Office of Clinical Pharmacology Review

NDA Number/Supplement Number	204042/043, 204353/046, 205879/023
Link to EDR	**\\CDSESUB1\evsprod\NDA204042\0458**
Submission Date	06/18/2024
Submission type	Pediatric Supplement, Priority Review
Brand Name	INVOKANA®, INVOKAMET®, INVOKAMET® XR
Generic Name	Canagliflozin, canagliflozin + metformin, canagliflozin + metformin extended release
Dosage Form and Strength	Canagliflozin Tablets: 100 mg, 300 mg FDC formulation (INVOKAMET): Oral tablets containing IR canagliflozin at strengths of 50 and 150 mg, in combination with IR metformin HCl at strengths of 500 or 1000 mg. FDC formulation (INVOKAMET XR): Oral tablets containing IR canagliflozin at strengths of 50 and 150 mg, in combination with XR metformin HCl at strengths of 500 or 1000 mg.
Route of Administration	Oral
Proposed Indication	As an adjunct to diet and exercise to improve glycemic control in children and adolescents (≥10 to <18 years) with type 2 diabetes mellitus (T2DM).
Applicant	Janssen Pharmaceuticals Inc
OCP Review Team	Anusha Ande, Ph.D., Abiy Eyakem, Ph.D., Jiajun Liu, PharmD., MSc., Jayabharathi Vaidyanathan, Ph.D.

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1. Executive Summary

Canagliflozin (Invokana), is approved as an adjunct to diet and exercise for improving glycemic control in adults with type 2 diabetes mellitus (T2DM). In the current submission, the Applicant is seeking to expand the indication for the three canagliflozin formulations (INVOKANA®, INVOKAMET®, and INVOKAMET® XR) approved in adults to include pediatric patients with type 2 diabetes who are aged ≥10 to <18 years. The canagliflozin formulation, INVOKANA, consists of immediate-release oral tablets containing canagliflozin at strengths of 100 and 300 mg. The fixed-dose combination formulations of INVOKAMET and INVOKAMET XR consist of oral tablets containing immediate-release canagliflozin at strengths of 50 and 150 mg, in combination with immediate-release metformin at strengths of 500 or 1000 mg (INVOKAMET) or extended-release metformin at strengths of 500 or 1000 mg (INVOKAMET XR), respectively. INVOKAMET dosing is one tablet, twice daily with meals, while INVOKAMET XR dosing is two tablets, once daily with morning meal.

The efficacy and safety of canagliflozin in pediatric patients with T2DM was established with confirmatory evidence from a single placebo-controlled pediatric study (DIA 3018), conducted to fulfill the PMR 2027-2. The dose selection for DIA 3018 study was based on an open label multiple dose PK/PD trial (DIA 1055) in pediatric patients aged ≥10 to <18 years with T2DM, which was a PMR study (2027-1) fulfilled in March 2017. The overall canagliflozin exposures observed in pediatric participants in Study DIA1055 receiving either 100 mg or 300 mg doses are consistent with the exposures observed in the adult populations. Following 14-days daily dosing, both doses of canagliflozin lowered the renal threshold for glucose (RT_G), increased urinary glucose excretion (UGE), and lowered plasma glucose concentrations in a manner that is consistent with the relationship defined in adult participants with T2DM.

Study DIA3018 was a randomized, double-blind, placebo-controlled, 2-arm, parallel-group, multi-center Phase 3 study in participants with T2DM ≥10 and <18 years of age who had inadequate glycemic control (i.e., HbA1c of ≥6.5% to ≤11.0%). The total duration of the study was approximately 52 weeks consisting of a 26-week core double-blind treatment period, followed by a 26-week double-blind extension treatment period. A total of 171 pediatric participants were 1:1 randomized and treated with either canagliflozin 100 mg QD (N=84) or placebo (N=87). Out of 171 participants, 129 (75.4%) were on background metformin (with or without insulin). Of the 84 participants on canagliflozin, 33 participants who did not achieve HbA1c of <7.0% at Week 12 were re-randomized to either continue with 100 mg canagliflozin QD (N=16) or up titrated to 300 mg canagliflozin QD (N=17). The primary efficacy endpoint was the change in HbA1c from baseline to Week 26.

The Applicant proposed a starting dose of 100 mg QD, taken before the first meal of the day with an option to increase the dose to 300 mg once daily in patients tolerating 100 mg once daily who have an eGFR of 60 mL/min/1.73 m^2 or greater and require additional glycemic control. This was based on the results of primary analysis of DIA 3018 study that showed a placebo adjusted mean lowering of HbA1c of -0.76% at Week 26 in the pooled canagliflozin

arms. The focus of this sNDA review was to evaluate if the proposed dosing regimen for canagliflozin was appropriate for treatment of pediatric patients (aged 10 years and older) with T2DM. Because the efficacy data for the canagliflozin treatment was pooled across two doses, we generated longitudinal HbA1c plots over time for 4 subgroups post re-randomization (i.e., placebo, Cana 100 mg responders, Cana 100 mg re-randomized, and Cana 300 mg re-randomized). In patients who did not achieve HbA1c < 7% at Week 12, there was no significant difference in the mean HbA1c levels between the group of patients who remained on 100 mg canagliflozin compared with the group up titrated to 300 mg canagliflozin after randomization at Week 12 suggesting that 300 mg does not provide additional benefit on HbA1c for non-responders. However, the responders who remained on 100 mg canagliflozin continued to have reduced HbA1c levels. 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. The advantage of titrating of dose from 100 mg to 300 mg for responders is unknown. The DIA 3018 study was not designed to assess dose or exposure response for the 100 and 300 mg doses used in this pediatric study. Taking the study limitation (e.g., lack of 300 mg arm from initial randomization, limited sample size) into consideration, the clinical pharmacology team defers the specific dose recommendations to the clinical review team.

Based on the pediatric PK/PD model, for total daily doses of 100 mg and 300 mg of canagliflozin, the exposure-response relationship between canagliflozin plasma concentrations and HbA1c at Week 26 in adult patients with T2DM adequately described the observed HbA1c data in pediatric participants with T2DM (≥10 to <18 years of age). In addition, based on PK/PD simulations, BID and QD canagliflozin dosing regimens at the same total daily dose are predicted to provide similar HbA1c lowering in pediatric patients with T2DM.

Based on the results from DIA 3018 study in the current submission, the Applicant has fulfilled all requirements for PMR 2027-2. The results from the study in this submission are updated to the currently approved package insert.

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 INVOKANA, INVOKAMET, or INVOKAMET XR in pediatric patients 10 years and older. The proposed dosage of 100 mg INVOKANA once daily taken before the first meal of the day is considered acceptable. The review team acknowledges the DIA 3018 study design limitations that preclude a dose or exposure-response assessments in support of the dose increase to 300 mg in pediatric patients tolerating 100 mg INVOKANA, and hence defer to the clinical review team to evaluate the benefit and risk of extending the approval to 300 mg for additional glycemic control.

The proposed labeling claim for similar exposures and PD responses in pediatric patients to be consistent with those found in adult patients with T2DM is acceptable.

Dosing in renal impairment - We consider the benefit risk conclusions in adult patients with reduced renal function i.e., lower response (reduction in HbA1c) and higher risk of renal function related adverse events would be applicable to pediatrics as well. Additionally, Study DIA 3018, did not show improvement on glycemic control upon titrating to 300 mg in non-responders. Therefore, the proposed labeling for pediatric patients with renal impairment similar to that of adults i.e., limiting the maximum recommended dosage to 100 mg once daily in patients with eGFR 30 to <60 mL/min/1.73 m^2 is acceptable.

Canagliflozin BID and QD dosing: Based on exposure-response simulations, canagliflozin dosing regimens at the same total daily dose are predicted to provide similar HbA1c lowering in pediatric patients with T2DM as that in adult patients with T2DM. Therefore, pediatric patients with T2DM who switch from canagliflozin and metformin single agent tablets to FDC of canagliflozin and metformin HCl taken on a BID basis are expected to attain similar glycemic control. Similar dosing and administration for INVOKAMET and INVOKAMET XR in adults and pediatrics is acceptable.

2. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

Regulatory History

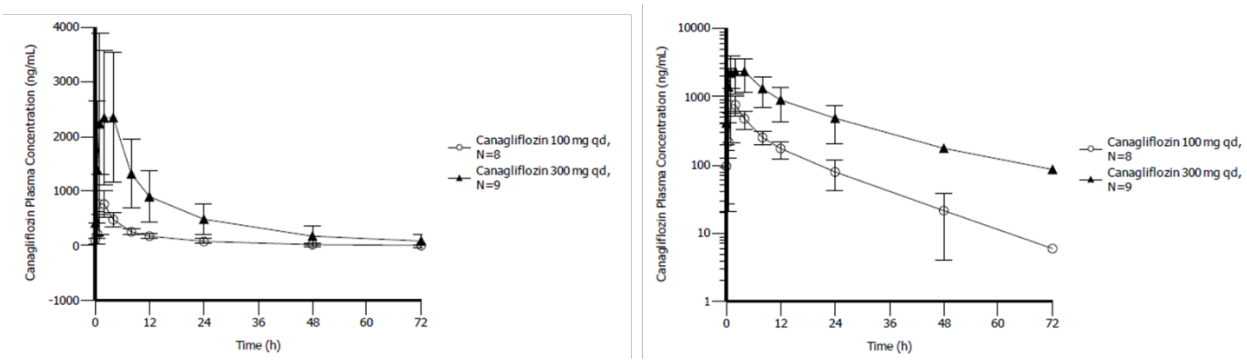
Janssen Pharmaceuticals, Inc., has submitted the supplemental New Drug Applications (sNDAs) to NDA 204042, NDA 204353, and NDA 205879 for the proposed indication of INVOKANA®, INVOKAMET®, and INVOKAMET® XR, respectively, as an adjunct to diet and exercise to improve glycemic control in children and adolescents (≥10 to <18 years) with type 2 diabetes mellitus (T2DM). Reference has been made to PMRs 2027-1 and 2027-2 established under the PREA in the FDA's approval letters for NDA 204042 dated 29 March 2013, NDA 204353 dated 08 August 2014, and NDA 205879 dated 20 September 2016. PMR 2027-1 was considered fulfilled by the FDA on March 20, 2017. Further reference has been made to the WRITTEN REQUEST for pediatric studies of canagliflozin for the purpose of pediatric exclusivity determination issued on 18 March 2014 and subsequently amended on 10 February 2015 (WRITTEN REQUEST - AMENDMENT 1), 15 October 2018 (AMENDMENT 2), 16 July 2020 (AMENDMENT 3), 28 July 2020 (AMENDMENT 4), 12 July 2022 (AMENDMENT 5), and 26 January 2024 (AMENDMENT 6). The sNDAs serve as the Applicant's complete response to the WRITTEN REQUEST for pediatric studies of canagliflozin for the purpose of pediatric exclusivity determination and to fulfill PREA PMR 2027-2. The Applicant discussed the format and content of the planned sNDAs in the Type B pre-sNDA Meeting on 26 January 2024.

Overall, the Applicant proposed to update the labeling of three canagliflozin containing products with the pediatric study results that are collected from the DIA 3018 study by submitting efficacy supplements to NDA 204042 for INVOKANA, NDA 204353 for INVOKAMET®, and NDA 205879 for INVOKAMET® XR.

General Pharmacology and Pharmacokinetic Characteristics

The general pharmacology and pharmacokinetics of canagliflozin in healthy volunteers, adult patients withT2DM, and special populations has been previous reviewed [Refer to NDA 204042 OCP review; Reference ID: 3256450 dated 06 Feb 2013]. Canagliflozin is not studied in children less than 10 years of age because T2D is not a disease expected to affect this younger population. A summary of pediatric information from the post marketing study DIA1055 is summarized below. This study was an open-label, sequential, multiple-dose (14 days of dosing), multicenter study of canagliflozin with 2 dose groups of 8 participants in 100 mg canagliflozin group and 9 participants in 300 mg canagliflozin group with T2DM who were ≥10 to <18 years of age and on a stable regimen of metformin (at a dose of at least 1000 mg per day) for at least 8 weeks before screening.

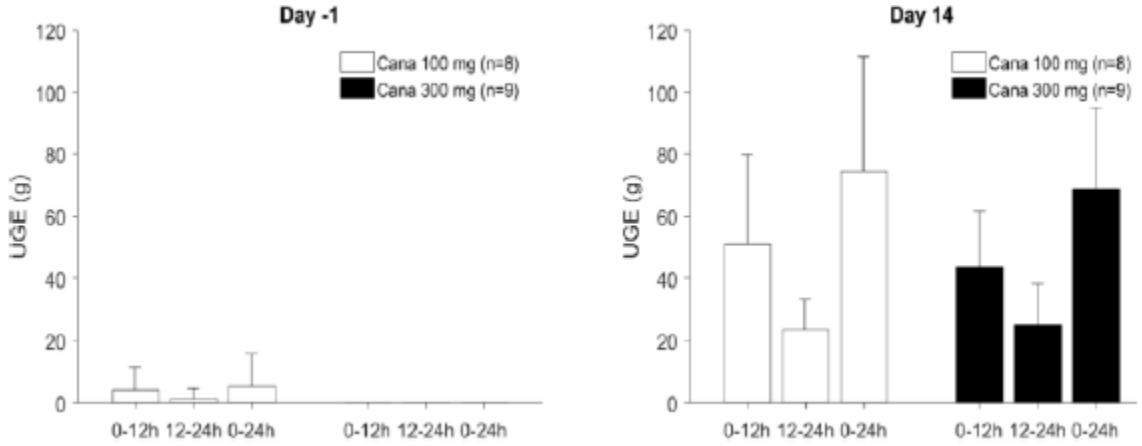
Figure 1: Mean (SD) Linear-Linear and Linear-Log Plasma Canagliflozin Concentration-Time Profiles (Study DIA1055 PK Analysis Set)



Source: Study DIA1055 report Figure 1

Plasma canagliflozin concentrations increased rapidly following canagliflozin administration in both groups. Median tmax for canagliflozin after 14 days of QD 100 mg or 300 mg dose administration was 1.98 and 2.00 hours, respectively (range of 1 to 4 hours) across both groups (**Figure 1**). Mean Cmax and AUCτ values in the 9 pediatric participants with T2DM receiving canagliflozin 300 mg QD were higher than in the 8 pediatric participants with T2DM receiving canagliflozin 100 mg QD. Mean $t_{1/2}$ for canagliflozin after 14 days of QD 100 mg or 300 mg dose administration ranged from 11.3 to 15.2 hours (range of 8.0 to 29.3 hours) across both groups. A cross study comparison of PK exposures (AUC0-24) of canagliflozin for the adult (Study 1023) and pediatric population (Study 1055) was conducted, and the results showed that the PK exposures at 100 and 300 mg dose of canagliflozin were comparable between adult and adolescent patients with T2DM [Refer to sNDA 204042 OCP review; Reference ID: 3973077 dated 16 August 2016].

Figure 2: Mean (SD) UGE on Day-1 and Day 14 for the 100 mg and 300 mg canagliflozin dose groups (Study DIA 1055)



Source: Study DIA1055 report Figure 3

On Day -1, 15 of 17 patients had $UGE_{0\text{-}24h}$ < 0.18 g. On Day 14, mean (SD) $UGE_{0\text{-}24h}$ was 74 (37) g for the 100 mg dose group and 69 (27) g for the 300 mg dose group (**Figure 2**). The mean $UGE_{0\text{-}24h}$ for the 100 mg and 300 mg canagliflozin dose groups of adolescent T2DM patients is about 70 g, whereas the typical values of $UGE_{0\text{-}24h}$ for the 100 mg and 300 mg canagliflozin dose groups of adult T2DM patients is about 100 g. However, the adolescent $UGE_{0\text{-}24h}$ is higher than the $UGE_{0\text{-}24h}$ (45 – 60 g) of healthy normoglycemic adults. The UGE results are consistent with the expectations that the adolescent UGE is between the normoglycemic adult and adults with T2DM.

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?

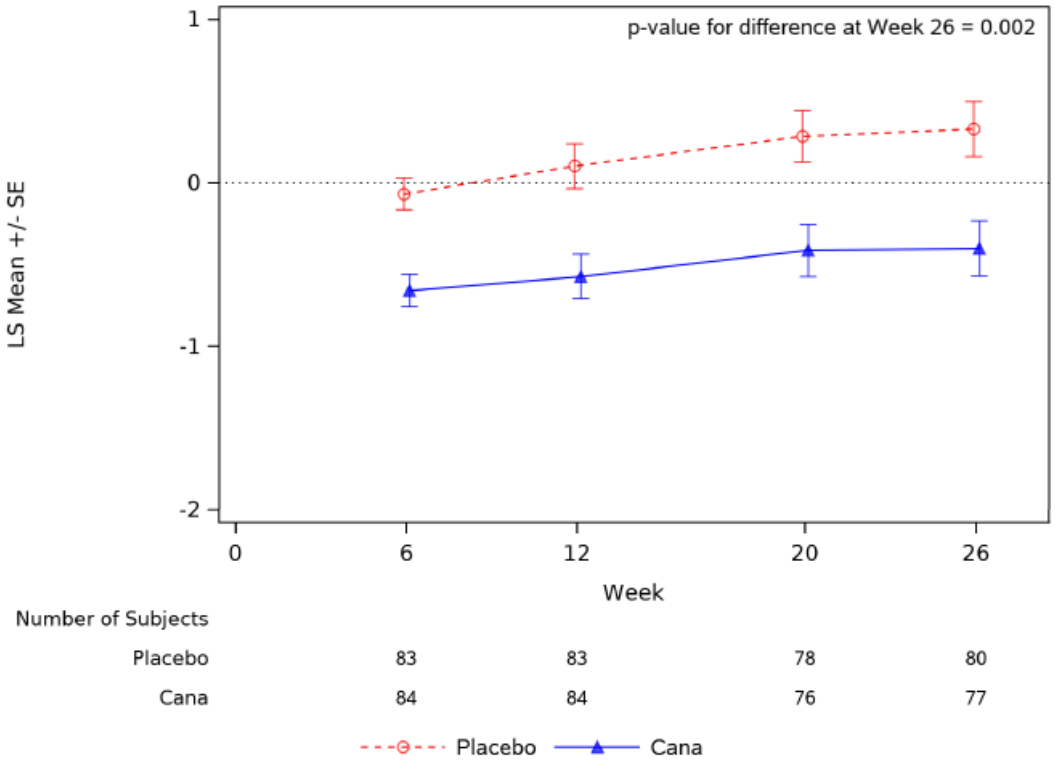
Yes, the clinical pharmacology information in this pediatric supplement based on studies PMR 2027-1 (study DIA 1055) and PMR 2027-2 (study DIA 3018) provided the supportive evidence of effectiveness. Study DIA 1055 evaluated the PK and PD data for canagliflozin in pediatric patients aged ≥10 to <18 years old with T2DM, and the results were compared to the historical data in adult patients with T2DM to support dose selection of the DIA 3018 study. The recommended dosage of canagliflozin as an adjunct to treat T2DM in this pediatric age group is mainly supported by the efficacy, PK and safety data from the DIA 3018 study. Additional simulation data using exposure response models from pooled adult and pediatric data were presented as supportive evidence for efficacy.

<u>Primary efficacy analysis: pooled canagliflozin treatment vs placebo</u>
Study DIA 3018 did not include separate arms for 100 mg and 300 mg of canagliflozin. All patients were randomized initially to the canagliflozin 100 mg (N=84) or placebo (N=87) treatment arms. All patients have background antidiabetic medication (75.4 % on metformin,

with or without insulin). The mean baseline HbA1c (%) was also comparable among two treatment arms (8.3 ± 1.35, 7.8 ± 1.31 in canagliflozin, and placebo treatment arms, respectively). For the canagliflozin 100 mg arm, those who failed to achieve HbA1c < 7% at Week 12, underwent a second randomization at Week 13 to remain on the 100 mg dose or increase to 300 mg dose of canagliflozin. The mean baseline HbA1c (%) was 8.8 ± 1.30 for the 300 mg group (N=17) which was higher than 7.5 ± 1.20 for the 100 mg dose group (N=67; includes both N=51 responders at Week 12 and N= 16 nonresponders randomized to 100 mg at Week 13)

The primary analysis for change from baseline in HbA1c at Week 26 evaluated the pooled treatment effect for canagliflozin 100 and 300 mg. Based on the primary analysis of the primary efficacy endpoint, canagliflozin showed a statistically significant improvement with respect to change from baseline in HbA1c at Week 26 compared to placebo (LS means difference = -0.76% [SE: 0.249; 95% CI: -1.25, -0.27; p=0.002]. A statistically significant improvement in HbA1c was achieved as early as Week 12 and sustained through Week 52 with pooled canagliflozin treatment group vs placebo group (**Figure 3**). In addition, canagliflozin treatment resulted in a statistically significant and clinically meaningful improvement with respect to change from baseline in HbA1c at Week 26 compared to placebo in the subgroup on background metformin (with or without insulin) therapy (in support of INVOKAMET). DIA 3018 study excluded the use of metformin XR in participants on background antihyperglycemic (AHA) therapy. Participants who were on metformin XR prior to screening were instructed to switch to metformin IR. With the expected similarity in efficacy of metformin IR versus metformin XR for adults, the data that supports the efficacy of INVOKAMET in children and adolescents (≥10 to <18 years) with T2DM can be extrapolated to support the efficacy for INVOKAMET XR.

Figure 3: LS Mean Change from Baseline in HbA1c (%) Over Time (Up to Week 26) Using Mixed Model for Repeated Measures (MMRM)) - All Subjects; Full Analysis Set (Study JNJ28431754- DIA3018)



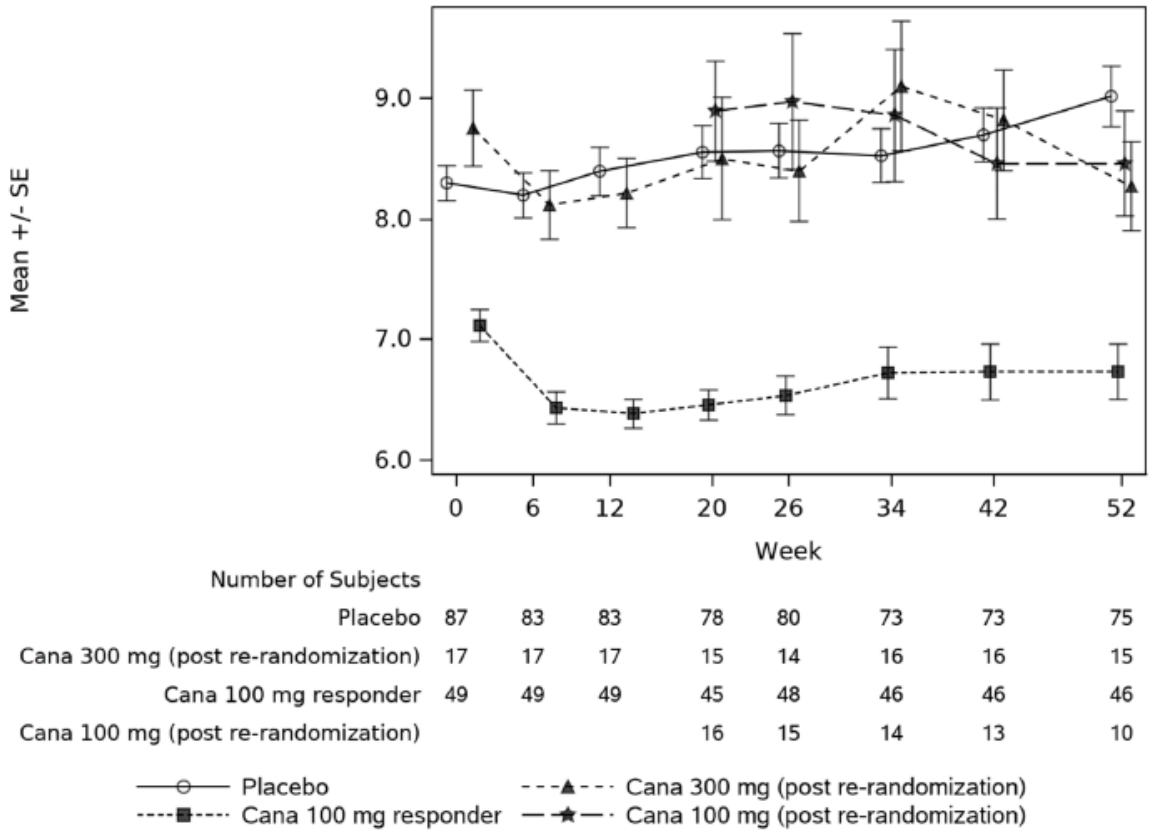
Source: Study DIA3018 report Figure 2

As a secondary efficacy endpoint, the LS mean change in fasting plasma glucose (FPG) from baseline, which was computed based on an LOCF approach, was found to be statistically significantly greater in the canagliflozin group compared to the placebo group at Week 26 and Week 52. The difference in LS means at Week 26 were: -26.9 (SE: 8.84; 95% CI: -44.3, -9.4; p = 0.003), and at Week 52 were -35.6 (SE: 9.05; 95% CI: -53.5, -17.8; p: <0.001).

Exploratory Analyses based on Longitudinal HbA1c Plots

Figure 4 illustrates longitudinal HbA1c levels over time based on observed data for 3 subgroups of interest: placebo, Cana 100 mg (responders who continued to receive 100 mg after Week 12), and Cana 100 mg (non-responders who were re-randomized to 300 mg after Week 12) from Week 0 to Week 12 and 4 subgroups post re-randomization (i.e., placebo, Cana 100 mg responders, Cana 100 mg re-randomized, and Cana 300 mg re-randomized).

Figure 4: Mean and SE for observed HbA1c levels over time Full Analysis Set (Study JNJ28431754-DIA3018)



At Week 13, the non-responders (N=33 of 84 treated) in canagliflozin 100 mg arm (who failed to achieve HbA1c <7.0% at Week 12, indicating insufficient glycemic control) were dose up-titrated to 300 mg (N=17) or remained at 100 mg (N=16) 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 canagliflozin 100 mg, as shown in **Figure 4**. However, the up titration of dose to 300 mg in non-responders did not reveal a dose response, as the reduction in HbA1c levels is not observed in the 300 mg group compared to the 100 mg non-responder group. Overall, due to the study design where a small sample size of non-responders was randomized to 100 and 300 mg, confounded by differences in baseline values for HbA1c, a clear dose-response for 100 mg and 300 mg could not be identified for canagliflozin in this pediatric population.

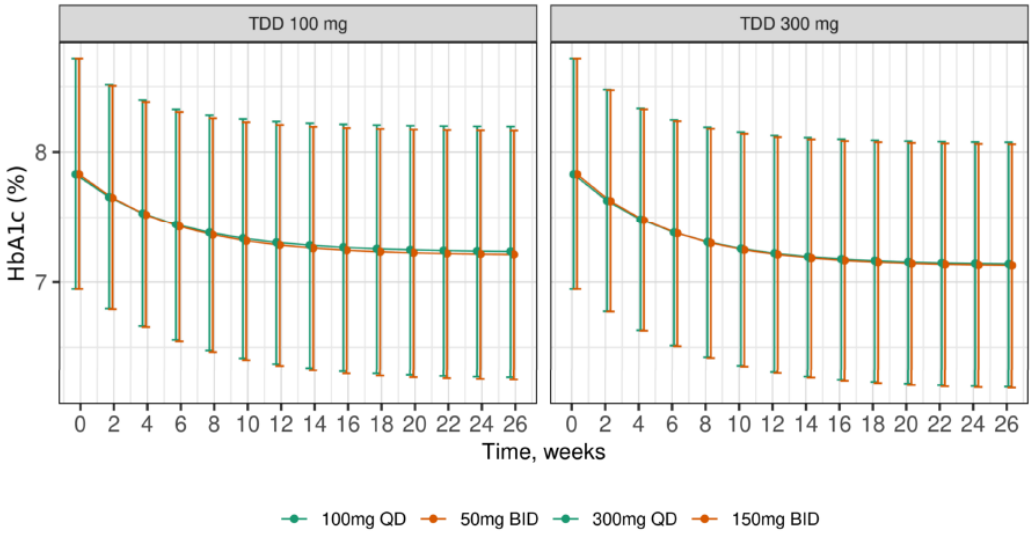
2.3.2 Is the proposed dosing regimen appropriate for pediatric patients with type 2 diabetes that are 10 years and older?

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 DIA 3018 study, the canagliflozin treatment (pooled of 100 and 300 mg data) was superior to placebo and achieved a statistically significant decrease from baseline in HbA1c in the overall study population as well

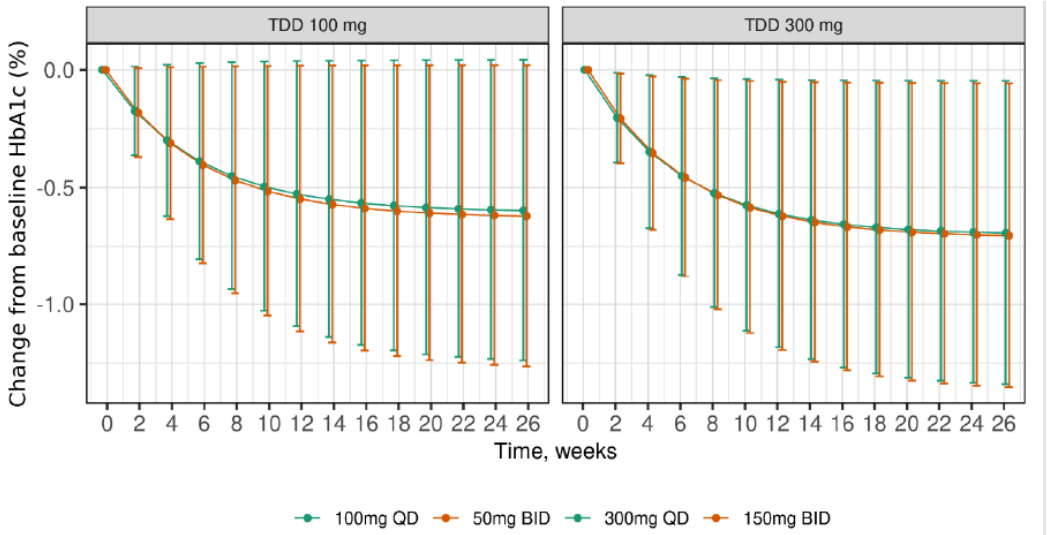
as in the subgroup on background metformin (with or without insulin) which was sustained up to Week 52 (Refer to response to question 2.3.1). An improvement in glycemic control was similarly observed, including a significant improvement in FPG with canagliflozin at Week 26 which was sustained up to Week 52.

Simulations based on PopPK analysis demonstrated that in pediatric participants with T2DM, the predicted $AUC2_{4h}$ at steady state was comparable following BID or QD dosing of canagliflozin at the same total daily dose of 100 mg or 300 mg (Figure 13). This is in line with Phase 1 study observations in adults (Study DIA1032) and supports the use of canagliflozin in combination with metformin (IR) in a BID regimen in pediatric patients with T2DM. The PK/PD analysis indicated that the exposure-response relationship estimated between canagliflozin plasma concentrations and HbA1c in adult patients with T2DM adequately described the observed HbA1c data in pediatric participants with T2DM (≥10 to <18 years of age) and that BID and QD canagliflozin dosing regimens at the same total daily dose are predicted to provide similar HbA1c lowering in pediatric patients with T2DM as that in adult patients with T2DM (**Figure 5**). Therefore, pediatric patients with T2DM who switch from canagliflozin and metformin single agent tablets to FDC of canagliflozin and metformin HCl taken on a BID basis are expected to attain similar glycemic control. Overall, these results indicate that no dose adjustment of canagliflozin as a single agent (INVOKANA) or as an FDC with metformin HCl (INVOKAMET or INVOKAMET XR) is required to obtain the same canagliflozin plasma exposures in pediatric as in adult patients with T2DM.

Figure 5: Simulated HbA1c (top panels) and Change from Baseline HbA1c (bottom panels) Following Oral Administration of Canagliflozin at 50 mg BID, 100 mg QD, 150 mg BID, and 300 mg QD in Pediatric T2DM Patients



Dots represent mean HbA1c at each time point, while error bars represent mean ± SD; TDD of 100 mg (left panel: 50 mg BID, 100 mg QD) and TDD of 300 mg (right panel: 150 mg BID, 300 mg QD).



Dots represent mean change from baseline HbA1c at each time point, while error bars represent mean ± SD; TDD of 100 mg (left panel: 50 mg BID, 100 mg QD) and TDD of 300 mg (right panel: 150 mg BID, 300 mg QD).

Source: PK/PD Model Update Report; Pages 41-42

3. Appendices

3.1 Summary of Bioanalytical Method Validation and Performance

The partial validation of the LC-MS/MS method for the determination of canagliflozin in human EDTA plasma samples from DIA 3018 study, transferred to another LC system (b) (4) was performed and the results demonstrate that the validated method is suitable for the determination of canagliflozin in human plasma samples. In addition, the results demonstrate long-term frozen stability in human EDTA plasma samples at -20°C for 1431 days for canagliflozin. An overview of the validation parameters for the validated method is provided in below table.

(b) (4) (Mod5.3.1.4/BA13665)	JNJ-28431754
Matrix	Human EDTA Plasma
Validated concentration range	5.00 – 5000 ng/mL
Inter-run accuracy (%)	NA
Inter-run precision (%CV)	NA
Intra-run accuracy (%)	−3.9 to 1.9
Intra-run precision (%CV)	≤5.2
Intra-run accuracy (%)	NA
Intra-run precision (%CV)	NA
Incurred sample reproducibility	Not tested (for the purpose of the method upgrade)
Selectivity and matrix	6 lots tested Selectivity within criteria Matrix effect bias: −3.3%
Stability in blood	Not tested (for the purpose of the method upgrade)
Stability in plasma	Demonstrated for at least 1,431 days at −20°C
Processed sample stability	Not tested (for the purpose of the method upgrade)
Hemolysis effect	1 lot tested Bias: 2.2% to −10.2%
Lipemic effect	1 lot tested Bias: −3.3% to −4.7%
Stability in stock solution	Not tested (for the purpose of the method upgrade)
Cross-validation with previous assay PBRL-RD-1040	3 QC levels, 3 replicates, within acceptance criteria

Abbreviations: CV=coefficient of variation; EDTA=ethylenediaminetetraacetic acid; NA=not available; QC=quality control.

3.2. Pharmacometrics Review

3.2.1. Population PK analysis

3.2.1.1. Review Summary

The Applicant conducted a population pharmacokinetic (PopPK) modeling and simulation analysis of canagliflozin for T2DM patients of 10 to less than 18 years of age. Previously, a PopPK model for canagliflozin was developed using pooled PK data from healthy adult participants and adult patients with T2DM (refer to NDA 204042 Office of Clinical Pharmacology Review; DARRTS link; reference ID, 3256450). In the current submission, the Applicant seeks to expand canagliflozin indication (NDA 204042 S-41, 204353 S-45, and 205879 S-22 for canagliflozin, canagliflozin and metformin, and canagliflozin and metformin extended release

tablets, respectively) based on the results of the clinical studies DIA1055 (a Phase 1, open-label, sequential, multiple-dose, multicenter study) and DIA3018 (a Phase 3, randomized, double-blind, placebo-controlled, parallel-group, multicenter study) to children and adolescents who are ≥10 to <18 years of age with T2DM.

The PK of canagliflozin is characterized by a 2-compartment disposition model with a sequential zero- and first-order absorption after a lag time and first-order elimination structural PopPK model. The statistically significant covariates are age, sex, body weight, estimated glomerular filtration rate (eGFR), over-encapsulation and total daily dose; however, the effects of these covariate were not considered clinically relevant for dose adjustment (refer to Applicant's PopPK Model Report; Page 17). Briefly, the Applicant had initially applied the previously developed adult PopPK model to externally validate the PK data obtained from the DIA1055 and DIA3018 studies by fixing all the parameter estimates to the adult model estimates. Subsequently, a model update was deemed necessary and was carried out by removing the covariates of the adult model (age on *Vc/F* (apparent volume of distribution of the central compartment), eGFR on ke (elimination rate constant), BMI (body mass index) on ka (absorption rate constant) and lag time, body weight on apparent central volume of distribution or *Vc/F*, sex on *Vc/F* and total daily dose on elimination rate constant or *ke*) one at a time. In the final PopPK model, the covariate impacts of sex and body weight on *Vc/F*, total daily dose on *ke*, and over-encapsulation (i.e., formulation) on lag time were retained, while age on *Vc/F*, eGFR on *ke*, and BMI on *ka* and lag time from the original adult model were removed.

The approved adult dosage for canagliflozin and metformin (NDA 204353) is twice daily with meals. To support bridging of the canagliflozin component (in canagliflozin and metformin) from 100 mg once daily (QD) to 50 mg twice daily (BID) and from 300 mg QD to 150 mg BID in the target pediatric patients, the final PopPK model was used to simulate steady-state exposure metrics (AUC24h and Cmax). The simulated canagliflozin exposure metrics were comparable between QD and BID regimens (50 mg BID vs. 100 mg QD; 150 mg BID vs. 300 mg QD; same total daily doses of 100mg and 300mg, respectively).

Overall, the review team considers the final PopPK model acceptable in: 1) characterizing the canagliflozin PK in pediatric patients of ≥10 to <18 years of age with T2DM, 2) deriving Bayesian posterior predictions for exposure comparisons between the target pediatric patients and adult patients, and 3) simulating exposures to support bridging from once daily to twice daily dose regimens in pediatric patients. Based on the simulation results, the review team agrees with the updated labeling language as summarized in the table below. Collectively, the pharmacometric assessment supports the indication expansion to pediatric patients of 10 to less than 18 years of age with T2DM.

3.2.1.2. Summary and Assessment of Population PK Analysis

The table below summarizes the studies and data included in the pharmacometric analysis, the Applicant's the primary objectives of the analysis, and model development processes. The table also outlines the model evaluations and conclusions based on model goodness-of-fit (GOF),

prediction-corrected Visual Predictive Checks (pc-VPCs), parameter-covariate relationships and simulations based on the final PopPK model. The corresponding assessments of the review team are provided.

General Information			
Objectives		• To characterize the canagliflozin PK in pediatric T2DM patients (≥10 to <18 years) who participated in studies DIA1055 and DIA3018. • To estimate the individual PopPK parameters and individual exposure metrics, eg, AUC24h of canagliflozin at steady state in pediatric T2DM patients, and to compare with those estimated in adult T2DM patients. • To compare canagliflozin exposure metrics (steady-state AUC24h and Cmax) for QD and BID dose regimens in pediatric T2DM patients and adult T2DM patients using a PopPK simulation approach, to bridge from QD to BID dosing of canagliflozin to support canagliflozin and metformin tablet in pediatric T2DM patients.	
Study Included		**Table 1**	
Dose(s) Included		**Table 1**	
Population Characteristics	General	**Table 2**	
	Pediatrics (if any)	Yes, T2DM patients (≥10 to <18 years).	
No. of Patients, PK Samples, and BLQ		**Table 1**	
Sampling Schedule	Rich Sampling	**Table 1**	
	In ITT Population	**Table 1**	
Covariates Evaluated	Static	**Figure 6**	
	Time-varying	**Figure 6**	
Final Model		**Applicant's Description** **Summary** • The selected final model: • Two-compartment disposition model with	**Review Team Assessment** Acceptable. The review team agrees with the selected final model. Two-compartment distribution model with

	first-order elimination and a sequential zero- and first-order absorption with lag time. Model parameters were fixed to the previously developed adult PopPK parameter estimates except for the Phase 1 and Phase 2/3 residual error variances, which were re-estimated based on the pediatric data. **(Figure 7).** • Inter-subject variability (IIV) was quantified on the model parameters for *Vc*/*F*, *ke*, *k32* (distribution rate constant from the peripheral to the central compartment), *ka*, and *Tlag* (lag time), assuming a lognormal distribution. The *CL*/*F* (apparent clearance) was derived from the estimated apparent volume of distribution and the estimated *ke* through *CL*/*F*=*Vc*/*F***ke*. **(PopPK Model Update Report; Page 23)** • An additive error model was used to quantify the RUV (residual unexplained variability) on the log-transformed plasma concentration scale, assuming different variances for rich and sparse PK data	first-order elimination and a sequential zero- and first-order absorption after a lag time adequately described the data **(Figure 7)**. The review team noted that model parameters were fixed to the previously developed adult PopPK parameter estimates except for residual error variances. The team requested clarifications on this, and the Applicant responded that the parameter estimates are unlikely to be significantly different given the number of pediatric T2DM patients enrolled and analyzed in the current studies. ETA terms were characterized on Vc/F, ke, k32 and ka. The residual error model was characterized by an additive error model on the log-transformed plasma concentration and the assumption of different variances for rich and sparse PK data are reasonable. The review team also agrees with the effects of body weight, sex, over-encapsulation, and total daily dose being retained as covariates in the pediatric PopPK model.

	(PopPK Model Update Report; Page 23). • The effects of body weight, sex, over-encapsulation, and total daily dose were identified as covariates in the pediatric PopPK model **(PopPK Model Update Report; Page 51).**	
Software and Version	NONMEM 7, Version 7.4 and higher (ICON Development Solutions; Ellicott City, Maryland, USA) and R 3.6.2 or higher (R Foundation for Statistical Computing, Vienna, Austria) **(PopPK Model Update Report; Page 29).**	Acceptable.
Estimation Algorithm	First Order Conditional Estimation with Interaction (FOCE-I) **(PopPK Model Update Report; Page 29).**	Acceptable.
Model Structure	Canagliflozin PK data was characterized by a 2-compartment disposition model with first order elimination and lag time **(Figure 7)**.	Acceptable. The previous structural model developed for adult data was adopted with no updates on the structural model. The review team agrees that the PopPK model structure for canagliflozin adequately described the data **(Figure 7)**.
Model Parameter Estimates	**Table 4**	Acceptable. The review team verified the model parameter estimates as shown in **Table 4**.
Uncertainty and Variability (RSE, IIV, Shrinkage, Bootstrap)	Adequate precision was obtained for the estimated residual error variances as measured by RSEs below 15%. In addition, the shrinkages of the random effects on *Vc/F*, *ke*,	After reproducing the model, the review team agrees that uncertainty measure of most estimated model parameters was within acceptable range (<

	k32, *ka*, and *Tlag* were high (>39%), which can be attributed to the sparse sampling scheme with mainly trough samples of study DIA3018 **(PopPK Model Update Report; Page 36 & Table 4).**	15%). The review team also noted that the ETA-shrinkage values for the model parameters were high (39% to 70%). This suggests that the individual empirical Bayes estimates of the model parameters may be less reliable as they tend to fold towards the population estimates **(Table 4)**. Careful consideration should be taken when interpreting the model parameter estimates for both pediatric and adult populations.
BLQ for Parameter Accuracy	Canagliflozin plasma concentrations below the quantification limit (BQL) were kept as commented out and were excluded from the analysis, as was done in the previous PopPK model. The percentage of PK samples below LLOQ was 15.1%. BQL samples with time since last dose of <28 hours were considered implausible given the elimination half-life of canagliflozin (10.6 and 13.1 hours for 100 and 300 mg, respectively) and were therefore excluded from the PopPK analysis. After omitting these BQL samples, the percentage of BQL samples were <10% and therefore these samples were also removed from the PopPK analysis (M1 method) **(PopPK Model Update Report; Page 21 & Table 3).**	Based on the M1 method, the review team agrees with censoring the BLQ PK observations with time since last dose of <28 hours given the elimination half-life of canagliflozin (10.6 and 13.1 hours for 100 mg and 300 mg, respectively). Of note, the number of the remaining BLQ observations after the omission of the above-mentioned BLQ samples were below the acceptable 10% of the total PK samples **(Table 3)**.

GOF, VPC	Based on the population- and individual-level GOF plots **(Figure 8**Figure 8**)**, the pooled data from studies DIA1055 and DIA3018 appear to be well described both at a population and at an individual level, with no major trends in the residuals **(PopPK Model Update Report; Page 29)**. Furthermore, the predictive performance of the model was evaluated using a pcVPC based on 1000 replicates **(Figure 9)**. Based on the pcVPC plots, the model appears to adequately capture the central tendency and the variability of the data from studies DIA1055 and DIA3018, as attested by the agreement between the observed 10^{th}, 50^{th} , and 90^{th} percentiles **(PopPK Model Update Report; Page 37).**	Upon reproducing similar GOF plots, the review team agrees that the GOFs plots show reasonable agreement between predicted and observed concentrations both at population and individual level. The lines of identity and unity of the observed vs predicted concentrations generally align and divide the data nearly in equal parts. The residual plots do not also show model bias or misspecification **(Figure 8**Figure 8**)**. Further, the review team agrees that the central tendency and the variability between the studies DIA1055 and DIA3018 based on the evidence that the 10^{th}, 50^{th} and 90^{th} percentiles of observed canagliflozin concentration-time profiles were reasonably captured by the model **(Figure 9)**.
Significant Covariates and Clinical Relevance	In the previous adults final PopPK model, statistically significant covariates were sex, age, and body weight on *Vc/F*, BMI on *ka,* BMI and over-encapsulation (over-encapsulated versus non-encapsulated tablets) on *Tlag*, and eGFR and total daily dose on *ke*. The covariate effects were deemed not clinically relevant and therefore no dose adjustment based on those covariates was warranted **(PopPK Model Update Report; Page 23)**. In the final pediatric	The review team verified the covariates (identified in the previous adult model) that were tested with the current pediatric PK data. Sex and body weight on *Vc/F*, total daily dose on *ke*, and over-encapsulation on lag time improved the model-fit, and therefore, they were retained in the model while age on *Vc/F*, eGFR on *ke*, and BMI on *ka* and lag time were removed. In the previously developed adult PopPK

	PopPK model, the adult model was updated such that covariate relationships of sex and body weight on *Vc/F*, total daily dose on *ke*, and over-encapsulation on lag time were retained, while age on *Vc/F*, eGFR on *ke*, and BMI on *ka* and lag time were removed **(PopPK Model Update Report; Page 36)**. Based on a graphical parameter-covariate relationship analysis, no additional covariate effects were detected. These diagnostics based on EBEs should be interpreted with caution, because shrinkage was high (>39%) for all random effects **(Figure 10 & Figure 11)**.	model for canagliflozin, the Applicant concluded that exposure changes based on statistically significant covariates were not clinically relevant, and therefore, no dose adjustment was warranted **(PopPK Model Update Report; Page 23)**. Review team agrees with this assessment. The review team also agrees that no additional covariate effects were identified **(Figure 10 & Figure 11)**.
Analysis Based on Simulation	Using the final pediatric PopPK model, to support bridging from QD to BID dosing of canagliflozin for the use of canagliflozin and metformin canagliflozin in pediatric T2DM patients, exposure metrics (AUC24h and Cmax) at steady state were simulated for QD and BID dose regimens in pediatric T2DM patients and compared with those simulated in adult T2DM patients based on the previous PopPK model. PK profiles of N=1,000 female and N=1,000 male virtual T2DM patients were generated, accounting for IIV and RUV **(PopPK Model Update Report; Page 46)**. The simulated concentration-time profiles at steady state following 50 mg BID, 100 mg QD, 150 mg BID,	After reproducing the simulations, the review team agrees that the simulated steady-state concentration-time profiles and derived exposures (i.e, AUC and Cmax) were similar between pediatric and adult T2DM patients for canagliflozin at the simulated dose regimens of the same total daily doses (50mg BID vs.100mg QD; 150mg BID vs. 300mg QD) **(Figure 12 and Figure 13)**. The simulation results support the bridging of QD to BID dosing of canagliflozin (in canagliflozin and metformin) for pediatric patients with T2DM.

	and 300 mg QD canagliflozin administration demonstrate that within the same regimen, there is good correspondence in exposure between pediatric and adult participants with T2DM **(Figure 5)**. Furthermore, the summary statistics for AUC24h and Cmax at steady state following total daily doses of 100 mg and 300 mg of canagliflozin, are presented graphically in a boxplot in **Figure 13**.	
Labeling Language		Acceptable.
12.3 PK	**Pediatric Patients** The pharmacokinetics and pharmacodynamics of canagliflozin were investigated in pediatric patients aged 10 years and older with type 2 diabetes mellitus. Oral administration of canagliflozin at 100 mg and 300 mg resulted in exposures and responses consistent with those found in adult patients.	Based on the simulation results, the review team agrees with the proposed languages in the labeling.

Table 1. Summary of Studies Included in the PopPK Analysis

Study No., Phase	Study Title and Brief Description of Design	Dose (mg), Regimen, Route of Administration, Formulation	No. of Participants With PK Data Available	PK Sampling
28431754DIA1055 Phase 1	**Phase 1, multiple dose PK in pediatric T2DM patients** Open-Label, Multicenter, Multiple Oral Dose Study to Evaluate the Pharmacokinetics, Pharmacodynamics and Safety of Canagliflozin in Older Children and Adolescents ≥10 to <18 years of age with Type 2 Diabetes Mellitus on a Stable Dose of Metformin	Multiple dose 100 mg and 300 mg canagliflozin QD for 14 days	17	Predose, 0.5, 1, 2, 4, 8, 12, 24, 48, and 72 hours postdose on Day 14
28431754DIA3018 Phase 3	**Phase 3, multiple dose efficacy and safety in pediatric T2DM patients** A Randomized, Multicenter, Double-Blind, Parallel-Group, Placebo-Controlled Study to Investigate the Efficacy and Safety of Canagliflozin in Children and Adolescents (≥10 to <18 years) with Type 2 Diabetes Mellitus	**No up-titration:** 100 mg canagliflozin QD for 52 weeks; **Up-titration:** 100 mg canagliflozin QD for 12 weeks followed by 300 mg canagliflozin QD for 40 weeks	84	Plasma trough concentrations at Week 12, Week 26, and Week 52 (end of treatment) or early withdrawal

Source: PopPK Model Update Report; Page 20

Table 2. Descriptive Statistics of Baseline Categorical and Continuous Covariates for Pediatric Participants (DIA1055 and DIA3018) and Adult Participants Included in the PopPK Analysis Datasets

		DIA1055	DIA3018	Total pediatrics	Diabetic adults[b]	Total adults[b]
Analysis set, n		17	73	90	1219	1616
Total daily dose, n (%)	25 mg				12 (1)	12 (0.7)
	50 mg				69 (5.7)	164 (10.1)
	100 mg	8 (47.1)	61 (83.6)	69 (76.7)	506 (41.5)	610 (37.4)
	200 mg				69 (5.7)	148 (9.1)
	300 mg	9 (52.9)	12 (16.4)[a]	21 (23.3)	480 (39.4)	596 (36.6)
	400 mg				13 (1.1)	13 (0.8)
	600 mg				70 (5.7)	70 (4.3)
	800 mg				0 (0)	6 (0.4)
	1200 mg				0 (0)	6 (0.4)
	1600 mg				0 (0)	5 (0.3)
Sex, n (%)	Male	5 (29.4)	24 (32.9)	29 (32.2)	647 (53.1)	769 (47.6)
	Female	12 (70.6)	49 (67.1)	61 (67.8)	572 (46.9)	847 (52.4)
Race, n (%)	White, Not Hispanic or Latino	2 (11.8)	13 (17.8)	15 (16.7)	676 (55.5)	942 (58.3)
	Black, of African heritage or African American	12 (70.6)	6 (8.2)	18 (20)	52 (4.3)	102 (6.3)
	White, Hispanic, or Latino	0 (0)	20 (27.4)	20 (22.2)	154 (12.6)	203 (12.6)
	Asian	0 (0)	30 (41.1)	30 (33.3)	226 (18.5)	245 (15.2)
	Native Hawaiian or Other Pacific Islander	0 (0)	0 (0)	0 (0)	1 (0.1)	2 (0.1)
	American Indian or Alaskan Native	0 (0)	4 (5.5)	4 (4.4)	2 (0.2)	2 (0.1)
	Other	3 (17.6)	0 (0)	3 (3.3)	108 (8.9)	120 (7.4)
Over-encapsulation, n (%)	Non-encapsulated tablet	0 (0)	0 (0)	0 (0)	51 (4.2)	174 (10.8)
	Over-encapsulated tablet	17 (100)	73 (100)	90 (100)	1168 (95.8)	1442 (89.2)
Age (years)	Mean (SD)	14.6 (1.80)	14.1 (1.95)	14.2 (1.92)	56.6 (10.3)	53.4 (12.3)
	Median	15.0	15.0	15.0	57.0	55.0
	Range	(11.0; 17.0)	(10.0; 17.0)	(10.0; 17.0)	(22.0; 90.0)	(18.0; 90.0)
Body weight (kg)	Mean (SD)	108 (34.1)	81.9 (25.1)	86.8 (28.6)	86.9 (19.1)	88.0 (19.6)
	Median	116	75.1	79.5	85.0	86.0
	Range	(48.2; 170)	(44.8; 161)	(44.8; 170)	(42.5; 167)	(42.5; 167)
BMI (kg/m^2)	Mean (SD)	38.3 (9.25)	30.9 (7.37)	32.3 (8.22)	31.4 (5.56)	31.7 (6.09)
	Median	41.4	29.9	30.7	30.8	31.1
	Range	(17.9; 54.4)	(19.0; 50.4)	(17.9; 54.4)	(18.4; 54.7)	(18.0; 54.7)
eGFR ($mL/min/1.73m^2$)	Mean (SD)	147 (36.4)	163 (33.1)	160 (34.1)	86.6 (27.3)	86.3 (27.0)
	Median	142	165	160	87.0	87.0
	Range	(70.3; 222)	(104; 277)	(70.3; 277)	(25.0; 194)	(9.00; 194)

[a] After 12 weeks of 100 mg and re-randomization, participants were up-titrated to 300 mg.[7]

[b] Adult participants included in the previously developed PopPK model for canagliflozin[1]

eGFR - estimated glomerular filtration rate.

Source: PopPK Model Update Report; Page 68-9

Table 3. Summary of Dataset Exclusion in the PopPK Dataset

Reasons	Samples Affected	Samples Remaining	Participants Affected	Participants Remaining
Study 1055				
All Samples		168		17
BQL	3	165	3	17
Not_analyzed	2	163	1	17
Study 3018				
All Samples		235		84
BQL	50	185	32	77
BQL.Previous_Dose_Date/Time_Incomplete	4	181	1	76
BQL.Sample_Date/Time_Incomplete	4	177	4	75
Not_analyzed	1	176	1	75
Not_analyzed.Sample_Date/Time_Incomplete	8	168	7	73
Outlier for patient 100330	1	167	1	73
Total number of samples				
Before exclusion		403		101
Excluded		73		11
Included in the PopPK analysis dataset		330		90

Source: PopPK Model Update Report; Page 22

Table 4.Parameter Estimates of the Final Pediatric PopPK Model for Canagliflozin

Parameter	Population Mean Estimate	RSE (%)	IIV (CV%)	Shrinkage (%)
V_c/F (L) (males)	99.3 FIX		14.6 FIX	70.1
k_e (h^{-1})	0.145 FIX		23.1 FIX	39.1
k_a (h^{-1})	3.68 FIX		188 FIX	51.6
T_{lag} (h) (non-encaps. tablets)	0.147 FIX		93.6 FIX	65.7
D_1 (h)	0.604 FIX			
k_{23} (h^{-1})	0.101 FIX			
k_{32} (h^{-1})	0.0856 FIX		36.2 FIX	65.1
V_c/F (L) (females)	82.6 FIX			
T_{lag} (h) (over-encaps. tablets)	0.262 FIX			
Body weight on V_c/F	0.583 FIX			
Total daily dose on k_e	-0.0631 FIX			
Residual error (SD %) Phase 1 pediatric	22.7	13.4		
Residual error (SD %) Phase 2 and 3 pediatric	114	9.12		

FIX = model parameters, including covariate and random effects, were fixed to the estimates obtained from the adult PopPK model[1]

CV% calculated as $\left(\sqrt{\exp(\omega^2) - 1}\right) * 100$

Source: PopPK Model Update Report; Page 37

Table 5. Summary statistics of estimated AUC0-24h (h.ng/mL) steady state after 100mg QD and 300mg QD doses of canagliflozin in pediatric and adult T2DM patients, stratified by sex.

Dose (mg) QD	Sex	N[b]	Mean (SD)	Median	10th percentile	90th percentile
Pediatric						
100	Male	24	6574 (1774)	6353	4858	9072
	Female	54	8397 (2155)	8154	6143	10355
300	Male	8	22480 (7858)	19013	15501	32336
	Female	10	29930 (11839)	25502	21681	50845
Adult[a]						
100	Male	269	7183 (2146)	6684	4933	9975
	Female	237	8984 (2770)	8522	6048	12425
300	Male	254	22954 (6932)	21374	15768	32555
	Female	226	28391 (8111)	27408	19029	39071

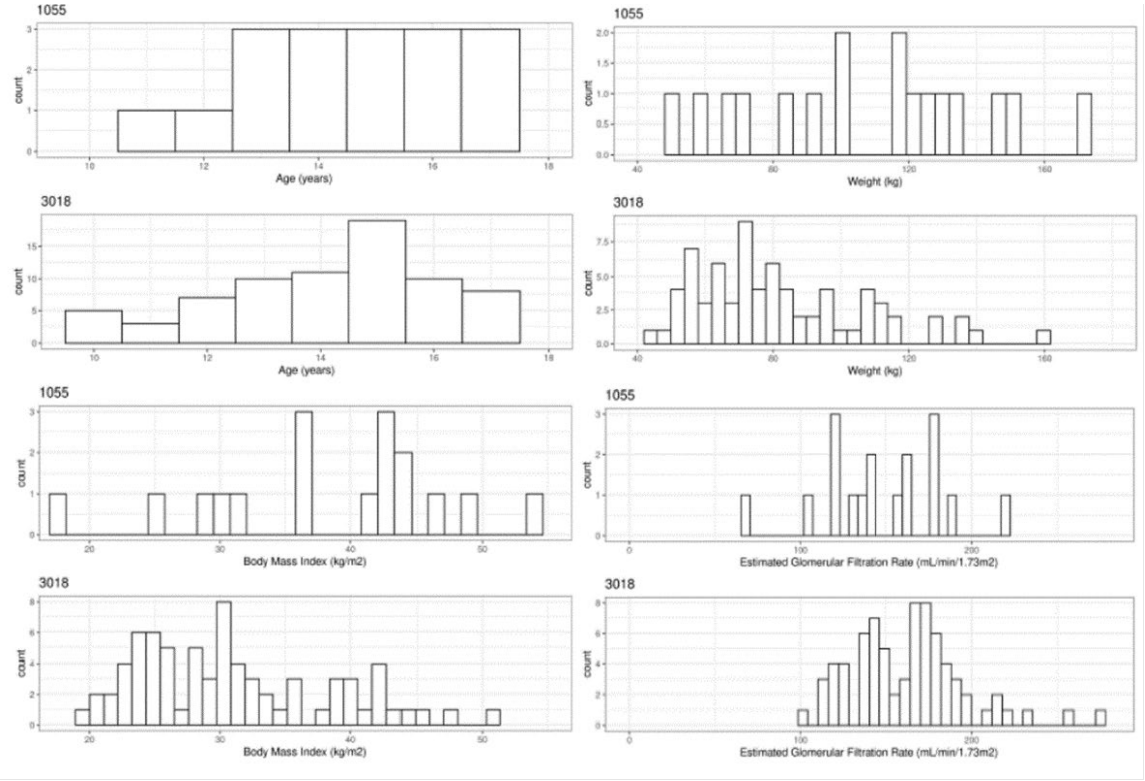
[a] Estimated mean (SD) AUC_{24h} at steady state for 300 mg QD of canagliflozin in male and female adult T2DM patients were presented previously[2]

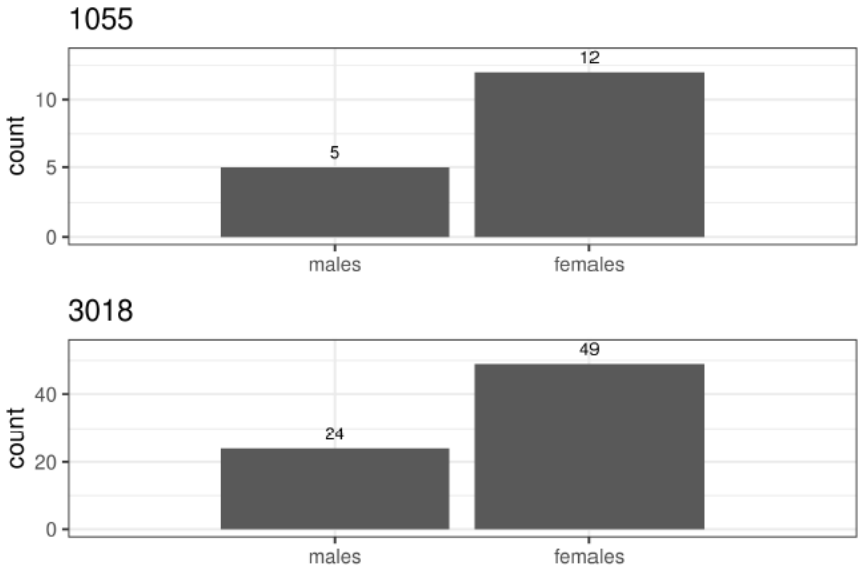
[b] All pediatric T2DM patients who contributed PK data on the specific dose regimen were considered, eg, participants in the DIA3018 300 mg group were included for 100 mg QD, 300 mg QD or both doses depending on the PK samples available.

SD, standard deviation

Source: PopPK Model Update Report; Page 46

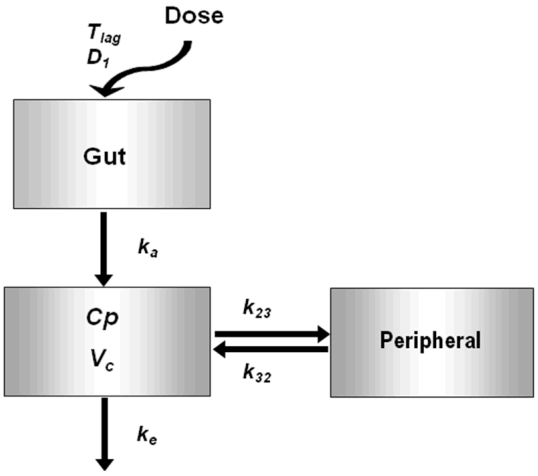
Figure 6. Distributions of Baseline Continuous and Catagorical Covariates for Pediatric Participants (DIA1055 and DIA3018)





Source: PopPK Model Update Report; Page 71 – 2

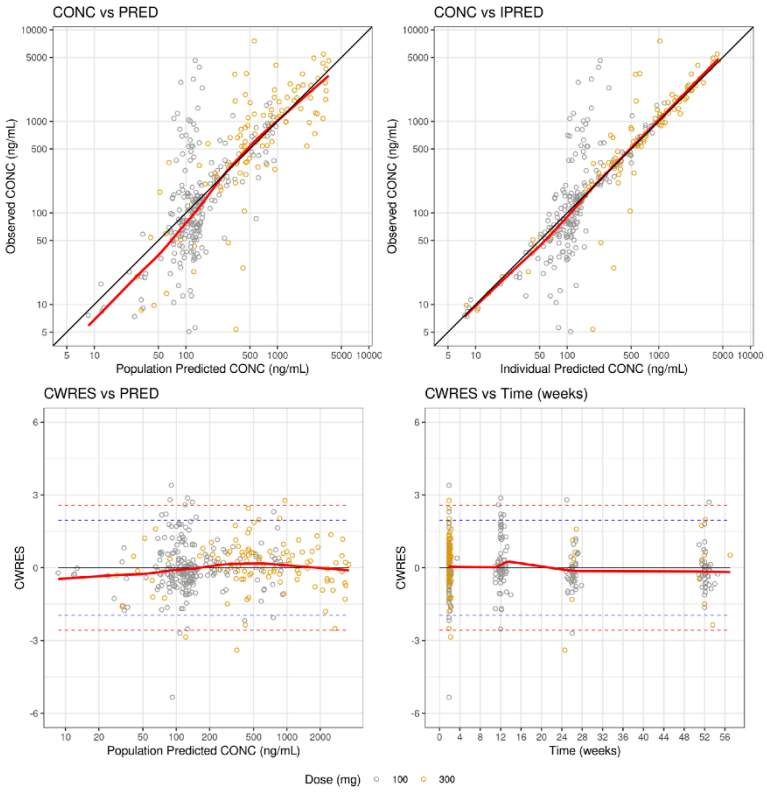
Figure 7. PopPK Model Diagram for Canagliflozin



Tlag, lag time; ka, absorption rate constant; Cp, central compartment concentration; ke, elimination rate constant; k23, intercompartment transfer rate constant from central to peripheral compartment; k32, intercompartment transfer rate constant from peripheral to central compartment.

Source: PopPK Model Update Report; Page 24

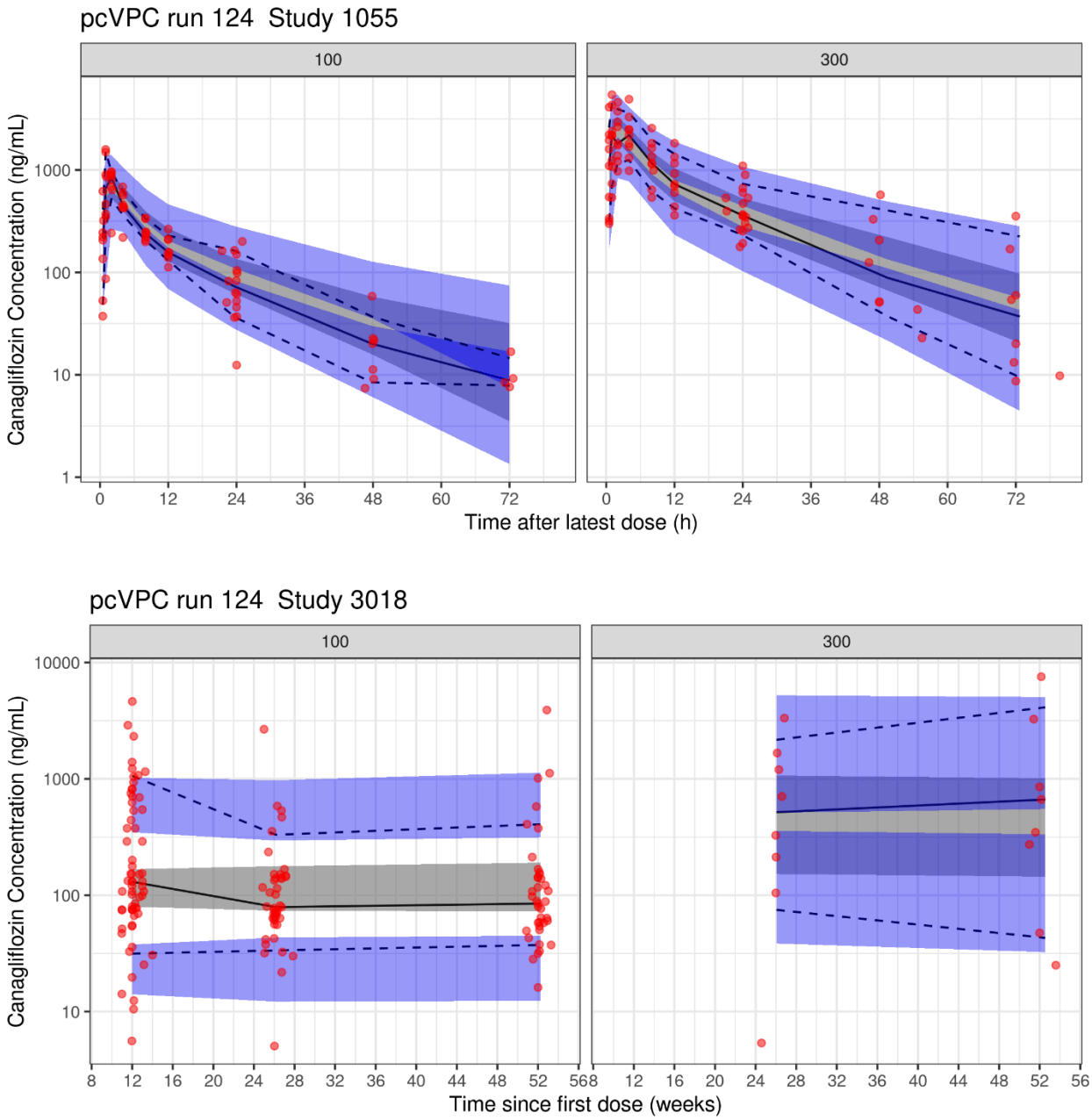
Figure 8. GOF Plots for the Final Pediatric PopPK Model for Canagliflozin



The black solid line is the line of identity or the zero line, and the red solid line is the trend line (lowess smoother); the blue and red dashed lines are the 95% and 99% probability intervals of the standard normal distribution; CONC, concentration; CWRES, conditional weighted residuals

Source: PopPK Model Update Report; Page 40

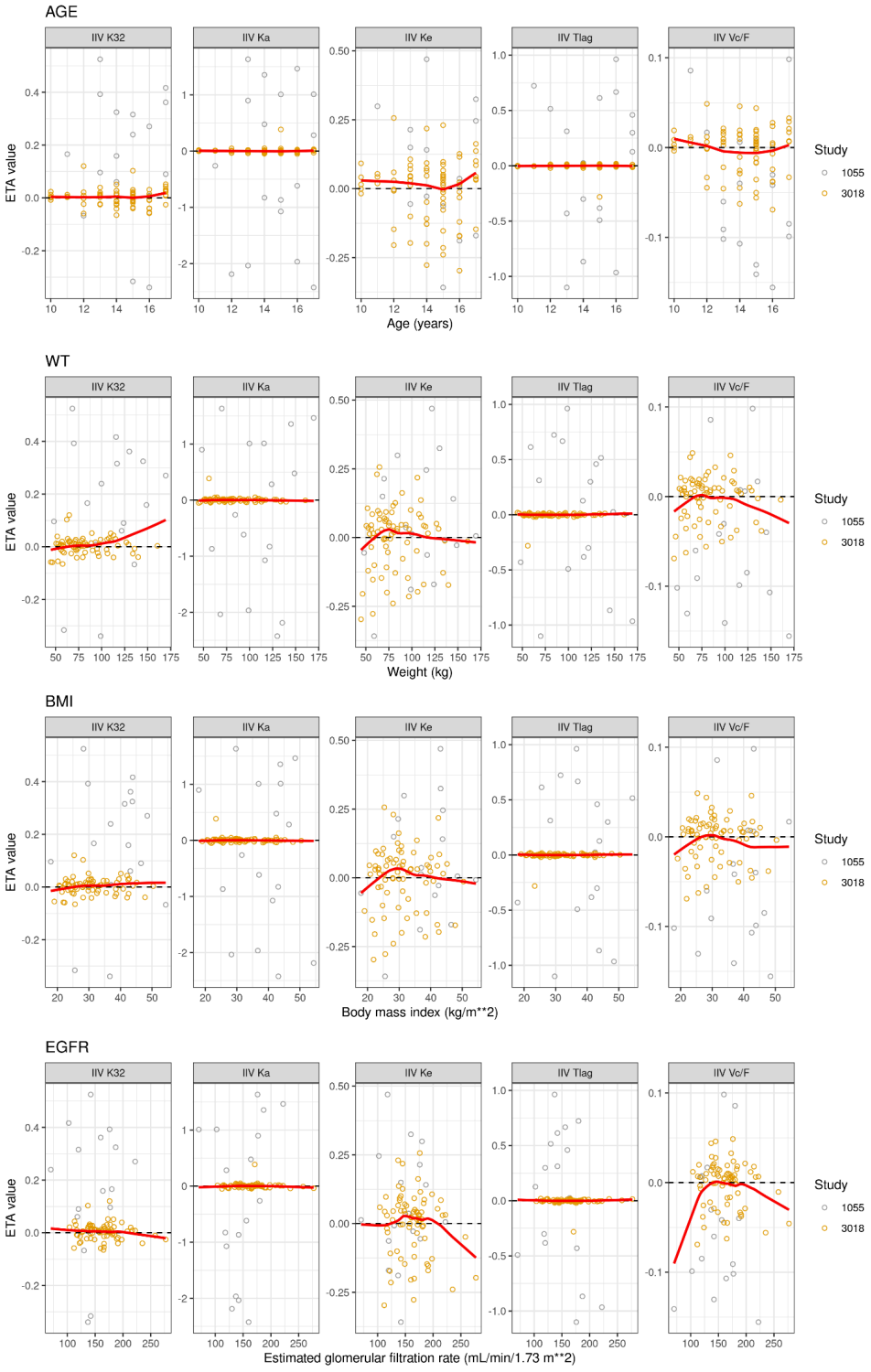
Figure 9. pcVPC of the Final Pediatric PopPK Model for Canagliflozin (run124) in DIA1055 (Top) and DIA3018 (Bottom) by Dose



Observed concentrations (red dots) with median (solid lines) and 10th, 90th percentiles (dashed lines). Areas show the simulation-based 95% PIs, in grey for the median and in blue for the 10th and 90th percentiles (N=1,000).

Source: PopPK Model Update Report; Page 38

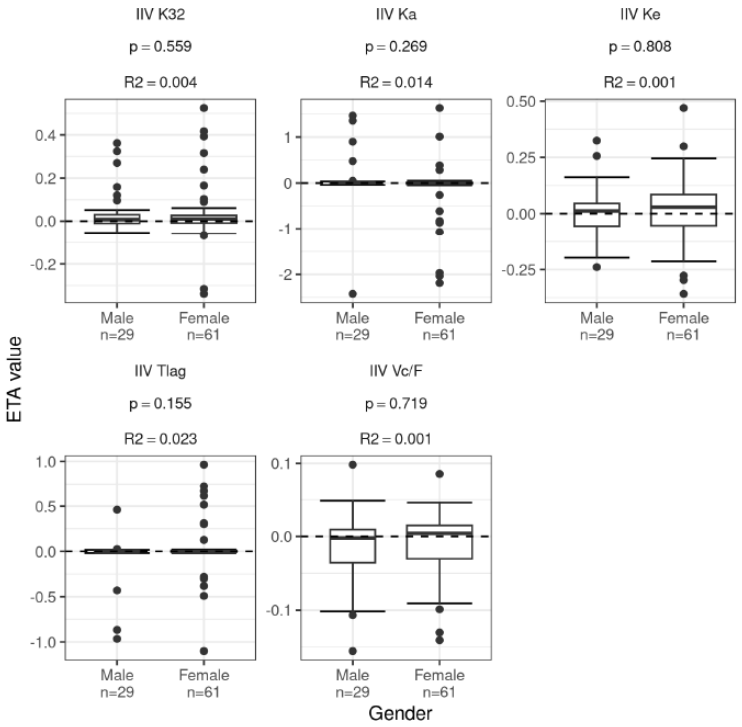
Figure 10. Parameter-covariate Relationships for the Final Pediatric PopPK Model for Canagliflozin (Continuous Covariates Age, Body Weight, BMI and eGFR)



Open circles are EBEs for IIV random effects. The black dashed line is the zero line, and the red solid line is the trend line (lowess smoother).

Source: PopPK Model Update Report; Page 42-43

Figure 11. Parameter-covariate Relationships for the Final Pediatric PopPK Model for Canagliflozin (Categorical Covariates Sex and Total Daily Dose)

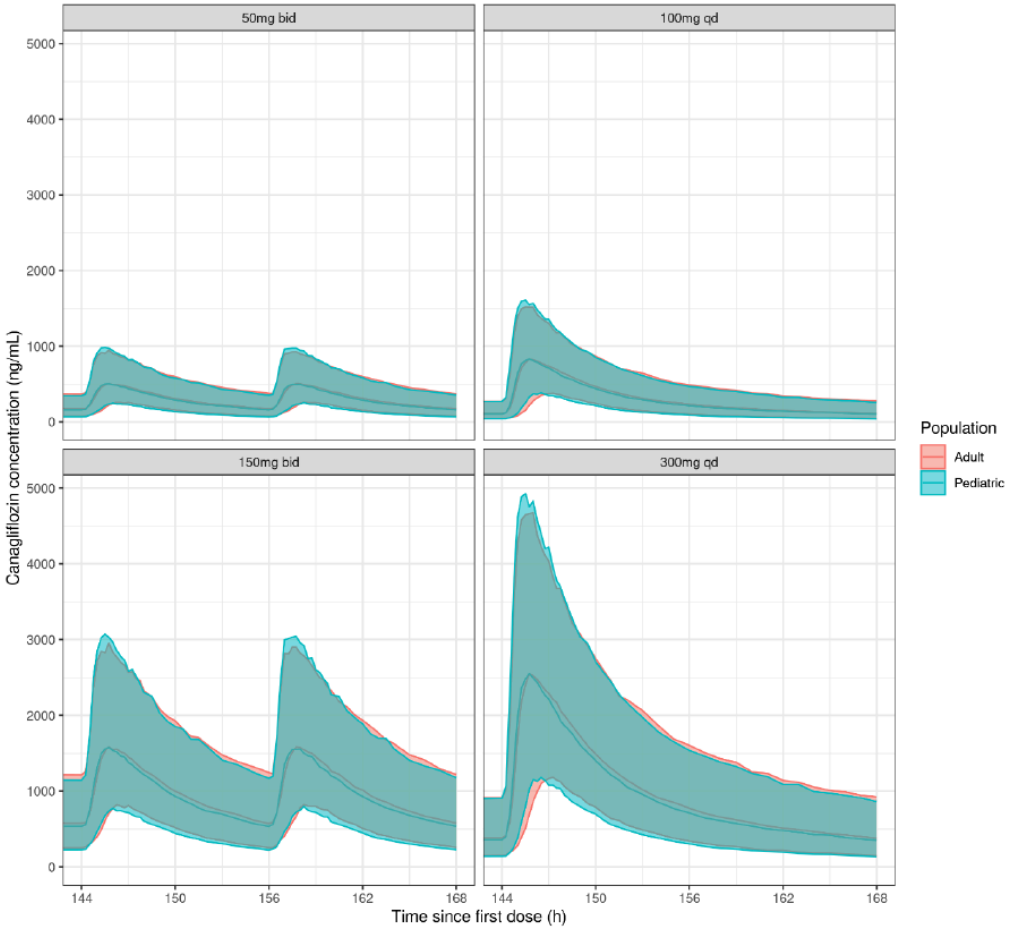


Boxplots of EBEs for IIV random effects. The lower and upper hinges correspond to the first and third quartiles (the 25th and 75th percentiles). The upper whisker extends from the hinge to the largest value no further than 1.5 * IQR from the hinge. The lower whisker extends from the hinge to the smallest value at most 1.5 * IQR of the hinge. Data beyond the end of the whiskers are plotted individually.
Dose indicates first dose taken that has associated PK observations.

Key: p = ANOVA p-value; R2 = ANOVA R-squared.

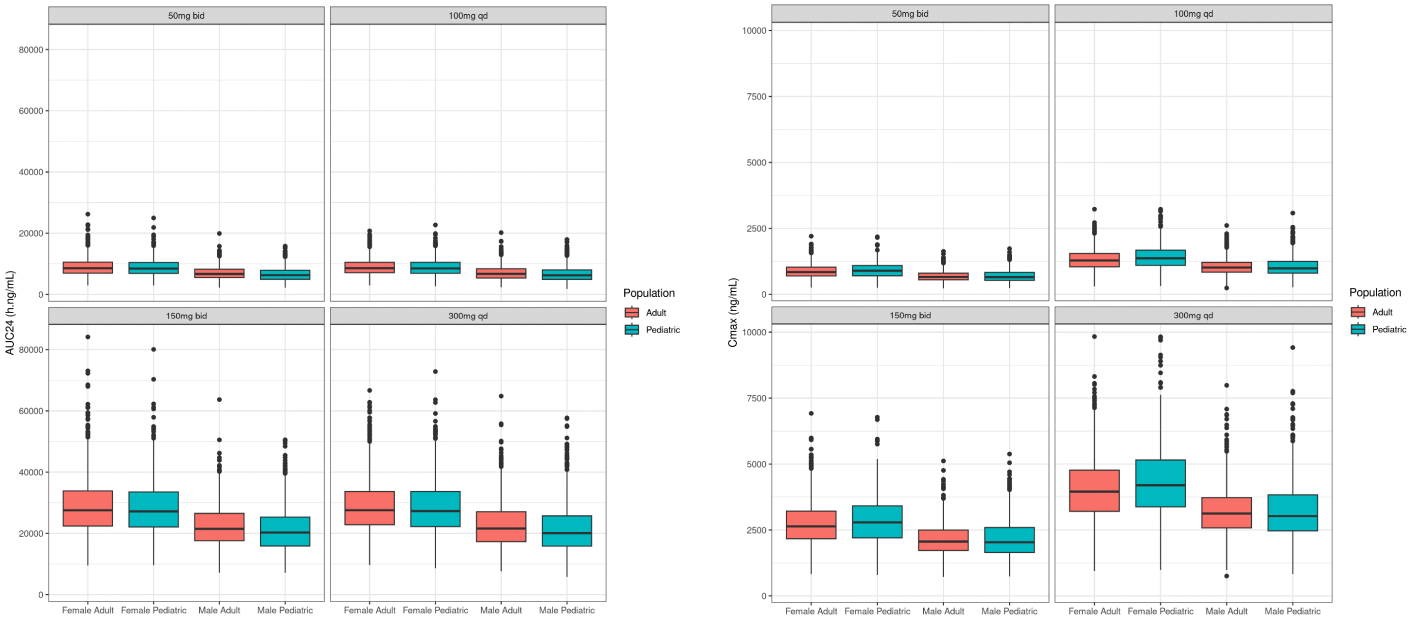
Source: PopPK Model Update Report; Pages 44-45

Figure 12. Simulated Concentration-time Profiles at Steady State After Oral Administration of Canagliflozin at 50 mg BID, 100 mg QD, 150 mg BID, and 300 mg QD in Pediatric and Adult T2DM Patients



Source: PopPK Model Update Report; Page 47

Figure 13. Boxplots of Simulated $AUC_{24}h$ and C_{max} at Steady State After Oral Administration of Canagliflozin at 50 mg BID, 100 mg QD, 150 mg BID, and 300 mg QD in Pediatric and Adult T2DM Patients, Stratified by Sex

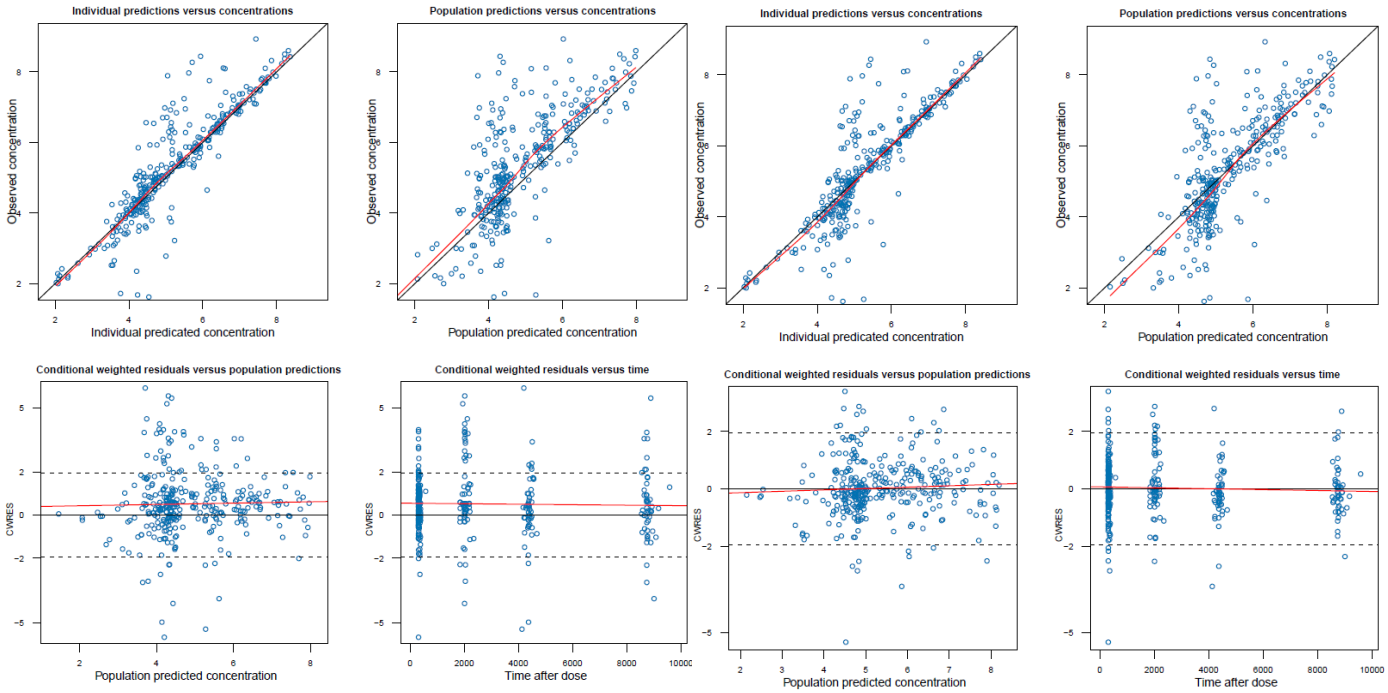


The lower and upper hinges of the boxplot correspond to the first and third quartiles (the 25th and 75th percentiles). The upper whisker extends from the hinge to the largest value no further than 1.5*IQR from the hinge. The lower whisker extends from the hinge to the smallest value at most 1.5*IQR of the hinge. Data beyond the end of the whiskers are plotted individually.

Source: PopPK Model Update Report; Pages 48-49

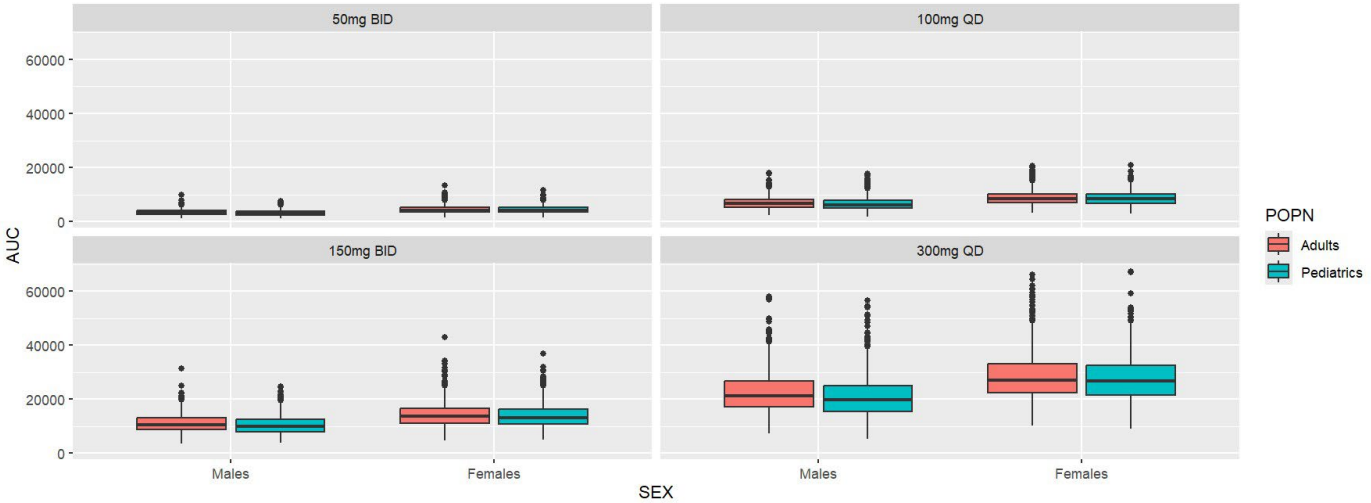
Figure 14. Goodness of Fit Plots Based on the Adult (a) and Pediatric (b) Models Applied to Pediatrics Data

(a) Adult PopPK Model Applied to Pediatric Data **(b) Pediatric PopPK Model Applied to Pediatric Data**



Source: Review Team Analysis

Figure 15. Comparisons of Simulated Steady State AUC24h Between Adults and Pediatrics and QD and BID Dose Regimens



The lower and upper hinges of the boxplot correspond to the first and third quartiles (the 25th and 75th percentiles). The upper whisker extends from the hinge to the largest value no further than 1.5*IQR from the hinge. The lower whisker extends from the hinge to the smallest value at most 1.5*IQR of the hinge. Data beyond the end of the whiskers are plotted individually.

Source: Review Team Analysis

3.2.1.3. Overall Summary of FDA's Assessment:

The review team assessed and verified the Applicant's final pediatric PopPK model in this review based on several standard criteria including visual inspection of diagnostic plots (observed vs. predicted concentration, residual/weighted residual vs. predicted concentration or time), scatterplots of individual random effects, successful convergence of the minimization, routine evaluation of precision and shrinkage estimates of the model parameters.

The GOF plots indicate that the model adequately describes the observed data (i.e., observed versus population and individual predictions plots were generally symmetrically distributed around the line of identity) **(Figure 14)**. Additionally, the distribution of the random effects appeared to be approximately zero-centered and normally distributed **(Figure 20)**. The review team reproduced the model results with successful convergence, indicating the model stability. The model parameters were fixed to the adult model parameter estimates, and cautious interpretation is warranted **(Table 4)**. Furthermore, since the inter-individual variability (IIV) terms were fixed to the original adult estimates, the shrinkages of the parameter estimates were also similar (i.e., between 39% and 70%), suggesting cautious interpretations of EBEs should be exercised. The pc-VPC plots of simulated concentrations showed that the median, 10^{th} and 90^{th} percentiles were reasonably contained within 95% confidence interval, suggesting the model reasonably described the observed pediatric data **(Figure 9)**. The parameter-covariate relationships indicated that no additional covariate correlating with any of the parameters other than those already accounted for in the model **(Figure 11)**. Based on the review team's assessment, the final PopPK model can be used to conduct simulations and support the expanded indication to pediatric patients of 10 years of above with T2DM.

The simulation results demonstrated that the steady-state concentration-time profiles of canagliflozin in pediatric and adults T2DM patients were similar between QD and BID dose regimens at the same total daily dose **(Table 5 and Figure 12)**. In addition, steady-state exposures (AUC24h and Cmax) were also similar between pediatric and adult T2DM patients for the 100 mg and 300 mg QD, 50 mg and 150 mg BID doses of canagliflozin **(Figure 13)**. The review team verified the model, and the findings were consistent with the Applicant's **(Figure 14 and Figure 15)**.

Collectively, the review team agrees with the Applicant's PopPK and simulation analysis results to support the indicated patient population expansion in canagliflozin, canagliflozin with metformin, and canagliflozin with metformin extended-release products to pediatric patients of 10 to less than 18 years of age with T2DM.

3.2.2. Exposure-Response Analysis

3.2.2.1. Review Summary

The Applicant performed a population pharmacokinetics and pharmacodynamics (PK/PD) modeling and simulations of canagliflozin to characterize the relationship between exposure and response in pediatric T2DM patients. The assessed PD endpoints were the time course levels of HbA1c and the change in HbA1c level from baseline. Previously, a population PK/PD model for canagliflozin was developed using PK and PD data from healthy adult participants and adult patients with T2DM. Canagliflozin was characterized by a turnover model for the HbA1c formation additively with an Emax model relating the concentration over time of canagliflozin to HbA1c-lowering effect.

The Applicant had initially applied the adult PK/PD model to evaluate the HbA1c dynamics in the pediatric T2DM patients from study DIA3018. Based on the results of the external evaluation, it was concluded that the adult model required updating to adequately describe the placebo and canagliflozin pediatric data. The final updated pediatric PK/PD model had similar base model structure with the previously developed adult model but included statistically significant covariate effects of background insulin and treatment group on baseline HbA1c and of background insulin on *Efp* (i.e., the effect of placebo treatment on HbA1c at steady state for a typical participant). In addition, the residual error variance was re-estimated based on the pediatric HbA1c data. All other model parameters were fixed to the estimates from the previously developed adult PK/PD model.

To support bridging from 50 mg BID to 100 mg QD and from 150 mg BID to 300 mg QD canagliflozin administration for the use of canagliflozin and metformin in pediatric T2DM patients, the final pediatric final PopPK and PK/PD models were used to simulate HbA1c profiles. Based on the PK/PD model simulations, the predicted HbA1c level and HbA1c change from baseline were comparable when canagliflozin was orally administered in QD and BID dosing regimens at the same total daily dose (TDD) to pediatric T2DM patients for 26 weeks.

Overall, the review team agrees that the updated PK/PD model can adequately describe the observed PD data in pediatric patients from study DIA3018. Based on the simulation results, the review team agrees that the change from baseline HbA1c was projected to be similar between QD and BID dosing at the same total daily dose in the target pediatric patients and agrees with the updated labeling language as summarized in the table below. Collectively, the PK/PD analysis supports the indication expansion to pediatric patients of 10 to less than 18 years of age with T2DM.

3.2.2.2. Summary and Assessment of ER Analysis

The table below summarizes the studies and data included in the analysis, the Applicant's the primary objectives of the analysis, and model development processes. The table also outlines the model evaluations and conclusions based on GOFs, pc-VPCs, the parameter-covariate plots and simulations results based on the final model. The corresponding assessments of the review team are provided.

<table>
<tr><th colspan="4">General Information</th></tr>
<tr><td colspan="2">Objectives of ER analysis</td><td colspan="2">• To investigate the relationship between canagliflozin plasma concentrations and time course of HbA1c in pediatric patients with diagnosis of T2DM (≥10 to <18 years).
• To compare the change from baseline HbA1c in pediatric T2DM patients for QD and BID dosing regimens at the same TDD of canagliflozin using a PK/PD simulation approach, to bridge from QD to BID dosing of canagliflozin to support canagliflozin and metformin in pediatric T2DM patients.</td></tr>
<tr><td colspan="2">Study Included</td><td colspan="2">Table 6</td></tr>
<tr><td colspan="2">No. of Patients (total, and with individual PK)</td><td colspan="2">Table 7</td></tr>
<tr><td rowspan="2">Population Characteristics</td><td>General</td><td colspan="2">Table 2</td></tr>
<tr><td>Pediatrics (if any)</td><td colspan="2">Yes.</td></tr>
<tr><td colspan="2">Dose(s) Included</td><td colspan="2">Total daily doses of 100 mg or 300mg of canagliflozin; 50 mg twice daily or 150 mg twice daily (for canagliflozin) in combination product with metformin (NDA 204353).</td></tr>
<tr><td colspan="2">Exposure Metrics Explored (range)</td><td colspan="2">Plasma concentration vs time profile</td></tr>
<tr><td colspan="2">Covariates Evaluated</td><td colspan="2">Table 8</td></tr>
<tr><td colspan="2" rowspan="2">Final Model Parameters</td><td>Applicant's Description</td><td>Review Team Assessment</td></tr>
<tr><td>Summary
Table 9 reports the parameter estimates of the final pediatric PK/PD model. All parameters had acceptable SEs and did not have correlations exceeding 0.90 in absolute value. The shrinkages of the individual random effects were below 21%, which was</td><td>The review team notes that the pediatric model parameters were fixed to the previously estimated model parameters (i.e., adult model), except for the placebo effect Efp, baseline HbA1c, and residual error variance</td></tr>
</table>

	considered acceptable **(PK/PD Model Update Report; Page 32)**. In this model, the PD parameters were fixed to the estimates from the adult PK/PD model, except for the placebo effect *Efp*, baseline HbA1c, and residual error variance that were re-estimated **(PK/PD Model Update Report; Page 44)**.	that were re-estimated **(PK/PD Model Update Report; Page 44)**. Based on an IR response regarding fixing model parameters for the pediatric data, the Applicant stated that one by one re-estimation of PK/PD parameters was explored, while keeping the other parameters fixed to those estimated in the adult model. However, this did not entail a statistically significant improvement in the model fit (IR Response). Overall, the review team agrees that fixing the parameter estimates is reasonable. The ETA shrinkages were also less than 21% **(Table 9)** which is generally considered acceptable in simulating PD responses **(PK/PD Model Update Report; Page 32)**.
Model Structure	A turnover model for HbA1c with an *Emax* model relating the HbA1c-lowering effect of canagliflozin to *C(t)*, the canagliflozin plasma concentration at time *t*, for the HbA1c-lowering effect of canagliflozin included additively on the HbA1c formation rate, adequately described the central tendency and the observed variability of the relationship between canagliflozin plasma	The same adult structural PK/PD model was applied to the current T2DM pediatric patient dataset (≥10 to <18 years). The review team agrees that the pediatric data from was reasonably described by a turnover model for the HbA1c formation additively with an Emax model relating the concentration over time of

	concentrations and HbA1c in pediatric T2DM patients (≥10 to <18 years). In this model, the PD parameters were fixed to the estimates from the adult PK/PD model, except for the placebo effect *Efp*, baseline HbA1c, and residual error variance that were re-estimated **(PK/PD Model Update Report; Page 44)**.	canagliflozin to HbA1c-lowering effect.
Model Parameter Estimates	**Table 9**	The model parameters presented in **Table 9** were verified by the review team, and the model parameter estimates were considered acceptable in describing the PD data.
Model Evaluation	Based on the population- and individual-level GOF and residual plots for the final PK/PD model **(Figure 16)**, the HbA1c data from study DIA3018 appear to be reasonably described both at a population and at an individual level, with no major trends in the residuals. Based on the pcVPC plots **(Figure 17)** , the final PK/PD model appears to adequately capture the central tendency and the variability of the data, as attested by the overall agreement between the observed 10^{th}, 50^{th}, and 90^{th} percentiles of the data and the respective 95% PIs obtained from the simulations **(PK/PD Model Update Report; Page 32-3)**.	The review team agrees that the GOF plots for population and individual predictions, as well as the residual plots appear reasonably unbiased, and therefore the model is acceptable in describing the PD data **(Figure 16)**. The review team verified the GOF plots **(Figure 21)**. The pcVPC plots demonstrate that the final model generally captures the central tendency (50^{th} percentile), as well as the spread (i.e., 10^{th} and 90^{th} percentiles) of the data **(Figure 17)**.
Covariates and Clinical Relevance	Background insulin was identified as a covariate on the baseline HbA1c, which is in line with an earlier PK/PD model for canagliflozin in	The review team agrees that background insulin was a significant covariate on both baseline HbA1c

	adult T2DM patients where AHA [antihyperglycemic agent] at screening was included as a covariate on baseline HbA1c. Furthermore, background insulin was also identified as a statistically significant covariate on the HbA1c-lowering effect of placebo treatment (*Efp*) **(Table 8)**. Additionally, treatment group was identified as a covariate on baseline HbA1c, accounting for the overall lower baseline HbA1c in the canagliflozin group compared to the placebo group **(Table 8)**. The parameter-covariate relationships plots do not reveal any additional covariate effects other than those already included in the model **(PK/PD Model Update Report; Page 36-41)**. A strong positive linear correlation is observed between the random effect on baseline HbA1c and (observed) baseline HbA1c, as expected **(Figure 18)**. T2DM patients who were white, not Hispanic or Latino, seemed to have a lower random effect on baseline HbA1c, but overall, the variability was within the variability of the other subgroups and therefore not further investigated **(Figure 18)**.	and the HbA1c-lowering effect of placebo treatment (*Efp*). Furthermore, treatment group was also identified as a covariate on baseline HbA1c, accounting for the overall lower baseline HbA1c in the canagliflozin group compared to the placebo group **(Table 8)**. The review team agrees with the expected positive correlation observed between the random effect on baseline HbA1c and (observed) baseline HbA1c **(Figure 18)**.
Simulation for Specific Population	To support canagliflozin and metformin in pediatric patients with T2DM, the final PopPK and PK/PD models were used to simulate HbA1c profiles to bridge from QD to BID dosing of canagliflozin. PK/PD	The review team agrees with the approach to simulate HbA1c profiles for pediatric T2DM patients population to support canagliflozin and

	model covariates (body weight and background insulin) were sampled jointly from the PK/PD analysis dataset, split by sex and kept the same for all simulated dosing regimens. The means of placebo and canagliflozin baseline HbA1c estimates (stratified by insulin background) were used for the simulations, ie, assuming a balanced baseline HbA1c between the treatment groups **(PK/PD Model Update Report; Page 41)**. For total daily dose (TDDs) of 100 mg and 300 mg of canagliflozin, there is a good overlap in simulated mean HbA1c and mean change from baseline HbA1c and their associated variability between QD and BID dosing regimens in pediatric T2DM patients **(Figure 5)**.	metformin pediatric dosing regimen. The review team also agrees that the stimulation results demonstrated comparable mean HbA1c and mean change from baseline HbA1c of BID and QD dose regimens for the same total daily doses of 100 mg and 300 mg canagliflozin **(Figure 5)**. The review team verified the simulation results (**Figure 21**).
Overall Clinical Relevance for ER	The PK/PD analysis shows that the ER relationship estimated between canagliflozin plasma concentrations and HbA1c in adult T2DM patients adequately described the observed HbA1c data in pediatric T2DM patients (≥10 to <18 years). In addition, the PK/PD model simulations for BID and QD canagliflozin dosing regimens at the same TDD are predicted to provide similar HbA1c lowering in pediatric T2DM patients. Therefore, pediatric T2DM patients who switch from canagliflozin and metformin single agent tablets to canagliflozin and metformin taken on a BID basis, are expected to attain similar glycemic	The review team agrees that the final PK/PD model reasonably describes the observed canagliflozin plasma concentrations and longitudinal HbA1c data in pediatric T2DM patients of ≥10 to <18 years. The review team agrees with the findings that: 1) the PK/PD simulations support bridging of QD to BID canagliflozin dosing regimens at the same total daily dose, and 2) BID regimens are predicted to provide similar HbA1c lowering in pediatric T2DM patients.

	control **(PK/PD Model Update Report; Page 45)**.	

Table 6. Summary of the Clinical Study DIA3018 Included in the PK/PD Analysis

Study	Study Title and Brief Description of Design	Dose (mg), Regimen, Route of Administration, Formulation	No. of Participants with HbA1c Data Available	PK/PD Sampling
28431754 DIA3018 Phase 3	**Phase 3, multiple dose efficacy and safety in pediatric T2DM patients** A Randomized, Multicenter, Double-blind, Parallel-group, Placebo-controlled Study to Investigate the Efficacy and Safety of Canagliflozin in Children and Adolescents (≥10 to <18 years) with T2DM	**No up-titration:** 100 mg canagliflozin QD for 52 weeks; **Up-titration:** 100 mg canagliflozin QD for 12 weeks followed by 300 mg canagliflozin QD for 40 weeks. Canagliflozin oral administration as over-encapsulated tablets.	171	**PK sampling:** plasma trough concentrations at Week 12, 26, and 52 (end of treatment) or early withdrawal. **HbA1c sampling:** Week -3 (screening visit), Day 1 (baseline), Week 6, 12, 20, 26, 34, 42, and 52 (end of treatment) or early withdrawal; at rescue visit.

Source: PK/PD Model Update Report; Page 16

Table 7. Summary of HbA1c Observations Excluded From the Analysis by Reason for Exclusion

Reasons	Samples Affected	Samples Remaining	Participants Affected	Participants Remaining
All Samples		1259		171
Participants not in final PopPK model	73	1186	11	160
Sample date/time incomplete	4	1182	3	160
Previous dose date/time incomplete	1	1181	1	160
Rescue medication	176	1005	48	160
Beyond Week 26	303	702	109	160
Total number of samples				
Before exclusion		1259		171
Excluded		557		11
Included in the PK/PD analysis dataset		702		160

Source: PK/PD Model Update Report; Page 18

Table 8. Covariates Included in the PK/PD Analyses Based on Dataset from DIA3018 Study

	Canagliflozin	Placebo	Total
Analysis set, n	73	87	160
Dose, n (%)			
100 mg	61 (83.6)	0 (0)	61 (38.1)
300 mg[a]	12 (16.4)	0 (0)	12 (7.5)
Placebo	0 (0)	87 (100)	87 (54.4)
Sex, n (%)			
Male	24 (32.9)	27 (31.0)	51 (31.9)
Female	49 (67.1)	60 (69.0)	109 (68.1)
Race, n (%)			
White, Not Hispanic or Latino	13 (17.8)	8 (9.2)	21 (13.1)
Black, of African heritage or African American	6 (8.2)	13 (14.9)	19 (11.9)
White, Hispanic or Latino	20 (27.4)	23 (26.4)	43 (26.9)
Asian	30 (41.1)	38 (43.7)	68 (42.5)
American Indian or Alaskan Native	4 (5.5)	4 (4.6)	8 (5.0)

	Canagliflozin	Placebo	Total
Other	0 (0)	1 (1.1)	1 (0.6)
AHA background, n (%)			
Diet and exercise only	12 (16.4)	10 (11.5)	22 (13.8)
Metformin	34 (46.6)	40 (46.0)	74 (46.2)
Insulin	8 (11.0)	10 (11.5)	18 (11.2)
Metformin and insulin	19 (26.0)	27 (31.0)	46 (28.7)
Age (years)			
Mean (SD)	14.1 (1.95)	14.4 (2.04)	14.3 (2.00)
Median	15.0	15.0	15.0
Range	(10.0; 17.0)	(10.0; 17.0)	(10.0; 17.0)
Body weight (kg)			
Mean (SD)	81.9 (25.1)	79.9 (25.3)	80.8 (25.1)
Median	75.1	75.2	75.2
Range	(44.8; 161)	(40.6; 162)	(40.6; 162)
BMI (kg/m^2)			
Mean (SD)	30.9 (7.37)	30.5 (7.66)	30.7 (7.51)
Median	29.9	29.2	29.6
Range	(19.0; 50.4)	(17.8; 56.6)	(17.8; 56.6)
eGFR ($mL/min/1.73m^2$)			
Mean (SD)	163 (33.1)	151 (29.7)	157 (31.8)
Median	165	146	154
Range	(104; 277)	(66.0; 284)	(66.0; 284)

	Canagliflozin	Placebo	Total
Baseline HbA1c (%)			
Mean (SD)	7.65 (1.24)	8.30 (1.35)	8.00 (1.34)
Median	7.50	8.00	7.70
Range	(5.80; 11.3)	(6.00; 11.2)	(5.80; 11.3)

[a] After 12 weeks of 100 mg and re-randomization, participants were up-titrated to 300 mg.[2]

Source: PK/PD Model Update Report; Pages 23-25

Reviewer's Comments: The data collected above appears to be sufficient to inform the goals of the E-R analysis.

Table 9. Parameter Estimates of the Final PK/PD Model for HbA1c

Parameter	Population Estimate	SE	Shrinkage (%)
Baseline HbA1c (%)			
Insulin placebo	8.50	0.213	
Insulin canagliflozin	7.82	0.270	
No insulin placebo	7.91	0.190	
No insulin canagliflozin	7.22	0.154	
HbA1c half-life $t_{1/2}$ (days)	28.2 FIX		
Ef_p insulin (%)	0.171	0.148	
Ef_p no insulin (%)	-0.238	0.107	
E_{max} (%)	-0.738 FIX		
Log EC_{50} (log ng/mL)*	4.12 FIX		
IIV of baseline HbA1c (variance)	0.011 FIX		1.00E-10
IIV of Ef_p (variance)	0.369 FIX		20.9
Residual error (SD)	0.0773	0.00522	

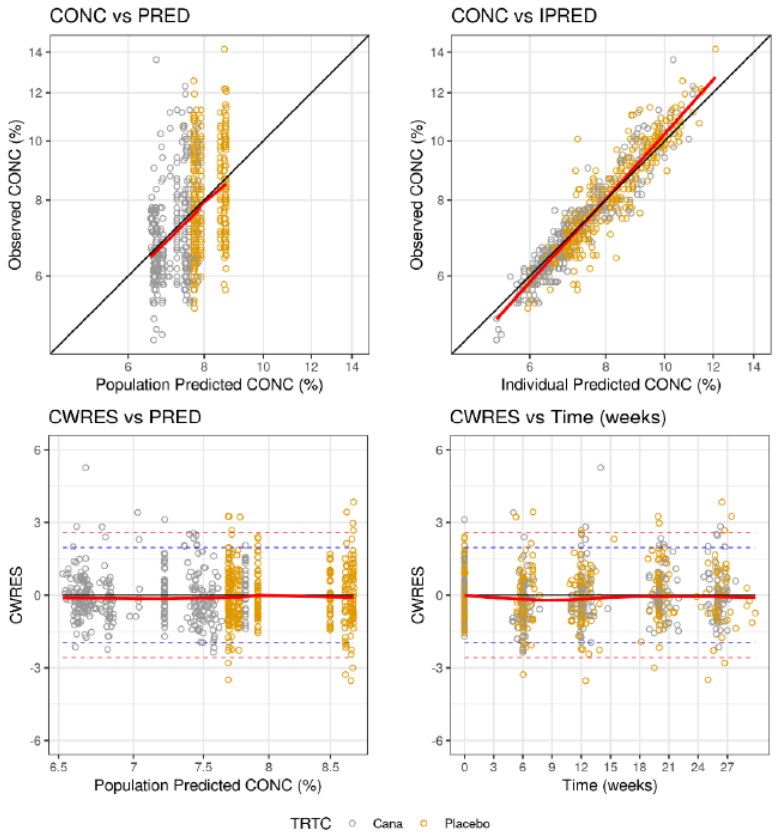
HbA1c half-life $t_{1/2} = \log(2)/k_{out}$
FIX = model parameters were fixed to the estimates obtained from the adult PK/PD model[4]
Random effect shrinkage as reported in NONMEM
* Corresponds to an EC_{50} estimate of 61.6 ng/mL

Source: PK/PD Model Update Report; Page 32

Reviewers' Comment:
The review team noted that the Applicant conducted the pediatric population PK/PD modeling by fixing some of model parameters to the original adult population PK/PD parameter estimates. The review team issued an information request (IR) to the Applicant seeking explanations on this and other additional issues as identified during the review. The Applicant

responded to the issued IR. Based on the response, the Applicant clarified that the re-estimation of PK/PD parameters were explored. However, this did not result a significant improvement in the model fit (Response). The review team accepted the provided justifications.

Figure 16. GOF Plots for the Final PK/PD Model for HbA1c

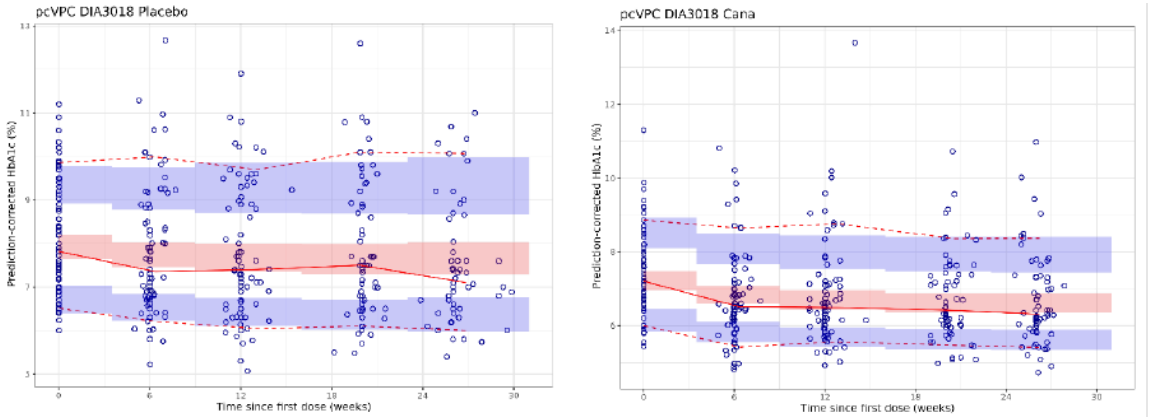


The black solid line is the line of identity or the zero line, and the red solid line is the trend line (lowess smoother). The blue and red dashed lines are the 95% and 99% probability intervals of the standard normal distribution.

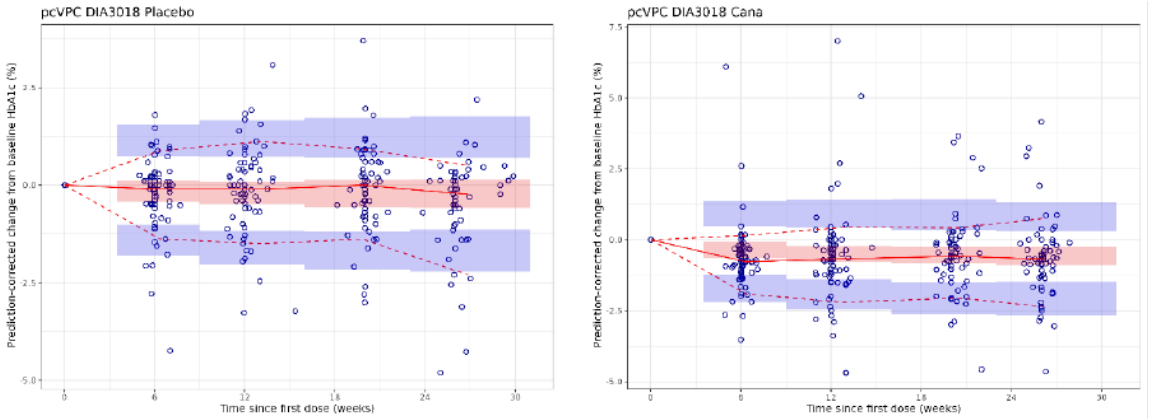
Key: CONC = HbA1c concentration; TRTC = treatment group; Cana = canagliflozin.

Source: PK/PD Model Update Report; Page 34

Figure 17. pcVPC of the Final PK/PD Model for HbA1c (top panels) and Change from Baseline HbA1c (bottom panels) in Placebo and Canagliflozin Groups



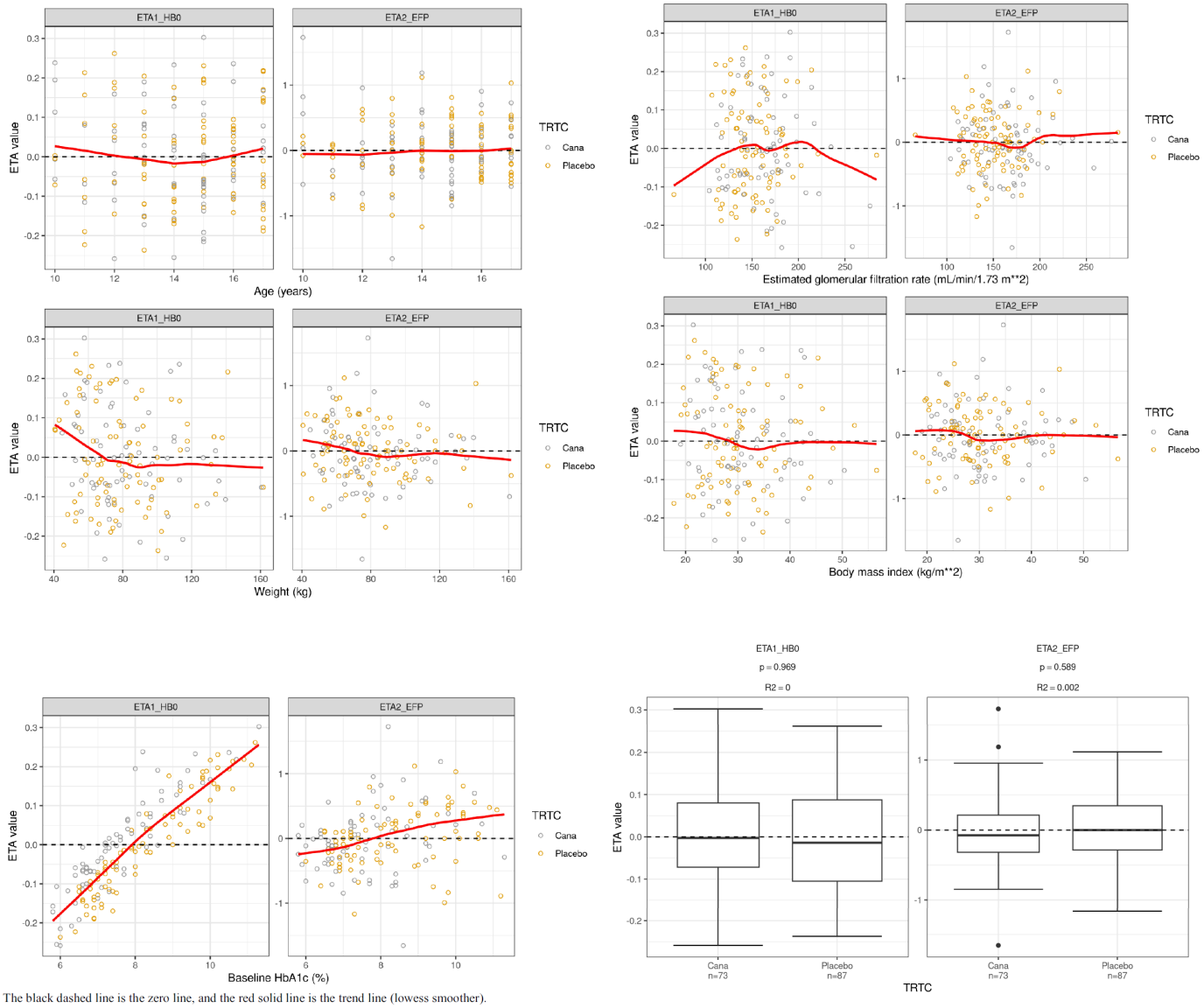
Lines are median (red solid line), 10th and 90th percentiles (red dashed lines) of observed concentrations (blue circles). Shaded intervals represent simulation-based 95% PIs, in red for the median and in blue for the 10th and 90th percentiles (N=1,000).



Lines are median (red solid line), 10th and 90th percentiles (red dashed lines) of observed concentrations (blue circles). Shaded intervals represent simulation-based 95% PIs, in red for the median and in blue for the 10th and 90th percentiles (N=1,000).

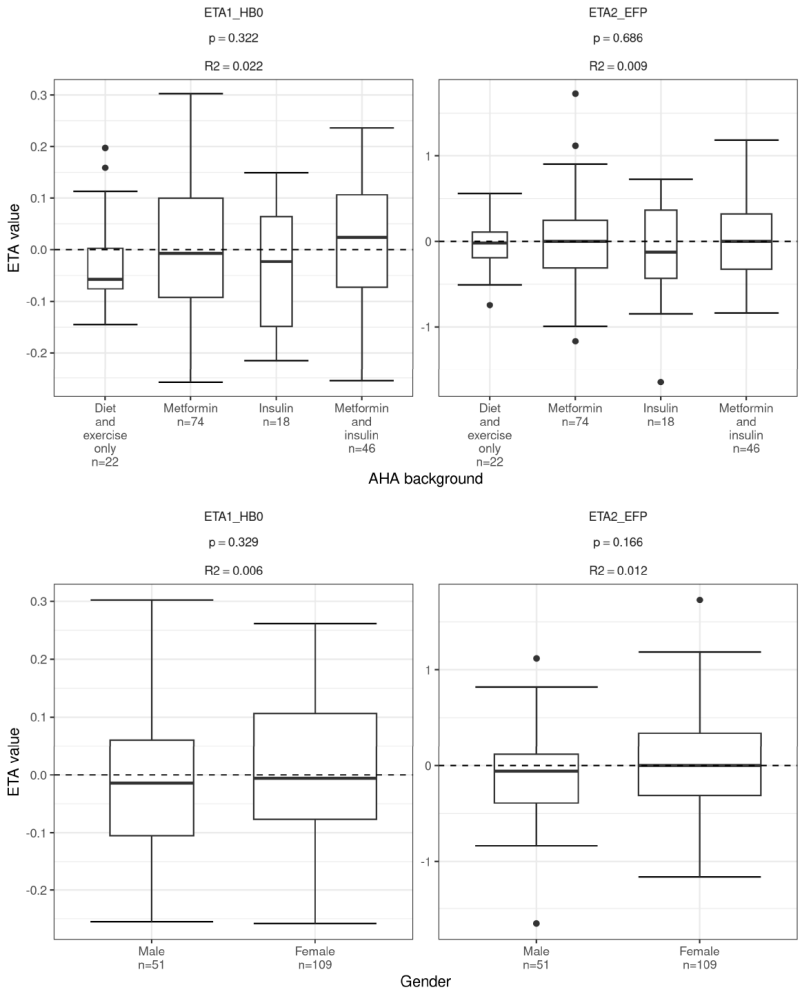
Source: PK/PD Model Update Report; Page 33

Figure 18. Parameter-covariate Relationships for the Final PK/PD Model for HbA1c



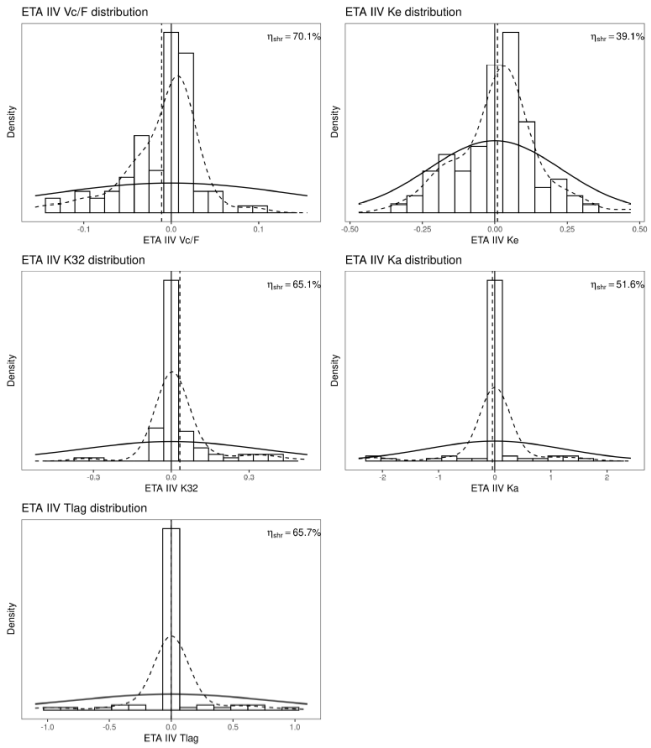
The black dashed line is the zero line, and the red solid line is the trend line (lowess smoother).

Key: ETA = random effect; HB0 = baseline HbA1c; EFP = HbA1c-lowering effect of placebo treatment; TRTC = treatment group; Cana = canagliflozin.



Source: PK/PD Model Update Report; Page 37 – 41

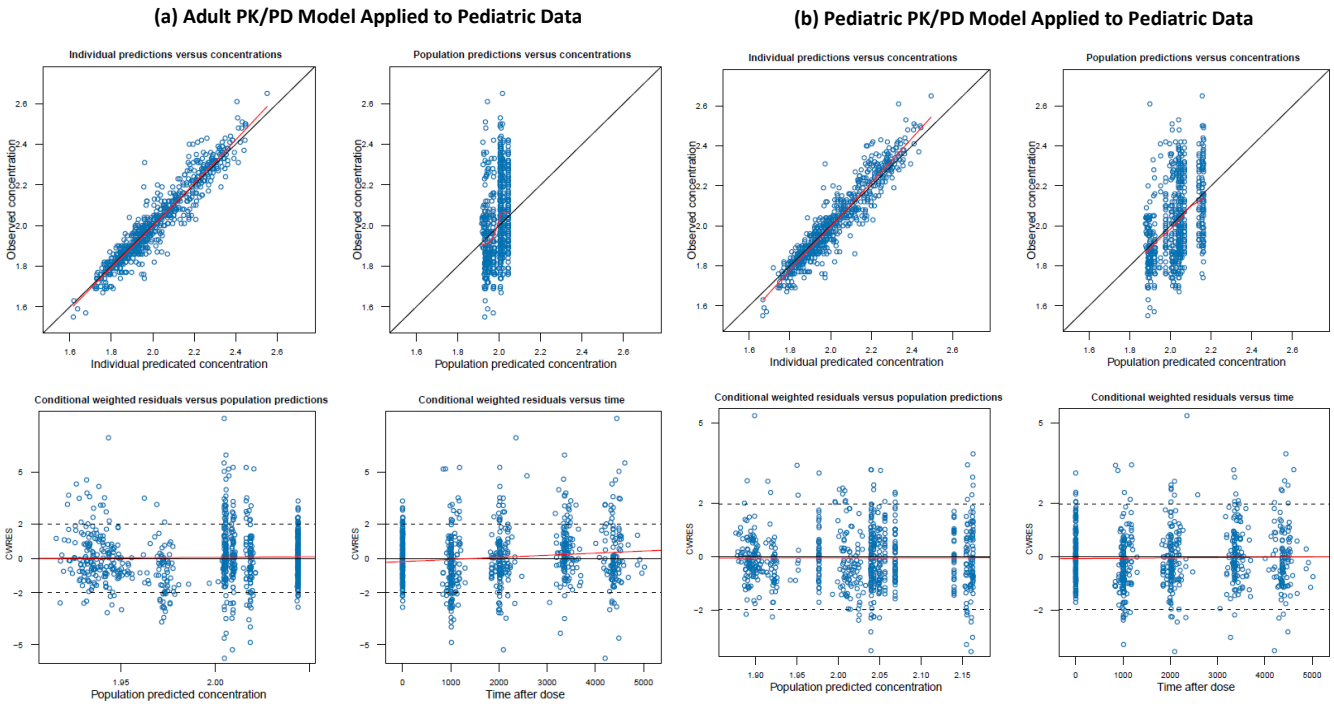
Figure 19. Distribution of IIV Random Effects for the Final Pediatric PopPK Model



Dashed black vertical line: mean of the individual EBEs; dashed black line: density line of the distribution of the individual EBEs; solid black line: density line of the theoretical distribution of the random effect (ETA) with mean equal to zero (solid black vertical line) and variance equal to the corresponding omega in the model. η_{shr}=shrinkage on ETA.

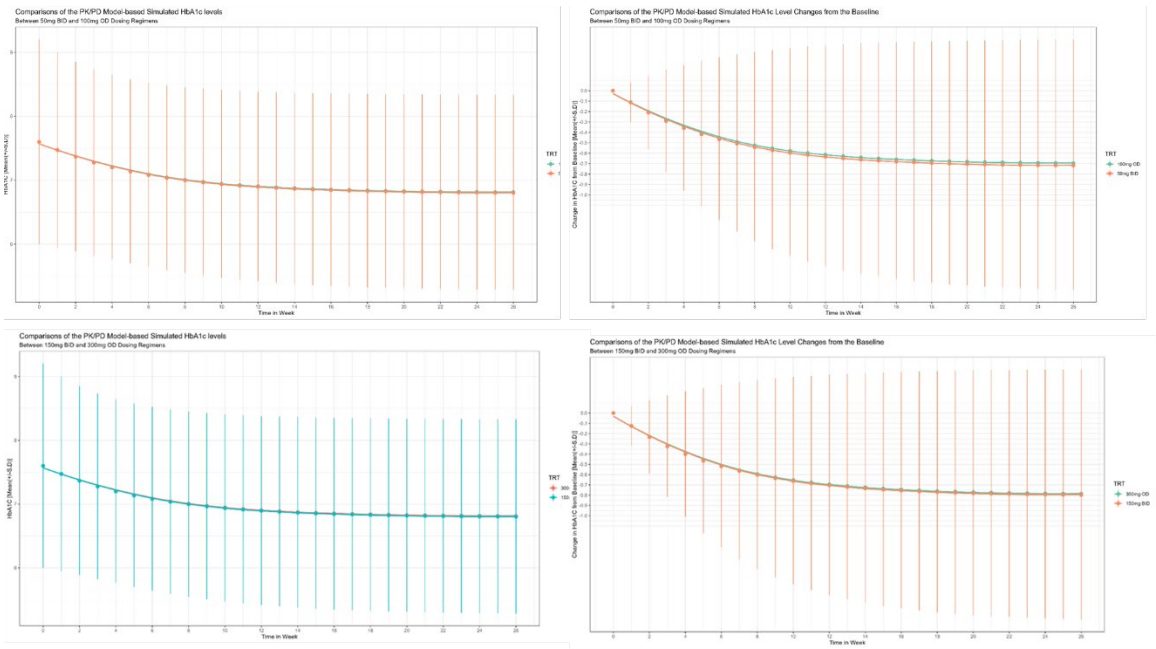
Source: PopPK Model Update Report; Page 41

Figure 20.Goodness-of-Fit Plots for PK/PD Models (Review teams' Analysis)



Source: Review teams' Analysis

Figure 21. Simulated HbA1c (left panels) and Change from Baseline HbA1c (right panels) Following at 50mg BID & 100mg QD (top panels) and 150mg BID & 300mg QD (bottom panels) in Pediatric T2DM Patients



Source: Review teams' Analysis

3.2.2.3. Overall benefit evaluation based on E-R analyses

The FDA's Assessment:

Based on the updated E-R relationship between exposure and PD endpoint (i.e., exposure and change in HbA1c from the baseline to Week 26), comparable PD outcomes were shown between QD and BID dose regimens for the same total daily dose administration of canagliflozin to pediatric T2DM patients (≥10 to <18 years). These simulation results also support the indication of canagliflozin and metformin for pediatric T2DM patients. Of note, the 300 mg simulation results should be interpreted with caution because the 300 mg PK and PD data of canagliflozin were from subjects who were enrolled into the 100 mg arm initially but were re-randomized to receive 300 mg dose at Week 12 due to HbA1c ≥ 7.0%. Refer to Section 2.3.1 for further details.

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/s/

ANUSHA ANDE
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ABIY H EYAKEM
11/22/2024 12:39:28 PM

JUSTIN C EARP on behalf of JIAJUN LIU
11/22/2024 03:22:58 PM

JAYABHARATHI VAIDYANATHAN
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