Office of Clinical Pharmacology Review

NDA Number	202293/S-031
Link to EDR	\\CDSESUB1\evsprod\NDA202293\1346
Submission Date	12/12/2023
Submission Type	Pediatric Supplement, Priority Review
Brand Name	Farxiga
Generic Name	Dapagliflozin
Dosage Form and Strength	Tablets
Route of Administration	Oral
Proposed Indication	As an adjunct to diet and exercise to improve glycemic control in adults and pediatric patients aged 10 years and older with type 2 diabetes mellitus (T2DM)
Applicant	AstraZeneca
Associated IND	IND 068652
OCP Review Team	Dong Guo, Ph.D., Justin Earp, Ph.D., Edwin Chiu Yuen Chow, Ph.D.
OCP Final Signatory	Edwin Chiu Yuen Chow, Ph.D.

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1. EXECUTIVE SUMMARY

Dapagliflozin (Farxiga), is 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 mellitus who are aged 10 to 17 years. The efficacy and safety of dapagliflozin in pediatric patients with type 2 diabetes mellitus was established with confirmatory evidence from a single placebo-controlled pediatric study (D1680C00019, CV181375), conducted to fulfill the PMR 3199-1. The dose selection for Study D1680C00019 (also refer as Study 19) was based on pharmacokinetics (PK) and pharmacodynamics (PD) data from an open label single dose PK/PD trial in pediatric patients aged 10 to 17 years with type 2 diabetes mellitus, Study D1680C00016 (MB102091, refer as Study 16) which was a PMR study (2121-1) fulfilled in March 2016.

Study 19 was a 26-week phase 3b, multicenter, randomized, placebo-controlled, double-blind, parallel-group, study with a 26-week, double-blind safety extension period plus a 4-week follow-up period to evaluating the safety and efficacy of dapagliflozin (5 mg followed by second randomization of non-responders to 5 mg or 10 mg), and saxagliptin (2.5 mg followed by second randomization of non-responders to 2.5 mg or 5 mg) in pediatric patients with type 2 diabetes mellitus who are between 10 and below 18 years of age. After the completion of the 26-week short-term period, all patients were to enter the long-term treatment period. A subset of eligible patients could undergo a third randomization at Week 32 or Week 40 to continue or withdraw background therapy with metformin to evaluate monotherapy with active study drug. After Week 52, all patients discontinued study drug and received medication at the discretion of the treating physician until the post-treatment visit at Week 104. The current submitted study report summarized the study results up to the Week 56 database lock.

A total of 245 pediatric patients aged 10 to 17 years with type 2 diabetes mellitus were randomized and treated with either dapagliflozin group (N=81), saxagliptin group (N=88), or placebo (N=76). In the dapagliflozin arm, patients on dapagliflozin (5 mg QD) who did not achieve HbA1c <7.0% at Week 12 (N=42) were re-randomized at Week 14 to either continue with 5 mg dapagliflozin QD or increase to 10 mg dapagliflozin QD. Similarly, patients on saxagliptin (2.5 mg QD) who did not achieve HbA1c <7.0% at Week 12 (N=52) were re-randomized at Week 14 to either continue with 2.5 mg saxagliptin QD or increase to 5 mg saxagliptin QD. Patients previously assigned to placebo with Week 12 HbA1c values ≥ 7% were to continue on placebo.

Patients enrolled in the study included background therapies was metformin alone for most patients (51.4%), followed by a combination of metformin and insulin (36.3%), and insulin alone (12.3%). Background therapies were balanced across the treatment groups.

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 could enter the double-blind safety extension period with the same treatment except a subset of eligible patients underwent a third randomization (randomized withdrawal of background metformin) at either Week 32 or Week 40. Eligibility was restricted to patients receiving background treatment with metformin only and had HaA1c < 7.5 at Week 26 or Week 32. During the third randomization, eligible patients receiving active treatment were

grouped into 2 separate strata for saxagliptin and dapagliflozin, and then randomized 1:1 within each of the strata to either continue or discontinue background medication with metformin. For patients randomized to withdraw background treatment with metformin, those currently receiving high doses of saxagliptin (5 mg) or dapagliflozin (10 mg) continued to receive the high doses, whereas those currently receiving low doses of saxagliptin (2.5 mg) or dapagliflozin (5 mg) had their doses uptitrated to the high doses. Patients in the active treatment groups who were randomized to continue background medication with metformin continued with their current dose of either saxagliptin or dapagliflozin. Eligible patients receiving placebo were randomized 1:1:1 to either withdraw background medication with metformin and switch to active treatment with either saxagliptin 5 mg or dapagliflozin 10 mg or to remain on background medication with metformin and continue with placebo.

The focuses of this sNDA review were to evaluate if the proposed dosing regimen for dapagliflozin was appropriate for treatment of pediatric patients (aged ≥ 10 years) with type 2 diabetes mellitus and whether the labeling claim for similar pharmacokinetics and pharmacodynamics (glucosuria) between pediatric patients (aged ≥ 10 years) and adult patients with type 2 diabetes mellitus are appropriate.

The Applicant proposed an oral dapagliflozin dose of 5 mg once daily, and for additional glycemic control, a dose increase to 10 mg, as the recommended dosing regimen. This was based on the results of primary analysis of Study 19 that showed a placebo adjusted mean change from baseline HbA1c of -1.03% at Week 26 in the pooled dapagliflozin arms. In patients who did not achieve HbA1c < 7% at Week 12, there was no significant difference in the placebo adjusted reduction of HbA1c from baseline at Week 26 between the group of patients who remained on 5 mg dapagliflozin compared with the group uptitrated to 10 mg dapagliflozin after randomization at Week 14. Taking the study limitation (e.g., limited sample size and efficacy comparison of dapagliflozin 5 mg and 10 mg conducted in a subset of patients who did not achieve HbA1c < 7%) into consideration, clinical pharmacology reviewers defer the specific dose recommendations to the clinical review team.

The Applicant claimed the pharmacokinetic exposure of dapagliflozin in pediatric (aged ≥ 10 years) and adult patients with type 2 diabetes mellitus were comparable based on cross study comparison of the observed data and population pharmacokinetics model derived area under the curve (AUC) normalized to dose. The dapagliflozin pharmacokinetics in pediatric (aged ≥ 10 years) with type 2 diabetes mellitus has been evaluated in Study 16. A cross-study comparison using NCA analysis found no difference in average dapagliflozin PK (C_{max} and $AUC_{0\text{-}inf}$) between pediatrics and adults at the same dose level. In addition, population pharmacokinetics model was conducted as supportive evidence using the steady state trough concentration data and 2 h post dose PK samples in Study 19 to estimate the systemic exposure to dapagliflozin in pediatric patients with type 2 diabetes mellitus. The population pharmacokinetics model was able to approximately describe the dapagliflozin concentrations in pediatrics (aged ≥ 10 years) patients with type 2 diabetes mellitus, healthy adults, and adult patients with type 2 diabetes mellitus. The estimated $AUC_{0\text{-}inf}$ normalized to dose in pediatric patients (aged ≥ 10 years) was within the range of that in adult patients with type 2 diabetes mellitus. And the median estimated $AUC_{0\text{-}inf}$ normalized to dose is comparable between pediatric (aged ≥ 10 years) and adult patients with type 2 diabetes mellitus. Therefore, the clinical pharmacology reviewers agree that

submitted PK data is sufficient to support the labeling claim that there is the similar pharmacokinetic exposure in pediatric (aged ≥ 10 years) and adult patients with T2DM.

The Applicant claimed the pharmacodynamics (glucosuria) marker of dapagliflozin in pediatric (aged ≥ 10 years) and adult patients with type 2 diabetes mellitus were similar. A cross-study comparison found that the observed mean 24-hours urine glucose excretion in pediatric (aged ≥ 10 years) patients with type 2 diabetes mellitus was higher than that in adult patients. The Applicant submitted a published population pharmacokinetics and pharmacodynamics model to support the higher observed 24-hours urine glucose excretion may mainly attribute to the higher estimated glomerular filtration rate and claimed the pharmacodynamic similarity between pediatric (aged ≥ 10 years) and adult patients based on similar exposure-response relationship between these two patient populations. Insufficient PK/PD data in pediatric patients, complicated by uncertainties in the submitted model, precluded the ability of the reviewers to make a direct statistical comparison between the adult and pediatric PK/PD data. However, the observed 24-hours urine glucose excretion in pediatric (aged ≥ 10 years) patients from study 16 does appears to fall in the range of that observed in adult patients after accounting for differences in renal function.

Based on the results from Study 19 in the current submission, the Applicant has fulfilled all requirements for PMR 3199-1. The results from the study in this submission are updated to the currently approved package insert.

1.1 Recommendations

The Office of Clinical Pharmacology has determined that there is sufficient clinical pharmacology information provided in this supplement NDA (sNDA) to support the approval of Farxiga in pediatric patients 10 years and older. The final proposed dose of 5 mg once daily 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 10 mg in pediatric patients with T2DM who are not responding well to Farxiga, and hence defer to the clinical review team to evaluate the benefit and risk of extending the approval to 10 mg for additional glycemic control.

The proposed labeling claim for similar pharmacokinetics (PK) in pediatric and adult patients with type 2 diabetes mellitus (T2DM) is acceptable. A statistical comparison of pharmacodynamics (glucosuria) in pediatric and adult patients with T2DM is not appropriate with the submitted PK/PD data due to limited pediatric numbers and limitations of the submitted PK/PD model. However, the pharmacodynamics (PD) in pediatric patients with T2DM was within the range of those observed in adult patients with T2DM after accounting for different renal function. The labelling language was revised accordingly.

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Regulatory History

The sNDA submission is an efficacy supplement with clinical data from the pediatric study (Study 19) to support dosing of dapagliflozin in pediatric patients aged 10 years and above. The Applicant had

discussed the protocol for Study 19 in several meetings in 2015 (refer to written response only dated 5/15/2015, 9/14/2015 and 12/22/2015, IND 068652). The Applicant has previously conducted Study 16 in pediatric patients (PMR 2121-1) to support dose selection of the Study 19. The protocol for Study 16 has been agreed by the Agency (Refer to Dr. Ritesh's clinical pharmacology review dated 9/20/2011 in DARRTS, IND 068652). The final clinical study report (CSR) for Study 16 submitted March 31, 2015, and PMR 2121-1 has been determined to be fulfilled (refer to PMR fulfill letter dated 3/21/2016 in DARRTS). The CSR for Study 16 has been reviewed (refer to clinical pharmacology review dated 2/16/2016, NDA 202293) and FDA's comments about the dose selection for Phase 3 study (Study 19) in pediatrics was sent to the Applicant (Advice letter dated 2/23/2016, IND 068652). FDA agreed with the proposed dose for the phase 3 study based on the pharmacodynamics, efficacy and safety data in pediatrics and adults (refer to advice letter dated 6/17/2016 in DARRTS, NDA 202293). The Applicant and Agency had reached consensus upon the design of Study 19 in the written request issued on 3/22/2016. The Applicant discussed the content and format of the planned supplement NDA for the new proposed indication of dapagliflozin and saxagliptin, an adjunct to diet and exercise to improve glycemic control in adults and children aged 10 years and above with T2DM in a Type B Pre-sNDA meeting (refer to written response only dated 12/20/2022 in DARRTS for IND 068652).

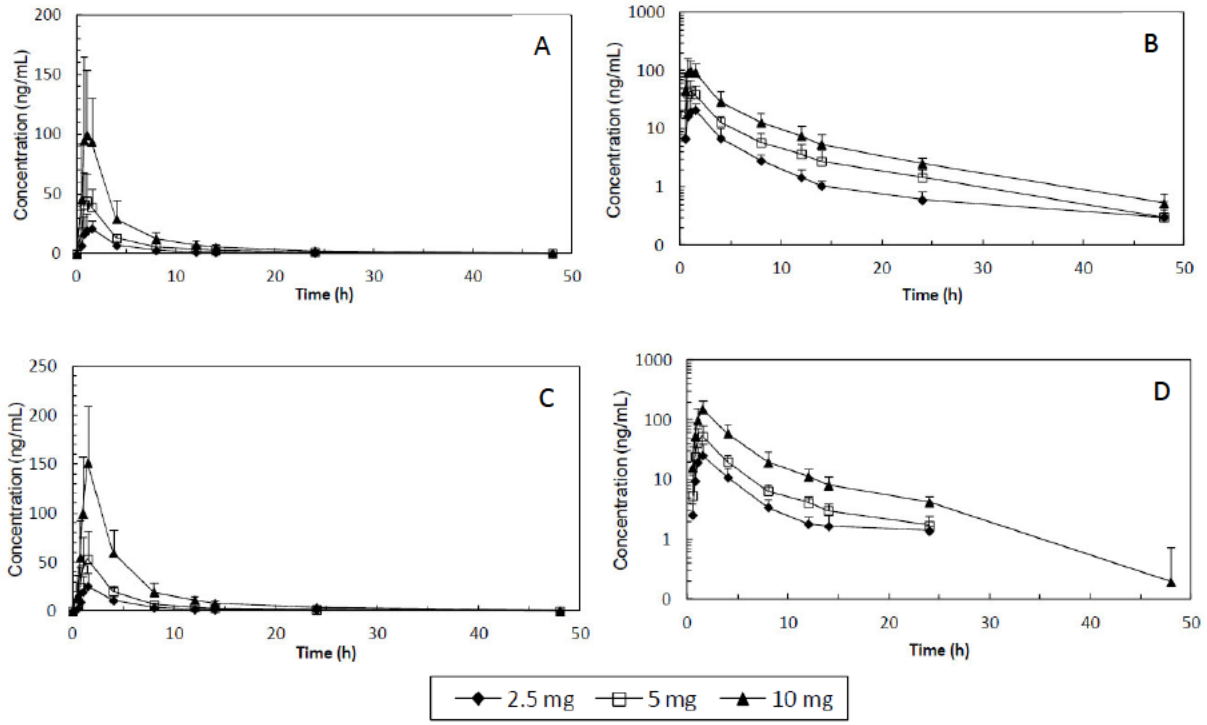
The Applicant is seeking pediatric indication and proposing to update the labelling of two dapagliflozin containing products with the pediatric study results that are collected from Study 19 by submitting efficacy supplements to NDA 202293 for Farxiga (dapagliflozin) and NDA 205649 for Xigduo XR (dapagliflozin and metformin hydrochloride extended release).

2.2 General Pharmacology and Pharmacokinetics Characteristics

The general pharmacology and PK of dapagliflozin in healthy volunteers, adult patients with T2DM, and special population has been previous reviewed (Refer to NDA 202293 Clinical pharmacology review, reference ID 3423696, dated 12/17/2013 and reference ID 3009432 dated 9/1/2011). Dapagliflozin is not studied in children less than 10 years of age including neonates because the prevalence of T2DM in this younger population is low.

The pediatric PK and PD from the post-marketing study 16 is summarized below. Study 16 was a single dose, open-label, Phase 1 trial to evaluate the PK and PD (24 hours urine glucose excretion [UGE]) of 2.5 mg, 5 mg and 10 mg dapagliflozin in children and adolescents from 10 to less than 18 years of age with T2DM. Eight subjects were randomized to each dapagliflozin dose cohort (2.5 mg, 5 mg and 10 mg). The mean age was 14.5 years (11 to 17 years), mean weight was 99.7 kg (61.5 – 169.5 kg), median eGFR was 110.5 ml/min/1.73 m^2 (82.0 to 154 ml/min/1.73 m^2), and median baseline mean fasting glucose was 6.9 mmol/L (4.6 to 16.2 mmol/L), the median baseline HbA1c was 6.9 % (6.1 – 9.7 %). The baseline UGE was not available and UGE after single dose dapagliflozin was collected from 0 to 24 hours post dose.

Figure 1. Mean plasma concentration-time profiles of dapagliflozin (A, B) and dapagliflozin 3-O-glucuronide (C, D) after single dose of 2.5 mg, 5 mg or 10 mg dapagliflozin to pediatric patients in linear (A, C) and semi log (B, D) plots.



In pediatric subjects aged 10 to 17 years, following a single oral dose, peak concentration (C_{max}) was achieved approximately 1 h after administration. Mean terminal elimination half-life of dapagliflozin appeared independent of dose and ranged between 10 to 14 h across the studied dose range and is similar to the reported half-life of dapagliflozin of 12.9 h in adults. The increase in C_{max} and total systemic exposure of dapagliflozin was dose proportional with geometric mean of C_{max} ranging from 24.8 ng/mL (2.5 mg group) to 118 ng/mL (10 mg group) and geometric mean area under the time-concentration profile ($AUC_{0\text{-}inf}$) ranging from 101 ng*h/mL (2.5 mg group) to 427 ng*h/mL (10 mg group). A cross study comparison of the exposure level of dapagliflozin after single dose 2.5 mg, 5 mg and 10 mg administration in pediatric patients with T2DM from Study 16 and those in adults from Study MB102002 (healthy subjects) and MB102003 (patients with T2DM) were performed in previous clinical pharmacology review (Reference ID: 3887636, dated 2/16/2016) and found the average dapagliflozin PK (C_{max} and $AUC_{0\text{-}inf}$) did not differ between pediatrics and adults at the same dose levels. The steady-state exposure level comparison between pediatric and adult patients with T2DM were performed by $AUC_{0\text{-}inf}$ normalized to dose derived from a popPK model which will be detailed reviewed below. The PK of the major metabolite, dapagliflozin-3-O-glucuronide, was not compared between pediatric and adult patients with T2DM because it is an inactive metabolite.

2.3 Clinical Pharmacology Review Questions

2.3.1 Does the proposed dose regimen in pediatric patients aged 10 and above with type 2 diabetes mellitus reasonable?

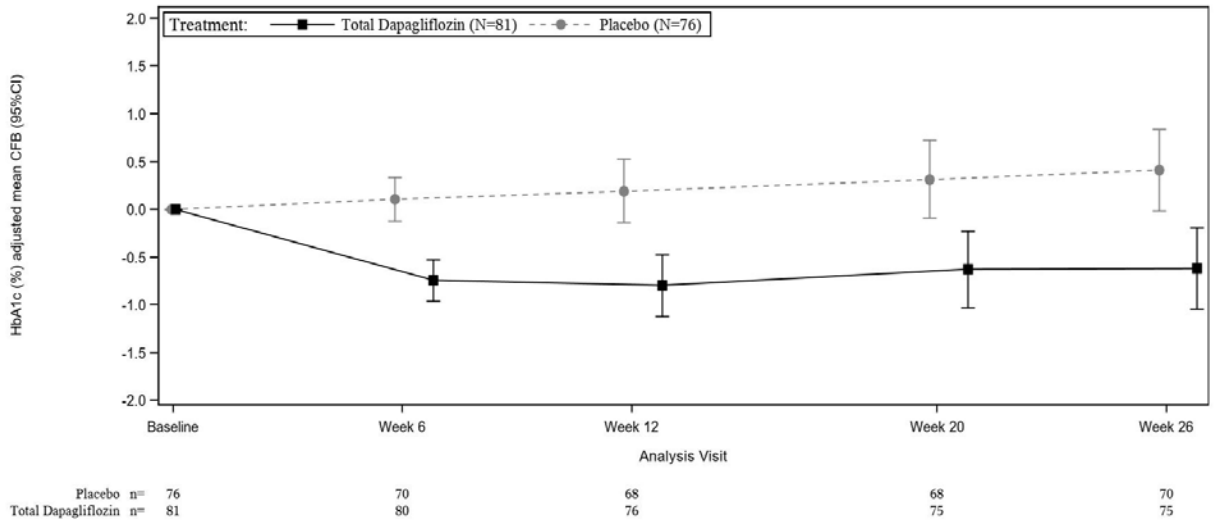
Yes, the proposed dosage is acceptable for the treatment in pediatric patients aged 10 years and older with T2DM.

Primary efficacy analysis: pooled dapagliflozin treatment vs placebo

The Study 19 did not include separate arms for 5 mg and 10 mg of dapagliflozin. All patients were randomized initially to the dapagliflozin 5 mg (n=81) or placebo (n=76) or saxagliptin (n=88) treatment arms. All patients have background antidiabetic medication (51.4 % on metformin, 12.2% on insulin and 36.3% on combination), and the background treatment was balanced in three treatment arms. The baseline HbA1c (%) was also comparable among three treatment arms (8.22 ± 1.46, 8.02 ± 1.43 and 7.96 ± 1.63 in dapagliflozin, saxagliptin and placebo treatment arms, respectively). For the dapagliflozin 5 mg arm, those who failed to achieve HbA1c < 7% at Week 12, underwent a second randomization at Week 14 to remain on the 5 mg dose or increase to 10 mg dose of dapagliflozin. Hence, the primary analysis for change from baseline in HbA1c at Week 26 evaluated the pooled treatment effect for dapagliflozin 5 and 10 mg. At Week 26, the difference in adjusted mean change from baseline HbA1c (adjusted with baseline HbA1c, sex, age group and background antidiabetic medication) between the dapagliflozin treatment group (pooled of 5 mg and 10 mg) and the placebo group was -1.03% (95% confident interval [CI]: -1.57 to -0.49, P< 0.001). A statistically significant improvement in HbA1c was achieved at Week 6 and sustained through Week 26 with pooled dapagliflozin treatment group vs placebo group (Figure 2).

As a secondary analysis, the fasting plasma glucose (FPG) also showed a significant decrease from baseline at Week 26, the difference in adjusted mean change from baseline FPG between the pooled dapagliflozin treatment group and placebo group was -1.08 mmol/L (95% CI: -1.76 to -0.62, P < 0.001).

Figure 2: Mean Plot of Change from Baseline in HbA1c (%) Between Overall Dapagliflozin and Placebo by Visit in 26-Week Short-Term period, Regardless of Rescue (Randomized Patients Data Set, Study 19)



Source: Figure 7 of the Clinical Study Report for Study 19 (Page 110)

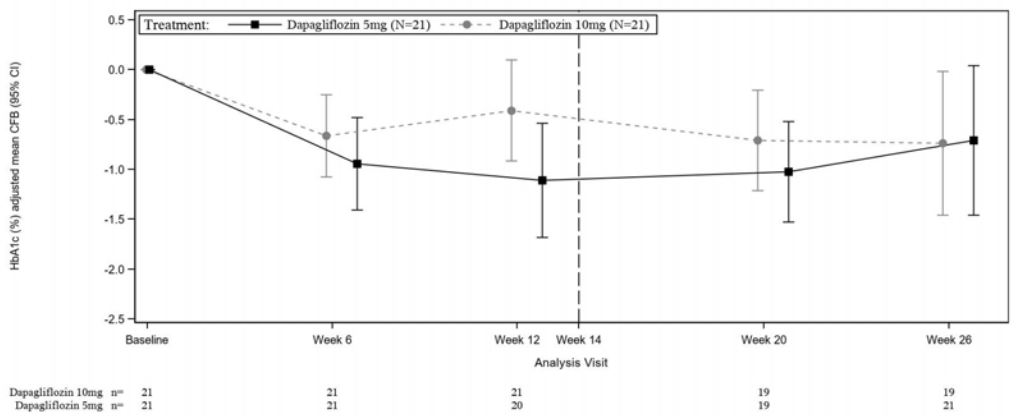
Exploratory subgroup analysis of non-responders:

At week 14, the patients who failed to achieve HbA1c < 7% at Week 12 (42 subjects out of 81 treated), underwent a second randomization at Week 14 to remain on the 5 mg dose (21 subjects) or increase to 10 mg dose of dapagliflozin (21 subjects). In these re-randomized patients, there were no significant differences in adjusted HbA1c change from baseline to Week 26 (adjusted by treatment, sex, age group, background antidiabetic medication and baseline HbA1c) between the group of patients who remained on 5 mg dapagliflozin (-0.74%) compared with the group uptitrated to 10 mg dapagliflozin (-0.71%) after randomization at Week 14, with the difference between two groups are -0.03% (95% CI -1.00 to 0.94, P = 0.955) (Figure 3). However, this result should be interpreted will caution for the following reasons.

1. The change from baseline of HbA1c at Week 12 (i.e., before the second randomization and uptitration) is not well balanced between the patients with $\geqslant$ 7% HbA1c at Week 12 who underwent uptitration randomization at Week 14 and those who remained on 5 mg dapagliflozin (-0.41% in the group that were later uptitrated to 10 mg dapagliflozin group and -1.11% in the group that remained on the low-dose, Figure 3). The larger reduction in HbA1c from baseline to Week 12 in the group that was not uptitrated may have influenced the results at Week 26.
2. The comparison between 10 mg dapagliflozin and 5 mg dapagliflozin is not powered because the sample size is limited with only 21 and 20 subjects were re-randomized to dapagliflozin 10 mg and remained on dapagliflozin 5 mg, respectively.

The Applicant did not submit an exposure-efficacy or exposure-safety relationship in pediatric patients with T2DM to review in this sNDA. Acknowledging the study design limitations that preclude a dose or exposure-response assessments in support of the dose increase to 10 mg in pediatric patients with T2DM who are not responding to Farxiga, and hence the clinical pharmacology review team defers to the clinical review team to evaluate the benefit and risk of extending the approval to 10 mg for additional glycemic control.

Figure 3. Mean Plot of Change from Baseline in HbA1c (%) Between 10 mg and 5 mg Dapagliflozin for Patients Who Did Not Achieve HbA1c < 7% at Week 12 by Visit During the short-time period, Regardless of rescue (Uptitration Randomized Patients Data Set)



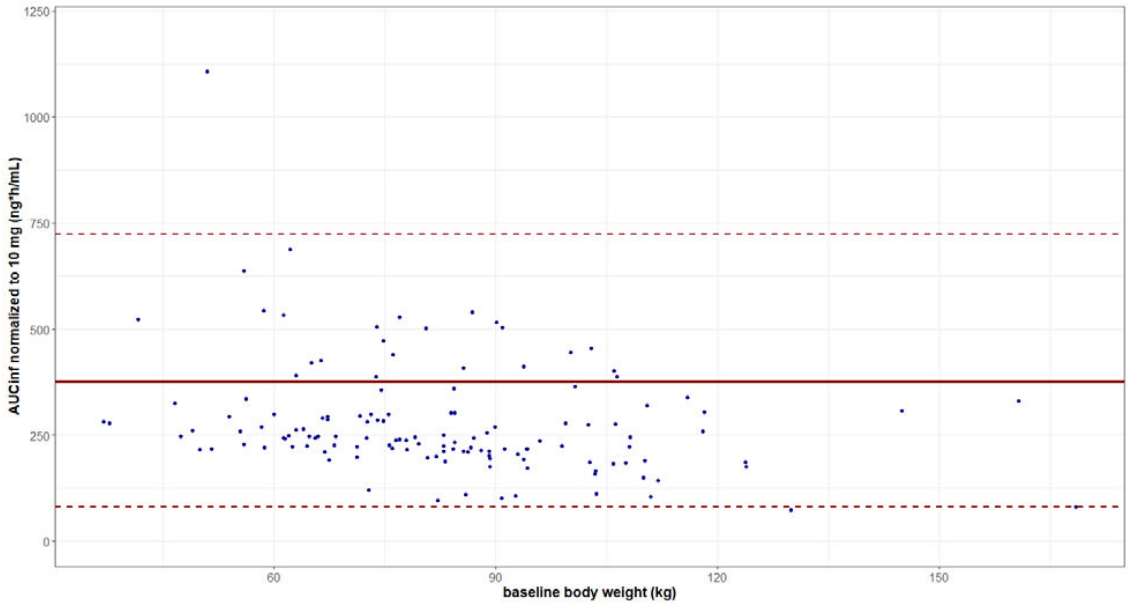
Source: Figure 9 of the Clinical Study Report for Study 19 (Page 120)

2.3.2 Is the proposed label language for pharmacokinetics and pharmacodynamics in pediatric patients with T2DM reasonable?

The Applicant proposed the following labelling language in section 12.3 "The pharmacokinetics and pharmacodynamics (glucosuria) of dapagliflozin in pediatric patients aged 10 to 17 years with type 2 diabetes mellitus were similar to those observed in adults (b) (4)

As stated in the previous clinical pharmacology review, a cross-study comparison found no difference in the average dapagliflozin PK (C_{max} and $AUC_{0\text{-}inf}$) between pediatrics and adults after single dose of 2.5 mg, 5 mg and 10 mg dapagliflozin administration based on PK from pediatric patients with T2DM (Study 16) and adult (Study MB102002 [healthy subjects] and MB102003 [T2DM]). The Applicant submitted a population PK (popPK) report to support the similar PK between pediatric aged ≥ 10 years and adult patients with T2DM. The PopPK model included data from 1 healthy adult volunteer study, 4 T2DM studies in adults, and 3 T2DM studies in pediatrics (MB102091/D1690C00016, MB102002, MB102003, MB102013, MB102032, D1690C00006, D1690C00017 and D1690C00019). The model was reviewed and considered as approximately described the dapagliflozin concentration in pediatric and adult patients with T2DM (Refer to Appendix 3.2 popPK review, for detail). The popPK model derived $AUC_{0\text{-}inf}$ normalized by dose in pediatric patients with T2DM were within the range of those in adult patients with T2DM (Figure 4) and the median $AUC_{0\text{-}inf}$ was also similar between pediatric and adult patients with T2DM at the same dose level (Table 6 in Appendix 3.2).

Figure 4. Predicted $AUC_{0\text{-}inf}$ normalized to 10 mg in pediatric T2DM patients over baseline body weight. Solid and dashed red lines are the median, and 5% and 95% percentile of the predicted AUC0-inf normalized to 10 mg in adult T2DM patients.



Source: Reviewers' analysis.

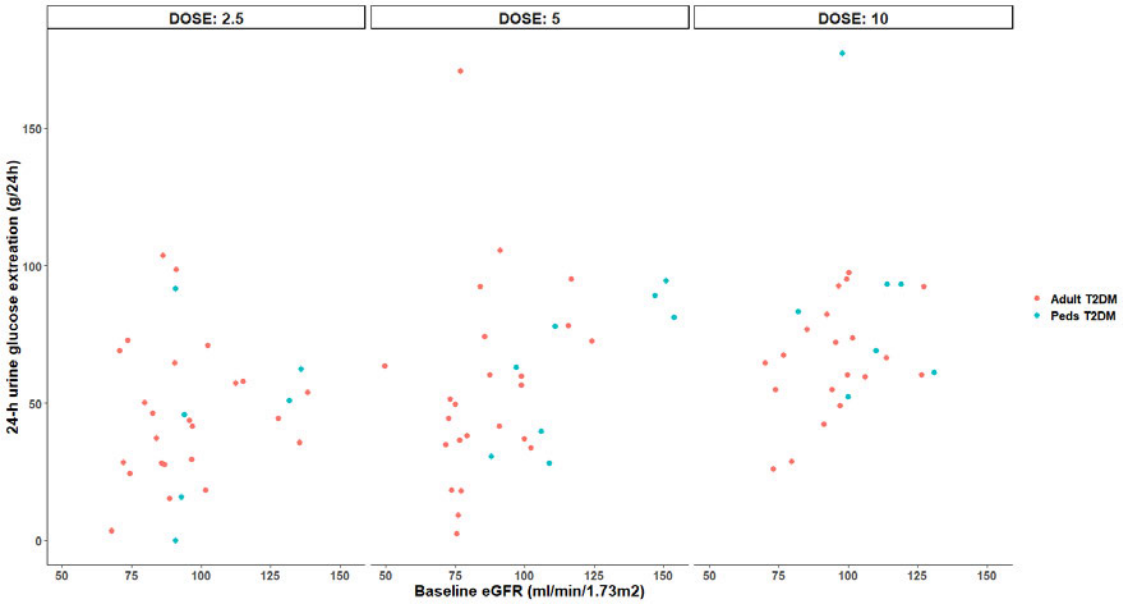
In study 16 (MB102091), 24-hour urine glucose extraction (UGE) increased with dose after single dose of dapagliflozin in 20 pediatric patients with T2DM (52.8 [n=5], 62.4 [n=8] and 89.0 [n=7] g/24 h for 2.5, 5

and 10mg). Of note, the baseline 24-hour UGE was not collected before dapagliflozin administration in this pediatric PK/PD study. A cross-study comparison found that the observed mean 24-hours urine glucose excretion in pediatric (aged ≥ 10 years) patients with type 2 diabetes mellitus was numerically higher than that in adult patients. To support similar pharmacodynamics (glucosuria) in pediatric and adult patients with T2DM, the Applicant submitted a published exposure (AUC) -response (24 hours urine glucose extraction [UGE]) relationship of dapagliflozin established based on data from clinical studies of single-dose (2.5, 5 and 10 mg), orally administered dapagliflozin in adult (n=63, MB102003 and MB102025) and pediatric (n=20, study 16) patients with T2DM. Baseline FPG, eGFR, baseline 24-h UGE (only available for adults), sex, and race were evaluated as covariates and only baseline eGFR, FPG and sex were significant covariates in both populations. The model predicted UGE after administration of the same single doses of dapagliflozin (2.5, 5 and 10mg) increased with dose and were higher in pediatric (47.4, 67.5 and 85.9 g/24 h, respectively) patients than those in adult (31.2, 43.5 and 54.3 g/24 h, respectively) patients with T2DM. Since the eGFR was identified as a covariate for the exposure-response model that has a significant impact on UGE response, the Applicant claimed that the higher observed UGE was attributed to the higher baseline eGFR in pediatric patients with T2DM in study 16 (110.5 [range 82.0 – 154.0] ml/min/1.73m^2) compared to that in adult patients with T2DM (86.0 range [56.7 – 138.4] ml/min/1.73m^2). The clinical pharmacology reviewers believes that the Applicant's claim (i.e., the higher 24-h UGE in pediatric patients may due to the higher eGFR in pediatric patients) is reasonable because the mechanism of action of sodium glucose cotransporter 2 (SGLT2) inhibitor is through increasing the amount of glucose excreted in urine and it has been reported that the 24-h UGE and glycemic control response after SGLT2 inhibitors administration was related to eGFR. However, there is insufficient data to provide conclusive evidence that the pharmacodynamics (glucosuria) is statistically the same between pediatric and adult patients with T2DM based on current data due to following reasons.

1. The eGFR was calculated from the Schwartz formula and MDRD formula in pediatrics and adults, respectively. 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 pediatrics and adults.
2. The baseline UGE (i.e., before dapagliflozin administration) was absent in pediatric patients with T2DM.
3. There are limited numbers of pediatric patients with T2DM included in the exposure-response analysis.

However, we agree that, in general, the observed 24-hours UGE in pediatric patients with T2DM does fall in the range of (i.e., similar to) those observed in adult patients with T2DM after accounting for differences in renal function (Figure 5).

Figure 5. 24-hour Urine Glucose Excretion in Pediatric and Adult Patients with T2DM stratified by Dose levels



Source: Reviewers' analysis using data from MB102003 and MB102025 for adult T2DM and Study 16 for pediatric T2DM

3. APPENDICES

3.1 Summary of Bioanalytical Method Validation and Performance

Concentrations of dapagliflozin in plasma samples for the pediatric studies were determined by a validated LC-MS/MS assay (liquid chromatography tandem mass spectrometry). The method validation (b) (4) project OAZ2 [document No. 930065686]) for dapagliflozin measurement in human plasma used in Study 16 and bioanalysis report for Study 16 have been reviewed and determined to be acceptable in previous OCP review (Reference ID: 3887636 dated 2/16/2016). The determination of dapagliflozin in human plasma for study 19 ((b) (4) Study Number 8316647) has been reviewed and found acceptable by the OCP previously (Reference ID:4038399 dated 1/6/2017). The bioanalysis report for Study 19 has been submitted in this sNDA. The study samples were analyzed within the validated stability period of 1163 days and the assay performance was found acceptable, as below. The accuracy of the low, medium, high and 10-fold dilution quality control samples for the 10 analytical runs were 100.5%, 100.8%, 100.6% and 99.5%, respectively. The precision of the low, medium, high and 10-fold dilution quality control samples for the 10 analytical runs were 9.3%, 2.6%, 2.2% and 1.8%, respectively. Incurred sample reproducibility was assessed by re-assaying 68 out of the 618 patient samples (11.0% of the sample size), and 97.1% of the re-assayed patient samples results were within 20%, thus meeting the acceptance criteria. The bioanalytical method performance to quantify dapagliflozin in plasma samples was found to be acceptable.

3.2 Population PK Assessments

3.2.1 Review Summary

In general, the applicant's population PK analysis is considered acceptable for the purpose of evaluating if the AUC of dapagliflozin in pediatric patients (aged 10 to < 18 years) with T2DM are comparable to that observed in adult patients with T2DM. 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 1.

Table 1. Specific Comments on Applicant's Final Population PK model

Utility of the final model		Reviewer's Comments
Derive exposure metrics for comparison between pediatric and adult patients with T2DM	AUC	The applicant's final model is generally acceptable for generating AUC for pediatric patients with T2DM and comparing the AUC between pediatric and adult patients with T2DM

3.2.2 Introduction

The primary objectives of applicant's analysis were to:

- Characterize the PK of dapagliflozin in Study 19 using a popPK model previously established in healthy adults and in children and adult patients with T2DM.
- To evaluate if the PK behavior of dapagliflozin in pediatric patients with T2DM who are between 10 and < 18 years of age from Study 19 is similar to that observed in previous clinical studies conducted in healthy adults and in pediatric and adult patients with T2DM.

3.2.3 Model development

Data

The analysis was based on PK data from 8 studies. The study design, study population, and timing of blood samples varied among the 8 clinical studies. Brief descriptions of the studies included are presented in Table 2.

The final NONMEM data file for analysis contained 8866 PK observations from 1443 subjects. Table 3 provides summary statistics of the baseline demographic covariates in the analysis dataset.

Table 2. Summary of Studies with PK Sampling Included in Population PK Analysis (include if available from the applicant's report)

Protocol # & Study Design	Dose	Number of Subjects in PopPK	PK sampling time points
Studies in pediatric and adolescents/young adults with T2DM			
D1680C00019: Randomized, double-blind, placebo-controlled, parallel group, Phase 3 study.	5 mg and 10 mg, tablets	85, T2DM patients (between 10 and < 18 years of age)	Pre-dose and 2-hour post-dose at week 4, 16 and 24.
D1690C00017: Randomized, double-blind, placebo-controlled, parallel group, Phase 3 study.	10 mg	35, T2DM aged 10-24 years	Pre-dose and 2-hour post-dose at week 16 and 24
MB102091: Randomized, parallel group, multicenter, single dose, Phase 1 study.	2.5, 5 and 10 mg, tablets,	24, Pediatric T2DM (between 10 and < 18 years of age)	Pre-dose, and 0.5, 0.75, 1, 1.5, 4, 8, 12, 14, 24 and 48 hours post-dose
Studies in healthy adults and adults with T2DM			
MB102002: Ascending multiple dose study, phase 1 study	2.5, 10, 20, 50 and 100 mg once daily for 14 days, capsule	30, healthy adults	Pre-dose, and 0.25, 0.5, 1, 1.5, 2, 4, 6, 8, 10, 12, 14, 18, 22, 24 hours post-dose at days 1 and 7. Trough samples at days 4, 6, 10, 12. Pre-dose, and 0.25, 0.5, 1, 1.5, 2, 4, 6, 8, 10, 12, 14, 18, 22, 24, 48, 72, 96, 120, 144, and 312 hours post dose after the last dose at Day 14.
MB102003: Randomized, double-blind, placebo-controlled, parallel group, phase 2 study	5, 25 and 100 mg once daily, capsule	39, T2DM adults	Pre-dose, 0.5, 1, 2, 4, 8, 12, 18, 24 hours post-dose at days 1 and 14. Trough PK samples at Days 4 and 6.
MB102013: Randomized, double-blind, placebo-controlled, parallel group, multicenter, Phase 3 study	2.5, 5 and 10 mg once daily, tablets	480, T2DM adults	Pre-dose and 3 hours post dose at Day 1 and Week 20. Additional predose samples at weeks 16, 20 and 24.
D1690C00006: Randomized, double-blind, placebo-controlled, parallel group, multicenter, phase 3 study	2.5, 5 and 10 mg once daily, tablets	567, T2DM adults	Pre-dose, 1 and 3 hours post-dose at Weeks 8 and 20.
MB102032: Randomized, double-blind, placebo-controlled, parallel group, multicenter, Phase 3 study.	1, 2.5 and 5 mg, tablets	183, T2DM adults	Pre-dose, 0.5, 1, 2 and 3 hours post-dose at week 20.

Source: Applicant's Population PK report for study 19, Table 1.

Table 3. Summary of Baseline Demographic Covariates for Analysis

Variable	Total	D1690C00017	D1690C00019	MB102091	Adult T2DM	Adult Healthy
N	1396	34	85	24	1223	30
Age (yr) (medidan [range])	55 [10, 79]	16 [11, 23]	15 [10, 17]	15 [11, 17]	57 [18, 79]	34 [25, 42]
Baseline Body Weight (kg) (medidan [range])	88 [37, 168]	84 [42, 149]	77 [37, 124]	94 [61, 168]	90 [42, 164]	80 [66, 99]
Baseline eGFR ($mL/min/1.73\ m^2$) (medidan [range])	85 [31, 223]	119 [81, 162]	117 [68, 175]	110 [82, 154]	82 [31, 223]	95 [71, 114]
Male (N (%))	691 (49.5)	13 (38.2)	35 (41.2)	9 (37.5)	604 (49.4)	30 (100.0)
Race (N (%))	-	-	-	-	-	-
Caucasian	1224 (87.7)	24 (70.6)	42 (49.4)	11 (45.8)	1132 (92.6)	15 (50.0)
Black	68 (4.9)	7 (20.6)	7 (8.2)	11 (45.8)	30 (2.5)	13 (43.3)
Asian	65 (4.7)	0 (0.0)	18 (21.2)	0 (0.0)	46 (3.8)	1 (3.3)
Other	39 (2.8)	3 (8.8)	18 (21.2)	2 (8.3)	15 (1.2)	1 (3.3)
CKD stage (N (%))						
eGFR 30-44	20 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	20 (1.6)	0 (0.0)
eGFR 45-59	115 (8.2)	0 (0.0)	0 (0.0)	0 (0.0)	115 (9.4)	0 (0.0)
eGFR 60-89	706 (50.6)	3 (8.8)	9 (10.6)	2 (8.3)	681 (55.7)	11 (36.7)
eGFR >90	555 (39.8)	31 (91.2)	76 (89.4)	22 (91.7)	407 (33.3)	19 (63.3)

Abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; N, number of subjects.
Source: Applicant's Population PK report for study 19, Table 4.

Methods

Using the previous popPK model established on studies mentioned above except Study 19, an external evaluation by visual predictive check (VPC) methodology was able to predict the new pediatric PK data from Study 19. Therefore, the previous model were re-evaluated (including additional inter-individual and residual variability term) after incorporating PK data from Study 19 and the covariates have also been re-assessed.

The final base model was a two-compartment PK model with lag time, first-order absorption, and first-order elimination from the central compartment. The lag time was set as a fixed value of 0.248 hour due to lacking PK data on absorption phase in pediatrics from Study 19.

Inter-individual variability (IIV) was modelled assuming a log-normal distribution for patient level random effects. Residual variability was tested as additive, proportional or both on the ln-transformed dependent variable and allowed different residual model for healthy adults, pediatric and adult T2DM patients.

Covariates included in the previous popPK model (eGFR and sex on CL/F and body weight on Vc/F) were removed one by one to assess their impact on dapagliflozin and limited parameters, including body weight, age and sex were tested on CL/F, Vc/F, Q/F and Qp/F.

Model evaluation and selection were based on standard statistical criteria of goodness-of-fit such as a decrease in the minimum objective function value (OFV), accuracy of parameter estimation (i.e., 95% confidence interval excluding 0), successful model convergence, and diagnostic plots.

3.2.4 Final Model

The final model was two compartment model with first-order absorption, lag time and first-order elimination. IIV was exponentially characterized on absorption rate (Ka), apparent clearance (CL/F), apparent peripheral volume (Qp/F) and intercompartmental (Q/F) clearance. A combined error model for log transformed data was applied to account for residual variability for healthy adults and a separate estimate using approximate proportional error was estimated for patients with T2DM, obtaining one error for adults with T2DM and one error for pediatric patients with T2DM. The covariates included in the final model were baseline total body weight, eGFR, and sex on CL/F and baseline total body weight on Vc/F.

The parameter estimates for the final covariate model and its comparison to previous models are listed in Table 4. The apparent clearance kept consistent throughout all three models. The eta shrinkage for apparent clearance in the current model is acceptable, e.g., < 30%.

The goodness-of-fit (GOF) plots for the final covariate model for all data are shown in Figure 6. The GOF stratified by population are presented in Figure 7. The GOF plots showed approximate agreement between the model prediction and the observed dapagliflozin concentration, no apparent bias or trend in the conditional weighted residuals (CWRES) across predicted concentrations and over chronological time in pooled population, and pediatric and adult T2DM patients.

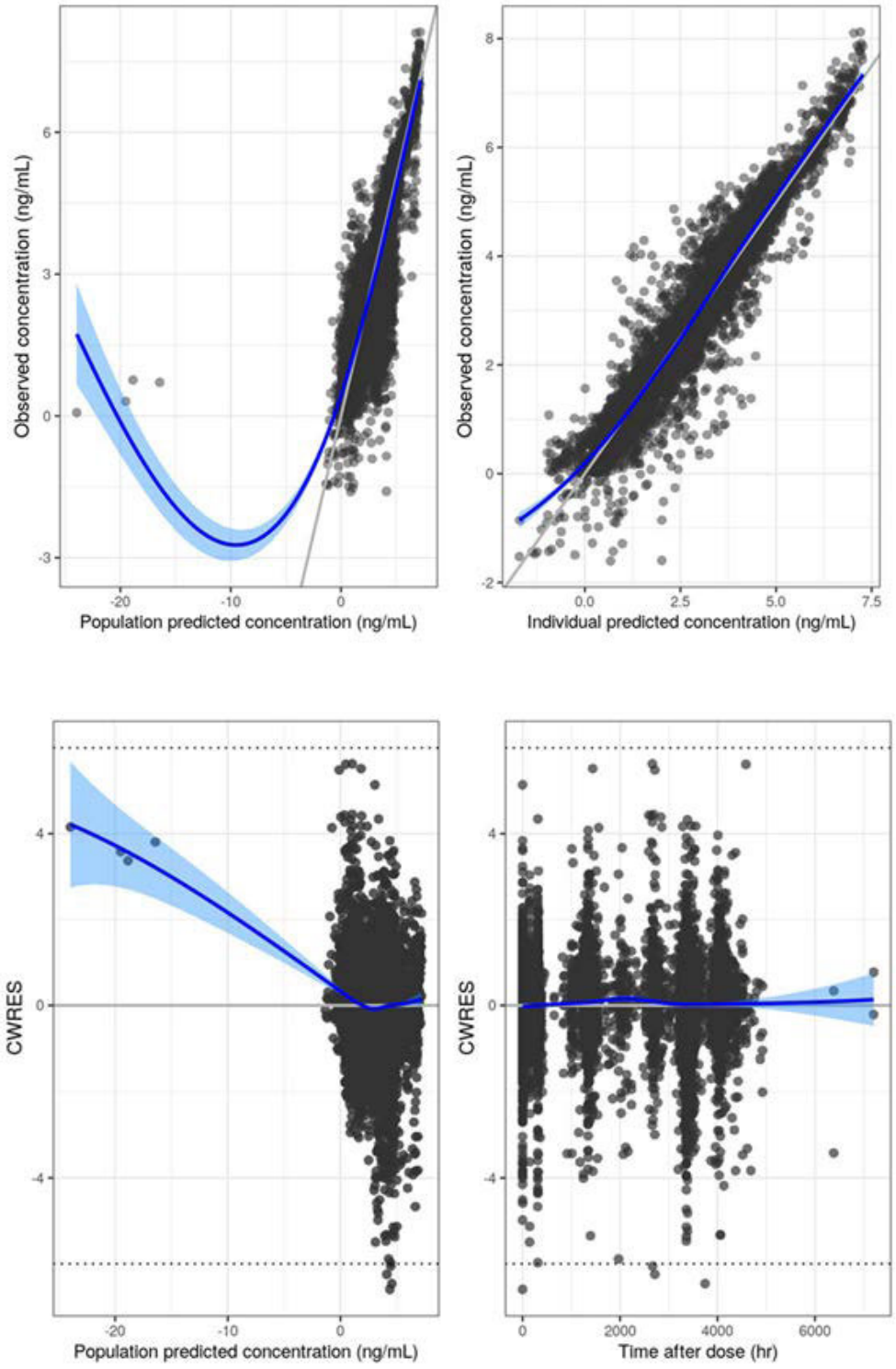
The prediction corrected VPC (pcVPC) plots for the final covariate model stratified by population are shown in Figure 8. The pcVPC plots show the approximate adequate model performance in pediatric and adult with T2DM. Although the high dispersion observed in pediatric PK data, the large degree of overlap between the observed and model derived concentrations in subjects 10 to < 18 years of age indicated that the current model could approximately describe dapagliflozin PK in pediatric subjects with T2DM.

Table 4. Parameter Estimates (RSE) and Median (95% CI) for the Final Model

	Current model[&]			Adult only model*		D1690C00017 model[#]		
Parameter	Estimate	RSE(%)	Shrinkage (%)	Estimate	RSE(%)	Estimate	RSE(%)	unit
Polulation Parameter								
Ka	3.09	13.7	-	2.97	14.4	2.96	13.5	h-1
CL/F	21	1.54	-	22.9	1.76	23.4	1.78	L/h
Vc/F	74.4	1.52	-	73.9	1.61	74.1	1.49	L
Vp/F	233	8.51	-	113	4.82	116	4.72	L
Q/F	9.91	3.25	-	8.85	3.02	8.87	2.98	L/h
EP1	0.864	8.13	-	0.725	3.79	0.728	3.76	-
Covariate								
eGFR on CL/F	0.519	7.5	-	0.552	6.67	0.515	9.6	-
Sex on CL/F	-0.111	18.4	-	-0.161	13.9	-0.182	13.2	-
BW on CL/F	0.518	8.62	-	0.705	10.7	0.593	11.4	-
BW on Vc/F	0.663	10.7	-	-	-	-	-	-
IIV								
Eta_Ka	7.91	8.31	39.2	8.68	8.33	8.42	7.79	-
Eta_CL/F	0.0734	4.49	24.7	0.106	4.87	0.13	4.32	-
Eta_Vp/F	0.633	10.5	66.7	0.147	24.5	0.144	23.8	-
Eta_Q/F	0.0877	19.3	69.8	-	-			-
Residual								
Additive adult	0.0948	1.81	4.05	0.197	0.889	0.197	0.883	ng/mL
Prop adult	0.0943	28.1	4.05	0.0979	12.6	0.0978	12.6	-
Prop adult t2dm	0.191	0.983	4.05	-	-			-
Prop ped t2dm	0.647	2.61	4.05	-	-	0.356	4.37	-

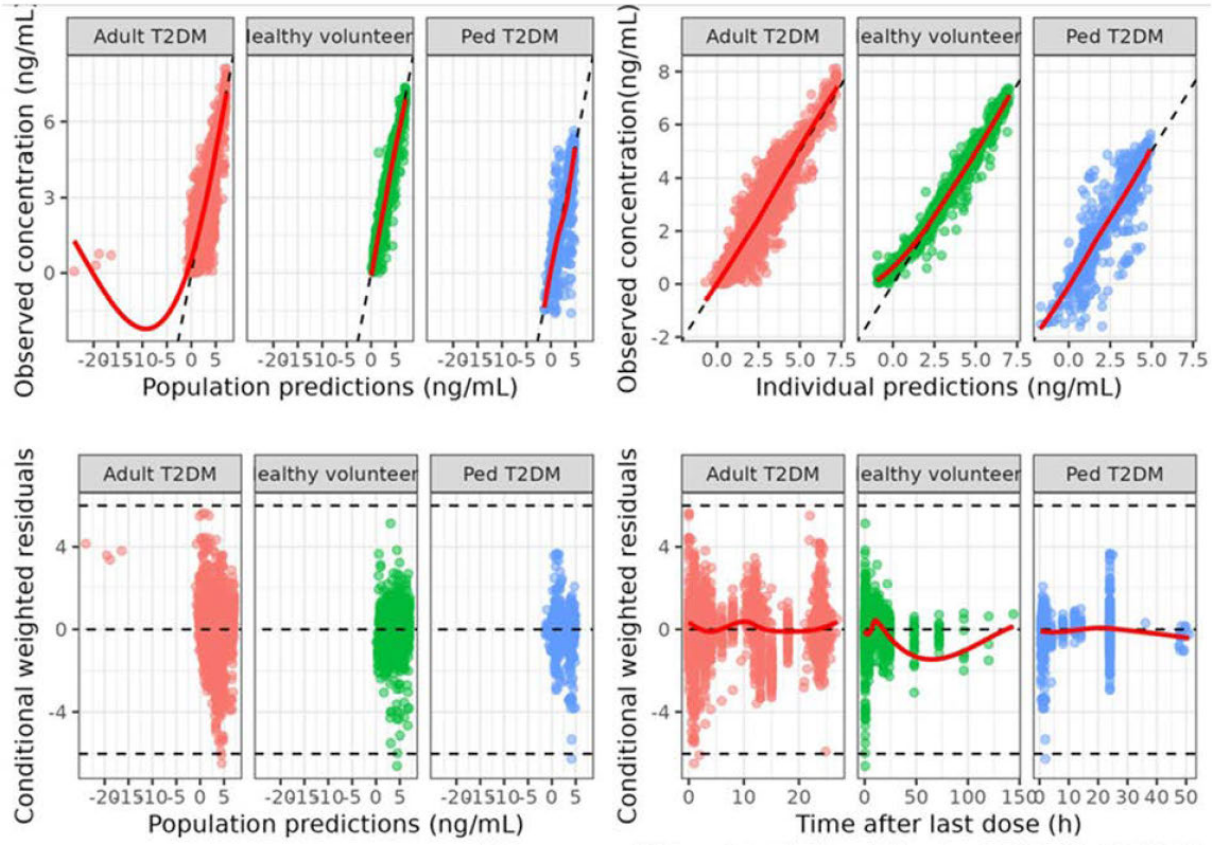
&: From Applicant's popPK report for study D1690C00019 Table 6;
**: From FDA pharmacometrics review for NDA 202293 Table 3*
#: From Applicant's popPK report for study D1690C00017 Table 5

Figure 6. Goodness-of-fit Plots for Final Covariate Model.



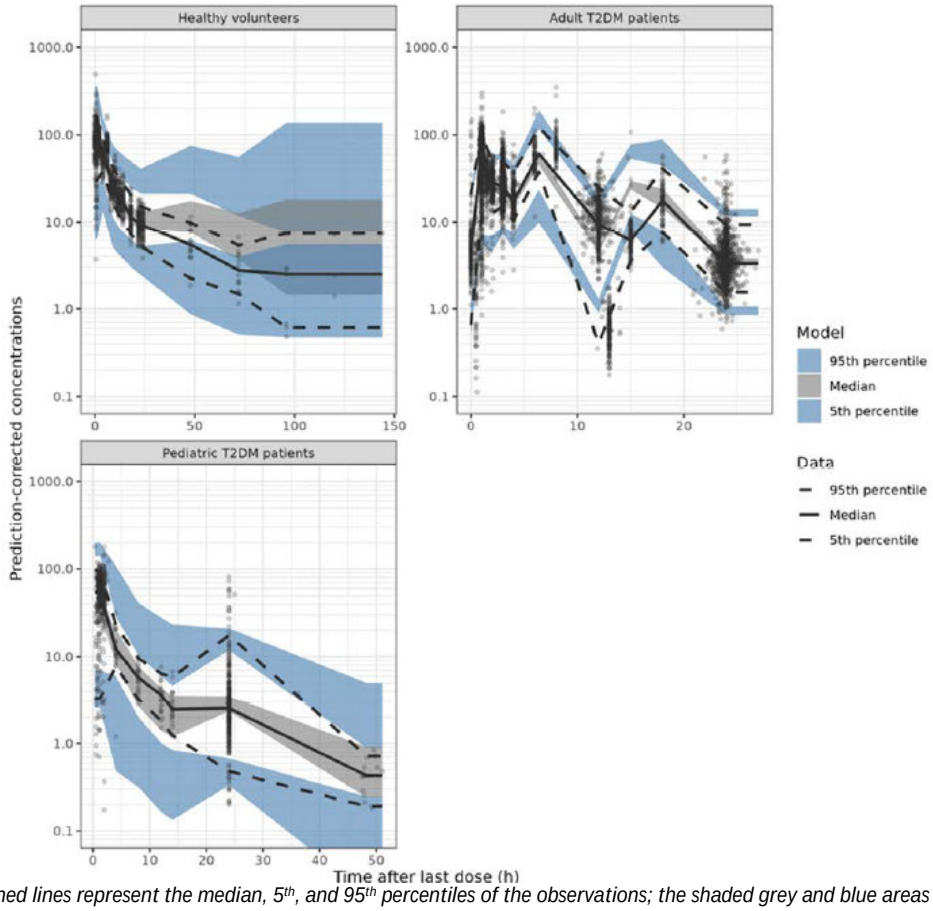
Concentrations are expressed in logarithmic scale; the blue line is a trend line through the data points, the blue area is the 95% confidence interval around it. CWRES, conditional weighted residuals.
Source: Applicant's popPK report for Study D1690C00019 Figure 6.

Figure 7. Goodness of Fit Plots for the Final Covariate Model Stratified by Population: Adult T2DM, Healthy adults and Pediatric T2DM.



Source: Applicant's popPK report for Study D1690C00019 Figure C4.

Figure 8. pcVPC vs Time after Last Dose of the Final Model Stratified by Populations.

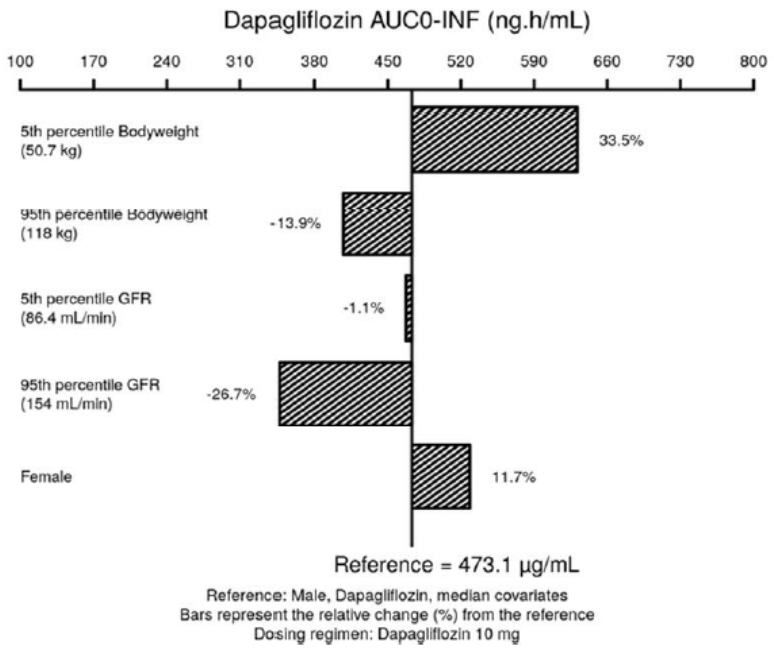


The solid and dashed lines represent the median, 5th, and 95th percentiles of the observations; the shaded grey and blue areas represent the 95% confidence interval of the median, 5th, and 95th percentiles predicted by the model. The time after last dose was truncated to 50hours. CI, confidence interval; pcVPC, prediction-corrected visual predictive check.
Source: Applicant's popPK report for Study D1690C00019 Figure 7.

Exposure comparison in sub-population:

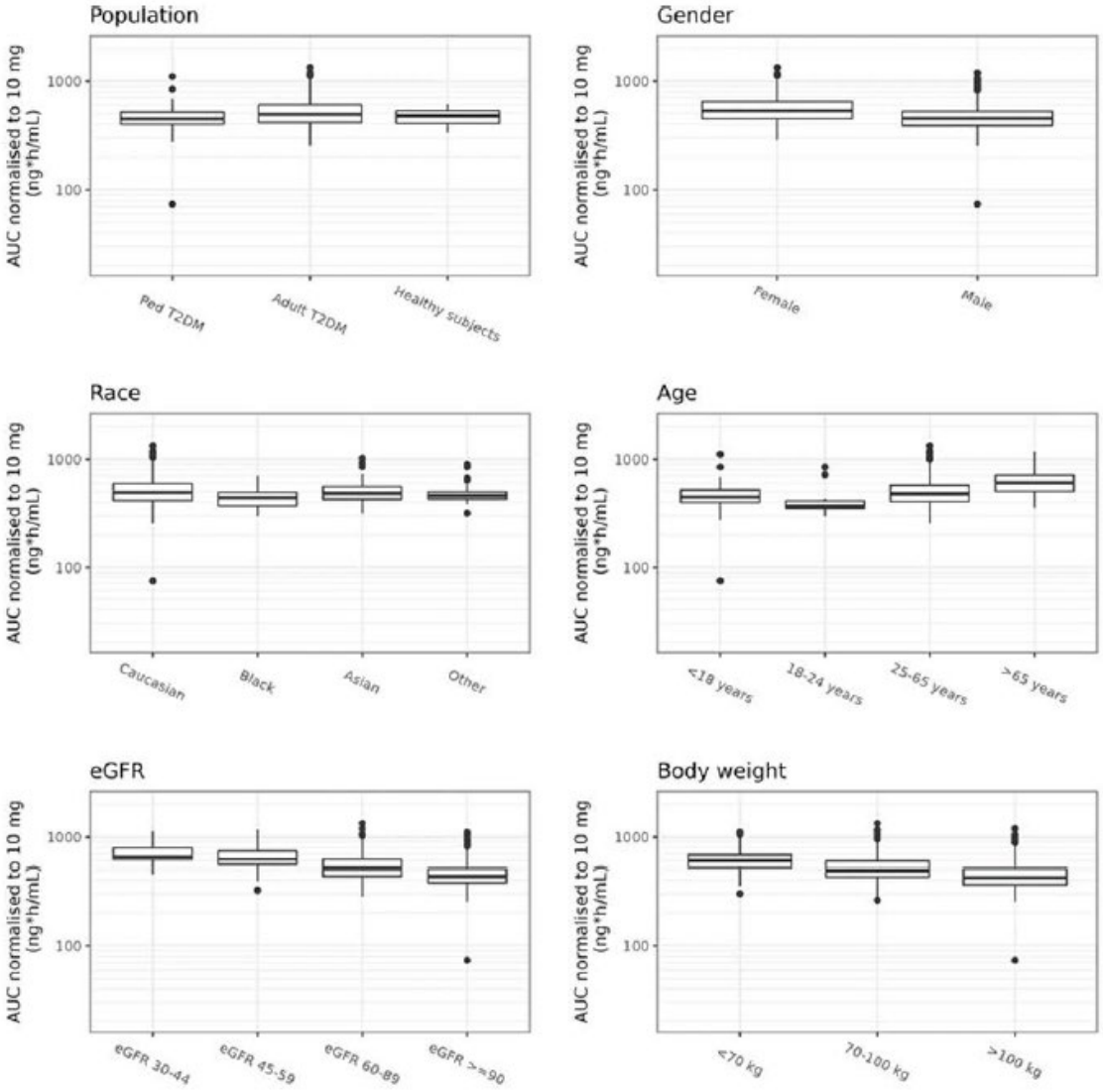
The model estimated covariate effects on $AUC_{0\text{-inf}}$ relative to the reference subject are illustrated in Figure 9. The dapagliflozin systemic exposure ($AUC_{0\text{-inf}}$ normalized 10 mg) were compared between different sub-population (e.g., healthy adults/adult T2DM patients/pediatrics with T2DM, female/male, different races, different age groups, different renal function and different body weight). There is only somewhat tendency to increase $AUC_{0\text{-inf}}$ was only observed at decreasing eGFR and at decreasing total body weights. No evident trend was observed for population groups, gender and race (Figure 10 and Table 5). As summarized in Table 5, median $AUC_{0\text{-inf}}$ normalized to 10 mg was similar for subjects < 18 years (449 ng*h/mL) and 25-65 years (481 ng*h/mL). Patients > 65 years had 1.3-fold higher dapagliflozin AUC compared to patients aged 25-65 years. The median dapagliflozin $AUC_{0\text{-inf}}$ normalized to 10 mg was similar for healthy adults (478 ng*h/mL), adults with T2DM (493 ng*h/mL) and pediatric T2DM patients (449 ng*h/mL).

Figure 9. Covariate Effects on $AUC_{0\text{-}inf}$



Source: Applicant's popPK report for Study D1690C00019 Figure 9.

Figure 10. Dapagliflozin AUC0-inf Normalized to 10 mg Stratified on Different Covariates



Source: Applicant's popPK report for Study D1690C00019 Figure 10.

Table 5. Descriptive Statistics for Dapagliflozin $AUC_{0\text{-}inf}$ (ng*h/mL) Normalized to 10 mg, Stratified by Population Sex, Race, Age, eGFR and Body Weight in All Studies.

Covariate Group	n	Median	5th perc	95th perc	Gmean	GSD
Age <18 years	134	449	318	603	450	1.3
Age 18-24 years	13	369	299	773	407	1.37
Age 25-65 years	1060	481	329	781	489	1.3
Age >65 years	189	606	397	966	606	1.3
Body weight <70 kg	190	597	421	919	605	1.27
Body weight 70-100 kg	801	494	352	789	509	1.28
Body weight >100 kg	405	426	301	699	438	1.32
eGFR 30-44	20	654	522	1010	691	1.25
eGFR 45-59	115	620	440	943	638	1.27
eGFR 60-89	706	512	354	831	521	1.29
eGFR >90	555	436	306	671	443	1.28
Ped T2DM	134	449	318	603	450	1.3
Adult T2DM	1232	493	332	833	505	1.32
Healthy subjects	30	478	352	573	467	1.18
Sex, Male	691	453	317	693	457	1.29
Sex, Female	705	534	365	862	543	1.3
Race, Caucasian	1224	493	331	820	503	1.32
Race, Black	68	443	320	646	436	1.23
Race, Asian	65	486	362	897	503	1.29
Race, Other	39	462	388	850	485	1.25

Source: Applicant's popPK report for Study D1680C00019 Table 7.

Exposure of dapagliflozin in pediatric (10 to < 18 years) and adult patients with T2DM:
As shown in Table 6, the median of dapagliflozin exposure ($AUC_{0\text{-}inf}$) approximately doubled as the dose doubled (453 and 229 ng*h/mL for 10 mg and 5 mg, respectively) in pediatrics (10 to < 18 years) with T2DM, which is similar to adult patients with T2DM (477 and 244 ng*h/mL for 10 mg and 5 mg, respectively).

Table 6. Descriptive Statistics for Dapagliflozin AUC0-inf (ng*h/mL) at Dose Levels of 5 and 10 mg, stratified by Population and studies.

Population	Dose = 5 mg			Dose = 10 mg		
Group	n	Median	CV (%)	n	Median	CV (%)
Clinical studies with pediatric patients with T2DM						
D1680C00019	85	233	19	21	493	21
D1690C00017	-	-	-	34[a]	412	38
MB102091/D1690C00016	8	217	13	8	389	20
Clinical studies only with adults with T2DM						
D1690C00006	194	255	30	185	516	27
MB102003	11	252	25	-	-	-
MB102013	155	235	28	174	443	31
MB102032	56	235	30	-	-	-
Subpopulations						
Pediatric patients (10 to < 18 years) T2DM	93	229	19	54[b]	453	31
Adult patients with T2DM	416	244	29	368[b]	477	30
Healthy adults[c]	-	-	-	6	539	18

a. 9 patients were >18 years of age at baseline.
b. The 9 patients from D1690C00017 > 18 years of age at baseline were included under adult patients with T2DM.
c. Healthy adult PK study results were from study MB102002.
Source: Applicant's popPK report for Study D1680C00019 Table 8 and Applicant's response to FDA's information request SDN2509 Table 1.

3.2.5 Reviewer's Independent Analysis

3.2.5.1 Introduction

One additional plot (Figure 11) with predicted $AUC_{0\text{-inf}}$ normalized to 10 mg over baseline body weight was presented to compare the exposure of dapagliflozin in pediatric and adult patients with T2DM.

3.2.5.2 Objectives

Analysis objective is to verify whether the $AUC_{0\text{-inf}}$ normalized to 10 mg in pediatric T2DM patients is comparable to that in adult T2DM patients.

3.2.5.3 Methods

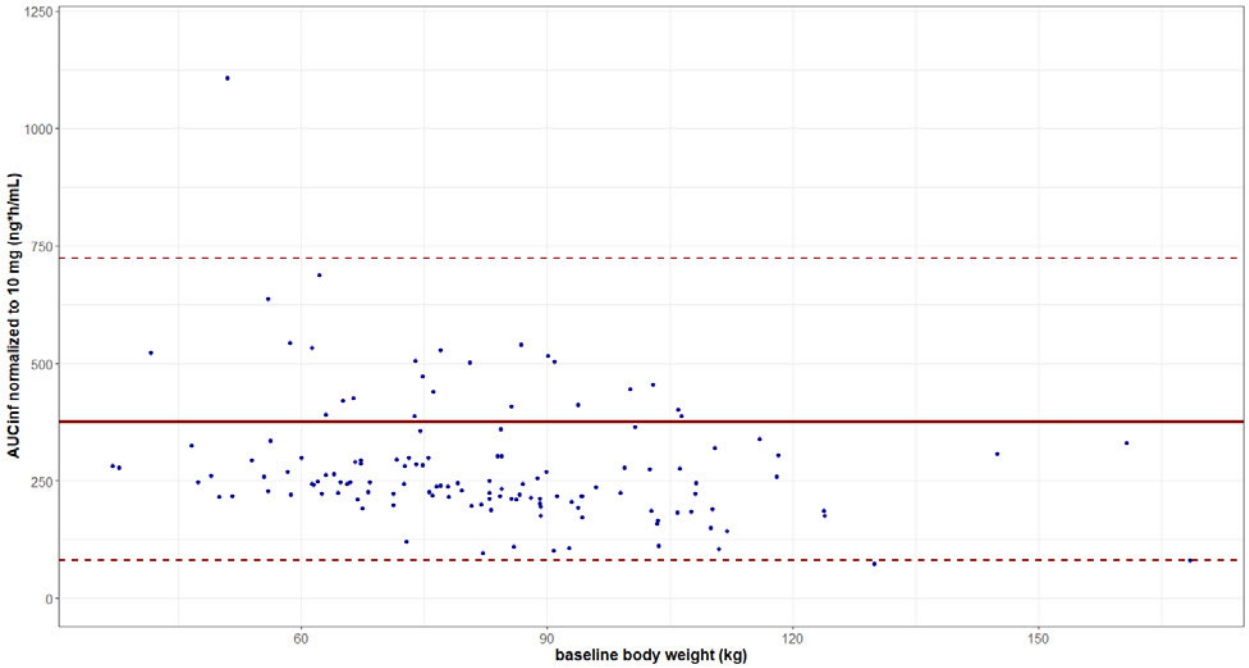
An output dataset with predicted $AUC_{0\text{-inf}}$ normalized to 10 mg for all populations was generated by using the Applicant's full dataset and final popPK model. Then, the predicted $AUC_{0\text{-inf}}$ normalized to 10 mg in pediatric patients with T2DM was plotted over baseline body weight. The median, and 5% and 95% percentile of the $AUC_{0\text{-inf}}$ normalized to 10 mg from adult patients with T2DM were shown as solid and dashed horizontal lines.

NONMEM version VII was used for population PK analysis. The plot was generated with R ggplot2 package.

3.2.5.4 Results

With the exception of two points, all other $AUC_{0\text{-inf}}$ values from pediatric subjects with T2DM fall in 5% and 95% percentiles of the $AUC_{0\text{-inf}}$ in adult subjects with T2DM (Figure 11).

Figure 11. Predicted $AUC_{0\text{-inf}}$ normalized to 10 mg in pediatric T2DM patients over baseline body weight. Solid and dashed red lines are the median, and 5% and 95% percentile of the predicted AUC0-inf normalized to 10 mg in adult T2DM patients.



3.2.5.5 Listing of analyses codes and output files

File Name	Description	Location in \\cdsnas\pharmacometrics\
NONMEM dataset for the final model	pooled_pk_data_paed_adult_t2dm_d168c019.csv	\\CDSESUB1\EVSPROD\nda202293\1346\m5\datasets\d1680c00019-poppk-dapa\misc\02_dapa_d01_data_02_derived-pooled_pk_data_paed_adult_t2dm.csv
NONMEM code for the final model	Final_model-run1019_lst	\\CDSESUB1\EVSPROD\nda202293\1346\m5\datasets\d1680c00019-poppk-dapa\analysis\adam\programs\02_dapa_d02_models_01_final_model-run1019_lst.txt

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