Office of Clinical Pharmacology Review

NDA Number	204629/S-042
Link to EDR	\\CDSESUB1\evsprod\NDA204629\1321
Submission Date	12/20/2022
Submission Type	Pediatric Supplement, Priority Review
Brand Name	Jardiance
Generic Name	Empagliflozin
Dosage Form and Strength	Tablets
Route of Administration	Oral
Proposed Indication	As an adjunct to diet and exercise to improve glycemic control in patients 10 years and older with type 2 diabetes mellitus (T2DM)
Applicant	Boehringer Ingelheim Pharmaceuticals, Inc.
OCP Review Team	Harisudhan Thanukrishnan, Ph.D., Xiaolei Pan, Ph.D., Justin Earp, Ph.D., Edwin Chow, Ph.D.

Table of Contents

Contents

1. EXECUTIVE SUMMARY

Empagliflozin (Jardiance), has been approved as an adjunct to diet and exercise for improving glycemic control in adults with type 2 diabetes mellitus. In the current submission, the Applicant is seeking to expand the indication to include pediatric patients with type 2 diabetes who are aged 10 to 17 years. The efficacy and safety of empagliflozin in pediatric patients with type 2 diabetes was established with confirmatory evidence from a single placebo-controlled pediatric study (DINAMO), conducted to fulfill the PMR 3300-1. The dose selection for DINAMO study was based on an open label single dose PK/PD trial in pediatric patients aged 10 to 17 years with type 2 diabetes, which was a PMR study (2755-1) fulfilled in Feb 2017.

The DINAMO (Diabetes study of linagliptin and empagliflozin in children and adolescents) was a 26-week, double-blind, randomized, placebo-controlled, parallel group study, with a double-blind active treatment period for 26 weeks and a safety extension period up to 52 weeks to assess the efficacy and safety of empagliflozin (10 mg followed by second randomization of non-responders to 10 mg or 25 mg) and a 5 mg dose of linagliptin. Patients enrolled in the study included background therapies such as metformin (51%), a combination of metformin and insulin (40.1%), insulin (3.2%), or none (5.7%). A total of 157 pediatric patients aged 10 to 17 years with type 2 diabetes mellitus were randomized and treated with either empagliflozin 10 mg QD (N=52), linagliptin (N=52), or placebo (N=53). In the empagliflozin arm, patients on empagliflozin who did not achieve HbA1c <7.0% at Week 12 were re-randomized at Week 14 to either continue with 10 mg empagliflozin QD or increase to 25 mg empagliflozin QD. The primary efficacy endpoint is the change in HbA1c (%) from baseline at Week 26. After primary clinical data have been collected at Week 26, patients on placebo were re-randomized to treatment with either empagliflozin 10 mg or 25 mg or linagliptin until Week 52.

The Applicant proposed an oral empagliflozin dose of 10 mg once daily in the morning with or without food, and for additional glycemic control, a dose increase to 25 mg in patients who can tolerate empagliflozin, as the recommended dosing regimen. This was based on the results of primary analysis of DINAMO study that showed a placebo adjusted mean lowering of HbA1c of -0.84% at Week 26 in the pooled empagliflozin arms. The focus of this sNDA review was to evaluate if the proposed dosing regimen for empagliflozin was appropriate for treatment of pediatric patients (aged 10 years and older) with Type 2 diabetes. The steady state trough concentration and 1.5 h post dose PK samples in DINAMO study were used to estimate the systemic exposure to empagliflozin in pediatric patients of the DINAMO study. The PK exposure and HbA1c data from DINAMO Study was then used in the development of pediatric population PK and exposure-response models for empagliflozin. Because the efficacy data for the empagliflozin treatment was pooled across two doses, additional exploratory analyses were assessed to evaluate dose-response relationship of empagliflozin, and additional exposure-response (ER) analyses and simulations based on Applicant's final population ER model describing the longitudinal HbA1c data in pediatric patients with placebo treatment incorporated as a marker for disease progression. Based on exploratory analysis, we concluded that

- The disease progression rates for pediatric T2D patients are inherently different. In general, pediatric patients with a baseline HbA1c ≥ 7.5 % and/or combination use of insulin are likely to have a faster disease progression rate and could be a non-responder. Whereas pediatric patients with a baseline

HbA1c < 7.5 % and/or without combination use of insulin are likely to have a slower disease progression rate and could be a responder.

- For both responders/non-responders, there is a significant treatment effect as compared to matched placebo group using propensity score matching.
- Contradicting results were observed comparing the treatment effect between 10 mg and 25 mg. However, totality of evidence suggest that 25 mg does not provide additional benefit on HbA1c for non-responders.
- The advantage of titrating of dose from 10 mg to 25 mg for responders is unknown, due to limited sample size. Refer to clinical review regarding the benefit-risk assessment for the use of 25 mg dose to get additional glycemic control.

Due to these reasons and given the low sample size and exploratory nature of analyses, the results for dose-response should be interpreted with caution.

The DINAMO study was not designed to assess dose or exposure response for the 10 and 25 mg doses used in this pediatric study. The clinical review team evaluated the supporting evidence for 25 mg dosing using the primary outcome analysis with pooled data that included efficacy data for 25 mg as well as from the open-label phase of study wherein placebo patients were re-randomized to be treated with 25 mg from Week 26 until Week 52. Please refer to the clinical review regarding the benefit-risk assessment for the use of 25 mg dose targeting the additional glycemic control in pediatric patients with Type 2 diabetes.

Based on the results from DINAMO study in the current submission, the Applicant has fulfilled all requirements for PMR 3300-1. The results from the study in this submission are updated to the currently approved package insert.

1.1 Recommendation

The Office of Clinical Pharmacology has determined that there is sufficient clinical pharmacology information provided in this NDA supplement (sNDA) to support the approval of Jardiance in pediatric patients 10 years and older. The final proposed dose of 10 mg once daily in the morning with or without food, is considered acceptable. The review team acknowledges the study design limitations that preclude a dose or exposure-response assessments in support of the dose increase to 25 mg in pediatric patients tolerating Jardiance, and hence defer to the clinical review team to evaluate the benefit and risk of extending the approval to 25 mg for additional glycemic control.

2. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

2.1 Regulatory History

The supplemental NDA (sNDA) submission is an efficacy supplement with clinical data from the pediatric study (DINAMO) to support dosing of empagliflozin in pediatric patients aged 10 years and above. In addition to DINAMO, Applicant (Boehringer Ingelheim Pharmaceuticals, Inc.) has previously conducted pediatric PMR studies as listed below to support dose selection of the DINAMO study. The Applicant discussed the content and aspects of the planned sNDAs to support a new indication of linagliptin and empagliflozin as an adjunct to diet and exercise to improve glycemic control in patients 10 years and older

with T2DM in a Type C guidance meeting on September 3, 2021.

Table 1. Post marketing pediatric studies for empagliflozin and linagliptin

Trial	Phase	Study Design	Randomized subjects	Treatment duration	Doses of study drug	Study population
1245.87 (PMR 2755-1)	1	Open label, randomized, parallel group	27	Single dose	Empagliflozin: 5 mg, 10 mg, 25 mg	10 to 17 years with T2DM
1218.56 (PMR 1766-1)	2b	Double-blind, randomized, placebo- controlled parallel group	39	12 weeks	Linagliptin: 1 mg,5 mg daily	10 to 17 years with T2DM
1218.91 (DINAMO) (PMR 3300-1)	3	Double-blind, randomized, placebo- controlled, paralle group plus double- blind active treatment safety extension period	157	26 weeks plus safety extension up to 52 weeks	Empagliflozin: 10 mg, 25 mg daily Linagliptin: 5 mg daily	10 to 17 years with T2DM

Source: Applicant's Clinical Overview Documents in Module 2

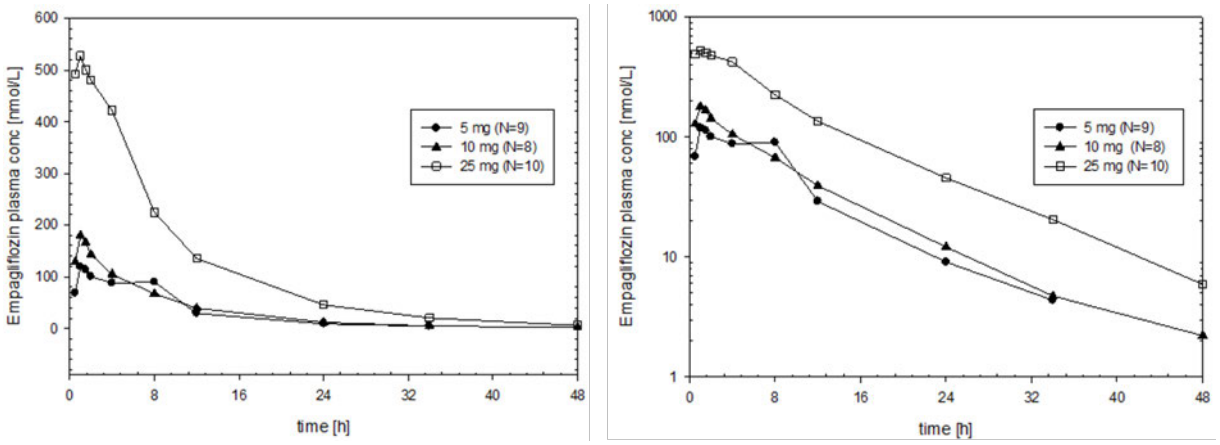
Overall, the Applicant proposed to update the labeling of three linagliptin containing products and the three empagliflozin products with the pediatric study results that are collected from the DINAMO (trial 1218.91) by submitting efficacy supplements to NDA 201280 for Tradjenta (linagliptin), NDA 201281 for Jentadueto (linagliptin and metformin hydrochloride), NDA 208026 for Jentadueto XR (linagliptin and metformin hydrochloride extended-release), NDA 204629 for Jardiance (empagliflozin), NDA 206111 for Synjardy (empagliflozin and metformin hydrochloride), and NDA 208658 for Synjardy XR (empagliflozin and metformin hydrochloride extended-release). The Applicant is seeking pediatric indication only for the empagliflozin containing products.

2.2 General Pharmacology and Pharmacokinetic Characteristics

The general pharmacology and pharmacokinetics of empagliflozin in healthy volunteers, adult patients with T2DM, and special populations has been previous reviewed [Refer to NDA 204629 OCP review; Reference ID: 3403875 dated 08 Nov 2013]. Empagliflozin is not studied in children less than 10 years of age including neonates because T2D is not a disease expected to affect this younger population. A summary of pediatric information from the post marketing study 1245.87 is summarized below. The study was a single dose, open-label, Phase 1 trial to evaluate the pharmacokinetics and pharmacodynamics of 5 mg, 10 mg, or 25 mg empagliflozin in children and adolescents from 10 to less than 18 years of age with T2D.

The data was obtained from 26 pediatric patients wherein 8 patients each received 5 and 10 mg dose and 10 patients received the 25 mg dose. The median age was 14.5 years, median weight was 92 kg, median eGFR was 162 ml/min/1.73 m^2 (120 to 225 ml/min/1.73 m^2), and median baseline mean daily glucose was 124 mg/dL (90.3 to 292 mg/dL).

Figure 1. Mean plasma concentration-time profiles of empagliflozin after single-dose of 5 mg, 10 mg, or 25 mg

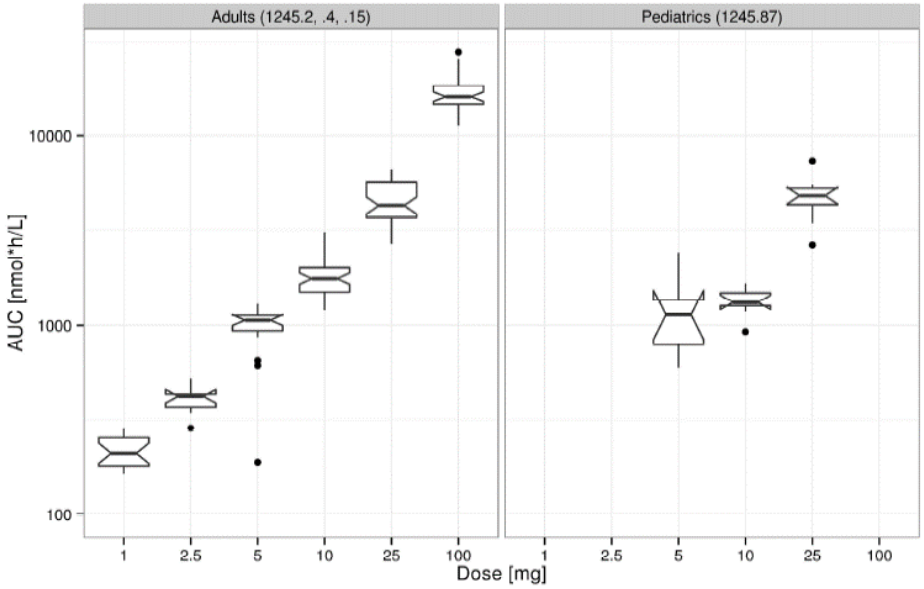


empagliflozin to pediatric patients in linear and semi log (right panel) plots

Following a single dose administration, peak concentrations of empagliflozin was reached at approximately 1.5 hours and the plasma concentrations increased with increasing dose. Empagliflozin exposure increased with increasing dose, with mean C_{max} ranging from 175 nmol/L (5 mg dose group) to 692 nmol/L (25 mg dose group) and mean $AUC_{0-\infty}$ ranging from 1270 nmol·h/L (5 mg dose group) to 5250 nmol·h/L (25 mg dose group). Mean $t_{1/2}$ values were in the range of 7 hours to 8 hours for all empagliflozin doses. The cumulative fraction of empagliflozin excreted in urine fe_{0-24} was comparable across the dose range tested with ~19% of the dose excreted in urine.

A cross study comparison of PK exposures (AUC_{0-24}) of empagliflozin for the adult and pediatric population was conducted, and the results showed that the PK exposures at 10 and 25 mg dose of empagliflozin were comparable between adult and adolescent patients with T2DM as shown in Figure 2. The adult PK dataset were comprised of data from 3 clinical studies (1245.2 (c01801234), 1245.4 (c01796495), 1245.15 (c01793570)) with a total number 226 adult patients with T2DM.

Figure 2. Observed 24 h AUC [nmol·h/L] per dose group in the adult (left panel) and pediatric (right panel) population



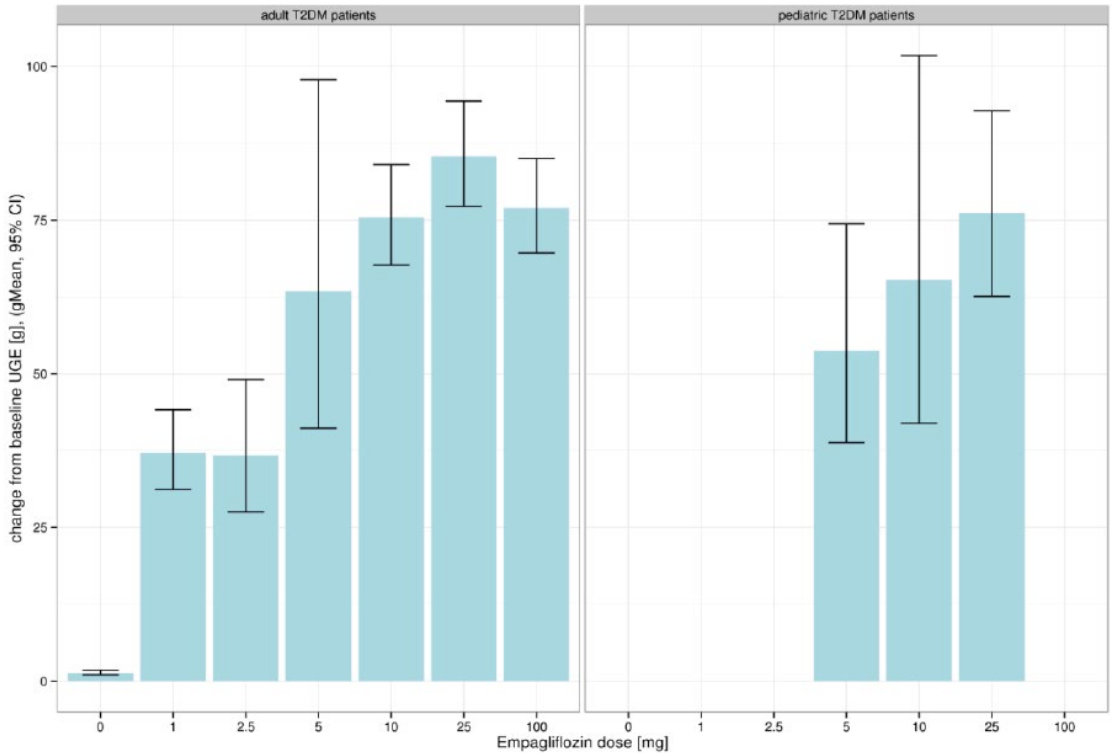
2.3 Clinical Pharmacology Review Questions

2.3.1 Does the available clinical pharmacology information provide supportive evidence of effectiveness in pediatric patients with type 2 diabetes?

Yes, the clinical pharmacology information in this pediatric supplement based on studies PMR 2755-1 (study 1245.87) and PMR 3300-1 (study 1218.91 or DINAMO) provided the supportive evidence of effectiveness. Study 1245.87 evaluated the PK and PD data for empagliflozin in pediatric patients aged 10-17 years old with Type 2 Diabetes mellitus (T2DM), and the results were compared to the historical data in adult patients with T2DM to support dose selection of the DINAMO study. The recommended dosage of empagliflozin as an adjunct to treat T2DM in this pediatric age group is mainly supported by the efficacy, PK and safety data from the DINAMO study. Additional simulation data using exposure response models from pooled adult and pediatric data were presented as supportive evidence for efficacy.

Dose selection based on Study 1245.87:
The PK/PD study 1245.87 was previously reviewed by the OCP (Reference ID: 4044488, dated 20 Jan 2017) and determined to satisfy the clinical pharmacology pediatric PMR (2755-1) of NDA 204629.
Study 1245.87 (Phase 1, n=27) was a randomized, open-label, parallel group, multicenter single-dose trial with 3 treatment groups (5 mg, 10 mg, or 25 mg empagliflozin). Based on allometric scaling the Applicant predicted that the doses of 7 or 17 mg in 10-year-old patients and 10 or 25 mg in 17-year-old patients, should provide exposures equivalent to the approved clinical doses of 10 and 25 mg in adults. The doses selected for evaluation in this study (5 mg, 10 mg or 25 mg) were intended to cover the above 7-25 mg target dose range. Empagliflozin was administered via the oral route under fasting conditions, using the commercially available film-coated tablets (5 mg strength used the same final blend and slightly different amount of film-coat). Patients in the age range of 10 to less than 18 years with T2DM and who had insufficient glycemic control (HbA1c ≤10.5%) despite treatment with diet and exercise and/or stable metformin and/or stable basal or multiple dose injection (MDI) insulin therapy were included in the trial. The dosage regimen of these background therapies was to remain unchanged if medically appropriate throughout the trial. Nearly half of patients (n=13) were younger than 15 years of age and 67% were female. The PK and PD (urinary glucose excretion (UGE)) assessment was evaluated for 48 hours post-dose.
Following the single doses of 5, 10 or 25 mg of empagliflozin, a dose-dependent increase in exposure and UGE was observed in pediatric patients. Overall, the PK parameters and 24 h UGE after single doses of empagliflozin in pediatric patients were comparable to corresponding adult values observed in the Study 1245.4 (Figure 3). Due to the large variability in UGE values and limited sample size, the traditional assessment of PK/PD relationship was not feasible; however, a population PK/PD was developed and used to characterize the exposure-response relationship for UGE in adults and pediatrics. The predictions from population PK/PD model were similar to the observed results for UGE following administration of 10 and 25 mg in pediatric patients and the similarity of these results to adults, supported the further evaluation of these two doses (10 mg and 25 mg) in the pivotal DINAMO study.

Figure 3. Observed change from baseline UGE in the adult (left panel) and pediatric (right panel) population



Source: Figure 10.1.2.1, Population PK/PD analysis (document number: c09146085-01)

Dosing regimen in pivotal study 1218.91 (DINAMO):

The DINAMO trial provided the efficacy and safety data to support empagliflozin dosage in pediatric patients with T2DM, aged 10 to ≤ 17 years (mean age= 14.5 years).

DINAMO was a randomized, placebo-controlled, double-blind, and parallel group trial with 3 treatment arms (placebo, 5 mg linagliptin, 10 mg empagliflozin) lasting 26 weeks (Figure 4). Patients on empagliflozin who did not achieve HbA1c <7.0% at Week 12 were re-randomized at Week 14 to either continue with 10 mg empagliflozin or increase to 25 mg empagliflozin. The primary efficacy endpoint was the change in HbA1c (%) from baseline to the end of 26 weeks. The trial included a double-blind active treatment safety extension period up to 52 weeks: patients on placebo were re-randomized at Week 26 to receive either linagliptin or empagliflozin (10 mg or 25 mg).

Of the total study population, 48% of randomized patients were <15 years of age and 62% of randomized patients were female. Patients with insufficient glycemic control of HbA1c ≥6.5% and ≤10.5% could participate in this trial. About half of the patients had baseline HbA1c values of <8%; for the remaining patients, approximately similar proportions had either HbA1c values of 8.0% to 9.0% or of >9%. the trial included patients who were treated with diet and exercise plus a stable dose of metformin and/or insulin or who were not tolerating metformin. About half of the patients (85 patients, 54.1%) took 1 background antidiabetic treatment and 63 patients (40.1%) took 2 background antidiabetic medications. There were 80 patients (51.0%) with only metformin as background antidiabetic therapy, 5 patients (3.2%) with only insulin treatment, 63 patients (40.1%) with metformin and insulin treatment, and 9 patients (5.7%) with no background antidiabetic medication. The mean total daily dose of metformin at baseline was 1661.5 mg and the mean total daily dose of insulin was 54.3 IU/day.

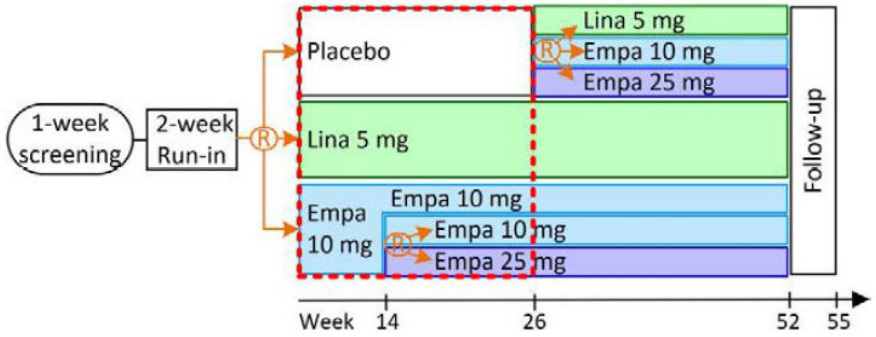
Figure 4. Overview of the study design for DINAMO (Study 1218.91)

Planned: Entered: approximately 150 patients (50 per treatment group)

Actual: Screened: 262 patients Randomised: 158 patients

	Randomised	Treated	Analysed (primary endpoint)
Primary analysis up to Week 26 for Treatment Grouping 1 (TG1)			
Placebo	53	53	53
Linagliptin 5 mg	53	52	52
Empagliflozin pooled (10 mg + 25 mg)	52	52	52

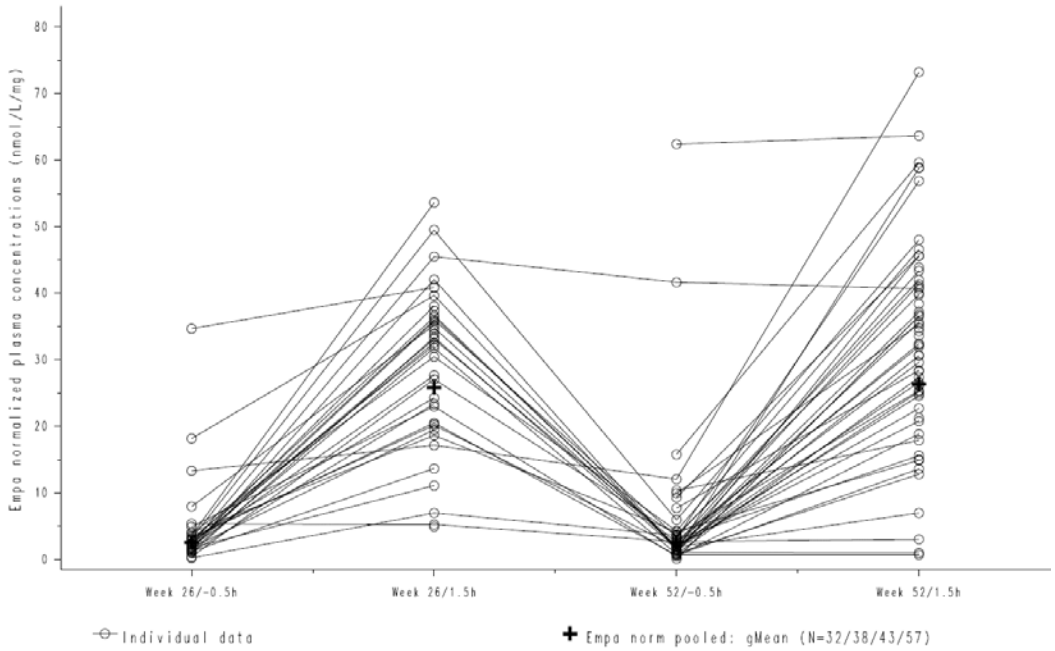
TG1 is marked in dashed red borderline:



Source: Synopsis, CTR for Study 1218.91 (document number: c 38245139-01)

Approximately, 50% were White, 6% were Asian, and 31% were Black. The mean BMI was 36.0 kg/m^2 and mean body weight was 99.9 kg. Patients with an eGFR less than 60 mL/min/1.73 m^2 were not enrolled in the study. PK samples for empagliflozin were obtained at pre-dose (approx. 24 h after dosing on previous day) and at 1.5 h post-dosing and taken at Week 26 and 52. The mean empagliflozin concentrations were similar between Week 26 and 52 and indicative of exposure being at steady state. The pooled dose-normalized concentrations at the sampled time points are shown in Figure 5. No influence of age on empagliflozin exposure was observed when comparing the exposure of patients aged below 15 years (n=22) with the exposure of patients aged 15 to <18 years (n=23). The dose normalized concentrations were observed to be higher in patients with lower body weight (below 70 kg) and in female gender.

Figure 5. Individual and geometric mean plot of pooled values of empagliflozin after multiple oral administration of 10 mg or 25 mg empagliflozin once daily dosing at Week 26 and 52 in DINAMO (Study 1218.91)

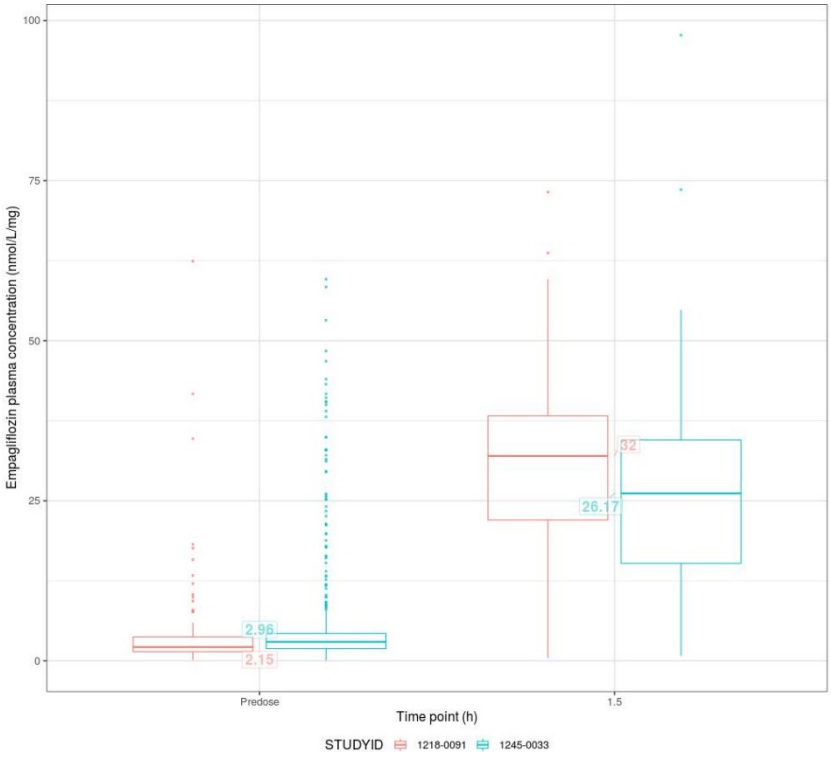


Source: Figure 15.6.5.1.1:2; CTR for Study 1218.91 (document number: c 38245139-01)

The plasma concentrations in children and adolescents with T2DM under steady state were generally comparable to those previously observed after the approved dosing regimen in adult patients with T2DM (Study 1245.33- Phase 2 study with once daily dosing over 78 weeks) and is illustrated in Figure 6.

.

Figure 6. Comparison of median (inter-quartile range) pooled dose normalized concentrations for empagliflozin after once daily dosing with 10 or 25 mg in pediatric (DINAMO Study 1218.91) and adult (Study 1245.33) patients with Type 2 diabetes



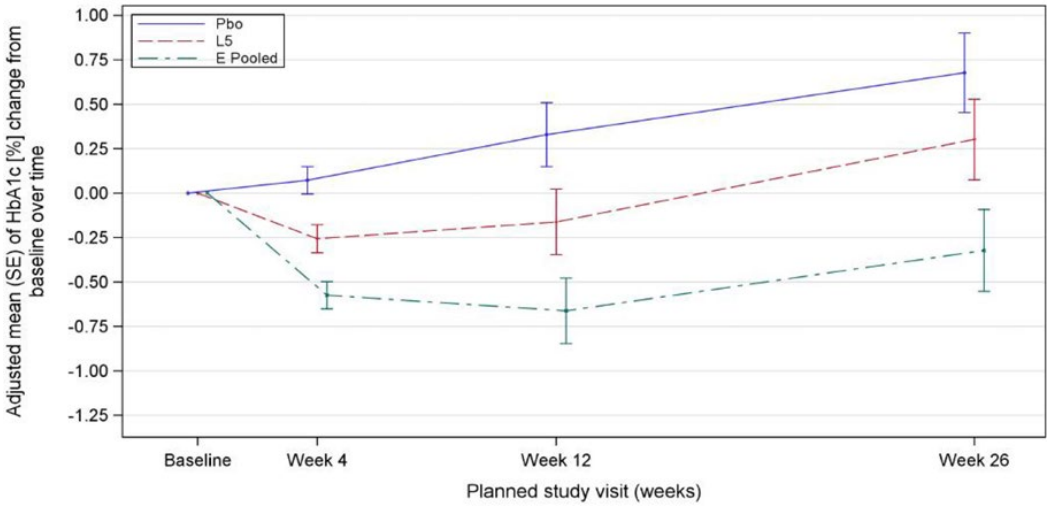
Source: Reviewer's analysis from pooled dataset adpkempa

2.3.2 Is the proposed dosing regimen appropriate for pediatric patients with type 2 diabetes that are 10 years and older?

Yes, the proposed dosage is acceptable for the treatment of type 2 diabetes in pediatric patients aged 10 years and older. Following 26 weeks of treatment in the DINAMO study, the empagliflozin treatment (pooled of 10 and 25 mg data) was superior to placebo and achieved a statistically significant decrease from baseline in HbA1c with placebo-adjusted mean reduction of −0.84% (95% CI: −1.50% to −0.19%; p = 0.0116). The fasting plasma glucose also showed a decrease from baseline for the pooled empagliflozin treatment with placebo-adjusted mean reduction of -35.2 mg/dl (95% CI: −58.6 to −11.7; not tested as a part of sequential testing procedure).

The study design of DINAMO did not include separate arms for 10 mg and 25 mg of empagliflozin. Instead, all patients were randomized initially to the empagliflozin 10 mg (n=52) or placebo (n=52) or linagliptin (n=52) treatment arms. Most of the treated patients (94.3%) had background antidiabetic treatment at baseline (metformin and/or insulin), and the baseline HbA1c was 8.03%. Only for the empagliflozin 10 mg arm, those who failed to achieve HbA1c <7.0% at Week 12, underwent a second randomization at Week 14 to remain on the 10 mg dose or increase to 25 mg dose of empagliflozin. Hence, the primary analysis for change from baseline in HbA1c at Week 26 evaluated the pooled treatment effect for empagliflozin 10 and 25 mg. Overall, in the empagliflozin pooled group, there was a drop in HbA1c at Week 4 (−0.57%) and Week 12 (−0.66%); at Week 26, mean HbA1c increased relative to Week 12, but was below the baseline (−0.32%; Figure 5).

Figure 7.HbA1c [%] change from baseline* over time up to Week 26 (DINAMO study)



Number of patients				
Pbo	52	50	52	50
L5	50	48	49	49
E Pooled	51	50	48	47

Pbo = Placebo, L5 = Linagliptin 5 mg, E Pooled = Empagliflozin pooled.

*LS Mean+/- SE, adjusted for categorical age, treatment, visit, treatment-by-visit interaction; re-randomization at Week 14 for non-responders to patients on 10 mg empagliflozin

In comparison, the placebo group that showed an increase in HbA1c at Week 4, 12 and 26, by mean values of 0.07%, 0.33% and 0.68%, which was considered to reflect the disease progression rate in pediatric patients in the presence of a stable background treatment. This observation for the increase in HbA1c over time for placebo was not apparent in the clinical studies of adult patients with T2DM.

Exploratory subgroup analysis of non-responders:

At Week 14, the non-responders (n=24 of 51 treated) in empagliflozin 10 mg arm (who failed to achieve HbA1c <7.0% at Week 12, indicating insufficient glycemic control) were dose up-titrated to 25 mg (n=13) or remained at 10 mg (n=11) for the remainder of the study. In general, there was a higher mean baseline value for HbA1c observed in the non-responders compared to responders to empagliflozin 10 mg, as shown in Table 2.

However, the up titration of dose to 25 mg in non-responders did not reveal a dose response, as the mean (SD) change in HbA1c from Week 12 to 26 for non-responder patients titrated to 10 mg or up-titrated to 25 mg was −0.10% (0.71) and 0.52% (0.63) with placebo-adjusted mean change from baseline of -1.18% (95% CI: −1.90% to −0.45%) and −0.52% (95% CI: −1.31% to 0.27%), respectively.

Further, there were differences in baseline HbA1c for non-responders re-randomized to 10 and 25 mg, as shown in Table 2, wherein a higher mean baseline HbA1c value was observed for 10 mg than 25 mg which was a chance variation, considering that randomization to treatment groups was done at baseline. In addition, one outlier patient with poor compliance in the 25 mg group showed an increase from baseline HbA1c of 7.9% to 15.1% at Weeks 12 and 26, increasing the overall mean hBA1c for the 25 mg group.

Table 2. Descriptive statistics of HbA1c [%] over time up to Week 26 in responders (continuing at 10 mg) vs non-responders (re-randomized to 10 mg or 25 mg at Week 14)

	Placebo			Empa 10 mg discontinued before Week 14			Empa 10 mg responders at Week 12			Empa 10 mg non-responders at Week 12 Re-randomized to 10 mg			Empa 10 mg non-responders at Week 12 Re-randomized to 25 mg		
Visit	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD
Baseline	53	8.05	1.23	5	9.36	1.49	23	7.20	0.91	11	8.76	1.15	13	8.24	1.08
Week 4	50	8.17	1.56	3	8.37	1.14	23	6.68	0.67	11	8.16	0.88	13	7.75	0.95
Week 12	52	8.40	1.96	2	6.40	0.28	23	6.37	0.37	11	8.04	0.87	12	8.30	2.26
Week 26	50	8.77	2.41	2	7.15	1.63	23	6.81	1.21	10	7.87	0.85	12	8.89	2.22

Overall, due to the study design where a small sample size of non-responders was randomized to 10 and 25 mg, confounded by differences in baseline values for HbA1c, and presence of outlier, a clear dose-response for 10 mg and 25 mg could not be identified for empagliflozin in this pediatric population.

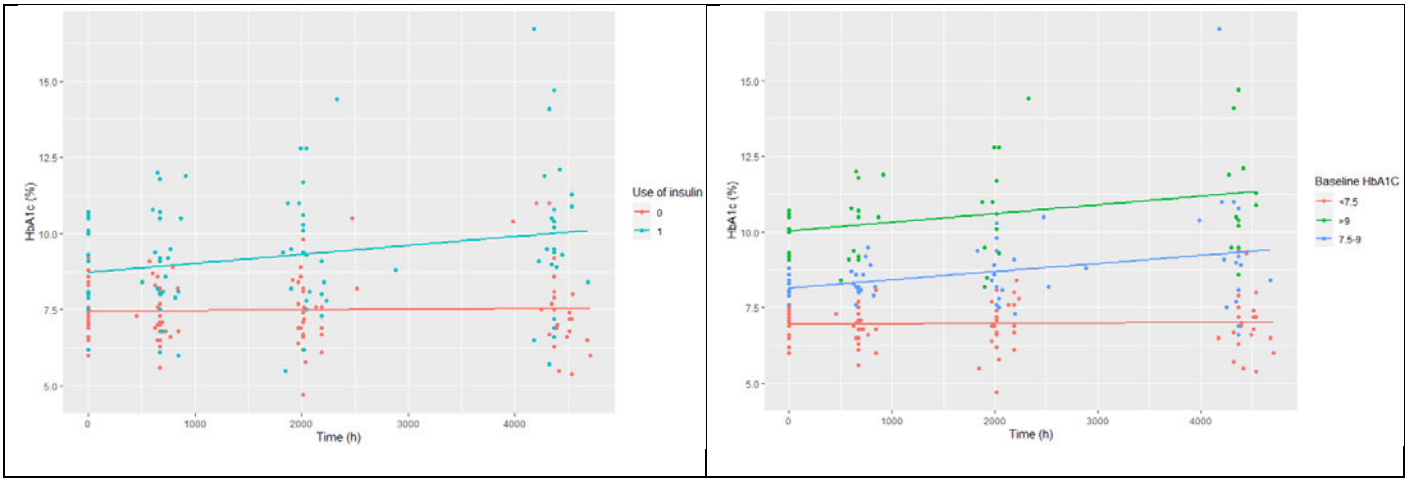
Placebo treated until Week 26 and re-randomized at Week 26 to empagliflozin until Week 52:
At Week 26, the placebo treated patients (n=47) were re-randomized to linagliptin 5 mg (n=16), empagliflozin 10 mg (n=15) or empagliflozin 25 mg (n=16). The mean (SD) change at Week 52 was 0.59% (1.95) for linagliptin 5 mg, −0.35% (1.50) for empagliflozin 10 mg and −0.53% (1.13) for empagliflozin 25 mg. The HbA1c change in response to empagliflozin treatment from weeks 26 to 52, were in the range of values observed for pooled treatment at the end of 26-week double-blind treatment and the 25 mg seemed to have a better response than 10 mg. However, in the absence of information on the proportion of responders and non-responders within the 10 mg and 25 mg treatment arms, a clear dose response was not interpretable.

Exposure-response analysis in pediatric patients:
In the pediatric efficacy Study 1218.91, a single dose (i.e., 10 mg) empagliflozin was evaluated for responders, while two doses (i.e., 10 mg or 25 mg) were evaluated for non-responders in Study 1218.91. It was observed that the absolute change of HbA1c from baseline following 25 mg dose empagliflozin was smaller than those following 10 mg dose for non-responders, indicating inferior efficacy at 25 mg of empagliflozin as compared to 10 mg.

In order to better understand the treatment effects at 10 mg or 25 mg, the reviewer further analyzed 1) the empagliflozin treatment effects at different doses using propensity score matching method, and 2) the data from placebo arm between Week 26 and Week 52, and 3) exposure-response model.

1) Based on the disease progression data from the placebo arm between Week 0 and Week 26, it was identified that patients with the baseline use of insulin had higher baseline HbA1c and faster disease progression as compared to patients not using insulin at baseline. In addition, patients with a baseline HbA1c < 7.5% also have a slower disease progression rate as compared to pediatric patients with higher baseline HbA1c.

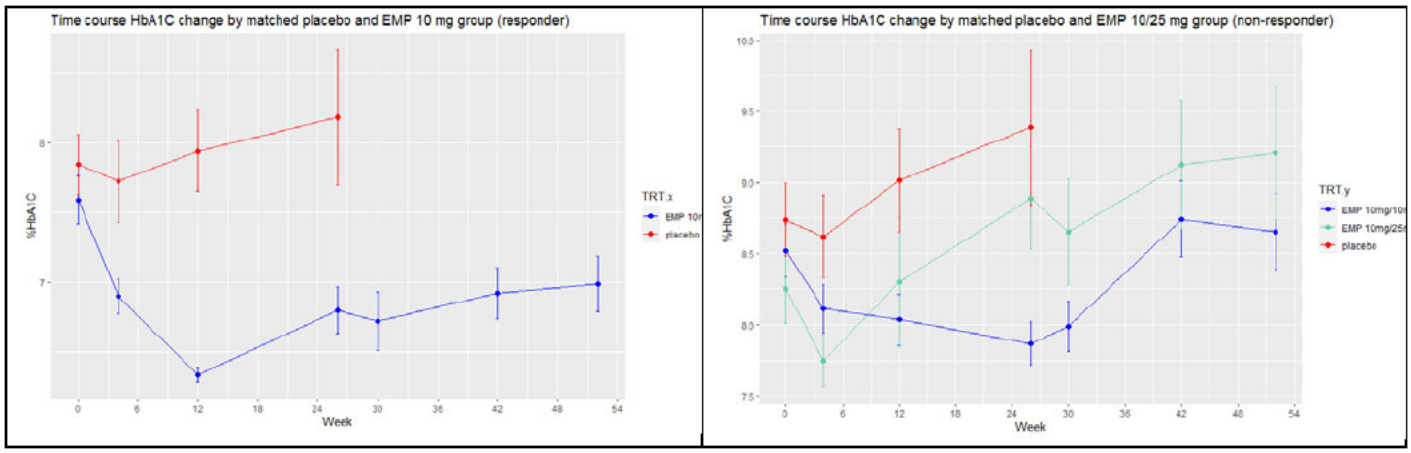
Figure 8. HbA1c (%) over time for the placebo arm in Study 1218.91 stratified by use of insulin (upper) or baseline HbA1c (lower).



Use of Insulin: 0 (red), patients were using insulin; 1 (blue), patients were not using insulin.
Baseline HbA1c: < 7.5 (red), the baseline HbA1c < 7.5 %; 7.5 – 9 (blue), the baseline HbA1c ≥ 7.5 % and < 9%; HbA1c: > 9 (green), the baseline HbA1c > 9 %.
Source: Reviewer's analyses.

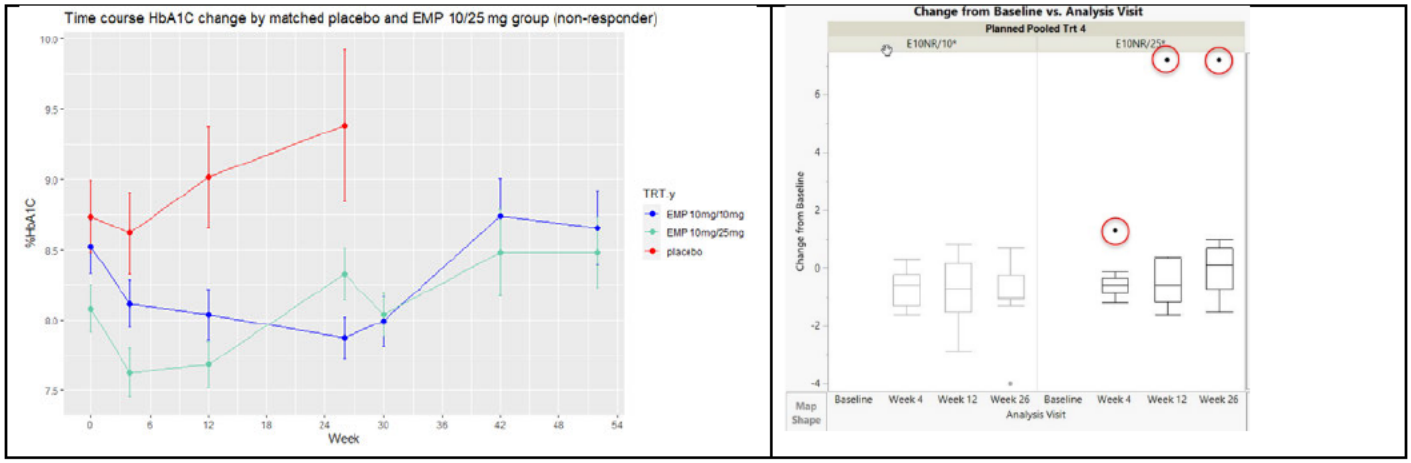
Therefore, propensity score matching was used to identify the matched placebo groups for responders and non-responders, respectively, based on baseline HbA1c and status of using of insulin. After identifying the matched placebo patients, the time course treatment effects of empagliflozin on HbA1c as compared to placebo were assessed. The results show that 10 mg empagliflozin significantly decreased HbA1c for T2D pediatric patients as compared to placebo for both responders and non-responders (**Figure *9***). The performance of 25 mg dose of empagliflozin for its effect on HbA1c seems to be worse as compared to 10 mg in the non-responder group (**Figure *9***). However, after removing a single outlier patient, the performance of 10 mg and 25 mg in the non-responder group was similar (**Figure *10***).

Figure 9. Time course treatment effects as compared to placebo after propensity score matching for responders (left) and non-responders (right).



Abbreviation: EMP, empagliflozin.
Source: reviewer's analyses.

Figure 10. Time course treatment effects for non-responders after removing the outlier subject.

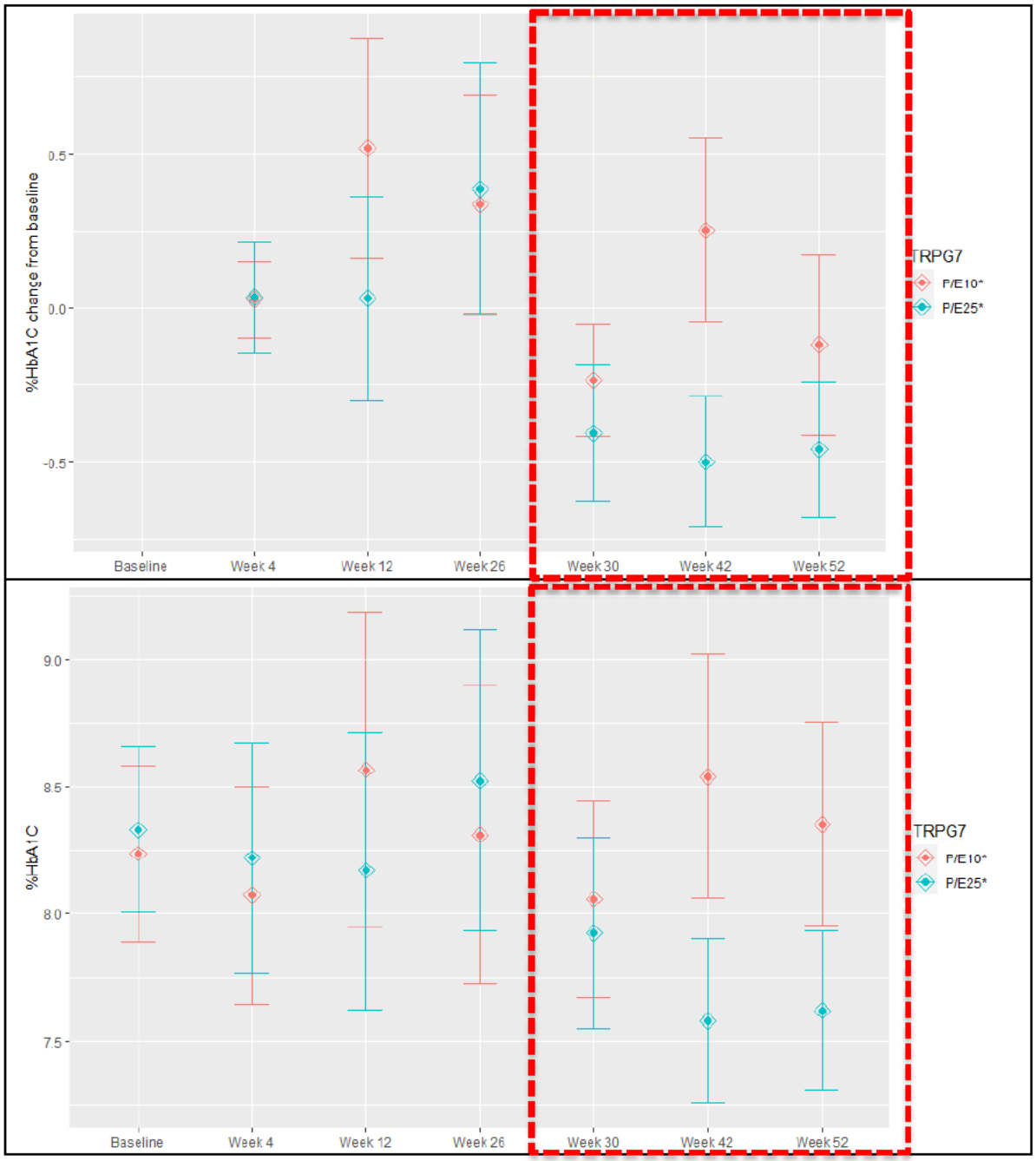


Outlier subject in red circle: ID (b) (6)
Source: reviewer's analyses.

2) The placebo arm results between Week 26 and Week 52

For patients in placebo arm, they were re-randomized to either empagliflozin 10 mg arm or 25 mg arm at Week 26. Therefore, the reviewer analyzed the time course of HbA1c (%) and HbA1c change from baseline for patients in the placebo group. The results show that patients in the placebo/25 mg group had a larger drop in HbA1c (%) from Week 26 to Week 52, as compared to placebo/10 mg group (**Figure 11**).

Figure 11. Time course of HbA1c (%) and HbA1c change from baseline for patients in the placebo group in Study 1218.91.



Source: reviewer's analyses.

3) ER model

The effects of empagliflozin exposure on HbA1c in pediatric patients with T2D was described by an indirect response model with a disease progression rate acting on k_{in} and a drug effect inhibiting k_{in} via an inhibitory I_{max} model. In this inhibitory I_{max} model, the AUC_{50} (AUC at 50% IMAX) was fixed at 703 nmol*hr/L. However, the estimated AUC_{ss} following 10 mg (2185 ± 617 nmol*hr/L) and 25 mg dose (5634

± 2057 nmol*hr/L) are much higher than 703 nmol*hr/L, indicating that the inhibition effect for empagliflozin is already at the plateau at the proposed dose levels. Further titration the dose from 10 mg to 25 mg is not expected to bring additional inhibitory effect on HbA1c.

Based on the above analyses, we concluded that

- The disease progression rates for pediatric T2D patients are inherently different. In general, pediatric patients with a baseline HbA1c ≥ 7.5 % and/or combination use of insulin are likely to have a faster disease progression rate and could be a non-responder. Whereas pediatric patients with a baseline HbA1c < 7.5 % and/or without combination use of insulin are likely to have a slower disease progression rate and could be a responder.
- For both responders/non-responders, there is a significant treatment effect as compared to matched placebo group using propensity score matching.
- Contradicting results were observed comparing the treatment effect between 10 mg and 25 mg (**Figure *10*** and **Figure 11**). However, totality of evidence suggest that 25 mg does not provide additional benefit on HbA1c for non-responders.
- The advantage of titrating of dose from 10 mg to 25 mg for responders is unknown. Refer to the pharmacometric review in Section 3.2 and clinical review regarding the dose/exposure-response and benefit-risk assessment for the use of 25 mg dose to get additional glycemic control.

3. APPENDICES

3.1 Summary of Bioanalytical Method Validation and Performance

Concentrations of empagliflozin in plasma samples for the pediatric studies were determined by a validated LC-MS/MS assay (liquid chromatography tandem mass spectrometry). The analysis of patient samples for study 1245.87 was reviewed and found acceptable by the OCP previously (Reference ID: 3403875 dated 08 Nov 2013 and Reference ID: 4044488, dated 20 Jan 2017). For analysis of DINAMO study samples, the validated method (Inotiv SAP.1217) was used and found to perform within the acceptance criterion. The calibration range for the assay was 1.11-1110 nmol/L with the low, medium and high levels of quality control (QCs) being 3.33 nmol/L, 44.4 nmol/L and 887 nmol/L, respectively.

The study samples were analyzed within the validated stability period of 1327 days and the assay performance was found acceptable, as below. The overall accuracy and precision of the quality control samples for the 12 analytical runs were 101.4% and 8.2%, respectively. Incurred sample reproducibility was assessed by re-assaying 56 out of the 529 patient samples (10.6% of the sample size), and 98.2% of the re-assayed patient samples results were within 20%, thus meeting the acceptance criteria. The bioanalytical method performance to quantify empagliflozin in plasma samples was found to be acceptable.

3.2 Pharmacometrics Review

3.2.1 Population PK analysis

1.1 Review Summary

In general, the Applicant's population PK analysis is considered acceptable for the purpose of description of empagliflozin exposure in plasma in pediatric patients aged 10 years and older with type 2 diabetes (T2D), and for generating empagliflozin exposures for the exposure-response (ER) analyses. The Applicant's analyses were verified by the reviewer, with no significant discordance identified.

More specifically, the developed model was used to support the current submission as outlined in **Table *3***.

Table 3. Specific Comments on Applicant's Final Population PK model

Utility of the final model		**Reviewer's Comments**
Derive exposure metrics for Exposure-response analyses	C_{max}, C_{min}, AUC_{ss}	The Applicant's final pediatric population PK (PopPK) model is generally acceptable for generating exposure metrics for exposure-response analyses. However, out of sample visual predictive check show this pediatric model overpredict the exposures for data from Trial 1245-0087, and therefore the post-hoc individual estimates of empagliflozin should be used with caution.

1.2 Introduction

The primary objective of Applicant's analysis was to:

- Characterize the PK of empagliflozin in adults and pediatric patients with type 2 diabetes mellitus (T2D).

1.3 Model development

Population PK model reports

Report number	Title
tmcp-1245-poppkpd-empa-stage12022 Document number: c37380422-01	Empagliflozin simplified PopPK and ER modeling for HbA1c
tmcp-1218-0091-pmx-dinamo-empa-ppk-er Document number: c39218173-01	PopPK and ER modeling of empagliflozin in pediatric patients with Type 2 Diabetes

- **Simplified adult/pediatric population PK (Report c37380422-01)**

Data

The analyses were based on PK data from 14 studies (3 Phase 1 studies, 5 Phase 2 studies, and 6 Phase 3 studies). The study design, study population, and timing of blood samples varied among the 14 clinical studies. Brief descriptions of the studies included are presented in **Table *4***.

The NONMEM data file from the Applicant's proposed simplified adult/pediatric population PK model for analysis contained 23,008 observed PK concentrations from 5771 subjects. **Table 5** provides summary statistics of the baseline demographic covariates in the analysis dataset.

Table 4. Summary of Studies with PK Sampling Included in Population PK Analysis.

Protocol # & Study Design	**Dosage Regimen & Study Description**	**Number of Subjects in PopPK**	**Dose:**
Study 1245-0002 (Study 2, Phase I MAD)	Safety, tolerability, pharmacokinetics and pharmacodynamics of four multiple rising oral doses (2.5 mg to 100 mg) of empagliflozin tablets in male and female type 2 diabetic patients **PK sampling:** Full PK Profiles* (days 1 and 9) plus daily troughs.	N = 36	2.5 mg, 10 mg, 25 mg and 100 mg QD for 9 days
Study 1245-0004 (Study 4, Phase I)	Safety, tolerability, pharmacokinetics and pharmacodynamics of four weeks treatment with three oral doses of empagliflozin as tablets in female and male patients with type 2 diabetes. **PK Sampling:** Full PK Profiles (days 1 and 28)# plus daily troughs on days 2-4, 7, 14, 21, 25, 26, 27, and 29.	M = 62	Dose: 10, 25, and 100 mg QD for 4 weeks.
1245-0009 (Study 9, Phase IIb)	A Phase IIb, randomized, parallel group safety, efficacy, and pharmacokinetics study of empagliflozin (5 mg, 10 mg, and 25 mg) administered orally once daily over 12 weeks compared double blind to placebo, as monotherapy, with an additional open-label metformin arm in T2D patients with insufficient glycemic control. **PK Sampling:** Pre-dose on Days 1, 28, 56, 84, plus 1-2 post-dose samples on Day 84.	N = 237	Dose: 5, 10, and 25 mg QD for 12 weeks

1245-0010 (Study 10, Phase IIb)	A Phase II, randomized, parallel group safety, efficacy, and pharmacokinetics study of empagliflozin (1 mg, 5 mg, 10 mg, 25 mg, and 50 mg) administered orally once daily over 12 weeks compared double blind to placebo with an additional open-label sitagliptin arm in type 2 diabetic patients with insufficient glycemic control despite metformin therapy. **PK Sampling:** Pre-dose on Days 1, 28, 56, 84, plus 1-2 post-dose samples on Day 84	N = 334	Dose: 1, 5, 10, 25, and 50 mg QD for 12 weeks
1245-0015 (Study 15, Phase II)	A Phase II, randomized, double-blind, placebo-controlled, multiple dose study to evaluate pharmacodynamics, pharmacokinetics, safety, and tolerability of once daily oral administration of BI 10773 (1 mg, 5 mg, 10 mg, and 25 mg) for 28 days in Japanese patients with T2D **PK sampling:** Full PK Profiles (days 1 and 28) plus daily troughs on days 2, 7 14, 21, 26, 27, 29, plus 12, 24, and 48 hours after last dose	N = 79 (Japanese patients)	Dose: 1, 5, 10, and 25 mg QD for 28 days
1245-0019 (Study 19, Phase III)	A randomized, double-blind, placebo-controlled parallel group efficacy and safety trial of BI 10773 (10 and 25 mg administered orally once daily) over 24 weeks in patients with T2D with insufficient glycemic control despite a background therapy of pioglitazone alone or in combination with metformin. **PK sampling:** Trough samples on Days 85 and 169	N = 303	Dose: 10 and 25 mg QD for 24 weeks with background pioglitazone +/- metformin
1245-0020 (Study 20, Phase III)	A phase III randomized, double-blind, placebo-controlled parallel group efficacy and safety study of empagliflozin and sitagliptin administered orally over 24 weeks, in drug naive patients with T2D and insufficient glycemic control despite diet and exercise **PK sampling:** Trough samples on Days 85 and 169 plus two post-dose samples on Day 169	N = 394 Treatment naïve patients	Dose: 10 and 25 mg QD for 24 weeks.

1245-0023 (Study 23, Phase III)	A phase III randomized, double-blind, placebo-controlled, parallel group, efficacy and safety study of empagliflozin (10 mg, 25 mg) administered orally, once daily over 24 weeks in patients with type 2 diabetes mellitus with insufficient glycemic control despite treatment with metformin alone or metformin in combination with a sulfonylurea. **PK sampling:** Trough samples on Days 85 and 169	N = 692	Dose: 10 and 25 mg QD for 24 weeks. Metformin background.
1245-0028 (Study 28, Phase III)	A phase III randomized, double-blind, active-controlled parallel group efficacy and safety study of empagliflozin compared to glimepiride administered orally during 104 weeks with a 104-week extension period in patients with type 2 diabetes mellitus and insufficient glycemic control despite metformin treatment. **PK sampling:** Trough samples on Weeks 12 and 28 plus two post-dose samples on Week 28	N = 731	Dose: Phase III (25 mg) for 104 weeks. Metformin background
1245-0033 (Study 33, Phase IIb)	Randomized, double-blind, placebo-controlled, parallel group, safety and efficacy study of empagliflozin (10 mg and 25 mg) administered orally, once daily over 78 weeks in type 2 diabetic subjects receiving treatment with basal insulin (glargine or detemir insulin only) with or without concomitant metformin and/or sulfonylurea therapy and insufficient glycemic control. **PK sampling:** Pre-dose on Weeks 6, 12, 18, and two post-dose samples on Week 18	N = 273	Dose: 10 and 25 mg QD for 78 weeks; Basal insulin background with and without metformin
1245-0036 (Study 36, Phase III)	A phase III, randomized, double-blind, placebo-controlled, parallel group, efficacy and safety study of BI 10773 (10 mg and 25 mg administered once daily) as add on to pre-existing antidiabetic therapy over 52 weeks in patients with type 2 diabetes mellitus and renal impairment and insufficient glycemic control. **PK sampling:** Trough samples on Days 85 and 169 plus two post-dose samples on Day 169	N = 349 Subjects with mild to severe renal impairment	Dose: 10 and 25 mg QD for 52 weeks

1245-0087 (Study 87, Phase I)	An open-label, randomized, multicenter, single-dose, parallel group trial to evaluate pharmacokinetics and pharmacodynamics of empagliflozin in children and adolescents from 10 to less than 18 years of age with T2D. **PK sampling:** Full PK profile[&] for single dose	N = 27 Pediatrics patients 10–18-year-old	Dose: 5, 10, and 25 mg QD for a single dose.
1276-0001 (Study 71, Phase III)	A 24-week Phase III randomized, double-blind, parallel group study to evaluate the efficacy and safety of twice daily oral administration of empagliflozin + metformin compared with the individual components of empagliflozin or metformin in drug naive patients with T2D **PK sampling:** Trough samples on Weeks 12, 18, and 24	N = 1023	Dose: Empagliflozin 10 and 25 mg QD monotherapy and fixed dose combination with metformin for 24 weeks
1276-0010 (Study 72, Phase IIb)	A randomized, double blind, placebo controlled, parallel group efficacy and safety study of oral administration of empagliflozin twice daily versus once daily in two different daily doses over 16 weeks as add-on therapy to a twice daily dosing regimen of metformin in patients with T2D and insufficient glycemic control **PK sampling:** Trough samples on Weeks 4 and 16	N = 844	Dose: 10 and 25 mg QD for 16 weeks; Metformin background therapy

[*] *-0:05, 0:10, 0:20, 0:30, 0:40, 1:00, 1:30, 2:00, 3:00, 4:00, 6:00, 8:00, 12:00, 16:00, 24:00, 30:00, 36:00, and 48:00 h after drug administration.*
[#] *-0:05, 0:15, 0:30, 0:45, 1:00 (immediately before OGTT), 1:30, 2:00, 2:30, 3:00, 4:00, 6:00, 8:00, 10:00 (before dinner), 12:00, 16:00, 24:00 h after drug administration on Day 1 and 28. 12:00 h after dose administration on day 29.*
[&] *Predose as well as 0.5 h, 1 h, 1.5 h, 2 h, 4 h, 8 h, 12 h, 24 h, 34 h, and 48 h post dose.*
Source: Reviewer's summary.

Table 5. Summary of Baseline Demographic Covariates for Analysis

Covariate	Statistic	Total
Body Weight (kg)	N	6560
	Mean (SD)	84.1
	SD	19.5
Age (yr)	N	6560
	Mean	56.3
	SD	10.9
Serum Creatinine (mg/dL)	N	6560
	Mean	0.873
	SD	0.279

eGFR (ml/min/1.73m^2)	N Mean SD	6560 87.1 23.7
Sex		
Male	N (%)	3723 (56.8%)
Female	N (%)	2837 (43.2%)
Race		
White	N (%)	4045 (61.7%)
Black	N (%)	234 (3.6%)
Asian	N (%)	2018 (30.8%)
American Indian or Alaskan Native	N (%)	253 (3.9%)
Native Hawaiian or Other Pacific Islander	N (%)	10 (0.2%)
Smoking Status		
Never smoker	N (%)	3963 (60.4%)
Ex-smoker	N (%)	1575 (24.0%)
Current smoker	N (%)	1022 (15.6%)

a; Abbreviations: eGFR: Estimated Glomerular Filtration Rate, N=Number of subjects, SD=Standard deviation
Source: Applicant's population PK report c37380422-01. Tables 3 – 5, Page 53 – 55.

Reviewer's comments:

In the simplified adult/pediatric population PK model, the only study that included pediatric subjects with T2D is 1245-0087 (N= 27). The DINAMO study data was not included in the adult/pediatric population PK model.

Applicant's simplified adult/pediatric population PK model development/results

The simplified adult/pediatric model proposed by the Applicant was a two-compartment model with sequential zero-first order absorption. The covariate model included the effect of body weight on CL, Vc, Q, and Vp, with fixed allometric exponents, and estimated the effects of eGFR, age, race, and sex on CL. The residual error model was defined by a combined additive and proportional error term. Population and individual model parameters were estimated using the SAEM estimation method followed by 10 iteration of importance sampling (expectation only) to assess the OFV and covariance matrix.

The parameter estimates for the covariate model are listed in **Table *6***. The goodness-of-fit plots for the covariate model for all data are shown in **Figure 12**.

Table 6. Parameter Estimates for the Applicant's Simplified Adult/Pediatric Population PK Model

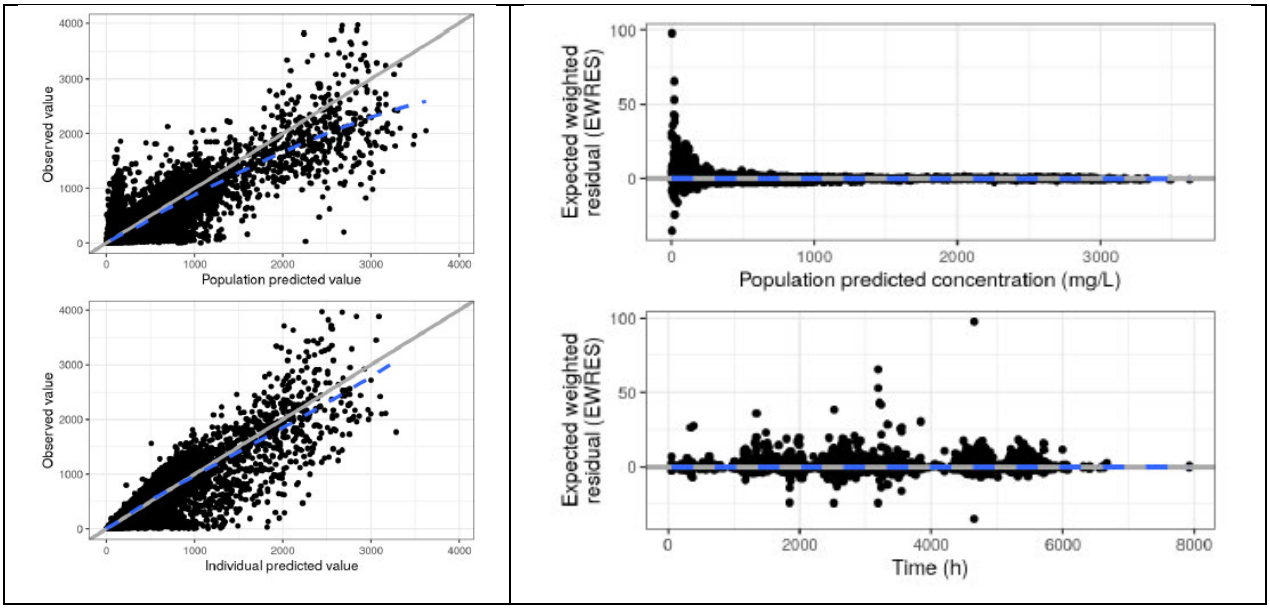
			Median	95% CDI	Bulk ESS	Tail ESS	$\hat{R}$
$WT_{CL/F}$	θ_7	Weight effect on CL/F	0.750	(0.750, 0.750)	40000	40000	1.00
$WT_{V2/F}$	θ_8	Weight effect on V2/F	1.00	(1.00, 1.00)	40000	40000	1.00
$WT_{Q/F}$	θ_9	Weight effect on Q/F	0.750	(0.750, 0.750)	40000	40000	1.00
$WT_{V3/F}$	θ_{10}	Weight effect on V3/F	1.00	(1.00, 1.00)	40000	40000	1.00
$EGFR_{CL/F}$	θ_{11}	eGFR effect on CL/F	0.408	(0.362, 0.455)	609	1307	1.01
$AGE_{CL/F}$	θ_{12}	Age effect on CL/F	-0.183	(-0.259, -0.106)	4774	14905	1.00
$BLACK_{CL/F}$	$\exp(\theta_{13})$	Race=Black effect on CL/F	0.885	(0.817, 0.957)	10384	19279	1.00
$ASIAN_{CL/F}$	$\exp(\theta_{14})$	Race=Asian effect on CL/F	0.933	(0.902, 0.965)	22840	33172	1.00
$FEMALE_{CL/F}$	$\exp(\theta_{15})$	Sex=Female effect on CL/F	1.02	(0.985, 1.05)	26946	34857	1.00

		Description	Median	95% CDI	Bulk ESS	Tail ESS	$\hat{R}$	Shrinkage %
Interindividual variability								
IIV-CL/F	$\sqrt{\exp(\Omega_{11})-1}\times 100\%$	Variance of CL/F	55.2	(53.6, 56.9)	4358	14679	1.00	6.26
IIV-V3/F	$\sqrt{\exp(\Omega_{22})-1}\times 100\%$	Variance of V3/F	40.5	(33.9, 48.4)	246	693	1.01	62.3
V3/F-CL/F	Ω_{21}	Covariance of V3/F - CL/F	0.0837	(0.0575, 0.111)	661	1715	1.01	
Residual variability								
Proportional	$\sqrt{\Sigma_{11}}\times 100\%$	Proportional RUV	35.9	(35.4, 36.4)	3095	5251	1.00	
Additive	$\sqrt{\Sigma_{22}}$	Additive RUV	2.09	(1.98, 2.22)	4407	6136	1.00	

The model used mu-referencing: estimates presented here were back-transformed from the log-domain for clarity. CDI = credible interval; ESS = effective sample size; $\hat{R}$ = Gelman-Rubin diagnostic

Source: *Applicant's population PK report c37380422-01. Tables 11 – 12, Page 61 – 62.*

Figure 12. Standard Goodness-of-fit Plots for the Applicant's Simplified Adult/Pediatric Population PK Model.



Source: *Applicant's population PK report c37380422-01. Figure 38 -39, Page 112-113.*

Ind. = individual; Pop. = population; PopPK = population pharmacokinetic.
The circles represent individual data points; the red lines represent loess smooth curves; and the dashed lines represent either the line of unity (y = x), or the unity line at 0 (y = 0).
Source: Applicant's *population PK report, Figure 23*

Reviewer's Comments:
The reviewer determined that Applicant's simplified adult/pediatric population PPK is acceptable. However, this model only included limited number (N= 27) of pediatric subjects, and therefore, it needs to be further refined for use for describing empagliflozin exposures in pediatric subjects.

- **Pediatric PopPK Model (Report Number: c39218173-01)**

The previous simplified adult/pediatric population PK model was developed based on data from 14 clinical trials. Since limited pediatric data was included in that model, the model was re-estimated using data from pediatric Phase III Study 1218.91.

Data

The pediatric population PK model was based on PK data from Phase 3 Study 1218.91. Brief descriptions of this study included are presented in **Table *7***.

The NONMEM data file from the Applicant's proposed pediatric population PK model for analysis contained 278 observed PK concentrations from 74 subjects. **Table 5** provides summary statistics of the baseline demographic covariates in the analysis dataset.

Table 7. Summary of Studies with PK Sampling Included in Population PK Analysis.

Protocol # & Study Design	Dosage Regimen & Study Description	Number of Subjects in PopPK Analysis, Subject	Dose:
Study 1218.91 (Study 91, Phase III)	A double-blind, randomized, placebo-controlled, parallel group trial to evaluate the efficacy and safety of empagliflozin and linagliptin over 26 weeks, with a double-blind active treatment safety extension period up to 52 weeks, in children and adolescents with T2DM **PK sampling:** weeks 26 and 52 (pre-dose trough (24h) and 1.5 hours post-dose).	N = 157 (placebo, linagliptin and empagliflozin arms) 157 children and adolescents from 10 to 17 years of age with T2DM	Linagliptin 5 mg daily, empagliflozin 10 mg or 25 mg daily, or placebo.

Source: Reviewer's summary from Study Report 1218.91.

Table 8. Summary of Baseline Demographic Covariates for Analysis

Covariate	Statistic	Total
Body Weight (kg)	N Mean (SD) SD Min/Max	103 98.3 26.9 42.5 / 169
Age (yr)	N Mean SD Min/Max	103 14.5 1.86 10.0 / 17.0

eGFR (ml/min/1.73m^2)	N	103
	Mean	127
	SD	25.2
	Min/Max	85.2 / 241
HbA1c (%)	N	103
	Mean	8.04
	SD	1.27
	Min/Max	6.00 / 10.7
Sex		
Male	N (%)	38 (36.9%)
Female	N (%)	65 (63.1%)
Race		
White	N (%)	52 (50.5)
Black	N (%)	35 (34.0)
Asian	N (%)	5 (4.9)
American Indian or Alaskan Native	N (%)	5 (4.9)
Native Hawaiian or Other Pacific Islander	N (%)	1 (1.0)
Multiple	N (%)	4 (3.9)
Unknown	N (%)	1 (1.0)
Insulin Co-Therapy at Baseline		
Yes	N (%)	51 (49.5)
No	N (%)	52 (50.5)
Metformin Co-Therapy at Baseline		
Yes	N (%)	93 (90.3)
No	N (%)	10 (9.7)

a; Abbreviations: eGFR: Estimated Glomerular Filtration Rate, N=Number of subjects, SD=Standard deviation
Source: Applicant's population PK report c39218173-01. Tables 13 – 14, Page 65 - 66.

Reviewer's Comments:

The reviewer conducted internal analyses for the baseline demographic covariates across all 15 studies. The only studies that included pediatric are Studies 1245-0087 and 1218.91. Since these two studies mainly enroll adolescent subjects ≥ 10 years, the body weights of these pediatric subjects are in the similar range as adults from other studies. It is also noted that the pediatric subjects from Studies 1245-0087 and 1218-91 have a higher baseline eGFR distribution as compared to adults from other studies, with the mean/median baseline eGFR greater than 120 mL/min/1.73m^2. For Study 1218-91, eGFR was calculated from Zappitelli et al formula [1]. For Study 1245-0087, eGFR was calculated from the Schwartz formula [2]. Whereas for all the adult studies, eGFR was calculated from MDRD formula [3]. It is not clear whether the relative higher eGFR distribution observed for pediatrics as compared to adults was partly due to different eGFR formulas used for eGFR calculation for each study.

In addition, the demographic analyses also show that 90% of the subjects in Study 1218-91 were coadministered with metformin, while only approximately 50% were co-administered with insulin.

Zappitelli Formula:

$$\text{GFR (mL/min/1.73m}^2) = (507.76 \times e^{0.003 \times \text{height}}) / (\text{Cystatine C}^{0.635} \text{x Serum Creatinine}^{0.547}\ [\mu\text{mol/L}]) \quad [1]$$

If renal transplant, × 1.165

Schwartz Formula:

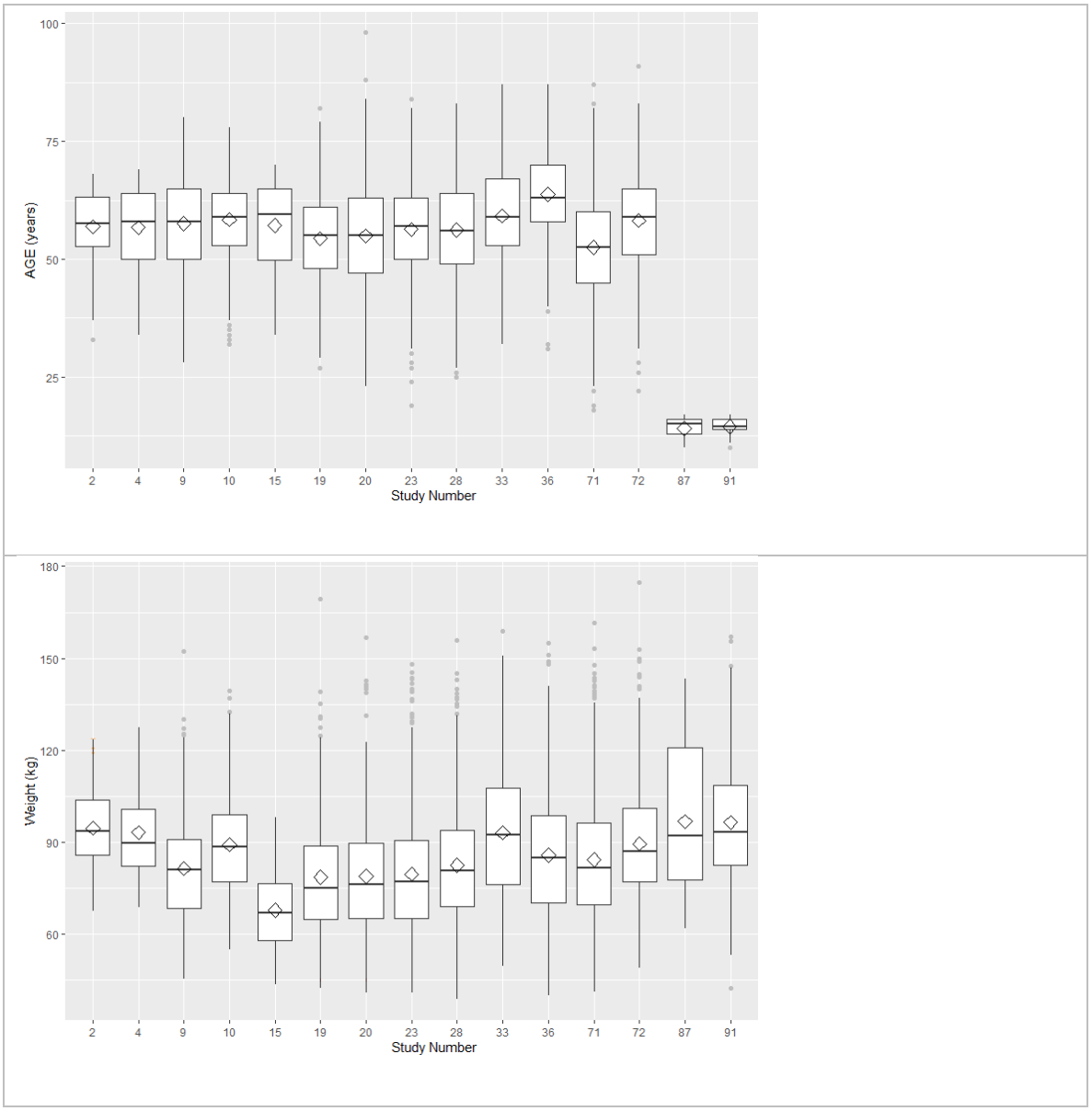
eGFR (ml/min/1.73m²)=k x height/serum creatinine (mg/dL) [2]

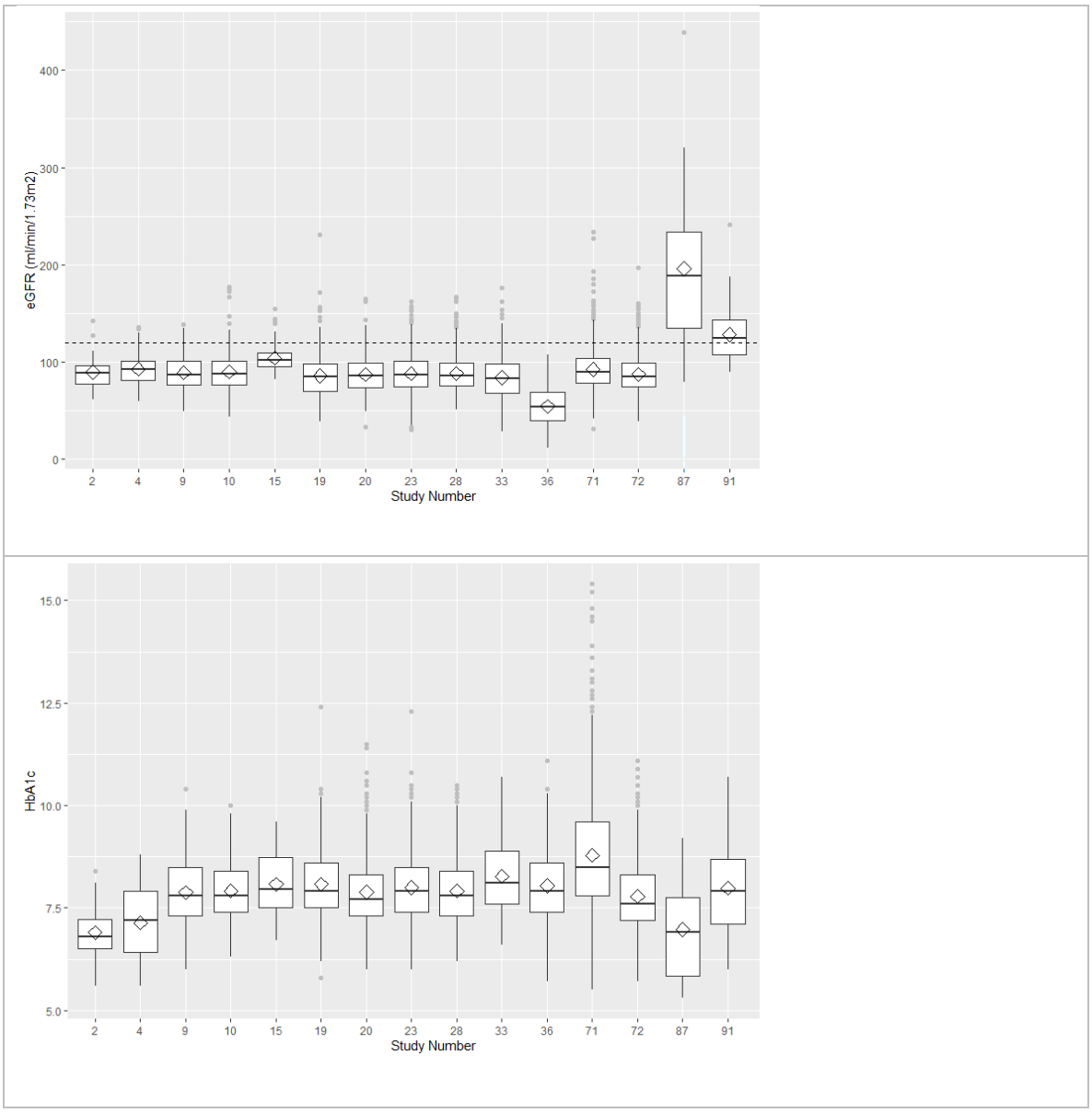
k is a constant that depends on muscle mass, which will vary with the patient's age and gender.

MDRD Formula

eGFR (ml/min) = 175 x [Screatinine (umol/L)/88.4]$^{-1.154}$ x [age]$^{-0.203}$ x [0.742 if patient is female] x [1.212 if patient is of African origin] [3]

Figure 13. Baseline Demographic for Age, Weight, eGFR and HbA1c Across 15 Studies Included in the Population PK Models.





Study ID Abbreviations: 2 = 1245-0002, 4 = 1245-0004, 9 =1245-0009, 10 = 1245-0010, 15 =1245-0015, 19 = 1245-0019, 20 = 1245-0020, 23 = 1245-0023, 28 = 1245-0028, 33 = 1245-0033, 36 = 1245-0036, 71 =1276-0001, 72 = 1276-0010, 87 = 1245-0087, 91 = 1218.91. The dashed line in the eGFR plot is 120ml/min/1.73m^2.
Source: Reviewer's analyses.

Applicant's Final Pediatric Population PK Model

In order to develop the pediatric population PK model for empagliflozin, the previous structural model was re-estimated using the data from Study 1218.91 using full Markov chain Monte Carlo (MCMC) Bayesian estimation methods. The parameter estimates from the previous empagliflozin simplified adult/pediatric population PK model were used as informative priors to inform the model parameters without direct support from the sparse pediatric data. For parameters of primary interest, namely CL/F and V2/F, weakly informative priors were used. All parameter estimates were reported as point estimates from NONMEM with 95% credible intervals (CDI), derived from the posterior distribution of the parameter estimates. Model

performances were evaluated by using predictive checks and Bayesian diagnostics.

The final pediatric population PK model was a two-compartment model with sequential zero-order and first-order absorption parameterized in terms of apparent clearance after oral dosing (CL/F), apparent central volume of distribution after oral dosing (V2/F), apparent (oral) intercompartmental clearance (Q/F), apparent peripheral volume of distribution after oral dosing (V3/F), absorption rate constant (ka) and zero order absorption duration (D1). Weight (WT) was used to scale clearances and volumes.

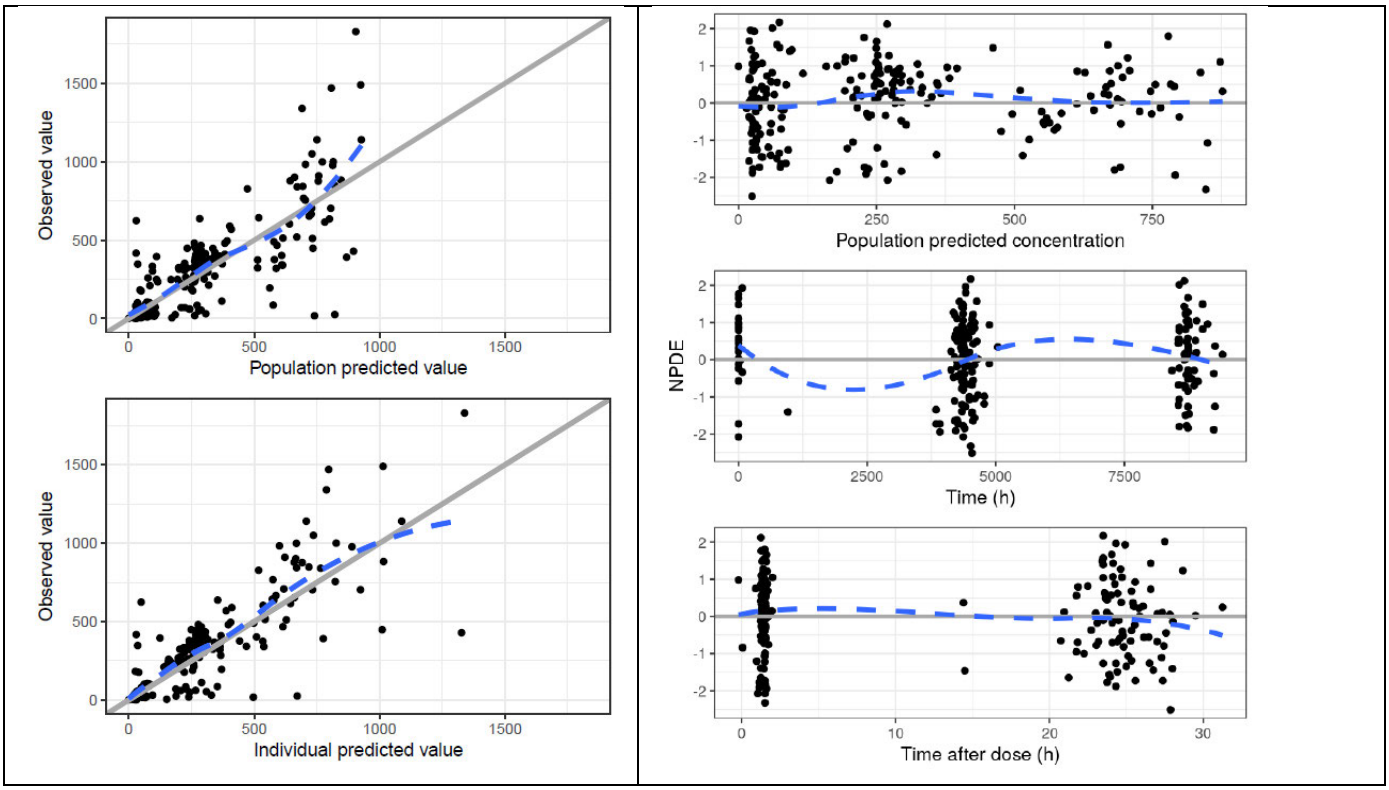
The parameter estimates for the final covariate model are listed in **Table *6***. The goodness-of-fit plots for the final covariate model for all data are shown in **Figure 14**. Prediction-corrected visual predictive check (VPC) plots for empagliflozin were shown in **Figure 15** and **Figure 16**.

Table 9. Parameter Estimates for the Applicant's Final Simplified Adult/Pediatric Population PK Model

			Median	95% CDI	Bulk ESS	Tail ESS	$\hat{R}$	Shrinkage (%)
Structural model								
CL/F (L/hr)	$\exp(\theta_1)$	Apparent clearance	6.74	(5.71, 7.90)	3213	3269	1.00	
V2/F (L)	$\exp(\theta_2)$	Apparent central volume of distribution	4.12	(1.30, 6.63)	3247	2807	1.00	
KA (1/hr)	$\exp(\theta_3)$	First order absorption rate constant	0.239	(0.232, 0.246)	4391	2750	1.00	
Q/F (L/hr)	$\exp(\theta_4)$	Apparent intercompartmental clearance	5.51	(5.22, 5.83)	5278	3074	1.00	
V3/F (L)	$\exp(\theta_5)$	Apparent peripheral volume of distribution	71.7	(67.6, 76.2)	3767	2718	1.00	
D1 (hr)	$\exp(\theta_6)$	Zero order absorption duration	0.326	(0.199, 0.542)	5140	2704	1.00	
Covariate effects								
$EGFR_{CL/F}$	θ_7	eGFR effect on CL/F	0.407	(0.363, 0.454)	4478	3034	1.00	
$BLACK_{CL/F}$	$\exp(\theta_8)$	Race=Black effect on CL/F	0.897	(0.834, 0.967)	4682	3255	1.00	
$ASIAN_{CL/F}$	$\exp(\theta_9)$	Race=Asian effect on CL/F	0.934	(0.904, 0.965)	5653	3348	1.00	
$FEMALE_{CL/F}$	$\exp(\theta_{10})$	Sex=Female effect on CL/F	1.19	(0.977, 1.45)	3313	3287	1.00	
Interindividual variability								
$\Omega_{CL/F}$	$\Omega_{1,1}$	IIV-CL/F (CV%)	33.3	(25.3, 44.0)	1728	2067	1.00	24.8
Residual variability								
Σ_{11}	$\Sigma_{1,1}$	RUV - proportional, non-outliers (CV%)	47.4	(41.9, 54.2)	3068	3045	1.00	
Σ_{22}	$\Sigma_{2,2}$	RUV - additive, non-outliers (SD)	1.67	(0.664, 5.94)	4053	3063	1.00	
Σ_{33}	$\Sigma_{3,3}$	RUV - additive, outliers (SD)	353	(213, 731)	4928	2414	1.00	

Abbreviations: CDI = credible interval; ESS = effective sample size; R^ = Gelman-Rubin diagnostic; IIV = interindividual variability; RV = residual variability; CV
= coefficient of variation; SD = standard deviation
*CV% of omegas = sqrt(exp(estimate) - 1) * 100*
*CV% of sigma = sqrt(estimate) * 100*
SD of sigma = sqrt(estimate)
Source: *Applicant's population PK report c39218173-01. Tables 6, Page 58.*

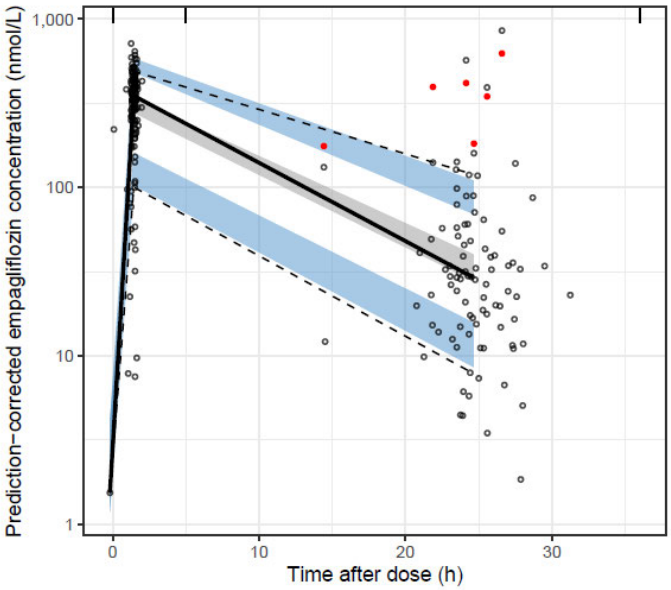
Figure 14. Standard Goodness-of-fit plots for the Applicant's final Pediatric Population PK Model



Source: *Applicant's population PK report c37380422-01. Figure 38 -39, Page 97-98.*

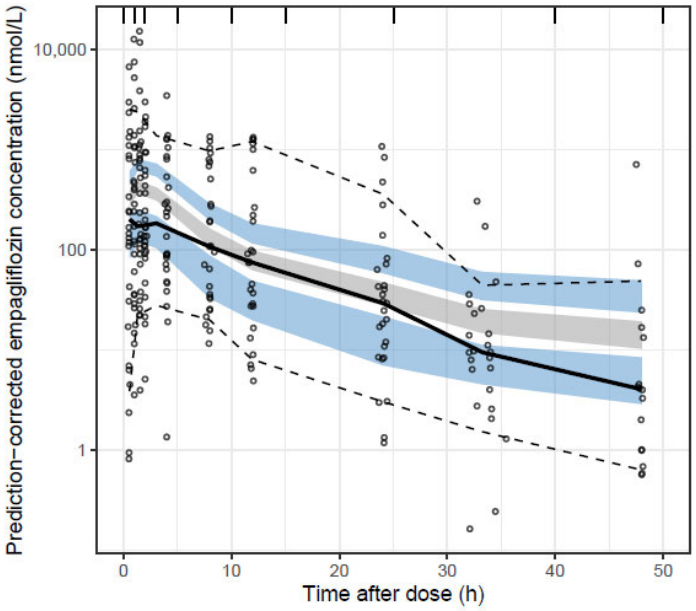
Ind. = individual; Pop. = population; PopPK = population pharmacokinetic.
The circles represent individual data points; the red lines represent loess smooth curves; and the dashed lines represent either the line of unity (y = x), or the unity line at 0 (y = 0).
Source: Applicant's *population PK report c39218173-01, Figures 25 - 26*

Figure 15. Prediction-corrected visual predictive check (VPC) for empagliflozin concentration versus time after dose before remove outliers.



The lines represent the median (solid) or 10th / 90th (dashed) percentiles of the observed data. The shaded areas represent 90% prediction intervals for median (grey) or 10th / 90th percentiles for data simulated under the model. Circles represent the observed data.
Source: Applicant's *population PK report c39218173-01, Figure 38*

Figure 16. PPK model: Out of sample visual predictive check (VPC) for Study 1245.87 empagliflozin concentration versus time after dose.



The lines represent the median (solid) or 10th / 90th (dashed) percentiles of the observed data. The shaded areas represent 90% prediction intervals for median (grey) or 10th / 90th percentiles for data simulated under the model. Circles represent the observed data.
Source: Applicant's *population PK report c39218173-01, Figure 35*

Reviewer's Comments:

In general, the reviewer determined that the Applicant's final pediatric PopPK model is acceptable for generating exposure metrics for empagliflozin in plasma for pediatric patients and descriptive labeling. The VPC plots show that the final pediatric PopPK model provided an adequate estimation of empagliflozin concentration over time for Study 1218.91. Several key issues for this pediatric population PK model are discussed as below:

- *External/cross validation using Study 1245.87*

*Since the final PopPK model was refined from the previous simplified adult/pediatric model using spare PK samples from Study 1218.91, external/cross validation was performed using pediatric data from Study 1245.87. Out of sample predictive check for the final model was generated for the longitudinal empagliflozin concentrations versus time after dose in pediatric patients in Study 1245.87 (**Figure 16**). The results show that this model slightly overpredicted the C_{max} and C_{min} of empagliflozin of Study 1245.87. However, the current model provides a reasonable fit for the steady-state drug exposures across Study 1218.91 and was acceptable for generating post-hoc exposure predictions (AUC_{ss}) for the ER analysis.*

- *eGFR*

The eGFR values above 120 mL/min/1.73m^2 were set to 120 mL/min/1.73m^2 for the covariate analysis. The FDA asked the Applicant to provide justifications for capping eGFR >120 in the PopPK model. The Applicant responded that this was done to avoid introduction of bias since measures of GFR become less accurate as

GFR increases.

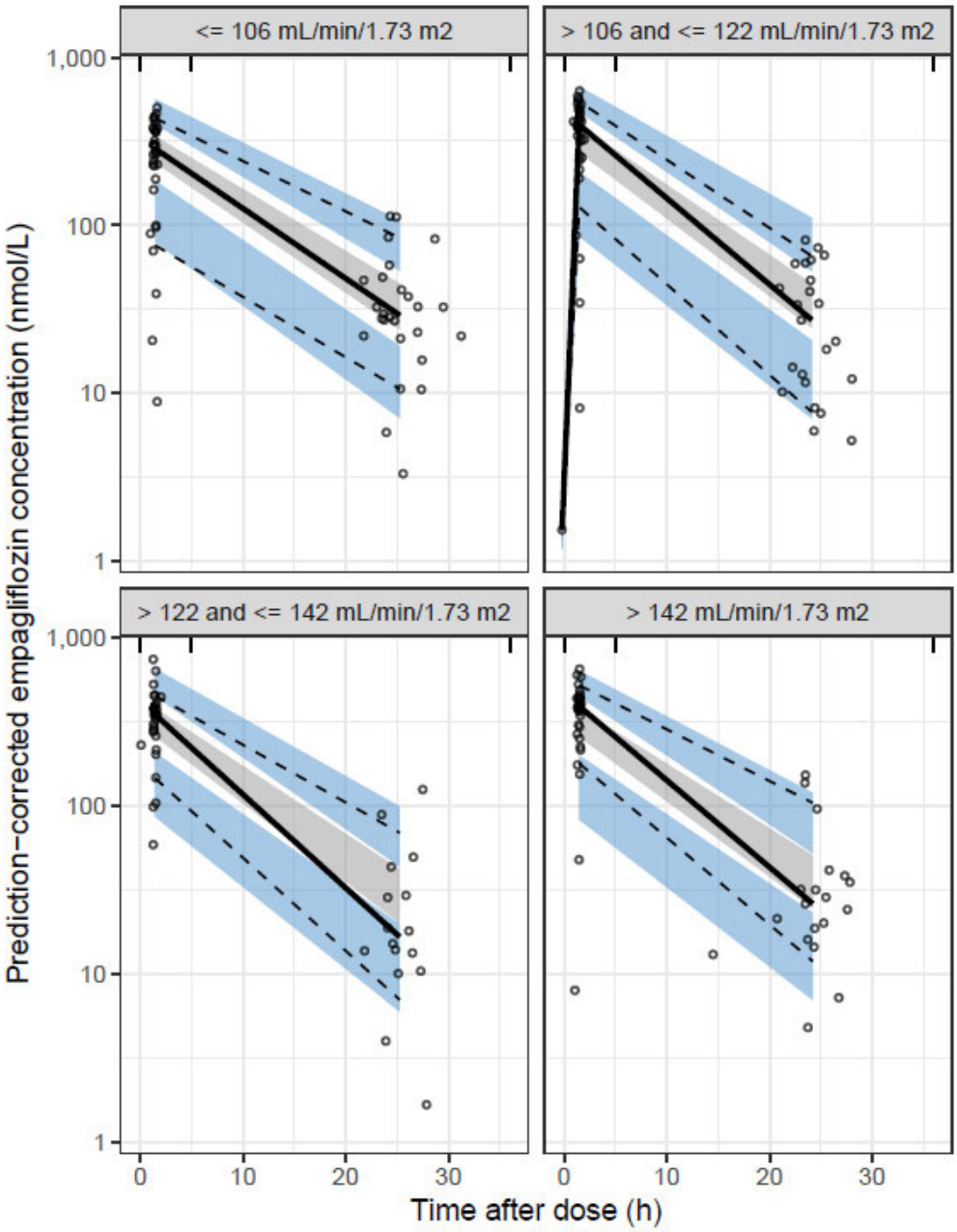
In addition, the effects of capping eGFR at 120 mL/min/1.73 m² was assessed by sensitively analyses comparing among different PopPK models by the reviewer: eGFR capping at 150 mL/min/1.73 m², without eGFR capping, and eGFR capping at 120 mL/min/1.73 m². The results show that the PopPK model with eGFR capping at 120 mL/min/1.73 m² provided lowest objective function value (OFV) among three models **Table 10***. In addition, prediction corrected VPC plots (***Figure 17***) by stratifying different eGFR bands show that the final pediatric PopPK model provide adequate estimation for empagliflozin for different eGFR categories. In general, the reviewer determined that capping eGFR at 120 mL/min/1.73 m² in the final pediatric PopPK model is acceptable.*

Table 10. Sensitivity analyses for the effects of capping eGFR in the PopPK model.

Model	*OFV*	*Δ OFV*
PopPK model with eGFR capping at 120 mL/min/1.73 m²	*2061.840*	
PopPK model with eGFR capping at 150 mL/min/1.73 m²	*2062.177*	*0.34*
PopPK model without eGFR capping	*2067.652*	*5.8*

Source: reviewer's analyses.

Figure 17. Prediction-corrected visual predictive check (VPC) for empagliflozin concentration versus time after dose by eGFR.



The lines represent the median (solid) or 10th / 90th (dashed) percentiles of the observed data. The shaded areas represent 90% prediction intervals for median (grey) or 10th / 90th percentiles for data simulated under the model. Circles represent the observed data.
Source: Applicant's population PK report c39218173-01, Figure 43

3.2.2 Exposure-Response (ER) Analyses

Objective:

- To characterize the ER of empagliflozin on HbA1c in pediatric patients with T2DM using data from Study 1218.91.

Data

*The ER analysis dataset included 103 subjects receiving empagliflozin or placebo treatment and contributing a total of 394 observations (**Table 11**) from Study 1218.91. Of these subjects, 39 received 10 mg of empagliflozin during weeks 1 to 26, 13 subjects received 10 mg of empagliflozin from weeks 1 to 14 and 25 mg from weeks 15 to 26, and 51 subjects remained in the placebo arm for weeks 1 to 26. Among these observations, 16 observation records were excluded from the final analysis dataset based on inclusion and exclusion criteria.*

Table *12* *and* **Table *13*** provide summary statistics of the baseline demographic covariates in the analysis dataset.

Table 11. Data summary of subjects (number) and observations (number and percent) for subjects receiving empagliflozin stratified by treatment arm.

	Number		Percent
Treatment arm	SUBJ	OBS	OBS
Empagliflozin 10 mg	28	101	25.6
Empagliflozin 10 mg/ Empagliflozin 10 mg	11	44	11.2
Empagliflozin 10 mg/ Empagliflozin 25 mg	13	50	12.7
Placebo	51	199	50.5
All data	103	394	100.0

Source: Applicant's *population PK report c39218173-01, Table 10*

Table 12. Categorical covariate (baseline) summary stratified by treatment arm.

	Treatment arm				
	Empagliflozin 10 mg n = 28	Empagliflozin 10 mg/ Empagliflozin 10 mg n = 11	Empagliflozin 10 mg/ Empagliflozin 25 mg n = 13	Placebo n = 51	Summary n = 103
Sex					
Female	17 (60.7)	8 (72.7)	8 (61.5)	32 (62.7)	65 (63.1)
Male	11 (39.3)	3 (27.3)	5 (38.5)	19 (37.3)	38 (36.9)
Race					
White	13 (46.4)	3 (27.3)	7 (53.8)	29 (56.9)	52 (50.5)
Black	9 (32.1)	6 (54.5)	4 (30.8)	16 (31.4)	35 (34.0)
Asian	1 (3.6)	1 (9.1)	0 (0.0)	3 (5.9)	5 (4.9)
American Indian or Alaskan Native	4 (14.3)	0 (0.0)	0 (0.0)	1 (2.0)	5 (4.9)
Native Hawaiian or Other Pacific Islander	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	1 (1.0)
Multiple	1 (3.6)	1 (9.1)	2 (15.4)	0 (0.0)	4 (3.9)
Unknown	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	1 (1.0)
Insulin Co-Therapy at Baseline					
Yes	12 (42.9)	8 (72.7)	7 (53.8)	24 (47.1)	51 (49.5)
No	16 (57.1)	3 (27.3)	6 (46.2)	27 (52.9)	52 (50.5)
Metformin Co-Therapy at Baseline					
Yes	25 (89.3)	10 (90.9)	13 (100.0)	45 (88.2)	93 (90.3)
No	3 (10.7)	1 (9.1)	0 (0.0)	6 (11.8)	10 (9.7)

Source: Applicant's *population PK report c39218173-01, Table 12*

Table 13. Continuous covariate (baseline) summary stratified by treatment arm.

Variable	n	Mean	Median	SD	Min / Max
Empagliflozin 10 mg					
Weight (kg)	28	101	94.8	25.2	58.5 / 157
Age (years)	28	14.5	15.0	1.97	11.0 / 17.0
Estimated GFR (ml/min/1.73m^2)	28	125	122	22.2	90.5 / 170
HbA1c (%)	28	7.59	7.10	1.31	6.20 / 10.6
Empagliflozin 10 mg/ Empagliflozin 10 mg					
Weight (kg)	11	92.2	87.8	27.6	42.5 / 153
Age (years)	11	14.6	14.0	1.63	11.0 / 17.0
Estimated GFR (ml/min/1.73m^2)	11	129	132	24.7	89.7 / 171
HbA1c (%)	11	8.76	9.00	1.15	6.60 / 10.6
Empagliflozin 10 mg/ Empagliflozin 25 mg					
Weight (kg)	13	98.4	93.4	20.8	62.1 / 134
Age (years)	13	13.9	14.0	2.18	10.0 / 17.0
Estimated GFR (ml/min/1.73m^2)	13	139	125	36.3	108 / 241
HbA1c (%)	13	8.24	8.10	1.08	6.90 / 10.6
Placebo					
Weight (kg)	51	98.4	92.5	29.5	52.0 / 169
Age (years)	51	14.6	14.0	1.79	11.0 / 17.0
Estimated GFR (ml/min/1.73m^2)	51	124	122	23.3	85.2 / 180
HbA1c (%)	51	8.08	7.60	1.25	6.00 / 10.7
All data					
Weight (kg)	103	98.3	92.9	26.9	42.5 / 169
Age (years)	103	14.5	15.0	1.86	10.0 / 17.0
Estimated GFR (ml/min/1.73m^2)	103	127	123	25.2	85.2 / 241
HbA1c (%)	103	8.04	7.90	1.27	6.00 / 10.7

Source: Applicant's *population PK report c39218173-01, Table 13*

Figure 18. HbA1c over time stratified by insulin co-therapy at baseline and colored by treatment arm.

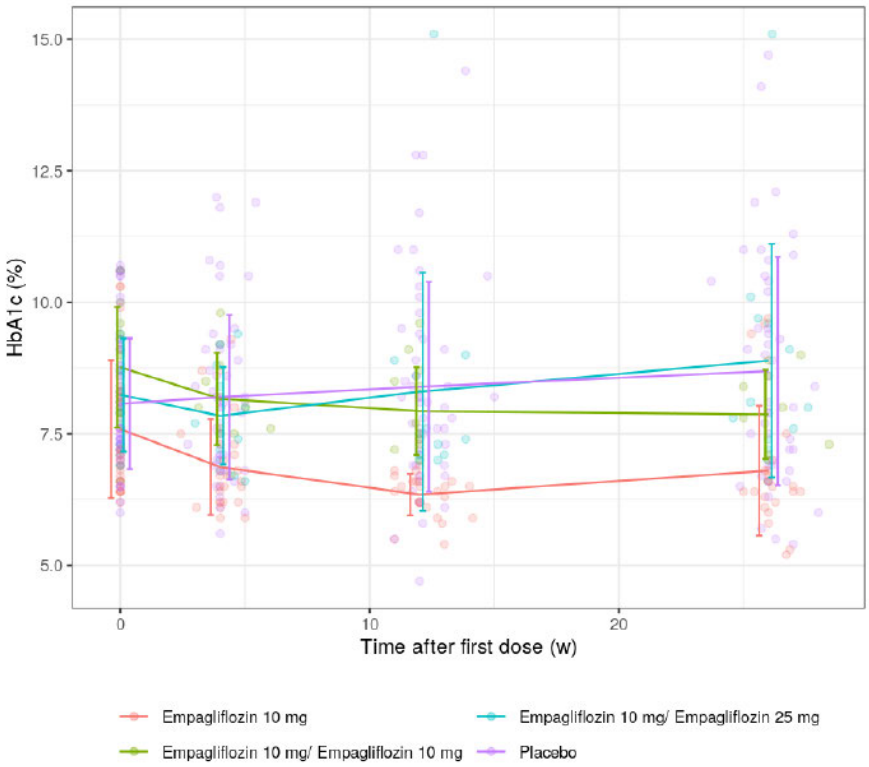


Figure 18 shows the observed HbA1c (%) change over time in Study 1218.91. Individual HbA1c versus time profiles showed high variability. The HbA1c increased in the placebo arm over time. In contrast, the average HbA1c in the 10 mg empagliflozin treatment arm showed a transient decrease from baseline by week 12, followed by a general increase through week 26, while the average HbA1c in the 10 mg/25 mg empagliflozin treatment arm showed a transient decrease from baseline by week 4, followed by a general increase through week 26.

Model Development/Results

A population ER model was previously developed for simplified adult/pediatric longitudinal HbA1c using adult data (Report c37380422-01). The model consisted of a turnover model parameterized in terms of baseline HbA1c, HbA1c synthesis rate constant (kin), and HbA1c degradation rate constant (kout), with empagliflozin exposure inhibiting the kin parameter through an inhibitory maximum effect (Emax) relationship, and a placebo effect incorporated on the kout parameter, to describe the change in HbA1c over time and with empagliflozin exposure. This adult/pediatric ER model was re-estimated for the new pediatric data from Study 1218.91 using full MCMC Bayesian estimation methods, with prior distributions defined from the point estimates and uncertainty of the simplified adult/pediatric ER model for model parameters without direct support from the pediatric data. A placebo effect was also incorporated which affected the k_{out} parameter.

$$\frac{HbA1c}{dt} = kin \cdot (1 - INH) - kout \cdot HbA1c \cdot (1 + PLAC)$$

Where:

$$INH = \frac{IMAX \cdot AUC_{ss}}{AUC50 + AUC_{ss}}$$

and:

- k_{in} is the zero-order HbA1c synthesis rate
- k_{out} is the first-order HbA1c degradation rate constant
- PLAC is the placebo response parameter
- I_{MAX} is the maximal inhibition
- AUC_{50} is the empagliflozin AUCss at which half the maximal effect is achieved
- AUC_{ss} is the subject-level empagliflozin area under the concentration time curve at steady state derived from the final population PK model

The final pediatric ER model was parameterized with a zero-order HbA1c synthesis rate (k_{in}), and a constant HbA1c first-order degradation rate (k_{out}). To capture the observed increases in HbA1c over time, a time dependent change in the synthesis process was used (i.e., increase of HbA1c) over time. Specifically, the effects of age, race, eGFR on I_{max}, and baseline HbA1c on Imax were estimated with informative priors while all other parameters were estimated with weakly informative priors. This disease progression parameter was only found to be estimable for patients requiring background insulin therapy. The empagliflozin effect was assumed to inhibit k_{in} via an I_{max} model. IIV was included on baseline HbA1c and the disease progression/placebo effect parameter. A proportional residual error was also included. All of the structural parameters, except, the area under the concentration-time curve at 50% of the maximum effect (AUC_{50}) were estimated with weakly informative priors.

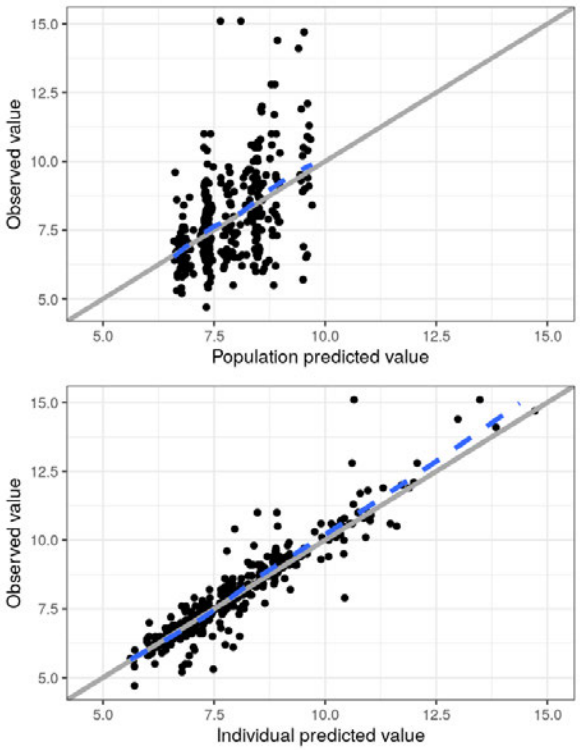
*The final model results were summarized across the four chains and showed each parameter had similar distributions and stable iterations of posterior parameter estimates (***Table 14***). The convergence of the posterior samples was supported by sufficiently large bulk and tail ESS (≥1595 and ≥2198, respectively) increasing approximately linearly over post-burnin iterations, and R-hat values equal to 1 indicating that each parameter was adequately sampled.*

Table 14. Final Pediatric ER Model Parameter Estimates.

			Median	95% CDI	Bulk ESS	Tail ESS	$\hat{R}$	Shrinkage (%)
Structural model								
kout (1/day)	$\exp(\theta_1)$	HbA1c degradation rate constant	0.0489	(0.0346, 0.0717)	5125	3498	1.00	
BASE (%)	$\exp(\theta_2)$	Baseline HbA1c	7.35	(6.99, 7.72)	1765	2624	1.00	
PROG (%/h/h)	$\exp(\theta_3)$	Zero-order disease progression rate constant	5.64e-07	(2.94e-07, 9.20e-07)	2937	2198	1.00	
IMAX (%)	$\exp(\theta_4)/(1+\exp(\theta_4))$	Maximum inhibition	10.1	(7.39, 12.9)	6062	4750	1.00	
AUC50 (nmol*hr/L)	θ_5	AUC at 50% IMAX	703	Fixed				
Covariate effects								
INS_{BASE}	$\exp(\theta_6)$	Prior insulin effect on BASE	1.15	(1.07, 1.24)	1595	2531	1.00	
$EGFR_{IMAX}$	θ_7	eGFR effect on IMAX	1.03	(0.917, 1.15)	8834	5348	1.00	
$HbA1c_{IMAX}$	θ_8	Baseline HbA1c effect on IMAX	2.04	(1.86, 2.21)	8205	5127	1.00	
Interindividual variability								
Ω_{BASE} (CV(%))	$\Omega_{2,2}$	IIV-BASE	16.1	(13.9, 19.0)	2373	3488	1.00	14.9
Ω_{PROG} (CV(%))	$\Omega_{3,3}$	IIV-PROG	7.35	(5.33, 10.7)	3950	3070	1.00	19.0
$\Omega_{PROG-BASE}$ (Corr)	$\Omega_{3,2}$	Covariance on PROG-BASE	0.00112	(-0.00201, 0.00422)	2525	3366	1.00	
Residual variability								
$\Sigma_{1,1}$ (CV(%))	$\Sigma_{1,1}$	Additive RUV on log scale	6.32	(5.71, 7.01)	2682	4283	1.00	

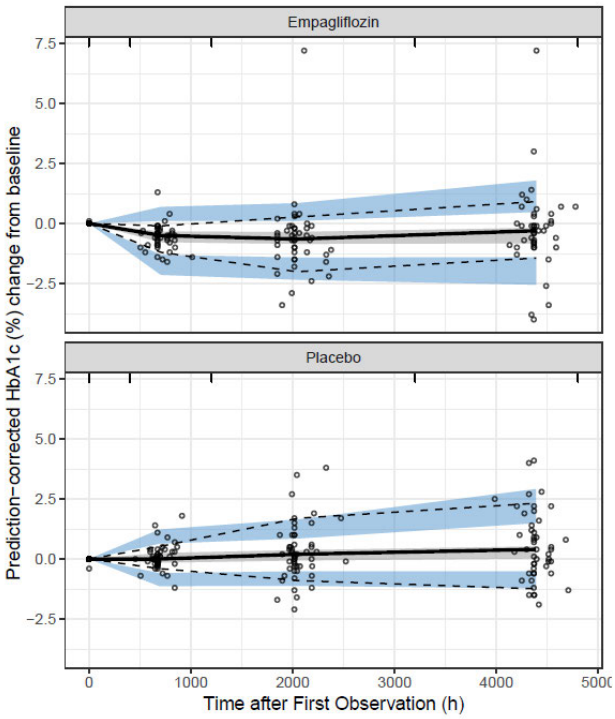
Parameters estimated in the log-domain were back-transformed for clarity. Credible intervals calculated from Bayesian posteriors.
Abbreviations: CDI: credible interval; Corr: correlation coefficient; ESS: effective sample size; Rˆ : Gelman-Rubin diagnostic; IIV: inter-individual variability; RV: residual variability; CV: coefficient of variation; SD: standard deviation CV% of omegas = sqrt(exp(estimate) - 1) * 100 CV% of sigma = sqrt(estimate) * 100
Source: Applicant's *population PK report c39218173-01, Table 16*

Figure 19. Observations versus population and individual predictions of empagliflozin concentration.



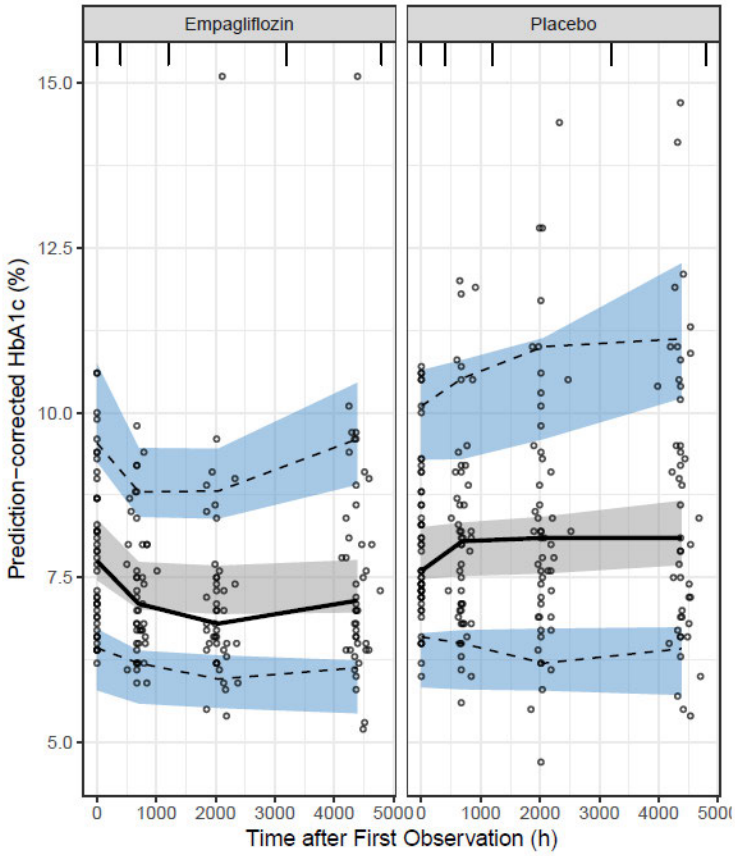
Source: Applicant's *population PK report c39218173-01, Figure 85*

Figure 20. Prediction-corrected HbA1c change from baseline versus time after first observation stratified by treatment.



The lines represent the median (solid) or 10th / 90th (dashed) percentiles of the observed data. The shaded areas represent 90% prediction intervals for median (grey) or 10th / 90th percentiles for data simulated under the model. Circles represent the observed data.
Source: Applicant's *population PK report c39218173-01, Figure 100*

Figure 21. Prediction-corrected HbA1c versus time after first observation; stratified by treatment



The lines represent the median (solid) or 10th / 90th (dashed) percentiles of the observed data. The shaded areas represent 90% prediction intervals for median (grey) or 10th / 90th percentiles for data simulated under the model. Circles represent the observed data.
Source: Applicant's *population PK report c39218173-01, Figure 111*

*The final model provided a reasonable description of the data, as judged by diagnostic plots (***Figure 19***). VPCs demonstrated that the model provided an adequate description of HbA1c over time by different treatment arms (***Figure 20** *and* **Figure 21***).*

Reviewer's Comments

In general, the reviewer determined that the Applicant's proposed ER model is acceptable and appropriately described the absolute HbA1C as well as HbA1C change from baseline over time for both placebo and treatment arms. There are several points that are discussed for this ER model as below:

- Impact of fixing the parameter of AUC_{50} in the ER model

In the ER model, the AUC_{50} for the drug effect was fixed to 703 nmol·hr/L. This fixed AUC_{50} value was estimated in the previous adult ER model (report c02090424) which included fasting plasma glucose (FPG) as an intermediary parameter between empagliflozin AUC and HbA1c. The available pediatric data alone, which does not include densely sampled FPG data, could not support estimation of AUC_{50} for pediatrics. As a result, AUC_{50} was fixed to the 703 nmol·hr/L based on adult information.

In order to understand the impact of fixing AUC_{50} in the pediatric ER model, a sensitivity analysis was conducted. Specifically, sensitivity analyses were conducted for AUC_{50} whereby the fixed estimate that was used in the final model was iteratively increased and decreased by 25% and 50%.

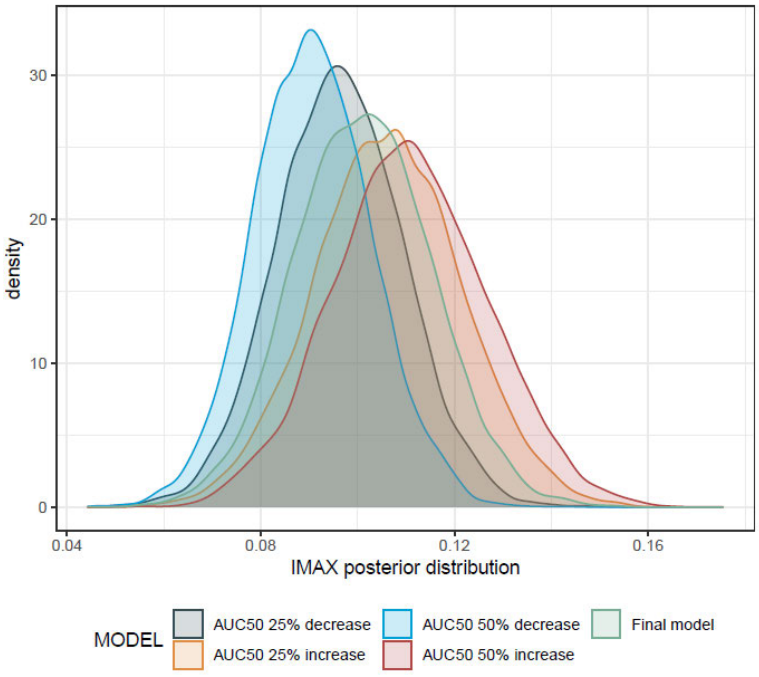
*Increasing and decreasing the AUC_{50} estimate resulted in the I_{max} posterior distribution shifting in an increased and decreased direction compared to the final model, respectively (**Figure 22**). This resulted in slightly shifted posterior predictive distributions of the typical placebo adjusted HbA1c at 26 weeks, but overall, the distributions had considerable overlap and were comparable (**Figure 23**). Additionally, there were negligible differences in ELPD values between the models (**Table 15**), which indicated comparable expected out of sample predictive accuracy across the models.*

Table 15. Expected log pointwise predictive densities (ELPD) for final model and sensitivity analysis models.

Model	ELPD	Standard error	Difference	Standard error of difference
Final model	-106.0	56.91	0.000	0.000
AUC50 adjustment				
AUC50 25% increase	-106.0	56.91	0.01937	0.3805
AUC50 25% decrease	-106.3	57.59	-0.2999	0.8799
AUC50 50% increase	-105.7	56.91	0.3398	0.6034
AUC50 50% decrease	-105.6	56.91	0.4536	1.387

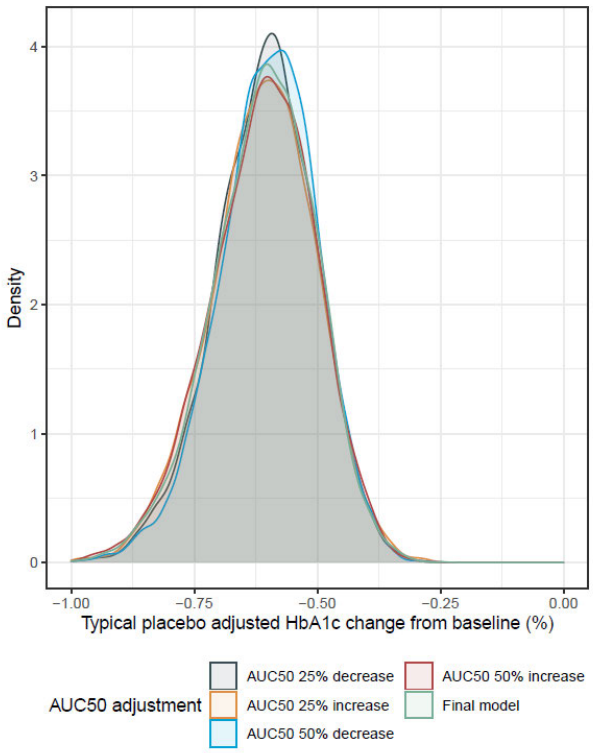
Source: Applicant's *population PK report c39218173-01, Table 18*

Figure 22. Impact of AUC_{50} fixed estimate on estimated IMAX posterior distribution in the pediatric ER model.



Source: Applicant's *population PK report c39218173-01, Figure 124*

Figure 23. Impact of AUC_{50} fixed estimate on typical model predicted placebo adjusted HbA1c change from baseline at week 26 in the pediatric ER model.

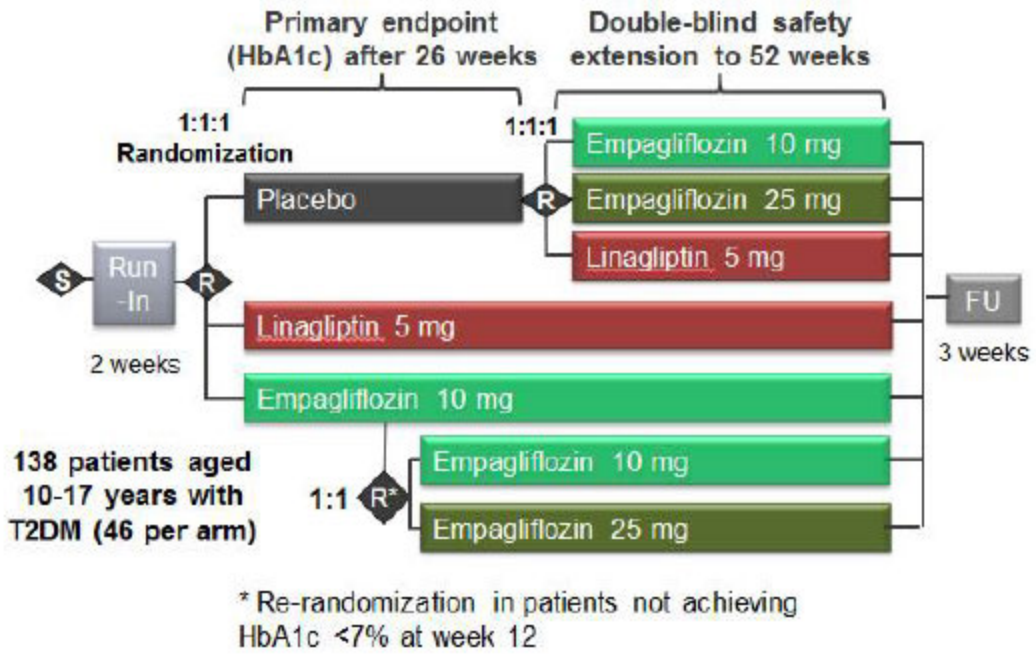


Source: Applicant's *population PK report c39218173-01, Figure 125*

Reviewer's Independent Analyses

Figure *24* illustrated the study design of 1218.91. This study includes 3 parallel treatment arms (placebo, linagliptin 5 mg, empagliflozin 10 mg) over 26 weeks. For patients randomized to 10 mg empagliflozin at randomization phase, patients were separated into responder group and non-responder group depending on whether they achieved HbA1c < 7.0% at Week 12 or not. For non-responders (HbA1c ≥ 7.0% at Week 12), patients were re-randomized 1:1 to either empagliflozin 10 mg/10 mg group or 10 /25 mg groups. Patients on placebo were re-randomized at Week 26 to receive either linagliptin or one of the empagliflozin doses (empagliflozin 10 mg or 25 mg).

Figure 24. Graphic presentation of Trial Design of Study 1218.91.



Source: Applicant's Study Report 1218.91

- T2D Disease Progression in Pediatric

*In order to understand the disease progression in pediatric T2D patients, the reviewer looked at the disease progression data in the placebo arm from week 0 to week 26. The results show that pediatric patients with T2D did not have the same disease progression rate (***Figure 8***). In the placebo arm, patients with the baseline use of insulin had higher baseline HbA1c as well as faster disease progression as compared to patients not using insulin at baseline. At the same time, patients with a baseline HbA1c < 7.5% also have a slower disease progression rate as compared to pediatric patients with higher baseline HbA1c.*

- Comparison of 10 mg versus 25 mg doses

Based on the Phase 3 study result (**Figure *18***), the absolute change of HbA1c from baseline for patients in the 10 mg/25 mg group was smaller than 10 mg/10 mg group for the non-responders. Therefore, it is not clear whether the dose titration is necessary for pediatric patients with T2D. In order to better understand the ER relationship for empagliflozin, the reviewer further looked at 1) the empagliflozin treatment arms using propensity score matching method, and 2) the placebo arm results between Week 26 and Week 52.

Table 16. Descriptive statistics of HbA1c (%) over time up to Week 26 by empagliflozin re-randomization

	Placebo			Empa 10 mg discontinued before Week 14			Empa 10 mg responders at Week 12			Empa 10 mg non-responders at Week 12 Re-randomized to 10 mg			Empa 10 mg non-responders at Week 12 Re-randomized to 25 mg		
Visit	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD
Baseline	53	8.05	1.23	5	9.36	1.49	23	7.20	0.91	11	8.76	1.15	13	8.24	1.08
Week 4	50	8.17	1.56	3	8.37	1.14	23	6.68	0.67	11	8.16	0.88	13	7.75	0.95
Week 12	52	8.40	1.96	2	6.40	0.28	23	6.37	0.37	11	8.04	0.87	12	8.30	2.26
Week 26	50	8.77	2.41	2	7.15	1.63	23	6.81	1.21	10	7.87	0.85	12	8.89	2.22

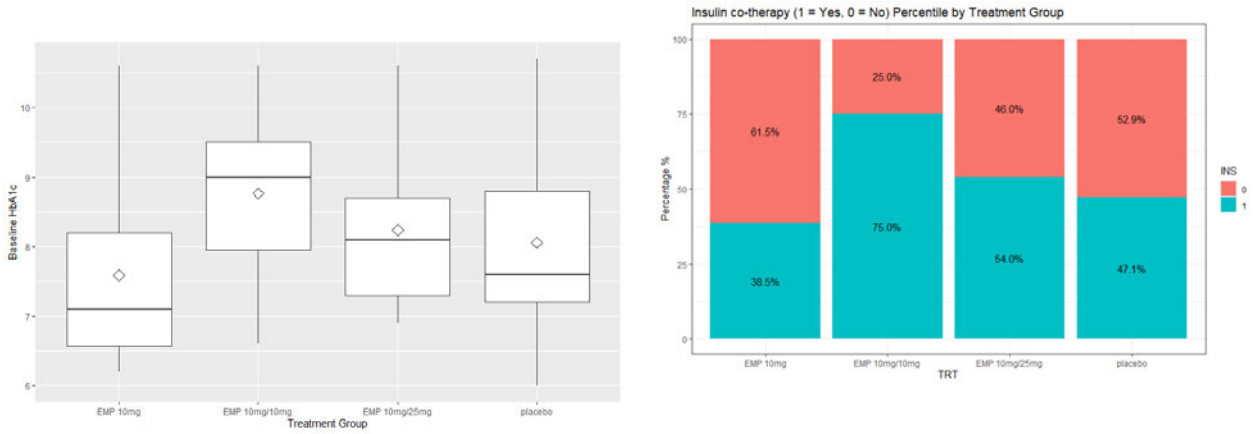
Source: Applicant's response to information request.

1) ER relationship using propensity score matching

Pooling data from responders and non-responders together makes it difficult for the ER analysis, because responders and non-responders had different disease progression rate. As a result, propensity score matching was used to find the corresponding placebo groups for responders and non-responders, respectively.

First of all, ANOVA test was used to determine the covariates that had a statistically significant different distribution among responder, non-responder and placebo groups. Among all the covariates tested (age, body weight, baseline AST, baseline eGFR, baseline HbA1C and use of insulin), the baseline HbA1C levels and % of patients using of insulin are statistically significant different among the three groups. Therefore, nearest neighbor propensity score matching was used to find matching placebo subjects for responder and non-responder, respectively based on baseline HbA1C and whether the patients use insulin or not.

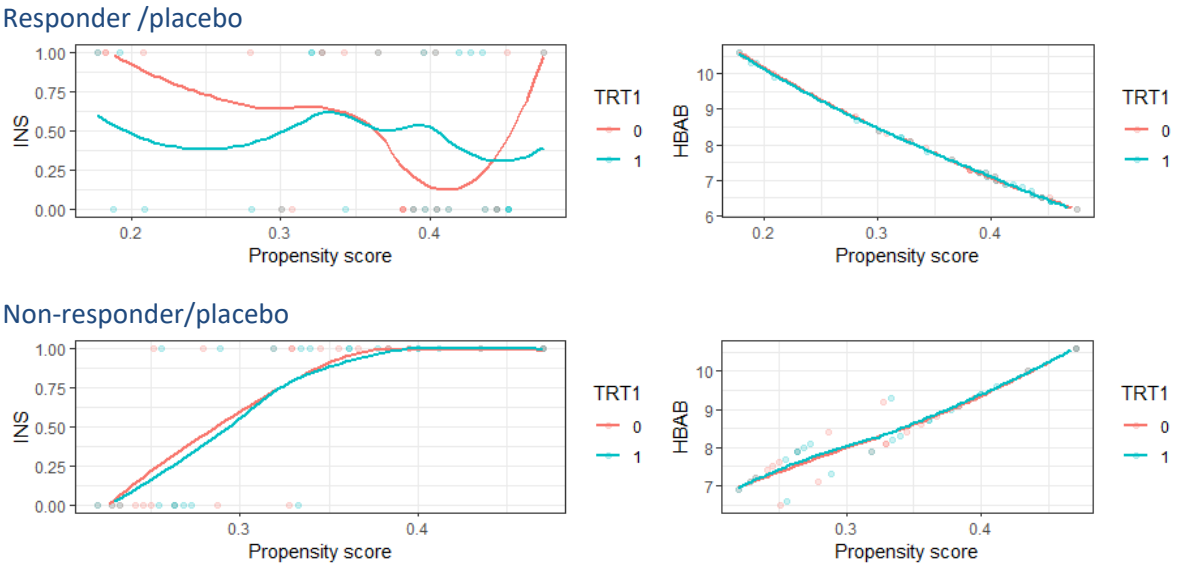
Figure 25. Distribution of baseline HbA1c (%) and status of using of insulin at baseline for patients in Study 1218.91 stratified by treatment groups.



Source: reviewer's analyses.

After propensity score matching, there are a total of 56 matched responder/placebo subjects and 48 matched non-responder/placebo subjects. The diagnostic plots for propensity score matching are shown in **Figure *26***.

Figure 26. Diagnostic plots for propensity score matching for responders/placebo (upper) and non-responder/placebo (lower).



Source: Reviewer's analyses

Figure 27. Baseline characteristics distributions for subjects in responders/placebo and non-responder/placebo groups after propensity score matching.

	Matched Group 1		Matched Group 2	
	Responder	*Placebo*	*Non-Responder*	*Placebo*
Baseline HbA1c (%)				
N	28	28	*24*	*24*
Mean	*7.59*	*7.75*	*8.48*	*8.36*
SD	*1.31*	*1.27*	*1.12*	*1.13*
Use of Insulin (N)				
No	*16*	*15*	*15*	*9*
Yes	*12*	*13*	*15*	*9*

Source: Reviewer's analyses

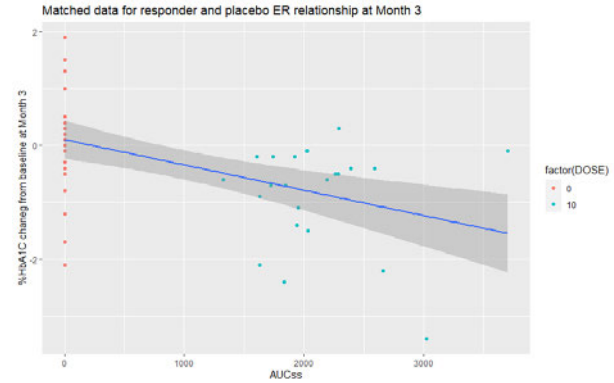
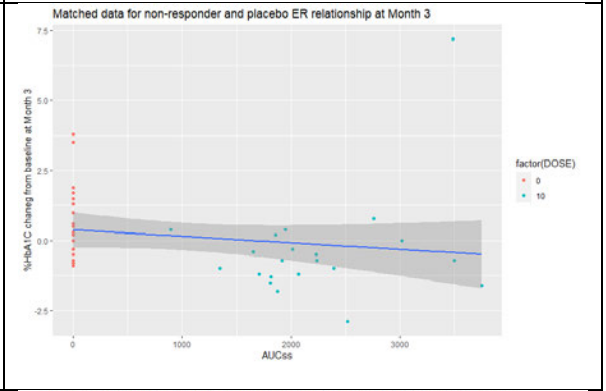
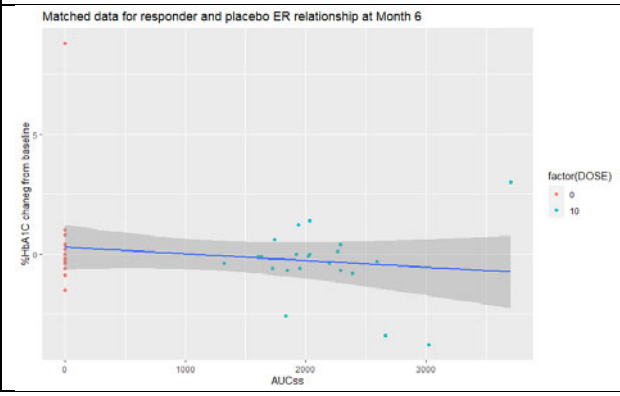
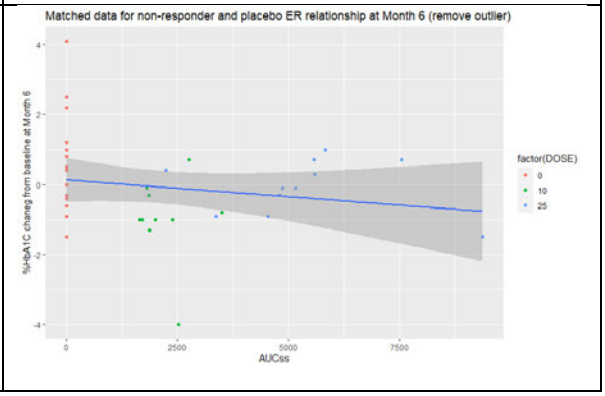
*After propensity score matching, the time course treatment effects were comparable among matched corresponding placebo groups (***Figure 9***). The results show that responders had a lower baseline HbA1c, and slower progression as compared to non-responder group. After receiving empagliflozin, the patients had a significant decrease in HbA1c from Weeks 0 to 12. There was a minor increase for HbA1c values after Week 12, but in general the treatment effect was persistent for responders from Week 26 to Week 52. For non-responders, patients receiving 10 mg/10 mg empagliflozin had a decline in HbA1c from Weeks 0 to 26. After Week 26, there was an increase of HbA1c for 10 mg/10 mg for the non-responder group. However, the*

mean HbA1c at Week 52 for subjects receiving 10 mg/10 mg empagliflozin in the non-responder group was lower than the mean HbA1c at Week 26 for subjects in the matched placebo group.

Further analysis showed than this worse response for HbA1c by 10 mg/25 mg as compared to 10 mg/ 10 mg non-responder group is mainly driven by a single patient identified as outlier (ID = (b) (6)) (**Figure *10***). After removing this outlier subject, the performance of 10 mg/10 mg and 10 mg/25 mg for non-responders were similar.

The results for ER analyses using propensity score matching data were shown in **Figure 28**. There is not a statistically significant ER relationship, except for responder group at week 12 (top left).

Figure 28. Exposure-response analyses after propensity score matching.

	Responder (10 mg)	Non-responder (10 mg/10 mg and 10 mg/25 mg)
Week 12		
Week 26		

Source: reviewer's analyses.

2) Placebo arm results between 26 weeks to 52 weeks.

For patients in placebo arm, they were re-randomized to either empagliflozin 10 mg arm or 25 mg arm at Week 26.

The reviewer analyzed the time course of HbA1c (%) and HbA1c change from baseline for patients in the placebo group. The results show that patients in the placebo/25 mg group had a larger drop in HbA1c (%) from Week 52 to Week 26, as compared to placebo/10 mg group (**Figure 11**).

3) ER model

The effects of empagliflozin exposure on HbA1c in pediatric patients with T2D was described by an indirect response model with a disease progression rate acting on k_{in} and a drug effect inhibiting k_{in} via an inhibitory

I_{max} model. In this inhibitory I_{max} model, the AUC_{50} (AUC at 50% I_{MAX}) was fixed at 703 nmol*hr/L. However, the estimated AUC_{ss} following 10 mg (2185 ± 617 nmol*hr/L) and 25 mg dose (5634 ± 2057 nmol*hr/L) are much higher than 703 nmol*hr/L, indicating that the inhibition effect for empagliflozin is already at the plateau at the proposed dose levels. Further titration the dose from 10 mg to 25 mg is not expected to bring additional inhibitory effect on HbA1c.

Based on the above analyses, we concluded that

1) The disease progression rates for pediatric T2D patients are inherently different. In general, pediatric patients with a baseline HbA1c ≥ 7.5 % and/or combination use of insulin are likely to have a faster disease progression rate and could be a non-responder. Whereas pediatric patients with a baseline HbA1c < 7.5 % and/or without combination use of insulin are likely to have a slower disease progression rate and could be a responder.
2) For both responders/non-responders, there is a significant treatment effect as compared to matched placebo group using propensity score matching.
3) There is a limited additional treatment effect by increasing the dose from 10 mg to 25 mg for non-responders for the tested subjects.
4) The advantage of titrating of dose from 10 mg to 25 mg for responders is unknown.

1.5.5 Listing of analyses codes and output files

File Name	Description	Location in \\cdsnas\pharmacometrics\
NONMEM dataset for the final pediatric PopPK model	bii0807f_pk	\\Cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\ Empagliflozin_NDA 204629_XP\NDA 204629 Empagliflozin\Pediatric Model
NONMEM code for the final pediatric PopPK model	Run 1.mod	\\Cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\ Empagliflozin_NDA 204629_XP\NDA 204629 Empagliflozin\Pediatric Model
Dataset for the final pediatric ER model	bii0807f_pd	\\Cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\ Empagliflozin_NDA 204629_XP\NDA 204629 Empagliflozin\Pediatric Model
Code for the final pediatric ER model	Run5 mod	\\Cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\ Empagliflozin_NDA 204629_XP\NDA 204629 Empagliflozin\Pediatric Model
Reviewer's Analyses	by sub-folders	\\Cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\ Empagliflozin_NDA 204629_XP\NDA 204629 Empagliflozin\Reviewer's Analyses

---

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

HARISUDHAN THANUKRISHNAN
06/13/2023 04:35:53 PM

XIAOLEI N PAN
06/14/2023 09:17:45 AM

JUSTIN C EARP
06/14/2023 09:59:16 AM

EDWIN C CHOW
06/14/2023 10:13:06 AM