1245.2)

Study Objective	Study Design and Type of Control	Healthy Subjects or patients Age: (median, range)	# Subjects Entered/ Completed (M/F)	Treatment (Dose, dosage Form Route) [Batch no.] ¹³	Mean Pharmacokinetic Parameters (%CV)						Mean Pharmacodynamic parameters (%CV) ¹⁴	
					AUC ₀₋₂₄ [nmol.h/L]	C _{max} [nmol/L]	t _{max} ¹⁵ [h]	t _{1/2} [h]	fe ₀₋₂₄ [%]	CL _{R,0-48} [mL/min]	UGE ¹⁶ [g/day]	FPG [mg/dL]
					AUC _{0-24, norm} [nmol.h/L/mg]	C _{max, norm} [nmol/L/mg]					Day -2 Day -1 Day 1 Day 8 Day 9	Day -2 Day -1 Day 1 Day 8 Day 9
AUC _{τ,ss} [nmol.h/L]	C _{max,ss} [nmol/L]	t _{max,ss} [h]	t _{1/2,ss} [h]	fe _{0-24,ss} [%]	CL _{R,τ,ss} [mL/min]							
8-day multiple rising dose study in Caucasian patients	Randomised, double-blind, placebo controlled	Patients (59.0, 51 – 67)	12/11 (10M/2F)	placebo, tablet, p.o.	--	--	--	--	--	--	5.44 (154) 7.60 (88.2) 5.84 (78.2)	166 (19.2) 157 (15.4) 154 (14.0)
					--	--	--	--	--	--	1.77 (227) 3.76 (117)	137 (16.4) 135 (18.9)
					402 (16.8) 161 (16.8)	62.4 (19.8) 24.9 (19.8)	1.50 (0.667 – 1.50)	11.4 (20.2)	11.4 (30.2)	29.1 (51.7)	5.35 (231) 7.58 (130) 46.3 (48.0)	155 (29.8) 144 (26.8) 141 (30.8)
					471 (23.0) 189 (23.0)	68.5 (24.5) 27.4 (24.5)	1.50 (0.983 – 2.00)	10.3 (18.1)	15.5 (32.9)	33.3 (55.4)	40.0 (61.3) 37.7 (66.7)	121 (26.5) 121 (26.3)
					1630 (14.2) 163 (14.2)	245 (21.0) 24.5 (21.0)	1.50 (0.983 – 2.00)	11.9 (11.5)	10.9 (37.1)	24.5 (27.0)	3.37 (192) 6.54 (125) 89.8 (20.9)	151 (20.7) 150 (21.4) 141 (21.2)
					2030 (17.8) 203 (17.8)	283 (31.9) 28.3 (31.9)	1.50 (0.983 – 2.00)	14.3 (16.6)	18.7 (24.1)	34.4 (22.9)	82.5 (67.6) 67.9 (46.3)	110 (11.9) 109 (12.2)

Study Objective	Study Design and Type of Control	Healthy Subjects or patients Age: (median, range)	# Subjects Entered/ Completed (M/F)	Treatment (Dose, dosage Form Route) [Batch no.] ¹⁷	Mean Pharmacokinetic Parameters (%CV)						Mean Pharmacodynamic parameters (%CV) ¹⁸	
					AUC ₀₋₂₄ [nmol.h/L] AUC _{0-24, norm} [nmol.h/L/mg]	C _{max} [nmol/L] C _{max, norm} [nmol/L/mg]	t _{max} ¹⁹ [h]	t _{1/2} [h]	f _{e0-24} [%]	CL _{R,0-48} [mL/min]	UGE ²⁰ [g/day]	FPG [mg/dL]
					AUC _{τ,ss} [nmol.h/L] AUC _{τ,ss, norm} [nmol.h/L/mg]	C _{max,ss} [nmol/L] C _{max,ss, norm} [nmol/L/mg]	t _{max,ss} [h]	t _{1/2,ss} [h]	f _{e0-24,ss} [%]	CL _{R,τ,ss} [mL/min]	Day -2 Day -1 Day 1 Day 8 Day 9	Day -2 Day -1 Day 1 Day 8 Day 9
8-day multiple rising dose study in Caucasian patients	Randomised, double-blind, placebo controlled	Patients (58.0, 40 – 68)	9/9 (7M/2F)	25 mg, tablet, p.o.	4310 (24.2)	606 (24.2)	1.50 (0.983)	10.8 (18.3)	9.00 (72.1)	21.1 (52.5)	1.43 (171)	144 (15.5)
					172 (24.2)	24.3 (24.2)	- 4.00)				3.64 (71.4)	142 (17.1)
					4990 (21.5)	630 (16.8)	2.00 (0.667)	10.7 (19.1)	12.7 (50.2)	23.5 (37.0)	77.9 (32.3)	144 (25.2)
					200 (21.5)	25.2 (16.8)	- 4.20)				75.5 (49.8)	121 (26.5)
		Patients (61.0, 50 – 68)	9/9 (7M/2F)	100 mg, tablet, p.o.	20000 (18.2)	2750 (25.5)	3.00 (0.983)	13.6 (27.5)	7.88 (37.4)	15.0 (39.6)	5.01 (193)	166 (16.4)
					200 (18.2)	27.5 (25.5)	- 4.00)				8.89 (88.5)	164 (16.2)
					22800 (25.0)	2750 (22.0)	1.75 (0.983)	18.8 (55.6)	12.2 (64.2)	27.4 (61.5)	88.5 (35.3)	162 (16.6)
					228 (25.0)	27.5 (22.0)	- 4.00)				93.0 (28.9)	123 (8.68)
								88.7 (30.2)	126 (11.7)			

Reviewer’s Comments: The sponsor’s assessments and conclusions from this study are acceptable. There were no notable protocol violation and deviations. The trial reasonably captured the pharmacokinetic and pharmacodynamic effect (Urinary glucose excretion) of empagliflozin after multiple once daily doses.

4.1.3 Multiple dose PKPD in patients (1245.4)

Study Objective	Study Design and Type of Control	Healthy Subjects or patients Age: (median, range)	# Subjects Entered/ Completed (M/F)	Treatment (Dose, dosage Form Route) [Batch no.]	Mean Pharmacokinetic Parameters (%CV)						Mean Pharmacodynamic parameters (%CV) ²¹	
					AUC ₀₋₂₄ [nmol.h/L]	C _{max} [nmol/L]	t _{max} ²² [h]	t _{1/2} [h]	fe ₀₋₂₄ [%]	CL _{R,0-24} [mL/min]	UGE ²³ [g/day]	FPG [mg/dL]
					AUC _{0-24, norm} [nmol.h/L/mg]	C _{max, norm} [nmol/L/mg]					Day -2	Day -2
					AUC _{τ,ss} [nmol.h/L]	C _{max,ss} [nmol/L]	t _{max,ss} [h]	t _{1/2,ss} [h]	fe _{0-24,ss} [%]	CL _{R,τ,ss} [mL/min]	Day 1	Day 1
					AUC _{τ,ss, norm} [nmol.h/L/mg]	C _{max,ss, norm} [nmol/L/mg]					Day 27	Day 27
											Day 28	Day 28
4-week multiple rising dose study in Caucasian patients	Randomised, double-blind, placebo controlled	Patients (60.5, 37 - 68)	16/16 (15M/1F)	placebo, tablet, p.o. B0630003 29, B0630003 30, B0630003 31	--	--	--	--	--	--	4.27 (185)	155 (26.0)
					--	--	--	--	--	--	6.49 (136)	154 (26.3)
					--	--	--	--	--	--	3.97 (197)	145 (24.6)
		Patients (57.0, 41 - 69)	16/16 (13M/3F)	10 mg, tablet, p.o. B0630003 65	1550 (16.2)	309 (45.2)	1.50 (1.00 – 2.50)	8.76 (13.0)	12.5 (24.0)	30.1 (25.1)	7.76 (161)	158 (22.3)
					155 (16.2)	30.9 (45.2)					8.45 (114)	186 (49.9)
					1870 (15.9)	259 (24.8)	1.50 (0.983 – 4.00)	13.2 (44.7)	18.3 (25.0)	37.0 (31.1)	81.5 (35.7)	149 (28.2)
										78.0 (44.1)	155 (24.1)	
										75.4 (44.6)	147 (20.1)	

Study Objective	Study Design and Type of Control	Healthy Subjects or patients Age: (median, range)	# Subjects Entered/ Completed (M/F)	Treatment (Dose, dosage Form Route) [Batch no.]	Mean Pharmacokinetic Parameters (%CV)						Mean Pharmacodynamic parameters (%CV) ²⁴			
					AUC ₀₋₂₄ [nmol.h/L] AUC _{0-24, norm} [nmol.h/L/mg]	C _{max} [nmol/L] C _{max, norm} [nmol/L/mg]	t _{max} ²⁵ [h]	t _{1/2} [h]	fe ₀₋₂₄ [%]	CL _{R,0-24} [mL/min]	UGE ²⁶ [g/day]	FPG [mg/dL]		
					AUC _{τ,ss} [nmol.h/L] AUC _{τ,ss, norm} [nmol.h/L/mg]	C _{max,ss} [nmol/L] C _{max,ss, norm} [nmol/L/mg]	t _{max,ss} [h]	t _{1/2,ss} [h]	fe _{0-24,ss} [%]	CL _{R,τ,ss} [mL/min]	Day -2 Day -1 Day 1 Day 27 Day 28	Day -2 Day -1 Day 1 Day 27 Day 28		
4-week multiple rising dose study in Caucasian patients	Randomised, double-blind, placebo controlled	Patients (57.5, 34 - 65)	16/16 (12M/4F)	25 mg, tablet, p.o. B0630003 68	3930 (22.9)	722 (20.0)	1.50 (0.750 - 2.00)	8.24 (14.9)	13.3 (24.5)	32.4 (28.1)	5.34 (123)	178 (25.2)		
					157 (22.9)	28.9 (20.2)					8.15 (91.0)	167 (23.6)		
					189 (21.2)	27.5 (18.4)					95.7 (30.4)	169 (22.2)		
					187 (21.2)	23.9 (18.4)					82.9 (32.9)	139 (19.9)		
		Patients (58.0, 40 - 68)	30/30 (27M/3F)	100 mg, tablet, p.o. B0630003 69	4740 (21.2)	687 (18.4)	1.50 (0.750 - 3.02)	13.3 (32.6)	17.8 (17.8)	36.2 (26.3)	83.4 (26.4)	133 (16.0)		
					15900 (21.2)	2630 (25.8)	1.50 (0.750 - 3.00)	8.67 (18.7)	13.7 (34.1)	33.0 (39.3)	6.05 (190)	151 (29.7)		
					159 (21.2)	26.3 (25.8)					6.19 (134)	150 (21.1)		
					18700 (25.2)	2390 (28.1)	1.50 (0.750 - 6.00)	16.5 (47.9)	17.5 (28.3)	36.5 (35.2)	87.0 (36.9)	141 (22.9)		
						81.3 (50.1)	125 (17.7)							
						73.9 (61.6)	120 (16.8)							

Reviewer's Comments: The sponsor's assessments and conclusions from this study are acceptable. There were no notable protocol violation and deviations. The trial reasonably captured the pharmacokinetic and pharmacodynamic effect (Urinary glucose excretion) of empagliflozin after multiple once daily doses.

4.1.4 DDI-Evaluations

DDI between Empagliflozin and Metformin (1245.6):

Study Design and Type of Control	Test Product ID (Batch no.)	Study population # Subjects Entered/ Completed (M/F)	Treatments		Mean Pharmacokinetic Parameters (%CV) ^{35,36}					Geometric mean ratio (90% confidence interval)	
			Substrate	Interacting Drug	AUC _{τ,ss} [nmol.h/L]	C _{max,ss} [nmol/L]	t _{max,ss} ³⁷ [h]	t _{1/2,ss} [h]	CL/F _{ss} [mL/min]	AUC _{τ,ss} [%]	C _{max,ss} [%]
Open-label, randomised, crossover	empagliflozin – 50 mg, tablet, p.o. B073000869 metformin – 1000 mg, tablet, p.o. 200847/ 201180	HV 16/16 (16M)	empagliflozin 50 mg, q.d., 5d		9810 (15.0)	1340 (15.3)	1.50 (0.667 – 2.00)	8.49 (18.6)	192 (15.1)	--	--
			empagliflozin 50 mg, q.d., 5d	metformin 1000 mg, b.i.d., 5 d	9540 (16.7)	1400 (31.0)	1.51 (0.667 – 2.52)	14.0 (53.6)	200 (19.0)	96.88 (92.29 – 101.70)	100.45 (88.76 – 113.70)
			metformin 1000 mg, b.i.d., 5 d		8660 (22.7)	1530 (21.9)	1.02 (0.667 – 2.50)	16.1 (65.8)	2030 (25.7)	--	--
			metformin 1000 mg, b.i.d., 5 d	empagliflozin 50 mg, q.d., 5d	8490 (17.1)	1570 (18.8)	2.00 (0.667 – 3.00)	15.8 (77.9)	2020 (17.9)	100.67 (95.93 – 105.64)	103.59 (96.52 – 111.18)

Plasma concentration units for metformin and glimepiride are ng/mL.

For glimepiride, PK parameters were calculated following single oral administration. PK parameters listed are AUC_{0-∞}, C_{max}, t_{max}, t_{1/2}, and CL/F. T_{max} presented as median (range).

The cumulative fraction of empagliflozin excreted in urine were similar when empagliflozin was administered alone (18%) and with metformin co-administration (18.4%). Renal clearance of empagliflozin was also similar with (36.3 mL/min) and without (34.5 mL/min) metformin co-administration.

The cumulative amounts of metformin excreted in urine were similar when metformin was administered alone (277 mg) and with empagliflozin co-administration (266 mg). Renal clearance of metformin was high and was similar with (532 mL/min) and without (551 mL/min) empagliflozin co-administration.

Bioanalytical method performance for metformin in plasma (left) and urine (right):

Analyte:	Metformin	Internal Standard:	Metformin-d ₆	Analyte:	Metformin	Internal Standard:	Metformin-d ₆		
Matrix:	Human plasma	Detection Method:	LC/MS/MS	Matrix:	Human urine	Detection Method:	LC/MS/MS		
Standard Curve Range:	10.0 – 3500 ng/mL	Assay Volume:	50 µL	Standard Curve Range:	5.00 – 5000 ng/mL	Assay Volume:	50 µL		
Extraction Method:	Protein precipitation	Regression Type:	Quadratic, 1/x weighting	Extraction Method:	Protein precipitation	Regression Type:	Quadratic, 1/x weighting		
Room Temperature Plasma Stability:	26 h	Processed Sample Stability:	112 h, ambient	Room Temperature Plasma Stability:	25 h	Processed Sample Stability:	89 h, ambient		
Freeze/Thaw Stability, (-20°C):	6 cycles	Long-term Freezer Stability, (-20°C):	395 days	Freeze/Thaw Stability, (-20°C):	6 cycles	Long-term Freezer Stability, (-20°C):	112 days		
Matrix	QC name	Concentration	Inaccuracy [%]	Imprecision [%]	Matrix	QC name	Concentration	Inaccuracy [%]	Imprecision [%]
Plasma	LLOQ	10.0 ng/mL	1.0	3.4	Urine	LLOQ	5.00 ng/mL	0.8	6.4
	QC_low	30.0 ng/mL	0.0	2.6		QC_low	15.0 ng/mL	0.7	4.9
	QC_mid	800 ng/mL	0.6	3.8		QC_mid	800 ng/mL	-2.1	3.4
	QC_high	3000 ng/mL	1.3	3.9		QC_high	4000 ng/mL	-0.5	3.0
	QC_dil	10000 ng/mL	4.0	1.6		QC_dil	10000 ng/mL	-0.4	2.3
	(df = 50)						(df = 50)		

Reviewers Comments: The sponsor's assessments and conclusions from this study are acceptable. There were no notable protocol violation and deviations. The bioanalytical method adequately supported the pharmacokinetic evaluation of the co-administered drug.

DDI between Empagliflozin and Glimepiride (1245.7):

Study Design and Type of Control	Test Product ID (Batch no.)	Study population # Subjects Entered/ Completed (M/F)	Treatments		Mean Pharmacokinetic Parameters (%CV) ^{38,39}					Geometric mean ratio (90% confidence interval)		
			Substrate	Interacting Drug	AUC _{τ,ss} [nmol.h/L]	C _{max,ss} [nmol/L]	t _{max,ss} ⁴⁰ [h]	t _{1/2,ss} [h]	CL/F _{ss} [mL/min]	AUC _{τ,ss} [%]	C _{max,ss} [%]	
Empagliflozin PK:												
Open-label, randomised, crossover	empagliflozin – 50 mg, tablet, p.o. B073000869	HV 16/16 (16M)	empagliflozin 50 mg, q.d., 6d		9370 (15.4)	1350 (23.0)	1.50 (1.00 – 4.00)	8.20 (10.7)	202 (15.4)	--	--	
			empagliflozin 50 mg, q.d., 6d	glimepiride, 1 mg, single dose	8910 (14.2)	1280 (14.1)	1.50 (1.00 – 2.50)	12.8 (59.2)	211 (14.1)	95.23 (92.03 – 98.54)	95.55 (88.24 – 103.46)	
Glimepiride PK:												
Open-label, randomised, crossover	empagliflozin – 50 mg, tablet, p.o. B073000869	HV 16/16 (16M)	glimepiride, 1 mg, single dose		233 (30.9)	47.4 (31.0)	2.01 (1.00 – 10.0)	3.62 (44.5)	78.5 (32.8)	--	--	
			glimepiride, 1 mg, single dose	empagliflozin 50 mg, q.d., 6d	218 (34.9)	47.6 (19.7)	1.50 (1.00 – 2.53)	3.84 (60.7)	83.7 (28.2)	93.26 (86.08 – 101.04)	104.18 (89.47 – 121.30)	

³⁸ Plasma concentration units for glimepiride and pioglitazone are ng/mL
³⁹ For glimepiride, PK parameters were calculated following single oral administration. PK parameters listed are AUC_{0-∞}, C_{max}, t_{max}, t_{1/2}, and CL/F.
⁴⁰ median (range)

The total amounts of BI 10773 excreted in urine (UGE0-24) were similar when BI 10773 was administered alone (20.0% of dose) and with glimepiride co-administration (20.5% of dose). Renal clearance of BI 10773 was also similar with (40.3 mL/min) and without (43.5 mL/min) glimepiride co-administration. Glimepiride urine concentrations were below the limit of quantification in almost all subjects.

Bioanalytical method performance for glimepiride in plasma (left) and urine (right):

Analyte:	Glimepiride	Internal Standard:	(b) (4)		Analyte:	Glimepiride	Internal Standard:	Glimepiride-d ₃	
Matrix:	Human Plasma	Detection Method:	LC/MS/MS		Matrix:	Human urine	Detection Method:	LC/MS/MS	
Standard Curve Range:	1.00 – 500 ng/mL	Assay Volume:	100 µL		Standard Curve Range:	1.00 – 500 ng/mL	Assay Volume:	100 µL	
Extraction Method:	Liquid-liquid	Regression Type:	Linear, 1/x ² weighting		Extraction Method:	Liquid-liquid	Regression Type:	Linear, 1/x ² weighting	
Room Temperature Plasma Stability:	26 h	Processed Sample Stability:	91 h, ambient		Room Temperature Plasma Stability:	28 h	Processed Sample Stability:	77 h, ambient	
Freeze/Thaw Stability, (-20°C):	4 cycles	Long-term Freezer Stability, (-20°C):	155 days		Freeze/Thaw Stability, (-20°C):	3 cycles	Long-term Freezer Stability, (-20°C):	71 days	
Matrix	QC name	Concentration	Inaccuracy [%]	Imprecision [%]	Matrix	QC name	Concentration	Inaccuracy [%]	Imprecision [%]
Plasma	LLOQ	1.00 ng/mL	-7.0	4.2	Urine	LLOQ	1.00 ng/mL	2.0	6.6
	QC_low	3.00 ng/mL	-8.7	3.5		QC_low	3.00 ng/mL	-0.7	4.5
	QC_mid	250 ng/mL	-4.0	2.5		QC_mid	250 ng/mL	2.8	1.1
	QC_high	400 ng/mL	-2.0	3.5		QC_high	400 ng/mL	1.8	1.6
	QC_dil	5000 ng/mL	-6.2	3.1		QC_dil	5000 ng/mL	-4.6	0.6
	(df = 20)					(df = 100)			

Reviewers Comments: The sponsor’s assessments and conclusions from this study are acceptable. There were no notable protocol violation and deviations. The bioanalytical method adequately supported the pharmacokinetic evaluation of the co-administered drug.

DDI between Empagliflozin and Pioglitazone (1245.17):

Study Design and Type of Control	Test Product ID (Batch no.)	Study population # Subjects Entered/ Completed (M/F)	Treatments		Mean Pharmacokinetic Parameters (%CV) ^{38,39}					Geometric mean ratio (90% confidence interval)	
			Substrate	Interacting Drug	AUC _{τ,ss} [nmol.h/L]	C _{max,ss} [nmol/L]	t _{max,ss} ⁴⁰ [h]	t _{1/2,ss} [h]	CL/F _{ss} [mL/min]	AUC _{τ,ss} [%]	C _{max,ss} [%]
Open-label, randomised, crossover	empagliflozin – 50 mg, tablet, p.o. B073000869 pioglitazone – 45 mg, tablet, p.o. 3250055B	HV 20/18 (20M)	empagliflozin								
			empagliflozin 50 mg, q.d., 5d		8990 (12.4)	1370 (18.8)	1.74 (1.00 – 3.00)	8.59 (15.5)	209 (14.2)	--	--
			empagliflozin 50 mg, q.d., 7d	pioglitazone, 45 mg, q.d., 7d	8980 (10.5)	1280 (15.3)	2.00 (1.48 – 3.00)	11.7 (36.9)	208 (11.3)	100.32 (96.08 – 104.75)	93.44 (85.08 – 102.62)
			pioglitazone								
			pioglitazone, 45 mg, q.d., 7d		9330 (31.6)	1140 (39.7)	1.75 (0.667 – 4.00)	15.6 (57.1)	88.4 (31.8)	--	--
Open-label, randomised, crossover	empagliflozin – 50 mg, tablet, p.o. B073000869 pioglitazone – 45 mg, tablet, p.o. 3250055B	HV 20/18 (20M)	pioglitazone M-III (metabolite)								
			pioglitazone, 45 mg, q.d., 7d		8700 (31.7)	463 (32.5)	4.99 (2.48 – 10.0)	22.2 (15.4)	--	--	--
			pioglitazone, 45 mg, q.d., 7d	empagliflozin 50 mg, q.d., 7d	10200 (15.7)	532 (15.4)	8.00 (3.00 – 12.1)	20.5 (14.3)	--	--	--
			pioglitazone M-IV (metabolite)								
			pioglitazone, 45 mg, q.d., 7d		20600 (30.9)	1030 (31.3)	4.00 (1.00 – 12.0)	22.1 (19.1)	--	--	--
		pioglitazone, 45 mg, q.d., 7d	empagliflozin 50 mg, q.d., 7d	23700 (17.6)	1240 (16.7)	4.00 (2.50 – 10.0)	21.6 (25.1)	--	--	--	

Plasma concentration units for pioglitazone and its metabolites (M-III and M-IV) are ng/mL, Tmax presented as median (range)

DDI between Empagliflozin and Pioglitazone Study 2(1245.50):

Study Design and Type of Control	Test Product ID (Batch no.)	Study population # Subjects Entered/ Completed (M/F)	Treatments		Mean Pharmacokinetic Parameters (%CV) ^{38,39}					Geometric mean ratio (90% confidence interval)		
			Substrate	Interacting Drug	AUC _{τ,ss} [nmol.h/L]	C _{max,ss} [nmol/L]	t _{max,ss} ⁴⁰ [h]	t _{1/2,ss} [h]	CL/F _{ss} [mL/min]	AUC _{τ,ss} [%]	C _{max,ss} [%]	
Open-label, randomised, crossover	empagliflozin – 10 mg, 25 mg, 50 mg, tablet, p.o. pioglitazone – 45 mg, tablet, p.o.	HV 20/16 (20M)	pioglitazone Day 1 ⁴³									
			pioglitazone, 45 mg, q.d., 7d		8670 (28.2)	908 (35.5)	2.00 (0.50 – 4.02)	10.8 (52.0)	75.5 (28.7)	--	--	
			pioglitazone, 45 mg, q.d., 7d	empagliflozin 10 mg, q.d., 9d	8410 (33.1)	924 (37.3)	1.75 (0.5 – 4.00)	9.63 (30.7)	83.0 (34.1)	--	--	
Open-label, randomised, crossover	empagliflozin – 10 mg, 25 mg, 50 mg, tablet, p.o. 10 mg: 909475 25 mg: 909473 pioglitazone – 45 mg, tablet, p.o. 4250009D	HV 20/16 (20M)	pioglitazone Day 1 ⁴⁶									
			pioglitazone, 45 mg, q.d., 7d	empagliflozin 25 mg, q.d., 9d	--	--	--	--	--	--	--	
			pioglitazone, 45 mg, q.d., 7d	empagliflozin 50 mg, q.d., 9d	8960 (33.1)	1020 (38.0)	2.00 (1.00 – 4.02)	8.75 (40.5)	82.1 (46.0)	--	--	
			pioglitazone Day 7									
			pioglitazone, 45 mg, q.d., 7d		10500 (38.2)	1260 (60.9)	2.00 (0.5 – 8.00)	11.3 (48.9)	82.3 (39.8)	--	--	
			pioglitazone, 45 mg, q.d., 7d	empagliflozin 10 mg, q.d., 9d	8820 (22.0)	988 (29.3)	2.00 (1.00 – 4.00)	12.3 (59.8)	90.1 (27.7)	90.01 (77.91 – 103.99)	87.74 (73.88 – 104.21)	
			pioglitazone, 45 mg, q.d., 7d	empagliflozin 25 mg, q.d., 9d	9200 (39.7)	1110 (60.1)	2.00 (0.517 – 8.00)	12.2 (68.1)	95.4 (43.0)	88.98 (72.69 – 108.92)	90.23 (66.84 – 121.82)	
pioglitazone, 45 mg, q.d., 7d	empagliflozin 50 mg, q.d., 9d	9200 (31.4)	1060 (37.5)	1.50 (0.5 – 6.00)	13.2 (41.7)	90.8 (36.2)	91.10 (77.40 – 107.22)	89.85 (71.03 – 113.66)				

Study Design and Type of Control	Test Product ID (Batch no.)	Study population # Subjects Entered/ Completed (M/F)	Treatments		Mean Pharmacokinetic Parameters (%CV) ⁴⁷					Geometric mean ratio (90% confidence interval)		
			Substrate	Interacting Drug	AUC _{τ,ss} [nmol.h/L]	C _{max,ss} [nmol/L]	t _{max,ss} ⁴⁸ [h]	t _{1/2,ss} [h]	CL/F _{ss} [mL/min]	AUC _{τ,ss} [%]	C _{max,ss} [%]	
Open-label, randomised, crossover	empagliflozin – 10 mg, 25 mg, 50 mg, tablet, p.o. 10 mg: 909475 25 mg: 909473 pioglitazone – 45 mg, tablet, p.o. 4250009D	HV 20/16 (20M)	pioglitazone M-III - Day 1 ⁴⁹									
			pioglitazone, 45 mg, q.d., 7d		3350 (45.7)	188 (42.9)	12.0 (10.0 – 23.9)	--	--	--	--	
			pioglitazone, 45 mg, q.d., 7d	empagliflozin 10 mg, q.d., 9d	3310 (31.2)	183 (31.2)	11.0 (6.00 – 23.9)	--	--	--	--	
			pioglitazone, 45 mg, q.d., 7d	empagliflozin 25 mg, q.d., 9d	--	--	--	--	--	--	--	
			pioglitazone, 45 mg, q.d., 7d	empagliflozin 50 mg, q.d., 9d	3480 (42.2)	192 (46.7)	12.0 (9.98 – 23.9)	--	--	--	--	
			pioglitazone M-III - Day 7									
			pioglitazone, 45 mg, q.d., 7d		10200 (40.5)	626 (77.5)	6.00 (1.50 – 10.0)	23.2 (17.8)	--	--	--	
pioglitazone, 45 mg, q.d., 7d	empagliflozin 10 mg, q.d., 9d	9740 (39.5)	514 (36.4)	6.00 (0.00 – 10.0)	24.8 (26.8)	--	--	--				

Study Design and Type of Control	Test Product ID (Batch no.)	Study population # Subjects Entered/ Completed (M/F)	Treatments		Mean Pharmacokinetic Parameters (%CV) ⁵⁰					Geometric mean ratio (90% confidence interval)		
			Substrate	Interacting Drug	AUC _{τ,ss} [nmol.h/L]	C _{max,ss} [nmol/L]	t _{max,ss} ⁵¹ [h]	t _{1/2,ss} [h]	CL/F _{ss} [mL/min]	AUC _{τ,ss} [%]	C _{max,ss} [%]	
Open-label, randomised, crossover	empagliflozin – 10 mg, 25 mg, 50 mg, tablet, p.o. 10 mg: 909475 25 mg: 909473 pioglitazone – 45 mg, tablet, p.o. 4250009D	HV 20/16 (20M)	pioglitazone M-III - Day 7									
			pioglitazone, 45 mg, q.d., 7d	empagliflozin 25 mg, q.d., 9d	9910 (39.4)	601 (82.1)	6.00 (1.00 – 12.0)	23.0 (21.7)	--	--	--	
			pioglitazone, 45 mg, q.d., 7d	empagliflozin 50 mg, q.d., 9d	9510 (35.6)	497 (36.2)	5.00 (2.00 – 12.0)	25.6 (36.6)	--	--	--	
			pioglitazone M-IV - Day 1 ⁵²									
			pioglitazone, 45 mg, q.d., 7d		8130 (29.8)	438 (26.1)	17.9 (7.98 – 23.9)	--	--	--	--	
			pioglitazone, 45 mg, q.d., 7d	empagliflozin 10 mg, q.d., 9d	8040 (25.2)	432 (26.9)	17.9 (7.98 – 23.9)	--	--	--	--	
			pioglitazone, 45 mg, q.d., 7d	empagliflozin 25 mg, q.d., 9d	--	--	--	--	--	--	--	
			pioglitazone, 45 mg, q.d., 7d	empagliflozin 50 mg, q.d., 9d	8370 (30.4)	449 (28.1)	12.0 (8.00 – 23.9)	--	--	--	--	

Study Design and Type of Control	Test Product ID (Batch no.)	Study population # Subjects Entered/ Completed (M/F)	Treatments		Mean Pharmacokinetic Parameters (%CV) ⁵³					Geometric mean ratio (90% confidence interval)	
			Substrate	Interacting Drug	AUC _{τ,ss} [nmol.h/L]	C _{max,ss} [nmol/L]	t _{max,ss} ⁵⁴ [h]	t _{1/2,ss} [h]	CL/F _{ss} [mL/min]	AUC _{τ,ss} [%]	C _{max,ss} [%]
Open-label, randomised, crossover	empagliflozin – 10 mg, 25 mg, 50 mg, tablet, p.o. 10 mg: 909475 25 mg: 909473 pioglitazone – 45 mg, tablet, p.o. 4250009D	HV 20/16 (20M)	pioglitazone M-IV - Day 7								
			pioglitazone, 45 mg, q.d., 7d		24600 (25.4)	1430 (74.8)	4.00 (2.00 – 12.0)	23.2 (21.5)	--	--	--
			pioglitazone, 45 mg, q.d., 7d	empagliflozin 10 mg, q.d., 9d	23100 (24.3)	1190 (25.0)	4.00 (0.50 – 12.0)	24.5 (23.7)	--	--	--
			pioglitazone, 45 mg, q.d., 7d	empagliflozin 25 mg, q.d., 9d	25000 (34.3)	1540 (68.4)	4.02 (1.00 – 12.0)	25.2 (24.2)	--	--	--
			pioglitazone, 45 mg, q.d., 7d	empagliflozin 50 mg, q.d., 9d	22800 (25.4)	1140 (27.7)	4.00 (1.50 – 12.0)	26.9 (31.9)	--	--	--

Plasma concentration units for pioglitazone and its metabolites (M-III and M-IV) are ng/mL, Tmax presented as median (range), For Day 1, PK parameters listed are AUC₀₋₂₄, C_{max}, t_{max}, t_{1/2}, and CL/F.

Bioanalytical method performance for pioglitazone for study 1245.17 (top row) and for study 1245.50 (bottom row) in plasma:

Analyte:	Pioglitazone	Internal Standard:	Pioglitazone-d ₄	Analytes:	Pioglitazone HCl ^a Keto Pioglitazone (M-III) ^b Hydroxy Pioglitazone (M-IV) ^c	Internal Standard:	Pioglitazone-d ₄ ^a M-III-d ₄ ^b M-IV-d ₄ ^c						
Matrix:	Human plasma	Detection Method:	LC/MS/MS	Matrix:	Human plasma	Detection Method:	LC/MS/MS						
Standard Curve Range:	25.0 – 2500 ng/mL	Assay Volume:	100 µL	Standard Curve Range:	25.0 – 2500 ng/mL	Assay Volume:	100 µL						
Extraction Method:	Solid phase	Regression Type:	Quadratic, 1/x ² weighting	Extraction Method:	Solid phase extraction	Regression Type:	Quadratic, 1/x ² weighting						
Room Temperature Plasma Stability:	24 h	Processed Sample Stability:	58 h, ambient	Room Temperature Plasma Stability:	24 h	Processed Sample Stability:	42 h, ambient						
Freeze/Thaw Stability, (-20°C):	4 cycles	Long-term Freezer Stability, (-20°C):	73 days	Freeze/Thaw Stability, (-20°C):	5 cycles	Long-term Freezer Stability, (-20°C):	29 days						
Matrix	QC name	Concentration	Inaccuracy [%]	Imprecision [%]	Matrix	QC name	Concentration (a,b,c)	Inaccuracy [%]			Imprecision [%]		
Plasma	LLOQ	25 ng/mL	0.0	2.5	Plasma	LLOQ	25 ng/mL	1.6	8.0	5.2	5.0	5.1	8.8
	QC_low	75 ng/mL	0.3	7.2		QC_low	75 ng/mL	-0.4	0.0	1.7	3.2	5.2	5.0
	QC_mid	900 ng/mL	-2.6	7.6		QC_mid	900 ng/mL	0.4	-0.1	4.6	2.8	4.2	6.5
	QC_high	1900 ng/mL	-2.6	4.0		QC_high	1900 ng/mL	-2.6	-1.1	3.7	2.4	3.3	5.6
	QC_dil (df = 10)	10000 ng/mL	-5.8	1.4		QC-dil (df = 4)	3200 ng/mL	-4.7	-14.4	-4.4	5.7	4.7	5.8

Study 1245.50: This study was conducted to investigate the effect of BI 10773 on the bioavailability of pioglitazone and to determine a dose of empagliflozin that would have no relevant effect on pioglitazone plasma levels. There were several treatments evaluated in this study:

Treatment A Pioglitazone 45 mg q.d. on Days 1 to 7

Treatment B Pioglitazone 45 mg q.d. on Days 1 to 7 + BI 10773 10 mg q.d. on Days 1 to 9

Treatment C Pioglitazone 45 mg q.d. on Days 1 to 7 + BI 10773 25 mg q.d. on Days 1 to 9

Treatment D Pioglitazone 45 mg q.d. on Days 1 to 7 + BI 10773 50 mg q.d. on Days 1 to 9

Treatment E Pioglitazone 45 mg q.d. on Days 1 to 7 + BI 10773 25 mg q.d. 1 h after pioglitazone on Days 1 to 9

Treatment F Pioglitazone 30 mg q.d. on Days 1 to 7 + BI 10773 50 mg q.d. on Days 1 to 9.

The results of this trial did not indicate any increase in exposure of pioglitazone and its active moieties following coadministration with 3 clinically relevant dose levels of empagliflozin when compared to pioglitazone alone.

Reviewers Comments: The sponsor's assessments and conclusions from this study are acceptable. There were no notable protocol violation and deviations. The bioanalytical method adequately supported the pharmacokinetic evaluation of the co-administered drug.

DDI between Empagliflozin and Warfarin (1245.27):

Study Design and Type of Control	Test Product ID (Batch no.)	Study population # Subjects Entered/ Completed (M/F)	Treatments		Mean Pharmacokinetic Parameters (%CV) ⁵³					Geometric mean ratio (90% confidence interval)	
			Substrate	Interacting Drug	AUC _{τ,ss} [nmol.h/L]	C _{max,ss} [nmol/L]	t _{max,ss} ⁵⁴ [h]	t _{1/2,ss} [h]	CL/F _{ss} [mL/min]	AUC _{τ,ss} [%]	C _{max,ss} [%]
Open-label, randomised, crossover	empagliflozin – 25 mg, tablet, p.o. 909473 warfarin – 25 mg, tablet, p.o. 9K23	HV 18/18 (18M)	empagliflozin 25 mg, q.d., 5d		4620 (13.0)	774 (19.2)	1.50 (1.00 – 3.00)	6.71 (10.8)	189 (14.8)	--	--
			empagliflozin 25 mg, q.d., 7d	warfarin, 25 mg, single dose	4670 (15.5)	785 (23.0)	1.00 (0.667 – 6.00)	7.12 (11.9)	185 (16.2)	100.89 (96.86 – 105.10)	100.64 (89.79 – 112.80)
Open-label, randomised, crossover	empagliflozin – 25 mg, tablet, p.o. 909473 warfarin – 25 mg, tablet, p.o. 9K23	HV 18/18 (18M)	R-warfarin								
			warfarin, 25 mg, single dose		64900 (21.2)	1420 (14.3)	0.842 (0.333 – 4.00)	47.5 (12.0)	6.68 (19.8)	--	--
			warfarin, 25 mg, single dose	empagliflozin 25 mg, q.d., 7d	64400 (24.5)	1390 (16.9)	1.00 (0.333 – 7.98)	46.3 (15.1)	6.83 (23.0)	98.49 (95.29 – 101.80)	97.89 (91.12 – 105.15)
			S-warfarin								
			warfarin, 25 mg, single dose		38100 (18.5)	1460 (14.2)	0.683 (0.333 – 4.00)	37.3 (13.6)	11.3 (17.1)	--	--
	warfarin, 25 mg, single dose	empagliflozin 25 mg, q.d., 7d	36400 (16.9)	1440 (16.3)	0.842 (0.333 – 7.98)	36.9 (12.0)	11.7 (15.3)	95.88 (93.40 – 98.43)	98.88 (91.84 – 106.47)		

For R- and S-warfarin, plasma concentration units are ng/mL. PK parameters listed are AUC_{0-∞}, C_{max}, t_{max}, t_{1/2}, and CL/F. T_{max} presented as median (range)

Summary of pharmacodynamic parameters of warfarin administered alone or in combination with (empagliflozin):

Parameter	Warfarin alone		Warfarin + BI 10773		gMean ratio of BI 10773 + warfarin to warfarin (95% CIs)
	N	gMean	N	gMean	
PT _{max} [s]	16	20.2	16	18.1	0.90 (0.79, 1.02)
PT AUEC ₀₋₁₆₈ [s*h]	10	2508	15	2282	0.91 (0.84, 0.98)
INR _{max}	16	1.76	16	1.53	0.87 (0.73, 1.04)
INR AUEC ₀₋₁₆₈	10	203	15	178	0.88 (0.79, 0.98)

Co-administration of BI 10773 with warfarin did not significantly alter effects of warfarin on PT and INR.

Bioanalytical method performance for warfarin in plasma:

Analytes:	R-warfarin S-warfarin	Internal Standard:	Warfarin-d ₅
Matrix:	Human plasma	Detection Method:	LC/MS/MS
Standard Curve Range:	10.0 – 2500 ng/mL	Assay Volume:	50 µL
Extraction Method:	Liquid-liquid	Regression Type:	Quadratic, 1/x ² weighting
Room Temperature Plasma Stability:	24 h	Processed Sample Stability:	115 h, 2-8°C
Freeze/Thaw Stability, (-20°C):	5 cycles	Long-term Freezer Stability, (-20°C):	59 days

Matrix	QC name	Concentration	Inaccuracy [%]		Imprecision [%]	
			R-warfarin	S-warfarin	R-warfarin	S-warfarin
Plasma	LLOQ	10.0 ng/mL	-4.9	-6.2	3.3	5.7
	QC_low	30.0 ng/mL	-3.7	-4.7	1.7	2.3
	QC_mid	250 ng/mL	-4.4	-4.4	2.1	2.8
	QC_high	2000 ng/mL	-3.5	-3.0	1.9	1.4
	ULOQ	5000 ng/mL (df=10)	-2.6	-1.2	1.1	1.4

Reviewers Comments: The sponsor’s assessments and conclusions from this study are acceptable. There were no notable protocol violation and deviations. The bioanalytical method adequately supported the pharmacokinetic evaluation of the co-administered drug.

DDI between Empagliflozin and Sitagliptin (1245.27):

Study Design and Type of Control	Test Product ID (Batch no.)	Study population # Subjects Entered/ Completed (M/F)	Treatments		Mean Pharmacokinetic Parameters (%CV) ⁵³					Geometric mean ratio (90% confidence interval)	
			Substrate	Interacting Drug	AUC _{τ,ss} [nmol.h/L]	C _{max,ss} [nmol/L]	t _{max,ss} ⁵⁴ [h]	t _{1/2,ss} [h]	CL/F _{ss} [mL/min]	AUC _{τ,ss} [%]	C _{max,ss} [%]
Open-label, randomised, crossover	empagliflozin – 50 mg, tablet, p.o. B073000869 sitagliptin – 100 mg, tablet, p.o. B091000116	HV 16/16 (16M)	sitagliptin, 100 mg, q.d., 5d		2600 (18.7)	341 (26.5)	3.00 (0.667 – 6.00)	12.7 (15.0)	664 (19.0)	--	--
			sitagliptin, 100 mg, q.d., 5d	empagliflozin 50 mg, q.d., 5d	2680 (21.3)	370 (27.1)	2.99 (0.667 – 4.00)	13.2 (19.1)	645 (18.8)	103.06 (98.97 – 107.34)	108.48 (100.68 – 116.88)
Open-label, randomised, crossover	empagliflozin – 50 mg, tablet, p.o. B073000869 sitagliptin – 100 mg, tablet, p.o. B091000116	HV 16/16 (16M)	sitagliptin, 100 mg, q.d., 5d		2600 (18.7)	341 (26.5)	3.00 (0.667 – 6.00)	12.7 (15.0)	664 (19.0)	--	--
			sitagliptin, 100 mg, q.d., 5d	empagliflozin 50 mg, q.d., 5d	2680 (21.3)	370 (27.1)	2.99 (0.667 – 4.00)	13.2 (19.1)	645 (18.8)	103.06 (98.97 – 107.34)	108.48 (100.68 – 116.88)

The total amount of empagliflozin excreted in urine was similar when empagliflozin was co-administered with sitagliptin (19.3% of dose) compared to empagliflozin alone (17.1% of dose). Renal clearance of empagliflozin was similar with (39.4 mL/min) and without (38.6 mL/min) sitagliptin co-administration.

The total amount of sitagliptin excreted in urine was similar when sitagliptin was administered alone (60.3% of dose) and with empagliflozin co-administration (62.8% of dose). Renal clearance of sitagliptin was also similar without (392 mL/min) and with (399 mL/min) empagliflozin co-administration.

Bioanalytical method performance for sitagliptin in plasma and urine:

Analyte:	Sitagliptin	Internal Standard:	Sitagliptin-d ₄	Analyte:	Sitagliptin	Internal Standard:	Sitagliptin-d ₄		
Matrix:	Human plasma	Detection Method:	LC/MS/MS	Matrix:	Human urine	Detection Method:	LC/MS/MS		
Standard Curve Range:	1.00 – 1000 ng/mL	Assay Volume:	100 µL	Standard Curve Range:	1.00 – 1000 ng/mL	Assay Volume:	100 µL		
Extraction Method:	Liquid-liquid	Regression Type:	Quadratic, 1/x ² weighting	Extraction Method:	Liquid-liquid	Regression Type:	Quadratic, 1/x ² weighting		
Room Temperature Plasma Stability:	24 h	Processed Sample Stability:	53 h, ambient	Room Temperature Plasma Stability:	24 h	Processed Sample Stability:	58 h, ambient		
Freeze/Thaw Stability, (-20°C):	4 cycles	Long-term Freezer Stability, (-20°C):	28 days	Freeze/Thaw Stability, (-20°C):	4 cycles	Long-term Freezer Stability, (-20°C):	96 days		
Matrix	QC name	Concentration	Inaccuracy [%]	Imprecision [%]	Matrix	QC name	Concentration	Inaccuracy [%]	Imprecision [%]
Plasma	LLOQ	1.00 ng/mL	-10.7	4.6	Urine	LLOQ	1.00 ng/mL	-4.9	5.8
	QC_low	3.00 ng/mL	-2.0	1.8		QC_low	3.00 ng/mL	-0.3	3.0
	QC_mid	250 ng/mL	-6.0	1.2		QC_mid	250 ng/mL	-3.6	1.8
	QC_high	800 ng/mL	-3.6	2.5		QC_high	800 ng/mL	-2.1	2.2
	QC_dil	5000 ng/mL	-7.0	1.2		QC_dil	20000 ng/mL	3.0	4.6
	(df = 20)					(df = 250)			

Reviewers Comments: The sponsor’s assessments and conclusions from this study are acceptable. There were no notable protocol violation and deviations. The bioanalytical method adequately supported the pharmacokinetic evaluation of the co-administered drug.

DDI between Empagliflozin and Linagliptin 1245.30:

Study Design and Type of Control	Test Product ID (Batch no.)	Study population # Subjects Entered/ Completed (M/F)	Treatments		Mean Pharmacokinetic Parameters (%CV) ⁵³					Geometric mean ratio (90% confidence interval)	
			Substrate	Interacting Drug	AUC _{τ,ss} [nmol.h/L]	C _{max,ss} [nmol/L]	t _{max,ss} ⁵⁴ [h]	t _{1/2,ss} [h]	CL/F _{ss} [mL/min]	AUC _{τ,ss} [%]	C _{max,ss} [%]
Open-label, randomised, crossover	empagliflozin – 50 mg, tablet, p.o. B073000869 linagliptin – 5 mg, tablet, p.o. P01005567	HV 16/16 (16M)	empagliflozin 50 mg, q.d., 5d		9300 (12.5)	1450 (17.1)	1.00 (1.00 – 3.00)	8.30 (11.4)	202 (11.8)	--	--
			empagliflozin 50 mg, q.d., 7d	linagliptin, 5 mg, q.d., 7d	9520 (17.1)	1310 (26.9)	1.50 (1.00 – 4.02)	8.44 (10.7)	200 (17.2)	101.71 (96.54 – 107.16)	88.31 (78.83 – 98.94)
			linagliptin, 5 mg, q.d., 7d		155 (16.8)	11.5 (28.8)	1.50 (0.5 – 4.00)	--	1170 (16.8)	--	--
			linagliptin, 5 mg, q.d., 7d	empagliflozin 50 mg, q.d., 7d	159 (14.8)	11.6 (31.0)	1.50 (0.5 – 4.00)	--	1130 (14.5)	103.31 (96.10 – 111.06)	101.47 (86.87 – 118.52)

Urinary excretion of empagliflozin was similar when the drug was administered with (20.4% of dose) and without linagliptin (20.7% of dose) after treatment with empagliflozin alone.

Urinary excretion of linagliptin was similar when the drug was administered with (4.77% of dose) and without empagliflozin (4.26% of dose). Inhibition of DPP-4 activity in plasma at steady state 24 h after dosing (E_{24,ss}) was similar when 5 mg linagliptin was administered in combination with 50 mg BI 10773 and when linagliptin was given alone.

Bioanalytical method performance for linagliptin in plasma and urine:

Analyte:	BI 1356 BS (Linagliptin)	Internal Standard:	¹³ C ₃ -BI 1356 BS	Analyte:	BI 1356 BS (Linagliptin)	Internal Standard:	¹³ C ₃ BI 1356 BS		
Matrix:	Human plasma	Detection Method:	LC/MS/MS	Matrix:	Human urine (acidified with citric acid)	Detection Method:	LC/MS/MS		
Standard Curve Range:	0.0 – 100 nmol/L	Assay Volume:	150 µL	Standard Curve Range:	1 -1000 nmol/L	Assay Volume:	40 µL		
Extraction Method:	Solid phase extraction	Regression Type:	Linear, 1/x ² weighting	Extraction Method:	Solid phase extraction	Regression Type:	Linear, 1/x ² weighting		
Room Temperature Plasma Stability:	26 h	Processed Sample Stability:	66 h, 12°C	Room Temperature Plasma Stability:	26 h	Processed Sample Stability:	76.5 h, 4°C		
Freeze/Thaw Stability, (-20°C):	3 cycles	Long-term Freezer Stability, (-20°C):	197 days	Freeze/Thaw Stability, (-20°C):	3 cycles	Long-term Freezer Stability, (-20°C):	56 days		
Matrix	QC name	Concentration	Inaccuracy [%]	Imprecision [%]	Matrix	QC name	Concentration	Inaccuracy [%]	Imprecision [%]
Plasma	LLOQ	0.1 nmol/L	0.0	5.4	Urine	LLOQ	1 nmol/L	-5.4	6.8
	QC_low	0.25 nmol/L	0.4	3.6		QC_low	2.5 nmol/L	-2.0	7.4
	QC_mid	5 nmol/L	4.4	1.9		QC_mid	50 nmol/L	2.8	2.8
	QC_high	80 nmol/L	-3.4	1.8		QC_high	800 nmol/L	-5.7	2.2

Reviewers Comments: The sponsor's assessments and conclusions from this study are acceptable. There were no notable protocol violation and deviations. The bioanalytical method adequately supported the pharmacokinetic evaluation of the co-administered drug.

DDI with Digoxin1245.40:

Study Design and Type of Control	Test Product ID (Batch no.)	Study population # Subjects Entered/ Completed (M/F)	Treatments		Mean Pharmacokinetic Parameters (%CV) ^{59,60}					Geometric mean ratio (90% confidence interval)	
			Substrate	Interacting Drug	AUC _{τ,ss} [nmol.h/L]	C _{max,ss} [nmol/L]	t _{max,ss} ⁶¹ [h]	t _{1/2,ss} [h]	CL/F _{ss} [mL/min]	AUC _{τ,ss} [%]	C _{max,ss} [%]
Open-label, randomised, crossover	empagliflozin – 25 mg, tablet, p.o. 909473 digoxin – 0.5 mg, tablet, p.o. 1001	HV 20/20 (11M/9F)	digoxin, 0.5 mg, single dose		38.7 (23.7)	2.14 (40.3)	1.00 (0.667 – 1.50)	68.7 (47.3)	226 (22.9)	--	--
			digoxin, 0.5 mg, single dose	empagliflozin 25 mg, q.d., 8d	41.2 (25.9)	2.36 (31.7)	1.00 (0.667 – 1.50)	55.4 (27.3)	215 (25.2)	106.11 (96.71 – 116.41)	113.94 (99.33 – 130.70)

No major differences in renal excretion of digoxin were observed. The mean fraction of digoxin excreted in urine was 40.1% of the dose when digoxin was given with empagliflozin and 40.6% when digoxin was given alone. The renal clearance of digoxin (mean CLR₀₋₂₄: 139 mL/min vs 153 mL/min) was also similar with and without empagliflozin.

Bioanalytical method performance for digoxin in plasma and urine:

Analyte:	Digoxin	Internal Standard:	Digoxin-d ₃	Analyte:	Digoxin	Matrix:	Human urine	
Matrix:	Human plasma	Detection Method:	LC/MS/MS	Standard Curve Range:	1.0 – 40 ng/mL	Assay Volume:	100 µL	
Standard Curve Range:	0.100 – 50.0 ng/mL	Assay Volume:	100 µL	Extraction Method:	Radioimmunoassay	Regression Type:	4-parameter logistic regression algorithm	
Extraction Method:	Supported liquid	Regression Type:	Quadratic, 1/x ² weighting	Room Temperature Plasma Stability:	48 h	Freezer Stability (-20°):	75 days	
Room Temperature Plasma Stability:	24 h	Processed Sample Stability:	72 h, 2-8°C	Freeze/Thaw Stability, (-80°C):	10 cycles	Freezer Stability (-80°):	34 days	
Freeze/Thaw Stability, (-20°C):	3 cycles	Long-term Freezer Stability, (-20°C):	663 days					
				Matrix	QC name	Concentration	Inaccuracy [%]	Imprecision [%]
				Urine	LLOQ	1 ng/mL	6.70	6.65
					QC_low 1	2.00 ng/mL	-0.92	8.60
					QC_low 2	3.00 ng/mL	-1.29	4.46
					QC_mid	15.00 ng/mL	-0.436 (0.329 ^a)	4.95 (3.99 ^a)
					QC_high 1	30.0 ng/mL	0.353	4.37
					QC_high 2	35.0 ng/mL	-3.02	5.28
					ULOQ	40.0 ng/mL	8.48 (2.42 ^a)	27.8 (5.25 ^a)
					QC_dil	75.0 ng/mL	-0.796	0.88
					(df = 20)			

Reviewers Comments: The sponsor's assessments and conclusions from this study are acceptable. There were no notable protocol violation and deviations. The bioanalytical method adequately supported the pharmacokinetic evaluation of the co-administered drug.

DDI with Oral Contraceptives 1245.41:

Study Design and Type of Control	Test Product ID (Batch no.)	Study population # Subjects Entered/ Completed (M/F)	Treatments		Mean Pharmacokinetic Parameters (%CV) ^{59,60}					Geometric mean ratio (90% confidence interval)	
			Substrate	Interacting Drug	AUC _{τ,ss} [nmol.h/L]	C _{max,ss} [nmol/L]	t _{max,ss} ⁶¹ [h]	t _{1/2,ss} [h]	CL/F _{ss} [mL/min]	AUC _{τ,ss} [%]	C _{max,ss} [%]
Open-label, randomised, crossover	empagliflozin – 25 mg, tablet, p.o. 909473 Microgynon [®] tablet (30 µg ethinylestradiol + 150 µg levonorgestrel) 91955B, 93842C	HV 18/18 (18F)	ethinylestradiol, 30 µg, q.d., 14d		932 (24.4)	99.0 (17.0)	1.26 (1.00 – 3.05)	15.9 (32.4)	567 (23.5)	--	--
			ethinylestradiol, 30 µg, q.d., 7d	empagliflozin 25 mg, q.d., 7d	956 (24.2)	99.0 (22.1)	1.50 (1.00 – 4.00)	16.7 (21.7)	549 (20.8)	102.82 (97.58 – 108.35)	99.22 (93.40 – 105.39)
			levonorgestrel 150 µg, q.d., 14d		99.6 (38.6)	8.24 (27.0)	1.00 (0.5 – 1.52)	38.6 (34.0)	27.9 (29.5)	--	--
			levonorgestrel 150 µg, q.d., 7d	empagliflozin 25 mg, q.d., 7d	102 (41.2)	8.71 (26.5)	1.00 (0.5 – 1.50)	40.8 (47.4)	27.5 (30.7)	101.94 (98.54 – 105.47)	105.81 (99.47 – 112.55)

Bioanalytical method performance for digoxin in plasma and urine:

Analytes:	Ethinylestradiol ^a Levonorgestrel ^b	Internal Standards:	Ethinylestradiol-d ₄ ^a Levonorgestrel-d ₆ ^b
Matrix:	Human plasma	Detection Method:	LC/MS/MS
Standard Curve Range:	5-500 pg/mL ^a 100-10000 pg/mL ^b	Assay Volume:	1000 µL
Extraction Method:	Solid phase extraction with liquid-liquid	Regression Type:	Linear, 1/x ² weighting
Room Temperature Plasma Stability:	24 h	Processed Sample Stability:	39 h, ambient
Freeze/Thaw Stability, (-80°C):	4 cycles	Long-term Freezer Stability, (-80°C):	92 days

Matrix	QC name	Concentration	Inaccuracy [%]		Imprecision [%]	
			Ethinyl-estradiol ^a	Levonor-gestrel ^b	Ethinyl-estradiol ^a	Levonor-gestrel ^b
Plasma	LLOQ	5.0 pg/mL ^a 100 pg/mL ^b	-6.8	-5.6	11.3	8.0
	QC_low	15.0 pg/mL ^a 300 pg/mL ^b	-0.7	-1.0	8.8	4.0
	QC_mid	75.0 pg/mL ^a 1500 pg/mL ^b	3.1	0.7	3.9	2.5
	QC_high	375 pg/mL ^a 7500 pg/mL ^b	1.1	-1.7	5.2	3.3
	ULOQ	2500 pg/mL ^a 50000 pg/mL ^b	4.8	2.8	3.0	2.6
	(df=50)					

Reviewers Comments: The sponsor's assessments and conclusions from this study are acceptable. There were no notable protocol violation and deviations. The bioanalytical method adequately supported the pharmacokinetic evaluation of the co-administered drug.

DDI with Diuretics 1245.42:

Study Design and Type of Control	Test Product ID (Batch no.)	Study population # Subjects Entered/ Completed (M/F)	Treatments		Mean Pharmacokinetic Parameters (%CV) ⁶²					Geometric mean ratio (90% confidence interval)	
			Substrate	Interacting Drug	AUC _{τ,ss} [nmol.h/L]	C _{max,ss} [nmol/L]	t _{max,ss} ⁶³ [h]	t _{1/2,ss} [h]	CL/F _{ss} [mL/min]	AUC _{τ,ss} [%]	C _{max,ss} [%]
Open-label, randomised, crossover	empagliflozin – 25 mg, tablet, p.o. 909473	patients 22/20 (15M/7F)	empagliflozin 25 mg, q.d., 5d		5090 (21.8)	961 (23.1)	1.50 (1.00 – 2.00)	15.3 (47.4)	189 (20.3)	--	--
			empagliflozin 25 mg, q.d., 5d	hydrochlorothiazide, 25 mg, q.d., 5d	5720 (24.1)	1070 (29.0)	1.50 (1.00 – 1.50)	14.8 (18.1)	171 (25.4)	107.08 (97.11 – 118.07)	102.78 (88.55 – 119.29)
	empagliflozin 25 mg, q.d., 5d		torasemide 5 mg, q.d., 5d	5340 (18.9)	969 (21.0)	1.00 (1.00 – 1.50)	16.1 (14.4)	179 (19.3)	107.83 (100.14 – 116.11)	107.50 (97.90 – 118.04)	
	hydrochlorothiazide, 25 mg, q.d., 4d			1050 (18.3)	211 (26.2)	1.50 (1.00 – 3.00)	10.6 (27.0)	408 (17.2)	--	--	
	hydrochlorothiazide, 25 mg, q.d., 5d		empagliflozin 25 mg, q.d., 5d	1020 (18.1)	213 (28.7)	1.75 (1.00 – 2.00)	13.5 (26.7)	422 (18.9)	96.27 (89.09 – 104.05)	101.77 (88.63 – 116.85)	
	torasemide		1340 (14.4)	721 (18.4)	0.5 (0.5 – 1.50)	4.77 (17.1)	63.4 (13.4)	--	--		
	torasemide 5 mg, q.d., 5d			1360 (16.2)	747 (12.1)	0.5 (0.5 – 1.00)	4.56 (13.9)	62.7 (15.7)	101.44 (99.06 – 103.88)	104.43 (93.81 – 116.25)	
	torasemide 5 mg, q.d., 5d		empagliflozin 25 mg, q.d., 5d								

Study Design and Type of Control	Test Product ID (Batch no.)	Study population # Subjects Entered/ Completed (M/F)	Treatments		Mean Pharmacokinetic Parameters (%CV) ⁶⁴					Geometric mean ratio (90% confidence interval)				
			Substrate	Interacting Drug	AUC _{τ,ss} [nmol.h/L]	C _{max,ss} [nmol/L]	t _{max,ss} ⁶⁵ [h]	t _{1/2,ss} [h]	CL/F _{ss} [mL/min]	AUC _{τ,ss} [%]	C _{max,ss} [%]			
Open-label, randomised, crossover	empagliflozin – 25 mg, tablet, p.o. 909473	patients 22/20 (15M/7F)	torasemide-M1 (metabolite)					75.7 (16.4)	43.7 (25.0)	0.5 (0.5 – 1.50)	2.55 (24.5)	1130 (15.2)	--	--
			torasemide 5 mg, q.d., 5d											
	hydrochlorothiazide – 25mg, tablet, p.o. 73502		empagliflozin 25 mg, q.d., 5d	79.2 (17.4)	44.4 (18.0)	0.5 (0.5 – 1.00)	2.49 (28.4)	1080 (17.6)	104.42 (100.39 – -108.62)	102.67 (94.13 – 111.97)				
	torasemide-M3 (metabolite)					41.5 (23.1)	8.64 (12.7)	1.50 (1.00 – 2.00)	3.70 (21.8)	2110 (23.9)	--	--		
	torasemide 5 mg, q.d., 5d													
	torasemide – 5 mg, tablet, p.o. 94002		empagliflozin 25 mg, q.d., 5d	42.4 (17.9)	8.90 (17.1)	1.50 (1.00 – 2.00)	3.75 (25.3)	2020 (18.0)	103.19 (95.93 – 111.01)	102.42 (97.65 – 107.42)				

While there was no relevant effect on PK of either of the drugs, effect on urine osmolality, urine volume, and micturition frequency were noted in this study.

- Urine osmolality was increased after treatment with empagliflozin alone and with a diuretic, while diuretics alone had no apparent effect. Mean urine volume was higher (341 mL/day) than baseline after single doses of empagliflozin and tended to be higher (135 mL/day) than baseline after multiple doses of empagliflozin. However, urine volume was similar to baseline with diuretics alone, and was higher than baseline after empagliflozin was added to either diuretic. At baseline, mean micturition frequencies were 4 to 5 voids in the day and 3 voids at night. On the first and fifth days of empagliflozin treatment, daytime micturition increased to about 6 voids per day while night-time micturition frequency was similar to baseline. The mean increase in total micturition frequency was about 1 to 2 voids per day.

- Treatment with HCT or TOR tended to increase both urinary glucose excretion and fasting serum glucose levels. When empagliflozin was added to either diuretic, the effects on urinary glucose excretion were maintained while the reductions in the fasting serum glucose concentration were less pronounced than when empagliflozin was given alone.
- Clearance and urinary excretion of sodium tended to decrease after multiple doses of empagliflozin or diuretics alone, were increased after empa+HCT, and were similar to baseline after empa+TOR. The serum sodium concentration increased slightly after multiple doses of empagliflozin, was similar to baseline after diuretics alone and empa+HCT, and tended to increase after empa+TOR.
- Clearance and urinary excretion of chloride tended to decrease after multiple doses of empagliflozin, after either diuretic alone, and after empa+TOR but tended to increase after empa+HCT. The serum chloride concentration was increased after multiple doses of empagliflozin, decreased after HCT alone and empa+HCT, and tended to increase after TOR alone and empa+TOR.
- Multiple doses of empagliflozin, alone and with HCT or TOR, resulted in increases in the clearance and urinary excretion of magnesium, potassium, and phosphate and reductions in the clearance and urinary excretion of calcium along with slight increases in the serum levels of magnesium and phosphate and slight reductions in the serum levels of potassium and calcium.
- Multiple doses of empagliflozin, alone and with HCT or TOR, resulted in increases in the clearance and urinary excretion of uric acid and tended to reduce the serum uric acid concentration.
- Empagliflozin alone had no clear effects on plasma renin or serum aldosterone concentrations, but treatment with either diuretic, alone or with empagliflozin, tended to increase circulating levels of both renin and aldosterone.
- Urine pH tended to be reduced after treatment with diuretics but generally demonstrated no consistent changes. In capillary blood, no meaningful changes in pH were observed, but both bicarbonate concentration and base excess were slightly reduced after multiple doses of empagliflozin, slightly increased after HCT and empa+HCT, and tended to be slightly reduced after TOR and empa+TOR. The capillary blood ionised calcium concentration tended to be slightly reduced after each treatment.
- The plasma iPTH concentration was slightly increased after each treatment. The increase after empa+TOR was greater than after either drug was given alone. The serum FGF-23 concentration tended to be slightly increased after empagliflozin, alone and with either diuretic. Diuretics had no apparent effect. No clear effects on serum calcitriol concentrations were observed. The serum ALP concentration was slightly increased after each treatment. Urinary NTx excretion was slightly increased after empagliflozin alone, after TOR alone, and empa+TOR. Small changes in serum and urinary electrolytes (Ca, Na, Cl, P) were observed in this mechanistic trial under standardized conditions of food and fluid intake.

Reviewers Comments: The sponsor's assessments and conclusions from this study are acceptable. There were no notable protocol violation and deviations. The bioanalytical method adequately supported the pharmacokinetic evaluation of the co-administered drug.

Bioanalytical method performance for hydrochlorothiazide (top row) and torasemide (bottom row) in plasma and urine:

Analyte:	Hydrochlorothiazide	Internal Standard:	Hydrochlorothiazide- ¹³ C ₂	Analyte:	Hydrochlorothiazide	Internal Standard:	Hydrochlorothiazide- ¹³ C, d ₂		
Matrix:	Human plasma	Detection Method:	LC/MS/MS	Matrix:	Human urine	Detection Method:	LC/MS/MS		
Standard Curve Range:	1.00 – 500 ng/mL	Assay Volume:	150 µL	Standard Curve Range:	100 – 10000 ng/mL	Assay Volume:	50 µL		
Extraction Method:	Protein precipitation	Regression Type:	Quadratic, 1/x ² weighting	Extraction Method:	Liquid-liquid	Regression Type:	Quadratic, 1/x ² weighting		
Room Temperature Plasma Stability:	25 h	Processed Sample Stability:	94 h, 2-8°C	Room Temperature Plasma Stability:	24 h	Processed Sample Stability:	108 h, 2-8°C		
Freeze/Thaw Stability, (-20°C):	5 cycles	Long-term Freezer Stability, (-20°C):	24 days	Freeze/Thaw Stability, (-20°C):	5 cycles	Long-term Freezer Stability, (-20°C):	232 days		
Matrix	QC name	Concentration	Inaccuracy [%]	Imprecision [%]	Matrix	QC name	Concentration	Inaccuracy [%]	Imprecision [%]
Plasma	LLOQ	1 ng/mL	-7.4	5.5	Urine	LLOQ	100 ng/mL	2.0	3.4
	QC_low	3.00 ng/mL	-2.0	1.8		QC_low	250 ng/mL	-1.6	2.1
	QC_mid	75.0 ng/mL	-4.5	2.0		QC_mid	1500 ng/mL	-2.0	1.6
	QC_high	400 ng/mL	0.5	1.7		QC_high	8500 ng/mL	-2.6	1.5
	QC_dil (df = 20)	5000 ng/mL	3.0	0.6		QC_dil (df = 50)	50000 ng/mL	-2.6	1.5
Analytes:	Torasemide ^a Torasemide M1 ^b Torasemide M3 ^c	Internal Standards:	Torasemide-d ₇ ^a Torasemide M1-d ₇ ^b Torasemide M3-d ₇ ^c	Analytes:	Torasemide ^a Torasemide M1 ^b Torasemide M3 ^c	Internal Standards:	Torasemide-d ₇ ^a Torasemide M1-d ₇ ^b Torasemide M3-d ₇ ^c		
Matrix:	Human plasma	Detection Method:	LC/MS/MS	Matrix:	Human urine	Detection Method:	LC/MS/MS		
Standard Curve Range:	1.00 – 1000 ng/mL ^a 0.500 – 500 ng/mL ^{bc}	Assay Volume:	50 µL	Standard Curve Range:	10.0 – 10000 ng/mL ^a 1.00 – 1000 ng/mL ^{bc}	Assay Volume:	50 µL		
Extraction Method:	Solid phase extraction	Regression Type:	Quadratic, 1/x ² weighting	Extraction Method:	Protein precipitation	Regression Type:	Quadratic, 1/x ² weighting		
Room Temperature Plasma Stability:	26 h	Processed Sample Stability:	83 h, 2-8°C	Room Temperature Plasma Stability:	24 h	Processed Sample Stability:	26 h, 2-8°C ^a		
Freeze/Thaw Stability, (-20°C):	4 cycles	Long-term Freezer Stability, (-20°C):	19 days	Freeze/Thaw Stability, (-20°C):	4 cycles	Long-term Freezer Stability, (-20°C):	142 h, 2-8°C ^{bc} 35 days ^{ac} 11 days ^b		
Matrix	QC name	Concentration	Inaccuracy [%]			Imprecision [%]			
Plasma	LLOQ	1.00 ng/mL ^a	-10.1	-12.8	-3.8	8.7	8.6	5.2	
		0.500 ng/mL ^{bc}							
	QC_low	3.00 ng/mL ^a	-7.7	-8.7	-5.3	3.9	4.4	6.2	
		1.50 ng/mL ^{bc}							
	QC_mid	400 ng/mL ^a	-3.0	-2.0	-2.5	1.8	1.8	2.9	
		200 ng/mL ^{bc}							
	QC_high	800 ng/mL ^a	-2.4	-3.3	-3.8	3.0	2.3	3.6	
400 ng/mL ^{bc}									
ULOQ (df = 20)	4000 ng/mL ^a 2000 ng/mL ^{bc}	-2.8	-5.5	-5.0	1.2	1.6	0.9		
Matrix	QC name	Concentration	Inaccuracy [%]			Imprecision [%]			
Urine	LLOQ	10.0 ng/mL ^a	-3.1	5.0	-4.0	7.7	11.8	11.7	
		1.0 ng/mL ^{bc}							
	QC_low	30.0 ng/mL ^a	-3.0	-1.0	-3.7	4.7	7.1	7.6	
		3.0 ng/mL ^{bc}							
	QC_mid	4000 ng/mL ^a	-4.5	-1.3	-4.3	3.6	4.8	5.2	
		400 ng/mL ^{bc}							
	QC_high	8000 ng/mL ^a	-2.6	-4.6	-2.5	4.4	3.8	3.4	
800 ng/mL ^{bc}									
ULOQ (df = 50)	40000 ng/mL ^a 4000 ng/mL ^{bc}	-7.0	-7.0	-7.3	4.6	5.3	3.8		

DDI between Verapamil 1245.43:

Study Design and Type of Control	Test Product ID (Batch no.)	Study population # Subjects Entered/ Completed (M/F)	Treatments		Mean Pharmacokinetic Parameters (%CV) ⁶⁴					Geometric mean ratio (90% confidence interval)	
			Substrate	Interacting Drug	AUC _{τ,ss} [nmol.h/L]	C _{max,ss} [nmol/L]	t _{max,ss} ⁶⁵ [h]	t _{1/2,ss} [h]	CL/F _{ss} [mL/min]	AUC _{τ,ss} [%]	C _{max,ss} [%]
Open-label, randomised, crossover	empagliflozin – 25 mg, tablet, p.o. 909473	HV 16/16 (8M/8F)	empagliflozin 25 mg, single dose ⁶⁶		5330 (22.7)	818 (27.7)	1.50 (1.00 – 2.50)	12.5 (27.9)	184 (26.8)	--	--
			empagliflozin 25 mg, single dose ⁶⁷ ,	verapamil 120 mg, single dose	5500 (25.4)	752 (27.2)	1.75 (0.683 – 3.00)	13.6 (28.1)	178 (24.8)	102.95 (98.87 – 107.20)	92.39 (85.38 – 99.97)

Bioanalytical method performance for verapamil in plasma:

Analyte:	Verapamil	Internal Standard:	Verapamil d-6
Matrix:	Human plasma	Detection Method:	LC/MS/MS
Standard Curve Range:	1.00 – 1000 ng/mL	Assay Volume:	50 µL
Extraction Method:	Liquid-liquid	Regression Type:	Quadratic, 1/x ² weighting
Room Temperature Plasma Stability:	24 h	Processed Sample Stability:	95 h, 2-8°C
Freeze/Thaw Stability, (-20°C):	5 cycles	Long-term Freezer Stability, (-20°C):	84 days

Matrix	QC name	Concentration	Inaccuracy [%]	Imprecision [%]
Plasma	LLOQ	1.0 ng/mL	-2.4	3.5
	QC_low	3.00 ng/mL	2.3	3.4
	QC_mid	200 ng/mL	-1.5	3.6
	QC_high	750 ng/mL	1.5	1.5
	QC_dil (df = 50)	5000 ng/mL	-4.4	1.8

Reviewers Comments: The sponsor’s assessments and conclusions from this study are acceptable. There were no notable protocol violation and deviations. The bioanalytical method adequately supported the pharmacokinetic evaluation of the co-administered drug.

DDI with Ramipril 1245.45:

Study Objective	Study Design and Type of Control	Test Product ID (Batch no.)	Study population # Subjects Entered/ Completed (M/F)	Treatments		Mean Pharmacokinetic Parameters (%CV) ⁶⁸					Geometric mean ratio (90% confidence interval)	
				Substrate	Interacting Drug	AUC _{τ,ss} [nmol.h/L]	C _{max,ss} [nmol/L]	t _{max,ss} ⁶⁹ [h]	t _{1/2,ss} [h]	CL/F _{ss} [mL/min]	AUC _{τ,ss} [%]	C _{max,ss} [%]
DDI between empagliflozin and ramipril	Open-label, randomised, crossover	empagliflozin – 25 mg, tablet, p.o. 909473 ramipril – 2.5/5 mg ⁷⁰ , tablet, p.o., H488	HV 23/23 (8M/15F)	empagliflozin 25 mg, q.d. 5d		5930 (16.8)	899 (23.1)	1.02 (0.667 – 3.00)	13.6 (40.2)	161 (19.5)	--	--
				empagliflozin 25 mg, q.d. 5d	ramipril 5 mg, q.d. 5d	5750 (15.5)	929 (20.0)	1.50 (1.00 – 4.00)	15.0 (43.2)	165 (17.1)	96.55 (93.05 – 100.18)	104.47 (97.65 – 111.77)
				ramipril		6.98 (32.8)	9.18 (41.3)	0.333 (0.333 – 1.00)	3.58 (72.1)	13500 (40.9)	--	--
				ramipril 5 mg, q.d. 5d	empagliflozin 25 mg, q.d. 5d	7.73 (35.4)	10.0 (46.0)	0.333 (0.333 – 1.00)	3.37 (85.1)	12200 (39.2)	108.14 (100.51 – 116.35)	103.61 (89.73 – 119.64)
				ramiprilat (metabolite)		88.2 (15.4)	11.9 (38.0)	2.00 (1.48 – 4.02)	75.2 (24.6)	966 (15.5)	--	--
				ramipril 5 mg, q.d. 5d	empagliflozin 25 mg, q.d. 5d	86.7 (20.2)	11.6 (45.7)	2.00 (1.50 – 4.00)	80.0 (34.2)	998 (20.2)	98.67 (96.00 – 101.42)	98.29 (92.67 – 104.25)
				ramipril 5 mg, q.d. 5d								

Bioanalytical method performance for ramipril and ramiprilat in plasma:

Analytes:	Ramipril ^a Ramiprilat ^b	Internal Standard:	Ramipril-d ₅ ^a Ramiprilat-d ₅ ^b
Matrix:	Human plasma	Detection Method:	LC/MS/MS
Standard Curve Range:	0.500 – 50.0 ng/mL	Assay Volume:	250 µL
Extraction Method:	Solid phase extraction	Regression Type:	Linear, 1/x ² ^a Linear, 1/x ^b
Room Temperature Plasma Stability:	24 h	Processed Sample Stability:	123 h, 2-8 °C
Freeze/Thaw Stability, (-70°C):	5 cycles	Long-term Freezer Stability, (-70°C):	304 days

Matrix	QC name	Concentration	Inaccuracy [%]		Imprecision [%]	
			Ramipril ^a	Ramiprilat ^b	Ramipril ^a	Ramiprilat ^b
Plasma	LLOQ	0.050 ng/mL	-3.70	1.62	7.67	12.0
	QC_low	0.140 ng/mL	0.286	3.86	4.63	8.91
	QC_mid 1	0.400 ng/mL	1.92	2.41	4.67	4.86
	QC_mid 2	1.50 ng/mL	1.61	3.29	4.87	3.84
	QC_high 1	6.00 ng/mL	1.83	1.61	4.84	3.70
	QC_high 2	38.0 ng/mL	0.227	2.21	5.94	5.44
	QC_dil	250 ng/mL	-2.09	-1.45	0.663	2.00
	(df = 10)					

Reviewers Comments: The sponsor’s assessments and conclusions from this study are acceptable. There were no notable protocol violation and deviations. The bioanalytical method adequately supported the pharmacokinetic evaluation of the co-administered drug.

DDI with gemfibrozil 1245.58:

Study Design and Type of Control	Test Product ID (Batch no.)	Study population # Subjects Entered/ Completed (M/F)	Treatments		Mean Pharmacokinetic Parameters (%CV) ^{71, 72, 73}					Geometric mean ratio (90% confidence interval)	
			Substrate	Interacting Drug	AUC _{τ,ss} [nmol.h/L]	C _{max,ss} [nmol/L]	t _{max,ss} ⁷⁴ [h]	t _{1/2,ss} [h]	CL/F _{ss} [mL/min]	AUC _{τ,ss} [%]	C _{max,ss} [%]
Open-label, randomised, crossover	empagliflozin – 25 mg, tablet, p.o. 909473 gemfibrozil – 600 mg, tablet, p.o., 0939070	HV 18/18 (11M/7F)	empagliflozin 25 mg, single dose		4770 (16.7)	610 (16.2)	2.75 (1.00 – 4.02)	13.3 (50.0)	199 (18.3)	--	--
			empagliflozin 25 mg, single dose ⁷⁵	gemfibrozil 600 mg, b.i.d. 5d	7630 (20.8)	713 (22.1)	3.00 (1.50 – 4.05)	13.6 (30.2)	127 (23.1)	158.50 (151.77 -165.53)	115.00 (106.15 -124.59)

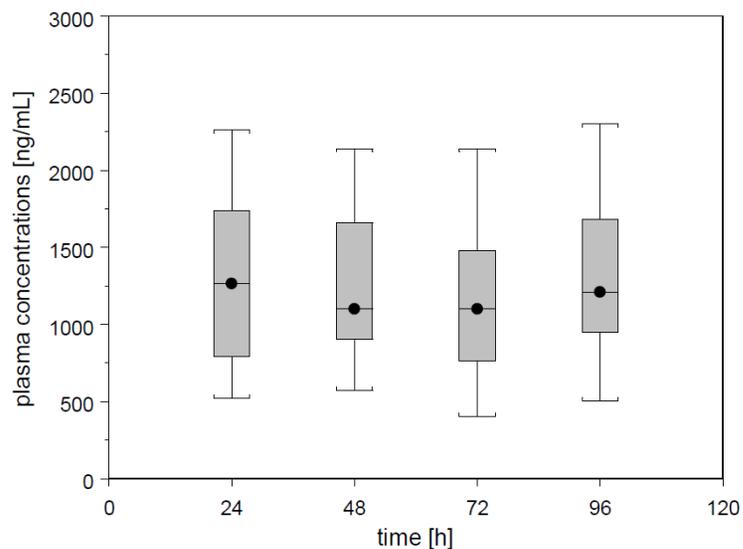
In the gemfibrozil DDI study, a single dose of empagliflozin was administered and PK parameters listed are AUC_{0-∞}, C_{max}, t_{max}, t_{1/2}, and CL/F. A single dose of empagliflozin was administered on the third day of a 5-day treatment with gemfibrozil.

The trial was designed to investigate whether co-administration of gemfibrozil had any effect on empagliflozin bioavailability, which is especially relevant for patients with type 2 diabetes mellitus also treated with fibrates for dyslipidemia. In addition, gemfibrozil is an inhibitor of hepatic uptake transporter OATP1B1¹ in humans, for which empagliflozin is a substrate based on in vitro studies. The study results are in agreement to the in vitro findings.

¹ Effects of fibrates on human organic anion-transporting polypeptide 1B1-, multidrug resistance protein 2- and P-glycoprotein-mediated transport. Yamazaki M, Li B, Louie SW, Pudvah NT, Stocco R, Wong W, Abramovitz M, Demartis A, Laufer R, Hochman JH, Prueksaritanont T, Lin JH. Xenobiotica. 2005 Jul;35(7):737-53.

PK Results for Gemfibrozil and Bioanalytical method performance for gemfibrozil in plasma:

Gemfibrozil morning trough concentrations of gemfibrozil on Days -1, 1, 2, and 3 (corresponding to 24, 48, 72, and 96 h after first gemfibrozil administration) during multiple oral administration of 600 mg gemfibrozil twice daily for 5 days with a single dose of 25 mg:



Analyte:	Gemfibrozil	Internal Standard:	Gemfibrozil-d ₆	
Matrix:	Human plasma	Detection Method:	LC/MS/MS	
Standard Curve Range:	50 – 50000 ng/mL	Assay Volume:	50 µL	
Extraction Method:	Liquid-liquid	Regression Type:	Quadratic, 1/x weighting	
Room Temperature Plasma Stability:	24 h ambient	Processed Sample Stability:	98 h, 2-8°C	
Freeze/Thaw Stability, (-20°C):	5 cycles	Long-term Freezer Stability, (-20°C):	64 days	
Matrix	QC name	Concentration	Inaccuracy [%]	Imprecision [%]
Plasma	LLOQ	50.0 ng/mL	-9.6	5.5
	QC_low	150 ng/mL	-3.3	2.8
	QC_mid	2750 ng/mL	-1.1	1.6
	QC_high 1	25000 ng/mL	1.2	1.6
	QC_high 2	38000 ng/mL	0.5	1.2
	QC_dil	500000 ng/mL	-3.8	1.0
(df = 50)				

Reviewers Comments: The sponsor’s assessments and conclusions from this study are acceptable. There were no notable protocol violation and deviations. The bioanalytical method adequately supported the pharmacokinetic evaluation of the co-administered drug.

DDI with simvastatin 1245.63:

Study Design and Type of Control	Test Product ID (Batch no.)	Study population # Subjects Entered/ Completed (M/F)	Treatments		Mean Pharmacokinetic Parameters (%CV) ^{71, 72, 73}					Geometric mean ratio (90% confidence interval)		
			Substrate	Interacting Drug	AUC _{τ,ss} [nmol.h/L]	C _{max,ss} [nmol/L]	t _{max,ss} ⁷⁴ [h]	t _{1/2,ss} [h]	CL/F _{ss} [mL/min]	AUC _{τ,ss} [%]	C _{max,ss} [%]	
Open-label, randomised, crossover	empagliflozin – 25 mg, tablet, p.o. 909473 simvastatin – 40 mg, tablet, p.o. 302431	HV 18/17 (12M/6F)	empagliflozin 25 mg, single dose		5680 (20.8)	806 (30.0)	1.00 (0.667 – 3.00)	14.9 (48.1)	169 (18.3)	--	--	
			empagliflozin 25 mg, single dose	simvastatin 40 mg, single dose	5800 (22.7)	876 (27.2)	1.00 (0.667 – 2.98)	13.8 (35.0)	165 (18.2)	102.05 (98.90 – 105.29)	109.49 (96.91 – 123.69)	
			simvastatin									
			simvastatin 40 mg, single dose		40.4 (57.2)	9.93 (67.8)	0.667 (0.400 – 6.00)	9.57 (50.3)	23700 (62.4)	--	--	
			simvastatin 40 mg, single dose	empagliflozin 25 mg, single dose	40.2 (54.6)	9.40 (62.2)	0.983 (0.667 – 2.50)	8.23 (36.8)	24200 (74.1)	101.26 (80.06 – 128.07)	97.18 (76.30 – 123.77)	
Open-label, randomised, crossover	empagliflozin – 25 mg, tablet, p.o. 909473 simvastatin – 40 mg, tablet, p.o. 302431	HV 18/17 (12M/6F)	simvastatin acid (metabolite)									
			simvastatin 40 mg, single dose		21.7 (71.9)	1.90 (68.2)	4.00 (1.00 – 6.00)	9.76 (77.3)	50100 (72.3)	--	--	
			simvastatin 40 mg, single dose	empagliflozin 25 mg, single dose	22.7 (77.0)	1.84 (73.1)	4.00 (1.50 – 6.02)	8.93 (40.6)	50200 (96.6)	104.87 (90.09 – 122.07)	97.27 (84.90 – 111.44)	

In the simvastatin DDI study, both empagliflozin and simvastatin were administered as single doses and PK parameters listed are AUC_{0-∞}, C_{max}, t_{max}, t_{1/2}, and CL/F.

Bioanalytical method performance for simvastatin and its metabolite in plasma:

Analytes:	Simvastatin ^a Simvastatin acid ^b	Internal Standard:	Smivastatin-d ₆ ^a Simvastatin acid-d ₆ ^b			
Matrix:	Human plasma	Detection Method:	LC/MS/MS			
Standard Curve Range:	0.0500 – 100 ng/mL	Assay Volume:	200 µL			
Extraction Method:	Liquid-liquid	Regression Type:	Quadratic, 1/x ² weighting			
Room Temperature Plasma Stability:	6 h	Processed Sample Stability:	51 h, 2-8°C			
Freeze/Thaw Stability, (-20°C):	4 cycles	Long-term Freezer Stability, (-20°C):	86 days			
Matrix	QC name	Concentration	Inaccuracy [%]		Imprecision [%]	
			Simvastatin ^a	Simvastatin Acid ^b	Simvastatin ^a	Simvastatin Acid ^b
Plasma (df = 10)	LLOQ	0.0500 ng/mL	-0.8	-4.0	5.2	6.9
	QC_low	0.150 ng/mL	-2.7	-3.3	5.8	3.0
	QC_mid	5.00 ng/mL	-0.6	1.0	3.7	2.4
	QC_high	75.0 ng/mL	-0.9	-1.3	3.2	2.9
	ULOQ	250 ng/mL	-0.4	0.4	1.9	1.1

Reviewers Comments: The sponsor’s assessments and conclusions from this study are acceptable. There were no notable protocol violation and deviations. The bioanalytical method adequately supported the pharmacokinetic evaluation of the co-administered drug.

DDI with Rifampicin and Probenecid 1245.83:

Study Design and Type of Control	Test Product ID (Batch no.)	Study population # Subjects Entered/ Completed (M/F)	Treatments		Mean Pharmacokinetic Parameters (%CV) ^{76,7778}					Geometric mean ratio (90% confidence interval)	
			Substrate	Interacting Drug	AUC _{τ,ss} [nmol.h/L]	C _{max,ss} [nmol/L]	t _{max,ss} ⁷⁹ [h]	t _{1/2,ss} [h]	CL/F _{ss} [mL/min]	AUC _{τ,ss} [%]	C _{max,ss} [%]
Open-label, randomised, crossover	empagliflozin – 10 mg, tablet, p.o. 003436	HV 18/16 (10M/8F)	empagliflozin 10 mg, single dose		2330 (31.4)	313 (27.7)	1.50 (1.00 – 3.00)	11.8 (34.2)	171 (24.9)	--	--
			empagliflozin 10 mg, single dose	rifampicin 600 mg, single dose	3150 (32.9)	546 (29.0)	1.00 (0.667 – 1.50)	7.53 (21.4)	126 (24.4)	135.20 (129.58–141.06)	175.14 (160.14–191.56)
			empagliflozin 10 mg, single dose ⁸⁰	probenecid 500 mg, b.i.d. 4d	3540 (33.1)	389 (29.6)	1.50 (1.00 – 3.00)	13.0 (23.1)	113 (25.1)	153.47 (146.41–160.88)	125.60 (113.67–138.78)

In vitro data showed that empagliflozin is a substrate of organic anion transporters, such as OAT3 and OATP1B1 (organic anion-transporting polypeptide 1B1). OAT3 is an uptake transporter in the proximal tubule epithelia of the kidney that mediates the basolateral entry step in renal secretion of many organic anions; thus an inhibition may result in reduced renal clearance. OATP1B1 is an uptake transporter expressed in the human liver that transports a broad range of compounds, such as bile acids, sulphate and glucuronate conjugates, thyroid hormones, peptides, and drugs (e.g. methotrexate and HMG-CoA reductase inhibitors). Therefore, the aim of this DDI study was to assess if and to which extent disposition and excretion of a single dose of empagliflozin is influenced by co-administration with drugs that inhibit either OATP1B1 or OAT3. Rifampicin (given as a single dose) was chosen as a model OATP1B1 inhibitor and probenecid (given as multiple doses) served as a model OAT3 inhibitor.

When co-administered with probenecid, increased systemic exposure of empagliflozin was associated with a more than 50% decrease in the mean renal clearance of empagliflozin after co-administration with probenecid (15.2 mL/min) compared with empagliflozin alone (32.7 mL/min). The mean fraction of empagliflozin excreted in urine was 13.8% after co-administration with probenecid compared with 19.7% after the administration of empagliflozin alone.

The UGE results of both treatments were similar, whether empagliflozin was given alone or with probenecid. The mean (%CV) cumulative amount of glucose recovered in urine over 24 h post-dose 10 mg empagliflozin was 50.7 g (16.8%) when empagliflozin was administered alone and 49.7 g (18.0%) when it was co-administered with 500 mg probenecid twice daily (from Day -1 to Day 3). The effect of increased exposure with rifampicin on amount of empagliflozin in urine or urinary glucose excretion was not evaluated.

Bioanalytical method performance for rifampicin and probenecid in plasma:

Analytes:	Rifampin ^a (Rifampicin) Probenecid ^b	Internal Standards:	Rifampin-d ³ Probenecid-d ¹⁴
Matrix:	Human plasma	Detection Method:	LC/MS/MS
Standard Curve Range:	10.0 – 10000 ng/mL ^a 250 -250000 ng/mL ^b	Assay Volume:	0.05 mL
Extraction Method:	Liquid-liquid extraction	Regression Type:	Linear, 1/x ² weighting
Room Temperature Plasma Stability:	7 h	Processed Sample Stability:	259 h
Freeze/Thaw Stability, (20°C):	5 cycles	Long-term Freezer Stability, (20°C):	95 days

Matrix	QC name	Concentration	Inaccuracy [%]		Imprecision [%]	
			Rifampin ^a	Probenecid ^b	Rifampin ^a	Probenecid ^b
Plasma	LLOQ	10.0 ng/mL ^a 25 ng/mL ^b	-1.10	-11.6	7.48	15.8
	QC_low	30.0 ng/mL ^a 750 ng/mL ^b	3.67	-1.73	10.2	11.6
	QC_mid	750 ng/mL ^a 18800 ng/mL ^b	6.40	3.47	4.79	4.81
	QC_high	7500 ng/mL ^a 188000 ng/mL ^b	3.47	-0.267	6.61	5.94
	ULOQ	20000 ng/mL ^a 50000ng/mL ^b	10.0	3.00	2.66	5.67
	(df = 20)					

Reviewers Comments: The sponsor’s assessments and conclusions from this study are acceptable. There were no notable protocol violation and deviations. The bioanalytical method adequately supported the pharmacokinetic evaluation of the co-administered drug. However, this study does not address the potential of UGT induction by rifampicin and its impact on empagliflozin exposure in a single dose setting.

4.1.5 PKPD in Renal Impairment (1245.12)

Study Design	Treatments (Dose, dosage Form Route) [Batch no.]	Study population # Subjects Entered/ Completed (M/F)	Results – Study Parameters Mean (%CV)							Geometric mean ratio (90% confidence interval)	
			AUC _{0-∞} [nmol.h/L]	C _{max} [nmol/L]	t _{max} ⁸¹ [h]	t _{1/2} [h]	f _{e,0-96h} (%)	CL _{R,0-96h} [mL/min]	UGE ⁸² [g]	AUC _{0-∞} [%]	C _{max} [%]
Open-label, parallel group, single dose	50 mg tablet p.o. [B09100097 8]	8 subjects MDRD: >90 mL/min/1.73 m ² (1M/7F)/(1M/7F)	10600 (16.4)	1240 (23.5)	1.00 (1.00 – 3.00)	19.9 (58.8)	16.1 (26.7)	28.5 (20.5)	97.6 (7.20)	--	--
		9 subjects MDRD: 60-89 mL/min/1.73 m ² (3M/6F)/(3M/6F)	12700 (20.8)	1500 (29.4)	2.50 (2.00 – 4.00)	24.6 (84.5)	11.7 (36.4)	18.6 (46.9)	61.6 (6.89)	118.24 (96.17 – 145.38)	118.83 (93.62 – 150.84)
		7 subjects MDRD: 30-59 mL/min/1.73 m ² (4M/3F)/(4M/3F)	13000 (25.1)	1290 (37.9)	2.00 (1.50 – 3.00)	23.8 (87.9)	7.69 (70.1)	11.8 (69.6)	55.7 (16.9)	119.94 (96.25 – 149.47)	102.27 (79.33 – 131.85)
		8 subjects MDRD: <30 mL/min/1.73 m ² (7M/1F)/(7M/1F)	17700 (17.8)	1520 (31.6)	2.00 (0.667 – 4.00)	27.9 (76.8)	3.64 (36.1)	3.95 (30.6)	18.3 (3.93)	166.29 (134.44 – 205.68)	120.68 (94.42 – 154.25)
		8 subjects Kidney failure/ ESRD (4M/4F)/(4M/4F)	16600 (38.7)	1290 (27.5)	2.50 (1.50 – 3.00)	22.0 (74.3)	0.345 (56.4)	0.502 (59.1)	0.779 (0.904)	148.29 (119.89 – 183.42)	103.75 (81.18 – 132.61)

Reviewers Comments: The sponsor's assessments and conclusions from this study are acceptable. There were no notable protocol violation and deviations. The bioanalytical method adequately supported the pharmacokinetic evaluation of the co-administered drug.

4.1.6 PKPD in Hepatic Impairment (1245.13)

Study Design	Treatments (Dose, dosage Form Route) [Batch no.]	Study population # Subjects Entered/ Completed (M/F)	Results – Study Parameters Mean (%CV)							Geometric mean ratio (90% confidence interval)	
			AUC _{0-∞} [nmol.h/L]	C _{max} [nmol/L]	t _{max} ⁸³ [h]	t _{1/2} [h]	f _{e,0-96h} (%)	CL _{R,0-24h} [mL/min]	UGE ⁸⁴ [g]	AUC _{0-∞} [%]	C _{max} [%]
Open-label, parallel group, single dose	50 mg tablet p.o. [B09300019 6]	empagliflozin									
		12 subjects normal (4M/8F)/(4M/8F)	10800 (22.6)	1370 (33.9)	2.00 (1.00 – 4.00)	19.9 (43.1)	16.6 (26.5)	28.7 (30.3)	42.6 (31.9)	--	--
		9 subjects mild (Child-Pugh class A) (4M/4F)/(4M/4F)	13800 (38.6)	1430 (36.8)	1.50 (0.667 – 4.00)	18.1 (25.9)	15.2 (20.6)	23.7 (48.0)	36.2 (31.2)	123.15 (98.89 – 153.36)	103.81 (82.29 – 130.95)
		7 subjects moderate (Child- Pugh class B) (5M/3F)/(5M/3F)	16100 (26.2)	1660 (26.4)	2.00 (0.667 – 2.50)	17.1 (45.9)	16.7 (35.0)	19.9 (36.8)	38.4 (60.7)	146.97 (118.02 – 183.02)	123.31 (97.74 – 155.55)
		8 subjects severe (Child- Pugh class C) (4M/4F)/(4M/4F)	19000 (27.1)	1970 (22.1)	1.50 (0.667 – 2.50)	17.7 (67.4)	20.3 (23.5)	21.3 (37.1)	40.2 (54.8)	174.70 (140.29 – 217.55)	148.41 (117.65 – 187.23)
		empagliflozin-2-O-glucuronide									
		12 subjects normal (4M/8F)/(4M/8F)	1070 (24.3)	146 (38.4)	2.50 (1.50 – 4.00)	9.06 (25.7)	8.47 (25.7)	144 (23.8)	--	--	--

Study Design	Treatments (Dose, dosage Form Route) [Batch no.]	Study population # Subjects Entered/ Completed (M/F)	Results – Study Parameters Mean (%CV)							Geometric mean ratio (90% confidence interval)	
			AUC _{0-∞} [nmol.h/L]	C _{max} [nmol/L]	t _{max} ⁸⁵ [h]	t _{1/2} [h]	f _{e,0-96h} (%)	CL _{R,0-24h} [mL/min]	UGE [g]	AUC _{0-∞} [%]	C _{max} [%]
Open-label, parallel group, single dose	50 mg tablet p.o. [B09300019 6]	empagliflozin-2-O-glucuronide									
		9 subjects mild (Child-Pugh class A) (4M/4F)/(4M/4F)	1290 (41.4)	124 (36.4)	2.25 (1.50 – 4.00)	10.8 (40.1)	8.88 (23.4)	136 (31.3)	--	--	--
		7 subjects moderate (Child- Pugh class B) (5M/3F)/(5M/3F)	1140 (38.0)	116 (34.6)	2.50 (1.50 – 2.50)	10.5 (49.6)	7.15 (19.8)	126 (31.0)	--	--	--
		8 subjects severe (Child- Pugh class C) (4M/4F)/(4M/4F)	969 (66.6)	82.6 (30.8)	2.50 (1.50 – 3.00)	12.0 (55.9)	6.09 (25.3)	148 (59.1)	--	--	--
		empagliflozin-3-O-glucuronide									
		12 subjects normal (4M/8F)/(4M/8F)	1150 (25.0)	166 (41.4)	2.50 (2.00 – 4.00)	8.47 (22.0)	12.1 (25.6)	192 (30.2)	--	--	--
9 subjects mild (Child- Pugh class A) (4M/4F)/(4M/4F)	2380 (34.5)	225 (37.8)	2.50 (1.50 – 4.00)	12.5 (57.9)	16.4 (16.8)	134 (27.6)	--	--	--		

Study Design	Treatments (Dose, dosage Form Route) [Batch no.]	Study population # Subjects Entered/ Completed (M/F)	Results – Study Parameters Mean (%CV)								Geometric mean ratio (90% confidence interval)	
			AUC _{0-∞} [nmol.h/L]	C _{max} [nmol/L]	t _{max} ⁸⁶ [h]	t _{1/2} [h]	f _{e,0-96h} (%)	CL _{R,0-24h} [mL/min]	UGE [g]	AUC _{0-∞} [%]	C _{max} [%]	
Open-label, parallel group, single dose	50 mg tablet p.o. [B09300019 6]	empagliflozin-3-O-glucuronide										
		7 subjects moderate (Child- Pugh class B) (5M/3F)/(5M/3F)	3150 (37.8)	243 (28.6)	2.75 (1.50 – 4.00)	19.7 (99.8)	16.8 (34.1)	109 (25.7)	--	--	--	
		8 subjects severe (Child- Pugh class C) (4M/4F)/(4M/4F)	3180 (57.2)	220 (33.6)	2.50 (2.00 – 6.00)	13.1 (58.7)	19.5 (20.1)	144 (49.5)	--	--	--	
		empagliflozin-6-O-glucuronide										
		12 subjects normal (4M/8F)/(4M/8F)	1140 (17.4)	97.6 (21.2)	4.00 (2.50 – 6.00)	10.3 (44.7)	3.57 (25.3)	57.0 (28.5)	--	--	--	
		9 subjects mild (Child- Pugh class A) (4M/4F)/(4M/4F)	1430 (52.1)	88.3 (38.2)	4.00 (3.00 – 8.00)	10.7 (42.1)	3.38 (20.8)	48.3 (32.9)	--	--	--	
7 subjects moderate (Child- Pugh class B) (5M/3F)/(5M/3F)	1190 (39.8)	69.9 (41.0)	4.00 (3.00 – 10.0)	12.5 (44.3)	2.86 (22.7)	49.1 (29.0)	--	--	--			

Study Design	Treatments (Dose, dosage Form Route) [Batch no.]	Study population # Subjects Entered/ Completed (M/F)	Results – Study Parameters Mean (%CV)							Geometric mean ratio (90% confidence interval)	
			AUC _{0-∞} [nmol.h/L]	C _{max} [nmol/L]	t _{max} ⁸⁷ [h]	t _{1/2} [h]	f _{e,0-96h} (%)	CL _{R,0-24h} [mL/min]	UGE [g]	AUC _{0-∞} [%]	C _{max} [%]
			empagliflozin-6-O-glucuronide								
Open-label, parallel group, single dose	50 mg tablet p.o. [B09300019 6]	8 subjects severe (Child- Pugh class C) (4M/4F)/(4M/4F)	771 (58.4)	45.5 (35.7)	5.00 (2.00 – 10.0)	10.7 (43.0)	2.49 (21.6)	70.1 (46.7)	--	--	--

Reviewers Comments: The sponsor's assessments and conclusions from this study are acceptable. There were no notable protocol violation and deviations. The bioanalytical method adequately supported the pharmacokinetic evaluation of the co-administered drug.

Pharmacometrics Review and OCP Filing Memo

4.2 Pharmacometric Review

OFFICE OF CLINICAL PHARMACOLOGY: PHARMACOMETRIC REVIEW

Application Number	204629
Submission Number (Date)	03/05/2013
Compound/Formulation/ Dosing regimen	Empagliflozin Film Coated, Immediate Release Tablets: Starting dose 10 mg, can be increased to 25 mg for additional glycemic control
Indication	Indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
Clinical Division	DMEP
Primary PM Reviewer	Manoj Khurana, Ph.D.
PM Team Leader	Nitin Mehrotra, Ph.D.

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1 SUMMARY OF FINDINGS

1.1 Key Review Questions

The purpose of this review is to address the following key questions.

1.1.1 Is there dose-response for effectiveness for Empagliflozin?

There is lack of evidence of clear dose-response when data from monotherapy and add on therapy trials was examined. From efficacy perspective, the dose-response data suggests that the use of 25 mg once daily dose of empagliflozin does not always produce higher reduction in HbA1c than 10 mg once daily.

In case of add on therapy to metformin or add on to metformin+sulfonylurea, the responses seen with 10 and 25 mg were similar. In some specific treatment settings, such as when administered as monotherapy, as add-on therapy to patients on pioglitazone with or without metformin or as add on to insulin, 25 mg once daily dose offers an additional HbA1c reduction of up to 0.14% units. There was however, a dose-dependent increase in proportion of patients who achieved <7% HbA1c by the time of primary end-point measurement (Figure 3).

The HbA1c reduction appeared to reach plateau by Week 24 in the Phase 3 monotherapy trial 1245.20, thus allowing for a reasonable dose-response evaluation at Week 24 (See Figure 1 below). This was also true for other Phase 3 trials (See Appendix 4.1 to the Pharmacometric Review).

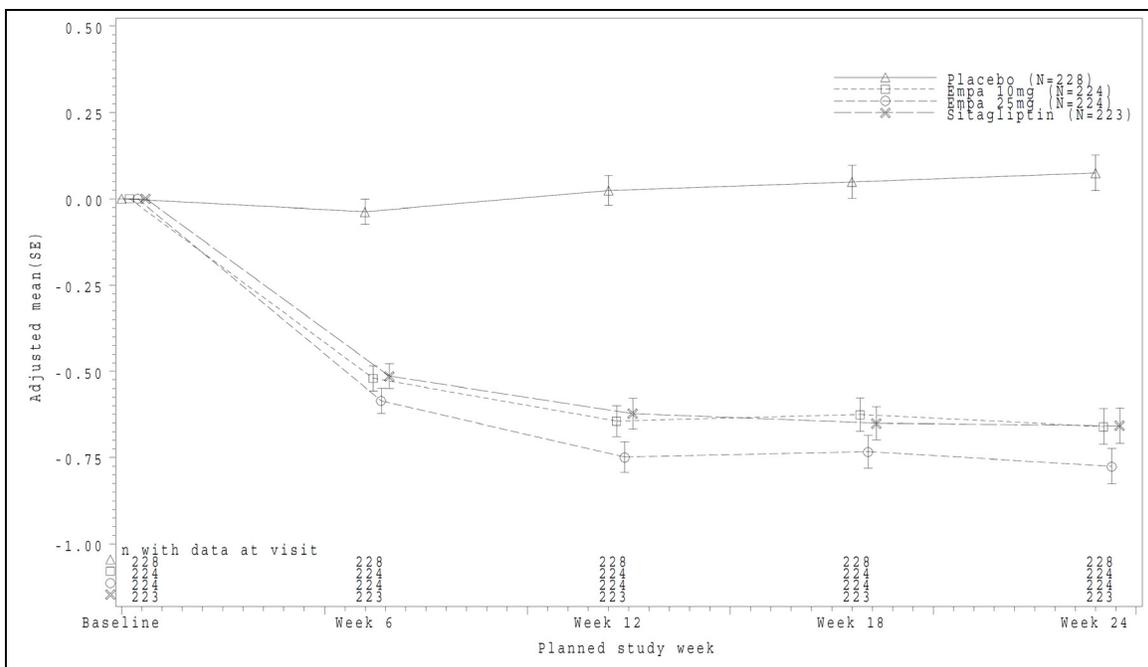
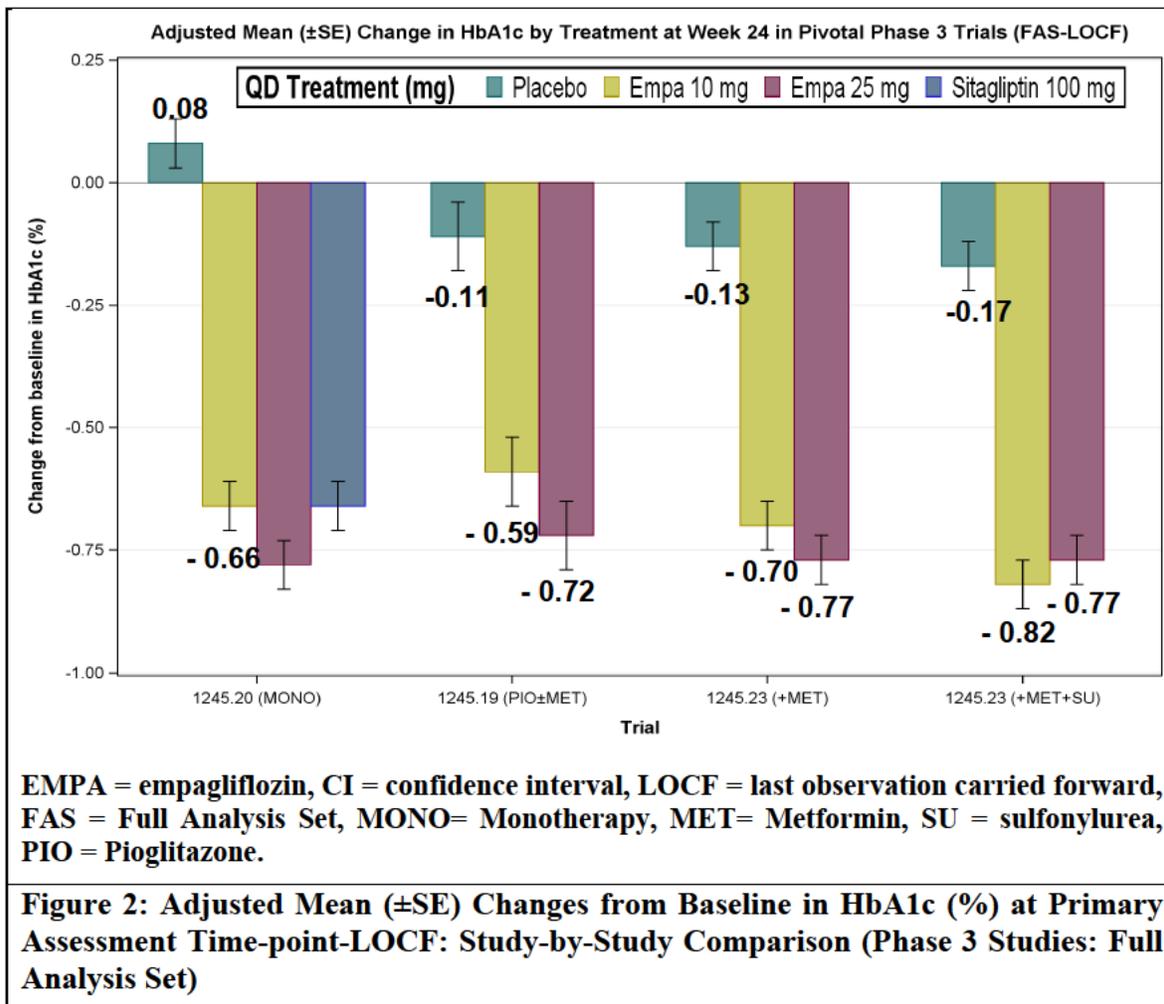


Figure 1: Time-profiles for adjusted mean (SE) change from baseline in HbA1c in Phase 3 monotherapy trial 1245.20. [Source: Sponsor's Figure 15.2.1.2.2:5 - HbA1c (%) ANCOVA results over time - FAS(LOCF) in Report U12-1517-01 Page 388. Model included treatment, baseline eGFR (MDRD), background medication and region as fixed effects and baseline HbA1c as a linear covariate.]

The mean (95%CI) change from baseline in HbA1c by treatment from the confirmatory Phase 3 trials is shown in Figure 2 below. The mono-therapy trial (1245.20) and add-on to pioglitazone and/or metformin trial (1245.19) showed numerically higher reduction in HbA1c from baseline (about 0.13%) for the 25 mg once daily dose. Whereas, in add on to metformin and add on to metformin plus sulfonylurea trials, both 10 mg and 25 mg treatments showed almost similar response against the placebo group (Figure 2) with modest to no separation in mean HbA1c reduction from baseline between the two active treatment arms (see Figure 2). This suggests that in certain treatment settings, the 25 mg dose could provide additional benefit for some patients with regards to HbA1c reduction.



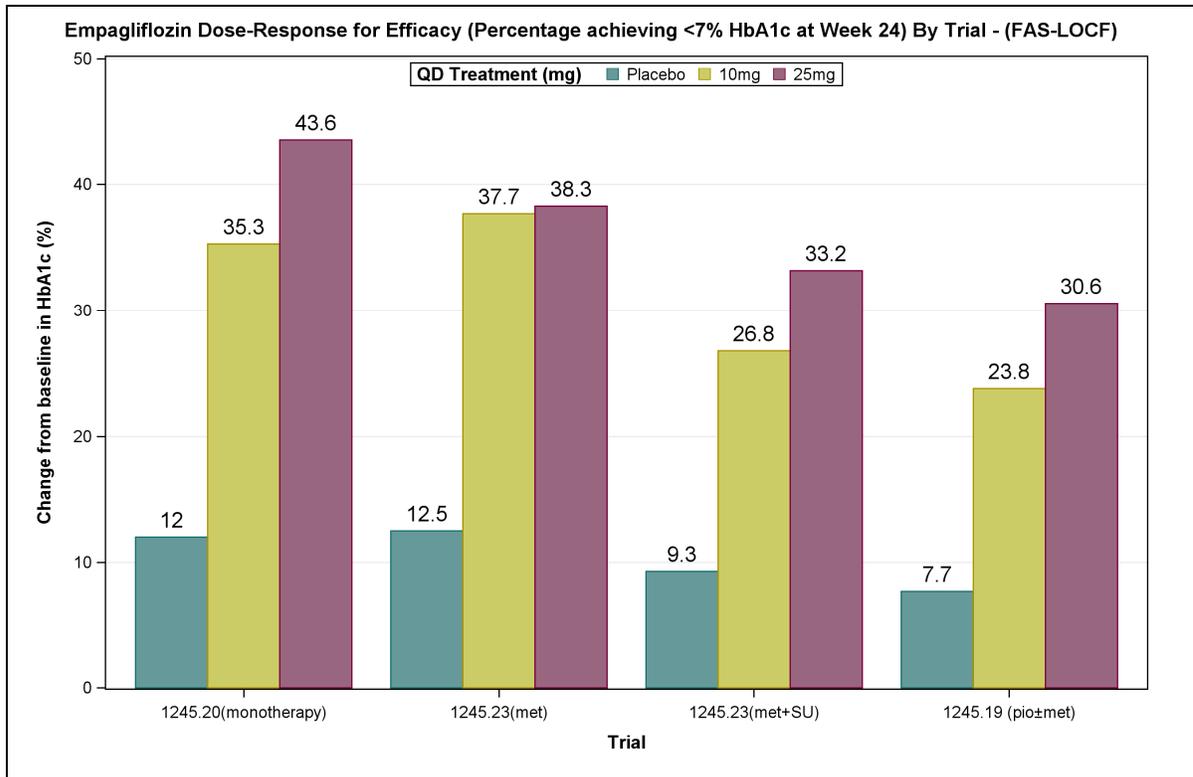


Figure 3: Proportion of Patients who Achieve <7% HbA1c by End of Trial: Study-by-Study Comparison (Phase 3 Studies: Full Analysis Set)

Results from the Monotherapy Trial (1245.20):

At week 24, the adjusted mean change (SE) in HbA1c from baseline at Week 24 was -0.08 (0.05)%, -0.66 (0.05)%, and -0.78 (0.05)% for placebo, empagliflozin 10 mg once daily, and empagliflozin 25 mg once daily, respectively. Accordingly, the difference versus placebo for the adjusted mean change (95%CI) in HbA1c from baseline at Week 24 was -0.74 (-0.88, -0.59) % for the empagliflozin 10 mg once daily group and -0.85 (-0.99, -0.71)% for the empagliflozin 25 mg once daily group, showing numerically higher HbA1c reduction with the latter. The proportion of subjects who achieved target HbA1c levels of <7.0% by Week 24 was higher for the 25 mg once daily dose group (43.6%) than the 10 mg once daily dose group (35.3%), while both being higher than placebo (12.0%) (see Figure 3).

Results from the Add-on therapy Trials:

Add-on to (pioglitazone ± metformin): In the dual/triple therapy setting in trial 1245.19 (~25% Add on to pioglitazone and ~75% Add on to pioglitazone plus metformin), the adjusted mean change (SE) in HbA1c from baseline at Week 24 was -0.11 (0.07)%, -0.59 (0.07)%, and -0.72 (0.07)% for placebo, empagliflozin 10 mg once daily, and empagliflozin 25 mg once daily, respectively. Accordingly, the difference versus placebo for the adjusted mean change (95%CI) in HbA1c from baseline at Week 24 was -0.48 (-0.66, -0.29) % for the empagliflozin 10 mg once daily group and -0.61 (-0.79, -0.42)% for the empagliflozin 25 mg once daily group, showing numerical advantage of

the latter. The proportion of subjects who achieved target HbA1c levels of <7.0% by Week 24 was also slightly higher for the 25 mg once daily dose group (30.6%) than the 10 mg once daily dose group (23.8%), while both doses being higher than placebo (7.7%).

Add-on to metformin: In the dual therapy setting in trial 1245.23 (Add-on to metformin), the adjusted mean change (SE) in HbA1c from baseline at Week 24 was -0.13 (0.05)%, -0.70 (0.05)%, and -0.77 (0.05)% for placebo, empagliflozin 10 mg once daily, and empagliflozin 25 mg once daily, respectively. Accordingly, the difference versus placebo for the adjusted mean change (95%CI) in HbA1c from baseline at Week 24 was -0.57 (-0.70, -0.43) % for the empagliflozin 10 mg once daily group and -0.64 (-0.77, -0.50)% for the empagliflozin 25 mg once daily group, showing only slight numerical advantage of the latter. The proportion of subjects who achieved target HbA1c levels of <7.0% by Week 24 was comparable for the 25 mg once daily dose group (38.7%) and the 10 mg once daily dose group (37.7%), while both doses being higher than placebo (12.5%).

Add-on to (metformin + sulphonylurea): In trial 1245.23 (Add-on to metformin plus sulphonylurea), the adjusted mean change (SE) in HbA1c from baseline at Week 24 was -0.18 (0.05)%, -0.80 (0.05)%, and -0.77 (0.05)% for placebo, empagliflozin 10 mg once daily, and empagliflozin 25 mg once daily, respectively. Accordingly, the difference versus placebo for the adjusted mean change (95%CI) in HbA1c from baseline at Week 24 was -0.64 (-0.77, -0.51) % for the empagliflozin 10 mg once daily group and -0.59 (-0.73, -0.46)% for the empagliflozin 25 mg once daily group, showing a lack of dose response between the two doses. The proportion of subjects who achieved target HbA1c levels of <7.0% by Week 24 however, was slightly higher numerically for the 25 mg once daily dose group (32.2%) than the 10 mg once daily dose group (26.3%), while both doses being higher than placebo (9.3%).

Dose-Response from other Phase 2/3 Trials:

Dose-response data from Phase 2 dose finding trials and other short term Phase 2/3 trials also indicate similar dose-response trend for 10 mg once daily and 25 mg once daily doses (Figure 4).

Add-on to basal insulin (1245.33): In add-on to basal insulin trial (Phase 2b, 1245.33), the adjusted mean differences versus placebo were -0.56% in the empagliflozin 10 mg group (97.5% CI: -0.78, -0.33) and -0.70% in the empagliflozin 25 mg group (97.5% CI: -0.93, -0.47) showing a dose response between the two doses for HbA1c reduction. For the key secondary endpoint of basal insulin dose, the adjusted mean differences from placebo at Week 78 were -6.66 IU in the empagliflozin 10 mg group (97.5% CI: -11.56, -1.77) and -5.92 IU in the empagliflozin 25 mg group (97.5% CI: -11.00, -0.85). At Week 18, among patients with a baseline HbA1c of 7.0% or greater, 18.0% of the patients in the empagliflozin 10 mg group and 19.5% of the patients in the empagliflozin 25 mg group had attained HbA1c values of less than 7.0% compared with 5.5% of patients in the placebo group.

Placebo adjusted Mean (95%CI) Change in HbA1c by Treatment at Week 12 in Phase 2/3 Trials (FAS-LOCF)

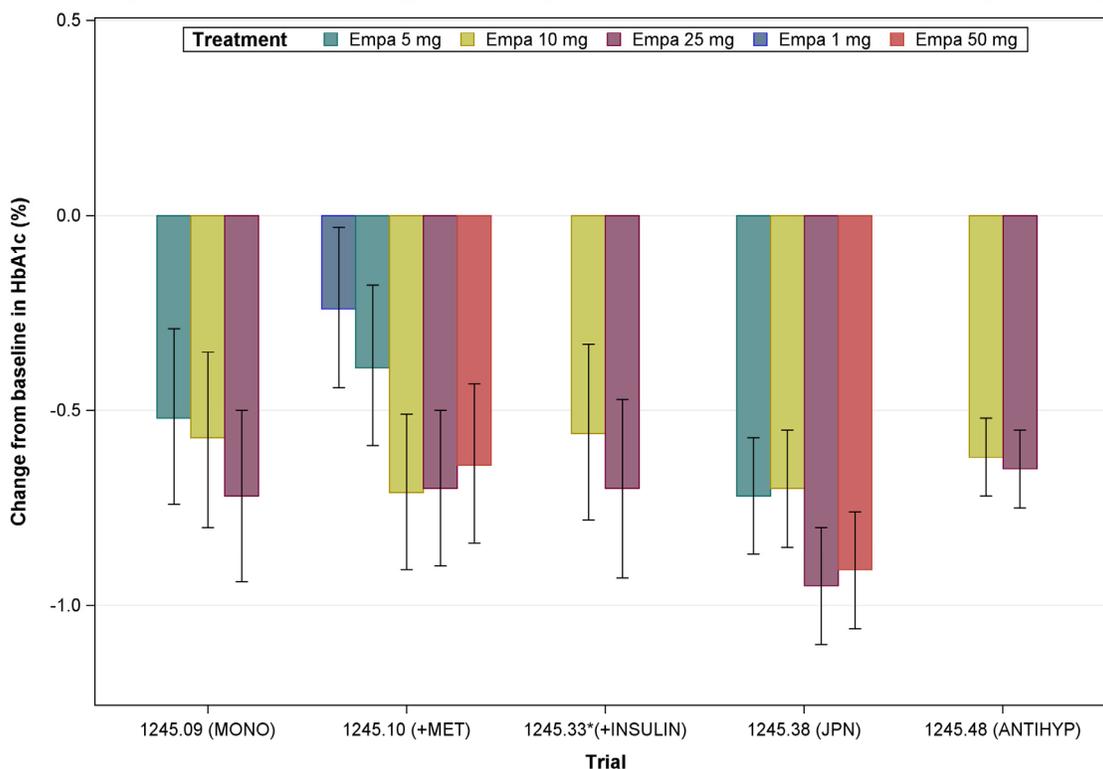


Table Shows Number of Patients by Treatment for Each Trial
*Week 18 end-point in Trial 1245.33

Figure 4: Placebo adjusted mean (95%CI) Changes from Baseline in HbA1c (%) at Primary Assessment Time-point-LOCF: Study-by-Study Comparison (Phase 2/3 Studies: Full Analysis Set)

1.1.2 Is there an impact of renal impairment on the efficacy of empagliflozin?

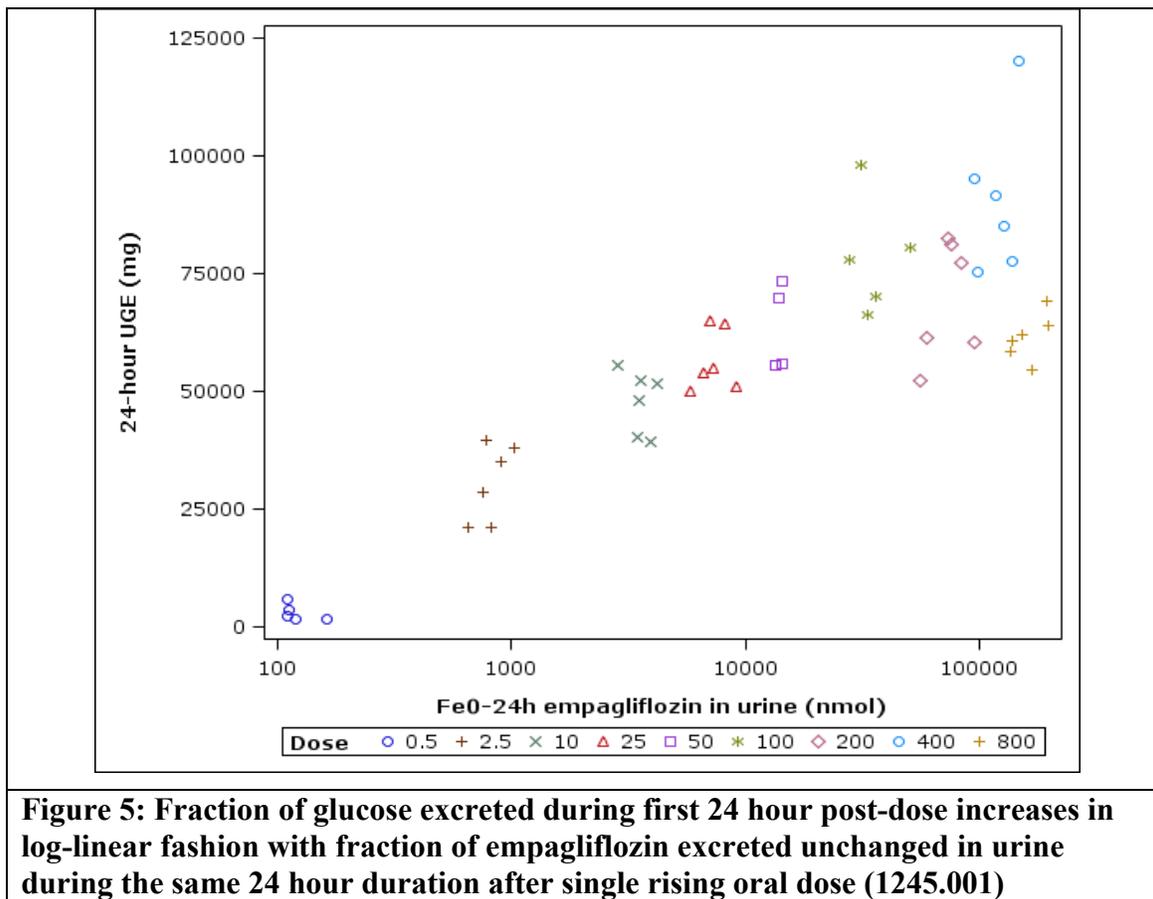
Yes, the evaluation of impact of renal function on empagliflozin demonstrates that:

- Consistent with the known mechanism of action of empagliflozin, there is a lower reduction in HbA1c levels with increasing degree of renal impairment in subjects with type 2 diabetes. The reduction in HbA1c from baseline in subjects with moderate renal impairment (1245.36) was of lower magnitude (approximately half) when compared to the magnitude observed in type 2 diabetic subjects majority with normal renal function or with mild renal impairment in trial 1245.20 or add-on therapy trials 1245.19 and 1245.23 (Figure 2).
- Even though the mean response is lower in type 2 diabetic subjects with mild renal impairment compared to those with normal renal function, efficacy of empagliflozin is preserved in these subjects for both 10 mg and 25 mg once daily doses.
- In subjects with moderate renal impairment only 25 mg dose was evaluated, limiting any dose-response assessment. However, decrease in HbA1c was observed following 24 weeks treatment with empagliflozin (Figure 7). When

evaluated based on baseline renal function, this response was found to be primarily driven by subjects with $eGFR \geq 45 \text{ mL/min/1.73m}^2$ (Figure 5). Based on absolute response, empagliflozin 25 mg once daily dose showed modest efficacy in patients with $eGFR 30$ to $<45 \text{ mL/min/1.73m}^2$ *per se*, and placebo adjusted response seems to be inflated by worsening of HbA1c response in the placebo group.

Mechanistic basis of lower efficacy in patients with impaired renal function:

Lower efficacy in patients with impaired renal function is consistent with the primary mechanism of action of empagliflozin [sodium glucose co-transporter 2 (SGLT2) inhibition in the proximal renal tubules], which is dependant on the functional capacity of the renal filtration. In kidneys, re-absorption of virtually all filtered glucose occurs primarily via SGLT2 and to a lesser extent via SGLT1. Inhibition of SGLT2 by empagliflozin in proximal renal tubules resulted in increased urinary glucose excretion from baseline, which was highly correlated to the fraction of unchanged empagliflozin excreted in urine (see Figure 5).



The decrease in this primary pharmacodynamics effect with increasing degree of renal impairment was evident in dedicated pharmacokinetic/pharmacodynamic study in renal impairment (see Figure 6).

Following administration of empagliflozin in subjects with reduced capacity of renal filtration, both fraction of empagliflozin excreted unchanged in urine and urinary glucose excretion (UGE) during first 24 hour post-dose declined based on the degree of renal impairment (Figure 4), as expected mechanistically. Although it is unclear if the glucose filtration and re-absorption cycle is intact and not affected by the degree of renal impairment, drug filtration was certainly dramatically reduced with increasing degree of renal impairment. Therefore, lower pharmacodynamic response could be an artifact of a combination of disturbed renal filtration/re-absorption cycle of glucose and reduced renal filtration of drug.

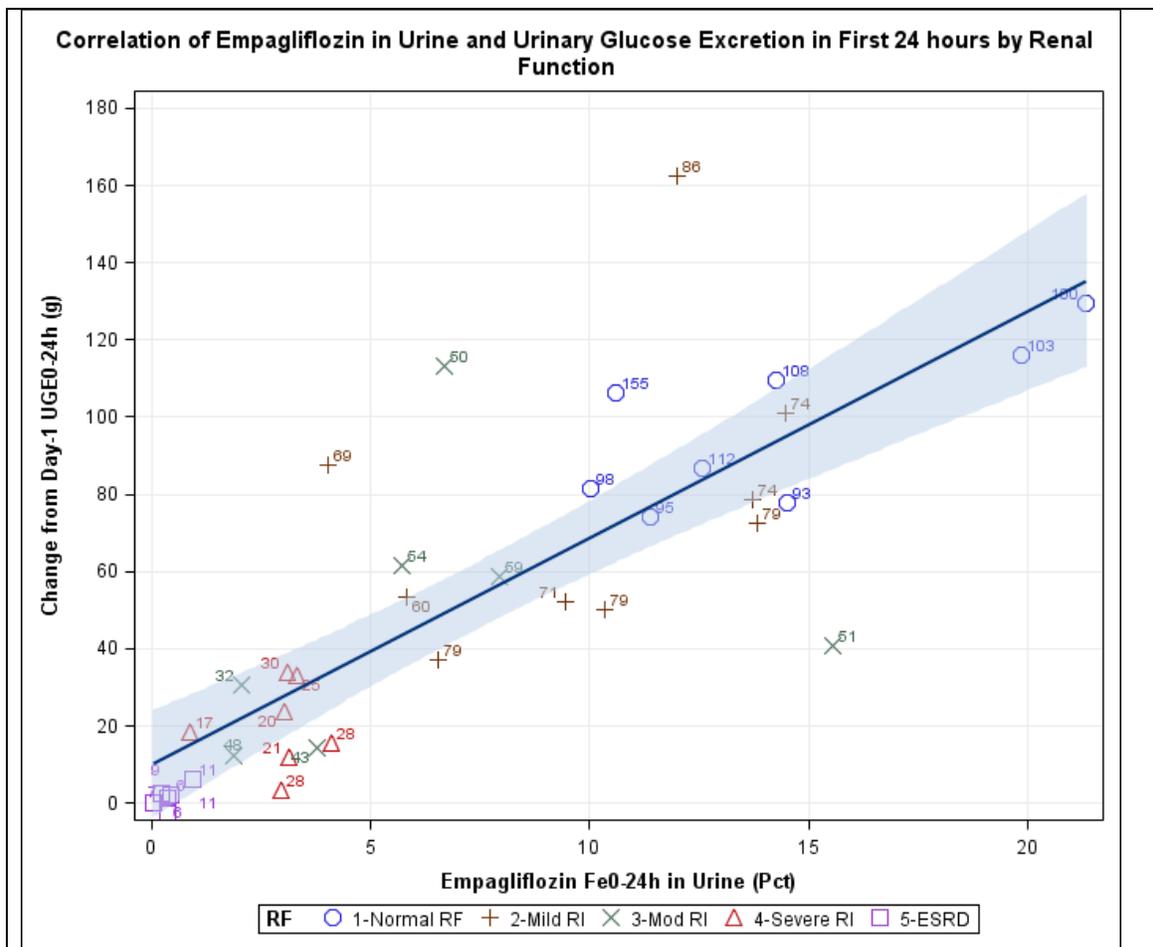


Figure 6: Urinary glucose excretion (UGE) changes from baseline (Day -1) during first 24 hour post-dose decreases in linear fashion with decreasing fraction of empagliflozin excreted unchanged in urine during the same 24 hour duration after single 50 mg oral dose in subjects with varying degrees of renal function (1245.012)

Observed clinical trial data indicating lower efficacy in moderate renal impairment:

The sponsor conducted a dedicated efficacy and safety evaluation (Trial 1245.36) in subjects with type 2 diabetes mellitus who had mild, moderate or severe renal impairment. Subjects on stable anti-hyperglycemic agent (AHA) therapy [including SUs, glinides, pioglitazone, insulin and their combinations, or other antidiabetics excluding

SGLT2 inhibitors] were randomly stratified by the baseline renal function category and assigned to Empagliflozin 10 mg once daily or 25 mg once daily or placebo treatment. Of the patients with mild or moderate renal impairment, more than half (61.1%) were taking metformin (as monotherapy or in combination with other antidiabetic drugs); most of these were in the group of patients with mild renal impairment (see below). Just over half of the patients (51.1%) were taking insulin as background medication.

The result of sponsor's pre-specified statistical analysis for efficacy in mild and moderate RI patients is shown in Table 1 below.

Table 1: Change in HbA1c is affected by baseline renal function and treatment in type 2 diabetes mellitus subjects with renal impairment (1245.36)

Trial Treatment group	N	Baseline HbA _{1c} mean (SE)	Change from baseline		Difference from placebo		
			Mean (SE)	Adjusted mean (SE)	Adjusted mean (SE)	95% CI	p-value
1245.36 mild renal impairment³							
Endpoint assessed after 24 weeks							
Placebo	95	8.09 (0.08)	0.04 (0.08)	0.06 (0.07)			
Empa 10 mg	98	8.02 (0.09)	-0.46 (0.07)	-0.46 (0.07)	-0.52 (0.10)	(-0.72, -0.32)	<0.0001
Empa 25 mg	97	7.96 (0.07)	-0.61 (0.07)	-0.63 (0.07)	-0.68 (0.10)	(-0.88, -0.49)	<0.0001
1245.36 moderate renal impairment³							
Endpoint assessed after 24 weeks							
Placebo	187	8.04 (0.06)	0.05 (0.05)	0.05 (0.05)			
Empa 25 mg	187	8.03 (0.06)	-0.37 (0.05)	-0.37 (0.05)	-0.42 (0.07)	(-0.56, -0.28)	<0.0001

³ Renal impairment was assessed by eGFR calculated with the MDRD formula: mild (eGFR of 60 to <90 mL/min/1.73 m²), moderate (eGFR of 30 to <60 mL/min/1.73 m²). ANCOVA model includes baseline HbA_{1c}, baseline background medication, and treatment.

Analysis to explore efficacy within patients with moderate renal impairment:

A post-hoc analysis was also conducted for trial 1245.36 (trial conducted in patients with renal impairment), evaluating efficacy by renal function subgroups: eGFR 60 to <90 (Mild RI), eGFR 45 to <60 (generally regarded as Moderate RI-A), eGFR 30 to <45 (generally regarded as Moderate RI-B), and eGFR<30 (Severe RI) mL/min/1.73m². Overall, the data demonstrate a trend for reduced efficacy with decrease in eGFR.

Figure 7 describes the mean (95%CI) change in HbA1c from baseline to week 24 across treatment groups (placebo, empagliflozin 10 mg and 25 mg). Overall, in patients with mild renal impairment a trend of modest, dose-dependant decrease in HbA1c is observed following 24 weeks treatment with empagliflozin. In moderate RI, however, this trend is primarily driven by changes in HbA1c from baseline in subjects with eGFR 45 to <60 mL/min/1.73 m² [Adjusted mean (SE) HbA1c change from baseline of -0.54 (0.07) for empagliflozin and -0.08 (0.07) for placebo].

Based on absolute response, empagliflozin showed modest efficacy in patients with eGFR 30 to <45 mL/min/1.73 m² *per se* [absolute mean (SE) change from baseline in HbA1c of -0.21 (0.07)]. However, placebo adjusted response for empagliflozin 25 mg once daily dose (Mean reduction in HbA1c of -0.39% unit) seems to be inflated by worsening of HbA1c response in placebo group [absolute mean (SE) change from baseline in HbA1c of 0.17 (0.07)] in eGFR 30 to < 45 ml/min/1.73 m² subgroup. At week 24, magnitude of change in HbA1c from baseline in subjects with eGFR < 30 mL/min/1.73m² appears similar between placebo and treatment groups.

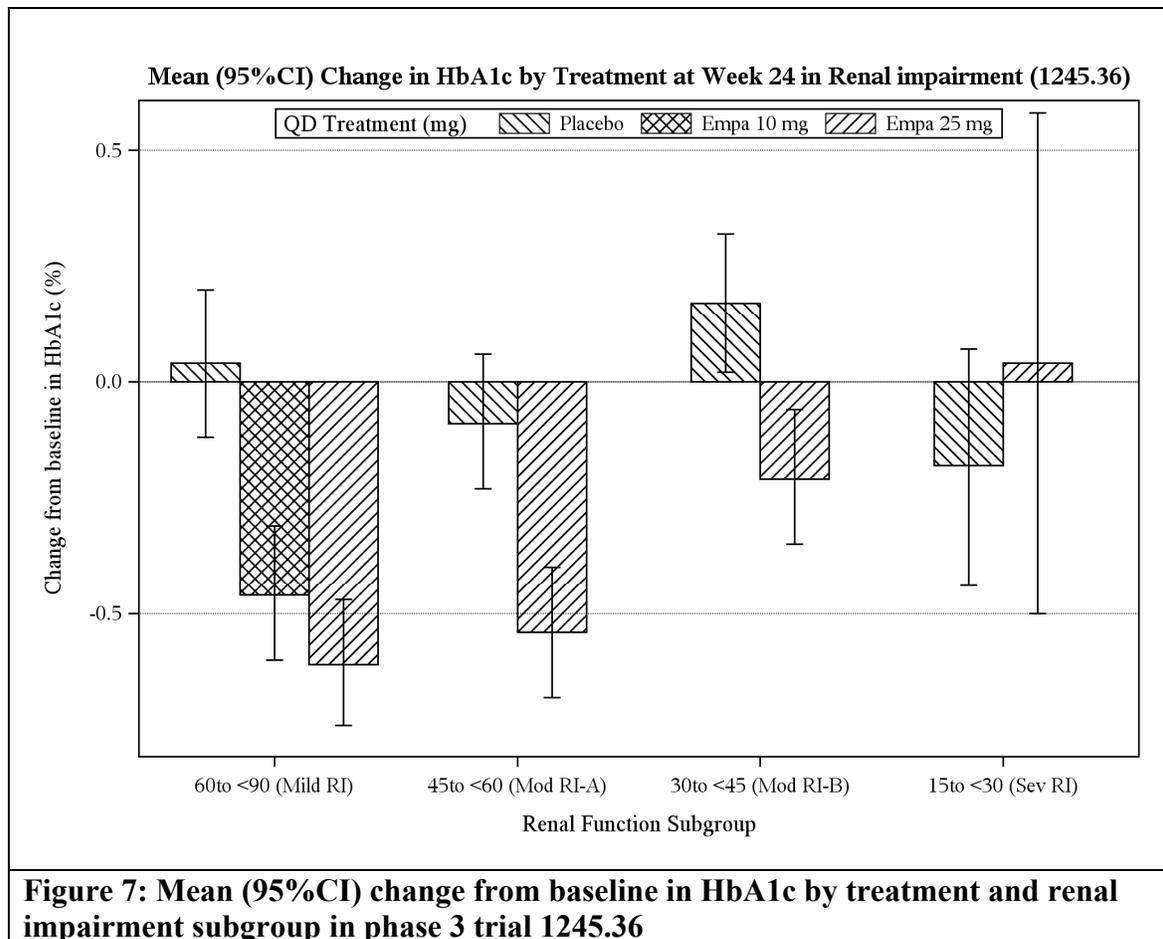


Figure 7: Mean (95%CI) change from baseline in HbA1c by treatment and renal impairment subgroup in phase 3 trial 1245.36

Proportion of subjects, who achieved target HbA1c levels of <7.0% by Week 24, was higher for the 25 mg once daily dose group (24.2%) compared to the 10 mg once daily dose group (17.0%) versus that observed with placebo (6.7%) among patients with mild RI. In moderate RI patients, this proportion was 12% for 25 mg once daily dose group versus 7.9% in placebo. Empagliflozin was not efficacious in patients with severe RI.

1.1.3 What are the dose-safety characteristics of Empagliflozin for relevant safety outcomes?

Dose-safety analysis revealed that:

- Empagliflozin causes only modest decreases in eGFR from baseline in a dose-dependent manner. On average, the decline in eGFR appeared to regress over time towards baseline.
- In all empagliflozin treated subjects, the adverse event profile of 10 mg once daily and 25 mg once daily dose was similar except for hypoglycemia incidences being higher with 25 mg once daily dose.
- Elderly population (> 65 year age) and patients with moderate renal impairment showed higher susceptibility for hypoglycemia, volume depletion, and urinary tract infection AEs for both doses.

Empagliflozin Impact on Renal Function:

Empagliflozin lowered the eGFR from baseline in both, dose and baseline renal function dependent manner. Effect of empagliflozin on renal function was evaluated based on longitudinal change from baseline in eGFR, and by evaluating the reduction in eGFR as a function of baseline renal function.

a. Longitudinal Change in eGFR following Treatment with Empagliflozin

Figure 7 shows the longitudinal change from baseline in eGFR by treatment for placebo controlled monotherapy trial 1245.20 wherein, most of the patients were with normal renal function or mild renal impairment.

The first observation was collected at week 12 and then at end-point week 24. The eGFR values did not show any trend for decline from baseline over 24 week assessment.

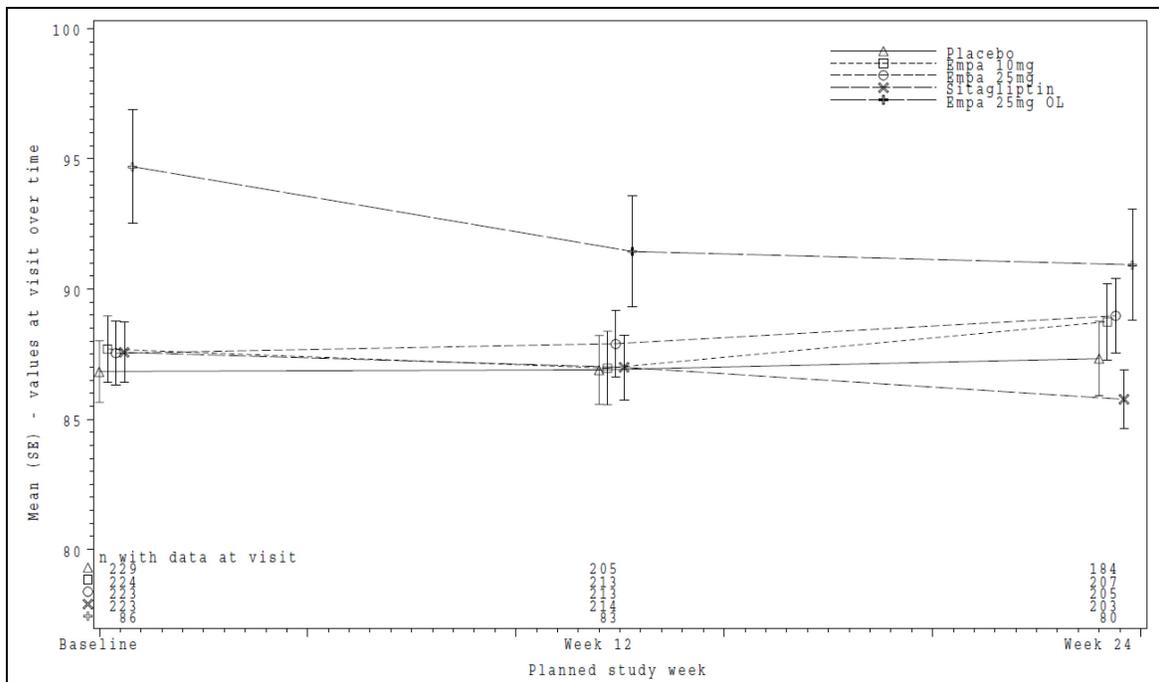


Figure 8: Mean (SE) eGFR (mL/min/1.73m²) over time (Phase 3 Placebo-Controlled Monotherapy Trial (1245.20))

The impact of empagliflozin on longitudinal change in renal function was also evaluated in two specific populations: hypertensive population in Trial 1245.48 and subjects with moderate renal impairment in Trial 1245.36 (already compromised renal function).

Figure 8 shows the longitudinal change from baseline in eGFR by treatment for type 2 diabetic subjects who have hypertension. This was perhaps the only trial that included a week 6 assessment for eGFR. On average, the eGFR decrease from baseline was maximal [Mean (SD) decline in eGFR of -0.07 (8.94), -1.52 (9.17), and -3.90 (9.65) mL/min/1.73m², respectively for placebo, 10 mg and 25 mg dose of empagliflozin] at the first observation of week 6 after initiation of the treatment. The eGFR values regressed towards baseline by Week 12.

Figure 9 shows the longitudinal change from baseline in eGFR by treatment for type 2 diabetic subjects who have renal impairment. On average, the eGFR decrease from baseline was maximal at the first observation of week 12 after initiation of the treatment. The eGFR values regressed towards baseline by Week 12 for some groups but not all in this trial.

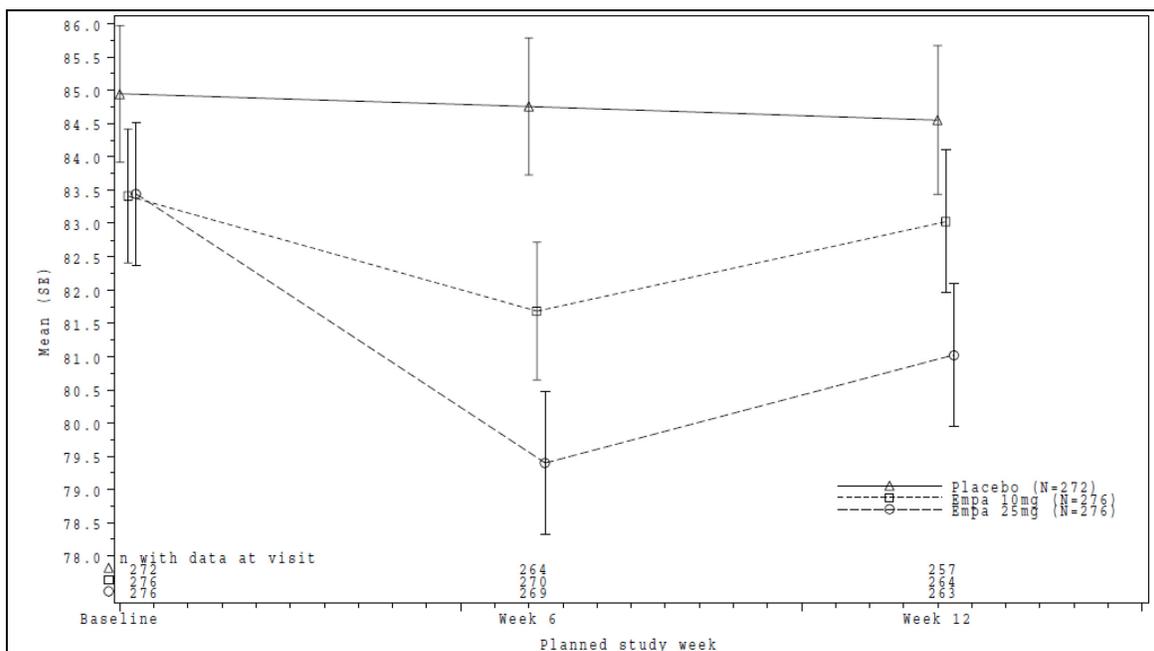


Figure 9: Empagliflozin reduces eGFR from baseline in type 2 diabetic subjects with Hypertension (Trial – 1245.48).

Figure 10, 11, 12, and 13 show the individual change from baseline in eGFR by treatment at week 12 (first assessment after initiation of treatment) for type 2 diabetic subjects with mild, moderate (A), moderate (B), or severe renal impairment, respectively (trial 1245.36). Overall in comparison to placebo, the magnitude of eGFR decrease from baseline was higher for both doses and more number of patients had decline in eGFR with empagliflozin treatment, although, dose dependence for the eGFR change was not evident in this subgroup.

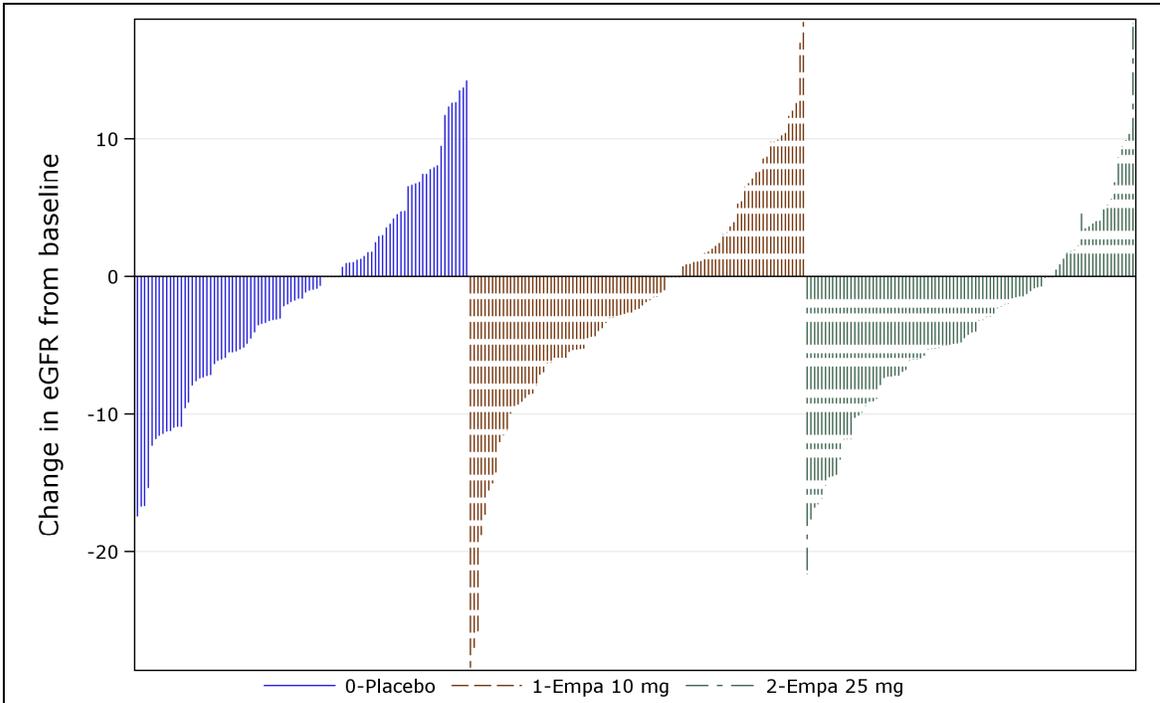


Figure 10: Empagliflozin reduces eGFR from baseline in type 2 diabetic subjects with mild renal impairment (Week 12, Trial 1245.36)

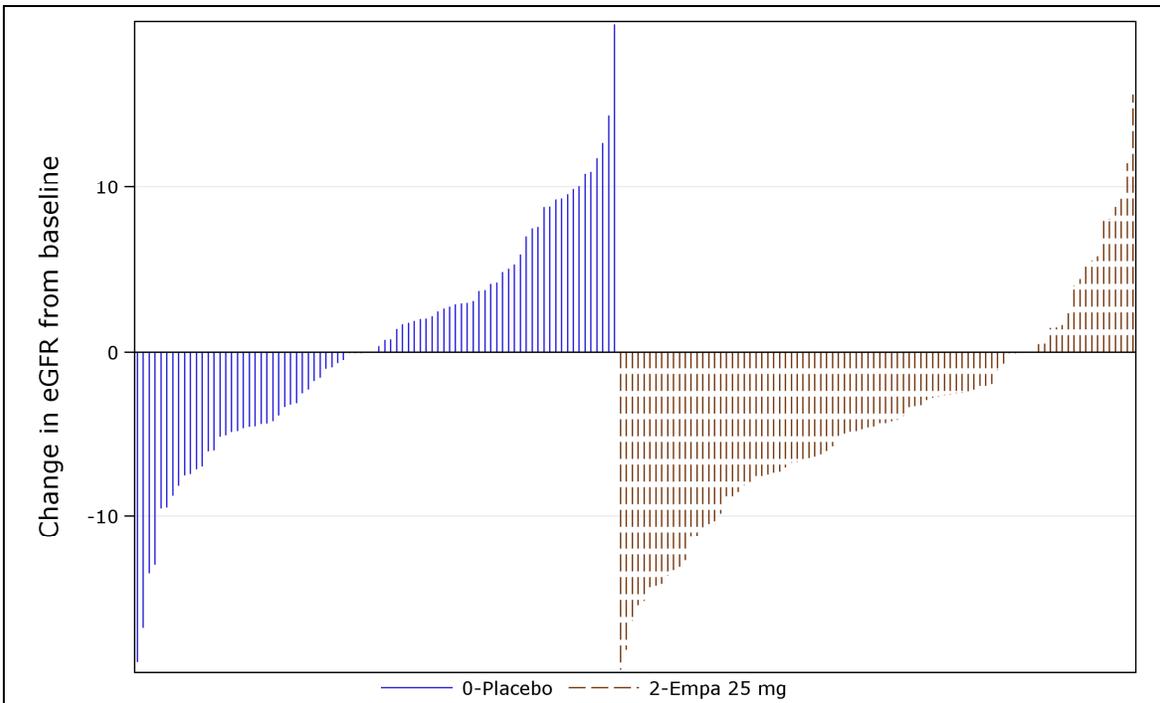


Figure 11: Empagliflozin reduces eGFR from baseline in type 2 diabetic subjects with Moderate Renal Impairment A (eGFR45-<60) (Week 12, Trial 1245.36)

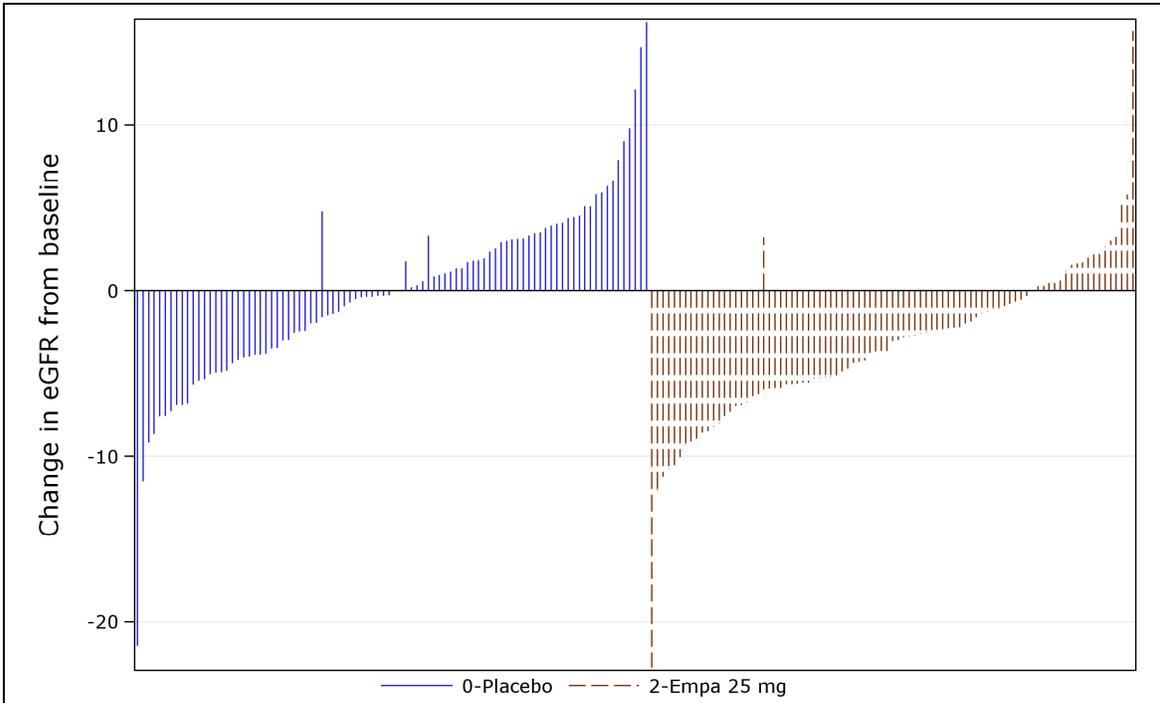


Figure 12: Empagliflozin reduces eGFR from baseline in type 2 diabetic subjects with Moderate Renal Impairment B (eGFR30-<45) (Week 12, Trial 1245.36)

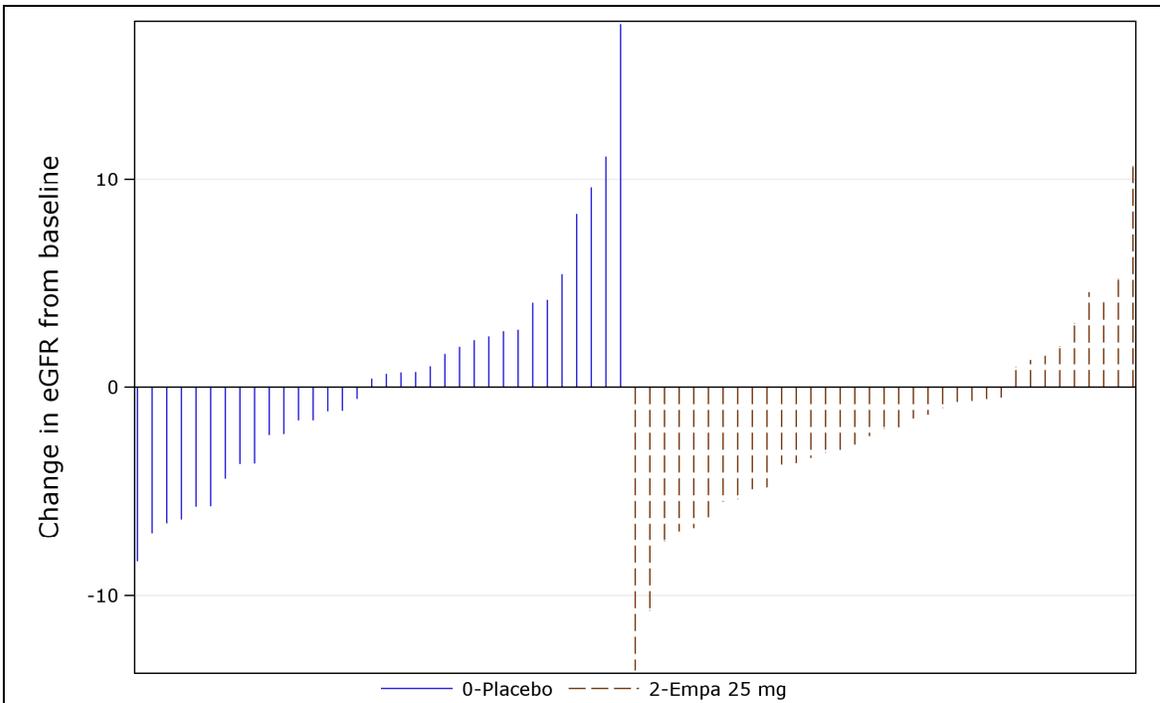


Figure 13: Empagliflozin reduces eGFR from baseline in type 2 diabetic subjects with severe renal impairment (Week 12, Trial 1245.36)

Patients with Adverse Events

Dose safety of empagliflozin was evaluated with respect to proportion of subjects with adverse events versus treatments.

The pooling strategy adopted by the sponsor is summarized in the Figure 14 below. This review focused on the SAF-5 datasets, which contained all type 2 diabetes patients in the clinical program.

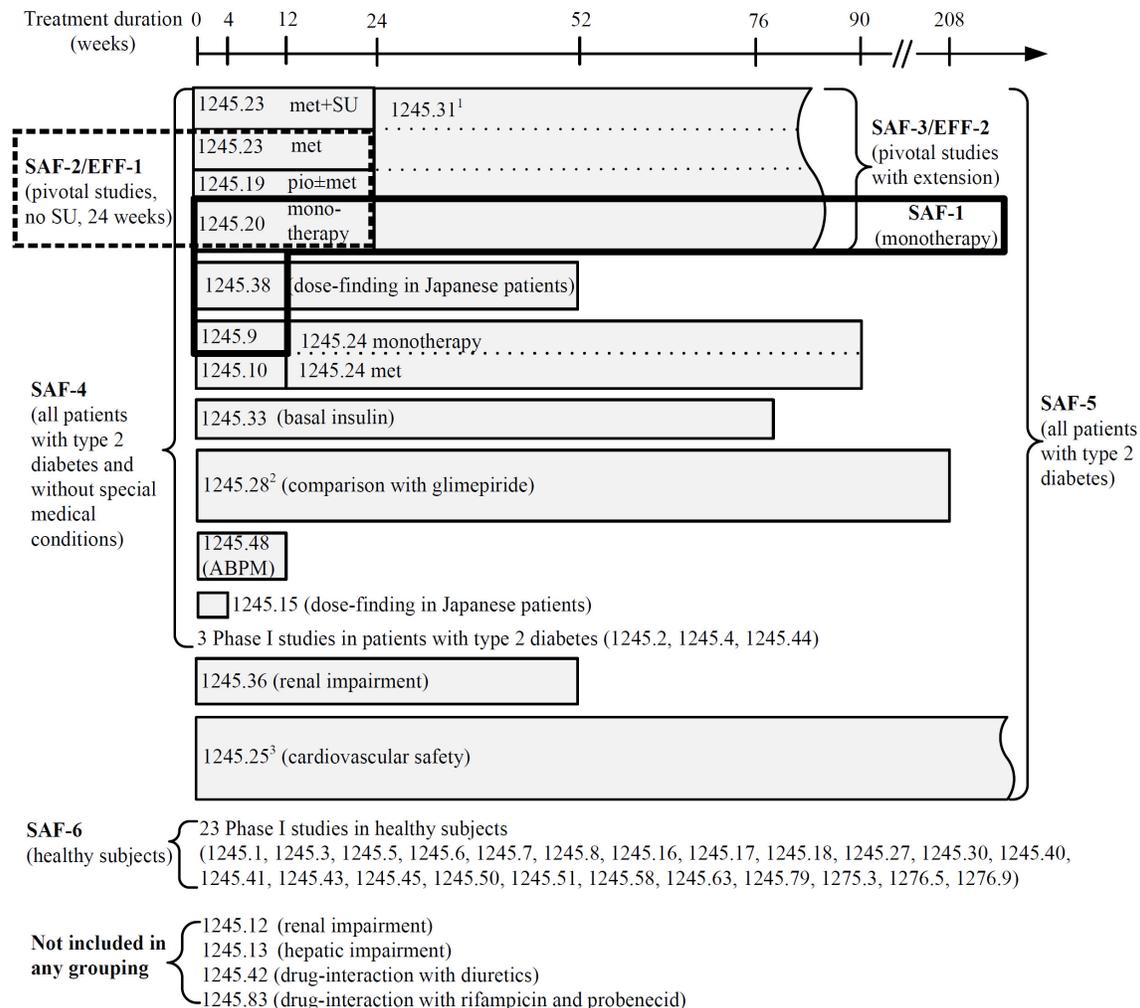


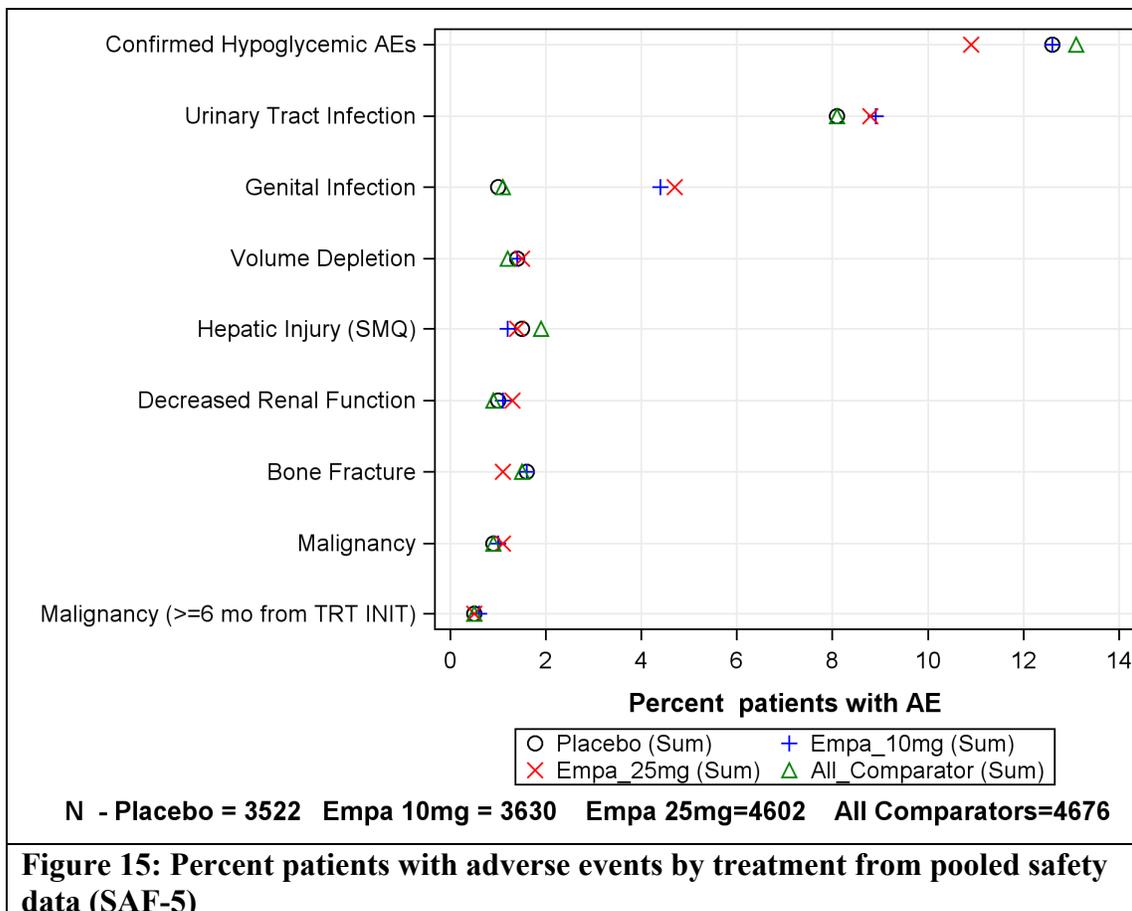
Figure 14: Pooling strategy for safety assessment

Overall safety assessment showed the following (see Figure 15):

- There was no dose-dependent trend for AEs related to decreased renal function, hepatic injury, bone fracture, volume depletion and malignancy, and the proportion of patients (%) with these AEs were similar to placebo (Table 2).
- Analyses of urinary tract infection using a pre-specified customized MedDRA query showed similar frequencies for all groups (8.9% for empagliflozin 10 mg, 8.8% for empagliflozin 25 mg, and 8.1% for placebo). However, the frequencies of patients with urinary tract infections were higher with empagliflozin treatment

than with placebo for patients older than 64 years (age between 65 and 74 years: 8.9% for empagliflozin 10 mg, 10.7% for empagliflozin 25 mg, and 7.5% for placebo; age 75 years and above: 15.7% for empagliflozin 10 mg, 15.1% for empagliflozin 25 mg, and 10.5% for placebo).

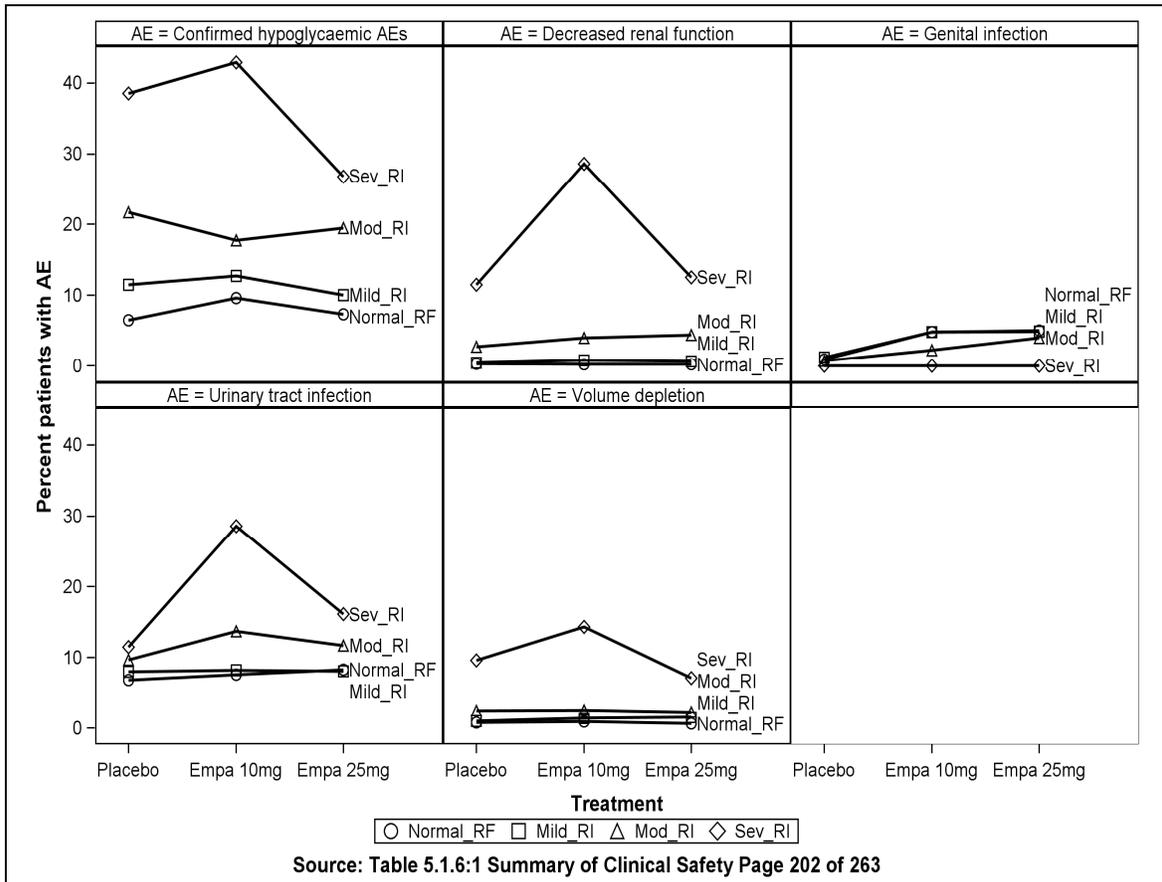
- Analyses of genital infection showed that the frequencies were higher in the empagliflozin groups (4.4% for 10 mg and 4.7% for 25 mg) than in the placebo group (1.0%). However, almost all events were mild or moderate in intensity; genital infections of severe intensity were only reported for 1 patient in the empagliflozin 10 mg (0.03%), 2 patients in the empagliflozin 25 mg (0.04%), and 1 patient in the placebo group (0.03%). The frequency of premature discontinuations of empagliflozin due to genital infection was very low (0.4% for 10 mg and 0.3% for 25 mg; 0.03% for placebo). Genital infection was identified as a side effect of empagliflozin.



- Treatment with empagliflozin did not increase the frequency of patients with confirmed hypoglycaemic adverse events (plasma glucose of 70 mg/dL or below or requiring assistance of another person). Only if patients received metformin plus a sulphonylurea background therapy was the frequency of patients with confirmed hypoglycemic adverse events higher with empagliflozin (16.1% for 10 mg and 11.5% for 25 mg) than with placebo (8.4%). Additionally, if patients received a fixed dose of

basal insulin, the frequency of patients with confirmed hypoglycemic adverse events was higher with empagliflozin 25 mg (28.4%) than with empagliflozin 10 mg (19.5%) or placebo (20.6%); no differences among the groups were seen when the dose of basal insulin could be adjusted. In an active-controlled study, there was a statistically significantly lower frequency of confirmed hypoglycemic adverse events with empagliflozin 25 mg treatment (1.6%) than with glimepiride (20.4%).

- The subgroup analyses by renal function did not show a different trend of dose-dependence for AEs as seen for the overall safety analysis. Although, increase in susceptibility for some AEs (such as decrease in renal function, urinary tract infection, bone fractures, volume depletion, and hypoglycemia) with increase in degree of RI was seen in all treatment groups (Figure 16).



Source: Table 5.1.6:1 Summary of Clinical Safety Page 202 of 263

Figure 16: Percent patients with adverse events by treatment from pooled safety data (SAF-5)

1.1.4 Does the dose-response relationship for effectiveness and safety support the proposed doses in type 2 diabetes patients with normal renal function, mild renal impairment, and with moderate renal impairment?

- Dosing in type 2 diabetic patients with normal renal function ($eGFR \geq 90$ mL/min/1.73 m²) and mild renal impairment ($90 > eGFR \geq 60$ mL/min/1.73 m²):

- Benefit in Patients with normal renal function:

There is lack of evidence of clear dose-response when data from monotherapy and add on therapy trials was examined. From efficacy perspective, the dose-response data suggests that the use of 25 mg once daily dose of empagliflozin does not always produce numerically higher reduction in HbA1c than 10 mg once daily, which does not support the sponsor's original proposal of 25 mg once daily dose. However, in some specific treatment settings, such as when administered as monotherapy, as add-on therapy to patients on pioglitazone with or without metformin or as add on to insulin, 25 mg once daily dose offers an additional HbA1c reduction of up to 0.14% units. In addition, there was a dose-dependent increase in proportion of patients who achieved <7% HbA1c by the time of primary end-point measurement. Therefore, there is merit in having both doses available for use. Placebo adjusted mean reductions in HbA1c (% units) for monotherapy/dual therapy/triple therapy Phase 3 trials ranged from -0.48 to -0.74 % units and -0.59 to -0.85 % units for 10 mg once daily and 25 mg once daily dose, respectively. Notably, most of the diabetic patients need combination therapies in order to get an optimal glycemic control and empagliflozin is also likely to be used in background of metformin or other antidiabetic therapies. The combination therapy trials that sponsor conducted for empagliflozin showed a modest incremental benefit (up to 0.14% unit additional reductions in HbA1c) of using 25 mg once daily as compared to the 10 mg once daily. Even with lower mean response in comparison to subjects with normal renal function, efficacy of empagliflozin was preserved in type 2 diabetes mellitus subjects with mild renal impairment with both 10 mg once daily and 25 mg doses.

- Risk:

There are slight dose-dependent changes in eGFR, whereas both doses were essentially similar in their adverse event profiles.

- Conclusion:

Given dose related benefit present in select treatment settings along with no increased risk of adverse events for 25 mg once daily dose, compared to the 10 mg once daily dose, approval of both 10 mg and 25 mg once daily doses is recommended. The recommended dose for empagliflozin is 10 mg once daily, which can be increased to 25 mg once daily. Although, it has not been established if 25 mg once daily dose provides additional benefit in patients who show less than optimal response at 10 mg once daily dose, there is a general trend for greater benefit with 25 mg once daily dose in select treatment settings. Therefore, some patients may benefit from 25 mg once daily dose and for some patients, a lower dose of 10 mg once daily may be

sufficient. We recommend that dose increases above 10 mg once daily should be made only after clinical reassessment including assessment of tolerability. When dose increase is indicated, the maximum recommended dose is 25 mg once daily.

▪ Dosing in type 2 diabetic patients with moderate renal impairment ($60 > eGFR \geq 30$ mL/min/1.73 m²):

○ Benefit in Patients with moderate renal impairment:

Consistent with the known dependence of empagliflozin mechanism of action on integrity of the renal function, the 25 mg once daily dose showed only a modest efficacy in subjects with moderate renal impairment (Figure 5 1245.36 results) when compared to type 2 diabetes mellitus subjects with normal renal function or mild renal impairment. The magnitude of response is markedly attenuated in the presence of moderate renal impairment. Further, reduction in HbA1c (week 24 end-point) from baseline are dependent on dose and baseline eGFR in patients with RI (1245.36).

The post-hoc evaluation of the data from Trial 1245.36, evaluating efficacy in moderate RI subgroups using an eGFR cut-off of 45 mL/min/1.73m², demonstrated that the efficacy in patients with moderate renal impairment was primarily driven by the subjects with baseline eGFR ≥ 45 mL/min/1.73m² where, HbA1c reduction with 25 mg once daily empagliflozin dose [-0.54 (0.07)] was well separated from placebo [(-0.08 (0.07))].

○ Risk:

There was a trend for decrease in eGFR in patients with moderate renal impairment following treatment with empagliflozin. In addition, the susceptibility to several adverse events was notably increased with worsening degree of renal impairment.

○ Conclusion:

Empagliflozin efficacy was preserved in patients with eGFR 45 to <60 mL/min/1.73m² with the 25 mg once daily dose, though attenuated in comparison to that observed in patients with normal renal function. Based on absolute response, empagliflozin 25 mg once daily dose showed modest efficacy in patients with eGFR 30 to <45 mL/min/1.73m² *per se*, and placebo adjusted response seems to be inflated by worsening of HbA1c response in the placebo group. A further reduced response can be anticipated for the 10 mg once daily dose in this subgroup. In addition, it is not certain what factors were responsible for the trend of worsening placebo response in eGFR 30 to <45 mL/min/1.73m² subgroup. Also note that similar post-hoc analysis for two other SGLT-2 inhibitors (canagliflozin and dapagliflozin) showed that HbA1c response for patients with eGFR 30 to <45 mL/min/1.73m² didn't worsen on placebo treatment. Further, there was increase in susceptibility for adverse events such as hypoglycemia, decreased renal function, urinary tract infection, genital infection with increase in degree of renal impairment. Between eGFR 45 to <60 mL/min/1.73m² (generally regarded as Moderate RI-A) and eGFR 30 to <45 mL/min/1.73m² (generally regarded as Moderate

RI-B), the latter group is likely to experience more adverse events because these patients have relatively poor renal function and further, eGFR changes could bring them closer to severe renal impairment group. Patients with severe renal impairment appeared to be more susceptible to adverse events, such as confirmed hypoglycemia and volume depletion, even on placebo treatment, compared to mild/moderate renal impairment. Therefore, given the lack of certainty in efficacy and higher susceptibility towards adverse events, the benefit-risk does not seem to favor the use of empagliflozin in patients with eGFR 30 to <45 mL/min/1.73m². Therefore, we recommend that among patients with moderate renal impairment empagliflozin should be used in patients with eGFR 45 to <60 mL/min/1.73m² and according to the dosage regimen recommended for patients with normal renal function or mild renal impairment. Empagliflozin should not be used in patients with eGFR 30 to <45 mL/min/1.73m².

▪ Type 2 diabetes mellitus patients, eGFR <30 mL/min/1.73m² (Severe Renal Impairment and End-stage Renal Disease):

○ Benefit:

For patients with eGFR < 30 mL/min/1.73m² empagliflozin 25 mg did not show any efficacy.

○ Risk:

There was a trend for decrease in eGFR and higher susceptibility for adverse events in patients with severe renal impairment following treatment with empagliflozin.

○ Conclusion:

Empagliflozin should not be used in patients with eGFR < 30 mL/min/1.73m².

1.2 Recommendations

Division of Pharmacometrics finds the NDA 204629 acceptable from a clinical pharmacology perspective and recommends approval. Please refer to section 1.1 of the clinical pharmacology QBR for OCP recommendations.

1.3 Labeling Recommendations

The following are the labeling recommendations relevant to clinical pharmacology for NDA 204629 that were based on population PK analysis. 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.

Highlights of Prescribing Information

(b) (4)

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosing

The recommended (b) (4) dose of (b) (4) JARDIANCE is 10 mg once (b) (4)

which can be increased to 25 mg once daily. The recommended dose for empagliflozin is 10 mg once daily, which can be increased to 25 mg once daily. 25 mg once daily dose provides additional benefit only in select settings (see Section 14, Clinical Trials); therefore, not all patients may get additional benefit by increasing the dose to 25 mg once daily dose. Patient tolerability should also be considered while increasing the dose to 25 mg once daily.

(b) (4)

(b) (4)

2.3 Renal Impairment

(b) (4)

].

8.6 Renal Impairment

(b) (4)

8.7 Hepatic Impairment

TRADENAME may be used in patients with (b) (4) hepatic impairment [see (b) (4) Clinical Pharmacology (12.3)].

12.3 Pharmacokinetics

Specific Populations

Renal Impairment

In patients with mild (eGFR: 60 - <90 mL/min/1.73 m²), moderate (eGFR: 30 - <60 mL/min/1.73 m²), severe (eGFR: <30 mL/min/1.73 m²) 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. (b) (4) population pharmacokinetic analysis showed that the apparent oral clearance of empagliflozin decreased with a decrease in eGFR leading to an increase in drug exposure (b) (4)

Effects of Age, Body Mass Index, Gender, and Race

Based on the population PK analysis with data collected from 1526 subjects, age, BMI, gender and race (Asians versus primarily Whites) do not have a clinically meaningful effect on pharmacokinetics of empagliflozin [see Dosage and Administration (2); Warnings and Precautions (5.2); Adverse Reactions (6.1); Specific Populations (8.5)].

(b) (4)

Reviewer's comments:

- *Proposed labeling claim by the Sponsor that “there is no clinically meaningful effect of age, BMI, gender and Race (Asians versus primarily Whites) on empagliflozin pharmacokinetics” is acceptable. However, the information on covariate effects is combined to keep the label concise.*

2 RESULTS OF SPONSOR'S ANALYSIS

Text in Sections 2.1 and 2.2 below is copied from the Sponsor's Population PKPD Analysis reports except the reviewer's comments.

2.1 Population PK and PKPD Analyses

According to the sponsor's population PK and population PKPD analysis reports, a preliminary population pharmacokinetic model was developed for empagliflozin using data from Phase 1 studies 1245.1, 1245.2, 1245.4, and 1245.5. This model was later adopted for obtaining the final population pharmacokinetic and pharmacokinetic-

pharmacodynamic model for empagliflozin. The data used in the final analysis for empagliflozin population PKPD included pooled data from six Phase 1/2 studies (i.e., 1245.2, 1245.4, 1245.9, 1245.10, 1245.15, and 1245.33), two Phase 2 studies (i.e., DIA2001, OBE2001) and four Phase 3 studies (i.e., 1245.19, 1245.20, 1245.23, 1245.36). Primary objective of the population PKPD analysis was to:

- To describe the population PK of empagliflozin.
- To describe the PK-PD (exposure-response) efficacy relationships of empagliflozin with fasting plasma glucose (FPG) and glycosylated hemoglobin (HbA1c).
- To evaluate the exposure-response relationships of empagliflozin with pre-selected adverse/tolerability events and with changes from baseline in MDRD estimated glomerular filtration rate in mL/min/1.73m² (eGFR).
- To quantify population PK and PD parameters for this system, including typical values and random interindividual and residual variabilities.
- To identify any individual-specific covariate factors (e.g., demographics, disease state, etc.) that are predictive of the unexplained random variability (PK and exposure-response).
- To provide modeling and simulation support of dosing recommendations, if treatment adjustments are necessary for specific subpopulations.

2.1.1 Methods

The empagliflozin PK data set was comprised of 2761 patients contributing a total of 12503 empagliflozin concentrations, dosing and covariate data. Orally-administered, active empagliflozin doses ranged from 1 to 100 mg, with 1129 patients (40.9%) receiving 10 mg empagliflozin and 1269 patients (46.0%) receiving 25 mg empagliflozin doses. Patients receiving placebo treatment were not included in the PK analysis.

Population pharmacokinetic (PK) and pharmacodynamic (PD) efficacy (FPG and HbA1c) data, including concentration observations, dosing histories, event times, and covariate factors (e.g., age, height, body mass index (BMI), sex, and race) were assembled and formatted for analysis. All listed studies contributed PK and FPG data; HbA1c data were contributed from studies 1245.9 (U10-2261), .10 (U10-3573), .19 (U12-1516), .20 (U12-1517), .23 (U12-1518), .33 (U12-3817), and .36 (U12-1522).

Population PK and efficacy PK-PD analyses for repeated-measures endpoints were conducted via nonlinear mixed-effects modeling with a qualified installation of the nonlinear mixed effects modeling (NONMEM®) software, Version 7.2 (ICON Development Solutions, Hanover, MD). NMQual 8.1.5 or greater was used to track all code patches/options and install the NONMEM software. The first-order conditional estimation method with η - ϵ interaction (FOCEI) was employed for all PK and PK-PD model runs.

A covariate modeling approach emphasizing parameter estimation rather than stepwise hypothesis testing was implemented for the population PK and PK-PD analyses. For each, predefined covariate parameter relationships were first identified based on scientific interest and mechanistic plausibility, or prior knowledge, and a full model was constructed with care to avoid correlation or collinearity in predictors. Model parameters were estimated and assessment of any remaining trends was conducted by graphical

inspection of all covariate effects. Inferences about clinical relevance of parameters were based on the resulting parameter estimates of the full model and measures of estimation precision. Individual PK parameters were also estimated, and the derived parameter AUC_{ss} was calculated. A predictive check model evaluation step was performed to assess the performance of the final model and parameters.

Safety/tolerability data from all studies but 1245.2 (U09-1271), 1245.4 (U09-1970), and 1245.15 (U10-2326) were included as dichotomous endpoints for logistic regression analysis as a function of empagliflozin exposure (area under the concentration-time curve for a dosing interval at steady-state (AUC_{ss})) and other potentially explanatory covariates. Safety endpoints included urinary tract infection (UTI), confirmed hypoglycemic event (HYPO), and genital infection (GBV).

2.1.2 Final Model

The PK data were described by a two-compartment model with first-order absorption. Since no reference intravenous data were available, the absolute oral bioavailability (F) of empagliflozin was not identifiable and this model was parameterized in terms of CL/F, apparent (oral) central volume of distribution in L (V₂/F), apparent (oral) intercompartmental clearance in L/hr (Q/F), apparent (oral) peripheral volume of distribution in L (V₃/F), and a first-order absorption rate-constant absorption rate constant in 1/hr (k_a). Apparent (oral) steady-state volume of distribution in L (V_{SS}/F) was derived from V₂/F and V₃/F. An oral absorption lag time was fixed to 0.5 hr based on previous empagliflozin population PK modeling work (U12-2524). Inter-individual random-effect distributions were modeled for CL/F, V₃/F, and k_a using exponential variance models, with a covariance term between CL/F and V₃/F, while residual random effects were described with a proportional model.

The final model was an adaptation of the population PK model described in the Preliminary POPPK report U12-2524:

$$\begin{aligned} \frac{CL}{F_i} &= \theta_1 \cdot \left(\frac{WT_i(\text{kg})}{70(\text{kg})} \right)^{0.75} \cdot \left(\frac{AGE_i(\text{years})}{50(\text{years})} \right)^{\theta_7} \cdot (\theta_8)^{\text{SMOK}_i[=1]} \cdot (\theta_9)^{\text{SMOK}_i[=2]} \\ &\quad \cdot (\theta_{10})^{\text{ALC}_i[=1]} \cdot (\theta_{11})^{\text{RACE}_i[\text{ASIAN}]} \cdot \left(\frac{\text{TPRO}_i(\text{g/dL})}{6.8(\text{g/dL})} \right)^{\theta_{12}} \cdot \left(\frac{0.8(\text{mg/dL})}{\text{SCR}_i(\text{mg/dL})} \right)^{\theta_{13}} \cdot \exp^{\eta_{(\frac{CL}{F})},i} \\ \frac{V_2}{F_i} &= \theta_2 \cdot \left(\frac{WT_i(\text{kg})}{70(\text{kg})} \right) \cdot \left(\frac{AGE_i(\text{years})}{50(\text{years})} \right)^{\theta_{14}} \cdot (\theta_{15})^{\text{RACE}_i[\text{ASIAN}]} \cdot \left(\frac{\text{TPRO}_i(\text{g/dL})}{6.8(\text{g/dL})} \right)^{\theta_{16}} \cdot \exp^{\eta_{(\frac{V_2}{F})},i} \\ \frac{V_3}{F_i} &= \theta_4 \cdot \left(\frac{WT_i(\text{kg})}{70(\text{kg})} \right) \cdot \left(\frac{AGE_i(\text{years})}{50(\text{years})} \right)^{\theta_{17}} \cdot (\theta_{18})^{\text{RACE}_i[\text{ASIAN}]} \cdot \left(\frac{\text{TPRO}_i(\text{g/dL})}{6.8(\text{g/dL})} \right)^{\theta_{19}} \cdot \exp^{\eta_{(\frac{V_3}{F})},i} \\ \frac{Q}{F_i} &= \theta_3 \cdot \left(\frac{WT_i(\text{kg})}{70(\text{kg})} \right)^{0.75} \cdot \exp^{\eta_{(\frac{Q}{F})},i} \\ k_{a,i} &= \theta_5 \cdot (\theta_{20})^{\text{RACE}_i[\text{ASIAN}]} \cdot \exp^{\eta_{k_a,i}} \\ \text{AMRT}_i &= \theta_6 \cdot (\theta_{21})^{\text{RACE}_i[\text{ASIAN}]} \cdot \exp^{\eta_{\text{AMRT},i}} \\ F1_i &= 1 \cdot (\theta_{22})^{\text{Study}_i[1245.1]} \cdot (\theta_{23})^{\text{Dose}_i[400\text{mg}]} \cdot (\theta_{24})^{\text{Dose}_i[800\text{mg}]} \end{aligned}$$

Final Population PK Model:

$$\begin{aligned} \frac{CL}{F_i} = & \theta 1 \cdot \left(\frac{BMI_i(\text{kg}/\text{m}^2)}{25(\text{kg}/\text{m}^2)} \right)^{\theta 8} \cdot \left(\frac{TPRO_i(\text{g}/\text{dL})}{70(\text{g}/\text{dL})} \right)^{\theta 14} \\ & \cdot \left(\frac{eGFR_i(\text{ml}/\text{min}/\text{m}^2)}{100(\text{ml}/\text{min}/\text{m}^2)} \right)^{\theta 13} \cdot \left(\frac{AGE_i(\text{years})}{50(\text{years})} \right)^{\theta 7} \cdot \left(\frac{LDH_i(\text{U}/\text{L})}{160(\text{U}/\text{L})} \right)^{\theta 18} \\ & \cdot \left(\frac{AP_i(\text{U}/\text{L})}{70(\text{U}/\text{L})} \right)^{\theta 17} \cdot \left(\frac{ALT_i(\text{U}/\text{L})}{20(\text{U}/\text{L})} \right)^{\theta 15} \cdot \left(\frac{AST_i(\text{U}/\text{L})}{70(\text{U}/\text{L})} \right)^{\theta 16} \\ & \cdot \theta_{32}^{\text{RACE}[\text{ASIAN}]} \cdot \theta_9^{\text{SEX}[\text{Female}]} \\ & \cdot \theta_{11}^{\text{SMOKE}[\text{ex-smoker}]} \cdot \theta_{12}^{\text{SMOKE}[\text{current-smoker}]} \cdot \exp^{\eta_{CL/F_i}} \end{aligned}$$

$$\begin{aligned} \frac{V_2}{F_i} = & \theta 2 \cdot \left(\frac{BMI_i(\text{kg}/\text{m}^2)}{25(\text{kg}/\text{m}^2)} \right)^{\theta 23} \cdot \left(\frac{TPRO_i(\text{g}/\text{dL})}{70(\text{g}/\text{dL})} \right)^{\theta 22} \\ & \cdot \left(\frac{AGE_i(\text{years})}{50(\text{years})} \right)^{\theta 19} \cdot \theta_{33}^{\text{RACE}[\text{ASIAN}]} \cdot \theta_{20}^{\text{SEX}[\text{Female}]} \cdot \exp^{\eta_{V2/F_i}} \end{aligned}$$

$$\frac{Q}{F_i} = \theta 3$$

$$\begin{aligned} \frac{V_3}{F_i} = & \theta 4 \cdot \left(\frac{BMI_i(\text{kg}/\text{m}^2)}{25(\text{kg}/\text{m}^2)} \right)^{\theta 28} \cdot \left(\frac{TPRO_i(\text{g}/\text{dL})}{70(\text{g}/\text{dL})} \right)^{\theta 27} \\ & \cdot \left(\frac{AGE_i(\text{years})}{50(\text{years})} \right)^{\theta 24} \cdot \theta_{34}^{\text{RACE}[\text{ASIAN}]} \cdot \theta_{25}^{\text{SEX}[\text{Female}]} \cdot \exp^{\eta_{V3/F_i}} \end{aligned}$$

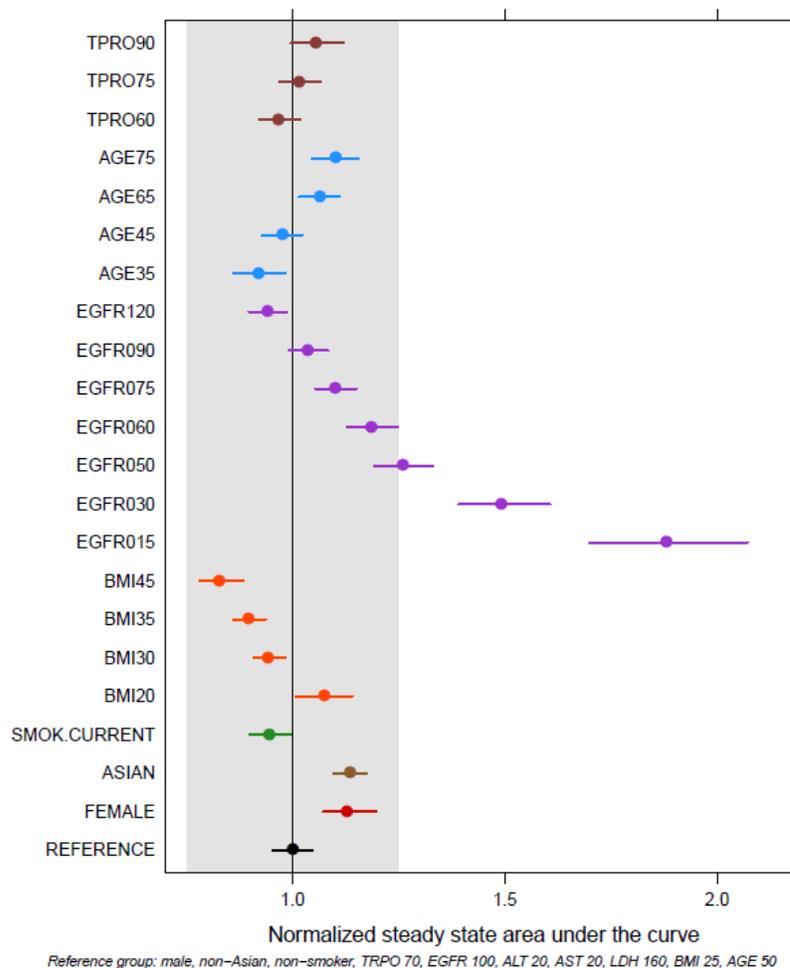
$$k_{ai} = \theta 5 \cdot \left(\frac{AGE_i(\text{years})}{50(\text{years})} \right)^{\theta 29} \cdot \theta_{35}^{\text{RACE}[\text{ASIAN}]} \cdot \theta_{30}^{\text{SEX}[\text{Female}]} \cdot \exp^{\eta_{k_{ai}}}$$

Typical population PK parameters (asymptotic 95% CI) given the reference covariates (50-year-old non-smoking male, non-Asian race, with BMI 25 kg/m², eGFR 100 mL/min/1.73 m², total protein (TPRO) 70 g/L, alanine transaminase (ALT) 20 U/L, aspartate transaminase (AST) 20 U/L, alkaline phosphatase (AP) 70 U/L, and lactate dehydrogenase (LDH) 160 U/L) were:

- CL/F: 10.6 (10.2, 11.1) L/hr
- V2/F: 3.14 (2.41, 4.10) L
- Q/F: 6.34 (5.84, 6.89) L/hr
- V3/F: 70.6 (64.6, 77.3) L
- ka : 0.196 (0.186, 0.207) 1/hr
- VSS/F: 73.8 L

Random effect variance estimates describing log-normal population variability in CL=F, V3=F, and ka were 0.142 (%RSE: 5.69%), 0.0744 (15.3%), and 0.0262 (22.9%), with covariance between random effects on CL/F and V3/F of 0.0447 (21.3%). These variance estimates correspond to percent coefficient of variation (CV%) values of 39.1%, 27.8%, and 16.3% for CL/F, V3/F, and ka interindividual variance, respectively.

The effects of covariate factors on empagliflozin PK were investigated. Variability in empagliflozin CL/F, and consequently in AUC_{ss}, was affected, albeit to varying degrees, by eGFR, age, BMI, TPRO, current smoking, female sex, and Asian race.



Estimated covariate effects on relative empagliflozin exposure ($AUC_{ss} / \text{reference } AUC_{ss}$) from the population pharmacokinetic model.

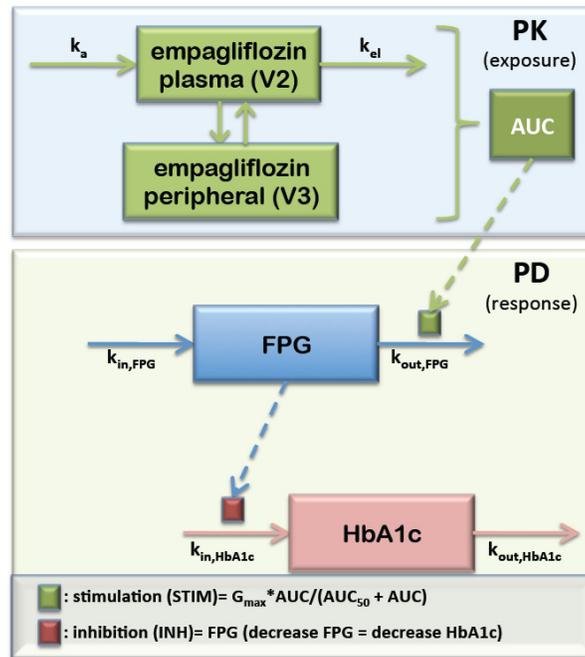
The solid point represents the median and horizontal lines represent the 95% CI for each covariate effect. CIs were determined from a nonparametric bootstrap ($n = 500$) of the final population PK model. Covariate effects for continuous covariates (TPRO, AGE, EGFR and BMI) were evaluated at fixed values (e.g., EGFR of 15, 30, 50, mL/min/1.73m²) to represent the observed range for each variable. The gray shaded area represents a $\pm 25\%$ reference region.

Figure 17: Estimated covariate effects on empagliflozin exposure

Population Pharmacodynamics: FPG and HbA1c Exposure-Response

- The empagliflozin PK-PD data set for exposure-FPG and HbA1c response modeling was comprised of 4289 patients (2761 on active empagliflozin therapy and 1528 on placebo) contributing a total of 25361 FPG observations and dosing and covariate data, and 4065 patients (2584 on active empagliflozin therapy and 1481 on placebo) contributing a total of 22012 HbA1c observations and dosing and covariate data. More subjects were available for FPG analysis since it included data from studies 1245.2 (U09-1271), 1245.4 (U09-1970), and 1245.15 (U10-2326) in addition to the data sets included in HbA1c modeling. Model

development proceeded by first fitting an indirect response model, driven by empagliflozin exposure (AUCs), to the FPG data.



$$\frac{d(FPG_{ij})}{dt} = k_{FPG_{in},i} - k_{FPG_{out}} \cdot FPG_{i,j} \cdot (1 + STIM_{i,j})$$

where *STIM* was a nonlinear Emax expression describing the effect of exposure (*AUC*s_{*s*,*j*}) on FPG.

$$STIM_{i,j} = \frac{GMAX_i \cdot AUCs_{s,i,j}}{AUC_{50} + AUCs_{s,i,j}}$$

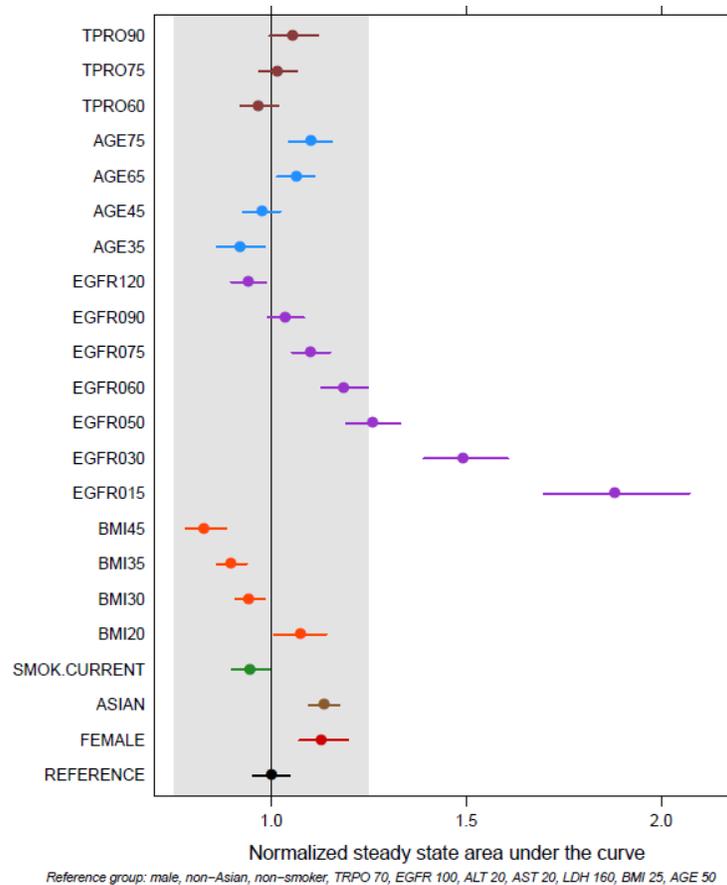
A steady-state ($\frac{d(FPG_{ij})}{dt} = 0$) assumption was made to solve for $k_{FPG_{in},i}$ under initial conditions. This parameterization included estimation of a baseline FPG (*BFPG*).

$$k_{FPG_{in},i} = BFPG_i \cdot k_{FPG_{out}}$$

for the *i*th individual at the *j*th collection time.

- Covariate effects (baseline FPG, AGE, BMI, SEX, RACE [Asian, Black, or Non-Asian/non-black], eGFR, concomitant oral anti-diabetic agents [MET, SU, pioglitazone (PIO)], and the duration of diabetes [< 1y, 1–5 y, or > 5y]) were included in this model as descriptors of variability in the baseline FPG (*BFPG*) and the extent of stimulation (*GMAX*) for FPG removal (*STIM*).
- The median baseline FPG was approximately 8mM (144 mg/dL) for most of the studies included (1245.2 (U09-1271), .4 (U09-1970), .19 (U12-1516), .20 (U12-1517), .23 (U12-1518), .33 (U12-3817) and .36 (U12-1522)). This value was approximately 9 mM (162 mg/dL) for studies 1245.9 (U10-2261), .10 (U10-3573) and .15 (U10-2326). Covariate effects on *BFPG* were precisely estimated, i.e., wholly contained within –25% of the reference baseline; this indicated only minimal differences in baseline for the covariate ranges observed. For example, the estimated *BFPG* increased by only 6.31% (2.80, 10.2%) with a decrease in EGFR from 100 to 15 mL/min/1.73 m². All other covariates tested had even less

effect on BFGP differences. The observed baseline FPG was included as covariate effect on BFGP. With this effect, BFGP was estimated to be 8.67mM (7.57, 9.95 mM) (156 mg/dL [136, 179 mg/dL]) for an observed baseline FPG of 8mM(144 mg/dL), the approximate median of the Phase III studies.



Estimated covariate effects on relative empagliflozin exposure ($AUC_{ss}/$ reference AUC_{ss}) from the population pharmacokinetic model.

The solid point represents the median and horizontal lines represent the 95% CI for each covariate effect. CIs were determined from a nonparametric bootstrap (n = 500) of the final population PK model. Covariate effects for continuous covariates (TPRO, AGE, EGFR and BMI) were evaluated at fixed values (e.g., EGFR of 15, 30, 50, mL/min/1.73m²) to represent the observed range for each variable. The gray shaded area represents a ±25% reference region.

Figure 18: Estimated covariate effects on empagliflozin response

- The maximal observed decrease in FPG appeared to occur within 1–2 weeks after initiation of empagliflozin treatment and was described as being dependent on exposure (AUC_{ss}). The additional post-treatment FPG data added to this analysis, compared to those included in the previous population PKPD analysis (U12-2524), were typically collected at visits beyond this 1–2 week initial window. The rate constant $k_{FPGout,i}$ describing the time to achieve the maximal drug effect was therefore fixed at the estimate

- (0.0407 1/hr) from the previous model (U12-2524). The estimated (95% CI) AUC₅₀ (658 [481, 871] nmol*hr/L) for the function stimulating FPG removal (STIM) corresponded to the median empagliflozin exposure from a once daily (once daily) dose of approximately 3 mg. The AUC₅₀ parameter corresponds to the exposure expected to produce half of the maximal effect. This maximal decrease (GMAX) in FPG, expressed as a percentage of the baseline FPG, was estimated to be 20.0% (17.9, 22.7) with a BFPG of 8mM(144 mg/dL).GMAX was estimated to increase with increased baseline FPG; for example, an increase in BFPG from 8 to 9 mM (144 to 162 mg/dL) was expected to increase GMAX by 9.75% (6.32, 13.6), and from 8 to 10mM(144 to 180 mg/dL) GMAX increased by 18.2% (13.4, 23.7); of note, these values are relative percentage increases rather than percentage point increases. As reference, the GMAX estimate at an observed baseline FPG of 8 mM (144 mg/dL), corresponding to BFPG of 8.67mM (156 mg/dL), was 23.0% (20.2, 26.6).Covariate effects included on GMAX indicated that eGFR most notably impacted the empagliflozin exposure-response relationship: relative to a reference eGFR of 100 mL/min/1.73m², GMAX was estimated to decrease by -59.4 (-69.0, -45.9)%, -43.5 (-52.4, -32.3)%, -21.5 (-27.0, -15.3)%, and -12.8 (-16.3, -8.91)% for eGFR of 15, 30, 60, and 75 mL/min/1.73m², respectively.
- An approximate increase in GMAX of 24.1% (12.7, 36.2) was estimated with concomitant SU administration. Other concomitant medications (MET, PIO) did not significantly impact GMAX, nor did the duration of T2DM or Asian race, where a precise and non-significant parameter estimate was considered if the 95%CI contained the null value and was contained within the ±25% minimal effect region. The imprecision of the covariate effect for Black race (-16.2% [-44.6, 15.0]) resulted in an inconclusive effect of Black race on empagliflozin exposure-response. Females, although significantly lower than the reference GMAX, were estimated to have only a -10.4% (-16.5, -4.07) decrease in this parameter.
- The remaining covariate effects, BMI and AGE, were expected to only marginally impact empagliflozin exposure-response through the GMAX parameter. Notably, though, these effects were independent of each other and eGFR. In addition, these effects were noted after accounting for their independent effects on exposure (PK) described above. Relative to a reference BMI of 25 kg/m², GMAX was expected to decrease by -21.6% (-33.0, -8.74), -13.0% (-20.5, -5.10), -7.29% (-11.7, -2.80) for BMI of 45, 35 and 30 kg/m², respectively; and increase by 9.70% (3.53, 16.4) for BMI of 20 kg/m². Similarly, relative to the reference age of 50 years, GMAX was expected to decrease by -16.1% (-22.9, -8.41) and -10.7% (-15.5, -5.53) for ages of 75 and 65, respectively, and increase by 4.66% (2.31, 6.99) and 16.7% (8.03, 25.7) for ages of 45 and 35 years, respectively.
- Interindividual variability for BFPG and GMAX, and FPG residual variability estimates (CV%) were 12.9%, 50.7%, and 15.7%, respectively.

The described changes in FPG were then used within another indirect response model to describe longitudinal changes in HbA1c:

$$\frac{d(HbA1c_{i,j})}{dt} = k_{HbA1c_{in,i}} \cdot FPG_{i,j} - k_{HbA1c_{out,i}} \cdot HbA1c_{ij} \cdot \left(1 - \frac{HbA1c_{limit}}{HbA1c_{ij}} \right)$$

- The HbA1c half-life calculated from $k_{HbA1c,out}$ was approximately 3.35 (2.79, 4.04) weeks. Therefore, maximal changes in HbA1c following initiation of empagliflozin treatment would be approached by approximately 12 weeks (>3 half-lives) and almost entirely achieved by 24 weeks (>6 half-lives).
- Covariate effects specific to HbA1c, as estimated on the parameter $k_{HbA1c,out}$, were generally non-significant (i.e., 95% CIs included null value), although not precisely estimated, i.e., they included both the null value and extended beyond the -25% reference range. The exception was the effect for MET concomitant use, which was estimated to have an increase in $k_{HbA1c,out}$ of 57.4% (38.3, 81.3).
- Interindividual variability for $k_{HbA1c,out}$ and HbA1c residual variability estimates (CV%) were 15.2% and 5.73%, respectively.
- Overall, the FPG and corresponding HbA1c responses were dependent on drug exposure and the baseline FPG. For example, the predicted maximal decreases (steady-state) in FPG and HbA1c at the reference baseline FPG (8 mM, 144 mg/dL) were 1.6 mM (20%), or 28.8 mg/dL, and 0.8 percentage points, respectively. This reference baseline FPG (8 mM, 144 mg/dL) equated to a baseline HbA1c of 8.0%. In addition, targets of 80% and 90% of the maximal response after 24 weeks of treatment for FPG and HbA1c were obtained by empagliflozin doses of approximately 10 and 25 mg, respectively, based on the AUC50 estimate. Therefore, although both doses were expected to provide near maximal responses, the 25 mg once daily dose of empagliflozin may provide additional HbA1c lowering. For example, the median HbA1c was predicted to decrease by -0.62% (10 mg) and -0.71% (25 mg) after 24 weeks of empagliflozin treatment for a baseline HbA1c of 8.0% in the typical patient.

Basic goodness of fit plots for the Sponsor's final model are shown in Figure 19.

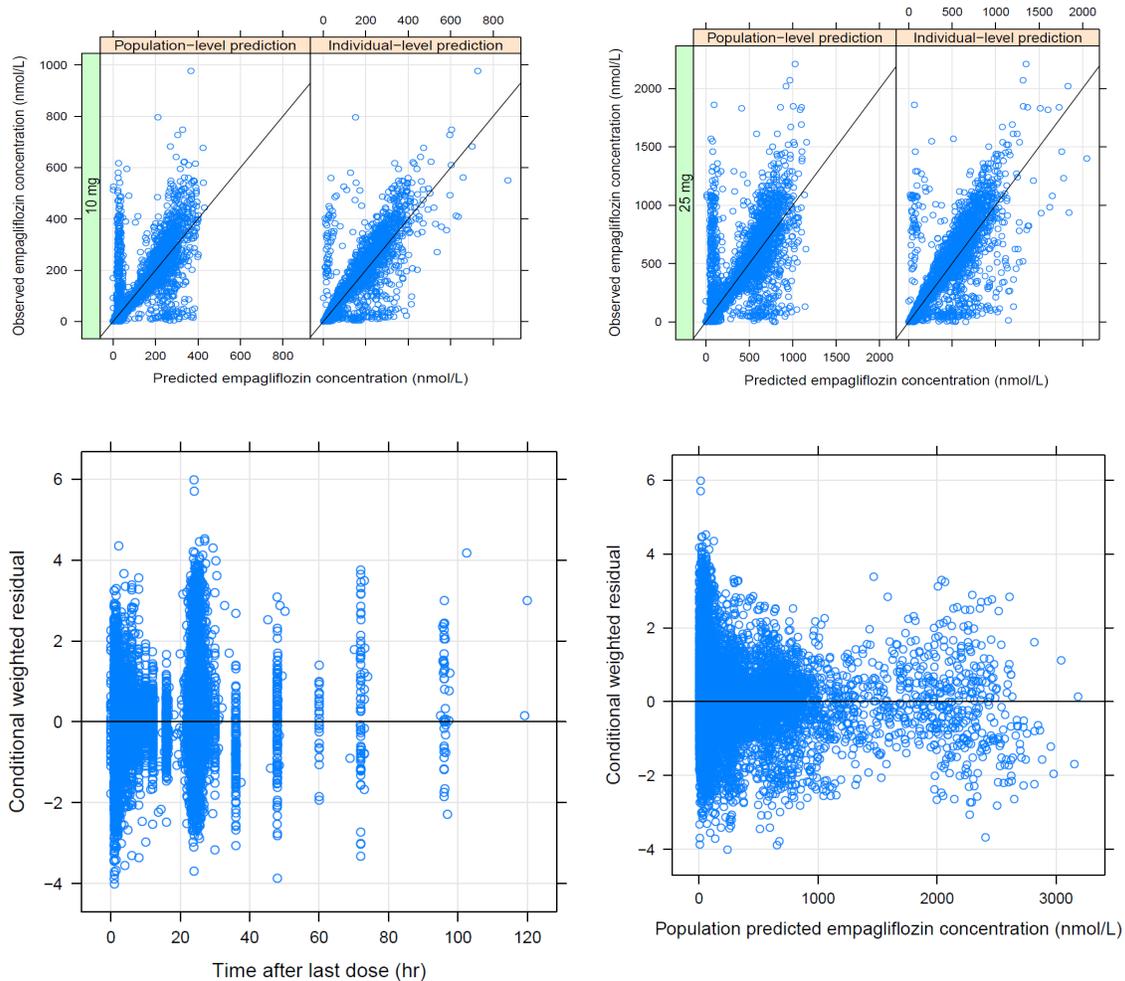


Figure 19: Basic goodness of fit plots for the Sponsor’s final PK model (Top row shows plots for two clinically relevant doses 10 mg and 25 mg)

Source: Population PKPD Study Report, Page 132, 133, 137, 138

The parameter estimates for the final PK and PKPD model are presented in Table 1 and 2 below.

Table 1: Parameter Estimates of Final PK Model

description	estimate	unit	RSE (%)	median (95% CI)	parameter
CL (liter per hour)	10.6	$L \cdot hr^{-1}$	2.24	10.6 (10.1, 11.1)	CL
$CL \sim (AGE/50)^{\theta_7}$	-0.241		23.0	-0.234 (-0.347, -0.128)	θ_7
$CL \sim (BMI/25)^{\theta_8}$	0.320		18.2	0.322 (0.207, 0.440)	θ_8
$CL \sim \theta_9^{female}$	0.886		2.04	0.886 (0.845, 0.919)	θ_9
$CL \sim \theta_{11}^{ex-smoker}$	1.02		1.81	1.02 (0.982, 1.05)	θ_{11}
$CL \sim \theta_{12}^{current-smoker}$	1.06		2.10	1.06 (1.02, 1.10)	θ_{12}
$CL \sim (eGFR/100)^{\theta_{13}}$	0.333		7.16	0.334 (0.282, 0.383)	θ_{13}
$CL \sim \theta_{32}^{asianrace}$	0.880		2.25	0.881 (0.843, 0.924)	θ_{32}
$CL \sim (TPRO/70)^{\theta_{14}}$	-0.219		32.8	-0.217 (-0.364, -0.0745)	θ_{14}
$CL \sim (ALT/20)^{\theta_{15}}$	0.0200		88.1	0.0204 (-0.0157, 0.0535)	θ_{15}
$CL \sim (AST/20)^{\theta_{16}}$	-0.0421		51.0	-0.0435 (-0.0860, 0.00296)	θ_{16}
$CL \sim (AP/70)^{\theta_{17}}$	-0.0488		44.9	-0.0493 (-0.0916, -0.00796)	θ_{17}
$CL \sim (LDH/160)^{\theta_{18}}$	0.0110		199	0.00852 (-0.0388, 0.0496)	θ_{18}
Vc (liter)	3.14	L	13.5	3.11 (0.00128, 4.03)	V_c
$Vc \sim (AGE/50)^{\theta_{19}}$	0.795		51.2	0.804 (-0.00742, 1.85)	θ_{19}
$Vc \sim \theta_{20}^{female}$	1.25		12.1	1.22 (0.971, 1.81)	θ_{20}
$Vc \sim (TPRO/70)^{\theta_{22}}$	2.07		35.1	2.10 (0.0972, 3.65)	θ_{22}
$Vc \sim (BMI/20)^{\theta_{23}}$	1.04		31.3	1.11 (0.300, 2.29)	θ_{23}
$Vc \sim \theta_{33}^{asian}$	1.27		15.3	1.29 (0.930, 1480)	θ_{33}
Q (liter per hour)	6.34	$L \cdot hr^{-1}$	4.22	6.31 (5.72, 6.91)	Q
Vp (liter)	70.6	L	4.59	70.0 (64.4, 76.6)	V_p
$Vp \sim (AGE/50)^{\theta_{24}}$	0.135		93.0	0.154 (-0.120, 0.381)	θ_{24}
$Vp \sim \theta_{25}^{female}$	0.831		4.70	0.832 (0.751, 0.909)	θ_{25}
$Vp \sim (TPRO/70)^{\theta_{27}}$	-0.196		95.8	-0.177 (-0.608, 0.179)	θ_{27}
$Vp \sim (BMI/25)^{\theta_{28}}$	0.672		19.6	0.690 (0.423, 0.937)	θ_{28}
$Vp \sim \theta_{26}^{asianrace}$	0.959		5.04	0.963 (0.865, 1.07)	θ_{26}
Ka (hour ⁻¹)	0.196	hr^{-1}	2.68	0.196 (0.185, 0.208)	K_a
$Ka \sim (AGE/50)^{\theta_{29}}$	0.108		55.8	0.114 (-0.0210, 0.238)	θ_{29}
$Ka \sim \theta_{30}^{female}$	1.17		2.38	1.16 (1.11, 1.23)	θ_{30}
$Ka \sim \theta_{35}^{asianrace}$	1.23		2.21	1.23 (1.18, 1.29)	θ_{35}
ALAG1 (hour)	0.500	hr	NA	0.500 (0.500, 0.500)	$ALAG_1$
ω_{CL}^2	0.142	39.1 (%CV)	5.69	0.140 (0.125, 0.157)	
$\omega_{V_3}^2$	0.0744	27.8 (%CV)	15.3	0.0719 (0.0519, 0.0981)	
$\omega_{K_a}^2$	0.0262	16.3 (%CV)	22.9	0.0253 (0.0165, 0.0388)	
ω_{CL,V_3}	0.0447	$\rho=0.435$	21.3	0.0432 (0.0240, 0.0632)	
σ_{prop}^2 Study 2, 4, 15	0.0281	16.9 (%CV)	4.17	0.0279 (0.0258, 0.0303)	
σ_{prop}^2 Study 9, 10, 19, 20, 23, 33, 36	0.128	37.0 (%CV)	3.25	0.128 (0.120, 0.135)	
σ_{add}^2 CWRES lt -3 or CWRES gt 3	3.50e+05	nmol/L	10.1	3.52e+05 (2.85e+05, 4.23e+05)	

Point estimates and relative standard errors (RSE) of the estimates from pk/2019.lst; Median and 95% confidence intervals (CI) of the estimates were obtained from nonparametric bootstrap estimates (N=500)

Source: Sponsors Response to Information Request, Page 34 dated 10/02/2013

Table 2: Parameter Estimates of Final Model

description	estimate	unit	RSE (%)	median (95% CI)	parameter
Intercept for BFPG (IBFPG, mM): Study 1245.2	12.8	mM	3.90	12.9 (11.9, 13.9)	θ_1
IBFPG (mM): Study 1245.4	14.1	mM	4.15	14.1 (13.1, 15.2)	θ_2
IBFPG (mM): Study 1245.9 and .10	14.7	mM	3.07	14.7 (13.9, 15.7)	θ_3
IBFPG (mM): Study 1245.15	14.8	mM	3.14	14.9 (14.1, 15.8)	θ_4
IBFPG (mM): Study 1245.19, .20, .23, .33, .36	14.2	mM	3.34	14.2 (13.2, 15.2)	θ_5
FPG elimination rate constant (hr^{-1})	0.0407	hr^{-1}	NA	0.0407 (0.0407, 0.0407)	θ_6
BFPG \sim IBFPG $\cdot \exp(8/\text{observed BFPG})^{\theta_{17}}$	-0.497		7.12	-0.498 (-0.567, -0.428)	θ_{17}
BFPG $\sim (AGE/50)^{\theta_{18}}$	-0.100		14.7	-0.1 (-0.129, -0.0713)	θ_{18}
BFPG $\sim (BMI/25)^{\theta_{19}}$	0.0248		74.2	0.0247 (-0.0103, 0.0608)	θ_{19}
BFPG $\sim (eGFR/100)^{\theta_{20}}$	-0.0364		26.5	-0.0352 (-0.0544, -0.0167)	θ_{20}
BFPG $\sim \theta_{21}^{female}$	0.996		0.510	0.996 (0.987, 1)	θ_{21}
BFPG $\sim \theta_{22}^{black}$	0.977		2.07	0.979 (0.941, 1.02)	θ_{22}
BFPG $\sim \theta_{23}^{asian}$	0.948		0.772	0.948 (0.933, 0.961)	θ_{23}
BFPG $\sim (DUR/2)^{\theta_{24}}$	0.0512		14.7	0.0513 (0.038, 0.066)	θ_{24}
BFPG $\sim \theta_{25}^{MET}$	0.995		0.669	0.995 (0.983, 1.01)	θ_{25}
BFPG $\sim \theta_{26}^{U}$	1.01		0.687	1.01 (0.998, 1.03)	θ_{26}
BFPG $\sim \theta_{16}^{O}$	0.999		0.701	0.999 (0.984, 1.01)	θ_{16}
FPG maximum effect (GMAX, %)	0.217	%	5.52	0.218 (0.197, 0.242)	θ_7
GMAX $\sim (\text{baseline FPG}/8)^{\theta_8}$	1.76		6.37	1.77 (1.54, 1.96)	θ_8
GMAX $\sim (AGE/50)^{\theta_{27}}$	-0.401		25.5	-0.398 (-0.597, -0.205)	θ_{27}
GMAX $\sim (BMI/25)^{\theta_{28}}$	-0.288		42.6	-0.289 (-0.537, -0.0553)	θ_{28}
GMAX $\sim (eGFR/100)^{\theta_{29}}$	0.512		14.6	0.515 (0.393, 0.648)	θ_{29}
GMAX $\sim \theta_{30}^{female}$	0.890		3.51	0.887 (0.828, 0.947)	θ_{30}
GMAX $\sim \theta_{31}^{black}$	0.979		13.7	0.959 (0.703, 1.23)	θ_{31}
GMAX $\sim \theta_{32}^{asian}$	1.07		4.66	1.07 (0.964, 1.16)	θ_{32}
GMAX $\sim (DUR/2)^{\theta_{33}}$	0.0117		524	0.0142 (-0.11, 0.118)	θ_{33}
GMAX $\sim \theta_{34}^{MET}$	0.931		4.39	0.931 (0.848, 1.01)	θ_{34}
GMAX $\sim \theta_{35}^{U}$	1.27		4.58	1.27 (1.16, 1.39)	θ_{35}
GMAX $\sim \theta_{36}^{O}$	1.02		4.39	1.02 (0.911, 1.13)	θ_{36}
FPG AUC50 (GC50, nmol*h/L)	703	nmol · h/L	14.2	704 (528, 888)	θ_9
ω_{BFPG}^2	0.0165	12.9 (%CV)	7.41	0.0163 (0.0138, 0.0187)	
ω_{GMAX}^2	0.237	51.7 (%CV)	7.11	0.233 (0.202, 0.267)	
σ_{prop}	0.0236	15.5 (%CV)	2.40	0.0237 (0.0226, 0.0248)	

description	estimate	unit	RSE (%)	median (95% CI)	parameter
HbA1c input rate (KHIN) = $\theta_{10} \cdot KHOT$	0.466		1.20	0.466 (0.452, 0.482)	θ_{10}
physiologic limit HbA1c (HLIM): 1245.9 and .10	3.57	%	1.32	3.57 (3.43, 3.72)	θ_{12}
physiologic limit HbA1c (HLIM): 1245.19, .20, .23, .33 and .36	3.99	%	1.12	3.98 (3.86, 4.10)	θ_{14}
HbA1c elimination rate constant (KHOT, $10^{-3} hr^{-1}$)	1.59	$10^{-3} hr^{-1}$	21.2	1.59 (1.17, 2.03)	θ_{15}
KHOT $\sim (AGE/50)^{\theta_{45}}$	-0.241		93.7	-0.273 (-0.790, 0.247)	θ_{45}
KHOT $\sim (BMI/25)^{\theta_{46}}$	0.328		134	0.324 (-0.230, 0.986)	θ_{46}
KHOT $\sim (eGFR/100)^{\theta_{47}}$	-0.119		279	-0.135 (-0.693, 0.313)	θ_{47}
KHOT $\sim \theta_{48}^{female}$	0.858		9.73	0.850 (0.704, 1.01)	θ_{48}
KHOT $\sim \theta_{50}^{asian}$	1.05		21.7	1.05 (0.847, 1.43)	θ_{50}
KHOT $\sim (DUR/2)^{\theta_{51}}$	-0.577		25.9	-0.590 (-0.890, -0.330)	θ_{51}
KHOT $\sim \theta_{52}^{MET}$	1.48		12.9	1.51 (1.21, 1.94)	θ_{52}
ω_{KHOT}^2	0.0242	15.7 (%CV)	3.83	0.0242 (0.0221, 0.0263)	
$\sigma_{prop, HbA1c}^2$	0.00321	5.67 (%CV)	1.95	0.00320 (0.00305, 0.00342)	

Source: Sponsors Response to Information Request, Page 34 dated 10/02/2013

Figure 20 shows the visual predictive check (VPC) plot of the PK data from final PKPD model (2019). Overall, after incorporating a number of covariates approximately 95% of the observations for major part of the concentration-time profile (except around trough) lie within the predicted interval, indicating that model reasonably describes the data.

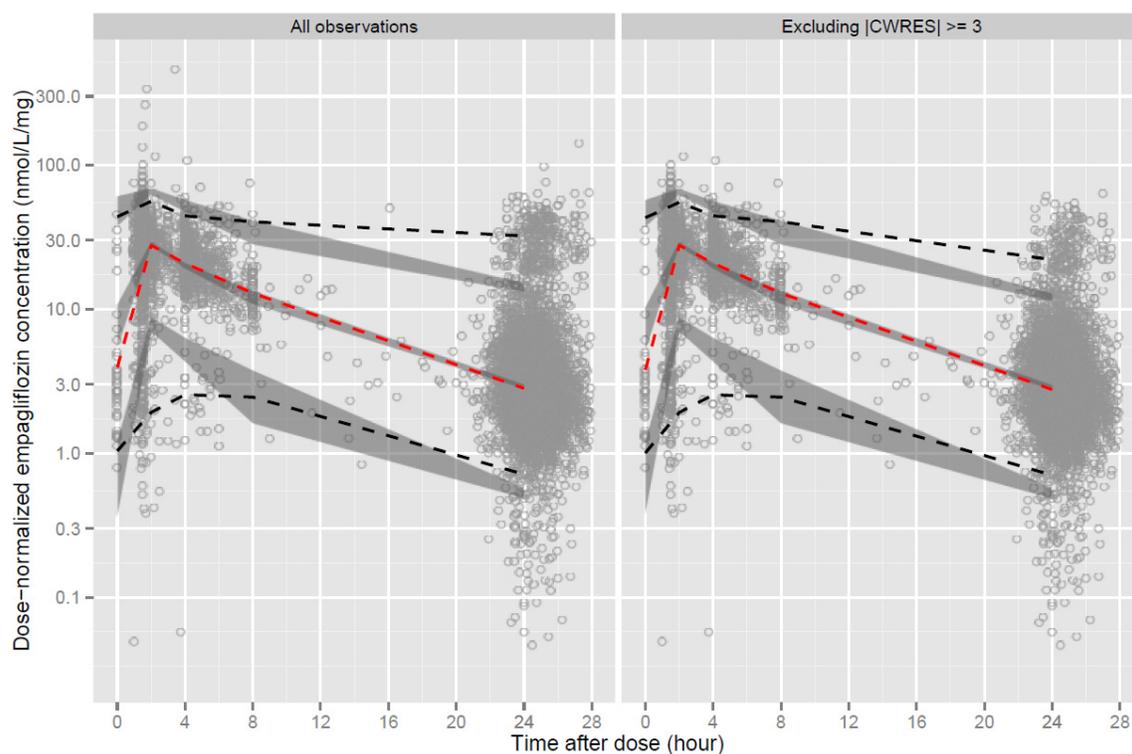


Figure 20: Visual predictive check of the final population PK model for studies 1245.9, .10, .19, .20, .23, 33, and .36. Dashed lines represent median (red), 2.5th and 97.5th (black) percentile of the observations; grey area represents 95% CI of the respective metrics from n=300 simulations. The left panel includes all observations and the right panel excludes those observations that were flagged having a |CWRES| >3. Source: *Sponsors Response to Information Request, Page 2 dated 10/02/2013*

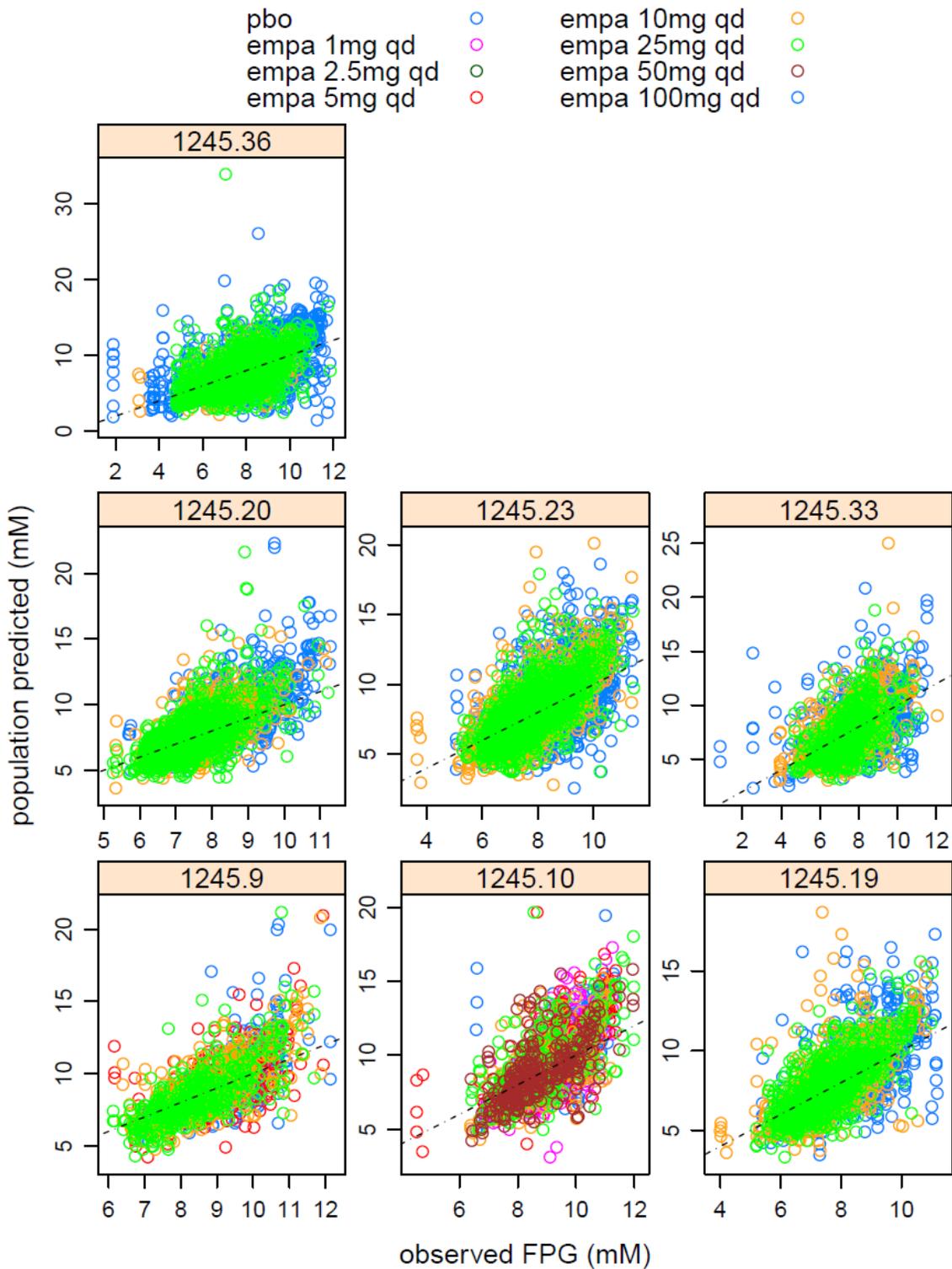


Figure 21: Goodness of fit plots for FPG data using final model 4030.ctf
 Source: *Sponsors Population PKPD Report, Page 190*

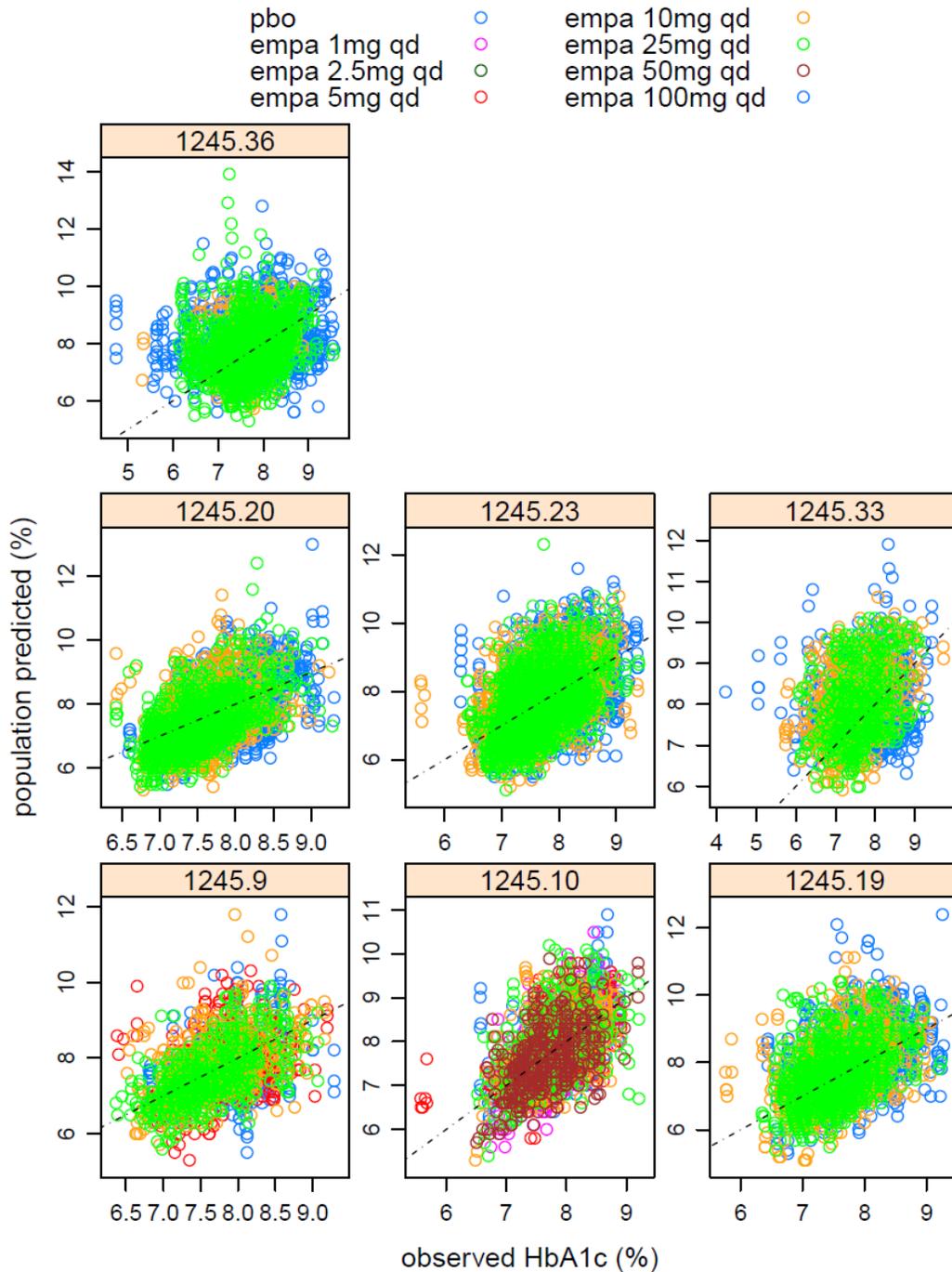


Figure 22: Goodness of fit plots for FPG data using final model 4030.ctl
Source: Sponsors Population PKPD Report, Page 192

2.2 Sponsor's Conclusions

- The population PK of empagliflozin in T2DM patients was described by a two-compartment model with first-order absorption.
- Variability in empagliflozin CL/F and AUC_{ss} was primarily affected by BMI, eGFR, TPRO, age, female sex, and Asian race. Under the PK model, typical CL/F and AUC_{ss} values were generally within 75 to 125% of the reference group value across the range of most commonly observed covariate values. The typical AUC_{ss} increased by 18.5% (95% CI: 13.0, 24.8), 49.2% (95% CI: 39.2, 60.6), 88.1% (95% CI: 69.9, 107) in patients with an eGFR of 60, 30, and 15 mL/min/1.73m², respectively, compared to a reference patient with an eGFR of 100 mL/min/1.73m². Other covariates tested included smoking status and liver enzymes (LDH, AST, ALT, and AP) did not have a significant effect on the PK of empagliflozin. FPG and HbA1c responses were described as being dependent on drug exposure. The maximal effect (20% lowering of FPG) achieved by empagliflozin treatment was increased with increasing baseline FPG.
- The maximal effect is attenuated with decreased eGFR despite an increase in empagliflozin exposure, but was still maintained to nearly half of the maximal effect with eGFR as low as 30 mL/min/1.73m². The exposure-response modeling estimated that targets of 80% and 90% of the maximal response after 24 weeks of treatment for FPG and HbA1c were obtained by oral empagliflozin once daily doses of approximately 10 and 25 mg.
- Overall, targets of 80% and 90% of the maximal response after 24 weeks of treatment for FPG and HbA1c were obtained by empagliflozin doses of approximately 10 and 25 mg, respectively, based on the AUC₅₀ estimate. Therefore, although both doses were expected to provide near maximal responses, the 25 mg once daily dose of empagliflozin may provide additional HbA1c lowering.

Reviewer's comments on Sponsor's Population PK Analysis:

- *Sponsor's population PK analysis appears reasonable to support the labeling statements. However, based on the goodness of fit plots (see Figure 19) and the visual predictive checks (VPCs; see Figure 20), there appears to be a systematic bias in the model predictions as the model was unable to explain trough concentrations. This indicates that PK model is not able to completely capture the inter-individual variability.*
- *Nevertheless, the covariates that were identified in the final model are likely not to be clinically significant as the magnitude of effect on systemic exposure of empagliflozin is within 20-30% (see Figure 17) except that for eGFR. However, since renal function affected systemic exposure (increased) and efficacy (decreased) in opposite directions, this increase in exposure is not considered clinically relevant. Therefore, no exposure based dose-adjustments are proposed for patients with renal impairment.*
- *Sponsor's conclusion that no dose adjustment based on age, gender, and body mass index, is supported by the population PK analysis results and is acceptable. There*

were adequate representation with regards to gender (~55% males and ~45% females), age (19-98 years), eGFR (9.5 – 218 mL/min/1.73m²), and BMI (15.4 – 89.8 kg/m²). However, the statement with regards to impact of Race, categorized based on Asians and Whites, on empagliflozin exposure are acceptable as the source data used in population PK or PKPD analysis was primarily derived from White (56%) or Asian (41%) and did not have adequate representation for black (2.5%) or others (<1%) populations. Population PKPD analysis data was primarily derived from Whites (52%) or Asian (46%) and did not have adequate representation for black (1.5%) or others (<1%) populations.

Reviewer’s comments on Sponsor’s Population PKPD Analysis:

- *Sponsor’s population PKPD analysis appears reasonable. Overall, the model explained the fasting plasma glucose and HbA1c data from various trials. However, the model was limited with respect to the predictability of the efficacy response in patients with moderate renal impairment and severe renal impairment (see Figure 25 in Appendix). One of the possible limitations of the model is that it is not fully mechanistic and is purely driven by the assumption of indirect response relationship between systemic exposure and stimulation of FPG utilization. This assumption seems to be true as long as the renal function is normal and renal handling of drug and glucose are unaltered. However, in presence of renal impairment, where the PKPD studies showed a decrease in both amount of drug excreted in urine as well as effect on 24-hour urinary glucose excretion with decrease in eGFR, this assumption was not entirely true. This aspect could not be explained by the model even if eGFR was a covariate on both, empagliflozin CL/F (accounting for increase in exposure) and GMAX (accounting for decrease in maximal stimulation of FPG utilization with decrease in renal function). This model was not utilized to predict the response for 10 mg dose in patients with moderate renal impairment (This dose was not studied in patients with moderate renal impairment in Phase 3 trial 1245.36). Also, this model was also not utilized for any regulatory decision making other than to conclude that exposure-response for HbA1C was relatively flat (see Figure 26 in Appendix), consistent with dose-response data from several phase 3 trials.*

3 RESULTS OF REVIEWER’S ANALYSIS

3.1 Objectives

The primary objective was to re-run and confirm the results of sponsor’s population PK and PKPD analyses using NONMEM and the adequacy of the proposed label claims that there are no clinically meaningful effects of gender, BMI, age, race on empagliflozin pharmacokinetics.

3.2 Methods

3.2.1 Data Sets

Data sets used are summarized in Table 3.

Table 3: Analysis Data Set

Description and Link to EDR\\Cdsesub1\evsprod\NDA204629\0000\m5\datasets\U12-2525\analysis		
Dataset	Description	Location
tran	Development dataset of the combined population pharmacokinetic analysis described in U12-2525 (tran.csv)	tran.xpt
tranaeal	Final dataset of the exposure-response analysis for tolerability endpoints: urinary tract infection, genital infection, confirmed hypoglycemia described in U12-2525 (tranAEall.csv)	tranaeal.xpt
tranegfr	Final dataset of the combined population pharmacokinetic/pharmacodynamic analysis for eGFR change from baseline described in U12-2525 (tranALLegfr.csv)	tranegfr.xpt
tranalpd	Final dataset of the combined population pharmacokinetic/pharmacodynamic analysis for FPG and HbA1c described in U12-2525 (tranALLPD.csv)	tranalpd.xpt
tranpk	Final dataset of the combined population pharmacokinetic analysis described in U12-2525 (tranALLpk.csv)	tranpk.xpt
tranpd	Development dataset of the combined population pharmacokinetic/pharmacodynamic analysis for FPG and HbA1c described in U12-2525 (tranPD.csv)	tranpd.xpt

3.2.2 Software

NONMEM version 7.2 and S-plus (TIBCO Spotfire S+ Version 8.1) were used for reviewer's analysis.

3.3 Results

Sponsors population PK and PKPD model runs were reproducible using the input data and model files provided by the sponsor.

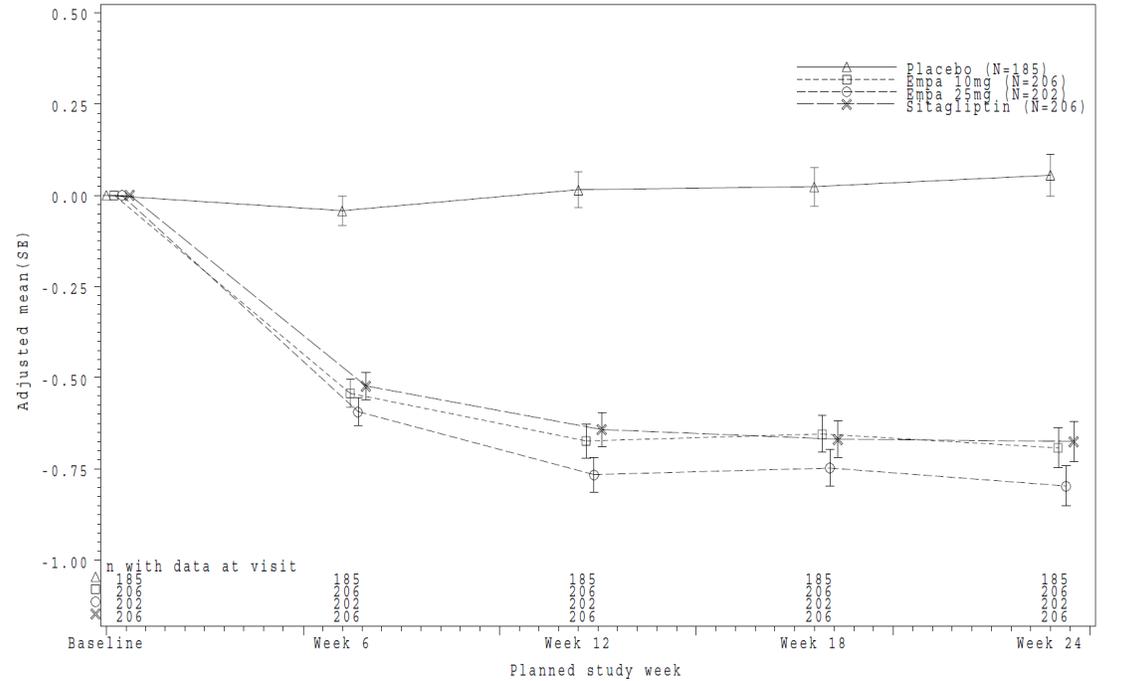
4 APPENDIX TO PHARMACOMETRIC REVIEW

Appendix 4.1: Longitudinal Efficacy Data from Add-on Therapy Trials

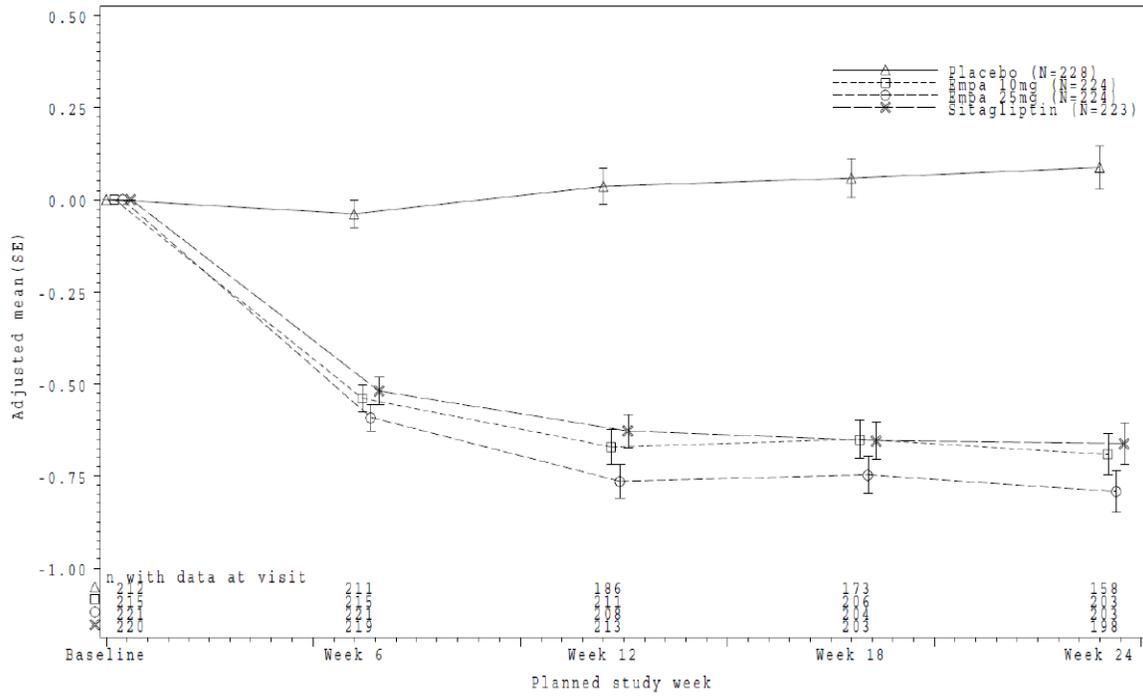
The time-profiles for the mean change from baseline in HbA1c in add-on therapy trials are shown in Figure 21, 22, 23, 24 below for FAS (full analysis set)-LOCF and FAS-OC (Observed case, non-LOCF data). HbA1c (%) change from baseline based on FAS-LOCF data is generated from ANCOVA results over time. Model included treatment, baseline eGFR (MDRD), background medication and visit as fixed effects and baseline HbA1c as a linear covariate. HbA1c (%) change from baseline based on FAS-OC data is generated using MMRM results over time. Model included treatment, baseline eGFR (MDRD), region, visit and visit by treatment interaction as fixed effects and baseline HbA1c as a linear covariate.

Figure 23: Time-profiles for adjusted mean (\pm SE) change from baseline in HbA1c in Phase 3 trials.

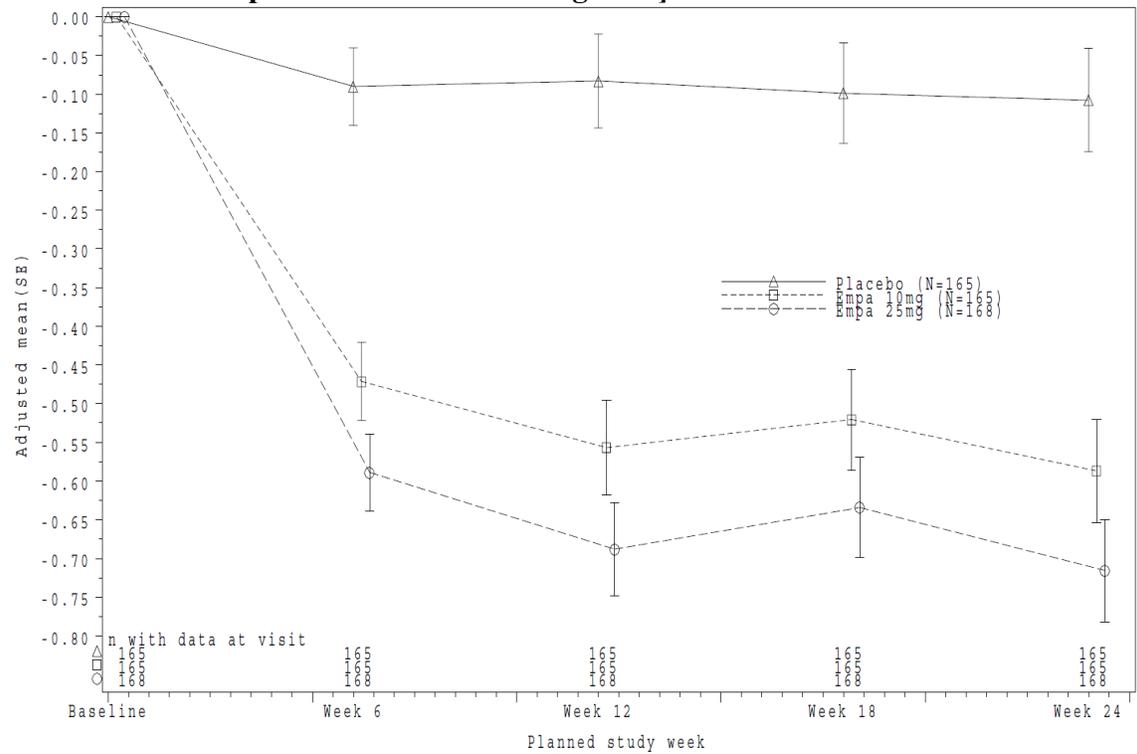
A: Monotherapy trial 1245.20 FAS-LOCF [Source: Sponsor's Figure 15.2.1.2.2: 7 in Report U12-12-1517-01 Page 390]



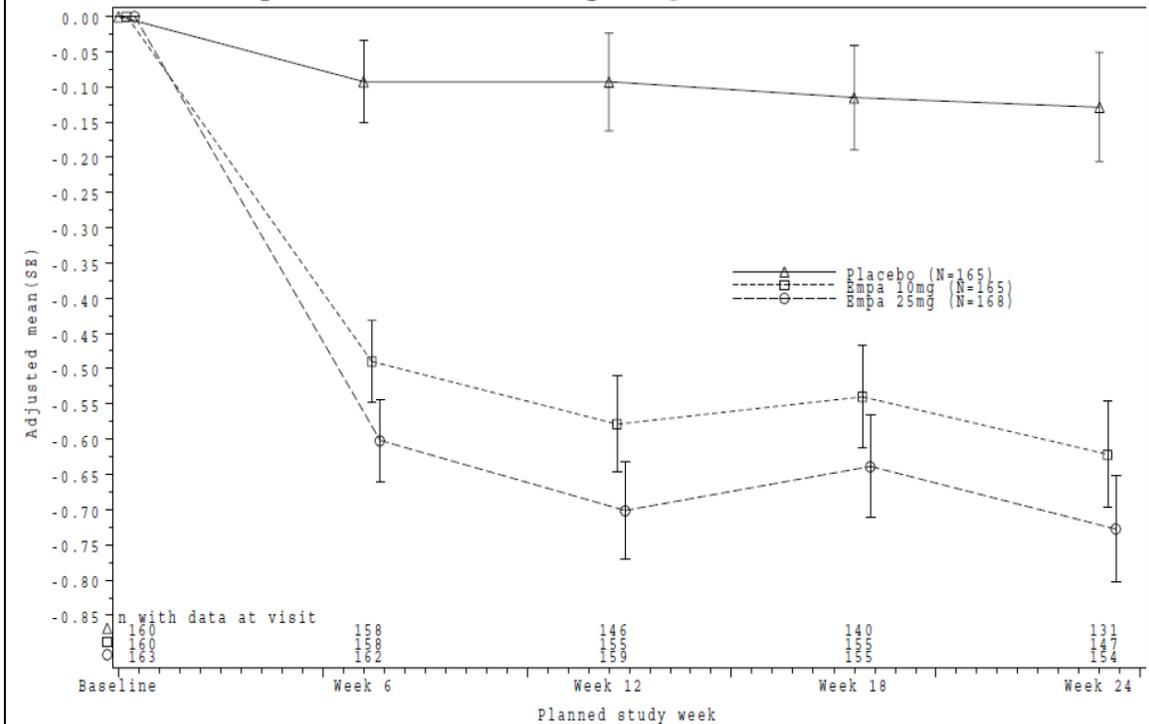
B: Monotherapy trial 1245.20 FAS-OC [Source: Sponsor's Figure 15.2.1.2.2: 1 in Report U12-12-1517-01 Page 384]



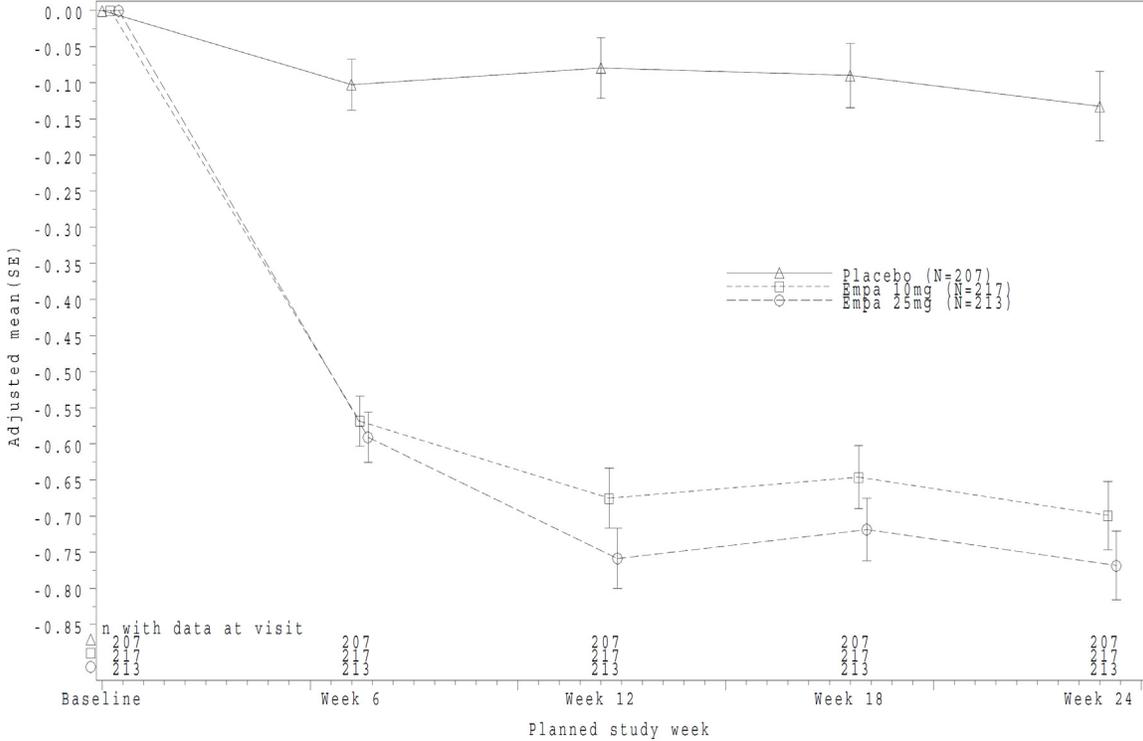
C: Add-on to Pio±Met trial 1245.19 FAS-LOCF [Source: Sponsor's Figure 15.2.1.2.2: 7 in Report U12-12-1517-01 Page 323]



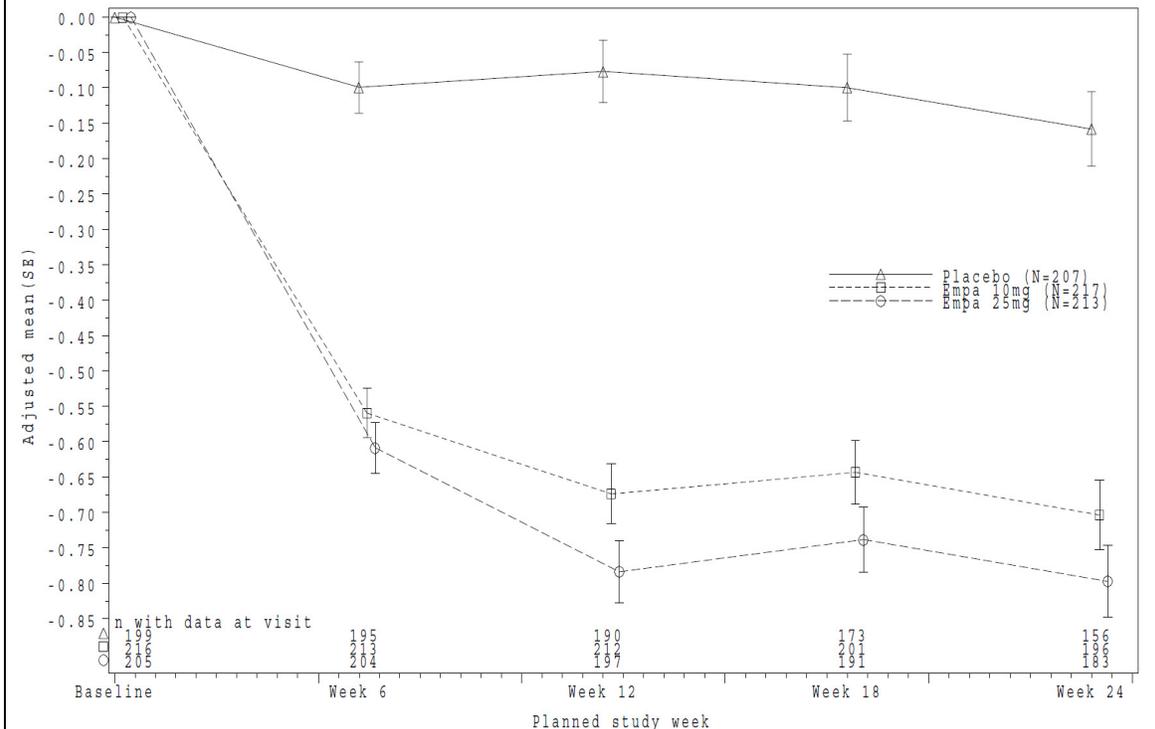
D: Add-on to Pio±Met trial 1245.19 FAS-OC [Source: Sponsor's Figure 15.2.1.2.2: 1 in Report U12-12-1516-02 Page 311]



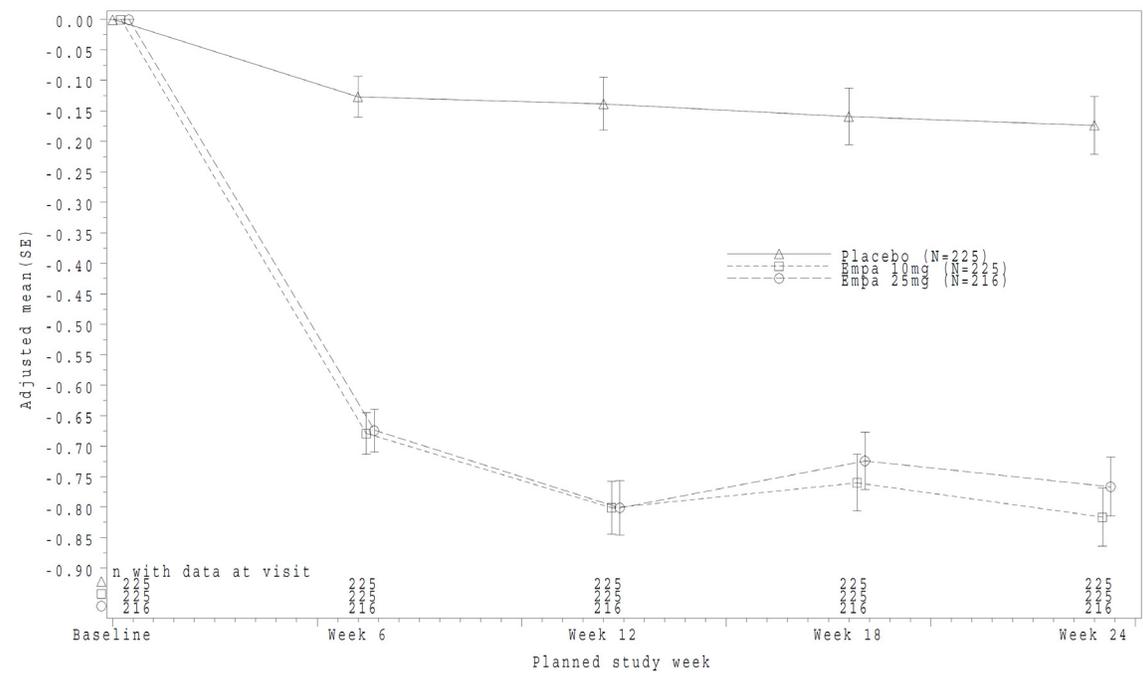
E: Trial 1245.23 Add on to Metformin only part [Source: Sponsor's Figure 15.2.1.2.2: 5 -FAS (LOCF) in Report U12-1518-01 Page 518]



F: Trial 1245.23 Add on to Metformin only part [Source: Sponsor's Figure 15.1.2.1.2.2: 1 -FAS (OC) in Report U12-1518-01 Page 514]



G: Trial 1245.23 Add on to Metformin+SU part [Source: Sponsor's Figure 15.2.1.2.2: 5 - FAS(LOCF) in Report U12-1518-01 Page 2265]



H: Trial 1245.23 Add on to Metformin+SU part [Source: Sponsor's Figure 15.2.2.1.2.2: 1 in Report U12-1518-01 on Page 2261]

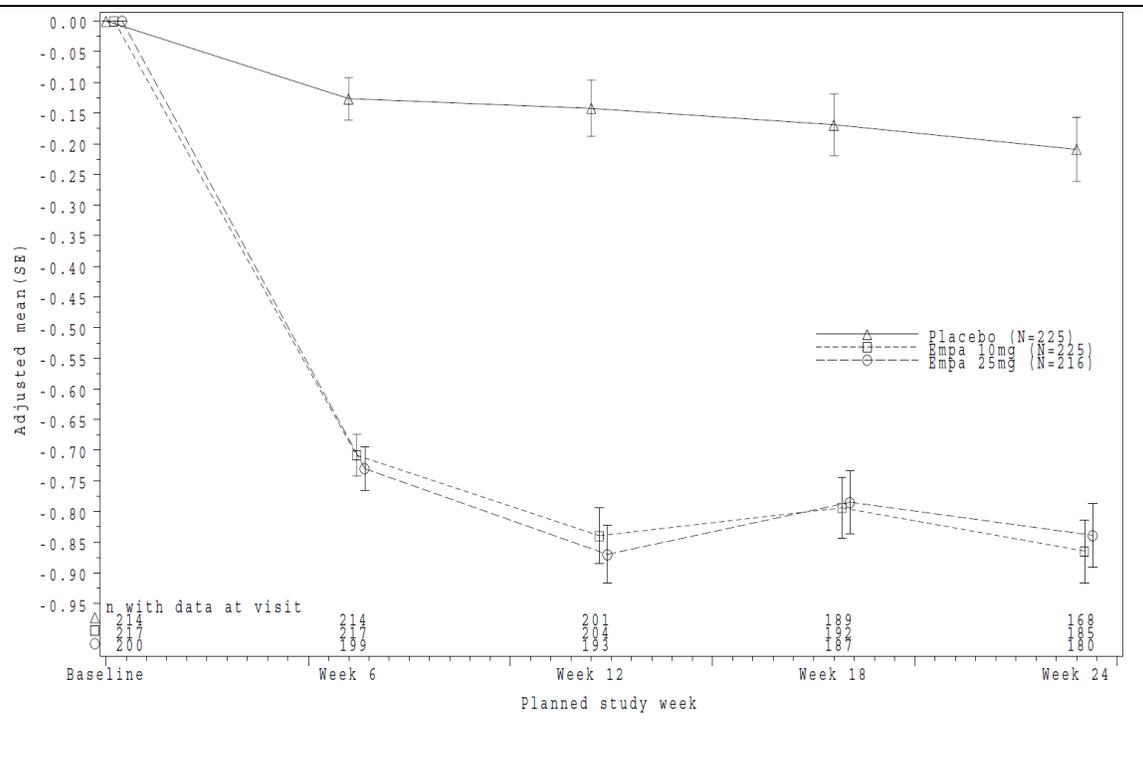
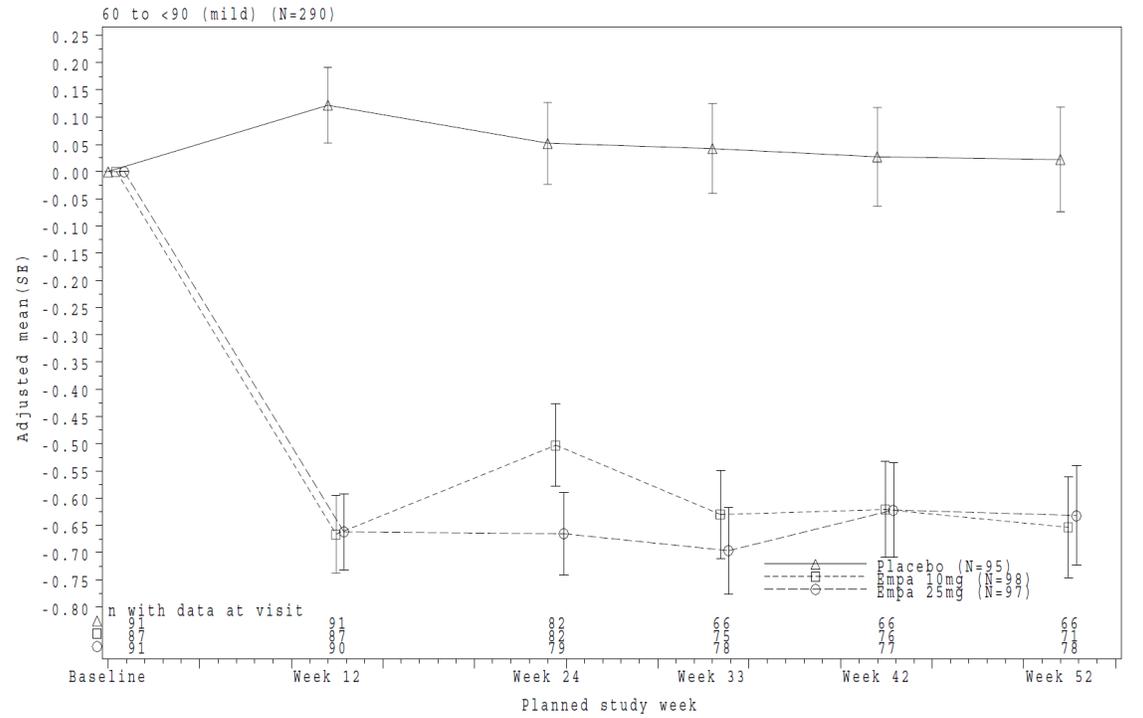
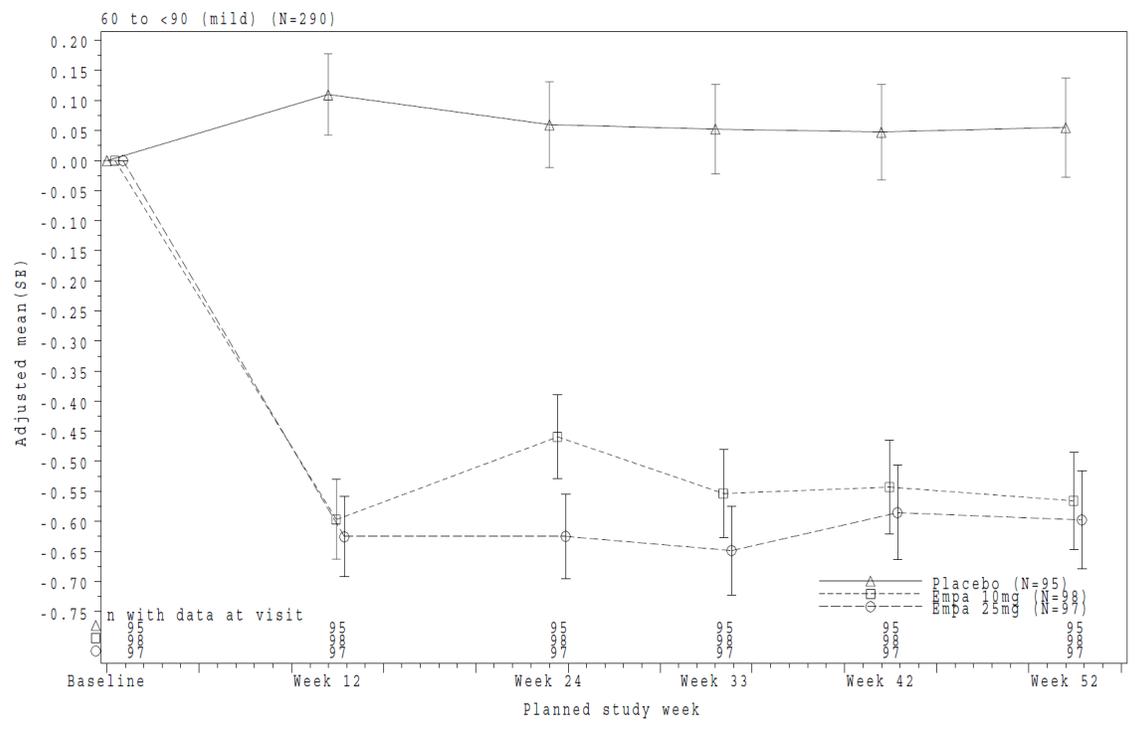


Figure 24: Time-profiles for adjusted mean (\pm SE) change from baseline in HbA1c in dedicated efficacy/safety trial in patients with Renal Impairment (RI) (1245.36)

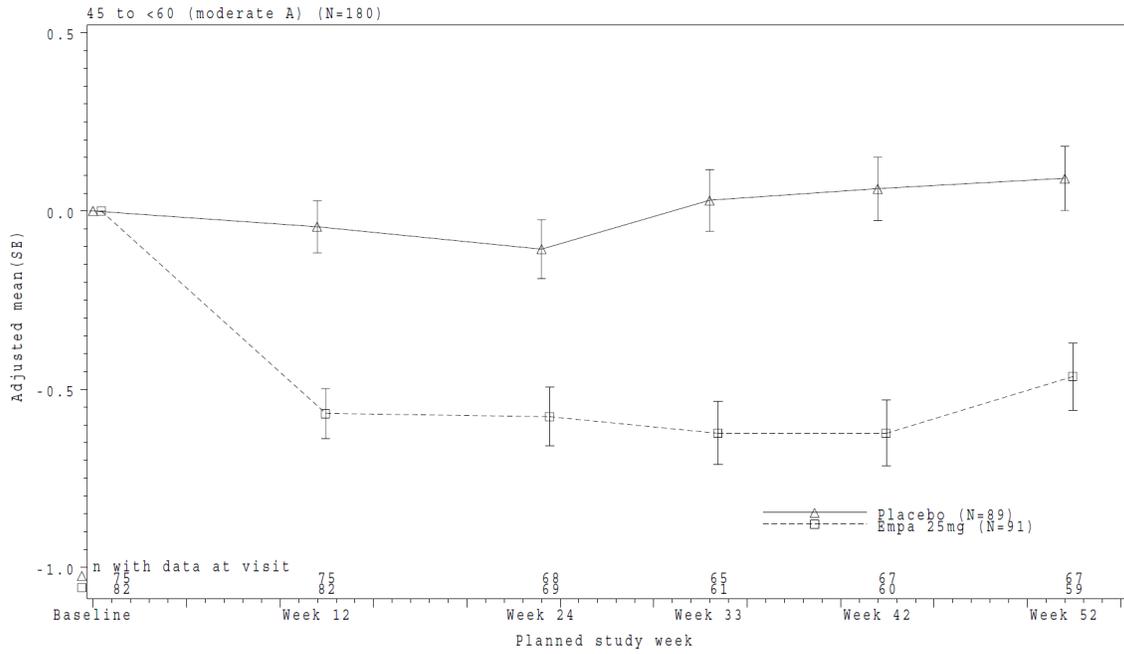
A: Trial 1245.36 FAS-OC in Mild RI [Source: Sponsor's Figure Figure 15.2.1.2.3.1: 1 - FAS(OC) in Report U12-1522-01 Page 1247]



B: Trial 1245.36 FAS-OC in Mild RI [Source: Sponsor's Figure Figure 15.2.1.2.3.1: 5 - FAS(LOCF) in Report U12-1522-01 Page 1279]



C: Trial 1245.36 FAS-OC in Moderate RI-A [Source: Sponsor's Figure 15.2.1.2.3.2: 1 in Report U12-1522-01 on Page 1308]



D: Trial 1245.36 FAS-OC in Moderate RI-B Figure 15.2.1.2.3.2: 1

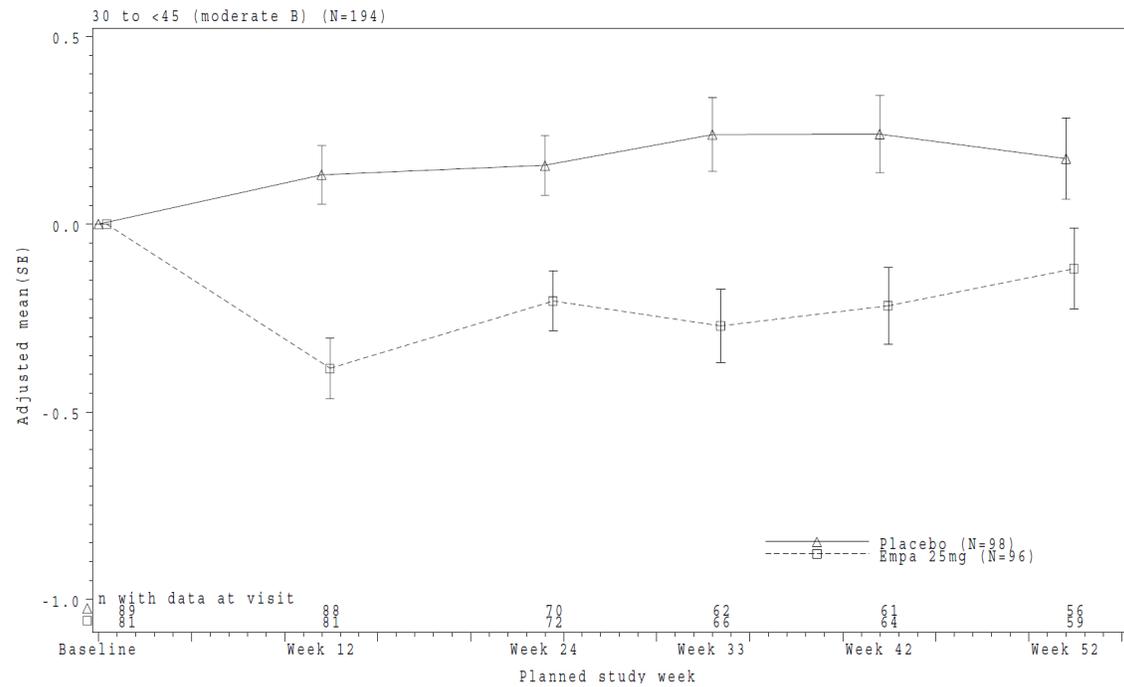
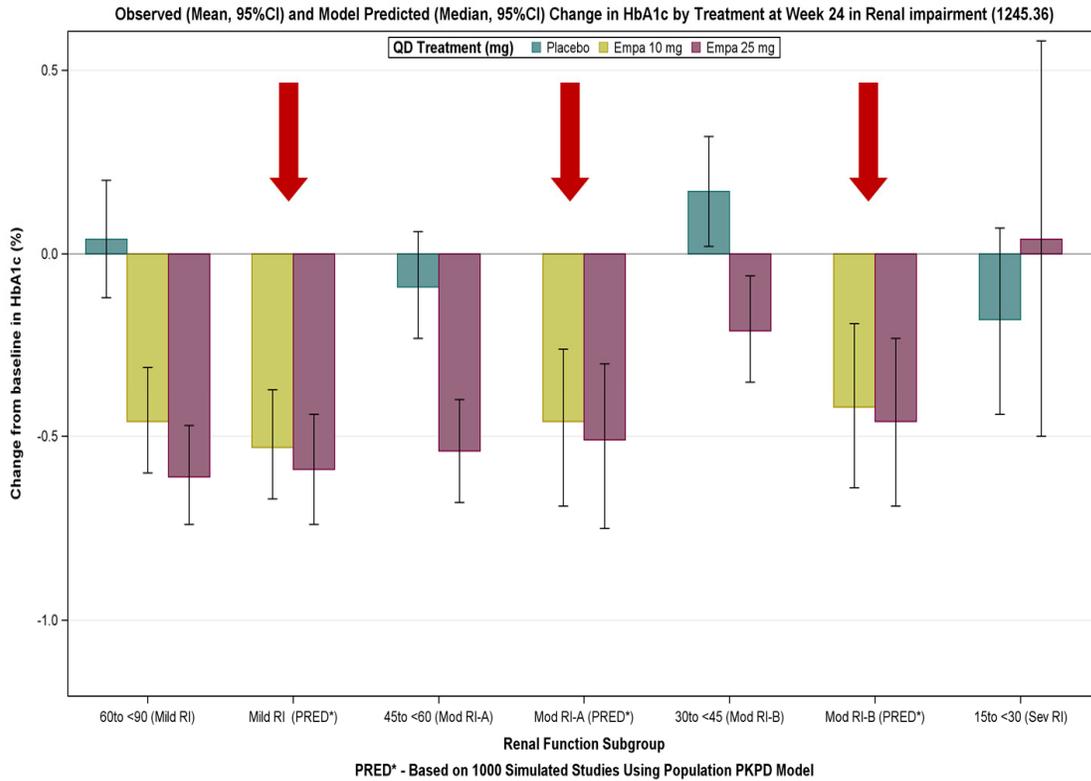
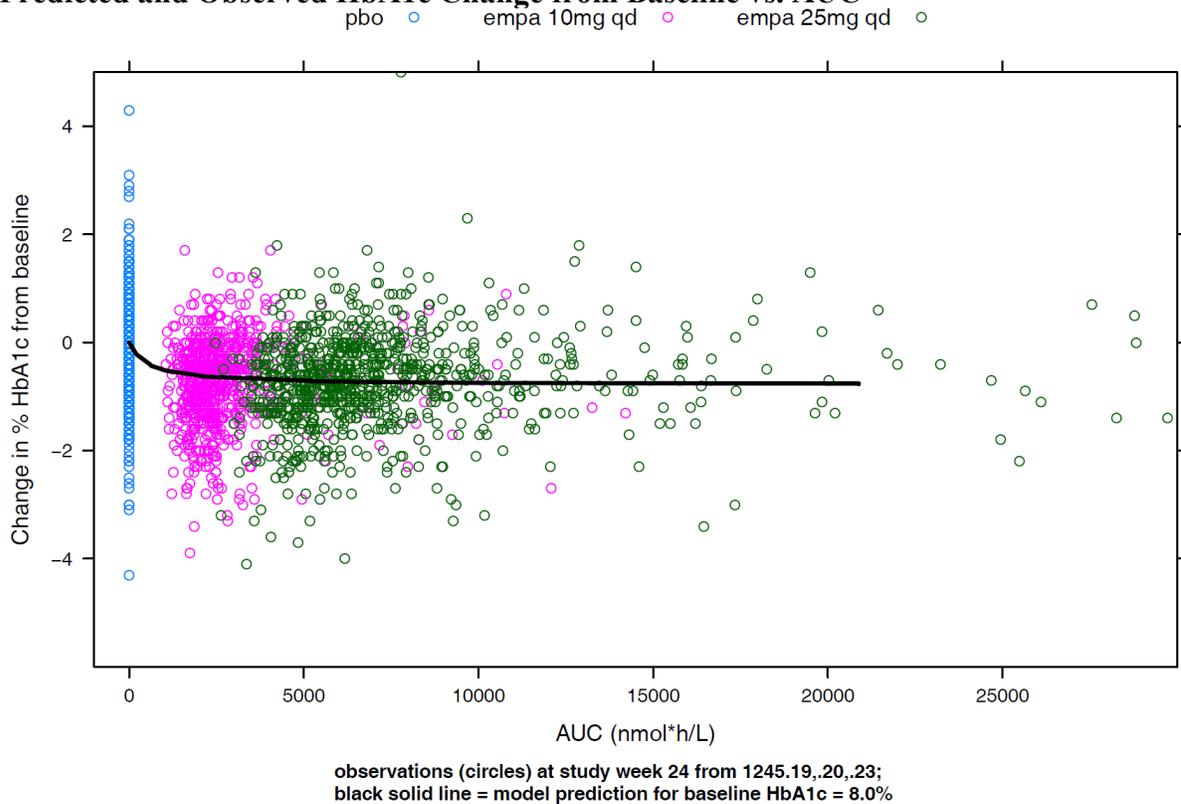


Figure 25: Observed and model simulated (indicated by down arrows) change from baseline in HbA1c for dedicated efficacy/safety trial in patients with Renal Impairment (RI) (1245.36)



[The model predicted data was provided by the sponsor in response to the information request sent after the Mid-Cycle discussion. See the sponsor's response to Information Request, dated 10/02/2013 in the EDR]

Figure 26: Efficacy E-R FPG-HbA1c Model 4030 Diagnostic Plots: Population Predicted and Observed HbA1c Change from Baseline vs. AUC



[Source: Figure 106 on Page 208 of Population PKPD report U12-2525-01]

4.3 OCP Filing Memo

Office of Clinical Pharmacology New Drug Application Filing and Review Form				
General Information about the Submission				
	Information		Information	
NDA Number	204629		Brand Name	JARDIANCE™ (Proposed)
OCP Division (I, II, III, IV, V)	DCP II		Generic Name	Empagliflozin
Medical Division	DMEP		Drug Class	SGLT-2 inhibitor
OCP Reviewer	Manoj Khurana, Ph.D.		Indication(s)	An adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.
OCP Pharmacometrics Reviewer	Manoj Khurana, Ph.D.		Dosage Form	Film-coated Immediate-release Tablets; 10 mg and 25 mg
OCP Team Leader	Lokesh Jain, Ph.D.		Dosing Regimen	Once daily
Date of Submission	March 5, 2012		Route of Administration	Oral
Estimated Due Date of OCP Review	November 05, 2013		Sponsor	Boehringer Ingelheim Pharmaceuticals, Inc.
PDUFA Due Date	March 5, 2014		Priority Classification	Standard
Division Due Date				
Clin. Pharm. and Biopharm. Information				
	"X" if included at filing	Number of studies submitted	Number of studies reviewed	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			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X	31		
I. Clinical Pharmacology				
Mass balance:	X	1		1245.08
Isozyme characterization:	X	5		studies including human liver microsomes; hepatocytes, transporters
Blood/plasma ratio:	X	1		DM-06-1083
Plasma protein binding:	X	1		DM-07-1001
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X	1		1245.01
multiple dose:	X			
Patients-				
single dose:				
multiple dose:	X	1		1245.02
Dose proportionality -				
fasting / non-fasting single dose:	X			1245.79
fasting / non-fasting multiple dose:				

Drug-drug interaction studies -				
In-vivo effects on primary drug:	X	15		1245-n, n=6, 7, 17, 18, 27, 30, 40, 41, 42, 43, 45, 50, 58, 63, 83
In-vivo effects of primary drug:	X	-do-		
In-vitro:	X	8		Enzyme/transporter interactions
Subpopulation studies -				
ethnicity:	X	2		1245.05 (JPN), 1245.44 (CHN)
gender:				
pediatrics:				
geriatrics:				
renal impairment:	X	1		1245.12
hepatic impairment:	X	1		1245.13
PD:				
Phase 2:	X			
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:	X	3		1245.16 (TQT) 1245.04 (MD T2DM), 1245.15 (MD, T2DM, JPN)
Phase 3 clinical trial:	X			See pop-pkpd analysis section
Population Analyses -				
Data rich:	X	1		U12-2524 (Used data from 1245.2, 1245.4, 1245.15, and 1245.12)
Data sparse:	X	1		U12-2525 (Used data from Phase 1 trials: 1245.2, 1245.4, 1245.9, 1245.10, 1245.15, Phase 2b trial 1245.33, and Phase 3 trials 1245.19, 1245.20, 1245.23, and 1245.36 for Pop-PKPD E/R Analysis)
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	X	1		1245.51 (TBM vs. TF2)
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:	X	2		1245.79 (with TBM formulation); 1245.03 (With TF1)
Dissolution: (IVIVC):				
Bio-wavier request based on BCS				
BCS class	X			
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				

Pediatric development plan	X		Waiver: (b) (4) Deferral PKPD Study 1245.87 plan 5, 10, 25 mg Phase 3 Study 1245.56 plan: 5, 10 or 25 mg based on PK study results
Literature References			
Total Number of Studies		76	
Filability			
	"X" if yes	Comments	
Is Application filable?	X	Comments to the Sponsor: Please submit raw electronic data sets for the DDI Study #1245.83 titled "A randomised, open-label, three-way crossover trial to investigate the effect of rifampicin and probenecid on empagliflozin pharmacokinetics in healthy male and female subjects".	
Submission in Brief: See the details below.	<p>Reviewer's Comments: The preNDA meeting minutes included the following discussion points, indicating that company should submit this data within 30 days:</p> <p>"Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. We agreed that the following minor application components may be submitted within 30 calendar days after the submission of the original application:</p> <p>Clinical Pharmacology assessment of in vivo chiral conversion of empagliflozin in human clinical samples."</p> <p>Sponsor included one study report with the NDA submission (Document No.: U13-3020-01 Report No.: DM-12-1184) that documents the evaluation of the chiral conversion of empagliflozin by quantitating (b) (4) in pooled human plasma samples obtained from a Clinical Study.</p>		

Submission in Brief:

The sponsor, Boehringer Ingelheim Pharmaceuticals, Inc. (hereafter BI), has submitted a new drug application (NDA) seeking approval for (b) (4) (Empagliflozin).

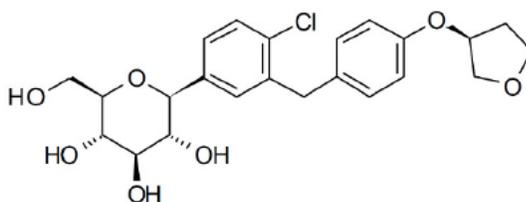


Figure 1 Molecular structure of empagliflozin

[D-Glucitol,1,5-anhydro-1-C-[4-chloro-3-[[4-[[[(3S)-tetrahydro-3-furanyl]oxy]phenyl]methyl]phenyl]-, (1S). Molecular formula: C₂₃H₂₇ClO₇, Molecular weight: 450.91 g/mol]

Empagliflozin is an inhibitor of sodium-glucose co-transporter 2 (SGLT2) with a claimed IC₅₀ of 1.3 nM. It has a 5000-fold selectivity over human SGLT1 (IC₅₀ of 6278 nM),

responsible for glucose absorption in the gut. In addition, high selectivity was shown toward other glucose transporters (GLUTs). SGLT2 is highly expressed in the kidney, and is the predominant transporter for re-absorption of glucose from the glomerular filtrate back into the systemic circulation. In patients with type 2 diabetes and hyperglycemia a higher amount of glucose is filtered and reabsorbed. By inhibiting SGLT2 empagliflozin reduces renal re-absorption of glucose. This promotes increased urinary glucose excretion resulting in reduction of blood glucose levels.

The clinical program comprises 30 phase I trials and 13 phase IIb/III trials. Overall, 13767 subjects were treated in these clinical trials, 6808 patients were treated with empagliflozin for at least 24 weeks, 4415 patients for at least 52 weeks, and 1486 patients for at least 76 weeks. In clinical studies, empagliflozin was evaluated as monotherapy and in combination with metformin, glimepiride, pioglitazone, insulin, and DPP-4 inhibitors. During the clinical development program, the sponsor also assessed the cardiovascular (CV) risk associated with empagliflozin therapy by conducting a prospective, pre-specified meta-analysis of independently adjudicated cardiovascular events.

Trial characteristics	Trial number	Reference	Geographical regions	Duration analysed
Pivotal double-blind phase III trials	1245.19	[U12-1516]	Europe, Asia, North America	24 weeks
	1245.20	[U12-1517]	Europe, Asia, North America	24 weeks
	1245.23 _(met)	[U12-1518]	Europe, Asia, North America, Latin America	24 weeks
	1245.23 _(met+SU)	[U12-1518]	Europe, Asia, North America, Latin America	24 weeks
Double-blind phase III extension trials	1245.31	[U12-1521]	Europe, Asia, North America, Latin America	52 weeks ¹
Additional phase IIb/III double-blind individual trials	1245.28	[U12-1520]	Europe, Asia, North America, Latin America, Africa/Middle East	52 weeks ²
	1245.33 ³	[U12-3817]	Europe, Asia, North America,	78 weeks
	1245.48	[U12-1526]	Europe, North America, Africa/Middle East	12 weeks
	1245.36	[U12-1522]	Europe, Asia, North America, Africa/Middle East	52 weeks
	1245.25	No clinical trial report available	Europe, Asia, North America, Latin America, Africa/Middle East	12 weeks ⁴
Open label phase IIb extension trial	1245.24	[U12-1213]	Europe, Asia, North America, Latin America	90 weeks ⁵

¹ Including the 24-week treatment duration in the preceding trials; 52-week efficacy data from a prespecified interim analysis are included in this submission. The overall planned duration (initial trials + extensions) is 76 weeks

² Minimum duration at time of interim analysis; overall planned duration is 208 weeks

³ Trial 1245.33 was conducted in patients with basal insulin as background therapy. This trial was originally designated as a phase IIb trial. Since it had confirmatory testing introduced via a protocol amendment, it is considered to be equivalent to a confirmatory phase III trial for the assessment of the efficacy and safety of empagliflozin

³ Minimum duration at time of interim analysis; overall anticipated duration is between 6 and 8 years

⁵ Data from a combined analysis with the preceding double-blind preceding trials 1245.9 and 1245.10 are presented

Formulation Development:

There were changes in the formulation during the drug development. However, the final formulation was used in the pivotal Phase 3 trials.

Table 1 Overview of formulations and manufacturing processes applied to clinical trial batches

Formulation type	General manufacturing principle	Clinical studies *
(b) (4) tablets (TF I)	(b) (4)	Phase I: 1245.1, 2, 3, 4
(b) (4) tablets (TF II)	(b) (4)	Phase I: 1245.5, 6, 7, 12, 13, 17, 27, 30, 51 Phase II: 1245.9, 10, 15, 24, 33
Film-coated tablets (FF)	(b) (4)	Phase I: 1245.16, 18, 40, 41, 43, 44, 45, 50, 51, 53, 58, 63, 79, 83 Phase II: 1245.38 Phase III: 1245.19, 20, 23, 25, 28, 31, 36, 48

* numbers in bold indicate pivotal clinical studies

Trial formulation II and Final Formulation FF, intended for commercial supply, were compared in a relative bioavailability study (1245.51, U11-1756).

The composition of the formulations is mentioned below:

Table 2 Qualitative and quantitative composition of empagliflozin film-coated tablets: 10 mg and 25 mg

Ingredient	[mg / tablet] 10 mg	[mg / tablet] 25 mg	Function	Reference to Standards
(b) (4)				
Empagliflozin	10.000	25.000	Drug substance	Company standard
Lactose monohydrate	(b) (4)	(b) (4)		NF
Microcrystalline cellulose	(b) (4)	(b) (4)		NF
Hydroxypropylcellulose	(b) (4)	(b) (4)		NF
Croscarmellose sodium	(b) (4)	(b) (4)		NF
Colloidal silicon dioxide	(b) (4)	(b) (4)		NF
Magnesium stearate	(b) (4)	(b) (4)		NF
(b) (4)				USP
(b) (4)				Company standard
(b) (4)				USP
Total mass of film-coated tablet	257.0	206.0		

*) Removed during processing; does not appear in the final drug product

Sponsor mentioned that Empagliflozin drug substance is (b) (4). The particle size for empagliflozin drug substance (b) (4).

is tightly controlled to

(b) (4)

(b) (4)

Key Clinical Pharmacology Review Questions:

- **What is the dose-response, systemic exposure-response relationship for Empagliflozin for efficacy?**
 - Does exposure-response information support the adequacy of the proposed dose of 25 mg QD?
 - Is there an impact of renal impairment on the efficacy of Empagliflozin?
- **What is the dose-response, systemic exposure-response relationship for Empagliflozin for safety?**
 - Does exposure-safety information support the proposed dose of 25 mg QD?
- **What is the concentration-QT relationship for Empagliflozin concerning safety? (IRT-QT Consult)**
- **What is the effect of food on pharmacokinetics of Empagliflozin?**
 - Do the results support sponsor's proposed language in the label that "Empagliflozin can be taken with or without food"?
 - Are analytical methods adequate?
- **What is the effect of Empagliflozin on other co-administered drugs and vice-versa?**
 - Does the DDI result warrant for any dose adjustments for Empagliflozin and the co-administered drugs?
 - Are analytical methods adequate?
- **Are sponsor's assessments for specific populations appropriate and do they adequately support the proposed labeling language?**
- **What is the relative bioavailability of to-be-marketed formulation in comparison to the formulations used in the development phase?**
 - Are analytical methods adequate?

The key aspects of the filing and questions for clinical pharmacology review are presented in the slides below:

Attachment 1: Clinical Pharmacology Filing Meeting Presentation

**NDA 204069 Filing Meeting
Clinical Pharmacology Perspective**

**Empagliflozin ("Empa")
(b) (4) (Proposed)**

Sponsor: Boehringer Ingelheim
Submitted: 03/05/2013

Manoj Khurana, PhD
Division of Metabolism and Endocrinology Products
Office of Clinical Pharmacology

OCF Review Team:
Clin. Pharm. and Pharmacometrics Reviewer: Manoj Khurana, PhD
Clin. Pharm. Team Leader: Lokesh Jain, PhD
Pharmacometrics Team Leader: Nilesh Mehrotra, PhD

Empagliflozin: A new molecular entity

Class: SGLT2 inhibitor in proximal renal tubule

Proposed Indication:
- adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus

Formulation: film-coated oral tablets:
- 10 mg
- 25 mg

Proposed dose:
- 25 mg QD, with or without food
- Not recommended in severe RI (eGFR <30 mL/min/1.73 m²)

Proposed use spans from Moderate RI to Normal RF
- Reduce dose of insulin/insulin secretagogue (e.g., SU)

Overview of Clinical Pharmacology Studies

Pharmacokinetic and pharmacodynamic trials in healthy volunteers

Trial 1241.1 Single rising dose study in Caucasian healthy volunteers
Trial 1241.2 Once daily vs. twice daily regimen in healthy volunteers
Trial 1241.3 Human ADME study
Trial 1241.4 Through OCT study

Pharmacokinetic and pharmacodynamic trials in patients with T2DM

Trial 1242.2 8-day multiple rising dose study in Caucasian patients
Trial 1242.4 4-week repeated dose study in Caucasian patients

Special population trials

Trial 1242.5 Single rising dose study in Japanese healthy volunteers
Trial 1242.6 Single rising dose study in Chinese patients
Trial 1242.7 In-vitro reproductive study in Japanese patients
Trial 1242.8 In-vitro reproductive study in Caucasian subjects
Trial 1242.9 In-vitro reproductive study in Caucasian subjects

Drug-drug interaction trials

Trial 1242.10 SOD with warfarin Trial 1242.40 SOD with Aspirin
Trial 1242.7 SOD with pioglitazone Trial 1242.41 SOD with oral contraceptive (norgestrel and levonorgestrel)
Trial 1242.8 SOD with pioglitazone Trial 1242.42 SOD with diuretic (hydrochlorothiazide and nifedipine)
Trial 1242.10 SOD with warfarin Trial 1242.43 SOD with aspirin
Trial 1242.11 SOD with warfarin Trial 1242.44 SOD with aspirin
Trial 1242.12 SOD with empagliflozin Trial 1242.45 SOD with pioglitazone
Trial 1242.13 SOD with empagliflozin Trial 1242.46 SOD with simvastatin
Trial 1242.14 SOD with empagliflozin Trial 1242.47 SOD with simvastatin and ezetimibe

Empagliflozin ADME

PK Profile – QD in T2DM (Trial 1245.4)

Fairly rapid absorption (t_{max} ~ 1.5 hour)
T_{1/2} ~ 12 hours (P_{0-100%} = 1.22 QD)
Absolute BA ~ 7-90-80% in animals
No t_{1/2} dependent PK

Metabolism:
- 2-O, 3-O, and 8-O glucuronides (~ 30% of total in plasma, formed by UGT2B7, UGT1A3, UGT1A6, and UGT1A9)
- 90% recovered.
- 41% in feces (~83% intact)
- 55% in urine (~50% intact)

No chiral conversion
RBC Partitioning ~ 30%
Pgp, OAT3, and BCRP substrate
Inhibitor of OAT3, OATP1B1, OATP1B3 and OATP2B1 (high IC50s)

Clin. Pharm. Review Questions

- Review Questions:**
- What are the PK and PD characteristics of Empagliflozin?
- Filing Issues:**
- Did sponsor submit all the information for review? – Yes

Overview of efficacy and safety trials of empagliflozin

Timeline: 0, 4, 12, 24, 52, 76, 96, 120 weeks

Number of patients: 706, 404, 666, 214, 1547, 874, 718, 4074, 406, 497

Trials:
- 1241.1, 1241.2, 1241.3, 1241.4, 1241.5, 1241.6, 1241.7, 1241.8, 1241.9, 1241.10, 1241.11, 1241.12, 1241.13, 1241.14, 1241.15, 1241.16, 1241.17, 1241.18, 1241.19, 1241.20, 1241.21, 1241.22, 1241.23, 1241.24, 1241.25, 1241.26, 1241.27, 1241.28, 1241.29, 1241.30, 1241.31, 1241.32, 1241.33, 1241.34, 1241.35, 1241.36, 1241.37, 1241.38, 1241.39, 1241.40, 1241.41, 1241.42, 1241.43, 1241.44, 1241.45, 1241.46, 1241.47, 1241.48, 1241.49, 1241.50, 1241.51, 1241.52, 1241.53, 1241.54, 1241.55, 1241.56, 1241.57, 1241.58, 1241.59, 1241.60, 1241.61, 1241.62, 1241.63, 1241.64, 1241.65, 1241.66, 1241.67, 1241.68, 1241.69, 1241.70, 1241.71, 1241.72, 1241.73, 1241.74, 1241.75, 1241.76, 1241.77, 1241.78, 1241.79, 1241.80, 1241.81, 1241.82, 1241.83, 1241.84, 1241.85, 1241.86, 1241.87, 1241.88, 1241.89, 1241.90, 1241.91, 1241.92, 1241.93, 1241.94, 1241.95, 1241.96, 1241.97, 1241.98, 1241.99, 1242.00, 1242.01, 1242.02, 1242.03, 1242.04, 1242.05, 1242.06, 1242.07, 1242.08, 1242.09, 1242.10, 1242.11, 1242.12, 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FDA U.S. Food and Drug Administration
Priority and Promoting Public Health
www.fda.gov

Extrinsic Factor – Food Effect

Mean plasma concentration-time profiles of empagliflozin after oral administration of single 25 mg empagliflozin tablet (25 mg empagliflozin final formulation tablet) under fasted and fed (standard high fat, high calorie meal) conditions (TRIAL: 1245.79).
Similar results for TF1 in TRIAL 1245.3

- **Sponsor:**
 - Food effect not clinically relevant for formulations TF1 and FF
 - Can be administered with and without food
- **Review Questions:**
 - Are sponsor's claims acceptable?
 - Is proposed language in label acceptable?
- **Filing Issues:**
 - Did sponsor submit all the information for review? – Yes

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

PK Comparability of Different Formulations

Mean plasma concentration-time profiles of empagliflozin after oral administration of 25 mg empagliflozin final formulation tablet or empagliflozin total formulation 2 tablets (TRIAL: 1245.51)

- **Sponsor:**
 - To-be-marketed formulation used in Phase 3
 - Formulations TF2 and FF are bioequivalent for PK
- **Review Questions:**
 - Are sponsor's claims acceptable?
- **Filing Issues:**
 - Did sponsor submit all the information for review? – Yes

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Application Filability and Consults

- Yes, the application is filable
- No OSI consults
- IRT-QT for the thorough QT study

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Attachment 2: GRMP Filing Memo

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING CHECKLIST FOR A NEW NDA/BLA**

**NDA/BLA Number: 204629 Applicant: Boehringer Ingelheim Stamp Date: 03/05/2013
Pharmaceuticals, Inc.**

Drug Name: Empagliflozin NDA/BLA Type: (505(b)(1))

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

	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	TBM formulation was used in Phase 3
2	Has the applicant provided metabolism and drug-drug interaction information?	X			
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	X			
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			
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			
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			
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	X			
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	X			

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Checklist for a New NDA_BLA 110307

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING CHECKLIST FOR A NEW NDA/BLA**

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.

Manoj Khurana	05/03/2013
Reviewing Pharmacologist	Date
Lokesh Jain	05/03/2013
Team Leader/Supervisor	Date

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Checklist for a New NDA_BLA 110307

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

/s/

MANOJ KHURANA
11/08/2013

NITIN MEHROTRA
11/08/2013

LOKESH JAIN
11/08/2013

BIOPHARMACEUTICS REVIEW			
Office of New Drug Quality Assessment			
Application No.:	NDA 204-629	Reviewer: Houda Mahayni, Ph.D.	
Division:	DMEP		
Applicant:	Boehringer Ingelheim Pharmaceuticals, Inc.	Acting Team Leader: Sandra Suarez, Ph.D.	
Trade Name:	Jardiance	Acting Supervisor: Richard T. Lostritto, Ph.D.	
Generic Name:	Empagliflozin (BI 10733)	Date Assigned:	March 5, 2013
Indication:	An adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus	Date of Review:	October 25, 2013
Formulation/strength	Film-coated immediate-release tablets/10 mg and 25 mg		
Route of Administration	Oral		
SUBMISSIONS REVIEWED IN THIS DOCUMENT			
Submission Dates		Date of Consult	PDUFA DATE
		March 5, 2013 October 1, 2013	March 5, 2014
Type of Submission:	505 (b) (1) NDA (NMEs being reviewed under the Program)		
Key review points	Dissolution Method and Acceptance Criterion		

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7. Is the proposed dissolution method biorelevant? What data are available to support this claim?	
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11. Is the setting of the dissolution acceptance criterion based on data from clinical and registration batches?	

12. Are mean (n=12) dissolution profile data used for the setting of the acceptance criterion?
13. Is the acceptance criterion acceptable? If not, what is the recommended criterion?

C) DRUG PRODUCT FORMULATION DEVELOPMENT AND BRIDGING ACROSS PHASES

14. What is the composition of the formulation of the proposed product? 24
15. What are the highlights of the drug product formulation development?
16. Are all the strengths evaluated in the pivotal clinical trials? If not, what data are available to support the approval of lower strengths?
17. Are there any manufacturing changes implemented (e.g. formulation changes, process changes, site change, etc.) to the clinical trial formulation? What information is available to support these changes?
18. Is the formulation of the clinical product the same formulation of the to-be-marketed product? If not, what information is available to support the formulation changes?
19. Is the manufacturing site the same for the clinical and to-be-marketed products? If not, what information is available to support the new site?

D) DISSOLUTION APPLICATIONS 27

D.1 BIOWAIVERS

20. Is there a waiver request of in vivo BA or BE data (Biowaiver)? If yes, what is/are the purpose/s of the biowaiver request/s? What data support the biowaiver request/s? Is the biowaiver request acceptable?
21. Is there any IVIVR or IVIVC information submitted? What is the regulatory application of the IVIVR or IVIVC in the submission? What data are provided to support the acceptability of the IVIVR or IVIVC model?

D.2 SURROGATES IN LIEU OF DISSOLUTION 28

22. Are there any manufacturing parameters (e.g. disintegration, drug substance particle size, etc.) being proposed as surrogates in lieu of dissolution testing? What data are available to support the approval of the proposed surrogate test?

D.3 DISSOLUTION AND QBD 28

23. Does the application contain QbD elements? If yes, is dissolution identified as a CQA for defining design space?

24. Was dissolution included in the DoE? What raw materials and process variables are identified as having an impact on dissolution? What is the risk assessment been performed to evaluate the criticality of dissolution?
25. What biopharmaceutics information is available to support the clinical relevance of the proposed design space?
26. Is there any dissolution model information submitted as part of QbD implementation? What is the regulatory application of the dissolution model in the submission? What data are provided to support the acceptability of the dissolution model?

D) SUMMARY OF BIOPHARMACEUTICS FINDINGS

Original NDA 204-629 for Empagliflozin (BI 10773) was submitted in accordance with the regulations set forth in section 505 (b) (1) of the FDC Act.

Empagliflozin (BI 10773) is a NME being reviewed under the Program. It is claimed to be a selective inhibitor of the sodium glucose co-transporter 2 (SGLT-2). The proposed indication is to be used as an adjunct to diet and exercise to improve glycemic control in adult with type 2 diabetes mellitus (b) (4)

The proposed drug product is a film-coated tablet formulation comprised of the drug substance (Empagliflozin), lactose monohydrate, microcrystalline cellulose, hydroxypropyl cellulose, croscarmellose sodium, colloidal silicon dioxide, magnesium stearate, and the film coat (b) (4)

Although the drug product has two dosage strengths (10 mg and 25 mg), the dosage strength of 25 mg is the only strength being proposed for marketing. The recommended dose administration is 25mg once daily, with or without food.

The proposed commercial process and formulation is the same as used for manufacture of the phase 3 clinical trials supplies.

The Applicant has QbD elements in the application, but a design space is not proposed, and alternative control strategies are not sought.

Empagliflozin film-coated tablets are manufactured (b) (4)

This review is focused on the evaluation of the acceptability of the dissolution test method and acceptance criterion.

The Applicant proposed the following dissolution method conditions and acceptance criterion:

Apparatus:	Paddle (Apparatus 2, Ph. Eur., USP, JP)
Agitation:	75 rpm
Medium:	900 mL phosphate buffer pH 6.8
Temperature:	37°C
Sampling time:	(b) (4) minutes
Analytical procedure:	isocratic HPLC, detection at 224 nm
Proposed regulatory Acceptance criterion:	"Q = (b) (4)% at (b) (4) minutes"

FDA considered the Applicant's proposed acceptance criterion ($Q = \frac{(b)}{(4)}\%$ in $\frac{(b)}{(4)}$ minutes) wide based on results obtained on representative batches, including batches used in Phase III clinical studies and primary stability studies. Therefore, FDA requested the Applicant $\frac{(b)}{(4)}$ the acceptance criterion to $Q = \frac{(b)}{(4)}\%$ in 15 minutes. FDA's request was communicated in an IR on September 16, 2013 as follow:

The proposed acceptance criterion of $Q = \frac{(b)}{(4)}\%$ at $\frac{(b)}{(4)}$ minutes is not supported by data. We recommend that you revise and implement the acceptance criterion of $Q = \frac{(b)}{(4)}\%$ at 15 minutes and provide an updated specifications table for the drug product.

The Applicant responded on October 1, 2013 and agreed $\frac{(b)}{(4)}$ the acceptance criterion for dissolution from $Q = \frac{(b)}{(4)}\%$ at $\frac{(b)}{(4)}$ minutes to $Q = \frac{(b)}{(4)}\%$ at 15 minutes for both release and shelf-life. Also, the Applicant updated the finished product specifications table in all the relevant sections of the NDA.

II) RECOMMENDATION

The ONDQA-Biopharmaceutics team reviewed NDA 204-629 for Jardiance (Empagliflozin) film-coated tablets, 25 mg.

The following dissolution method parameters and acceptance criterion are acceptable:

-paddle apparatus, 75 rpm, 900 mL, 0.05 M phosphate buffer pH 6.8

- $Q = \frac{(b)}{(4)}\%$ at 15 minutes

From the Biopharmaceutics perspective, NDA 204-629 for Jardiance (Empagliflozin) film-coated tablets, 25 mg is recommended for approval.

Houda Mahayni, Ph. D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Sandra Suarez, Ph.D.
Acting Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

cc: DARRTS/Lostritto

III) BIOPHARMACEUTICS ASSESSMENT-QUESTION BASED REVIEW APPROACH

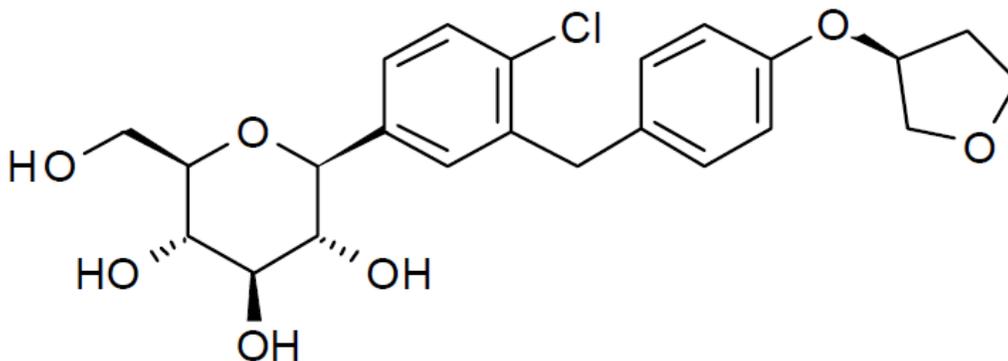
A) GENERAL ATTRIBUTES

1. *What are the highlights of the chemistry and physico-chemical properties of the drug substance (e.g. solubility) and formulation of the drug product?*

Drug Substance

Empagliflozin is described chemically as D-Glucitol, 1, 5-anhydro-1-C-[4-chloro-3-[[4-[[[(3S)-tetrahydro-3-furanyl] oxy] phenyl] methyl] phenyl]-, (1S). It is claimed to be a selective inhibitor of the sodium glucose co-transporter 2 (SGLT-2).

The empirical formula is $C_{23}H_{27}ClO_7$ and the molecular weight is 450.91 g/mol. The structural formula is shown below.



Empagliflozin has a (b) (4) and its solubility is pH independent in the physiological range. Empagliflozin has a solubility of 0.28 mg/ml in water at 20 °C (See Table 1).

Table 1: Solubility profile of Empagliflozin in aqueous media at room temperature

Medium	Solubility [mg/mL]	pH of the sat. sol.
Water	0.28	8.6
0.1 N HCl	0.30	1.1
McIlvaine buffer pH 4.0	0.21	4.1
McIlvaine buffer pH 7.4	0.14	7.5

Source data: Section 3.2.S.3.1 Physicochemical characteristics [U12-1202]

At 37 °C, Empagliflozin solubility in water increased to 0.47 mg/ml (See Table 2).

Table 2: Solubility data of Empagliflozin in aqueous media at 37 °C

Medium	Sample	Solubility mg/mL		Degradation (Sum) ^a	pH-value (23°C)	
		Single value	average	%	start	end
H ₂ O	1	0.469		≤ 0.1		6.1 ^b
	2	0.473	0.471	≤ 0.1	7.2 ^b	6.4 ^b
	3	0.471		≤ 0.1		6.3 ^b
pH 1.0 0.1M HCL	1	0.459		≤ 0.1		1.2
	2	0.459	0.460	≤ 0.1	1.2	1.2
	3	0.461		≤ 0.1		1.2
pH 3.0 McIlvaine buffer	1	0.462		≤ 0.1		3.0
	2	0.465	0.464	≤ 0.1	3.1	3.0
	3	0.465		≤ 0.1		3.0
pH 4.5 0.1 M Sodium- Acetate buffer	1	0.478		≤ 0.1		4.5
	2	0.473	0.475	≤ 0.1	4.5	4.5
	3	0.475		≤ 0.1		4.5
pH 6.8 0.1 M Potassium- Phosphate buffer	1	0.390		≤ 0.1		6.8
	2	0.398	0.395	≤ 0.1	6.8	6.8
	3	0.396		≤ 0.1		6.8
pH 7.5 0.1 M Potassium- Phosphate buffer	1	0.385		≤ 0.1		7.5
	2	0.389	0.386	≤ 0.1	7.5	7.5
	3	0.384		≤ 0.1		7.5

^a relative to the average value of dissolved substance

^b not buffered

Source data: Section 3.2.S.3.1 Physicochemical characteristics [U12-1202]

The octanol/water partition coefficient log P is 1.7.

The Applicant stated that Empagliflozin drug substance (b) (4) (b) (4) The particle size distribution was determined by a laser diffraction method. The 90th percentile (X90) of the cumulative particle size distribution is set to an acceptance criterion of X90 (b) (4) μm.

Drug Product

The proposed drug product is a film-coated tablet formulation comprised of the drug substance (Empagliflozin), lactose monohydrate, microcrystalline cellulose, hydroxypropyl cellulose, croscarmellose sodium, colloidal silicon dioxide, magnesium stearate, and the film coat (b) (4). Although the drug product has two dosage strengths (10 mg and 25 mg), the dosage strength of 25 mg is the only strength being proposed for marketing. The recommended dose administration is 25mg once daily, with or without food.

Empagliflozin film-coated tablets are manufactured (b) (4)

[REDACTED] (b) (4)

The two strengths (10 mg and 25 mg) are formulated [REDACTED] (b) (4)

Empagliflozin film-coated tablets, 10 mg are pale yellow, round, biconvex and bevel-edged film-coated tablets. One side is debossed with the code 'S10', the other side is debossed with the company symbol.

Empagliflozin film-coated tablets, 25 mg are pale yellow, oval, biconvex film-coated tablets. One side is debossed with the code 'S25', the other side is debossed with the company symbol.

The proposed market package presentations is plastic bottles containing 30, 90, [REDACTED] (b) (4) tablets and aluminum [REDACTED] (b) (4) blisters containing 10 tablets. The proposed package presentations for physician samples are aluminum [REDACTED] (b) (4) blister [REDACTED] (b) (4), [REDACTED] (b) (4) containing 7 tablets.

2. Is there any information on BCS classification? What claim did the Applicant make based on BCS classification? What data are available to support this claim?

A BCS Class III (high solubility/low permeability) is claimed for Empagliflozin. The Applicant reported that based on the pH solubility shown in Table 2 above, Empagliflozin can be classified as a highly soluble compound according to BCS for a dosage of up to 96.5 mg. Therefore, the highest dose (25 mg) is soluble in ≤ 250 mL of aqueous media over the pH range of 1-7.5 (> 0.4 mg/mL up to pH 7.5) and can be classified as a highly soluble compound.

The Applicant conducted in vitro permeability studies using Caco-2 monolayers. The Applicant stated that permeability results showed low absorptive permeability ($< 1 \times 10^{-6}$ cm/sec) and high secretory permeability ($\sim 18 \times 10^{-6}$ cm/sec) at donor compartment concentrations of 1, 10, and 50 μ m. Hence, the ratio of secretory to absorptive transport, or efflux ratio, for Empagliflozin is high (> 20). Additional mechanistic studies conducted using MDCK-MDR1 and Caco-2 cell monolayers demonstrated that Empagliflozin is a substrate for efflux transporters, i.e. P-glycoprotein (P-gp) and breast cancer resistant protein (BCRP), which are expressed in these cell lines. Therefore, based on in vitro permeability data, the Applicant classified Empagliflozin as a low permeability drug substance [U08-3676]. Also, the Applicant determined the lipophilicity of Empagliflozin drug substance by measuring the octanol/water partition coefficient (Log P = 1.7).

The Applicant stated that for this type of drug substance, the drug absorption (permeability) is rate limiting and not the dissolution of the drug product.

Reviewer's Note: Satisfactory.

Based on the solubility data of Empagliflozin, it can be concluded that Empagliflozin is a BCS class III substance. The permeability studies will be reviewed by OCP, as this NDA was submitted (March, 2013) before the implementation of the September 2013 MOU.

B) DISSOLUTION INFORMATION

B.1. DISSOLUTION METHOD

3. What is the proposed dissolution method?

The Applicant proposed the following dissolution method conditions and acceptance criterion:

Apparatus:	Paddle (Apparatus 2, Ph. Eur., USP, JP)
Agitation:	75 rpm
Medium:	900 mL phosphate buffer pH 6.8
Temperature:	37°C
Sampling time:	(b) (4) minutes
Analytical procedure:	isocratic HPLC, detection at 224 nm
Proposed regulatory	
Acceptance criterion:	"Q = (b) (4) % at (b) (4) minutes"

4. What data are provided to support the adequacy of the proposed dissolution method (e.g medium, apparatus selection, etc.)?

Apparatus Selection

The Applicant selected the paddle apparatus (Apparatus 2), as it is commonly used for dissolution testing of tablet formulations.

Rotation Speed Selection

The Applicant employed a rotation speed of 75 rpm (b) (4)
(b) (4) the agitation speed of 75 rpm is justified.

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(b) (4)

(b) (4)

6. *What information is available to support the robustness (e.g. linearity, accuracy, etc.) of the dissolution methodology?*

Dissolution testing of Empagliflozin film-coated tablets is performed using the paddle apparatus at 75 rpm in 900 ml phosphate buffer pH 6.8. The quantification of Empagliflozin was performed by HPLC-UV a (b) (4) nm.

The analytical method was validated with respect to specificity, linearity, accuracy, repeatability, intermediate precision, and robustness. The results show that the analytical method is suitable. Table 3 below provides a summary of the results of the validation parameters. Also, the Applicant assessed the stability of the sample and standard solutions and found that both solutions (sample and standard) are stable for 4 days.

Table 3: Validation summary for dissolution of Empagliflozin film-coated tablets, 25 mg

Validation Parameter	Method of Determination	Acceptance criteria / Results
Specificity	Visual evaluation of chromatograms of standard solution, solvent, and placebo	Acceptance criterion: Specific determination of active ingredient in presence of blank and placebo. Demonstrated non interference from blank and placebo at (b) (4) nm.
Linearity	7 concentration levels of empagliflozin	Acceptance criterion: The correlation coefficient should be (b) (4). The Y-intercept should be within (b) (4) % of the 100 % value. Linear range: (b) (4)%, correlation coefficient: (b) (4) Y-intercept: (b) (4) %
Accuracy	Mean accuracy (%) at about	Acceptance criterion: The mean recovery for the (b) (4) % concentration levels should be between (b) (4) and (b) (4) % of the theoretical value and for the (b) (4) % concentration levels between (b) (4) % of the theoretical value.
	20 % (n=3)	(b) (4) %
	75 % (n=3)	%
	130 % (n=3)	%
Repeatability	Overall RSD (%), spiked placebo at 3 different concentration levels	Acceptance criterion: The overall RSD should be (b) (4) % Overall RSD: (b) (4) %
Intermediate precision	Overall RSD (%) spiked placebo at 3 different concentration levels, including 2 operators, 2 dissolution apparatuses, 2 HPLC systems, analyses on different days	Acceptance criterion: The overall RSD should be (b) (4) % Overall RSD: (b) (4) %
Range	Derived from linearity, accuracy and precision	(b) (4) %

Validation Parameter	Method of Determination	Acceptance criteria / Results
Robustness	Stability of sample and standard preparation: Change in assay upon storage	Acceptance criterion: For test and standard solutions, the value determined after storage should be within (b) (4) % of the initial value. Test solution stable for 4 days at room temperature in glass vial; standard solution stable for 4 days at room temperature in glass flask and glass vial.
	Filter validation: Evaluation of the adsorption of the drug substance onto the filter	Two different filters (Membrex 25GC, Roby 25/GF 92) and the amount of initial filtrate, which needs to be discarded, are validated.
	Interchangeability of manual and automated measurements: Comparison of manual and semi automated determination	Acceptance criterion: The difference in the mean value between the dissolution results at (b) (4) minutes should be (b) (4) %. Difference in the mean value: (b) (4) %

Reviewer's Assessment: Satisfactory

7. Is the proposed dissolution method biorelevant? What data are available to support this claim?

The Applicant showed that two types of formulations (Trial Formulation:TFII and Final Formulation:FF) exhibit similar in vitro profiles which reflect the results obtained in vivo (the relative bioavailability study 1245.51). Therefore, the in vitro dissolution results reflect the in vivo performance of the formulation. But, there is no information to show that the method is able to reject batches that are not bioequivalent.

8. Is the proposed method acceptable? If not, what are the deficiencies?

The proposed dissolution method is acceptable. The Applicant provided an acceptable rationale to support selecting the proposed method parameters as optimal for routine dissolution testing.

B.2. ACCEPTANCE CRITERION

9. What is the proposed dissolution acceptance criterion for this product?

The Applicant proposed an acceptance criterion of “Q=(b) (4) % in (b) (4) minutes” which correspond to not less than (b) (4) % (n (b) (4)) of Empagliflozin dissolved in (b) (4) minutes.

10. What data are available to support the dissolution acceptance criterion?

The Applicant stated that the acceptance criterion is based on results obtained on representative batches, including batches used in Phase III clinical studies and primary stability studies.

A summary of the individual and mean dissolution data after (b) (4) minutes at release is presented in Table 4.

Table 4: Dissolution of Empagliflozin after (b) (4) minutes at release (Test conditions: Paddle 75 rpm, 900 mL buffer pH 6.8); Empagliflozin film-coated tablets, 25 mg

Batch Number	% Dissolved after (b) (4) minutes			Intended Use of Batch
	Individual value (n: (b) (4))	Mean	RSD	
909472	(b) (4)			Clinical studies
909473				Clinical studies
001747				Clinical studies
003530*				Clinical and primary stability studies
003531				Clinical and primary stability studies
003532				Primary stability studies
003533				Clinical studies
007768				Clinical studies
007769				Clinical studies
007770				Clinical studies
103698				Clinical studies
107786				Clinical studies
107787				Clinical studies

* The release data of this batch are also valid for the batch 003530A that was used for primary stability studies of the drug product packaged in (b) (4) blisters. The slightly differing batch number in (b) (4) blisters was allocated to allow for the differentiation of packaging runs.

11. Is the setting of the dissolution acceptance criterion based on data from clinical and registration batches?

Yes, all phase III clinical and primary stability batches of Empagliflozin film-coated tablets have been tested for dissolution at batch release and were found to be in compliance with the acceptance criterion of $Q = \frac{(b)}{(4)}\%$ at $\frac{(b)}{(4)}$ minutes. In fact, all batches can meet $Q = \frac{(b)}{(4)}\%$ at 15 minutes. Moreover, stability data remained within the acceptance criterion at long-term as well as at accelerated storage conditions. Hence, FDA requested the Applicant to tighten the acceptance criterion to $Q = \frac{(b)}{(4)}\%$ at 15 minutes.

12. Are mean (b) (4) dissolution profile data used for the setting of the acceptance criterion?

No, the mean ((b) (4)) is the data used for setting of the acceptance criterion.

In the Applicant response dated October 1, 2013 to FDA IR dated September 16, 2013, the Applicant summarized the results of a retrospective dissolution assessment for clinical and primary stability batches, applying FDA's recommended acceptance criterion of $Q = \frac{(b)}{(4)}\%$ at 15 minutes. The Applicant stated that the results indicate that the acceptance criterion of $Q = \frac{(b)}{(4)}\%$ at 15 minutes is appropriate to control the drug release of Empagliflozin film-coated tablets. Table 5 below shows the result for the 25 mg, and similar results were obtained for the 10 mg strength.

Table 5: Dissolution of Empagliflozin after 15 minutes sampling time point (test conditions: Paddle 75 rpm, 900 mL buffer pH 6.8); Empagliflozin film-coated tablets, 25 mg₁

Batch Number	% Dissolved after 15 minutes			Intended Use of Batch	
	Individual value (n=6)	Mean	RSD		
909472	(b) (4)			Clinical studies	
909473				Clinical studies	
001747				Clinical studies	
003533				Clinical studies	
007768 ²				Clinical studies	
007769 ²				Clinical studies	
007770				Clinical studies	
103698 ²				Clinical studies	
107786				Clinical studies	
107787				Clinical studies	
003530 ³				Clinical and primary stability studies	
003531 ³				Clinical and primary stability studies	
003532 ³				Primary stability studies	
003530A				(b) (4)	Primary stability, initial value, Alu blister
003531					(b) (4)
003532	(b) (4)	Primary stability, 30°C/75% r.h., 24 months, Alu blister			
003530A		(b) (4)	(b) (4)		
003531					
003532					

- 1 batches listed in section P 5.4 document [U12-2609-01]
- 2 no data available for the 15 minutes time point
- 3 dissolution results of bulk measurement

13. Is the acceptance criterion acceptable? If not, what is the recommended criterion?

FDA sent an IR on September 16, 2013 which included the following Biopharmaceutics request:

The proposed acceptance criterion of Q = (b) (4) % at (b) (4) minutes is not supported by data. We recommend that you revise and implement the acceptance criterion of Q = (b) (4) % at 15 minutes and provide an updated specifications table for the drug product.

The Applicant responded on October 1, 2013 and agreed (b) (4) the acceptance criterion for dissolution from Q = (b) (4) % at (b) (4) minutes to Q = (b) (4) % at 15 minutes for both release and shelf-life. Also, the Applicant revised the finished product specifications table in all the relevant sections of the NDA.

C) DRUG PRODUCT FORMULATION DEVELOPMENT AND BRIDGING ACROSS PHASES

14. What is the composition of the formulation of the proposed product?

The components and composition of the drug product and film-coat are provided in Table 6 and Table 7, respectively.

Table 6: Qualitative and quantitative composition of Empagliflozin film-coated tablets, 10 mg and 25 mg

Ingredient	[mg / tablet] 10 mg	[mg / tablet] 25 mg	Function	Reference to Standards
(b) (4)				
Empagliflozin	10.000	25.000	Drug substance	Company standard
Lactose monohydrate	(b) (4)	(b) (4)		NF
Microcrystalline cellulose			NF	
Hydroxypropylcellulose			NF	
Croscarmellose sodium			NF	
Colloidal silicon dioxide			NF	
Magnesium stearate			NF	
(b) (4)			USP	
(b) (4)			Company standard	
(b) (4)	USP			
Total mass of film-coated tablet	257.0	206.0		

*) Removed during processing; does not appear in the final drug product

Reviewer's Note: Although the Applicant is proposing only the 25 mg strength for marketing, the lower strength (10 mg) (b) (4)

In fact, the two strengths (10 mg and 25 mg) are formulated (b) (4)

Furthermore, the 10 mg dosage strength was studied in the Phase 3 trials and a biowaiver for this strength is not needed.

Table 7: Qualitative and quantitative composition of (b) (4)

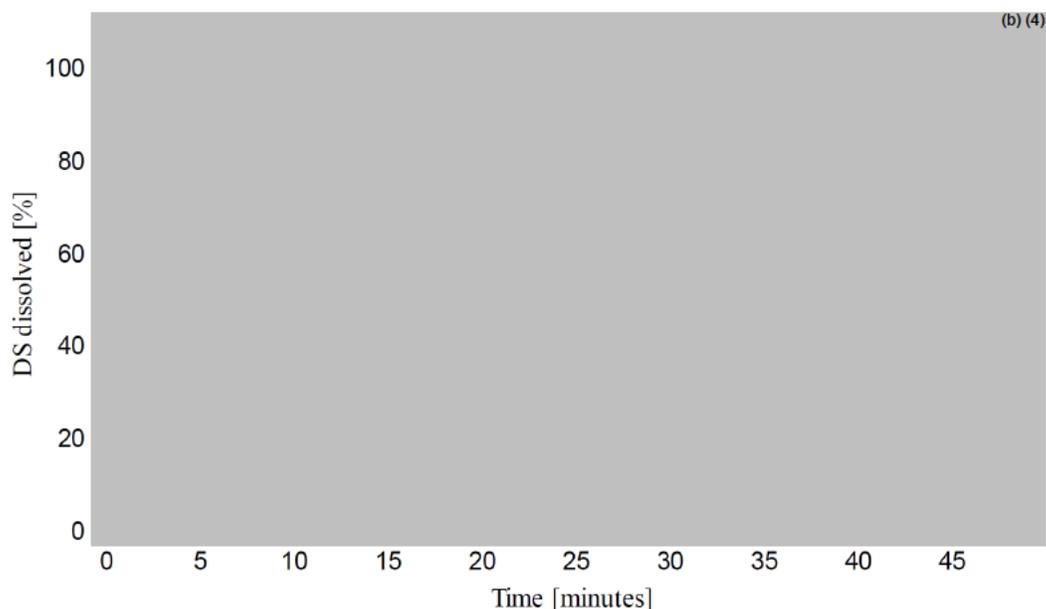
Hypromellose (b) (4)	(b) (4)	USP
Titanium dioxide	(b) (4)	USP
Talc	(b) (4)	USP
Polyethylene glycol (b) (4)	(b) (4)	NF
Ferric oxide yellow	(b) (4)	NF
Total	(b) (4)	

15. What are the highlights of the drug product formulation development?

Three tablet trial formulations (TF) were developed to support clinical trials: TF-I, TF-II, and the final formulation (FF). All 3 formulations had the same qualitative composition. TF-I and TF-II were (b) (4) tables, and FF is a film-coated tablet with a hypromellose-based standard film coat. TF-I and TF-II were used in phase I and II trials. The FF was used in several phase I trials and all phase III trials.

TF-II and FF (intended for commercial supply) were compared in a relative bioavailability study (1245.51, U11- 1756). The Applicant stated that the results of this relative bioavailability study showed comparable in vivo exposure. The relative bioavailability will be reviewed by the Office of Clinical Pharmacology. Also, the Applicant used the selected dissolution method and provided the dissolution profiles of both formulations used in the relative bioavailability study (TF-II and FF). The dissolution profiles of both formulations are similar (see Figure 14). The Applicant stated that the in vitro dissolution conditions reflected the observed in vivo performance.

Figure 14: Comparative dissolution profiles of Empagliflozin tablets, 25 mg, TF II and Empagliflozin film-coated tablets, 25 mg, FF tested in study 1245.51 (n=12) (dissolution method: paddle apparatus, 75 rpm, 900 mL, 0.05 M phosphate buffer pH 6.8)



The dissolution profiles of both formulation types are similar which reflect the results obtained in vivo (the relative bioavailability study 1245.51). Therefore, the in vitro dissolution results reflect the in vivo performance of the formulations.

16. Are all the strengths evaluated in the pivotal clinical trials? What data are available to support the approval of lower strengths?

Yes, all strengths are evaluated in the pivotal clinical trials. However, the Applicant wants to commercialize only one dosage strength (25 mg).

17. Are there any manufacturing changes implemented to the clinical trial formulation (e.g. formulation changes, process changes, site change, etc.)? What information is available to support these changes?

Early process development activities in lab scale were conducted by Boehringer Ingelheim at the development site located in Ridgefield, CT, USA. Subsequently, process development activities in pilot and full scale were conducted by Boehringer Ingelheim at the development site located in Biberach, Germany. The Final Formulation (FF) and manufacturing process was transferred to the production site located in Ingelheim, Germany. Therefore, clinical trial supplies for phase 3 studies using the Final Formulation were manufactured only at the production site located in Ingelheim, Germany, which is the proposed commercial site.

18. Is the formulation of the clinical product the same formulation of the to-be-marketed product? If not, what information is available to support the formulation changes?

Yes, the proposed formulation is the same as used for manufacture of the phase 3 clinical trial supplies. There are no manufacturing changes implemented to the clinical trial formulation.

19. Is the manufacturing site the same for the clinical and to-be-marketed products? If not, what information is available to support the new site?

The clinical trial supplies for phase 3 studies using the Final Formulation were manufactured only at the production site located in Ingelheim, Germany.

D) DISSOLUTION APPLICATIONS

D.1 BIOWAIVERS

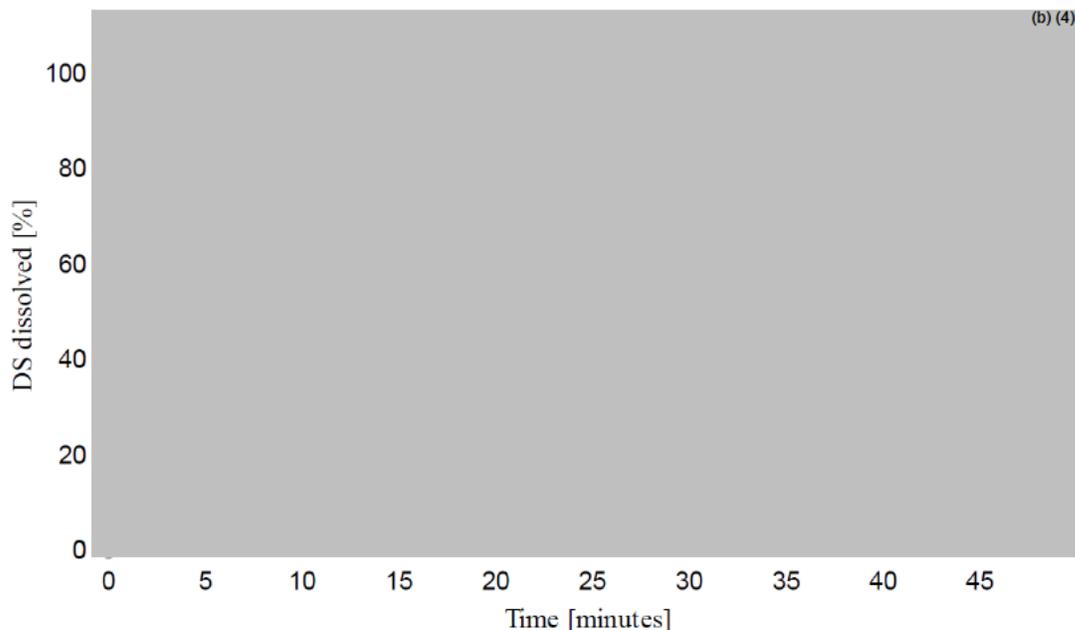
20. Is there a waiver request for in vivo BA or BE data (Biowaiver)? If yes, what is/are the purpose/s of the biowaiver request/s? What data support the biowaiver request/s? Is the biowaiver request acceptable?

The FF formulation which is intended for commercial supply was compared against TFII in a relative bioavailability study (1245.51) which will be reviewed by OCP. The Applicant stated that the results show comparable in vivo exposure (1254.51, U11-1756).

Although the Applicant intends to commercialize only the 25 mg strength and is not requesting a biowaiver for the lower strength (10 mg) because it was studied in Phase 3 trials, a comparison of dissolution profiles between the two dosage strengths of Empagliflozin film-coated tablets (10 mg and 25 mg) was performed. The dissolution profiles were generated using the proposed regulatory dissolution conditions. Although the 10 mg and 25 mg Empagliflozin film-coated tablets have (b) (4) the dissolution profiles of both dosage strengths are almost superimposable (See Figure 15). The comparative dissolution profiles are not relevant, as the lower strength (10 mg) (b) (4) the higher strength (25 mg) in its active and inactive ingredients, and the two strengths (10 mg and 25 mg) are formulated (b) (4)

Also, the lower strength (10 mg) was studied in Phase 3 trials and a biowaiver request is not requested or applicable in this case.

Figure 15: Dissolution profiles of Empagliflozin film-coated tablets (n=6) comparing different dosage strengths



21. Is there any IVIVR or IVIVC information submitted? What is the regulatory application of the IVIVC or IVIVC in the submission? What data is provided to support the acceptability of the IVIVC or IVIVC model?

There is no IVIVC data included in the submission.

D.2 SURROGATES IN LIEU OF DISSOLUTION

22. Are there any manufacturing parameters (e.g. disintegration, drug substance particle size, etc.) being proposed as surrogates in lieu of dissolution testing? What data is available to support this claim?

No, there are no manufacturing parameters being proposed as surrogates in lieu of dissolution testing.

D.3 DISSOLUTION AND QBD

23. If the application contains QbD elements, is dissolution identified as a CQA for defining design space?

The Applicant has some QbD elements in the application. However, the Applicant did not propose a design space, nor sought alternative control strategies. Also, dissolution is not identified as CQA for defining design space.

24. *Was dissolution included in the DoE? What raw materials and process variables are identified as having an impact on dissolution? What is the risk assessment performed to evaluate the criticality of dissolution?*

NA

25. *What biopharmaceutics information is available to support the clinical relevance of the proposed design space?*

NA

26. *Is there any dissolution model information submitted as part of QbD implementation? What is the regulatory application of the dissolution model in the submission? What data are provided to support the acceptability of the dissolution model?*

NA

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

/s/

HOUDA MAHAYNI
11/04/2013

SANDRA SUAREZ
11/04/2013

Office of Clinical Pharmacology New Drug Application Filing and Review Form				
General Information about the Submission				
	Information		Information	
NDA Number	204629	Brand Name	JARDIANCE™ (Proposed)	
OCP Division (I, II, III, IV, V)	DCP II	Generic Name	Empagliflozin	
Medical Division	DMEP	Drug Class	SGLT-2 inhibitor	
OCP Reviewer	Manoj Khurana, Ph.D.	Indication(s)	An adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.	
OCP Pharmacometrics Reviewer	Manoj Khurana, Ph.D.	Dosage Form	Film-coated Immediate-release Tablets; 10 mg and 25 mg	
OCP Team Leader	Lokesh Jain, Ph.D.	Dosing Regimen	Once daily	
Date of Submission	March 5, 2012	Route of Administration	Oral	
Estimated Due Date of OCP Review	November 05, 2013	Sponsor	Boehringer Ingelheim Pharmaceuticals, Inc.	
PDUFA Due Date	March 5, 2014	Priority Classification	Standard	
Division Due Date				
Clin. Pharm. and Biopharm. Information				
	"X" if included at filing	Number of studies submitted	Number of studies reviewed	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			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X	31		
I. Clinical Pharmacology				
Mass balance:	X	1		1245.08
Isozyme characterization:	X	5		studies including human liver microsomes; hepatocytes, transporters
Blood/plasma ratio:	X	1		DM-06-1083
Plasma protein binding:	X	1		DM-07-1001
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X	1		1245.01
multiple dose:	X			
Patients-				
single dose:				
multiple dose:	X	1		1245.02
Dose proportionality -				
fasting / non-fasting single dose:	X			1245.79
fasting / non-fasting multiple dose:				

Drug-drug interaction studies -				
In-vivo effects on primary drug:	X	15		1245-n, n=6, 7, 17, 18, 27, 30, 40, 41, 42, 43, 45, 50, 58, 63, 83
In-vivo effects of primary drug:	X	-do-		
In-vitro:	X	8		Enzyme/transporter interactions
Subpopulation studies -				
ethnicity:	X	2		1245.05 (JPN), 1245.44 (CHN)
gender:				
pediatrics:				
geriatrics:				
renal impairment:	X	1		1245.12
hepatic impairment:	X	1		1245.13
PD:				
Phase 2:	X			
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:	X	3		1245.16 (TQT) 1245.04 (MD T2DM), 1245.15 (MD, T2DM, JPN)
Phase 3 clinical trial:	X			See pop-pkpd analysis section
Population Analyses -				
Data rich:	X	1		U12-2524 (Used data from 1245.2, 1245.4, 1245.15, and 1245.12)
Data sparse:	X	1		U12-2525 (Used data from Phase 1 trials: 1245.2, 1245.4, 1245.9, 1245.10, 1245.15, Phase 2b trial 1245.33, and Phase 3 trials 1245.19, 1245.20, 1245.23, and 1245.36 for Pop-PKPD E/R Analysis)
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	X	1		1245.51 (TBM vs. TF2)
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:	X	2		1245.79 (with TBM formulation); 1245.03 (With TF1)
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class	X			
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				

Pediatric development plan	X			Waiver (b) (4) years Deferral: (b) (4) years PKPD Study 1245.87 plan 5, 10, 25 mg Phase 3 Study 1245.56 plan: 5, 10 or 25 mg based on PK study results
Literature References				
Total Number of Studies		76		
Filability				
	"X" if yes	Comments		
Is Application filable?	X	Comments to the Sponsor: Please submit raw electronic data sets for the DDI Study #1245.83 titled "A randomised, open-label, three-way crossover trial to investigate the effect of rifampicin and probenecid on empagliflozin pharmacokinetics in healthy male and female subjects".		
Submission in Brief: See the details below.	<p>Reviewer's Comments: The preNDA meeting minutes included the following discussion points, indicating that company should submit this data within 30 days:</p> <p>"Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. We agreed that the following minor application components may be submitted within 30 calendar days after the submission of the original application: Clinical Pharmacology assessment of in vivo chiral conversion of empagliflozin in human clinical samples."</p> <p>Sponsor included one study report with the NDA submission (Document No.: U13-3020-01 Report No.: DM-12-1184) that documents the evaluation of the chiral conversion of empagliflozin by quantitating (b) (4) in pooled human plasma samples obtained from a Clinical Study.</p>			

Submission in Brief:

The sponsor, Boehringer Ingelheim Pharmaceuticals, Inc. (hereafter BI), has submitted a new drug application (NDA) seeking approval for (b) (4) (Empagliflozin).

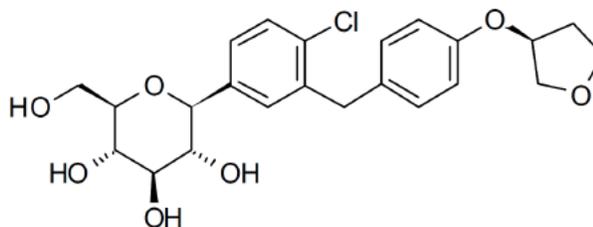


Figure 1 Molecular structure of empagliflozin

[D-Glucitol,1,5-anhydro-1-C-[4-chloro-3-[[4-[[[(3S)-tetrahydro-3-furanyl]oxy]phenyl]methyl]phenyl]-, (1S). Molecular formula: C₂₃H₂₇ClO₇, Molecular weight: 450.91 g/mol]

Empagliflozin is an inhibitor of sodium-glucose co-transporter 2 (SGLT2) with a claimed IC₅₀ of 1.3 nM. It has a 5000-fold selectivity over human SGLT1 (IC₅₀ of 6278 nM),

responsible for glucose absorption in the gut. In addition, high selectivity was shown toward other glucose transporters (GLUTs). SGLT2 is highly expressed in the kidney, and is the predominant transporter for re-absorption of glucose from the glomerular filtrate back into the systemic circulation. In patients with type 2 diabetes and hyperglycemia a higher amount of glucose is filtered and reabsorbed. By inhibiting SGLT2 empagliflozin reduces renal re-absorption of glucose. This promotes increased urinary glucose excretion resulting in reduction of blood glucose levels.

The clinical program comprises 30 phase I trials and 13 phase IIb/III trials. Overall, 13767 subjects were treated in these clinical trials, 6808 patients were treated with empagliflozin for at least 24 weeks, 4415 patients for at least 52 weeks, and 1486 patients for at least 76 weeks. In clinical studies, empagliflozin was evaluated as monotherapy and in combination with metformin, glimepiride, pioglitazone, insulin, and DPP-4 inhibitors. During the clinical development program, the sponsor also assessed the cardiovascular (CV) risk associated with empagliflozin therapy by conducting a prospective, pre-specified meta-analysis of independently adjudicated cardiovascular events.

Trial characteristics	Trial number	Reference	Geographical regions	Duration analysed
Pivotal double-blind phase III trials	1245.19	[U12-1516]	Europe, Asia, North America	24 weeks
	1245.20	[U12-1517]	Europe, Asia, North America	24 weeks
	1245.23 _(met)	[U12-1518]	Europe, Asia, North America, Latin America	24 weeks
	1245.23 _(met+SU)	[U12-1518]	Europe, Asia, North America, Latin America	24 weeks
Double-blind phase III extension trials	1245.31	[U12-1521]	Europe, Asia, North America, Latin America	52 weeks ¹
Additional phase IIb/III double-blind individual trials	1245.28	[U12-1520]	Europe, Asia, North America, Latin America, Africa/Middle East	52 weeks ²
	1245.33 ³	[U12-3817]	Europe, Asia, North America,	78 weeks
	1245.48	[U12-1526]	Europe, North America, Africa/Middle East	12 weeks
	1245.36	[U12-1522]	Europe, Asia, North America, Africa/Middle East	52 weeks
	1245.25	No clinical trial report available	Europe, Asia, North America, Latin America, Africa/Middle East	12 weeks ⁴
Open label phase IIb extension trial	1245.24	[U12-1213]	Europe, Asia, North America, Latin America	90 weeks ⁵

¹ Including the 24-week treatment duration in the preceding trials; 52-week efficacy data from a prespecified interim analysis are included in this submission. The overall planned duration (initial trials + extensions) is 76 weeks

² Minimum duration at time of interim analysis; overall planned duration is 208 weeks

³ Trial 1245.33 was conducted in patients with basal insulin as background therapy. This trial was originally designated as a phase IIb trial. Since it had confirmatory testing introduced via a protocol amendment, it is considered to be equivalent to a confirmatory phase III trial for the assessment of the efficacy and safety of empagliflozin

⁴ Minimum duration at time of interim analysis; overall anticipated duration is between 6 and 8 years

⁵ Data from a combined analysis with the preceding double-blind preceding trials 1245.9 and 1245.10 are presented

Formulation Development:

There were changes in the formulation during the drug development. However, the final formulation was used in the pivotal Phase 3 trials.

Table 1 Overview of formulations and manufacturing processes applied to clinical trial batches

Formulation type	General manufacturing principle	Clinical studies *
(b) (4) tablets (TF I)	(b) (4)	Phase I: 1245.1, 2, 3, 4
(b) (4) tablets (TF II)		Phase I: 1245.5, 6, 7, 12, 13, 17, 27, 30, 51 Phase II: 1245.9, 10, 15, 24, 33
Film-coated tablets (FF)		Phase I: 1245.16, 18, 40, 41, 43, 44, 45, 50, 51, 53, 58, 63, 79, 83 Phase II: 1245.38 Phase III: 1245.19, 20, 23, 25, 28, 31, 36, 48

* numbers in bold indicate pivotal clinical studies

Trial formulation II and Final Formulation FF, intended for commercial supply, were compared in a relative bioavailability study (1245.51, U11-1756).

The composition of the formulations is mentioned below:

Table 2 Qualitative and quantitative composition of empagliflozin film-coated tablets: 10 mg and 25 mg

Ingredient	[mg / tablet] 10 mg	[mg / tablet] 25 mg	Function	Reference to Standards
(b) (4)				
Empagliflozin	10.000	25.000	Drug substance	Company standard
Lactose monohydrate	(b) (4)	(b) (4)	(b) (4)	NF
Microcrystalline cellulose				NF
Hydroxypropylcellulose				NF
Croscarmellose sodium				NF
Colloidal silicon dioxide				NF
Magnesium stearate				NF
(b) (4)				USP
(b) (4)				Company standard
(b) (4)	USP			
Total mass of film-coated tablet	257.0	206.0		

*) Removed during processing; does not appear in the final drug product

Sponsor mentioned that Empagliflozin drug substance (b) (4). The particle size for empagliflozin drug substance

is tightly controlled to (b) (4) μm

(b) (4)

Key Clinical Pharmacology Review Questions:

- **What is the dose-response, systemic exposure-response relationship for Empagliflozin for efficacy?**
 - **Does exposure-response information support the adequacy of the proposed dose of 25 mg QD?**
 - **Is there an impact of renal impairment on the efficacy of Empagliflozin?**
- **What is the s dose-response, systemic exposure-response relationship for Empagliflozin for safety?**
 - **Does exposure-safety information support the proposed dose of 25 mg QD?**
- **What is the concentration-QT relationship for Empagliflozin concerning safety? (IRT-QT Consult)**
- **What is the effect of food on pharmacokinetics of Empagliflozin?**
 - **Do the results support sponsor's proposed language in the label that "Empagliflozin can be taken with or without food"?**
 - **Are analytical methods adequate?**
- **What is the effect of Empagliflozin on other co-administered drugs and vice-versa?**
 - **Does the DDI result warrant for any dose adjustments for Empagliflozin and the co-administered drugs?**
 - **Are analytical methods adequate?**
- **Are sponsor's assessments for specific populations appropriate and do they adequately support the proposed labeling language?**
- **What is the relative bioavailability of to-be-marketed formulation in comparison to the formulations used in the development phase?**
 - **Are analytical methods adequate?**

The key aspects of the filing and questions for clinical pharmacology review are presented in the slides below:

Attachment 1: Clinical Pharmacology Filing Meeting Presentation

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NDA 204069 Filing Meeting Clinical Pharmacology Perspective

Empagliflozin ("Empa")
 (b) (4) Proposed
Sponsor: Boehringer Ingelheim
Submitted: 03/05/2013

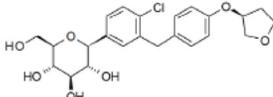
Manoj Khurana, PhD
 Division of Metabolism and Endocrinology Products
 Office of Clinical Pharmacology

OCP Review Team:
 Clin. Pharm. and Pharmacometrics Reviewer: Manoj Khurana PhD
 Clin. Pharm. Team Leader : Lokesh Jain, PhD
 Pharmacometrics Team Leader: Nitin Mehrotra, PhD

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Empagliflozin: A new molecular entity



- **Class:** SGLT2 inhibitor in proximal renal tubule
- **Proposed Indication:**
 - adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
- **Formulation:** film-coated oral tablets:
 - 10 mg
 - 25 mg
- **Proposed dose:**
 - 25 mg QD, with or without food
 - Not recommended in severe RI (eGFR <30 mL/min/1.73 m²)
 - **Proposed use spans from Moderate RI to Normal RF**
 - Reduce dose of insulin/insulin secretagogue (e.g., SU)

Empagliflozin

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Overview of Clinical Pharmacology Studies

Pharmacokinetic and pharmacodynamic trials in healthy volunteers

Trial 1245.1	Single rising dose study in Caucasian healthy volunteers
Trial 1276.9	Once daily vs. twice daily regimen in healthy volunteers
Trial 1245.8	Human ADME study
Trial 1245.16	Thorough QT study

Pharmacokinetic and pharmacodynamic trials in patients with T2DM

Trial 1245.2	8-day multiple rising dose study in Caucasian patients
Trial 1245.4	4-week repeated dose study in Caucasian patients

Special population trials

Trial 1245.5	Single rising dose study in Japanese healthy volunteers
Trial 1245.44	8-day multiple dosing study in Chinese patients
Trial 1245.15	4-week repeated dose study in Japanese patients
Trial 1245.12	Renal impairment study in Caucasians subjects
Trial 1245.13	Hepatic impairment study in Caucasians subjects

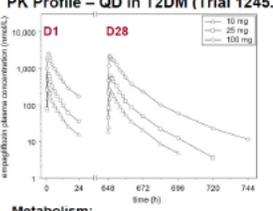
Drug-drug interaction trials

Trial 1245.6	DDI with metformin	Trial 1245.40	DDI with digoxin
Trial 1245.7	DDI with gimepiride	Trial 1245.41	DDI with oral contraceptives (ethinylestradiol and levonorgestrel)
Trial 1245.17	DDI with pioglitazone	Trial 1245.42	DDI with diuretics (hydrochlorothiazide and torsemide)
Trial 1245.50	DDI with pioglitazone	Trial 1245.43	DDI with verapamil
Trial 1245.18	DDI with warfarin	Trial 1245.45	DDI with ranitidine
Trial 1245.27	DDI with sitagliptin	Trial 1245.58	DDI with gemfibrozil
Trial 1245.27	DDI with sitagliptin	Trial 1245.63	DDI with simvastatin
Trial 1245.30	DDI with liraglutin	Trial 1245.83	DDI with rifampicin and probenecid

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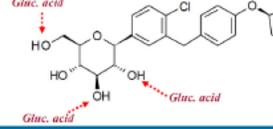
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Empagliflozin ADME



- Fairly rapid absorption ($t_{MAX} \sim 1.5$ hour)
- $T_{1/2} \sim 12$ hours (R_{accum} : 1.22 QD)
- Absolute BA – ? (80-90% in animals)
- No time dependent PK
- Metabolism:
 - 2-O, 3-O, and 6-O glucuronides (~ 10% of total in plasma; formed by UGT2B7, UGT1A3, UGT1A8, and UGT1A9)
- 96% recovered:
 - 41% in feces : (~83% intact)
 - 55% in Urine : (~50% intact)
- No chiral conversion
- RBC Partitioning ~ 36%
- Pgp, OAT3, and BCRP substrate
- Inhibitor of OAT3, OATP1B1, OATP1B3 and OATP2B1 (high IC50s)

Metabolism:



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Clin. Pharm. Review Questions

- **Review Questions:**
 - What are the PK and PD characteristics of Empagliflozin?
- **Filing Issues:**
 - Did sponsor submit all the information for review? – **Yes**

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Overview of efficacy and safety trials of empagliflozin

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Empagliflozin Efficacy from Pivotal Trials

Adjusted mean difference (with 95% confidence intervals) between empagliflozin and placebo in HbA_{1c} after 24 weeks for the pivotal trials – FAS (LOCF)

Trial ID	Dose	Adjusted mean difference (95% CI)
1245.20 (mono-therapy)	Empa 10	-0.73
	Empa 25	-0.87
1245.23 (met)	Empa 10	-0.58
	Empa 25	-0.71
1245.23 (met+SU)	Empa 10	-0.51
	Empa 25	-0.64
1245.19 (pio ± met)	Empa 10	-0.51
	Empa 25	-0.73

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Empagliflozin Efficacy in Renal Impairment

Change from baseline in HbA_{1c} [%] in Renal Impairment Trial – FAS (LOCF)

Trial Treatment group	N	Baseline HbA _{1c} mean (SE)	Change from baseline		Difference from placebo		p-value
			Mean (SE)	Adjusted mean (SE)	Adjusted mean (SE)	95% CI	
1245.36 mild renal impairment³							
Endpoint assessed after 24 weeks							
Placebo	95	8.09 (0.08)	0.04 (0.08)	0.06 (0.07)			
Empa 10 mg	98	8.02 (0.09)	-0.46 (0.07)	-0.46 (0.07)	-0.52 (0.10)	(-0.72, -0.32)	<0.0001
Empa 25 mg	97	7.96 (0.07)	-0.61 (0.07)	-0.63 (0.07)	-0.68 (0.10)	(-0.88, -0.49)	<0.0001
1245.36 moderate renal impairment³							
Endpoint assessed after 24 weeks							
Placebo	187	8.04 (0.06)	0.05 (0.05)	0.05 (0.05)			
Empa 25 mg	187	8.03 (0.06)	-0.37 (0.05)	-0.37 (0.05)	-0.42 (0.07)	(-0.56, -0.28)	<0.0001

³ Renal impairment was assessed by eGFR calculated with the MDRD formula: mild (eGFR of 60 to <90 mL/min/1.73 m²), moderate (eGFR of 30 to <60 mL/min/1.73 m²). ANCOVA model includes baseline HbA_{1c}, baseline background medication, and treatment.

*Adjusted mean treatment difference:
Chronic kidney disease 3A (180 patients overall, eGFR 45 to <60 mL/min/1.73 m²): **-0.46% (95% CI: -0.66, -0.27)**
Chronic kidney disease 3B (194 patients, eGFR 30 to <45 mL/min/1.73 m²): **-0.39% (95% CI: -0.58, -0.19)***

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Empagliflozin Exposure-Response for Safety

- **Sponsor:**
 - Neither HYPO nor UTI rates changed significantly with changes in empagliflozin AUCss
 - **Hypoglycemia:** odds ratio for 3500 nmol*hr/L increase in AUCss: **0.988, 95% CI: [0.863, 1.13]**
 - **UTI:** **1.06 [0.935, 1.20]**.
 - **GBV (genital infection rate):** decreased with increasing empagliflozin AUCss (odds ratio for 3500 nmol*hr/L increase in AUCss: **0.744, 95% CI: [0.574, 0.965]**)

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Empagliflozin TQT Study (1245.16) Results

Adjusted means and confidence intervals for the mean QTcN changes from baseline within the time interval 1 h to 4 h after administration of BI 10773 and placebo – full analysis set

Treatment	No of subjects	No of obs.	Adjusted mean [ms] Mean (SE)	Difference to placebo [ms]	
				Mean (SE)	90% CI (lower, upper)
Placebo	29	57	3.68 (1.00)		
25 mg BI 10773	28	28	4.27 (1.10)	0.59 (0.76)	-0.69, 1.87
Placebo	29	57	3.67 (0.86)		
200 mg BI 10773	30	30	3.44 (0.94)	-0.22 (0.69)	-1.39, 0.94

The statistical model included fixed effects for 'treatment', 'period', 'treatment sequence', 'baseline' as a covariate and the random effect 'subject within sequence'.

- IRT-QT Consult

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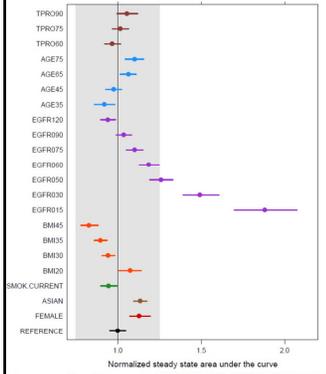
Clin. Pharm. Review Questions

- **Review Questions:**
 - What is the dose-response, systemic exposure-response relationship for Empagliflozin for efficacy?
 - Does exposure-response information support the adequacy of the proposed dose of 25 mg QD?
 - Is there an impact of renal impairment on the efficacy of Empagliflozin?
 - What is the dose-response, systemic exposure-response relationship for Empagliflozin for safety?
 - Does exposure-safety information support the proposed dose of 25 mg QD?
 - What is the concentration-QT relationship for Empagliflozin concerning safety? (IRT-QT Consult)
- **Filing Issues:**
 - Did sponsor submit all the information for review? – **Yes**

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Intrinsic Factors on PK



- **Sponsor:**
 - No dose adjustment for body mass index, body weight, sex, and race based on the results of population PK analysis.
 - None of these covariates had clinically relevant effect on PK of Empa
- **Review Questions:**
 - What is the impact of body mass index, body weight, sex, and race on PK of Empa?
 - Is sponsor's proposed language in the label acceptable?
- **Filing Issues:**
 - Did sponsor submit all the information for review? – **Yes**

Reference group: male, non-Asian, non-smoker, TPPO 75, EGFR 100, ALT 20, AST 20, LDH 160, BMI 25, AGE 50
 Estimated covariate effects on relative empagliflozin exposure (AUC_{1,ss}/reference AUC_{1,ss}) from the population pharmacokinetic model

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Specific Populations – Renal Impairment

- Sponsor:**
 - No dose adjustment in mild or moderate RI
 - Do not use in severe RI and ESRD (No efficacy)
- Review Questions:**
 - What is the impact of renal impairment on PK of Empa?
 - Is sponsor's proposed language in the label acceptable?
- Filing Issues:**
 - Did sponsor submit all the information for review? – **Yes**

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Specific Populations – Hepatic Impairment

- Sponsor:**
 - No dose adjustment in mild, moderate, or severe HI
- Review Questions:**
 - What is the impact of hepatic impairment on PK of Empa?
 - Is sponsor's proposed language in the label acceptable?
- Filing Issues:**
 - Did sponsor submit all the information for review? – **Yes**

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Extrinsic Factors: DDI – Effect on Empa

- Review Questions:**
 - What is the effect of other drugs with Empa?
 - Is proposed language in label acceptable?
- Filing Issues:**
 - Did sponsor submit all the information for review? **Yes**

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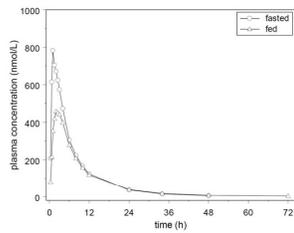
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Extrinsic Factors: DDI – Effect of Empa

- Review Questions:**
 - What is the effect of Empa on other drugs?
 - Is proposed language in label acceptable?
- Filing Issues:**
 - Did sponsor submit all the information for review? **Yes**

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Extrinsic Factor – Food Effect

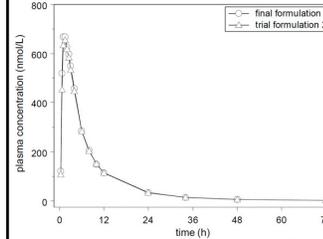


Mean plasma concentration-time profiles of empagliflozin after oral administration of single 25 mg empagliflozin tablet (25 mg empagliflozin final formulation tablet) under fasted and fed (standard high fat, high calorie meal) conditions (TRIAL 1245.79)

Similar results for TF1 in TRIAL 1245.3

- **Sponsor:**
 - Food effect not clinically relevant for formulations TF1 and FF
 - Can be administered with and without food
- **Review Questions:**
 - Are sponsor's claims acceptable?
 - Is proposed language in label acceptable?
- **Filing Issues:**
 - Did sponsor submit all the information for review? – **Yes**

PK Comparability of Different Formulations



Mean plasma concentration-time profiles of empagliflozin after oral administration of 25 mg empagliflozin final formulation tablet or empagliflozin trial formulation 2 tablet (TRIAL 1245.51)

- **Sponsor:**
 - To-be-marketed formulation used in Phase 3
 - Formulations TF2 and FF are bioequivalent for PK
- **Review Questions:**
 - Are sponsor's claims acceptable?
- **Filing Issues:**
 - Did sponsor submit all the information for review? – **Yes**

Application Filability and Consults

- Yes, the application is filable
- No OSI consults
- IRT-QT for the thorough QT study

Attachment 2: GRMP Filing Memo

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING CHECKLIST FOR A NEW NDA/BLA**

**NDA/BLA Number: 204629 Applicant: Boehringer Ingelheim Stamp Date: 03/05/2013
Pharmaceuticals, Inc.**

Drug Name: Empagliflozin NDA/BLA Type: (505(b)(1))

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

	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	TBM formulation was used in Phase 3
2	Has the applicant provided metabolism and drug-drug interaction information?	X			
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	X			
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			
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			
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			
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	X			
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	X			

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Checklist for a New NDA_BLA 110307

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING CHECKLIST FOR A NEW NDA/BLA**

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.

Manoj Khurana	05/03/2013
Reviewing Pharmacologist	Date
Lokesh Jain	05/03/2013
Team Leader/Supervisor	Date

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

/s/

MANOJ KHURANA
05/03/2013

LOKESH JAIN
05/03/2013