U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	NDAs 204042, 204353, 205879
Supplement #:	S-43, S-46, S-23
Drug Name:	Trade name (generic name): • INVOKANA®, (Canagliflozin) • INVOKAMET®, (Canagliflozin + metformin HCI) • INVOKAMET® XR (Canagliflozin + metformin HCI)
Indication(s):	Type 2 Diabetes Mellitus in Children and Adolescents (≥10 to <18 years)
Applicant:	Janssen Research & Development, LLC
Date(s):	Date Received: 06/18/2024 Primary Review Due Date: 11/25/2024 PDUFA Date: 12/18/2024 (6-month Priority)
Review Priority:	Priority
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Keywords:
Type 2 diabetes, pediatric study, analysis of covariance(ANCOVA), retrieved dropout, second randomization

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1 EXECUTIVE SUMMARY

The applicant, Janssen Pharmaceuticals, submitted NDA 204042/S-43, 204353/S-46, 205879/S-23 for INVOKANA® (canagliflozin), INVOKAMET® (canagliflozin + metformin HCI) and INVOKAMET® XR (canagliflozin + metformin HCI), in support of product label updates with respect to the pediatric indication. The label updates of three products were based on a single Phase 3 pediatric trial, DIA3018, with post marketing requirement (PMR) 2027-2 titled,

"A 26-week, randomized double-blind, placebo-controlled study, followed by a 26-week double-blind, placebo- or active-controlled extension, to evaluate the efficacy and safety of canagliflozin compared to placebo in pediatric patients ages 10 to <18 years with type 2 diabetes mellitus, as add-on to metformin and as monotherapy."

This review focuses on statistical results of A1C changes from baseline at Week 26 for overall population (Primary endpoint) and for subgroup of subjects with background therapy of metformin (Key secondary endpoint). The applicant proposed to update the T2DM indication based on pediatric study results in prescribing information for all three products:

- section 8.4: Pediatric Use,
- and a new section 14.2: Glycemic Control Trial in Pediatric Patients Aged 10 Years and Older with Type 2 Diabetes Mellitus.

1.1 Brief overview of Clinical Study

The Study DIA3018 was a randomized, double-blind, placebo-controlled, 2-arm, parallel-group, multicenter Phase 3 study intended to evaluate the efficacy and safety of canagliflozin 100 mg and 300 mg (Once daily administration) vs. placebo after 26 weeks of treatment in children and adolescents with T2DM, followed by a 26-week double-blind extension treatment period. A total of 171 subjects were randomized in a 1:1 ratio to one of the two treatment arms: canagliflozin 100 mg or placebo. At Week 13, subjects with an HbA1c value $\geq$ 7.0% and eGFR $\geq$ 60 mL/min/1.73m^2 underwent a second randomization to either 100 mg and 300 mg (canagliflozin or matching placebo) in a 1:1 ratio. Study objective is to evaluate the effect of the canagliflozin compared to placebo on HbA1c levels by assessing the HbA1c values of the pooled canagliflozin group and comparing them to those of the control group after 26 weeks of treatment.

1.2 Statistical Issues

The overall missing rate was 8.33% for canagliflozin, and 8.05% for placebo. Missing endpoints with intercurrent events (ICEs) were multiply imputed based on retrieved dropout observations. A minor review issue was about the implementation of missing value imputation. The applicant applied a multiple imputation (MI) regression to impute all monotone missing values, using treatment group, stratification factors, baseline HbA1c and the change from baseline in HbA1c at Weeks 6, 12 and 20 using all retrieved dropouts from both arms. Since the retrieved dropouts may differ by treatment arm, we prefer applying multiple imputation (MI) regressions to the missing values of each treatment group separately.

1.3 Collective Evidence

The study demonstrated a statistically significant treatment effect for canagliflozin compared to placebo with respect to the primary endpoint HbA1c change from baseline at Week 26 (Table 1). Results from sensitivity analyses demonstrated robustness of the primary efficacy results to untestable assumptions on missing data. Subgroup analyses on the primary efficacy endpoint found consistent treatment effect of canagliflozin in subgroup levels on age, sex, race, ethnicity, region, and background antidiabetic medications (Section 4). Risk of hypoglycemia was comparable in subjects treated with canagliflozin compared to those treated with placebo.

Table 1. Primary Efficacy Analysis: HbA1c Change from Baseline at Week 26, in FAS Population, DIA3018.

	Canagliflozin [pooled 100 mg and 300 mg] N = 84	**Placebo N=87**
Baseline, Mean (SD)	7.79 (1.31)	8.30 (1.57)
Week 26 Missing, n (%)	7 (8.33)	7 (8.05)
Change from baseline to Week 26* LS Mean (SE)	-0.35 (0.218)	0.37 (0.197)
Difference from Placebo* LS Mean (95% CI)	-0.73 (-1.26, -0.19)	
Two-sided P-value	0.008	

Abbreviations: CI = confidence interval, SD = standard deviation, Min.= minimum, Max. = maximum.
* The LS Mean estimate is based on an ANCOVA model adjusted for baseline HbA1c, stratification factors, and treatment after imputing missing data using retrieved dropout method
Source: Reviewer's Analysis Using Applicant Submitted Dataset adsl.xpt, adhba1c.xpt and ds.xpt.

1.4 Conclusion and Recommendations

Statistical analyses based on the clinical data from the Phase 3 pediatric study DIA3018 have demonstrated robust evidence to support the effectiveness of canagliflozin regarding glycemic control among pediatrics (10 to < 18 years) with T2DM. The statistical review team recommend approval of the proposed label updates with minor modifications for INVOKANA, INVOKAMET and INVOKAMET XR.

2 INTRODUCTION

2.1 Overview

Canagliflozin (INVOKANA), an orally active inhibitor of sodium-glucose co-transporter 2 (SGLT2), its fixed dose combination with metformin HCI (INVOKAMET), and its fixed dose combination with metformin HCI extended release (INVOKAMET XR) were approved by the FDA in 2013, 2014 and 2016, both as adjuncts to diet and exercise to improve glycemic control in adults with T2DM. In the current NDA supplements, the applicant proposed to expand the current adult indication as an adjunct to diet and exercise to improve glycemic control to include

children and adolescents (≥10 to <18years) with T2DM for INVOKANA, INVOKAMET, and INVOKAMET XR. Table 2 provides a summary of the trial characteristics.

Table 2. Summary Table of Trial Characteristics, DIA3018.

Trial ID	Design*	Treatment/ Sample Size/ Sample Size (proportion) in US	Endpoint/Analysis	Preliminary Findings
DIA3018	MC, R, DB, PG, PC (3-wk scr & run-in + 26-wk TrtP (second randomization at the end of wk 12) + 26-extension TrtP)	Canagliflozin (Cana) 100 mg or 300 mg / N = 84 / N** = 19 (23%)/ N***=13 (15%) Placebo / N = 87 / N** = 22 (25%)/ N***=18 (21%) Metformin subgroup Cana 100mg or 300mg N =62/ Placebo N=67	Primary: Change in HbA1c from baseline at Week 26 / ANCOVA with RDMI Key secondary: 1, Change in HbA1c from baseline at Week 26 in metformin subgroup / ANCOVA with PMI. Secondary (no multiplicity adjustment): 1, FPG, proportion of participants with HbA1c <7.5%, <7.0% and <6.5%, Time to rescue therapy and proportion of participants receiving rescue therapy, and Body weight at Week 26 / ANCOVA (with LOCF) + MMRM + odds ratio. 2, Change in HbA1c from baseline, FPG, proportion of participants with HbA1c <7.5%, <7.0% and <6.5%, Time to rescue therapy and proportion of participants receiving rescue therapy, and Body weight at Week 52/ ANCOVA (with LOCF) + MMRM + odds ratio.	Superiority of the primary endpoint was achieved for Cana. Difference [Cana-Placebo] in LS Means (CI) is -0.73 (-1.26, -0.19) with 2-sided p-value = 0.008.

* MC: multi-center, R: randomized, DB: double-blind, PG: parallel group, PC: placebo controlled, AC: active controlled, Cana: Canagliflozin, TrtP: treatment period, wk: week, scr: screening, FPG: fasting plasma glucose, LOCF: last observation carried forward, MMRM: mixed model for repeated measures, ANCOVA: analysis of covariance, N**: number of patients enrolled in domestic (USA), N***: number of patients on metformin background enrolled in domestic (USA), RDMI: retrieved dropouts multiple imputation, PMI: pattern-mixture imputation (refer to section 3 for details), LS: least squares.
Source: Reviewer's Analysis Using Applicant Submitted Dataset adsl.xpt and adhba1c.xpt.

2.2 Data Sources

The Electronic Document Room (EDR) location for the submission package is \\CDSESUB1\evsprod\NDA204042\0458.

The applicant’s responses to IRs are located at:

- \\CDSESUB1\evsprod\NDA204042\0462,
- \\CDSESUB1\evsprod\NDA204042\0469,
- and \\CDSESUB1\evsprod\NDA204042\0474.

The file folder named “0458” contains the original submission package of the pediatric study, which includes the study reports, SDTM dataset, ADSL dataset, and the associated SAS codes. The sponsor had submitted the missed subgroup analyses and codes, along with minor typo corrections, in the file folder titled “0462”, which replied to FDA’s information request(IR) dated 07/23/2024.

Since the sponsor's imputation method does not fully align with FDA’s current preferred imputation method, an IR was sent on 09/25/2024 and response received on 10/11/2024. The file folder named “0469” contains the sponsor's analyses with the revised imputation, referring to Section 3 for imputation details. Additional "g-computation" analyses for categorical endpoints were submitted to fulfill the FDA's request dated 09/25/2024. Since the sponsor's subgroup analyses does not align with FDA’s current preferred method, another IR was sent on 11/08/2024 and response received on 11/13/2024. The file folder named “0474” contains sponsor's updated subgroup analyses based on imputed datasets imputed by the whole dataset, updated FPG analyses and 2-way tipping point analyses for metformin subgroup.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

No issues have been identified with respect to data and analysis quality.

3.2 Evaluation of Efficacy

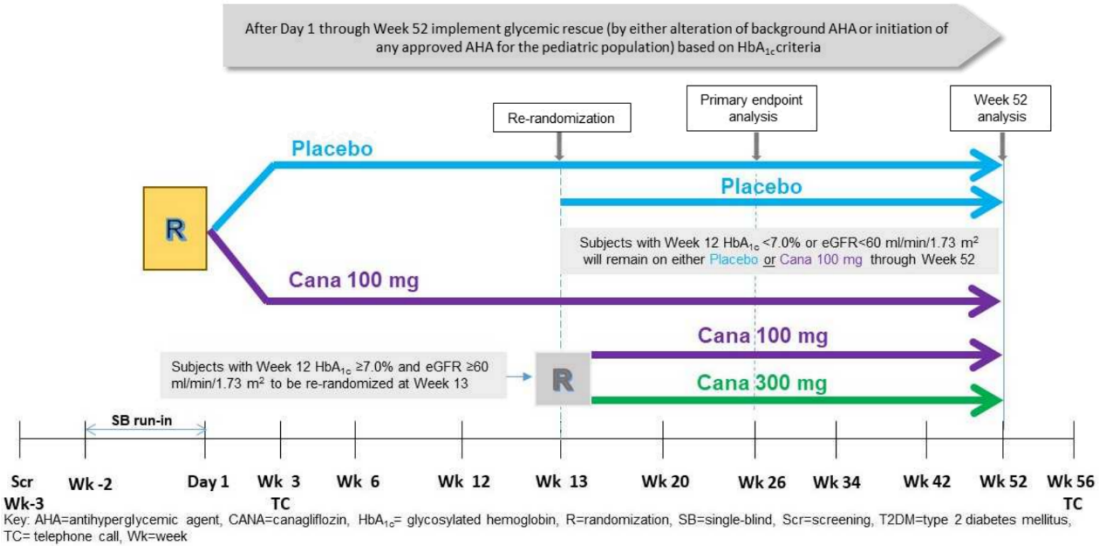
3.2.1 Study Design and Endpoints

The Study DIA3018 is a 52-week randomized, double-blind, placebo-controlled, parallel-group study, consisting of a 26-week core double-blind treatment period followed by a 26-week extension double-blind treatment period. Subjects who meet all enrollment criteria are randomly assigned in a 1:1 ratio to once-daily administration of canagliflozin 100 mg or placebo and enter a 52-week double-blind placebo-controlled treatment phase consisting of a 26-week core double-blind treatment period, followed by a 26-week double-blind extension treatment period.

Randomization was stratified by antihyperglycemic agent (AHA) background (i.e, diet and exercise only, metformin monotherapy, insulin monotherapy, or combination of insulin and metformin) and age group [≥10 to <15 years old, ≥15 to <18 years old]. Subjects who at Week

12 have an HbA1c of ≥ 7.0% and an estimated glomerular filtration rate (eGFR) ≥ 60 mL/min/1.73 m² had second randomization in a 1:1 ratio to either remain on double-blind canagliflozin 100 mg (or matching placebo) or to up titrate to double-blind canagliflozin 300 mg (or matching placebo). A diagram of the study design is showed in Figure 1.

Figure 1. Diagram of the Study Design, DIA3018.

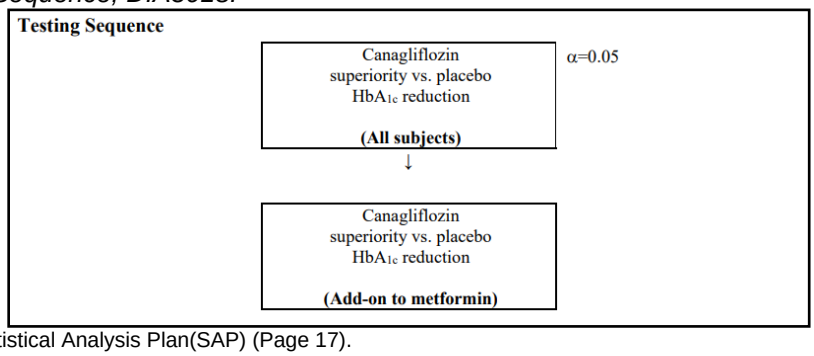


Source: Sponsor's Final Clinical Study Report (Page 25).

On Day 1 of the 26-week core period, 84 subjects were randomized to the treatment arm, while 87 subjects were randomized to the placebo arm. Of the 84 participants on canagliflozin, 33 participants were re-randomized at Week 12 (16 remained on 100 mg and 17 were up-titrated to receive 300 mg)

The primary objective of the study was to demonstrate the superiority of canagliflozin (100 mg or 300 mg pooled) to placebo as assessed by the primary endpoint: HbA1c (%) change from baseline at Week 26. A sequential testing procedure as illustrated in Figure 2 below was applied. The primary endpoint will be first tested in all subjects (i.e., FAS), and if the results are significant (2-sided alpha level of 0.05), it will then proceed to test the subset of subjects on a background of metformin (with or without insulin).

Figure 2. Testing Sequence, DIA3018.



Source: Sponsor's Statistical Analysis Plan(SAP) (Page 17).

In the supplemental SAP, Bayesian analysis of the primary efficacy endpoint is proposed to be performed if the study on its own does not yield significant result based on primary efficacy analysis. Since both tests achieved superiorities, Bayesian methods are not applied. (Refer to Section 3.2.4 for results of test details.)

3.2.2 Statistical Methodologies

Estimand Framework

The applicant pre-specified an estimand framework in the SAP as following.

- Population: children and adolescents (≥10 to <18 years) with T2DM who have an HbA1c ≥6.5% to ≤11.0%.
- Variable: change in HbA1c from baseline to Week 26.
- Treatment: canagliflozin (100 mg or 300 mg) vs placebo.
- Intercurrent events (ICEs) (events that preclude observation of the variable or affect its interpretation): treatment discontinuation or initiation of rescue medication; ICEs are addressed with the treatment policy strategy, targeting the effect of treatment assignment, regardless of the occurrence of ICE.
- Population-level summary: difference in means versus placebo.

Analyses Set

The safety analysis set consisted of the participants who are randomized and took at least 1 dose of study agent. Other than the safety analyses, all the other analyses use the full analysis set (FAS). FAS include all subjects who was randomly assigned to a treatment group, received at least one dose of the study drug, and has a baseline HbA1c measurement.

Handling of Missing Data and Primary Efficacy Analyses

The pre-specified primary analysis is based on pattern mixture (PM) imputation. The PM regression model proposed by the sponsor, which uses treatment group as a factor, assumes a treatment effect when calculating the Type I error and overlooks the interaction term between treatment and ICEs. This may result in inaccurate estimates and incorrect p-value and corresponding confidence interval calculations. Thus, a retrieved dropout (RD) imputation method was requested by IR. The details of RD imputation are as described below with 6 steps:

1. Any intermediate missing data will be multiply imputed using Monte Carlo Markov Chains (MCMC), under a Missing at Random (MAR) assumption.
2. For participants with intercurrent events (ICEs) and missing Week 26 HbA1c values from each of the two separate arms, impute missing values using a multiple imputation (MI) model based on participants with ICEs and non-missing Week 26 HbA1c values within each arm separately. An MI regression will be applied to impute all monotone missing values, using stratification factors, baseline HbA1c and the change from baseline in HbA1c at Weeks 6, 12 and 20. If the algorithm of certain imputation step does not converge, all stratification factors in the MI model of this step will be removed.

3. The MI imputation for participants without ICEs was applied for each treatment group separately.
4. A total of 1000 multiple imputations will be performed. A seed equal to 345 will be used in all MI models.
5. After MI, each of the multiply imputed datasets will be analyzed using analysis of covariance (ANCOVA) with terms for treatment, stratification factors, and baseline HbA1c.
6. Rubin's rules will be applied to combine the ANCOVA results across the imputed datasets, including the Week 26 LS Means for each treatment group and the difference vs placebo in LS Means.

The same imputed datasets are used for key secondary endpoint, A1C changes from baseline to Week 26 for the subset of subjects on a background of metformin to avoid convergence issue and/or inflated standard errors from limited sample size of retrieved dropouts in this subset.

Sensitivity Analyses

The following sensitivity analyses are performed, all aligned with the primary estimand:

- A Copy Reference MI model proposed by sponsor is performed to estimate and test the treatment efficacy.
- A 2-way tipping point analysis is performed based on the ANCOVA model with RD multiple imputation.

Reviewer's Supportive Sensitivity Analyses

In addition, wash-out imputation is applied by the reviewer to support the robustness of the primary analysis results.

Other Efficacy Analyses

Because of second randomization, two analyses were performed for subjects in canagliflozin 100 mg with no dose increase after week 12 compared to placebo and for subjects in canagliflozin 100 mg up-titrate to 300 mg after week 12 compared to placebo with weights (weight of 2 to subjects who remain in 100 mg, and who up-titrate to 300mg, respectively) after RD multiple imputation by the reviewer.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

A summary of subject disposition is presented in Table 3. At Week 12, 33 patients in the pooled canagliflozin arm got second randomization to either canagliflozin 100 mg (N = 16) or 300 mg (N = 17). Of the randomized subjects, 10 (11.9%) in the canagliflozin group and 30 (34.5%) in the placebo group encountered ICEs, and 1 (1.1%) in the placebo arm and 5 (6.0%) in the canagliflozin group missed their primary endpoint assessments without ICEs. Of 30 patients with ICEs in placebo arm at Week 26, 6 patients missed their primary endpoint assessments, and 24 patients provided their primary endpoint assessments. Of 10 patients with ICEs in canagliflozin

arm at Week 26, 2 patients missed their primary endpoint assessments, and 8 patients provided their primary endpoint assessments. Reasons for missing dropouts are described in the Table 3. Of note, efficacy assessment is based on only 26-week short term treatment period.

Table 3. Subject Disposition and Data Capture: HbA1c at Week 26, in FAS Population, DIA3018.

	Cana (N=84) **n**	**Placebo (N=87)** **n**
Randomized and treated	84	87
Second randomized at Week 13 **	33	60
Remain on placebo	0	60
Remain on 100 mg cana	16	0
Second randomized to 300 mg cana	17	0
Not Second randomized at Week 13 *	47	23
Subjects with ICEs	10	30
Discontinued treatment only	5	21
Received rescue medication only	1	6
Discontinued treatment + received rescue medication	4	3
Retrieved dropouts (non-missing data with ICEs)	8	24
Missing Values of A1C at Week 26	7	7
Missing without ICEs prior to Week 26	5	1
Missing with ICEs prior to Week 26	2	6
Adverse Event	1	1
Refusing Further Treatment	1	0
Withdrawal by Parent	0	2
Withdrawal by Subject (due to Lack of Improvement)	0	1
Lost to follow-up	0	1
Physician decision	0	1

Cana, canagliflozin; eGFR Criteria, eGFR <60 mL/min/1.73 m2; A1C Criteria, HbA1c value <7.0%; #, number; # of Subjects with ICEs = # of Retrieved dropouts + # of Missing with ICEs prior to Week 26; # of Missing Values of A1C at Week 26 = # of Missing without ICEs prior to Week 26 + # of Missing with ICEs prior to Week 26.
* For subjects with an HbA1c < 7% or an eGFR < 60 mL/min/1.73m2 .
** For subjects with an HbA1c level ≥ 7% and an eGFR ≥ 60 mL/min/1.73m2.
Source: Reviewer's Analysis Using Applicant Submitted Dataset adsl.xpt, adhba1c.xpt and addisp.xpt.

A summary of patient demographics and baseline characteristics is presented in Table 4. Based on the summary, demographics and baseline characteristics are balanced between the canagliflozin and placebo groups except the "Black or African American" subgroup in the race. There were more subjects in the Placebo group compared to Canagliflozin group (13 vs 6).

Table 4. Demographics and Baseline Characteristics in FAS Population, DIA3018.

Characteristic	Cana N = 84	Placebo N = 87
Age, years		
Mean (SD)	14.3 (2.0)	14.4 (2.0)
[Min, Max]	[10.0, 17.0]	[10.0, 17.0]
Age Category, n (%)		
10 to <15	39 (46%)	42 (48%)
15 to ≤18	45 (54%)	45 (52%)
Sex, n (%)		
Female	57 (68%)	60 (69%)
Male	27 (32%)	27 (31%)
Race, n (%)		
AMERICAN INDIAN OR ALASKA NATIVE	4 (4.8%)	4 (4.6%)
ASIAN	34 (40%)	38 (44%)
BLACK OR AFRICAN AMERICAN	6 (7.1%)	13 (15%)
MULTIPLE	0 (0%)	1 (1.1%)
WHITE	40 (48%)	31 (36%)
Ethnicity, n (%)		
HISPANIC OR LATINO	33 (39%)	29 (33%)
NOT HISPANIC OR LATINO	51 (61%)	57 (66%)
NOT REPORTED	0 (0%)	1 (1.1%)
Geographic Region, n (%)		
Eastern Asia	1 (1.2%)	3 (3.4%)
Eastern Europe	10 (12%)	6 (6.9%)
Latin America and the Caribbean	20 (24%)	16 (18%)
Northern America	19 (23%)	22 (25%)
South-eastern Asia	24 (29%)	29 (33%)
South America	4 (4.8%)	8 (9.2%)
Southern Asia	6 (7.1%)	3 (3.4%)
Body Mass Index (kg/m2) at Baseline		
Mean (SD)	31.1 (7.2)	30.5 (7.7)
[Min, Max]	[19.0, 50.4]	[17.7, 56.6]
Baseline HbA1c(%)		
Mean (SD)	7.8 (1.3)	8.3 (1.3)
[Min, Max]	[5.8, 11.3]	[6.0, 11.2]
Baseline eGFR(mL/min/1.73m2)		
Mean (SD)	163.8 (33.7)	151.1 (29.7)
[Min, Max]	[84.0, 277.0]	[66.0, 284.0]
AHA Background, n (%)		
DIET AND EXERCISE ONLY	13 (15%)	10 (11%)
INSULIN MONOTHERAPY	9 (11%)	10 (11%)
METFORMIN AND INSULIN	23 (27%)	27 (31%)
METFORMIN MONOTHERAPY	39 (46%)	40 (46%)

Abbreviations: SD = standard deviation, Cana = canagliflozin
Source: Statistical Reviewer's Analysis Using Applicant Submitted Dataset adsl.xpt.

3.2.4 Results and Conclusions

Primary Efficacy Results

As demonstrated in Table 5, the LSMean difference (95% CI) in HbA1c change from baseline at Week 26 is -0.73 (-1.27, -0.19) for canagliflozin pooled vs. placebo, with a two-sided p-value 0.008. The LSMean difference (95% CI) in HbA1c change from baseline at Week 26 is -0.74 (-1.37, -0.12) for canagliflozin pooled vs. placebo in patients on background metformin (with or without insulin), with a two-sided p-value 0.020. The patient level residual standard deviation was estimated to be 1.57. The study has successfully demonstrated superiorities of canagliflozin and canagliflozin with metformin to placebo with respect to glycemic control.

Table 5. Primary and Key Secondary Efficacy Analyses: HbA1c Change from Baseline at Week 26 in FAS Population, DIA3018.

Primary [Whole T2DM Population]	**Canagliflozin [pooled 100 mg and 300 mg] N = 84**	**Placebo N=87**
Baseline, Mean (SD),	7.79 (1.31)	8.30 (1.37)
Week 26 Missing, n (%)	7 (8.33)	7 (8.05)
Change from baseline to Week 26*, LS Mean (SE),	-0.35 (0.218)	0.37 (0.197)
Comparison to Placebo*, LS Mean difference (95% CI),	-0.73 (-1.26, -0.19)	
Two-sided P-value	0.008	
Key Secondary [Metformin Subpopulation]	**Canagliflozin [pooled 100 mg and 300 mg] N = 62**	**Placebo N=67**
Baseline, Mean (SD),	7.81 (1.37)	8.44 (1.37)
Week 26 Missing, n (%)	6 (9.68)	5 (7.46)
Change from baseline to Week 26*, LS Mean (SE),	-0.38 (0.225)	0.37 (0.218)
Comparison to Placebo*, LS Mean difference (95% CI),	-0.74 (-1.37, -0.12)	
Two-sided P-value	0.020	

Abbreviations: CI = confidence interval, SD = standard deviation, SE = standard error, Min.= minimum, Max. = maximum.
* The LS Mean estimate is based on an ANCOVA model adjusted for baseline HbA1c, stratification factors, and treatment after imputing missing data using retrieved dropout method
Source: Reviewer's analysis Using Applicant Submitted Dataset adsl.xpt, adhba1c.xpt.

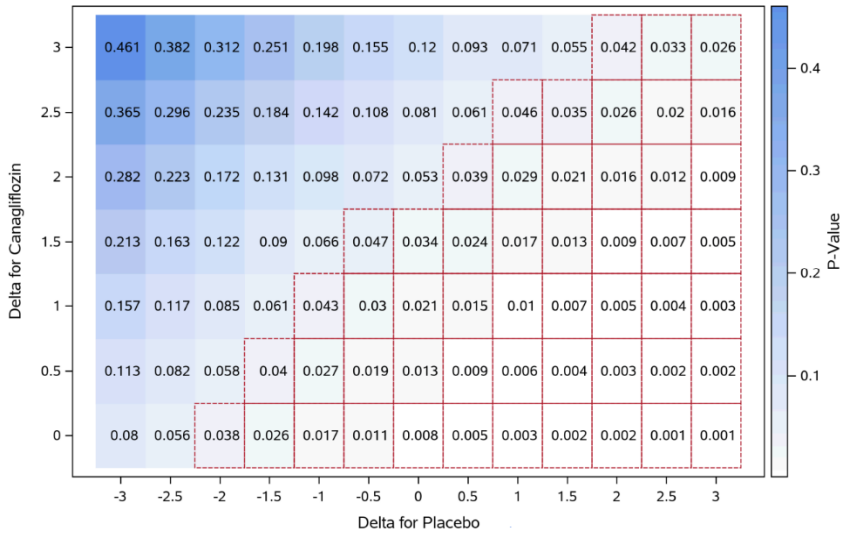
For sensitivity analysis, missing primary endpoints were multiply imputed based on the sponsor's copy-reference approach and reviewer's washout approach, as described in the Table 6. In addition, Figure 3 shows the p-value heatmap of the two-way tipping point analysis of primary efficacy endpoint, which implies the result of significant treatment benefit is robust.

Table 6. Primary and Key Secondary Efficacy Analyses: HbA1c Change from Baseline at Week 26 Based on Different Imputation Methods in FAS Population, DIA3018.

ANCOVA on All Patients	**Mean Difference Estimate (SE)**	**95% CI**	**P-value**
Retrieved Dropout	-0.73 (0.273)	(-1.27, -0.19)	0.008
Copy Reference	-0.71 (0.236)	(-1.17, -0.25)	0.003
Washout	-0.68 (0.236)	(-1.15, -0.22)	0.004
ANCOVA on Metformin Subgroup			
Retrieved Dropout	-0.74 (0.319)	(-1.37, -0.12)	0.020
Copy Reference	-0.73 (0.290)	(-1.30, -0.16)	0.012
Washout	-0.71 (0.286)	(-1.27, -0.15)	0.013

Abbreviations: CI = confidence interval; SE = standard error.
Source: Sponsor's Copy Reference Analyses in CSR (Page 71), Reviewer's Retrieved Dropout Analyses and Reviewer's Washout Analyses Using Applicant Submitted Dataset adsl.xpt, adhba1c.xpt and tefa1c03crm.txt.

Figure 3. Sensitivity Analysis: Graphical Representation of the P-Values of HbA1c Change from Baseline at Week 26 Derived from the Two-way Tipping Point Analysis in FAS Population, DIA3018.



Source: Sponsor's IR (Page 19), Dated 10/11/2024, Validated by the Reviewer.

Other Efficacy Results

The LS Mean differences in HbA1c change from baseline at Week 26 are -0.58 (95% CI: -1.16, -0.01) for subjects in canagliflozin 100 mg with no dose increase after week 12 to placebo and -0.89 (95% CI : -1.42, -0.36) for subjects in canagliflozin 100 mg up-titrate to 300 mg after week 12 to placebo. The group of subjects who were up-titrated to 300 mg of canagliflozin showed numerically larger reduction.

Reviewer's Note:

The reviewer used "PROC MIXED" in SAS by assigning weight value of 2 and 0 to different dose arms of subjects who got second randomized to get above LS mean differences results. The sponsor's efficacy results of LS mean differences using mixed model for repeated measures (MMRM) are -0.58 (95% CI: -1.08, -0.09) and -0.74 (95% CI : -1.21, -0.28) separately.

Other Exploratory Efficacy Results

As demonstrated in the below Table 7, the LSMean difference (95% CI) in fasting plasma glucose (FPG) change from baseline at Week 26 is -25.51 (-49.55, -1.47) for canagliflozin pooled vs. placebo. Similar estimate of LSMean difference in FPG change in patients on background metformin was observed.

Table 7. Secondary Efficacy Analysis: FPG (mg/dL) Change from Baseline at Week 26 in FAS Population, DIA3018.

	Canagliflozin [pooled 100 mg and 300 mg] N = 84	**Placebo N=87**
Baseline, Mean (SD),	154.8 (57.26)	156.5 (66.12)
Week 26 Missing, n (%)	9 (10.71)	7 (8.05)
Change from baseline to Week 26*, LS Mean (SE)	-8.2 (9.43)	17.3 (7.79)
Comparison to Placebo*, LS Mean difference (95% CI), Nominal P-value	-25.51 (-49.55, -1.47) 0.038	

Abbreviations: CI = confidence interval, SD = standard deviation, SE = standard error.
* The LS Mean estimate is based on an ANCOVA model adjusted for baseline FPG, stratification factors, and treatment after imputing missing data using retrieved dropout method
Source: Reviewer's Analyses Using Applicant Submitted Dataset adsl.xpt, adfpg52h.xpt and ada1c52h.xpt.

The results of proportion of patients with HbA1c (%) less than 7.5%, less than 7% or less than 6.5% at Week 52 using g-computation based on RD imputed datasets are shown in the below Table 8. Since all the standardized odds ratios are greater than 1 with nominal p-values less than 0.05, this further suggests a significant mean treatment benefit of canagliflozin at Week 26. Refer to Appendix Table 10 for proportion of subjects with HbA1c (%) < 7% at baseline.

Table 8. Secondary Efficacy Analysis: Proportion of Subjects with HbA1c (%) < 7.5%, < 7% or < 6.5% at Week 26 in FAS Population, DIA3018.

	Placebo (N=87)		Cana (N=84)		Cana versus Placebo		
	n	%	n	%	Odds Ratio	95% CI	p-value
< 7.5%	32	40.0	50	64.9			
>= 7.5%	48	60.0	27	35.1			
Total	80	100	77	100	Conditional 2.26	(0.86, 5.96)	0.099
					Standardized 1.65	(1.02, 2.67)	0.043
< 7%	22	27.5	40	51.9			
>= 7%	58	72.5	37	48.1			
Total	80	100	77	100	Conditional 2.22	(0.74, 6.66)	0.153
					Standardized 1.71	(1.03, 2.85)	0.039
< 6.5%	9	11.3	32	41.6			
>= 6.5%	71	88.8	45	58.4			
Total	80	100	77	100	Conditional 4.81	(1.59, 14.62)	0.006
					Standardized 3.25	(1.64, 6.42)	<.001

Abbreviations: CI = confidence interval.
Source: Sponsor's IR Response (Page 29), Dated 10/11/2024.

3.3 Evaluation of Safety

Subject-level hypoglycemia episodes (<70 mg/dL) for the 26-week core double-blind treatment period and the 52-week double-blind treatment phase in safety analysis set are analyzed by "g-computation" with negative binomial regression on safety analysis set. There was comparable safety observed since the event rate ratios for canagliflozin compared to placebo are either close to 1 or less than 1 as shown in the Table 9.

Table 9. Safety Analysis: Hypoglycemia Episodes for the Core Double-blind Treatment Period in Safety Analysis Set, DIA3018.

	Canagliflozin N = 84	**Placebo N = 87**
Week 26		
Number of Events (Total time at risk*)	32 (39.94)	24 (37.49)
Adjusted Event Rate Ratio (95% CI) ** Canagliflozin vs. placebo	1.08 (0.37, 3.15)	
Week 52		
Number of Events (Total time at risk*)	60 (72.72)	76 (59.47)
Adjusted Event Rate Ratio (95% CI) ** Canagliflozin vs. placebo	0.77 (0.19, 3.18)	

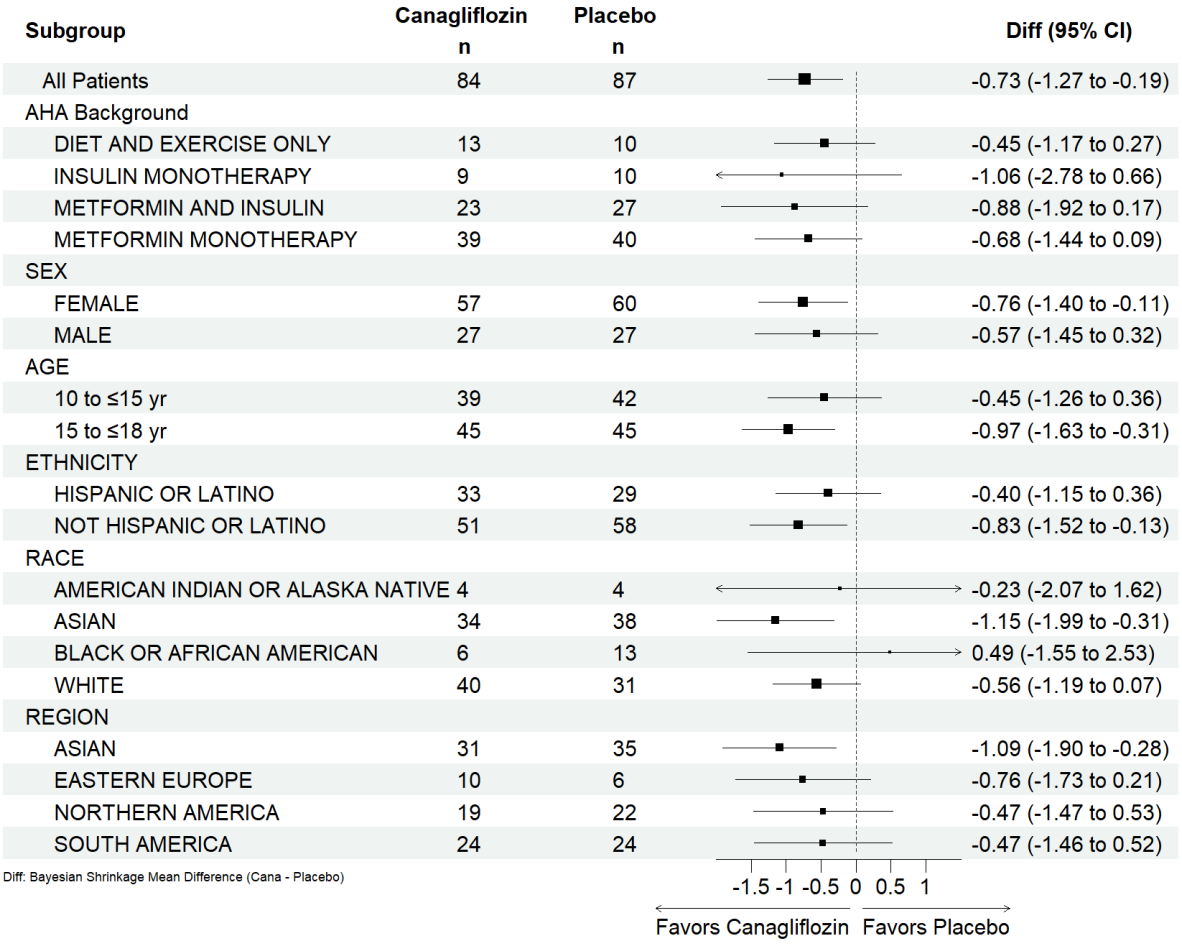
* The unit of the total time at risk is patient year.
** Smaller value of adjusted event rate ratio favors canagliflozin.
Source: Sponsor's IR Response (Page 30), Dated 10/11/2024.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, Ethnicity and Geographic Region

Subgroup analyses on HbA1c (%) change from baseline at Week 26 were conducted with respect to the baseline characteristics: sex, race, age, ethnicity, and region. Each analysis modeled the primary endpoint with an ANCOVA adjusted for baseline HbA1c, treatment, age stratum at randomization (except for the subgroup analysis on age), subgroup and subgroup-by-treatment interaction. Some subgroups are combined by the sponsor due to limited sample size. Similar to the primary efficacy analysis, missing data were first multiply imputed using retrieved dropout method based on FAS. Then for each of imputed subset, ANCOVA analyses are applied. Finally, the inference results were combined via Rubin's Rule. Figure 4 contains the forest plot of subgroup results. All the p-values of interaction terms between subgroup and treatment are larger than 0.1.

Figure 4. Primary Efficacy Subgroups Analyses: HbA1c Change from Baseline at Week 26 in FAS Population, DIA3018.



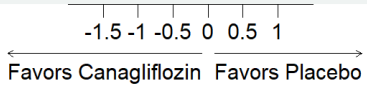
*The "Multiple" group (N=1) in the Race subgroup was not shown in this figure due to insufficient sample size for subgroup analyses.
**Size of black square (point estimate) in the forest plot is proportional to the precision (i.e., inverse of variance) of the estimates.
Source: Statistical Reviewer's Analysis Based on the Last 250 Multiple Imputations Using Applicant Submitted Dataset adsl.xpt, and adhba1c.xpt.

From Figure 4, all estimates of LSMean difference in primary endpoint favor canagliflozin except the race subgroup of Black or African American(BAA). Of 13 subjects in the placebo arm of BAA subgroup, mean observed primary endpoints was 0.53%, with 3 subjects had primary endpoint measurements missing. Of 6 subjects in the pooled canagliflozin arm of BAA subgroup, mean observed primary endpoints was 0.6%, 2 observed values for the primary endpoint were 5.2% and 2.7% with 1 ICE, and the rest 4 observed values were all negative, which implies that certain patients within BAA subgroups receive a benefit from the treatment.

4.2 Bayesian Shrinkage Subgroup Analyses

Figure 5. Primary Efficacy Subgroups Analyses: HbA1c Change from Baseline at Week 26 Based on Bayesian Shrinkage Methods in FAS Population, DIA3018.

Subgroup	Canagliflozin n	Placebo n	Diff (95% CI)
All Patients	84	87	-0.73 (-1.27 to -0.19)
AHA Background			
DIET AND EXERCISE ONLY	13	10	-0.58 (-1.15 to -0.01)
INSULIN MONOTHERAPY	9	10	-0.72 (-1.57 to 0.12)
METFORMIN AND INSULIN	23	27	-0.72 (-1.42 to -0.03)
METFORMIN MONOTHERAPY	39	40	-0.66 (-1.24 to -0.08)
SEX			
FEMALE	57	60	-0.72 (-1.30 to -0.14)
MALE	27	27	-0.63 (-1.35 to 0.10)
AGE			
10 to ≤15 yr	39	42	-0.59 (-1.31 to 0.12)
15 to ≤18 yr	45	45	-0.87 (-1.48 to -0.26)
ETHNICITY			
HISPANIC OR LATINO	33	29	-0.50 (-1.17 to 0.17)
NOT HISPANIC OR LATINO	51	58	-0.73 (-1.36 to -0.11)
RACE			
AMERICAN INDIAN OR ALASKA NATIVE	4	4	-0.52 (-1.59 to 0.54)
ASIAN	34	38	-0.87 (-1.59 to -0.16)
BLACK OR AFRICAN AMERICAN	6	13	-0.38 (-1.59 to 0.82)
WHITE	40	31	-0.60 (-1.16 to -0.04)
REGION			
ASIAN	31	35	-1.03 (-1.80 to -0.25)
EASTERN EUROPE	10	6	-0.78 (-1.68 to 0.11)
NORTHERN AMERICA	19	22	-0.58 (-1.55 to 0.39)
SOUTH AMERICA	24	24	-0.58 (-1.54 to 0.37)



Diff: Bayesian Shrinkage Mean Difference (Cana - Placebo)

*The "Multiple" group (N=1) in the Race subgroup was not shown in this figure due to insufficient sample size for subgroup analyses.
**Size of black square (point estimate) in the forest plot is proportional to the precision (i.e., inverse of variance) of the estimates.
Source: Reviewer's Analysis Based on the Last 250 Multiple Imputations Using Applicant Submitted Dataset adsl.xpt and adhba1c.xpt.

Additionally, the summary level Bayesian shrinkage analyses based on the sample estimates were performed. For a given baseline characteristic with k subgroups, let y_i $(i = 1,...k)$ be the observed sample estimate of the treatment effect in subgroup i. The shrinkage analysis in this review assumes the following:

- $y_i \sim N(\mu_i, \sigma_i^2)$ where μ_i is the expected treatment effect for subgroup i, and $\sigma_i^2$is the within-subgroup variance.
- $\sigma_i^2$is set to the variance for the sample estimate.
- $\mu_s \sim N(\mu, \tau^2)$, where $\mu \sim N(0, 16)$ and $\tau \sim Half\text{-}Normal(1)$.

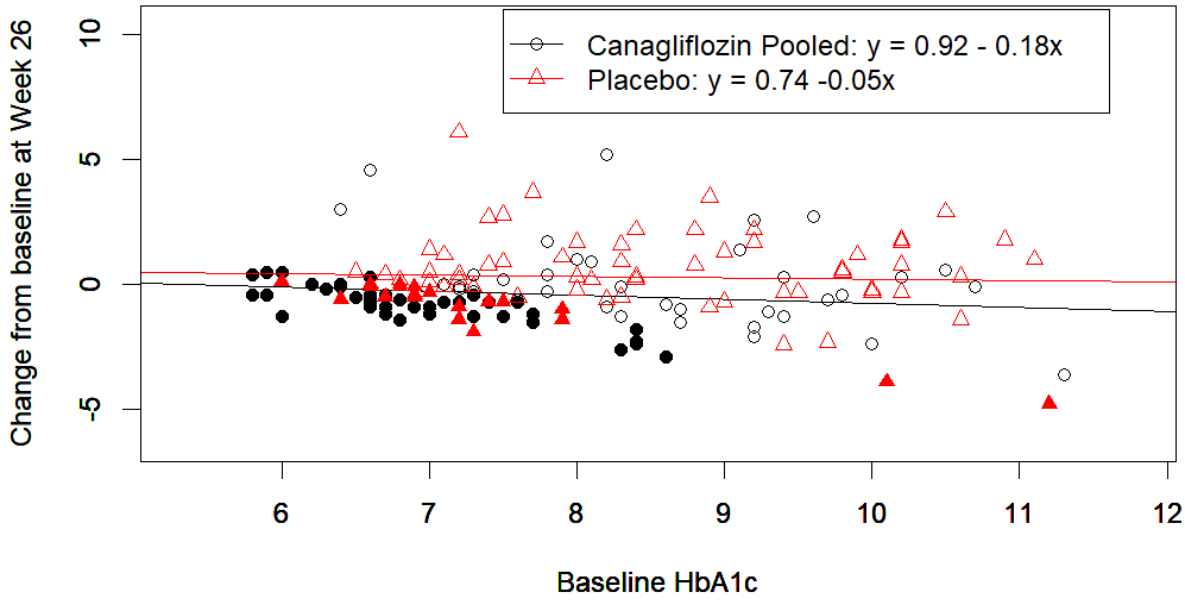
$N(0, 16)$ and $Half\text{-}Normal(1)$ are selected as weakly informative prior distributions for hyper-mean, μ and hyper-standard error, τ. Of note, all of subgroup estimates of LSMean

difference favor canagliflozin after Bayesian shrinkage, suggesting homogeneous treatment effects of canagliflozin across different subpopulations, as described in Figure 5.

4.3 Subgroup Analyses of Baseline HbA1c as an Effect Modifier

It is well known that baseline HbA1c is an effect modifier, (i.e., the treatment effect on HbA1c change will depend on a subject's baseline HbA1c measurement). Figure 6 below is a scatter plot of HbA1c change from baseline at Week 26 vs baseline HbA1c. The scatter points are color-coded by treatment arms. Hollow points represent observations with HbA1c values at or above 7% at Week 26, while solid points represent observations with HbA1c values below 7% at Week 26. Two regression lines based on completers (including retrieved dropouts) from canagliflozin pooled and placebo are superimposed over the scatter points. The regression line is y = 0.92-0.18x for canagliflozin pooled, and y= 0.74-0.05x for placebo. The difference in slopes is 0.13, which implies that for every 1% increase in baseline HbA1c, the placebo-adjusted treatment effect measured by HbA1c change from baseline increases by 0.13%. The higher the baseline HbA1c, the larger the treatment effect. In the primary analysis, baseline HbA1c was included in the ANCOVA model to adjust for this modification effect.

Figure 6. Scatterplot: Baseline HbA1c vs Change from Baseline at Week 26, in FAS Population, DIA3018.



Hollow points represent observations with HbA1c values at or above 7% at Week 26, while solid points represent observations with HbA1c values below 7% at Week 26.
Source: Statistical Reviewer's Analysis without Adjusting Stratification Factors Using Applicant Submitted Dataset adsl.xpt and adhba1c.xpt.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

The multiple imputation method proposed by the sponsor in the SAP does not correctly implement multiple imputation approach using the retrieved dropouts (RD). We perform the multiple imputation using RDs by treatment group separately to address this issue (Section 3.2.2).

5.2 Collective Evidence

For the primary efficacy analysis, the superiority of canagliflozin (pooled doses) compared to placebo was achieved by ANCOVA model with RD multiple imputation method, copy reference multiple imputation method and washout multiple imputation method. Also, the superiority was achieved in patients on background metformin (with or without insulin). Tipping point analyses further confirmed robustness of the primary efficacy results. Both of analyses of FPG and proportion of subjects with HbA1c (%) < 7.5%, < 7% or < 6.5% at Week 26 further suggest the treatment benefit. Subgroup analyses on the primary efficacy endpoint found consistent treatment effect of canagliflozin in subgroup levels based on AHA background, age, sex, race, ethnicity, and region. There were comparable hypoglycemia episodes between canagliflozin and placebo group at Week 26 and Week 52.

5.3 Conclusions and Recommendations

Statistical analyses based on the clinical data from the Phase 3 pediatric study, DIA3018, have demonstrated robust evidence to support the effectiveness of canagliflozin regarding glycemic control among pediatric subjects (10 to <18 years) with T2DM. The statistical team recommend approval of the proposed label updates for INVOKANA, INVOKAMET and INVOKAMET XR.

5.4 Labeling Recommendations

The sponsor proposed to add pediatric population to the T2DM indication as the following bold part:

- 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

In support of this pediatric indication, a new section with statistical inference on pediatric clinical studies (Section 14.2 Glycemic Control Trial in Pediatric Patients Aged 10 and Older with Type 2 Diabetes Mellitus) was added to Section 14 of the prescribing information. I recommend using the statistical results derived by retrieved dropout multiple imputations instead of the (b) (4) in the Section 14. The missing percentage should be added to tables. (b) (4) the sponsor proposed tables should be removed to ensure consistency and prevent overinterpretation. Additionally, the FPG table should be presented in text form without including potentially misleading nominal p-values.

APPENDICES

Table 10. Secondary Efficacy Analysis: Proportion of Subjects with HbA1c (%) < 7% at Baseline in FAS Population, DIA3018.

	Canagliflozin Pooled N = 84	**Placebo N = 87**
Baseline A1C <7%, n	26	16
Baseline A1C ≥ 7%, n	58	71

Source: Statistical Reviewer's Analysis Using Applicant Submitted Dataset adsl.xpt.

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

/s/

YUHAO LI
11/25/2024 01:24:36 PM

YOONHEE KIM
11/25/2024 01:35:00 PM
I concur