Clinical Review
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Supplemental NDAs 204042/S-43, 204353/S-46, 205879/S-23
Invokana (canagliflozin), Invokamet (canagliflozin and metformin hydrochloride), Invokamet XR (canagliflozin and metformin hydrochloride extended release)

CLINICAL REVIEW

Application Type	Supplemental NDA
Application Number(s)	NDA 204042/S-43, NDA 204353/S-46, NDA 205879/S-23
Priority or Standard	Priority
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Division/Office	Division of Diabetes, Lipid Disorders and Obesity (DDLO)/ Office of Cardiology, Hematology, Endocrinology and Nephrology (OCHEN)
Reviewer Name(s)	Susan Yuditskaya, MD
Review Completion Date	December 17, 2024
Established/Proper Name	Canagliflozin, canagliflozin and metformin hydrochloride, canagliflozin and metformin hydrochloride extended-release
(Proposed) Trade Name	Invokana, Invokamet, Invokamet XR
Applicant	Janssen Pharmaceuticals, Inc.
Dosage Form(s)	tablet
Applicant Proposed Dosing Regimen(s)	Invokana: 100mg once daily and 300mg once daily Invokamet: twice daily, 100 to 300 mg total daily dose of canagliflozin; 1000 to 2000 mg total daily dose of metformin HCl Invokamet XR: once daily, 100 to 300 mg total daily dose of canagliflozin; 1000 to 2000 mg total daily dose of metformin
Applicant Proposed Indication(s)/Population(s)	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.
Recommendation on Regulatory Action	Approval of proposed new indication; PMR 2027-2 fulfilled; grant pediatric exclusivity
Recommended Indication(s)/Population(s) (if applicable)	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.

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Glossary

AC	advisory committee
AE	adverse event
AESI	adverse event of special interest
AHA	antihyperglycemic agent
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CIs	clinical investigator
CI	confidence interval
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CVD	cardiovascular death
DBP	diastolic blood pressure
DMC	data monitoring committee
DKA	diabetic ketoacidosis
ECG	electrocardiogram
eCTD	electronic common technical document
eGFR	estimated glomerular filtration rate
ER	extended-release
ETASU	elements to assure safe use
FAS	full analysis set
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
FDCP	Fixed-dose combination product
FPG	fasting plasma glucose

GCP	good clinical practice
GLP-1	glucagon-like peptide 1
GRMP	good review management practice
HbA1c	hemoglobin A1c
HCG	human chorionic gonadotropin
ICE	intercurrent events
ICH	International Council for Harmonization
IND	Investigational New Drug Application
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
LS	least squares
MedDRA	Medical Dictionary for Regulatory Activities
MI	multiple imputation
mITT	modified intent to treat
MODY	maturity onset diabetes of youth
MTD	maximally tolerated dose
NDA	new drug application
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMM	pattern mixture model
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SD	standard deviation
SGE	special government employee
SGLT2	sodium-glucose cotransporter 2

SMBG	self-monitored blood glucose
sNDA	supplemental new drug application
SOC	standard of care
T1D	type 1 diabetes mellitus
T2D	type 2 diabetes mellitus
TEAE	treatment emergent adverse event
ULN	upper limit of normal
US	United States
USPI	United States Prescribing Information
WR	Written Request
XR	extended-release

1. Executive Summary

1.1. Product Introduction

Canagliflozin is a sodium-glucose cotransporter 2 (SGLT2) inhibitor. SGLT2 inhibitors have been used as treatments for type 2 diabetes (T2D), based on a mechanism of action in which plasma glucose levels are lowered by blocking reabsorption of filtered glucose in the proximal kidney tubules. Canagliflozin is available as Invokana tablets (canagliflozin NDA 204042), Invokamet tablets (canagliflozin and metformin hydrochloride, NDA 204353), and Invokamet XR tablets (canagliflozin and metformin hydrochloride extended release, NDA 208658). These products are indicated as an adjunct to diet and exercise to improve glycemic control in adults with T2D. Invokana and the canagliflozin component of Invokamet and Invokamet XR are also indicated reduce the risk of cardiovascular death (CVD) in adult patients with T2D and established cardiovascular disease, and to reduce the risk of end-stage kidney disease, doubling of serum creatinine, cardiovascular death, and hospitalization for heart failure in adults with type 2 diabetes mellitus and diabetic nephropathy with albuminuria. Pursuant to the Pediatric Research Equity Act (PREA), and in response to a Written Request (WR), Janssen Pharmaceuticals, Inc ("the Applicant") has conducted a pediatric postmarketing study [Study JNJ-28431754DIA3018 (referred to as "DIA3018" in this review)] to assess the safety and efficacy of canagliflozin for the glycemic control indication in pediatric patients with T2D, aged 10 years and older. Based on the results of Study DIA3018, the Applicant requests expansion of the glycemic control indication for Invokana, Invokamet, and Invokamet XR to adult and pediatric patients aged 10 years and older.

1.2. Conclusions on the Substantial Evidence of Effectiveness

Effectiveness of canagliflozin to improve glycemic control in pediatric patients with T2D was established based on results from one adequate and well-controlled study (DIA3018) plus confirmatory evidence[1]. After 26 weeks, treatment with canagliflozin was superior to placebo in reducing hemoglobin A1c (HbA1c) compared to baseline [placebo-adjusted treatment difference of -0.73% (95% confidence interval -1.27 to -0.19, p=0.008)]. Confirmatory evidence is derived from the previous finding of effectiveness of canagliflozin 100 mg and 300 mg in adult patients with T2D, based upon demonstration of durable and clinically meaningful reductions of A1c in nine pivotal, randomized, double-blind, controlled phase 3 trials (7 placebo-controlled, 2-active controlled) of canagliflozin in the adult T2D population, in which the efficacy of canagliflozin to reduce HbA1c when administered as monotherapy and as add-on therapy to

[1] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/demonstrating-substantialevidence-effectiveness-human-drug-and-biological-products

metformin and other background anti-diabetic agents, was demonstrated[2].

The efficacy of Invokana and the canagliflozin component of Invokamet and Invokamet XR in pediatric patients aged 10 years and older is demonstrated by the results of Study DIA3018, as presented in this review.

The safety and efficacy of the metformin component of Invokamet in pediatric patients has been previously established with the pediatric approval of Glucophage[3]. The Applicant is relying on Glucophage (metformin hydrochloride; NDA 020357) as the reference listed drug for the 505(b)2 applications of Invokamet.

The safety and efficacy of the metformin XR component of Invokamet XR in pediatric patients is supported by the Applicant's scientific justification to rely on the Agency's previous findings of safety and effectiveness for Glucophage in pediatric patients with T2D aged 10 years and older. To support this justification, the Applicant is relying on Glucophage as the reference listed drug for the 505(b)2 applications of Invokamet XR. The initial Invokamet XR NDA contained a right of reference to NDA 021748 for Glumetza (metformin hydrochloride extended release). The Applicant is continuing to rely on the Glumetza information available at the time of the approval of the original Invokamet XR NDA (NDA 205879, approved on 20 September 2016) to support the sNDA. The Applicant's scientific justification for the safety and efficacy of the metformin XR component of Invokamet XR contains the following key elements:

1. Similar pharmacokinetics, safety, and efficacy of Glucophage in adult and pediatric subjects, based on product labeling for Glucophage.
2. Similar exposures, safety, and efficacy of Glumetza as compared to Glucophage in adult subjects, based on product labeling for Glumetza.

The scientific arguments provided by the Applicant are considered appropriate to justify the Applicant's proposal to rely on the Agency's previous findings of safety and effectiveness Glucophage to broaden the glycemic control indication for Invokamet XR to include pediatric patients aged 10 and greater with T2D.

In addition, Study DIA3018 fulfills the Pediatric Research Equity Act Postmarketing Requirement (PMR) 2027-2.

The Pediatric Exclusivity Board agreed that Study DIA3018 fulfilled the WR, issued on March 18, 2014 and amended on February 10, 2015, October 15, 2018, July 16, 2020, July 28, 2020, July 12, 2022, and January 26, 2024, in accordance with the Best Pharmaceuticals for Children Act (BPCA). Pediatric exclusivity has been granted for studies conducted on canagliflozin, effective December 9, 2024, under section 505A of the FD&C Act (21 U.S.C. 355a).

[2] See primary clinical review by Dr. Hyon Kwon under NDA 204042, dated 02/11/2013.
[3] Sections 8.4, 12.3, and 14 of the product labeling for Glucophage

1.3. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

The incidence and prevalence of pediatric type 2 diabetes mellitus (T2D) has been increasing in the United States over the past two decades[1], with racial and ethnic groups that have historically experienced healthcare disparities disproportionately affected. Emerging data suggests pediatric patients may experience more rapid progression of disease and accelerated development of diabetes complications and comorbidities as compared to adults with T2D[2]. Treatment options for pediatric T2D are limited as compared to adults, including only a few choices for oral therapy (metformin hydrochloride, Farxiga, Xigduo XR, Jardiance, and Synjardy), several injectable glucagon-like peptide-1 (GLP-1) receptor agonists, and insulin products. There is an unmet need for additional oral treatment options for pediatric patients with T2D.

Janssen Pharmaceuticals, Inc ("the Applicant") has submitted supplemental new drug applications (sNDAs) for Invokana (canagliflozin), Invokamet (canagliflozin and metformin hydrochloride fixed dose combination product), and Invokamet XR (canagliflozin and metformin hydrochloride extended-release fixed dose combination product), proposing to broaden the indication to improve glycemic control to include pediatric patients with T2D aged 10 years and older, based on the results of a single adequate and well-controlled pediatric phase 3 study, Study DIA3018, plus confirmatory evidence derived from phase 3 studies of canagliflozin in the adult T2D population. Study DIA3018 was 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, in 171 pediatric T2D subjects aged 10 to <18 years of age. Subjects were randomized 1:1 to canagliflozin 100 mg or placebo. Subjects in the canagliflozin 100 mg group who failed to achieve HbA1c <7.0% at week 12 underwent a second randomization at Week 13 to remain on the 100 mg dose or increase to 300 mg; subjects in the placebo group remained on placebo. A total of 87 subjects received canagliflozin and 84 subjects received placebo. The average age was 14.3 years, the average duration of T2D was 2.0 years, and the mean HbA1c was 8.0%. The majority of subjects (75.4%) were treated with background metformin (with or without insulin), and 40.3% were treated with background insulin. Approximately 42% were Asian, 42% were White, 11% were Black or African-American, 5% were American Indian or Alaska Native, and 36% were of Hispanic or Latino ethnicity. The majority were obese (mean body mass index (BMI) was 30.8 kg/m^2 and mean BMI Z-score was 1.84).

The primary efficacy endpoint of Study DIA3018 was change from baseline in HbA1c at 26 weeks, for the pooled canagliflozin dosing group

versus placebo. Based on the primary efficacy analysis (which was adjusted for treatment, baseline HbA1c, and baseline age group), canagliflozin was superior to placebo in reducing HbA1c from baseline to Week 26 [placebo-adjusted treatment difference of -0.73% (95% confidence interval -1.27 to -0.19, p=0.008)]. Superiority of canagliflozin was also demonstrated in the subgroup of subjects on background metformin [placebo-adjusted treatment difference of -0.74% (95% CI -1.37 to -0.12; p = 0.02)]. Analyses of change from baseline in fasting plasma glucose (FPG) [placebo-adjusted treatment difference of -25.51 mg/dL (95% CI -49.55 to -1.47)] and of the proportion of subjects achieving glycemic thresholds at Week 26 were supportive of the primary efficacy result. A consistent treatment effect of canagliflozin was also observed in subgroup analyses based on background antidiabetic agent, age, sex, race, ethnicity, and region.

A clear dose-response for the canagliflozin 300 mg dose as compared to the 100 mg dose could not be identified in the pediatric study due to several limitations, including the small number of subjects who received canagliflozin 300 mg (N=17) and the differences in baseline characteristics among these subjects. Despite these limitations, labeling for the 300 mg dose in the pediatric population is supported by the previously demonstrated efficacy and dose-response in adult T2D phase 3 trials which can be extrapolated to the pediatric T2D population due to the similarity in PK and PD. Additional evidence for the efficacy of the canagliflozin 300 mg dose is derived from the primary outcome analysis which included data from subjects who received canagliflozin 300 mg, as well as the finding of a numerically greater treatment effect in canagliflozin-treated subjects who were uptitrated to 300 mg after week 12 as compared to those who remained on 100 mg with no dose increase [placebo-adjusted treatment difference in HbA1c change from baseline to Week 26 of-0.89% (95% CI : -1.42 to -0.36) vs. -0.58% (95% CI: -1.16 to -0.01)].

Substantial evidence of effectiveness of canagliflozin to improve glycemic control in pediatric patients with T2D was based on a single, adequate and well-controlled study (Study DIA3018) demonstrating the efficacy of canagliflozin to reduce HbA1c in pediatric T2D subjects when administered as monotherapy or as add-on therapy to metformin and/or insulin, plus confirmatory evidence derived from phase 3 studies of canagliflozin in the adult T2D population demonstrating the efficacy of canagliflozin to reduce HbA1c when administered as monotherapy and as add-on therapy to metformin and other background antidiabetic agents. The observed reduction in HbA1c from baseline in Study DIA3018 (-0.74%) is clinically meaningful, and of similar magnitude to the HbA1c reduction observed in adult studies (-0.62 to -1.16%). Although there are differences in disease progression between the adult and pediatric T2D populations, the use of adult data as confirmatory evidence for the substantial evidence of effectiveness determination is appropriate considering the similar underlying disease pathophysiology and similar exposure-response to canagliflozin between adult and pediatric T2D subjects as demonstrated in Study DIA3018. HbA1c is a validated surrogate endpoint for regulatory decision-making; improved glycemic control, as measured by HbA1c reduction, has clearly demonstrable benefits in improving microvascular outcomes and may also improve macrovascular outcomes. Therefore, the improved

glycemic control from canagliflozin treatment as demonstrated in Study DIA3018 is expected to result in a reduced risk of microvascular disease.

The risks of canagliflozin in adult T2D subjects are well characterized and include diabetic ketoacidosis, volume depletion, hypoglycemia with concomitant use of insulin and/or sulfonylureas, infections (including urinary tract infections, genital mycotic infections and necrotizing fasciitis), hypersensitivity reactions and bone fractures. In Study DIA3018, serious adverse events occurred in 8 (9.5%) subjects treated with canagliflozin and in 5 (5.7%) subjects treated with placebo. All SAEs and adverse events of special interest (AESIs) assessed as treatment-related or for which an imbalance was observed with canagliflozin treatment (including diabetic ketoacidosis, volume depletion, genital mycotic infections, and urinary tract infections) reflect known and labeled safety issues in adults. An increased incidence of hypoglycemia events was observed with canagliflozin as compared to placebo in the subgroup of patients treated with background insulin (25% vs. 16.2%), whereas a similar imbalance was not observed in the subgroup of subjects who were not treated with background insulin. These findings suggest that the hypoglycemia risk in pediatric T2D subjects is comparable to that described in adults as occurring in the setting of concomitant treatment with insulin or insulin secretagogues.

In summary, the data submitted from Study DIA3018 study plus confirmatory evidence from adult studies of canagliflozin support the benefit of canagliflozin to improve glycemic control in pediatric T2D patients. The safety profile of canagliflozin in pediatric subjects with T2D in Study DIA3018 was generally similar to the known and labeled safety profile in adults with T2D; no new pediatric-specific safety issues were identified. The overall evidence from Study DIA3018 study supports a favorable benefit-risk profile of canagliflozin in pediatric subjects aged 10 years and older with T2D. The safety and efficacy of the metformin component of Invokamet in pediatric patients has been previously established with the pediatric approval of Glucophage. The safety and efficacy of the metformin XR component of Invokamet XR in pediatric patients is supported by the Applicant's scientific justification to rely on the Agency's previous findings of safety and effectiveness for Glucophage in pediatric patients with T2D aged 10 years and older. All review disciplines support approval of this supplement.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• T2D is a serious and chronic medical condition associated with long term complications including both microvascular and macrovascular disease. • The prevalence of pediatric T2D is increasing in the U.S., with racial and ethnic groups that have historically experienced healthcare disparities disproportionately affected. • Although the pathophysiology of T2D is similar to adults, pediatric patients may experience more rapid disease progression and earlier beta-cell dysfunction compared with adults with T2D. • Pediatric patients also appear to have accelerated development of diabetes complications and comorbidities as compared to adults with T2D.	T2D in the pediatric population is a serious, chronic condition with increasing prevalence that disproportionately affects minority racial and ethnic groups. Pediatric T2D is characterized by more rapid disease progression, accelerated beta cell function decline, and accelerated development of diabetes complications compared to adults with T2D, resulting in earlier development of complications.
Current Treatment Options	• Prior to 2019, only metformin and insulin products were approved for the management of T2D in pediatric patients. • Since then, two SGLT2 inhibitors (empagliflozin and dapagliflozin) and three GLP-1 receptor agonists (liraglutide, exenatide, and dulaglutide) have been approved for glycemic control in pediatric patients with T2D. • Therapeutic options for pediatric patients with T2D remain limited.	Therapeutic options for pediatric patients with T2D remain an unmet need.
Benefit	• Study DIA3018 provides evidence of the efficacy of canagliflozin in improving glycemic control in the pediatric population with a statistically significant reduction in HbA1c from baseline for pooled canagliflozin doses (100 mg and 300 mg) vs placebo at Week 26: the placebo adjusted treatment difference was -0.73% (95% confidence interval -1.27 to -0.19, p=0.008).	Data from Study DIA3018 supports the effectiveness for canagliflozin in the pediatric population with T2D, with or without baseline metformin and/or baseline insulin therapy, by demonstrating a reduction in HbA1c from baseline which was both clinically significant

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Secondary efficacy analyses provided supportive evidence of efficacy of canagliflozin as compared to placebo, including demonstrated reductions in FPG from baseline and a greater proportion of subjects achieving HbA1c targets at Week 26 • Dose-response evaluation was limited due to small number of subjects treated with canagliflozin 300 mg (N=17) and differences in baseline characteristics among these subjects. Evidence for efficacy of the 300 mg dose can be extrapolated from adult studies due to similar exposure-response, and is supported by the primary outcome analysis and the numerically greater treatment effect in subjects uptitrated to the 300 mg dose as compared to those who remained on the 100 mg dose. • Fixed dose combinations of canagliflozin with metformin and metformin extended release (i.e., Invokamet and Invokamet XR) allow for simplification of treatment regimens by decreasing pill burden, and in the case of Invokamet XR, convenience of once daily dosing.	and statistically persuasive.
Risk and Risk Management	• No deaths occurred in Study DIA3018. • SAEs were infrequent (occurring in 9.5% of subjects treated with canagliflozin and 5.7% of subjects treated with placebo) and did not result in treatment discontinuation. • Treatment-related SAEs and AESIs occurring in Study DIA3018 reflect known and labeled safety issues in adults, including diabetic ketoacidosis, volume depletion, genital mycotic infections and urinary tract infections. Similar to adults, an increased risk of hypoglycemia was observed in pediatric subjects treated with	Canagliflozin was well-tolerated in the pediatric population with T2D with a safety profile similar to that described in adults as reflected in the current label.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	canagliflozin who received concomitant insulin therapy. • No new pediatric-specific safety signals were apparent. • Although conclusions are limited by the small sample size of Study DIA3018, the safety profile of canagliflozin in the pediatric population appears generally similar to that established in adults and is appropriately reflected in the proposed label.	

1.4. Patient Experience Data

This section is not relevant to the submission.

Patient Experience Data Relevant to this Application (check all that apply)

☐	The patient experience data that was submitted as part of the application include:			Section where discussed, if applicable
	☐	Clinical outcome assessment (COA) data, such as		[e.g., Sec 6.1 Study endpoints]
		☐	Patient reported outcome (PRO)	
		☐	Observer reported outcome (ObsRO)	
		☐	Clinician reported outcome (ClinRO)	
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		[e.g., Sec 2.1 Analysis of Condition]
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify)		
☐	Patient experience data that were not submitted in the application, but were considered in this review:			
		☐	Input informed from participation in meetings with patient stakeholders	
		☐	Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Current Treatment Options]
		☐	Observational survey studies designed to capture patient experience data	
		☐	Other: (Please specify)	
☒	Patient experience data was not submitted as part of this application.			

2. Therapeutic Context

2.1. Analysis of Condition

The incidence of pediatric type 2 diabetes mellitus (T2D) has been increasing over the past 2 decades.[1] As of 2017, the U.S. prevalence of pediatric T2D was estimated at 28,000, however, if current trends continue, the prevalence is projected to reach 220,000 by 2060.[3] The prevalence of pediatric T2D appears to be higher in certain racial and ethnic groups (including Non-Hispanic Blacks, Hispanics, Asians/Pacific Islanders and American Indians) and in adolescent girls (with a 60% higher prevalence rate than boys).[4] Nearly 80 to 90% of youth with T2D have overweight and obesity. The onset of pediatric T2D often coincides with pubertal insulin resistance and it is rarely diagnosed in patients below 10 years of age.

The pathophysiology of pediatric T2D is similar to that in adults, involving non-autoimmune pancreatic β-cell failure occurring on a background of insulin resistance. However, there are several differences in disease process and progression in pediatric versus adult T2D. The degree of insulin resistance in pediatric T2D appears to be more profound than in adults, even at the same degree of adiposity.[5,6] According to the TODAY study, nearly 50% of pediatric patients on metformin monotherapy failed glycemic control over a 4-year follow up with a median time to insulin of 11 months, far greater than the rates of glycemic failure reported in adults on metformin monotherapy.[7] Data from the TODAY study also suggest that some youth with T2D may experience more rapid deterioration of β-cell function as compared to adults,[8] while others may exhibit more durable glycemic control on metformin monotherapy.[9] The predictors of treatment response in pediatric T2D are not fully understood and currently under study. TODAY study participants who failed to maintain glycemic control had significantly lower β-cell function, higher fasting glucose concentration, higher HbA1c at randomization, and higher HbA1c after a short course of metformin compared to those who did not fail.[8,10,11] Diabetic ketoacidosis at the time of diagnosis of pediatric T2D also appears to predict greater β-cell decline over time.[12]

Youth with T2D also have accelerated development of diabetes complications and comorbidities. Based U.S. and Canadian registry studies, there is a higher prevalence of diabetic kidney disease, hypertension, retinal disease, and peripheral nerve disease in youth with T2D as compared to type 1 diabetes.[2,13] Compared to adults with T2D, diabetes-related complications appear early in youth with T2D and accumulate more rapidly. According to a longitudinal follow up study of youths with T2D,[2] at a mean time of 13.3 years since diagnosis (and mean age of 26.4 years), the incidence of diabetic kidney disease was 54.8%, the incidence of nerve disease was 32.4%, and the prevalence of retinal disease (including more advanced stages) was as high

as 51% within a 1-year period. At least 1 diabetes-related complication occurred in 60.1% of participants, at least two complications occurred in 28.4% of participants, and serious cardiovascular events occurred despite the young age of participants. The higher incidence of complications in youth-onset T2D may relate to more rapid disease progression, sub-optimal response to currently approved treatments, and additional age and socioeconomic-related challenges.[2]

2.2. Analysis of Current Treatment Options

There is an unmet need for additional treatment options for pediatric T2D. Current treatment options (other than insulin) approved for pediatric T2D are listed in Table 1. Glucophage (metformin hydrochloride) was approved for use in pediatric patients aged 10 years and older in 2004. A metformin extended-release product, Riomet ER (metformin hydrochloride extended-release oral suspension) was also approved in 2019 but is no longer marketed. In the past several years, three injectable glucagon-like peptide-1 (GLP-1) receptor agonist products have been approved for use in pediatric T2D: liraglutide (pediatric approval in 2019), exenatide (pediatric approval in 2021) and dulaglutide (pediatric approval in 2022). Before 2023, metformin hydrochloride was the only oral antihyperglycemic agent approved for use in pediatric type 2 diabetes; since then, the SGLT-2 inhibitors Jardiance (empagliflozin), and its fixed dose combination product (FDCP) Synjardy (empagliflozin and metformin hydrochloride), as well as Farxiga (dapagliflozin), and its FDCP Xigduo XR (dapagliflozin and metformin hydrochloride extended-release), have expanded their glycemic control indications to include pediatric patients age 10 years and above. However, no other oral antihyperglycemic agents are approved for use in pediatric patients, so options remain very limited. Recent pediatric trials of DPP-4 inhibitors have failed to demonstrate efficacy in pediatric T2D patients, despite the established efficacy in adults. The difference in pediatric versus adult efficacy for DPP-4 inhibitors may relate to the comparatively weaker glycemic lowering of DPP-4 inhibitors (as compared to GLP-1 receptor agonists) in the setting of a more progressive underlying disease. Some of the insulin products that have an indication “to improve glycemic control in adults and children with diabetes mellitus” are Humulin R (insulin human), Novolin R (insulin human), Humulin N (isophane insulin human), Novolin N (isophane insulin human), Novolin 70/30 (isophane insulin human and insulin human), Humulin R U-500 (insulin human), Apidra (insulin glulisine), Fiasp (insulin aspart), Humalog (insulin lispro), Levemir (insulin detemir), Novolog (insulin aspart), Ryzodeg (insulin degludec and insulin aspart), Toujeo (insulin glargine), Tresiba (insulin degludec), and Lyumjev (insulin lispro-aabc). No insulin product labels include any pediatric T2D efficacy trial data.

Table 1. Summary of Available Non-Insulin Therapies for Pediatric Type 2 Diabetes

Product (s) Name	Year of Approval	Currently Marketed (Yes/No)	Route and Frequency of Administration	Efficacy Information	Important Safety and Tolerability Issues
Glucophage (metformin hydrochloride)	2000	No* (several ANDAs available)	Oral, twice daily Dosage: 500 mg twice daily to be increased in 500 mg increments to a maximum of 2000 mg per day in divided doses	In a double-blind placebo- controlled study in pediatric patients, FPG change of -42.9 mg/dL in metformin group compared to + 21.4 mg/dL in placebo group ($p<0.0001$).	<u>Common AEs:</u> diarrhea, nausea, vomiting, flatulence, asthenia, indigestion, abdominal discomfort and headache. <u>Warning/Precaution:</u> lactic acidosis, vitamin B12 deficiency, hypoglycemia with concomitant use with insulin and insulin secretagogues.
Riomet (metformin hydrochloride oral suspension)	2003	No			
Riomet ER (metformin hydrochloride extended-release oral suspension)	2019	No	Oral, once daily Dosage: 500 mg once daily to be increased in 500 mg increments to maximum of 2000 mg per day.	Pediatric approval was based on 1) establishing similarity between Riomet ER and Glucophage XR (via a bioequivalence study), 2) similar efficacy, safety and pharmacokinetics between Glucophage XR and Glucophage IR in adults, and 3) similar efficacy, safety and pharmacokinetics between Glucophage IR in adults and pediatrics.	

Victoza (liraglutide)	2019	Yes	SC injection, once daily Dosage: 0.6 mg daily, to be increased to 1.2 mg and to 1.8 mg in weekly increments.	In a 26-week, double-blind, placebo-controlled clinical trial in 134 pediatric T2D patients aged 10 to 17 years, estimated treatment difference in HbA1c reduction from baseline between liraglutide and placebo was -1.06% (95% CI of -1.65% to -0.46%)	Common AEs: nausea, diarrhea, vomiting, decreased appetite, dyspepsia, constipation, and immunogenicity-related events (including urticaria). Warnings/Precautions: thyroid C-cell tumors (contraindicated in patients with a personal or family history of MTC or MEN2), pancreatitis, renal impairment, hypersensitivity and acute gallbladder disease, hypoglycemia regardless of concomitant insulin therapy in pediatric patients only*.
Bydureon (exenatide)	2021	Yes	SC injection, weekly Dosage: 2 mg once weekly	In a 24-week double-blind, placebo-controlled trial in 82 pediatric T2D patients aged 10 to 17 years, estimated treatment difference in HbA1c reduction from baseline between Bydureon and placebo was -0.71% (95% CI of -1.42% to 0%, p<0.05)	Common AEs: nausea, diarrhea, vomiting, constipation, headache, dyspepsia, injection-site site nodule, injection site pruritis. Warnings/Precautions: thyroid C-cell tumors (contraindicated in patients with a personal or family history of MTC or MEN2), acute pancreatitis, acute kidney injury, gastrointestinal disease, hypersensitivity reactions, drug-induced immune mediated thrombocytopenia, serious injection site reactions, immunogenicity-associated decreased glycemic control, acute gallbladder disease, hypoglycemia with concomitant use of insulin secretagogues or insulin.
Trulicity (dulaglutide)	2022	Yes	SC injection, once weekly Dosage: 0.75 mg once weekly, may increase to 1.5 mg once weekly after 4 weeks	In a 26-week double-blind, placebo-controlled trial of 154 pediatric T2D patients aged 10 years and older, estimated treatment difference in HbA1c reduction from baseline between pooled trulicity arms (0.75 mg and	Common AEs: nausea, diarrhea, vomiting, abdominal pain, decreased appetite, and injection site reactions (in pediatric patients only). Warnings/Precautions: thyroid C-cell tumors (contraindicated in patients with a personal or family history of

				1.5 mg) versus placebo was -1.4% (95% confidence interval of -1.9% to -0.8%).	MTC or MEN2), pancreatitis, hypoglycemia with concomitant use of insulin or insulin secretagogue, hypersensitivity reactions, acute kidney injury, severe gastrointestinal disease, diabetic retinopathy complications, acute gallbladder disease
Jardiance (empagliflozin)	2023	Yes	Oral, once daily Dosage: 10 mg once daily, can be increased to 25 mg once daily	In a 26-week, double-blind, placebo-controlled, parallel group trial with a double-blind active treatment safety extension period up to 52 weeks in 157 pediatric T2D patients aged 10 to 17 years, there was a -0.8% difference from placebo in HbA1c reduction from baseline (95% CI of -1.5% to -0.2%) and -36 mg/dL difference from placebo in fasting plasma glucose reduction from baseline (95% CI of -60.7 to -10.7 mg/dL) at 26 weeks.	Common AEs: urinary tract infections, genital mycotic infections Warnings/Precautions: ketoacidosis, volume depletion, urosepsis, pyelonephritis, hypoglycemia, necrotizing fasciitis of the perineum (Fournier's gangrene), genital mycotic infections, hypersensitivity reactions
Synjardy (empagliflozin/metformin)	2023	Yes	Oral, twice daily Dosage: 5 mg empagliflozin/500 mg metformin HCl twice daily, can be increased to a maximum dose of 12.5mg empagliflozin/1000 mg metformin HCl twice daily.	In a 26-week, double-blind, placebo-controlled, parallel group trial with a double-blind active treatment safety extension period up to 52 weeks of Jardiance in 157 pediatric T2D patients aged 10 to 17 years, 90.1% of whom were on background metformin therapy +/- insulin, there was a -0.8% difference from placebo in HbA1c reduction from baseline (95% CI of -1.5% to -0.2%) and -36 mg/dL difference from placebo in fasting plasma glucose reduction from baseline (95% CI of -60.7 to -10.7 mg/dL) at 26 weeks.	Common AEs: urinary tract infections, genital mycotic infections Warnings/Precautions: ketoacidosis, volume depletion, urosepsis, pyelonephritis, hypoglycemia, necrotizing fasciitis of the perineum (Fournier's gangrene), genital mycotic infections, lower limb amputation, hypersensitivity reactions, vitamin B12 deficiency

Farxiga (dapagliflozin)	2024	Yes	Oral, once daily Dosage: 5 mg once daily, can be increased to 10 mg once daily	In a 26-week, placebo-controlled, double-blind randomized clinical trial with a 26-week safety extension in 157 pediatric T2D patients aged 10 to 17 years, Farxiga provided a -1.0% difference from placebo in HbA1c reduction from baseline (95% CI of -1.6 to -0.5) and a -19.5 mg/dL difference from placebo in fasting plasma glucose reduction from baseline (95% CI of -36.4 to -2.6).	Common AEs: genital mycotic infections, nasopharyngitis, urinary tract infections Warnings/Precautions: diabetic ketoacidosis in patients with Type 1 diabetes mellitus and other ketoacidosis, volume depletion, urosepsis, pyelonephritis, hypoglycemia, necrotizing fasciitis of the perineum (Fournier's gangrene), genital mycotic infections.
Xigduo XR (dapagliflozin/metformin HCl extended-release)	2024	Yes	Oral, once daily Dosage: 5 mg dapagliflozin/500 mg metformin HCl extended-release once daily, can be increased to a maximum dose of 10 mg empagliflozin/2000 mg metformin HCl extended-release once daily.	In a 26-week, placebo-controlled, double-blind randomized clinical trial with a 26-week safety extension in 157 pediatric T2D patients aged 10 to 17 years, 88% of whom were on background metformin therapy +/- insulin, Farxiga provided a -1.0% difference from placebo in HbA1c reduction from baseline (95% CI of -1.6 to -0.5) and a -19.5 mg/dL difference from placebo in fasting plasma glucose reduction from baseline (95% CI of -36.4 to -2.6).	Common AEs: female genital mycotic infection, nasopharyngitis, urinary tract infection, diarrhea, nausea/vomiting, and headache. Warnings/Precautions: lactic acidosis, diabetic ketoacidosis in patients with Type 1 diabetes mellitus and other ketoacidosis, volume depletion, urosepsis, pyelonephritis, hypoglycemia, necrotizing fasciitis of the perineum (Fournier's gangrene), genital mycotic infections, hypoglycemia in patients taking insulin or insulin secretagogues, vitamin B12 deficiency

Source: Reviewer Created. Abbreviations: XR, ER= extended release, T2D= type 2 diabetes, FPG= fasting plasma glucose, HbA1c= hemoglobin A1c, AE= adverse events, MTC= medullary thyroid carcinoma, MEN2= multiple endocrine neoplasia type 2, SC= subcutaneous, ANDA= Abbreviated New Drug Application
**in adults, increased risk of hypoglycemia was seen only with concomitant insulin or insulin secretagogue therapy.*

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Invokana (canagliflozin, NDA 204042) was approved, as oral tablets, on March 29, 2013, at which time it was indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus and to reduce the risk of major adverse cardiovascular events in adults with type 2 diabetes mellitus and established cardiovascular disease. On Sept 27, 2019, a new indication was approved, to reduce the risk of end-stage kidney disease, doubling of serum creatinine, cardiovascular death, and hospitalization for heart failure in adults with type 2 diabetes mellitus and diabetic nephropathy with albuminuria.

Invokamet (canagliflozin and metformin hydrochloride, NDA 204353) and Invokamet XR (canagliflozin and metformin hydrochloride extended release, NDA 205879) were approved on August 08, 2014, and September 20, 2016, respectively. They are both indicated as an adjunct to diet and exercise to improve glycemic control in adults with T2D. The approval of Invokamet tablets (NDA 204353) was based on a 505(b)(2) application that relied upon the Agency's finding of safety and effectiveness for NDA 020357 Glucophage (metformin hydrochloride tablets) as the reference listed drug (LD). The approval of Invokamet XR tablets (NDA 205879) was based on a 505(b)(1) application that relied upon the Agency's finding of safety and effectiveness for Glumetza tablets (metformin hydrochloride extended release, NDA 021748), for which the Applicant had obtained a right to reference.

3.2. Summary of Presubmission/Submission Regulatory Activity

Regulatory History Relating to PREA PMRs:
According to the approval letters for Invokana (NDA 204042) and Invokamet (NDA 204353), the pediatric study requirement for ages 0 to 9 years (inclusive) was waived because the necessary studies were impossible or highly impracticable due to too few children in this age range with T2D, and the following deferred pediatric clinical studies for ages 10 to 17 years were required under the Pediatric Research Equity Act (PREA) as post-marketing requirements (PMRs):

- PMR 2027-1 A clinical pharmacology study to evaluate the pharmacokinetics, pharmacodynamics, and safety of canagliflozin in pediatric patients ages 10 to <18 years with type 2 diabetes mellitus on metformin monotherapy.
    - Final Protocol Submission: October 2013
    - Study Completion: December 2014
    - Final Report Submission: June 2015

- PMR 2027-2 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.
    - Final Protocol Submission: December 2015
    - Study Completion: June 2020
    - Final Report Submission: December 2020

- PMR 2761-1: A study to evaluate whether pediatric patients with type 2 diabetes ages 10 to 17 years (inclusive) or healthy pediatric subjects ages 10 to 17 years (inclusive) can safely swallow Invokamet tablets. The study should evaluate tablets that are the same dimensions as the largest Invokamet tablet, and placebo tablets should be used if the study population consists of healthy subjects.
    - Final Protocol Submission: May 2015
    - Study Completion: May 2017
    - Final Report Submission: November 2017

On September 12, 2014, the Sponsor requested deferral extensions for the PMR 2027-1 and 2027-2 due to enrollment issues experienced with the Phase 1 PK/PD pediatric study (28431754DIA1055). The Agency granted the deferral extension request on October 27, 2014 to the following:

- PMR 2027-1
    - Study Completion: December 31, 2015
    - Final Report Submission: June 30, 2016

- PMR 2027-2
    - Final Protocol Submission: December 31, 2016
    - Study Completion: June 30, 2021
    - Final Report Submission: December 31, 2021

On May 26, 2015, The Sponsor requested a second deferral extension for PMR 2027-1 due to continuing enrollment issues for Study 28431754DIA1055. On July 10, 2015, the Agency granted the deferral extension for the final report submission for PMR 2027-1 to June 30, 2017, but denied a deferral extension for PMR 2027-2 because there was insufficient information at the time to agree on the exact timeline for PMR 2027-2. In this correspondence, the Agency also agreed with the Sponsor's proposal to modify the 28431754DIA1055 study protocol for PMR 2027-1 by allowing the use of basal insulin as an acceptable concomitant background medication and allowing subjects on stable dose of metformin XR to participate after switching to metformin IR. This protocol amendment was intended to enhance study recruitment.

On June 29, 2015, the Agency issued a letter releasing PMR 2761-1. This was based on a determination that an evaluation of swallowability is no longer necessary because of a lack of clarity regarding the design and interpretation of such a study, and no prospect of benefit for study participants.

On October 30, 2015, the Agency provided a Written Response to a Type C Meeting request agreeing with the Sponsor's proposal to consolidate the previously proposed two Phase 3 studies to fulfill the WR (see regulatory history relating to the WR below) into a single study that would enroll subjects on a background of metformin or basal insulin in combination with metformin, but noted that if subjects on diet/exercise or insulin monotherapy alone are enrolled, the study should be sufficiently powered to assess the efficacy of canagliflozin on a background of metformin, if this study is intended to also satisfy the PREA requirement for the canagliflozin-metformin FDCPs.

On June 30, 2016, the final clinical study report for Study 28431754DIA1055 entitled "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 and Currently on a Stable Dose of Metformin," was submitted to NDA 204042.

On September 20, 2016, Invokamet XR (canagliflozin and metformin hydrochloride extended-release tablets, NDA 205879) was approved. The approval letter stated that PMRs 2027-1 and 2027-2 apply to Invokamet XR (NDA 205879) in addition to Invokana (NDA 204042) and Invokamet (NDA 204353).

On October 03, 2016, the Agency proposed considering an alternative trial design to address enrollment concerns for study JNJ-28431754DIA3018 (the planned phase 3 study to address PMR 2027-2), in which a re-randomization would be done at 12 weeks for a higher dose of canagliflozin versus current dose, if HbA1c is still >7%. This was discussed in the Type C Meeting Written Responses dated January 27, 2017.

On December 21, 2016, the final protocol for study JNJ-28431754DIA3018 was submitted to address PMR 2027-2.

On March 20, 2017, following the submission of the final report for Study JNJ-28431754DIA1055, PMR 2027-1 was fulfilled.

On December 15, 2021, the Agency granted a deferral extension on the Final Report Submission deadline for PMR 2027-2 to June 2024 to align with the new timeline established for study JNJ-28431754DIA3018 in the WR Amendment 2 (see regulatory history relating to the WR below).

<u>Regulatory History Relating to the Written Request (WR):</u>

On March 18, 2014, the original Written Request was issued to Invokana (NDA 204042). Three clinical studies were requested:

- Study 1: A phase 1 clinical pharmacology study to evaluate the pharmacokinetics (PK), pharmacodynamics (PD), and safety of canagliflozin in subjects ≥ 10 to < 18 years of age with T2D on a background of metformin.
- Study 2: A randomized, double-blind, placebo-controlled, phase 3, 52-week study to evaluate the efficacy and safety of canagliflozin when added on to metformin in subjects ≥ 10 to < 18 years of age with T2D who have been treated with a stable dose of metformin (≥1000 mg for at least 3 months before screening) and are experiencing inadequate glycemic control (HbA1c ≥7% and ≤10%).
- Study 3: A randomized, double-blind, placebo-controlled, phase 3, 52-week study to evaluate the efficacy and safety of canagliflozin in subjects ≥ 10 to < 18 years of age with T2D who have been treated with diet and exercise, have received less than seven days of any antidiabetic medications within eight weeks before screening, and are experiencing inadequate glycemic control (HbA1c ≥7% and ≤10%).

On February 10, 2015, the Agency issued Written Request Amendment 1 which amended the timeframes for submitting reports of the studies by one year to June 30, 2016, for Study 1; December 31, 2021, for Study 2; and December 31, 2026, for Study 3.

On October 15, 2018, the Agency issued Written Request Amendment 2 to consolidate the previously proposed two phase 3 studies into a single study that would enroll subjects on a background of diet and exercise with or without metformin and with or without insulin, and to have a re-randomization at week 12 for eligible participants still not at goal HbA1c, to either increase the dose or remain on the current dose of canagliflozin (or matching placebo).

On July 16, 2020, and July 28, 2020, the Agency issued Written Request Amendments 3 & 4, respectively, in response to several changes submitted by the Sponsor to broaden the enrollment criteria. Amendment 3 also included changes pertaining to the objective of Study 2, the major secondary objectives, and statistical analysis.

On July 12, 2022, the Agency issued Written Request Amendment 5 with changes pertaining to statistical analysis, including a plan to conduct a Bayesian analysis, among others.

On January 26, 2024, The Agency issued Written Request Amendment 6, qualifying that Bayesian analysis will be done only if the primary and secondary analyses of the primary efficacy endpoint do not result in a statistically significant result.

3.3. Foreign Regulatory Actions and Marketing History

As of March 28, 2024, canagliflozin is authorized in 70 countries. Canagliflozin/metformin fixed

dose combination (FDC) tablets are authorized in 48 countries. Canagliflozin/metformin XR FDC tablets are approved only in the United States.[4]

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

OSI conducted inspections for two domestic clinical investigators (CIs): Drs. Ulhas Nadgir, MD (Site #US10017) and Pedro A. Velasquez-Mieyer, MD (Site #US10050).

Site #US10017 screened 11 subjects, enrolled 7 subjects with 5 subjects completed the study. Source records for all 11 screened subjects were reviewed. The primary efficacy endpoint data of the change in HbA1c from baseline at Week 26 were verified with no discrepancies noted. There were no underreporting of AEs or SAEs. There was an investigational observation made that a subject (b) (6) was inappropriately enrolled despite a history of epilepsy and last use of phenytoin just a little over a month prior to enrollment. This would have met exclusion criterion #17 "Current use of anticonvulsant medication or is likely to require treatment with anticonvulsant medication." This error was also not reported as a protocol deviation. This subject was in the canagliflozin arm (100mg) and experienced a tonic-clonic seizure about 5 months into participating in Study DIA3018, which resulted in the subject being withdrawn from the study. Of note, this was one of the only two treatment emergent adverse events (TEAEs) that led to discontinuation in Study DIA3018.

Reviewer comment: Although this protocol deviation resulted in a TEAE that led to a discontinuation in the canagliflozin group, this was an isolated event that has minimal impact on the safety or efficacy evaluation of Study DIA3018.

Site #US10050 screened 11 subjects, enrolled 7 subjects (2 on canagliflozin group and 5 on placebo group) with 2 subjects (1 each on canagliflozin and placebo group) completed the study. Five subjects did not complete the study due to loss to follow up (3) and non-compliance (2). Source records of all 7 enrolled subjects were reviewed. The submitted data were verifiable with source records at the study site. The primary efficacy endpoint data of change in HbA1c from baseline at Week 26 were verified with no discrepancies noted. There were no underreporting of AEs or SAEs. There were two protocol deviations for Subjects (b) (6) (placebo group) and (b) (6) (placebo group) having been enrolled without repeated fasting self-monitoring blood glucose required to fully assess exclusion criterion #3; these were appropriately submitted as protocol deviations. Additionally, FDA inspection found that subject

[4] Development Safety Update Report (DSUR), covering period from March 29, 2023 to March 28, 2024, submitted to NDA for Invokana (NDA 204042)

(b) (6) (placebo group) and (b) (6) (placebo group) were documented as having been taking the anticonvulsant topiramate at the start of and during the study, which should have precluded their enrollment due to exclusion criterion #17. However, the clinical investigator responded to these investigational observations, that he had personally contacted these two subjects and confirmed that neither had taken topiramate before, during, or after the study, and therefore, concluded that these were documentation errors.

Reviewer comment: All four investigational observations made at site #US10050 were in subjects who were in the placebo group, and do not impact the efficacy or safety results of the study drug in Study DIA3018.

4.2. Product Quality

There are no new chemistry, manufacturing and controls (CMC) or sterility data.

4.3. Clinical Microbiology

There are no new data regarding microbiology information in the submission.

4.4. Nonclinical Pharmacology/Toxicology

There are no new data regarding pharmacology/toxicology information in the submission.

4.5. Clinical Pharmacology

This review references the primary review authored by Dr. Anusha Ande from the Office of Clinical Pharmacology, dated 11/22/2024. The clinical pharmacology package to support this submission included a dedicated PK/PD study (Study DIA1055) and a population PK model, which included serial PK samples from Study DIA1055 (from pre-dose to 72 hours post-dose on Day 14) and trough PK samples at week 12, Week 26, and Week 52 (or early withdrawal) from Study DIA3018.

Study DIA1055 was an open-label sequential, multiple-dose Phase 1 pharmacokinetic study conducted in 17 children and adolescents aged ≥10 to <18 years to evaluate the pharmacokinetics, pharmacodynamics, and safety and tolerability of canagliflozin after multiple oral doses of canagliflozin in children and adolescent subjects with T2D on a stable regimen of metformin at a dose of at least 1000 mg per day for at least 8 weeks prior to screening. Subjects were enrolled sequentially into the canagliflozin 100mg daily dose group (n=8) and the canagliflozin 300mg daily dose group (n=9). Subjects in each dose group received the respective dose of canagliflozin daily for 14 days. All 17 enrolled subjects completed the study. Study DIA1055 was reviewed in August 2016 by Clinical Pharmacology (Dr. S.W. Johnny Lau) and in March 2017 by clinical reviewer, Dr. Hyon Kwon. According to these reviews, the results of Study DIA1055 demonstrated lack of clinically meaningful differences in canagliflozin

pharmacokinetics and pharmacodynamics between pediatric patients (10 to 17 years inclusive) and adult patients, and no new or unexpected safety findings. Therefore, Study DIA1055 supported the use of the adult canagliflozin doses in the pediatric phase 3 study DIA3018.

According to Dr. Ande's review of clinical pharmacology data included in this submission, 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 T2D adequately described the observed HbA1c data in pediatric participants with T2D (≥10 to <18 years of age). In addition, based on PK/PD simulations, twice daily (BID) and daily (QD) canagliflozin dosing regimens at the same total daily dose are predicted to provide similar HbA1c lowering in pediatric patients with T2D. Therefore, pediatric patients with T2D 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. In addition, similar dosing and administration for INVOKAMET and INVOKAMET XR in adults and pediatrics is acceptable.

In Study DIA3018, the non-responders (N=33 of 84 treated) in the canagliflozin 100 mg arm who failed to achieve HbA1c <7.0% at Week 12 were re-randomized at Week 13 to increase to 300 mg (N=17) or to remain 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. According to the clinical pharmacology reviewer, the up-titration of dose to 300 mg in non-responders did not clearly reveal a dose response, since there was no significant difference in the mean HbA1c levels after week 12 between the group of patients who remained on 100 mg canagliflozin compared with the group uptitrated to 300 mg. However, Dr. Ande also notes that the interpretation of dose response was limited by the small sample size of patients re-randomized to up-titrate the dose to 300mg and confounded by differences in baseline values for HbA1c among the re-randomized non-responders versus those who did not meet criteria for re-randomization at Week 13; therefore, a clear dose-response for 100 mg and 300 mg could not be identified for canagliflozin in this pediatric population. Due to study design limitations that preclude a dose or exposure-response assessments in support of a dose increase to 300 mg in pediatric patients tolerating 100 mg, the clinical pharmacology team deferred to the clinical review team regarding labeling of the 300 mg dose for additional glycemic control.

As discussed in Section 6.1.2, the clinical review team has concluded that labeling of the 300 mg dose in the pediatric population is appropriate and supported by several lines of evidence, including the efficacy and dose-response of canagliflozin 300 mg that has previously been established in the adult population with T2D and evidence of efficacy from the primary outcome analysis of Study DIA3018 which was based on pooled data that included subjects who received the canagliflozin 300 mg dose. In addition, based on exploratory analyses completed by the statistical reviewer evaluating HbA1c change from baseline to Week 26, a numerically greater placebo-adjusted treatment difference was observed in pediatric subjects who were

uptitrated to canagliflozin 300 mg after week 12 as compared to all other subjects who remained on canagliflozin 100 mg with no dose increase [i.e., -0.89% (95% CI : -1.42 to -0.36) compared to -0.58% (95% CI: -1.16 to -0.01), see statistical review for further details].

For renal impairment, although there were no patients enrolled in either Study DIA1055 or Study DIA3018 with an eGFR <60 mL/min/1.73 m^2, based on the demonstrated similarity of PK and PD between adults and pediatric subjects ≥10 to <18 years of age, the clinical pharmacology team determined that the benefit-risk conclusions in adult patients with reduced renal function would be applicable to the pediatric population as well. Therefore, the clinical pharmacology team recommended a similar labeling approach for pediatric and adult patients with renal impairment, 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 and recommending against use in patients with eGFR < 30 mL/min/1.73 m^2.

4.6. Devices and Companion Diagnostic Issues

This section is not applicable to the submission.

4.7. Consumer Study Reviews

The Division of Medication and Error Prevention Analysis (DMEPA) review of the proposed US Prescribing Information (USPI) and Medication Guide dated November 22, 2024 did not identify areas of vulnerability that may lead to medication errors.

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

The primary efficacy and safety data to substantiate the proposed labeling claims and updates are based on a single, adequate and well-controlled phase 3 study, Study DIA3018.

5.2. Review Strategy

The primary documents reviewed were submitted under NDA 204042/S-043.

The review of efficacy focused on the Applicant's analyses and confirmatory analyses conducted by the statistician Dr. Yuhao Li.

The primary safety analysis is based on the 52-week placebo-controlled treatment period of Study DIA3018. Where applicable, I reviewed the safety data using the submitted datasets and also reviewed safety analyses completed by the Applicant.

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. [Study JNJ-28431754DIA3018 (Study DIA3018)]

6.1.1. Study Design

Overview and Objective

Study Title: 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

Primary Objective: To assess the effect of canagliflozin relative to placebo on HbA1c and the overall safety and tolerability of canagliflozin after 26 weeks of treatment in children and adolescents (10 to <18 years) with T2D who had inadequate glycemic control (i.e., HbA1c of 6.5% to 11.0%), either on diet and exercise only, diet and exercise and stable metformin monotherapy, diet and exercise and stable insulin monotherapy, or diet and exercise and a stable combination therapy with metformin and insulin.

Study Design

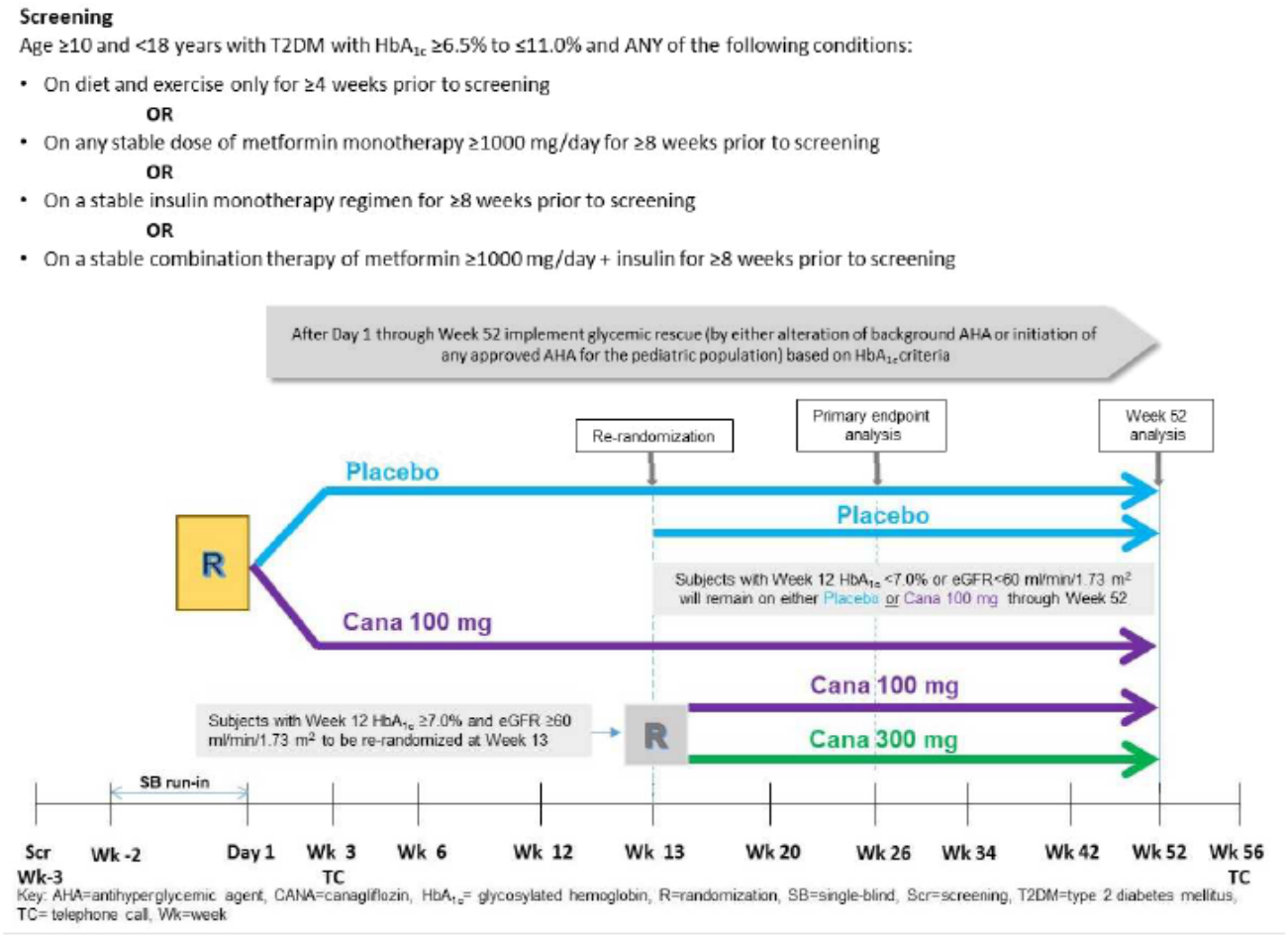
Study DIA3018 (Figure 1) was a 52-week randomized, double-blind, placebo-controlled, parallel-group study, consisting of a 26-week core double-blind treatment period followed by a 26-week safety extension double-blind treatment period, in patients with T2D ≥10 and <18 years of age who had inadequate glycemic control (i.e. HbA1c of 6.5% to 11.0%) either on diet and exercise only, diet and exercise and stable metformin monotherapy, diet and exercise and stable insulin monotherapy, or diet and exercise and a stable combination therapy with metformin and insulin.

Eligible subjects went directly into a 2-week single-blind placebo run-in period. Provided they met all other enrollment criteria at the conclusion of the run-in period, subjects were randomized in a 1:1 ratio to once-daily administration of canagliflozin 100 mg or placebo for 52 weeks. 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).

Canagliflozin-treated subjects who at Week 12 had an HbA1c of ≥7.0% and an estimated

glomerular filtration rate (eGFR) ≥60 mL/min/1.73 m2 were re-randomized at Week 13 in a 1:1 ratio to either remain on their original treatment (canagliflozin 100 mg) or to uptitrate to canagliflozin 300 mg. To maintain the study blinding, subjects treated with placebo were also re-randomized to matching placebo to canagliflozin 100 mg or 300 mg to undergo a mock uptitration.

Figure 1. Study Design of Study DIA3018



Source: Study DIA3018 CSR p. 25

Reviewer Comment: The study was designed to evaluate the efficacy of the pooled doses (100 mg and 300 mg) of canagliflozin. Because only subjects who were non-responders to canagliflozin 100 mg were eligible for re-randomization to a higher dose of canagliflozin through week 26, caution must be taken when interpreting efficacy information in this subgroup who may have had more rapid disease progression than the responders.

Trial Location and Administrative Structure:
Study DIA3018 was a multinational study conducted in 104 sites in 10 countries distributed as follows: Brazil (11), China (8), Greece (2), India (8), Malaysia (5), Mexico (10), Philippines (5), Poland (6), Russian Federation (15), and the US (34). The study included an internal medical safety review committee and an independent data monitoring committee, which was commissioned to review accumulated unblinded safety information during the study.

Dynamic randomization (i.e. covariate-adjusted randomization) was used to maintain balance between treatment groups with respect to the stratification factors – AHA background (i.e. diet and exercise only, metformin monotherapy, insulin monotherapy, or combination of metformin and insulin) and age group (≥10 to <15 years old, ≥15 to <18 years old). The stratification by age was to ensure that at least 30% of randomized subjects would be ≥10 to <15 years of age as required by the WR. Stratification and re-randomization occurred via Interactive Web Response System to maintain blinding.

Key Inclusion Criteria

- 10 to <18 years of age at the time of screening
- male or female patients
- diagnosis of T2D
- negative testing for markers of type 1 diabetes (random c-peptide, pancreatic autoimmunity)
- HbA1c of 6.5% to 11.0% and meeting 1 of the inclusion criteria below:
  - On diet and exercise only for at least 4 weeks prior to screening
  - On diet and exercise and a stable dose of metformin monotherapy 1,000 mg per day or maximally tolerated dose (MTD) per day (defined by the investigator) for at least 8 weeks prior to screening
  - On diet and exercise and a stable insulin monotherapy regimen for at least 8 weeks prior to screening (stable dose is defined as no change in the insulin regimen [i.e. type(s) of insulin] and up to a 15% change in the total daily dose of insulin [averaged over 1 week to account for day-to-day variability])
  - On diet and exercise and a stable combination therapy with metformin and insulin for at least 8 weeks prior to screening, as described above
- Each subject (or their legally acceptable representative) must have signed an informed consent form indicating that he or she understood the purpose of, and procedures required for the study and was willing to participate in the study. Assent was also required of children capable of understanding the nature of the study (approximately 7 years of age and older)
- For females of childbearing potential, use of highly effective birth control and a negative highly sensitive serum human chorionic gonadotropin (hCG) pregnancy test at the screening visit

- Adequate compliance with placebo single-blind run-in procedures, including 80% compliance (by tablet count) with single-blind placebo medication

Exclusion Criteria

Diabetes-Related/Metabolic

- History of diabetic ketoacidosis (DKA), type 1 diabetes (T1D), pancreas or cell transplantation, or diabetes secondary to pancreatitis or pancreatectomy or maturity onset diabetes of youth (MODY)
- On any AHAs other than metformin or injectable insulin within 8 weeks of the first dose of study agent
- Repeated (i.e., 2 or more over a 1-week period) fasting self-measured blood glucose (SMBG) >270 mg/dL (>15 mmol/L) during the pretreatment phase, despite reinforcement of diet and exercise counseling.
- Severe hypoglycemia within 6 months prior to Day 1
- History of hereditary glucose-galactose malabsorption or primary renal glucosuria

Renal/Cardiovascular

- Renal disease that required treatment with immunosuppressive therapy or a history of dialysis or renal transplant (except for those with a history of treated renal disease, without sequelae)

Gastrointestinal

- Known significant liver disease (e.g., acute hepatitis, chronic active hepatitis, cirrhosis)

Laboratory

- Persistent elevation in capillary blood ketones 0.6 mmol/L in the absence of concomitant illness or other identified precipitating factor during the screening period
- eGFR <60 mL/min/1.73m2 as assessed by Schwartz formula
- Alanine aminotransferase level >5.0 times the upper limit of normal (ULN) or total bilirubin >1.5 times the ULN at screening

Other Conditions

- History of malignancy within 5 years before screening (e.g., any evidence of active disease within 5 years, or diagnosis of malignancy within this period)
- Major surgery (i.e., requiring general anesthesia) within 12 weeks before screening, or had not fully recovered from surgery, or planned surgery during the participation of the current study
- History of non-traumatic amputation within past 12 months of screening, or an active skin ulcer, osteomyelitis, gangrene, or critical ischemia of the lower extremity within 6 months of screening

Medications/Therapies

- Previously been, or was currently being treated with an SGLT2 inhibitor, or the participant had participated or was currently participating in a canagliflozin study
- Known allergies, hypersensitivity, or intolerance to canagliflozin or its excipients

- Current use of corticosteroid medication or immunosuppressive agent, or likely to require treatment with a corticosteroid medication (for longer than 2 weeks in duration) or an immunosuppressive agent (except those using inhaled, intranasal, intra-articular, or topical corticosteroids, or corticosteroids in therapeutic replacement doses)
- Current use of anticonvulsant medication or was likely to require treatment with anticonvulsant medication
- Received an active investigational drug (including vaccines) or used an investigational medical device within 12 weeks before the planned start of treatment

Dose Selection:

The doses of canagliflozin used in Study DIA3018 were the same doses approved for use in adults with T2D. The selection of the canagliflozin 100mg and 300 mg doses was based on results of a single dose PK/PD study (Study JNJ-28431754DIA1055) showing a similar exposure-response relationship among adult and pediatric patients with T2D (see Section 4.5).

Study treatments:

Possible study treatments included canagliflozin 100mg tablets, canagliflozin 300mg tablets, and placebo to canagliflozin 100 mg and 300mg tablets. In the re-randomized participants, a double-dummy approach was used to maintain the blinding to dose assignments (protocol p. 54), as shown in Table 2.

Table 2. Summary of Dose Level and Number of Tablets by Study Period and Treatment

Study Period	Criteria for re-randomization	Treatment Group: canagliflozin	Treatment Group: placebo
Day 1 to re-randomization	Not applicable	1 tablet of canagliflozin 100 mg	1 tablet of placebo matching canagliflozin 100 mg
Re-randomization to Week 52	**NOT eligible for re-randomization if:** – HbA_{1c} <7.0% or – eGFR <60 mL/min/1.73m^2	1 tablet of canagliflozin 100 mg	1 tablet of placebo matching canagliflozin 100 mg
Re-randomization to Week 52	**Eligible for re-randomization if:** – HbA_{1c} ≥7.0% and eGFR ≥60 mL/min/1.73m^2	1 tablet of canagliflozin 100 mg **AND** 1 tablet of placebo matching canagliflozin 300 mg **or** 1 tablet of canagliflozin 300 mg **AND** 1 tablet of placebo matching canagliflozin 100 mg	1 tablet of placebo matching canagliflozin 100 mg **AND** 1 tablet of placebo matching canagliflozin 300 mg

Source: Study DIA3018 CSR p. 33

Discontinuation criteria:

Criteria to discontinue study treatment for individual subjects included:
(1) persistently poor compliance with study agent or procedures
(2) the investigator believed that for safety or tolerability reasons it was essential for the participant to discontinue study agent
(3) the subject experienced biochemically-confirmed DKA
(4) the investigator formally unblinded the subject's study treatment allocation
(5) the subject became pregnant
(6) the subject required disallowed therapy
(7) the subject had an eGFR of <45 mL/min/1.73m^2, confirmed by repeat
(8) the subject met the rescue therapy criteria, but the AHA to be initiated as rescue medication was not approved for use in the country of the investigational site, or the subject had a contraindication to the use of any approved AHA to be used as rescue medication, based upon the local label.

Treatment compliance:
The investigator or designated study research staff maintained a log of all drugs dispensed and returned. Drugs supplied for each subject were inventoried and accounted for throughout the study. Subjects who were poorly compliant with taking the study agent received counseling on the importance of dosing compliance and were permitted to continue in the study, at the investigator's discretion.

Subjects received clear instructions on compliance with study procedures at the screening visit. During the study, the investigator or designated study research staff was responsible for providing additional instructions to reeducate any subject who was not compliant with taking the study agent or with completing the diary, as required. Study agent interruption occurring for any reason was documented on the appropriate eCRF.

Background therapy:
Subjects were to remain on a stable AHA regimen (doses and medications) of metformin, insulin, or a combination of the two from screening to week 52, unless glycemic rescue criteria were met. Adjustment to the AHA regimen, including adjustments in insulin doses, insulin type, and metformin, was permitted in situations in which prolonged fasting was necessary.

Rescue Treatment:
To assure that subjects were not exposed to prolonged poor glycemic control, the investigator initiated glycemic rescue therapy (insulin or other approved glucose lowering agent for the pediatric population) based on the following criteria:

A baseline HbA1c <9.0% and a change from baseline >0.80%.
A baseline HbA1c ≥9.0% and a change from baseline >0.50%.

HbA1c levels were measured at least every 6-8 weeks.

No other SGLT2 inhibitors (including commercially available canagliflozin), or other AHAs that were not approved for use in pediatric populations, were to be used as concomitant medications, and subjects were not to take any other investigational agents during the study.

Study Procedures: Subject monitoring was conducted as per the schedule of events shown in Table 3:

Table 3. Time & Events Schedule, Study DIA3018

	Pretreatment Phase			Double-blind Treatment Phase[a]									Post-treatment
	Screening Visit	2-week SB PBO Run-In	Baseline										
	Wk -3	Wk -2[b]	Day 1	Wk 3 TC	Wk 6	Wk 12	Wk 13[c]	Wk 20	Wk 26	Wk 34	Wk 42	Wk 52/EOT /Early Withdrawal[d]	Rescue Visit	Telephone call at Wk 56 or 30 days post last dose[e]
Screening/Administrative														
Informed consent	X[f]													
Child or adolescent assent	X[f]													
Inclusion/Exclusion criteria[g]	X	X	X											
Medical history and demographics	X													
Prestudy therapy[h]	X													
Concomitant therapy[i]	X	X	X	X	X	X		X	X	X	X	X	X	
Randomization			X											
Assess eligibility for re-randomization[j]						X								
Re-randomization of eligible subjects							X[c]							
Study Drug Administration														
Dispense single-blind placebo		X												
Assess for single-blind placebo compliance			X											
Dispense double-blind study drug			X		X	X	X[k]	X	X	X	X			
Drug Accountability					X	X	X	X	X	X	X	X	X	
Assess/Reinforce double-blind study drug compliance				X	X	X	X	X	X	X	X		X	
Review thresholds for potential need for rescue medication[l]				X	X	X		X	X	X	X		X	

	Pretreatment Phase			Double-blind Treatment Phase[a]									Post-treatment
	Screening Visit	2-week SB PBO Run-In	Baseline										
	Wk -3	Wk -2[b]	Day 1	Wk 3 TC	Wk 6	Wk 12	Wk 13[c]	Wk 20	Wk 26	Wk 34	Wk 42	Wk 52/EOT /Early Withdrawal[d]	Rescue Visit	Telephone call at Wk 56 or 30 days post last dose[e]
Clinical Procedures														
Vital signs[m]	X		X		X	X		X	X	X	X	X	X	
Body weight[n]	X		X		X	X		X	X	X	X	X	X	
Height[o]	X		X		X	X		X	X	X	X	X	X	
Tanner Staging[p]			X						X			X	X	
Physical examination[q]			X						X			X	X	
Subject Counseling and Ongoing Review/Assessments														
Diet/exercise counseling[r]		X												
Diet/exercise monitoring and re-enforcement			X	X	X	X		X	X	X	X	X	X	
Counseling for hypoglycemia and recognition & treatment of ketosis-related medically important events[s]		X	X	X	X	X		X	X	X	X		X	
Review of subject diary[u]			X	X	X	X		X	X	X	X	X	X	
Record hypoglycemic episodes[t] and ketone levels		X	X	X	X	X		X	X	X	X	X	X	
Dispense glucose/ketone meter & test strips, urine ketone strips, and subject diary (as needed)[u]		X	X		X	X		X	X	X	X		X	
Safety Evaluations														
Foot examination[v]			X						X			X	X	
Record adverse events[w]		X	X	X	X	X	X	X	X	X	X	X	X	X[e]
Laboratory Assessments														
Fasting plasma glucose[x]			X						X			X	X	
Hemoglobin A_{1c}	X		X		X	X		X	X	X	X	X	X	
Site fingerstick glucose			X											
Random C- peptide	X													
Fasting C-peptide[x]			X						X			X	X	
Hematology[y]	X		X						X			X		
Serum chemistry panel[y]	X		X			X			X			X	X	

Source: Study DIA3018 Protocol, p.24-25

Subjects were provided a blood ketone meter and were recommended to obtain ketone measurements during periods of increased risk of ketonemia, such as acute illness, significant or sudden reduction in insulin dose, prolonged fasting or low carbohydrate diet, dehydration and/or a marked increase in physical activity, increased alcohol consumption, undergoing a minor procedure such as a dental extraction, or significant physiologic stress, regardless of the presence of symptoms of DKA. An algorithm was provided to subjects to determine, based on severity of illness, degree of ketosis, and ability to increase insulin dose and food intake, the appropriate frequency of retesting of ketones and glucose, action with blinded study drug, need to seek immediate medical attention or to contact the study site. Subjects were instructed to record information related to elevated ketones in a subject diary to be presented to the study site.

Study Endpoints

Primary Efficacy Endpoint:

- Change in HbA1c (%) from baseline to Week 26.

Key Secondary Efficacy Endpoint:

- Change in HbA1c (%) from baseline to Week 26 in the subgroup with metformin as background AHA

Secondary Efficacy Endpoints

- At Week 26 and Week 52:
  - Change from baseline in FPG
  - The proportion of participants with HbA1c <7.5%, <7.0%, and <6.5%
  - Time to rescue and proportion of participants receiving rescue therapy.
  - Percent change from baseline in body weight
  - Change from baseline in BMI.
  - Percent change from baseline Fasting plasma lipids (i.e., LDL-C, HDL-C, total cholesterol, non-HDLC, LDL-C to HDL-C ratio, non-HDL-C to LDL-C ratio, and triglycerides)
  - Change from baseline in systolic blood pressure (SBP) and diastolic blood pressure (DBP)
- Change from baseline in HbA1c to Week 12 and Week 52

Safety Endpoints:

- Adverse events (AEs) reported from baseline to Week 26 and from baseline to Week 52
  - Adverse events of Special Interest (AESI) included diabetic ketoacidosis, fractures, and pancreatitis
  - Selected AEs for additional analysis

        - Vulvovaginal candidiasis, balanitis or balanoposthitis, urinary tract infections, volume depletion, hepatic injury, renal impairment/renal failure, hypersensitivity, venous thromboembolic event, photosensitivity (canagliflozin absorbs light in the UV range that is a concern for photoirritation), malignancy, pancreatitis, and lower extremity amputation
- Treatment-emergent hypoglycemia at 26 weeks and 52 weeks, by background AHA subgroups
    - Diet and exercise only; or metformin monotherapy.
    - On insulin (with or without metformin)
- Percentage of subjects for each of the following glucose levels (70 mg/dL [3.9 mmol/L], <56 mg/dL [3.1 mmol/L], and <36 mg/dL [2.0 mmol/L]
- Subjects who had 0, 1, 2, or ≥3 documented episodes and subjects who had 0, 1, 2, or ≥3 severe hypoglycemic episodes
- Incidence of all episodes of hypoglycemia
- Change from baseline in serum electrolytes, lipids, insulin-like growth factor -1 (IGF-1) and insulin-like growth factor binding protein-3 (IGFBP-3), markers of calcium and phosphate homeostasis, and bone turnover markers after 26 and 52 weeks
- Change from baseline in Tanner staging and growth velocity after 26 and 52 weeks
- Change from baseline at 26 and 52 weeks of systolic blood pressure (SBP) and diastolic blood pressure (DBP).
- Urinary albumin to creatinine ratio

Statistical Analysis Plan

Sample Size Estimation:
The primary hypothesis of the study was that canagliflozin is superior to placebo in glycemic control, as measured by the change from baseline to Week 26 in HbA1c. The sample size calculation was based on the 2-stage randomization design using a 2-sample, 2-sided t-test with Type 1 error rate of 0.05. Assuming a treatment effect of a 0.4% to 0.5% change in HbA1c between the active treatment group (canagliflozin) and the placebo group, a 0.9% standard deviation (SD), and that 50% of the subjects would meet the re-randomization criteria at Week 12, it was estimated that at least 66 subjects per group would be required to achieve approximately 85% power.

To account for attrition due to study discontinuation in a longitudinal analysis (to be described below), a 10% sample size inflation factor was employed, and a total of at least 146 subjects (73 per arm) were planned to be randomized in this study.

For subjects who were on background metformin (with or without insulin), it was estimated that at least 33 subjects per group (after accounting for attrition due to study discontinuation)

would be required to achieve approximately 85% power to assess the efficacy of canagliflozin on a background of metformin.

Estimand:
The key components of the pre-specified estimand from the statistical analysis plan (SAP) are summarized as follows based on the statistical approaches used for the primary efficacy analysis:

The primary efficacy estimand was described according to the following attributes:

- 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.

Handling of Missing Data:
Multiple imputations (MI) approach was considered to impute missing data. There was no imputation of missing values for clinical laboratory test results and vital signs measurements in the safety analyses.

Multiplicity Adjustment
To strongly control the family-wise error rate at the 5% significance level, a sequential testing procedure was applied. The primary endpoint was first tested in all participants (the full analysis set [FAS]) (primary analysis of the primary efficacy endpoint), and if the results were significant (2-sided alpha level of 0.05), a test for the subset of participants on a background of metformin (with or without insulin) followed (secondary analysis of the primary efficacy endpoint). As the secondary efficacy endpoints were supportive in nature, no corresponding hypothesis testing was performed and therefore, these endpoints were not part of the testing sequence.

Primary analysis
The primary efficacy endpoint was the change in HbA1c from baseline at Week 26 in the overall study population. The primary analysis was based on the FAS dataset, including all HbA1c measurements collected from randomization to Week 26, including the measurements collected after treatment discontinuation or initiation of rescue medication. The primary analysis was to be based on a pattern mixture model (PMM).

Secondary analysis of the primary efficacy endpoint (key secondary endpoint)

The secondary analysis was based on a subset of participants on background metformin (with or without insulin) from the FAS dataset, including all HbA1c measurements collected from randomization to Week 26, including the measurements collected after treatment discontinuation or initiation of rescue medication. The attributes of estimand for this analysis were the same as the primary efficacy estimand except the population was a subset of participants with background metformin (with or without insulin). The same analysis based on PMM was performed as described above.

Bayesian analysis of the primary efficacy endpoint

Bayesian analysis of the primary efficacy endpoint for the overall study and for a subset of participants on background metformin (with or without insulin) was planned to be performed if the study on its own yielded non-significant results based on the planned primary efficacy analysis. However, as the primary efficacy analysis yielded significant results, the Bayesian analysis was not performed.

Subgroup Analyses

Additional analyses of the primary efficacy endpoint in the FAS were performed to examine if the treatment effect was different for the defined subgroups. The interaction of treatment with each of the subgroups was analyzed based on the mixed model for repeated measures (MMRM) model for the primary efficacy endpoint with the addition of the interaction term. If an interaction was observed (significance<0.10), then further evaluations were performed to assess and explain the nature of the interaction [quantitative or qualitative interaction]. The least square (LS) mean change from baseline and the 95% CI for the LS means differences between canagliflozin compared to placebo were presented for the subgroups. In the event of small subgroups, descriptive statistics were provided in lieu of model-based estimates.

Populations:

Referencing the statistical review by Dr. Yuhao Li, dated 11/25/2024, the applicant pre-specified an estimand framework in the SAP as follows:

- 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.

All amendments to the study protocol were discussed and agreed upon with FDA. Table 4 provides a summary of key modifications.

Table 4. Summary of Key Protocol Amendments, Study DIA3018

Number	Date Submitted	Key Changes
	12/21/2016	Final study protocol for DIA3018 initially submitted to meet the PMR 2027-2 submission milestone due date of 12/31/2016
1	04/14/2017	Protocol Amendment 1 • Applicant amended the protocol for Study DIA3018 to reflect the trial design proposed by FDA to modify the study design to allow the assessment of canagliflozin when used with and without titration • Ketone monitoring procedures added • Exclusion criterion for hyperglycemia revised to only rely on SMBG rather than FPG • Glycemic rescue criteria revised to rely on HbA1c rather than FPG (from Type C meeting written response dated 6/23/2017)
2	09/01/2017	Protocol Amendment 2 • To reflect recommendations from FDA on the statistical analysis of the primary efficacy endpoint to assign different weights depending on the comparison, on the treatment assignment and re-randomization after Week 12.
3	07/23/2018	Protocol Amendment 3 • To include analyses of the primary efficacy endpoint in an independently powered subset of subjects on a background of diet and exercise only, and to add a related major secondary objective and hypothesis.
4	08/14/2020	Protocol Amendment 4 • Due to slower than expected recruitment in the study and a high rate of screen failures, the power calculation was modified resulting in a reduced sample size. • Due to challenges in recruiting pediatric T2D subjects who are treatment naïve, the assessment of canagliflozin as add-on to diet and exercise only (i.e., as monotherapy) was also removed.

		• In addition, minor modifications to the inclusion and exclusion criteria were made.

Source: Reviewer created based on summary provided in the Study DIA3018 CSR. Note that the dates correspond to the date of submission to the FDA.

6.1.2. Study Results

Compliance with Good Clinical Practices

The Applicant attested that Study DIA3018 was performed in accordance with the ethical principles of the Declaration of Helsinki and that are consistent with Good Clinical Practices and applicable regulatory requirements.

Financial Disclosure

The Applicant has adequately disclosed financial arrangements and there do not appear to be conflicts of interest that would compromise data integrity. Refer to the Financial Disclosure information in Section 13.2.

Patient Disposition

Subject disposition within Study DIA3018 is summarized in Table 5. A total of 171 subjects were randomized to study treatment versus placebo, of which 129 subjects (75.4%) were on background metformin (with or without insulin). Of the 84 subjects on canagliflozin, 33 subjects were re-randomized at Week 13 (16 remained on 100 mg and 17 were up-titrated to 300 mg) due to HbA1c >7.0% and eGFR >60 mL/min/1.73 m^2. All randomized subjects were treated with at least 1 dose of study treatment, and the majority completed the 26-week core treatment period (87.1%) and the 52-week treatment period (83.0%). The number of subjects who completed each period was balanced between both treatment groups (85.7% receiving canagliflozin versus 88.5% receiving placebo for the 26-week treatment period, and 82.1% receiving canagliflozin versus 83.9% receiving placebo for the 52-week treatment period). There were no deaths.

One subject (treated with canagliflozin 100mg) was identified in CSR Table 6 as not having been re-randomized at Week 13 due to an HbA1c <7.0% and eGFR <60 mL/min/1.73 m^2. However, review of the datasets revealed that this subject (b) (6) had no eGFR measurements <60 mL/min/1.73 m^2 . In addition, no subjects were noted to have achieved an eGFR <60 mL/min/1.73 m^2 during the study. Following an Advice/Information Request, the Applicant confirmed that this was a miscategorization, and that this subject did not have an eGFR <60 mL/min/1.73 m^2 at any point during the study and was therefore not re-randomized at week 13 solely due to having an HbA1c <7.0%.

Table 5. Subject Disposition in Study DIA3018

	Canagliflozin pooled N (%)	Placebo N (%)	Total N (%)
Screened			378
All Randomized	84	87	171
· On background metformin +/- insulin · On diet and exercise only	62 (73.8) 13 (15.4)	67 (77.0) 10 (11.5)	129 (75.4) 23 (13.4)
Safety Analysis Set (i.e. randomized & treated with at least 1 dose)	84 (100.0)	87 (100.0)	171 (100.0)
Full Analysis Set	84 (100.0)	87 (100.0)	171 (100.0)
Re-randomized at Week 13	33 (39.3)	60 (69.0)	93 (54.4)
· Remained on placebo · Remained on canagliflozin 100 mg · Increased to canagliflozin 300mg	0 16 (19.0) 17 (56.0)	60 (69.0) 0 0	
Completed 26-week core treatment period	72 (85.7)	77 (88.5)	149 (87.1)
Completed 52-week treatment period	69 (82.1)	73 (83.9)	142 (83.0)
Discontinued treatment prior to week 52	15 (17.9)	14 (16.1)	29 (17.0)

· Adverse event
· Lost to follow-up
· Noncompliance with study drug
· Physician decision
· Pregnancy
· Protocol violation
· Site terminated by sponsor
· Subject refused further treatment
· Withdrawal by parent/guardian
· Withdrawal by subject
  · Schedule conflicts
  · Lack of improvement
  · Lack of transportation
  · Lost study drug & no longer wants to participate
  · Moved to a different state
· Other
  · Unable to come to site due to COVID-19 restrictions
  · Moved out of the country
  · Refused contraception method
	1 (1.2)
	1 (1.2)
	1 (1.2)
	0
	1 (1.2)
	1 (1.2)
	1 (1.2)
	2 (2.4)
	1 (1.2)
	5 (6.0)
	2 (2.4)
	0
	1 (1.2)
	1 (1.2)
	1 (1.2)
	2 (2.4)
	0
	1 (1.2)
	1 (1.2)
		1 (1.1)
		3 (3.4)
		1 (1.1)
		1 (1.1)
		0
		0
		0
		0
		2 (2.3)
		3 (3.4)
		1 (1.1)
		2 (2.3)
		0
		0
		0
		1 (1.1)
		1 (1.1)
		0
		0
			2 (1.2)
			4 (2.3)
			2 (1.2)
			1 (0.6)
			1 (0.6)
			1 (0.6)
			1 (0.6)
			2 (1.2)
			3 (1.8)
			8 (4.7)
			3 (1.8)
			2 (1.2)
			1 (0.6)
			1 (0.6)
			1 (0.6)
			3 (1.8)
			1 (0.6)
			1 (0.6)
			1 (0.6)

Completed 52-week trial period	74 (88.1)	75 (86.2)	149 (87.1)
Discontinued trial prior to week 52	10 (11.9)	12 (13.8)	22 (12.9)
Deaths	0	0	0

Source: Reviewer created, modified from CSR Tables 2 & 4

Reviewer comment: Subject discontinuation was relatively balanced between treatment arms, with few discontinuations due to adverse events. Overall, the study retention was acceptable and comparable to other recently completed pediatric T2D trials.

Protocol Violations/Deviations

According to the SAP, major protocol deviations were defined as deviations that may affect the interpretation of the primary efficacy endpoint (including but not limited to the initiation of

glycemic rescue therapy) which occurred within the 26 weeks of the core double-blind treatment period. Major protocol deviations are summarized in Table Table 6 and Table 7. A total of 53 subjects (31%) reported major deviations, of which, 30 subjects (34.5%) received placebo and 23 (27.4%) received canagliflozin. The most common protocol deviations were categorized as "other (37 subjects [21.6%]) and as "subjects who entered but did not satisfy [eligibility] criteria" (21 subjects [12.3%]). The majority of protocol deviations within these two categories reflected testing deviations during the run-in period (primarily improper ketone measurements) (19 subjects [11.1%]), consent form related deviations (18 subjects [10.5%]), and <75% compliance with study drug at some point during the 26-week core treatment period (9 subjects [5.3%]). Although protocol deviations due to noncompliance with study drug was higher in the canagliflozin group than the placebo group, the overall number of subjects falling into this category was low.

Table 6. Major Protocol Deviations During the 26-Week Core Treatment Period

Relevant protocol deviation	Pooled canagliflozin 100 mg & 300 mg (N=84) N(%)	Placebo (N=87) N(%)	Total (N=171) N(%)
Number of patients with at least 1 relevant deviation	23 (27.4)	30 (34.5)	53 (31.0)
Other	17 (20.2)	20 (23.0)	37 (21.6)
Entered but did not satisfy criteria	10 (11.9)	11 (12.6)	21 (12.3)
Received a disallowed concomitant treatment	0	5 (5.7)	5 (2.9)
Developed withdrawal criteria but not withdrawn	0	1 (1.1)	1 (0.6)

Source: Reviewer created, curated from CSR Table 9

Table 7. Reasons Given for Protocol Deviations Labeled "Other" or "Entered but did not satisfy criteria"

Relevant protocol deviation	Pooled canagliflozin 100 mg & 300 mg (N=84) N(%)	Placebo (N=87) N(%)	Total (N=171) N(%)
Other	17 (20.2)	20 (23.0)	37 (21.6)
Testing deviations during run-in period (ketones improperly measured, SMBG measurements not provided, urine specimen not sent)	4 (4.8)	11 (12.6)	15 (8.8)
Consent form related deviations	7 (8.3)	8 (9.2)	15 (8.8)
<75% compliance with study drug for variable periods of time during the 26-week core treatment period	7 (8.3)	2 (2.3)	9 (5.3)
IA2 and or GAD65 result(s) missing	0	2(2.3)	2 (1.2)
Week 26 protocol-related assessments not done, except for the AE/SAE review (COVID-19 related)	1 (1.2)	0	1 (0.6)
Not re-randomized at wk 13 even though criteria met	0	1 (1.1)	1 (0.6)
Entered but did not satisfy criteria	10 (11.9)	11 (12.6)	21 (12.3)
Ketones improperly measured during run-in period	3 (3.6)	1 (1.1)	4 (2.3)
Subject randomized even though compliance with placebo during run-in period was <80%, or not checked at all	2 (2.4)	2 (2.3)	4 (2.3)
Consent form related deviations	2 (2.4)	1 (1.1)	3 (1.8)

Randomized subjects not switched from metformin XR to metformin IR	1 (1.2)	2 (2.3)	3 (1.8)
Subject randomized before IA2 results were available	2 (2.4)	0	2 (1.2)
Subject randomized despite not being on a stable insulin dose x 8 weeks	1 (1.2)	1 (1.1)	2 (1.2)
Subject enrolled despite being on an anti-convulsant and therefore meeting an exclusion criterion	0	2 (2.3)	2 (1.2)
Subject enrolled despite having pancreatic autoimmunity	1 (1.2)	0	1 (0.6)
Enrolled female subject of childbearing potential did not have a β-HCG performed at the screening visit	1 (1.2)	0	1 (0.6)
Randomized subject discovered to have participated in another research protocol recently	0	1 (1.1)	1 (0.6)
Randomized subject may have used disallowed medication prior to enrolling in the study	0	1 (1.1)	1 (0.6)
Subject enrolled despite a documented history of DKA	0	1 (1.1)	1 (0.6)
Subject enrolled without confirming SMBG history during run-in period	0	1 (1.1)	1 (0.6)

Note: Subjects may appear in more than one category.
Source: Reviewer created, curated from listing LSIDEV01 in Appendix 14 of the CSR.

Reviewer comment: Review of protocol deviations did not reveal any imbalances that would materially impact interpretation of the study results.

Table of Demographic Characteristics

A summary of the demographic and baseline characteristics of the study population is provided in Table 8. The mean age was 14.3 years and the majority (68.4%) of the study population was female. Racial representation of subjects was 42.1% Asian, 41.5% White, 11.1% Black or African-American, 8% American Indian or Alaska Native, and 0.6% multiple categories. With respect to ethnicity, 36.3% were Hispanic or Latino. The majority of subjects (24.0%) were enrolled from the US, followed by Mexico (21.1%), Malaysia (17.5%), Philippines (13.5%), Brazil (7.0%), Russia (5.8%), India (5.3%), Poland (3.5%), and China (2.3%). The mean BMI was 30.8 kg/m2 and the mean BMI Z-score was 1.84[5].Provide, in a table, demographic and other important baseline information for the treatment groups (e.g., age, sex, race/ethnicity, body mass index, and geographic location (by site, by country, U.S., non-U.S.)). State the extent to which demographics data (i.e. age, sex, race/ethnicity) were missing and provide reasons for the missing data (e.g., unable to be collected due to either local regulations or other reasons). A sample table is provided below. Generally, the information presented in this table should be limited to the population datasets used for the primary efficacy analysis (e.g., ITT or mITT); if other datasets are included, explain your reasoning. You should comment on any differences across treatment groups in terms of demographic characteristics and whether the demographic group in whom the drug is to be ultimately used (if approved) are adequately represented and evaluated in the trial. In some cases, notably age, the groupings provided by the Applicant may not be adequate (e.g., dividing patients into those < 65 and those ≥ age 65), it may be useful to divide into other subsets (e.g. ≤ 50, ≥ 75, etc.).

[5] The Applicant provided data regarding BMI Z-score in response to an Advice/Information Request (IR).

Table 8. Demographic and Baseline Characteristics of Treated Subjects in Study DIA3018

	Canagliflozin (N=84)	Placebo (N=87)	Total (N=171)
Age (years)			
Mean (SD)	14.3 (2.00)	14.4 (2.04)	14.3 (2.02)
Median (Min, Max)	15.0 (10, 17)	15.0 (10, 17)	15.0 (10, 17)
Age groups, n(%)			
10 to <15	39 (46.4)	42 (48.3)	81 (47.4)
15 to <18	45 (53.6)	45 (51.7)	90 (52.6)
Sex, n (%)			
F	57 (67.9)	60 (69.0)	117 (68.4)
M	27 (32.1)	27 (31.0)	54 (31.6)
Race, n (%)			
AMERICAN INDIAN OR ALASKA NATIVE	4 (4.8)	4 (4.6)	8 (4.7)
ASIAN	34 (40.5)	38 (43.7)	72 (42.1)
BLACK OR AFRICAN AMERICAN	6 (7.1)	13 (14.9)	19 (11.1)
MULTIPLE	0	1 (1.1)	1 (0.6)
WHITE	40 (47.6)	31 (35.6)	71 (41.5)
Ethnicity, n (%)			
HISPANIC OR LATINO	33 (39.3)	29 (33.3)	62 (36.3)
NOT HISPANIC OR LATINO	51 (60.7)	57 (65.5)	108 (63.2)
NOT REPORTED	0	1 (1.1)	1 (0.6)
Geographic Region			
Asia	31 (36.9)	35 (40.2)	66 (38.5)
Eastern Europe	10 (11.9)	6 (6.9)	16 (9.4)
Latin America and the Caribbean	20 (23.8)	16 (18.4)	36 (21.1)
North America	19 (22.6)	22 (25.3)	41 (24.0)
South America	4 (4.8)	8 (9.2)	12 (7.0)
Population			
Non-US	65 (77.3)	65 (74.7)	130 (76.0)
US	19 (22.6)	22 (25.3)	41 (24.0)
Height (cm)			
Mean (SD)	161.2 (10.1)	160.9 (9.9)	161.0 (9.9)
Median (Min, Max)	159.5 (143, 190)	161.0 (141, 186)	161.0 (141, 190)
Weight (kg)			
Mean (SD)	81.6 (24.0)	79.9 (25.3)	80.8 (24.6)
Median (Min, Max)	75.8 (44.8, 160.6)	75.2 (40.6, 161.6)	75.2 (40.6, 161.6)
Body Mass Index			
Mean (SD)	31.1 (7.2)	30.5 (7.6)	30.8 (7.4)
Median (Min, Max)	29.9 (19.0, 50.4)	29.2 (17.7, 56.6)	29.8 (17.8, 56.6)

	Canagliflozin (N=84)	Placebo (N=87)	Total (N=171)

Source: Reviewer-created in OCS Analysis Studio, Custom Table Tool.
Columns - Dataset: Demographics; Filter: SAFFL = 'Y'.
Age (years) - Dataset: Demographics; Filter: SAFFL = 'Y'.
Age groups, n(%) - Dataset: Demographics; Filter: SAFFL = 'Y'.
Sex, n (%) - Dataset: Demographics; Filter: SAFFL = 'Y'.
Race - Dataset: Demographics; Filter: SAFFL = 'Y'.
Ethnicity - Dataset: Demographics; Filter: SAFFL = 'Y'.
Geographic Region - Dataset: Demographics; Filter: SAFFL = 'Y'.
Population - Dataset: Demographics; Filter: SAFFL = 'Y'.
Height (cm) - Dataset: Demographics; Filter: SAFFL = 'Y'.
Weight (kg) - Dataset: Demographics; Filter: SAFFL = 'Y'.
Body Mass Index - Dataset: Demographics; Filter: SAFFL = 'Y'.
SD = Standard Deviation.

Reviewer Comment: The demographics (i.e., mean age of around 14 years and majority female) are generally similar to other recently completed pediatric trials of antihyperglycemic therapies. Generally, the demographic characteristics are well-balanced between the treatment arms. The study population was diverse in terms of ethnicity (36.3% Hispanic or Latino) and inclusion of subjects of Asian (42.1%) and American Indian or Alaskan Native (4.7%) descent. However, Black or African American subjects, despite being the race with the highest prevalence of pediatric T2D in 2017[14], were under-represented in this study (~11.1% of the study population), and there was an imbalance in the number of Black or African American subjects between the two treatment arms, with notably fewer subjects in the canagliflozin arm (7.1%) versus the placebo arm (14.9%). However, the racial/ethnic distributions of the study population may have also been influenced by enrollment of the majority of subjects (76%) from non-US sites.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Table 9 displays the baseline characteristics relating to T2D. The mean HbA1c was 8.0% and 36.8% of the study population had a baseline HbA1c of 8.0% or higher. The mean duration of T2D was 2.0 years. The majority of subjects (75.4%) were on background metformin, 29.2% were on background metformin and insulin, 13.5% were only on a regimen of diet and exercise, and 11.1% were treated with insulin alone. The mean eGFR was 157.3 mL/min/1.73m^2. There was evidence of microalbuminuria and macroalbuminuria in 10.5% and 3.5% of subjects, respectively; however, baseline data relating to urine albumin to creatinine ratio was not available in 11.7% of subjects.

Table 9. Baseline Characteristics Relating to T2D -- All Treated Subjects, Study DIA3018

	Canagliflozin (N=84)	Placebo (N=87)	Total (N=171)
Baseline HbA1c (%)			
Mean (SD)	7.8 (1.3)	8.3 (1.3)	8.0 (1.3)
Median (Min, Max)	7.5 (5.8, 11.3)	8.0 (6, 11.2)	7.8 (5.8, 11.3)
Baseline HbA1c ranges			
< 7%	26 (31.0)	16 (18.4)	42 (24.6)
> 10%	5 (6.0)	11 (12.6)	16 (9.4)

	Canagliflozin (N=84)	Placebo (N=87)	Total (N=171)
7 - < 8%	25 (29.8)	25 (28.7)	50 (29.2)
8 - < 9%	15 (17.9)	16 (18.4)	31 (18.1)
9 - <= 10%	13 (15.5)	19 (21.8)	32 (18.7)
Duration of T2D (years)			
Mean (SD)	1.7 (2.0)	2.3 (1.77)	2.0 (1.9)
Median (Min, Max)	1.1 (0, 13.8)	1.9 (0.2, 10.0)	1.5 (0, 13.9)
Background AHA Therapy, n(%)			
DIET AND EXERCISE ONLY	13 (15.5)	10 (11.5)	23 (13.5)
INSULIN MONOTHERAPY	9 (10.7)	10 (11.5)	19 (11.1)
METFORMIN AND INSULIN	23 (27.4)	27 (31.0)	50 (29.2)
METFORMIN MONOTHERAPY	39 (46.4)	40 (46.0)	79 (46.2)
Baseline eGFR (mL/min/1.73m2)			
Mean (SD)	163.8 (33.7)	151.1 (29.7)	157.3 (32.2)
Median (Min, Max)	166.0 (84, 277)	146.0 (66, 284)	155.0 (66, 284)
Urine Albumin/Creatinine Ratio Ranges (mg/g)			
< 30 mg/g	61 (72.6)	66 (75.9)	127 (74.3)
<NO DATA>	11 (13.1)	9 (10.3)	20 (11.7)
> 300 mg/g	4 (4.8)	2 (2.3)	6 (3.5)
30 - 300 mg/g	8 (9.5)	10 (11.5)	18 (10.5)
Baseline Fasting Plasma Glucose (mg/dL)			
Mean (SD)	155 (57)	157 (66)	156 (62)
Median (Min, Max)	136 (58, 324)	140 (58, 448)	138 (58, 448)

Source: Reviewer created in OCS Analysis Studio, Custom Table Tool.
Columns - Dataset: Demographics; Filter: SAFFL = 'Y'.
Baseline HbA1c - Dataset: Demographics; Filter: SAFFL = 'Y'.
Baseline HbA1c ranges - Dataset: Demographics; Filter: SAFFL = 'Y'.
Duration of T2D (years) - Dataset: Demographics; Filter: SAFFL = 'Y'.
Background Diabetes Therapy - Dataset: Demographics; Filter: SAFFL = 'Y'.
Baseline eGFR (mL/min/1.73m2) - Dataset: Demographics; Filter: SAFFL = 'Y'.
Urine Albumin/Creatinine Ratio Ranges (mg/g) - Dataset: Demographics; Filter: SAFFL = 'Y'.
Baseline Fasting Plasma Glucose (mg/dL) - Dataset: Demographics; Filter: SAFFL = 'Y'.
SD = Standard Deviation.

Reviewer Comment: Generally, the treatment arms are well-balanced for factors which might affect glycemic control during the study (e.g., baseline disease characteristics, demographics, and background antidiabetic therapy). The mean HbA1c in this study (8.0%) was similar to that observed in other recently completed pediatric trials of antihyperglycemic agents. Subjects with eGFR <60 mL/min/1.73m2 were excluded from participating in the study. It is notable that the baseline mean eGFR is in the hyperfiltration range. This is consistent with published reports that 24 to 50% of pediatric patients with T2D can experience hyperfiltration as a predictor of progressive diabetic kidney disease[15]. Although most of the study population had a normal urine albumin/creatinine ratio, at least 13.5% had early evidence of diabetic kidney disease at baseline (i.e., microalbuminuria or macroalbuminuria), despite a mean duration of T2D of only about 2 years. This finding is consistent with the early-onset of diabetes-related complications that has been reported in children with T2D (as discussed in Section 2).

Treatment Compliance

During the trial, subjects were considered compliant with their investigational treatment regimen if their adherence rates, based on tablet counts, were ≥75%. During the 26-week core treatment period (Table 10) 88.3% of enrolled subjects met this definition, and the proportion of subjects meeting this definition was similar between treatment arms (89.3% for canagliflozin vs 87.4% for placebo). Compliance through Week 52 was only slightly lower but comparable between groups, at 82.1% for canagliflozin and 82.8% for placebo (Table 11).

Table 10. Summary of Study Agent Compliance Through Week 26, Study DIA3018

		Canagliflozin		
	Placebo	100 mg	300 mg	Combined
Analysis set: Full	87	67	17	84
Compliance category				
<75%	3 (3.4%)	4 (6.0%)	1 (5.9%)	5 (6.0%)
>=75%	76 (87.4%)	60 (89.6%)	15 (88.2%)	75 (89.3%)
Missing	8 (9.2%)	3 (4.5%)	1 (5.9%)	4 (4.8%)

[tsicomp01.rtf] [PROD/jnj-28431754b/dia3018/dbr_final_re2/re_csr/tsicomp01.sas] 28DEC2023, 17:49

Source: Study DIA3018 CSR Table 10 p. 61

Table 11. Summary of Study Agent Compliance Through Week 52, Study DIA3018

		Canagliflozin		
	Placebo	100 mg	300 mg	Combined
Analysis set: Full	87	67	17	84
Compliance category				
<75%	3 (3.4%)	3 (4.5%)	2 (11.8%)	5 (6.0%)
>=75%	72 (82.8%)	57 (85.1%)	12 (70.6%)	69 (82.1%)

[tsicomp01a.rtf] [PROD/jnj-28431754b/dia3018/dbr_final_re2/re_csr/tsicomp01a.sas] 28DEC2023, 17:49

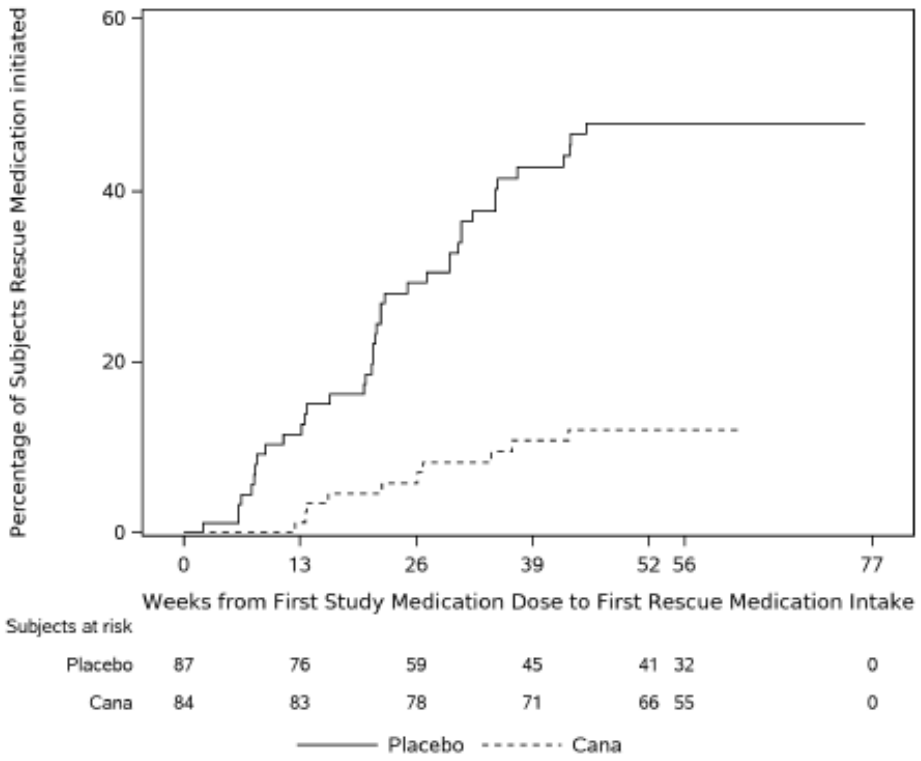
Source: Study DIA3018 CSR p. 989

Reviewer comment: Compliance with treatment was reasonable throughout the study, and well-balanced between the treatment arms.

Rescue Medications

The proportion of subjects who required glycemic rescue medication was lower in the canagliflozin group (11.9%) than the placebo group (46.0%) over the full 52-week treatment period (Figure 2). The time to initiate first rescue therapy was also longer in the canagliflozin versus the placebo group.

Figure 2. Time to Initiation of Rescue Medication, Study DIA3018



Source: Study DIA3018 CSR p. 86

Efficacy Results – Primary & Secondary Endpoints

According to the Statistical Review by Dr. Yuhao Li (dated 11/25/2024), the Applicant's imputation method used in the original submission (eCTD Sequence Number 0458) did not fully align with FDA's current preferred imputation method, so an information request (IR) was sent on 09/25/2024. The response received on 10/11/2024 (eCTD Sequence Number 0469) contains the Applicant's analyses with the revised imputation (please refer to Section 3 of the Statistical Review 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 did not align with FDA's current preferred method, another IR was sent on 11/08/2024; the response received on 11/13/2024 (eCTD Sequence Number 0474) contains the Applicant's updated subgroup analyses, updated FPG analyses and 2-way tipping point analyses for the metformin subgroup. FDA analyses done by Dr. Li replicated the Applicant's revised analyses.

The primary endpoint was the change in HbA1c (%) from baseline to the end of 26 weeks. A sequential testing procedure was applied in which the primary endpoint was first tested in all

subjects (i.e., FAS), and if the results were significant (2-sided alpha level of 0.05), it would then proceed to test the subset of subjects on a background of metformin (with or without insulin) as a key secondary efficacy endpoint. The secondary endpoint "change from baseline in FPG at Week 26" was not prespecified for multiplicity adjustment. The results of the primary and these secondary efficacy analyses are presented in Table 12.

The primary efficacy analysis demonstrated a statistically superior and clinically important treatment difference favoring canagliflozin. The mean difference in A1c change from baseline at Week 26 was -0.73% (95% CI: -1.26 to -0.19; p=0.008) for all subjects in the canagliflozin group versus placebo, and -0.74% (95% CI: -1.37 to -0.12; p=0.020) for the subset of subjects on background metformin.

The secondary endpoint, change from baseline in FPG at Week 26, also showed a significant difference favoring the canagliflozin group, with a placebo-adjusted treatment effect of -25.51 mg/dL (95% CI: -49.55 to -1.47; p = 0.038). This result further supports the finding of efficacy of canagliflozin demonstrated in the primary analysis.

Table 12. Primary and Secondary Analyses of A1C and FPG Change from Baseline at Week 26

	Canagliflozin (Pooled 100 mg & 300 mg) N=84	Placebo N=87
Primary Efficacy Analysis (Change from Baseline in A1C – All Subjects)		
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[6], LS Mean (SE)	-0.35 (0.218)	0.37 (0.197)
Comparison to Placebo[6], LS Mean difference (95% CI)	-0.73 (-1.26, -0.19)	
Two-sided P-value	0.008	
Key Secondary Efficacy Analysis (Change from Baseline in A1c – Metformin Subpopulation)		
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[6], LS Mean (SE)	-0.38 (0.225)	0.37 (0.218)
Comparison to Placebo[6], LS Mean difference (95% CI)	-0.74 (-1.37, -0.12)	
Two-sided P-value	0.020	

[6] 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

Secondary Efficacy Analysis (Change from Baseline in FPG – All Subjects)		
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[6], LS Mean (SE)	-8.2 (9.43)	17.3 (7.79)
Comparison to Placebo[6], LS Mean difference (95% CI)	-25.51 (-49.55, -1.47)	
Nominal P-value	0.038	

Source: Statistical Review Table 5 and Table 7
Abbreviations: CI = confidence interval, SD = standard deviation, LS = least square, SE = standard error.

The degree of missing endpoint data was ranged from 7 to9%) and was balanced between treatment arms. To account for missing data, Dr. Li performed a sensitivity analysis using two different imputation models (the retrieved drop-out imputation model and the washout imputation model) and these corroborated the Applicant's results, which were obtained using a copy-reference approach (Table 13). The 2-way tipping point analysis done by the Applicant was validated by Dr. Li. The findings of these analyses confirm the robustness of the primary analysis with respect to missing data assumptions. For additional details of this analysis, please see the Statistical Review, dated 11/25/2024 by Dr. Li.

Table 13. 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

Source: Statistical Review Table 6
Abbreviations: CI = confidence interval; SE = standard error.

Proportion of Subjects Achieving HbA1c targets of <7.5%, <7.0%, and <6.5% at 26 Weeks
Secondary efficacy assessments also included the proportion of subjects achieving HbA1c targets of <7.5%, <7.0%, and <6.5% at Week 26. The Applicant assessed this endpoint for the pooled canagliflozin group vs placebo. The standardized (unconditional) odds ratios of achieving these glycemic targets were 1.65 (95% CI: 1.02 to 2.67; p = 0.043), 1.71 (95% CI: 1.03 to 2.85; p=0.039), and 3.25 (95% CI: 1.64 to 6,42; p <0.001), respectively, for the pooled

canagliflozin group compared to placebo (Table 14).

Table 14. Proportion of Subjects with HbA1c (%) <7.5%, <7% or <6.5% at Week 26 – based on FDA-Requested Multiple Imputation and g-Computation – All subjects; Full Analysis Set

	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

Key: CI = confidence interval
Note: Odds ratios are based on the generalized linear mixed model for repeated measures including the fixed categorical effects of treatment, stratification factors (ie, background AHA and age group), visit, treatment-by-visit interaction, baseline value and baseline-by-visit interaction, and subject as a random effect. A compound symmetry covariance was used since the model did not converge using the unstructured covariance.
Source: Applicant's Information Request Response (Page 29), Dated 10/11/2024.

Data Quality and Integrity

Based on clinical inspections conducted at two study sites (see Section 4.1), the primary efficacy endpoint, change in HbA1c (%) from baseline to the end of 26 weeks, was verified using the source records with no discrepancies noted.

Dose/Dose Response

Due to the small number of subjects who received canagliflozin 300 mg (N=17) and the differences in baseline characteristics among the subjects who received the dose up-titration versus most of the subjects receiving the 100 mg dose, a clear dose-response could not be identified. However, the efficacy of the canagliflozin 300 mg dose in the pediatric population is supported by the following lines of evidence:

- The previously established efficacy and dose-response of canagliflozin 300 mg as compared to canagliflozin 100 mg in the adult T2D population. Extrapolation of these data to the pediatric T2D population is justified given the similarity in PK and PD (see Section 4.5 for details).

- The primary outcome analysis of Study DIA3018, which was based on pooled data that included subjects who received canagliflozin 300 mg.

- A numerically greater placebo-adjusted treatment difference of HbA1c change from baseline to Week 26 in subjects in the canagliflozin group who were uptitrated to 300 mg after week 12 [-0.89% (95% CI : -1.42 to -0.36)] compared to all other subjects who remained on canagliflozin 100 mg with no dose increase [-0.58% (95% CI: -1.16 to -0.01); as calculated by Dr. Li (Statistical Review 11/25/2025).

Reviewer's comment: Despite the limitations of Study DIA3018 in assessing the dose-response of canagliflozin in the pediatric population studied, the labeling for both the 100 mg and 300 mg dose in the pediatric population is supported by the evidence presented above.

Durability of Response

Study DIA3018 demonstrated evidence of durability of response to canagliflozin in the pediatric population studied. At week 52, a numerical difference in change in HbA1c from baseline was still observed for the pooled canagliflozin group as compared to the placebo group [placebo-adjusted treatment effect -1.02 (95% CI: -1.52 to -0.51]. Furthermore, there was progressive improvement in the estimated placebo-adjusted treatment effect over the course of 52 weeks (Table 15Table 15). Durability of effect was also supported by a placebo-adjusted mean difference in change from baseline in FPG at Week 52 of -35.6 mg/dL (95% CI -53.5 to -17.8), shown in Table 16.

Table 15. Change from Baseline in HbA1c (%) over 52 Weeks; Full Analysis Set

	Placebo (N=87)		Cana (N=84)		Difference (Cana-Placebo)		
	N[a]	LS Mean (SE)	N[a]	LS Mean (SE)	LS Mean (SE)	CI[b]	p-value[b]
WEEK 6	83	-0.08 (0.098)	84	-0.67 (0.098)	-0.59 (0.129)	(-0.85, -0.34)	<.001
WEEK 12	83	0.09 (0.137)	84	-0.58 (0.137)	-0.67 (0.187)	(-1.05, -0.30)	<.001
WEEK 20	78	0.26 (0.158)	76	-0.43 (0.159)	-0.69 (0.220)	(-1.13, -0.26)	0.002
WEEK 26	80	0.32 (0.168)	77	-0.41 (0.169)	-0.73 (0.234)	(-1.20, -0.27)	0.002
WEEK 34	73	0.28 (0.171)	76	-0.15 (0.170)	-0.43 (0.238)	(-0.90, 0.04)	0.072
WEEK 42	73	0.41 (0.165)	75	-0.23 (0.164)	-0.65 (0.229)	(-1.10, -0.19)	0.005
WEEK 52	75	0.70 (0.182)	71	-0.32 (0.184)	-1.02 (0.256)	(-1.52, -0.51)	<.001

[a]: Number of subjects with non-missing value of change from baseline.
[b]: CIs (confidence interval) and p-values are based on a mixed model for repeated measures including the fixed effects of treatment, stratification factors (i.e., background AHA and age group), visit, and treatment-by-visit interaction, as well as the fixed, continuous covariates of baseline and baseline-by-visit interaction. An unstructured covariance is used to model the within-patient errors.

[tefa1c02wk52.rtf] [PROD/jnj-28431754b/dia3018/dbr_final_re2/re_csr/tefa1c02wk52.sas] 28DEC2023, 17:49

Source: Study DIA3018 CSR p. 91.

Table 16. Change from Baseline in FPG (mg/dL) over 52 weeks; Full Analysis Set

	Placebo (N=87)		Cana (N=84)		Difference (Cana-Placebo)		
	N[a]	LS Mean (SE)	N[a]	LS Mean (SE)	LS Mean (SE)	CI[b]	p-value[b]
Week 52 (LOCF)	83	19.2 (6.90)	79	-16.4 (6.98)	-35.6 (9.05)	(-53.5, -17.8)	<.001

[a]: Number of subjects with non-missing value of change from baseline.
[b]: CI (confidence interval) and p-value are based on ANCOVA model with treatment and the stratification factors (AHA background and age group) as fixed effects and baseline FPG value as a covariate.
[teffpg04.rtf] [PROD/jnj-28431754b/dia3018/dbr_final_re2/re_csr/teffpg04.sas] 28DEC2023, 17:43

Source: Study DIA3018 CSR p. 83.

Persistence of Effect

Persistence of effect was not assessed in Study DIA3018.

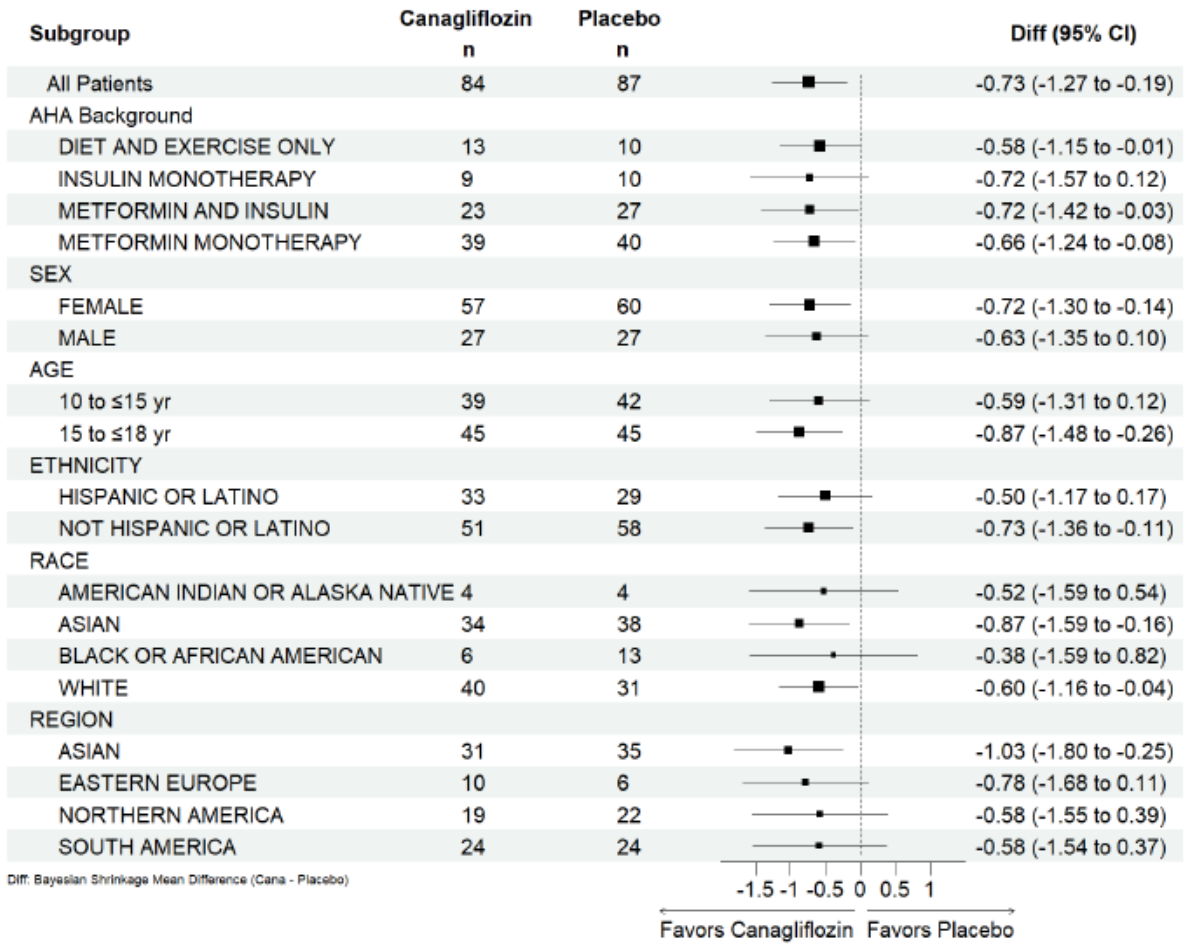
Additional Analyses Conducted on the Individual Trial

Subpopulations

Dr. Li conducted subgroup analyses on the primary efficacy endpoint. The shrinkage estimates (Figure 3) of the treatment difference with respect to A1C change from baseline at Week 26 are presented for subgroup levels defined by sex, age, race, ethnicity, region, and background antidiabetic medication. The plots include the corresponding 95% confidence and credible intervals for the shrinkage estimates, respectively. Subgroup analyses are consistent with primary analysis results which shows homogeneous treatment effects of canagliflozin across different subpopulations.

Figure 3. Primary Efficacy Subgroups Analyses: HbA1c Change from Baseline at Week 26 Based on Bayesian Shrinkage Methods (Study DIA3018; FAS)

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)



*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.

Source: Statistical Review, Figure 4

Reviewer's comment: The primary efficacy subgroup analysis was limited by the particularly small sample size of some of the subgroups, including the Black or African American subgroup and the American Indian or Alaska Native subgroup, as reflected by the wide 95% CI intervals for these subgroups.

7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

This section is not applicable to this review.

7.1.1. Primary Endpoints

This section is not applicable to this review.

7.1.2. Secondary and Other Endpoints

This section is not applicable to this review.

7.1.3. Subpopulations

This section is not applicable to this review.

7.1.4. Dose and Dose-Response

This section is not applicable to this review.

7.1.5. Onset, Duration, and Durability of Efficacy Effects

This section is not applicable to this review.

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Postmarket Setting

As discussed in Sections 4.5 and 6.1.1, subjects with moderate or severe renal impairment (eGFR < 60 mL/min/1.73m^2) were excluded from Study DIA3018, and despite the intention to enroll some pediatric patients with mild renal impairment, only 1 subject with eGFR between 60 to < 90 mL/min/1.73m^2 was actually enrolled in the study and renal function in this subject normalized during the study (see Section 8.4.6 for details). Therefore, there is insufficient data from Study DIA3018 draw any conclusions regarding the impact of renal impairment on the efficacy of canagliflozin in pediatric patients.

Although pediatric T2D patients are at risk for the development of diabetic kidney disease over time, 24 to 50% of patients may experience elevated eGFR relating to hyperfiltration. Therefore, the occurrence of eGFR < 60 mL/min/1.73m^2 would unlikely be related to diabetic nephropathy in a pediatric T2D patient aged < 18 years; however, a reduced eGFR could occur in the setting of a concomitant diagnosis of chronic kidney disease (CKD). Pediatric patients with CKD may also develop diabetes relating to treatments for CKD and/or post-renal transplantation.

In the adult program, Trial DIA3004 evaluated canagliflozin in T2D subjects with moderate renal impairment (GFR 30 to 50 mL/min/1.73m^2). Subjects in the canagliflozin group with eGFR ≥40 mL/min/1.73m^2 had a 10- to 12-fold higher rate of a >30% reduction in eGFR from baseline versus those in the placebo group. Those with eGFR <40 mL/min/1.73m^2 had a 2- to 3-fold

higher rate of a >30% reduction in eGFR with canagliflozin versus placebo. Additionally, there were 3 cases of >50% reduction in eGFR from baseline in Trial DIA3004, all of which occurred in subjects receiving canagliflozin. In general, Trial DIA3004 showed that among T2D subjects with moderate renal impairment, there was a higher proportion of subjects with a decrease in renal function and a larger magnitude of eGFR decline in subjects receiving canagliflozin compared to placebo. Based on these findings, along with the decreased efficacy of Invokana seen with eGFR <40 mL/min/1.73m^2, the original approval of Invokana (see primary clinical review dated 02/11/2013 by Dr. Kwon and primary clinical pharmacology review dated 02/06/2013 by Dr. Vaidyanathan under NDA 204042) recommended limiting the dose to 100 mg daily in subjects with eGFR between 45 and 60 mL/min/1.73m^2, and recommended against its use in patients with eGFR <45 mL/min/1.73m^2 due to the unfavorable risk-benefit profile in this subset of patients. These recommendations were reflected in Section 2 (Dosage and Administration) of the USPI at the time of approval.

Following the results of the CREDENCE trial,[16] which demonstrated that in T2D subjects with GFR 30 to <90 mL/min/1.73m^2, canagliflozin 100mg daily had benefit in significantly reducing the risk of the primary composite endpoint (end stage kidney disease [ESKD], doubling of serum creatinine, renal death, or CV death) based on a time-to-event analysis (HR: 0.70; 95% CI: 0.59, 0.82; p<0.0001), the USPI was subsequently updated to include a limitation of use for glycemic control in adults with T2D and eGFR < 30 mL/min/1.73m^2, and Section 2 of the USPI was also revised to recommend a dose increase to 300 mg for additional glycemic control only in subjects with eGFR >60 mL/min/1.73m^2. Although data regarding the use of canagliflozin in pediatric T2D subjects with renal impairment is not available, given the similarity in the PK and PD of canagliflozin in the adult and pediatric T2D populations, it appears reasonable to extrapolate the current limitation of use for glycemic control in adults with eGFR < 30 mL/min/1.73m2 and the dosing recommendation to increase to 300 mg for additional glycemic control only in those with eGFR > 60 mL/min/1.73m^2 to pediatric patients as well. See Section 10.1 for further discussion of the labeling approach.

7.2.2. Other Relevant Benefits

Prior to June 2023, metformin was the only approved oral antihyperglycemic agent for pediatric T2D. Since then, two other SGLT2 inhibitors have received pediatric indications for improvement of glycemic control in patients aged 10 years and older with type 2 diabetes mellitus – Jardiance (and its FDCP Synjardy) and Farxiga (and its FDCP Xigduo XR). However, these remain the only options in this limited arsenal of oral antihyperglycemic treatments for pediatric T2D patients, and the addition of Invokana (and its FDCPs Invokamet and Invokamet XR) would provide additional options for pediatric patients with T2D aged 10 years and older.

7.3. Integrated Assessment of Effectiveness

The Applicant submitted results from a single, adequate and well-controlled study (DIA3018) to support the effectiveness of canagliflozin in pediatric T2D subjects aged 10 to <18 years; efficacy results from the adult T2D program provide confirmatory evidence to establish substantial evidence of effectiveness in the pediatric T2D population.

The primary objective of Study DIA3018 was to demonstrate that treatment with canagliflozin provides superior glycemic control compared to placebo, as measured by the change from baseline HbA1C at Week 26. This study was well controlled: the control subjects were assigned concurrently and at random to a double-blinded placebo comparator. The study was considered adequate: the primary endpoint (HbA1c) is a validated surrogate clinical endpoint for microvascular disease risk reduction in the T2D population, study procedures reasonably approximated routine clinical practice, and the enrolled population reasonably represented the US pediatric T2D population.

In Study DIA3018, the primary efficacy analysis of the primary endpoint was met, demonstrating superiority of the pooled canagliflozin group compared to placebo for HbA1c change from baseline at Week 26: the placebo-adjusted treatment difference was -0.73% (95% CI: -1.26 to -0.19; p=0.008). The results of the primary analysis were robust to sensitivity analyses using alternative missing data assumptions. Statistically significant differences in HbA1c change from baseline at Week 26 were also observed in the subgroup of canagliflozin-treated subjects on background metformin as compared to those treated with placebo. Numerical differences in secondary endpoints were consistent with the results of the primary endpoint, including change from baseline in FPG at 26 and 52 weeks, change from baseline in A1c at 52 weeks, proportion of subjects achieving HbA1c <6.5% or <7.0% at 26 and 52 weeks, and time to rescue therapy. These findings, along with the robust clinical efficacy findings in adults, constitute substantial evidence of effectiveness for canagliflozin.

One key shortcoming of Study DIA3018 is that it was not adequately designed to rigorously establish a dose-response relationship for the 300 mg dose. Dose-response analyses of canagliflozin were limited by the small number of subjects receiving canagliflozin 300 mg (N=17) and apparent differences in baseline characteristics of the non-responder subjects who were re-randomized to uptitrate to canagliflozin 300 mg or to remain on canagliflozin 100 mg, as compared to the responder subjects who were not treated with the 300 mg dose. Because of these uncertainties, the clinical pharmacology review team did not provide a recommendation for labeling of 300 mg dose but deferred this decision to the clinical review team. The clinical review team recommends approval of both the 100 mg and 300 mg doses in the pediatric population, based on the efficacy of the canagliflozin 300 mg dose in the primary outcome analysis (which included data from subjects who received both canagliflozin 100 mg and 300 mg), the numerically greater placebo-adjusted treatment difference of HbA1c change from baseline to Week 26 in the subjects in the canagliflozin group that were uptitrated to 300 mg after week 12 compared to the subjects who remained on canagliflozin 100 mg with no dose

increase, and the dose-response relationship previously demonstrated in adults with T2D which may be extrapolated to pediatric T2D subjects given the similarity in PK and PD.

INVOKAMET (canagliflozin and metformin hydrochloride)
In addition to Invokana (canagliflozin), the pediatric indication is also being sought for the FDCPs Invokamet and Invokamet XR, through the 505(b)2 pathway, with Glucophage as the reference-listed drug. For both Invokamet and Invokamet XR, the effectiveness of the canagliflozin component is established by the information provided by Study DIA3018, as summarized above.

The bridge to the metformin component of Invokamet is established by the prior approval of Glucophage for use in pediatric patients aged 10 years and older, excerpts from the product label shown below:

> Section 8.4 Pediatric Use
> The safety and effectiveness of GLUCOPHAGE for the treatment of type 2 diabetes mellitus have been established in pediatric patients 10 to 16 years old.
>
> Section 14.1 Clinical Studies
> A double-blind, placebo-controlled study in pediatric patients aged 10 to 16 years with type 2 diabetes mellitus (mean FPG 182.2 mg/dL), treatment with GLUCOPHAGE (up to 2000 mg/day) for up to 16 weeks (mean duration of treatment 11 weeks) was conducted. The results are displayed below:
>
> ***Mean Change in Fasting Plasma Glucose at Week 16 Comparing GLUCOPHAGE vs Placebo in Pediatric Patients[a] with Type 2 Diabetes Mellitus***

FPG (mg/dL)	***GLUCOPHAGE (N=37)***	***Placebo (N=36)***	***p-Value***
Baseline	*162.4*	*192.3*	
Change at FINAL VISIT	*-42.9*	*21.4*	*<0.001*

> [a] *Pediatric patients mean age 13.8 years (range 10-16 years)*
> **Source**: Recreated from GLUCOPHAGE and GLUCOPHAGE XR USPI, revised May 2018.
>
> Mean baseline body weight was 205 lbs and 189 lbs in the GLUCOPHAGE and placebo arms, respectively. Mean change in body weight from baseline to week 16 was -3.3 lbs and -2.0 lbs in the GLUCOPHAGE and placebo arms, respectively.

INVOKAMET XR (canagliflozin and metformin hydrochloride extended-release)
The bridge to the extended-release metformin (metformin XR) component of Invokamet XR is further established by the following elements, each of which will be discussed in more detail below:

1. Similar pharmacokinetics, safety, and efficacy of Glucophage in adult and pediatric subjects, based on product labeling for Glucophage.

2. Similar exposures, safety, and efficacy of Glumetza as compared to Glucophage in adult subjects, based on product labeling for Glumetza

The initial Invokamet XR NDA contained a right of reference to NDA 021748 for Glumetza. The Applicant is continuing to rely on the Glumetza information available at the time of the approval of the original Invokamet XR NDA (NDA 205879, approved on 20 September 2016) to support this sNDA.

Similarity of PK, safety and efficacy of Glucophage in pediatric patients versus adults
Based on Glucophage's labeling, adult and pediatric subjects have similar pharmacokinetics, safety, and efficacy. Relevant excerpts from the product labeling for Glucophage are shown below:

> Section 8.4 Pediatric Use
> Use of GLUCOPHAGE in pediatric patients 10 to 16 years old for the treatment of type 2 diabetes mellitus is supported by evidence from adequate and well-controlled studies of GLUCOPHAGE in adults with additional data from a controlled clinical study in pediatric patients 10 to 16 years old with type 2 diabetes mellitus, which demonstrated a similar response in glycemic control to that seen in adults [see Clinical Studies (14.1)]. In this study, adverse reactions were similar to those described in adults. A maximum daily dose of 2000 mg of GLUCOPHAGE is recommended.
>
> Section 12.3 Pharmacokinetics
> After administration of a single oral GLUCOPHAGE 500 mg tablet with food, geometric mean metformin Cmax and AUC differed less than 5% between pediatric type 2 diabetic patients (12-16 years of age) and gender- and weight-matched healthy adults (20-45 years of age), all with normal renal function.

(b) (4)

Safety, efficacy, & exposure are similar between Glucophage and Glumetza in adults
Glumetza (metformin HCl extended-release tablets, NDA 021748) and Glucophage (metformin HCl tablets, NDA 020357) have similar exposures, safety, and efficacy in adult subjects. This was established in the original 505(b)(1) approval of Glumetza, which included a Phase 3 study that compared Glumetza with Glucophage and found similar efficacy and safety (NDA 021748 Clinical Review Memo by Dr. Robert Misbin, dated February 10, 2005). The Glumetza product labeling reflects this, as follows:

a. Section 2 of the Glumetza labeling does not recommend dosage adjustment when switching from Glucophage (metformin HCl) to Glumetza.

> Section 2 Dosage and Administration
> Patients receiving metformin hydrochloride (HCl) may be switched to GLUMETZA once daily at the same total daily dose, up to 2,000 mg once daily.

b. Section 12.3 describes that metformin absorption from Glumetza 1000 mg once daily is similar to absorption from the same total daily dose administered as metformin HCl tablets 500 mg twice daily, based on AUC.

> Section 12.3 Pharmacokinetics
> In both single-and multiple-dose studies in healthy subjects, once daily 1,000 mg (2x500 mg tablets) dosing provides equivalent systemic exposure, as measured by area under the curve (AUC), and up to 35% higher Cmax, of metformin relative to the immediate-release given as 500 mg twice daily.

c. Section 14 describes similar efficacy of Glumetza and metformin IR in clinical studies of adults with type 2 diabetes mellitus.

> Section 14 Clinical Studies
> In a multicenter, randomized, double-blind, active-controlled, dose-ranging, parallel group study conducted in patients type 2 diabetes mellitus, GLUMETZA 1,500 mg once daily, GLUMETZA 1,500 per day in divided doses (500 mg in the morning and 1,000 mg in the evening), and GLUMETZA 2,000 mg once daily were compared to immediate-release metformin HCl tablets 1,500 mg per day in divided doses (500 mg in the morning and 1,000 mg in the evening). This study included patients (n=338) who were newly diagnosed with diabetes, patients treated only with diet and exercise, patients treated with a single antidiabetic medication (sulfonylureas, alpha-glucosidase inhibitors, thiazolidinediones, or meglitinides), and patients (n=368) receiving metformin HCl tablets up to 1,500 mg/day plus a sulfonylurea at a dose equal to or less than one-half the maximum dose. Patients who were enrolled on monotherapy or combination antidiabetic therapy underwent a 6-week washout. Patients randomized to GLUMETZA began titration from 1,000 mg/day up to their assigned treatment dose over 3 weeks. Patients randomized to immediate-release metformin initiated 500 mg twice daily for 1 week followed by 500 mg with breakfast and 1,000 mg with dinner for the second week. The 3-week treatment period was followed by an additional 21-week period at the randomized dose.

Table 5: Mean Changes from Baseline in HbA1c and Fasting Plasma Glucose at Week 24 Comparing GLUMETZA versus Metformin HCl Tablets* in Patients with Type 2 Diabetes Mellitus

	GLUMETZA			Metformin HCl Tablets* 1,500 mg in Divided Doses (n=174)
	1,500 mg Once Daily (n=178)	1,500 mg in Divided Doses (n=182)	2,000 mg Once Daily (n=172)	
HbA1c (%), N	169	175	159	170
Baseline	8.2	8.5	8.3	8.7
Mean Change at Final Visit	-0.7	-0.7	-1.1	-0.7
Mean Difference from Metformin HCl Tablets* (98.4% CI)	0 (-0.3, 0.3)	0 (-0.3, 0.3)	-0.4 (-0.7, -0.1)	N/A
Fasting Plasma Glucose (mg/dL), N	175	179	170	172
Baseline	190	192.3	184	197
Mean Change at Final Visit	-39	-32	-42	-32
Mean Difference from Metformin HCl Tablets* (95% CI)	-6 (-15, 2)	0 (-8, 9)	-10 (-19, -1)	N/A

*Immediate-release metformin HCl tablets

Though the above elements are sufficient to establish the 505(b)2 bridge for Invokamet XR to the extended-release metformin component, the Applicant also submitted published studies from the literature that provide supportive evidence of the safety of metformin extended-release products in the pediatric population. These include a published study which reported similar safety of metformin and metformin extended release in pediatric T2D subjects as well as three additional studies reporting on the safety of metformin extended release in pediatric patients with either T2D or obesity. These studies have been summarized in Section 13.3.

The scientific bridge provided by the Applicant, as described above, is considered appropriate to justify the Applicant's proposal to rely on the Agency's previous findings of safety and effectiveness for Glucophage to broaden the glycemic control indication for the metformin extended-release component of Invokamet XR to pediatric patients aged 10 and older.

8. Review of Safety

8.1. Safety Review Approach

The safety of canagliflozin has been well-characterized in adult subjects with T2D. In adult studies of canagliflozin, the most common adverse events (AEs with > 2% incidence) were genital mycotic infections, urinary tract infections (UTIs), increased urination, thirst, nausea,

constipation, and vulvovaginal pruritis. The USPI for canagliflozin-containing products also describes Warnings and Precautions regarding the risks of ketoacidosis, lower limb amputation, volume depletion, urosepsis and pyelonephritis, hypoglycemia with concomitant use of sulfonylureas and insulin, necrotizing fasciitis of the perineum (Fournier's gangrene), genital mycotic infections, hypersensitivity reactions, and bone fracture.

The safety review focused primarily on previously identified risks of canagliflozin observed in adult studies, but also evaluated any potential risks that may be specific to pediatric patients.

For study DIA3018, the Applicant prespecified several AESIs and other specific AEs based on the known safety profile of canagliflozin, and pediatric-specific safety issues including effects on growth, bone development and puberty. These safety issues were also specified in the pediatric WR.

The safety analysis set consisted of the participants who were randomized and took at least 1 dose of study agent and was identical to the full analysis set.

The primary safety analysis is based on the 52-week placebo-controlled assessment period of study DIA3018. Safety data for this period is reported for the pooled canagliflozin arm (i.e., all subjects who received canagliflozin at any dose from baseline to week 52) and placebo arm.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

The duration of exposure through Week 26 and Week 52 is described in Table 17. The mean duration of exposure to canagliflozin during the placebo-controlled 26-week core treatment period was 25.5 weeks. The mean duration of exposure to canagliflozin during the placebo-controlled 52-week treatment period (core + extension) was 336 days, or 48.3 weeks. Exposure was comparable in both treatment arms.

Table 17. Duration of Exposure to Canagliflozin Pooled vs Placebo Regardless of Rescue (Safety Analysis Data Set)

	Canagliflozin Pooled N=84	Placebo N=87	Total N=171
Duration of Exposure through Week 26 [days]			
Mean (SD)	179.1 (31.45)	180.3 (30.35)	179.7 (30.81)
Median (Min, Max)	184.0 (15, 211)	185.0 (12, 211)	185.0 (12, 211)
Duration of Exposure through Week 52 [days]			
Mean (SD)	337.8 (79.01)	335.0 (85.79)	336.4 (82.30)
Median (Min, Max)	364.0 (15, 399)	364.0 (12, 533)	364.0 (12, 533)

Source: OCS Analysis Studio, Custom Table Tool.
Columns - Dataset: Demographics; Filter: SAFFL = 'Y'.
Duration of Exposure through Week 26 [days] - Dataset: Exposure; Filter: PARAM = 'Total Duration of Exposure Prior to Week 26 (Days)'.

	Canagliflozin Pooled N=84	Placebo N=87	Total N=171

Duration of Exposure through Week 52 [days] - Dataset: Exposure; Filter: PARAM = 'Total Duration of Exposure (Days)'.
SD = Standard Deviation.

The characteristics of the safety population for the primary safety analysis (i.e., the placebo-controlled treatment period through weeks 52) were described in Section 6.1.2.

8.2.3. Adequacy of the safety database:

In general, pediatric T2D programs are designed to demonstrate efficacy; the sample sizes are typically inadequate to constitute a rigorous, stand-alone assessment of safety and therefore extrapolation of some adult safety data is typically required. The sample size and total treatment exposure in this study is similar to that of other pediatric T2D programs. Because the safety profile for canagliflozin has been extensively evaluated in previous clinical trials in adults, the exposure and size of the safety database for canagliflozin in the pediatric population is generally considered adequate and has satisfied the requirements specified by the Agency in the Written Request. However, this clinical safety database is generally able to detect treatment differences for only the most frequently occurring AEs.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

The overall quality of the data submitted was acceptable. Based on clinical inspections conducted at two study sites (see Section 4.1) (OSI Clinical Inspection Summary, dated 11/12/2024), no discrepancies were noted in the source records for the safety data including adverse events, serious adverse events, laboratory tests and physical exam results, except for the below noted deficiencies:

- Subject (b) (6) (canagliflozin 100 mg group) should not have been enrolled in the study, due to meeting exclusion criterion #17 ("Current use of anticonvulsant medication or is likely to require treatment with anticonvulsant medication") due to a history of epilepsy and last use of phenytoin just 34 days prior to being consented for the study, and this was not reported as a protocol deviation pertaining to improper enrollment in the study. Subject (b) (6) went on to have a tonic-clonic seizure that required hospitalization and resumption of phenytoin.

  Reviewer's comment: Of note, this was one of the two TEAEs leading to discontinuation that occurred in this study. A protocol deviation for this subject was reported after Week 26 for having received a disallowed concomitant treatment.

- Two subjects in the placebo group (b) (6) were enrolled without repeated fasting self-monitoring blood glucose measurements required to fully assess exclusion criterion #3. These were properly reported as protocol deviations.

- Two subjects in the placebo group (b) (6) were recorded as taking the anticonvulsant topiramate at the start of and during the study, which would have met exclusion criterion #17. However, the clinical investigator reported that these cases were documentation errors, and that he confirmed with the subjects and their pharmacies that this medication was not actually being taken by these two subjects prior to or during enrollment in Study DIA3018.

Reviewer's Comment: Overall, the above deficiencies are not expected to materially impact the safety review.

8.3.2. Categorization of Adverse Events

All safety analyses and summaries were based on the safety analysis set. The safety analysis set consisted of the subjects who were randomized and took at least 1 dose of study drug. There was no imputation of missing values for clinical laboratory test results, vital signs measurements in the safety analyses and there was no hypothesis testing for results from safety analyses.

Protocol definitions for AEs, SAEs, and intensity of AEs were consistent with standard practice. AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 26.0. All AEs and AESIs were collected from the period of informed consent through the end of the study. All subjects, regardless of their completion status, were to have a follow-up telephone contact (or optional study visit, at the discretion of the investigator) approximately 30 days after their last dose of study drug is taken to collect information on any serious adverse events and adverse events of interest. If study drug was discontinued early, subjects were followed up for specific data collection, including vital signs, body weight, laboratory assessments, SAEs, AEs of interest, and AESIs for the duration of the study.

Subgroups were defined as follows:

- AHA subgroups: diet and exercise only; metformin monotherapy; insulin monotherapy; combination of metformin and insulin.
- Age: ≥10 to <15 years of age; ≥15 to <18 years.
- Sex: female; male.

A TEAE was defined as:

- an AE with an onset after the initiation of double-blind study medication and before the last study medication date + 30 days.
- AEs with a start date prior to initiation of the double-blind study medication which are

subsequently reported to have either an increase in intensity or change in attribution in relationship to study medication (i.e., no attribution to possible, probably, very likely) after the initiation of double-blind study medication.

TEAEs before the initiation of rescue therapy and TEAEs regardless of rescue therapy were summarized separately for the 26-week core double-blind treatment period and for the 52-week double-blind treatment phase.

An Independent Data Monitoring Committee (IDMC) was established to monitor safety data on an ongoing basis.

The AESIs and specific AEs that were identified for study DIA3018 were as follows:

- DKA and adverse events related to DKA, ketoacidosis, metabolic acidosis, or acidosis
- Fractures
- Lower extremity amputations
- Pancreatitis
- Serious adverse events related to UTIs such as urosepsis and pyelonephritis

Selected AEs of Interest[7] that were identified for study DIA3018 were as follows:

- Vulvovaginal candidiasis
- Balanitis or Balanoposthitis
- UTIs
- Volume Depletion
- Renal Impairment/Renal Failure
- Hypersensitivity
- Venous Thromboembolic Event
- Photosensitivity
- Hepatic Injury
- Renal Cell Cancer
- Bladder Cancer
- Pheochromocytoma
- Breast Cancer
- Testicular Malignancy

Fracture events identified by the investigator or the sponsor for meeting the criteria pre-specified in the charter were sent to an independent fracture adjudication committee to confirm that events were fractures, to determine fracture location (anatomic region) and type (low trauma or not). The summary of fracture events was based on the adjudicated events of

[7] Complete listing of preferred terms provided in Attachment 2 within the Statistical Analysis Plan (document "28431754dia3018-statistical.pdf")

Cases of DKA identified by investigator or the sponsor for meeting the criteria prespecified in the charter were sent to an independent DKA adjudication committee. The summary of DKA events was based on the adjudicated events of DKA.

Pancreatitis events identified by investigator or the sponsor for meeting the criteria pre-specified in the charter were sent to an independent pancreatitis adjudication committee. The summary of pancreatitis events was based on the adjudicated events of pancreatitis.

Lower extremity amputation was to be recorded on a dedicated amputation case report form page. There were no cases of lower extremity amputation in Study DIA3018.

Hypoglycemia

Hypoglycemia AEs were defined as follows:

- Symptomatic or asymptomatic hypoglycemia AEs with documented glucose $\leq$ 70 mg/dL
- Probable symptomatic hypoglycemia is defined as an event during which symptoms of hypoglycemia are not accompanied by a plasma glucose determination.
- Severe hypoglycemia is defined as an event requiring the assistance of another person to actively administer a carbohydrate, glucagon, or other resuscitative actions. A subject is considered to "require assistance" if he/she is unable to help himself/herself. An act of kindness to assist a subject when it is not necessary does not qualify as "requiring assistance". These episodes may be associated with sufficient neuroglycopenia to induce seizure or coma. Plasma glucose measurements may not be available during such an event, but neurologic recovery attributable to the restoration of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration.

Only treatment-emergent hypoglycemia episodes, reported on the eCRF for hypoglycemia, were summarized, as follows:

- Treatment emergent hypoglycemia regardless of rescue therapy
- Treatment-emergent hypoglycemia before the initiation of rescue therapy
- Treatment-emergent hypoglycemia episodes by background AHA groups at randomization
    - diet/exercise or metformin monotherapy
    - insulin with or without metformin
  - 26-week core double-blind treatment period regardless of rescue therapy
  - 26-week core double-blind treatment period before initiation of rescue therapy
  - 52-week double-blind treatment regardless of rescue therapy
  - 52-week double-blind treatment before the initiation of rescue therapy

For subjects with biochemically documented hypoglycemia episodes, the percentage of subjects was summarized for each of the following glucose levels (≤70 mg/dL [3.9 mmol/L], <56 mg/dL [3.1 mmol/L], and <36 mg/dL [2.0 mmol/L].

For subjects with severe hypoglycemia episodes, the percentage of subjects by each answer of the 2 questions for severe hypoglycemia on the eCRF were summarized by treatment group. Subjects who had 0, 1, 2, or ≥3 documented episodes and subjects who had 0, 1, 2, or ≥3 severe hypoglycemic episodes were also summarized by treatment group.

Reviewer's comment: The Applicant did not classify hypoglycemia events according to the currently accepted ADA definitions. However, the hypoglycemia data was analyzed using glucose level cutoffs that approximately correspond to the current definitions of Level 1 (< 70 mg/dL but ≥ 54 mg/dL) and Level 2 (<56 mg/dL) hypoglycemia, in addition to an additional tier of <36 mg/dL. The definition of severe hypoglycemia events was also consistent with ADA Level 3 hypoglycemia.

8.3.3. Routine Clinical Tests

In the Study DIA3018, the Applicant assessed safety by examination of adverse events, clinical laboratory measurements, physical examination findings, vital signs, standardized measurements of growth and development, electrocardiogram and self-monitoring of blood glucose and ketones according to the schedule detailed in Section 6.1.1.

Specific clinical laboratory tests are further described below:

Laboratory Category	Specific measurements
Hematology	Hemoglobin, hematocrit, red blood cell (RBC) count, platelet count, white blood cell (WBC) count with differential (neutrophils, eosinophils, basophils, monocytes, lymphocytes)
Clinical Chemistry	Sodium, potassium, chloride, bicarbonate, blood urea nitrogen (BUN), creatinine, calcium, phosphate, magnesium, albumin, alkaline phosphatase, creatinine (eGFR calculated by Schwartz formula) phosphokinase (CPK), lactic acid dehydrogenase (LDH), uric acid, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total protein, gamma-glutamyltransferase (GGT), total

	bilirubin, lipase, amylase Blood ketones Serum (β-human chorionic gonadotropin [β-hCG] pregnancy test for all female subjects of childbearing potential at screening visit, and additionally as needed as determined by the investigator.
Lipids	total cholesterol, high-density lipoprotein (HDL) cholesterol, calculated low density lipoprotein (LDL) cholesterol, triglycerides, non-HDL-C, LDL-C to HDL-C ratio, non-HDL-C to LDL-C ratio
Urine	Urine dipstick for specific gravity, pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase (for WBC) with microscopic as reflex test. First morning void urine for Urinary albumin/creatinine ratio (UACR). If the Week -2 first morning void showed +1 or higher proteinuria based on the central laboratory urine dipstick a 24-hour urine collection for protein was done prior to randomization and thereafter. Urinary excretion of calcium and phosphate
Markers of Bone Turnover and calcium/phosphate homeostasis	serum osteocalcin and serum collagen type 1 CTx, calcium, magnesium, phosphate, parathyroid hormone (PTH), 25-hydroxy Vitamin D, calcitonin, urinary excretion of calcium and phosphate

Source: Study DIA3018 Protocol & CSR

8.4. Safety Results

8.4.1. Deaths

No deaths occurred in Study DIA3018.

8.4.2. Serious Adverse Events

SAEs that occurred during the 52-week placebo-controlled safety assessment period are described in Table 18. There was a total of 13 SAEs in 13 subjects, including 8 participants (9.5%) receiving canagliflozin and 5 participants (5.7%) receiving placebo.

Table 18. Summary of Serious TEAEs in Study DIA3018

Preferred Term	Canagliflozin Pooled (100 mg & 300 mg) N = 84 n (%)	Placebo N = 87 n (%)
Any SAE	8 (9.5)	5 (5.7)
Abortion spontaneous	0 (0.0)	1 (1.1)
Anaphylactic reaction	1 (1.2)	0 (0.0)
Ankle fracture	0 (0.0)	1 (1.1)
Cholelithiasis	1 (1.2)	0 (0.0)
Diabetes mellitus inadequate control	0 (0.0)	1 (1.1)
Diabetic ketoacidosis	1 (1.2)	1 (1.1)
Erysipelas	1 (1.2)	0 (0.0)
Hyperglycemia	1 (1.2)	0 (0.0)
Pancreatitis acute	1 (1.2)	0 (0.0)
Pneumonia	1 (1.2)	0 (0.0)
Suicide attempt	1 (1.2)	0 (0.0)
Tonsillar hypertrophy	0 (0.0)	1 (1.1)

Source: OCS Analysis Studio, Safety Explorer.

Filters: TRTCA = "Cana" and SAFFL = "Y" (Canagliflozin Pooled (100 mg & 300 mg)); TRTCA = "Placebo" and SAFFL = "Y" (Placebo); TRTEMFL = "Y" and AESER = "Y" (Adverse Events).

Narratives for all SAEs associated with active drug treatment (i.e., canagliflozin) were reviewed and key findings and conclusions regarding relatedness of study treatment are summarized in Table 19 below:

Table 19. Narratives for SAEs Associated with Canagliflozin Treatment, Study DIA3018

SAEs associated with canagliflozin treatment	Clinical Reviewer Assessment of Relatedness to Study Treatment/Comments
Erysipelas Subject (b) (6) is a 17-year-old female who was randomized to the canagliflozin 100 mg arm who developed erysipelas on Study Day	Erysipelas is not a known adverse reaction to SGLT2 inhibitors. The subject has a family history of recurrent erysipelas, and the erysipelas did not recur with re-exposure to

33. The erysipelas was severe in intensity, and she was hospitalized. On admission, physical examination was notable for a low-grade fever (38.1°C), isolated purulent pustules on the cheeks, nose, chest, and arms, impaired nasal patency, and erythema of the throat. C-reactive protein (CRP) was elevated at 8.88 mg/dL (normal range <1.0). She was treated with antibiotics and paracetamol. CRP increased to 14.83 on Study Day 34, then decreased to 6.26 mg/dL on Study Day 35 and 1.05 by Study Day 42, when she was discharged home with mild erysipelas symptoms. Treatment with the study drug was interrupted for 3 days during the hospitalization for this SAE. Erysipelas resolved by day 51. Of note, she has a family history of recurrent erysipelas in her mother. She went on to continue treatment with the study drug until Day 148 when she withdrew from the study. She did not provide a specific reason for withdrawing from the study.	canagliflozin. This event was most likely not related to the study drug.
Cholelithiasis Subject (b) (6) is a 15-year-old female who was randomized to the canagliflozin 100mg arm who developed cholelithiasis on Study Day 158. Concomitant medications at study entry were metformin hydrochloride, vitamin D, calcium carbonate, and piracetam (a derivative of the neurotransmitter γ-aminobutyric acid (GABA) not approved for use in the US but available in the subject's country – Poland – for use as a CNS stimulant). On Study Day 158, this subject developed cholelithiasis of moderate intensity, was treated with antibiotics, analgesics, omeprazole, and Rowachol (an herbal remedy for gallstones), and underwent laparoscopic cholecystectomy on Study Day 176. She was discharged home on Study Day 177. No action was taken with the	Cholelithiasis is not a known adverse reaction to SGLT2 inhibitors. This is an isolated case and does not by itself raise concern as a potential safety signal.

study drug and the subject went on to complete the study.	
Diabetic Ketoacidosis Subject (b) (6) is a 10-year-old female who was randomized to the canagliflozin 100 mg arm who developed mild diabetic ketoacidosis (DKA) on Study Day 295. At study entry, she had an ongoing medical history of T2D, asthma, acanthosis nigricans, hepatic steatosis, vitamin D deficiency, and elevated blood pressure, but no prior history of DKA. Her concomitant medications at study entry were metformin, ergocalciferol, and clotrimazole. By Study Day 295 she was also being treated with insulin degludec and liraglutide, but reported being inconsistent with her insulin, metformin, and dietary regimen. On Study Day 295, fasting labs showed hyperglycemia (glucose 256 mg/dL), a ketone level of 0.7 mmol/L (ULN 0.6 mmol/L), and bicarbonate level of 16 mmol/L (LLN 19), so she was hospitalized for hyperglycemia, dehydration, and DKA. Of note, the subject reported having skipped her insulin dose the night before. She was treated with IV fluids and insulin, and the DKA was reported as resolved on Study Day 301. Due to the context of missed insulin dose and hyperglycemia, the investigator considered this DKA event to not be related to the study drug. No action was taken with the study drug and Subject (b) (6) went to complete the study. The endpoint adjudication committee confirmed the event to be DKA. The adjudication committee considered a recent reduction in the insulin dose to be the main precipitating factor.	The SGLT2 inhibitor class is known to increase the risk of ketoacidosis, so it is possible that canagliflozin treatment may have contributed to this DKA event.
Suicide Attempt Subject (b) (6) is a 13-year-old female who	Not related

was randomized to the canagliflozin 100mg arm. On Study Day 162, the subject attempted suicide by making life threatening wounds in her left forearm. Of note she had been diagnosed with depression on Study Day 123 based on symptoms she had been experiencing for at least 6 months prior to study enrollment, but was not being treated with an antidepressant. Risk factors for depression included social confinement due to the COVID-19 pandemic, emotional stress due to school activities, and low self-esteem. After the suicide attempt, she was started on sertraline and a program of psychiatric/psychological care. No action was taken with the study drug, and Subject (b) (6) went on to complete the study.	
Acute pancreatitis Subject (b) (6) is a 15-year-old male who was initially randomized to the canagliflozin 100 mg arm and, at Week 13 (Study Day 91), re-randomized to 300 mg. At study entry, his medical history was notable for T2D, type V hyperlipidemia, hypertriglyceridemia, and an episode of acute pancreatitis about 1-2 years earlier. Concomitant medications at study entry were insulin glargine, losartan, fish oil, and metformin. On Study Day 26, the subject presented to the ER with epigastric abdominal pain, headache, and nausea, and was found to have acute pancreatitis and hyperglycemia (483 mg/dL). At the time of the event, he was taking insulin degludec/liraglutide (Xultophy), metformin, losartan, and fish oil. On Study Day 27, lipase level was 1481 U/L and triglyceride level was 1041 mg/dL. Ultrasound was notable for fatty liver, and no gallstones nor evidence of cholecystitis; the pancreas was not well visualized. He was treated with ketorolac, tromethamine, bismuth subsalicylate,	The subject had a pre-existing history of acute pancreatitis, as well as risk factors for acute pancreatitis, including hypertriglyceridemia and recently-initiated treatment with a GLP-1 receptor agonist (liraglutide). Acute pancreatitis did not recur, despite a dose-increase of canagliflozin to 300 mg. Therefore, it is unlikely that this subject's acute pancreatitis event was related to the study drug. An increased risk of pancreatitis has not previously been described in clinical studies of canagliflozin. Section 6.1 of the Invokana Prescribing Information states "In the pool of eight clinical trials, the incidence rate of pancreatitis (acute or chronic) was 0.1%, 0.2%, and 0.1% receiving comparator, INVOKANA 100 mg, and INVOKANA 300 mg, respectively."

ondansetron, morphine, insulin, IV fluids, and fluconazole. The investigator considered the hypertriglyceridemia as well as Xultophy (which contains liraglutide and has a known side effect of pancreatitis) to be the factors responsible for the event. Xultophy was discontinued and insulin degludec was started. On Study Day 28, the subject was discharged from the hospital and, on Study Day 89, the acute pancreatitis was reported as resolved. The study drug was interrupted until Study Day 91, at which point he was re-randomized to canagliflozin 300 mg and study drug resumed at that dose. Despite the higher dose, acute pancreatitis did not recur on reinitiation of the study drug, and subject (b) (6) went on to complete the study. The endpoint adjudication committee confirmed the event to be pancreatitis.	
Hyperglycemia Subject (b) (6) is an 11-year-old female who was randomized to the canagliflozin 100 mg arm. On Study Day 2, she was hospitalized with hyperglycemia (286 to 300 mg/dL). She was asymptomatic, but her parents became alarmed due to hyperglycemic measurements and sought medical care. Her blood acid-base balance test results were unremarkable. She was treated with IV fluids, the hyperglycemia resolved that same day, and she was discharged home. No action was taken with the study drug, and Subject (b) (6) went on to complete the study.	This hyperglycemia event occurred very early in this subject's study participation, on Day 2 of canagliflozin therapy, before full effect of the drug would be expected to be reached for glycemic control (the Invokana label states that steady state is reached after 4 to 5 days of once-daily dosing) but did resolve with hydration alone. It may be possible that canagliflozin therapy may have contributed to this subject's dehydration due to its known volume depletion effect.
Pneumonia Subject (b) (6) is a 12-year-old Asian female who was randomized to the canagliflozin 100 mg arm. On Study Day 294, the subject developed pediatric community acquired pneumonia, of severe intensity, and was	Not related

hospitalized for that on Study Day 298. She was treated with antibiotics, paracetamol, omeprazole, and metoclopramide. She improved and was discharged home two days later. The pneumonia was reported as resolved on Study Day 301. No action was taken with the study drug, and Subject (b) (6) went on to complete the study.	
Anaphylactic Reaction Subject (b) (6) is a 17-year-old Asian female who was randomized to the canagliflozin 100 mg arm. On Study Day 20, she developed lightheadedness, hives, near-syncope, and possibly a brief syncope in the shower after a flying insect sting on the left arm. She had facial swelling, widespread hives, difficulty breathing, and wheezing, concerning for a severe allergic reaction or anaphylaxis. Epinephrine and diphenhydramine were given as first aid, and she was then taken to the local children's hospital emergency room for observation, where she was treated with methylprednisolone sodium succinate, prednisone, ibuprofen and famotidine. The anaphylactic reaction resolved the same day, and she was discharged home. Due to the temporal relationship between the insect sting and the anaphylactic reaction, the investigator considered this event to not be related to the study drug. No action was taken with the study drug and Subject (b) (6) continued in the study until Day 242 when she withdrew due to her college schedule.	While an anaphylactic reaction is possible with most drugs, including canagliflozin, in this case, there was a temporal relationship of this patient's anaphylactic reaction with a flying insect bite, and she did not experience anaphylaxis after multiple subsequent re-exposures to canagliflozin for 222 days after the anaphylactic reaction occurred. Therefore, this anaphylactic reaction event was not related to the study drug.

Source: Reviewer created.

Reviewer Comment: Overall, SAEs occurred in 8 (9.5%) canagliflozin-treated subjects during study DIA3018. Based on review of the subject narratives, canagliflozin treatment may have been a contributing factor to the SAEs of diabetic ketoacidosis and hyperglycemia that resolved with hydration (suggesting a causal role of volume depletion). Diabetic ketoacidosis and volume depletion are known safety issues associated with canagliflozin treatment that are described in

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

There were only two subjects who discontinued study treatment due to AE, one in each treatment arm (Table 20Table 20). The AE that prompted study treatment discontinuation in the canagliflozin arm was a generalized tonic-clonic seizure that occurred in a subject with a history of epilepsy (Subject # (b) (6) 17 year-old female), who had been treated with the anticonvulsant phenytoin up to 1 month prior to study enrollment, and was therefore inappropriately enrolled in the study due to meeting exclusion criterion #17: "Current use of anticonvulsant medication or is likely to require treatment with anticonvulsant medication." This study subject was not taking phenytoin at the start of the study and went on to have a generalized tonic-clonic seizure 5 months into study participation. This subject was at that point withdrawn from the study due to re-initiation of phenytoin. This protocol deviation was identified by the OSI review, and is also discussed in Section 4.1. Due to the subject's pre-existing history of epilepsy, it is unlikely that the tonic-clonic seizure was related to canagliflozin treatment.

A 13-year-old male in the placebo arm (Subject (b) (6)) discontinued study treatment due to mood swings.

Table 20. Summary of TEAEs Leading to Discontinuation

Preferred Term	Canagliflozin Pooled (100 mg & 300 mg) N = 84 n (%)	Placebo N = 87 n (%)
Any AE	1 (1.2)	1 (1.1)
Generalized tonic-clonic seizure	1 (1.2)	0 (0.0)
Mood swings	0 (0.0)	1 (1.1)

Source: OCS Analysis Studio, Safety Explorer.
Filters: TRTCA = "Cana" and SAFFL = "Y" (Canagliflozin Pooled (100 mg & 300 mg)); TRTCA = "Placebo" and SAFFL = "Y" (Placebo); TRTEMFL = "Y" and AEACN = "DRUG WITHDRAWN" (Adverse Events).

Reviewer's comment: The tonic-clonic seizure event was more likely related to the participant being off anti-epileptic medication rather than to treatment with canagliflozin.

8.4.4. Significant Adverse Events

Hypoglycemia
During Study DIA3018, subjects were provided study blood glucose meters and were advised to record SMBG at least 3 days per week with additional measurements made as considered

clinically appropriate by the investigator and per local guidelines.

Table 21 provides a summary of events of treatment-emergent hypoglycemia that were documented by blood glucose measurements during the 52-week double-blinded treatment period, whether symptomatic or not, and/or met the definition of being severe. Of note, there was only 1 episode of severe hypoglycemia, and this event occurred in a subject in the placebo group who was treated with background insulin therapy. There were no cases of severe hypoglycemia in the canagliflozin group. Overall, the proportion of patients reporting hypoglycemia was comparable between treatment groups, with the frequency of events numerically slightly higher for the placebo group (15 canagliflozin-treated subjects who experienced 58 events versus 14 placebo-treated subjects who experienced 74 events).

Table 21. Biochemically-documented and/or Severe Treatment-Emergent Hypoglycemia Prior to Rescue Medication - Safety Analysis Set

		Canagliflozin		
	Placebo	100 mg	300 mg	Combined
Analysis set: Safety	87	67	17	84
Subjects with any documented hypoglycemia	15 (17.2%)	14 (20.9%)	1 (5.9%)	15 (17.9%)
Biochemically documented hypoglycemia	14 (16.1%)	14 (20.9%)	1 (5.9%)	15 (17.9%)
Severe hypoglycemia	1 (1.1%)	0	0	0
Subjects with episodes of biochemically documented hypoglycemia*	14 (16.1%)	14 (20.9%)	1 (5.9%)	15 (17.9%)
<=70 mg/dL (3.9 mmol/L)	14 (16.1%)	14 (20.9%)	1 (5.9%)	15 (17.9%)
< 56 mg/dL (3.1 mmol/L)	7 (8.0%)	6 (9.0%)	0	6 (7.1%)
< 36 mg/dL (2.0 mmol/L)	2 (2.3%)	0	0	0
Total number of episodes	75	57	1	58
Subjects with numbers of documented hypoglycemia	15 (17.2%)	14 (20.9%)	1 (5.9%)	15 (17.9%)
1 episode	5 (5.7%)	5 (7.5%)	1 (5.9%)	6 (7.1%)
2 episodes	6 (6.9%)	3 (4.5%)	0	3 (3.6%)
>= 3 episodes	4 (4.6%)	6 (9.0%)	0	6 (7.1%)
Event rate per subject-year exposure	1.26	0.98	0.07	0.8

Note: Count and (%) are based on number of subjects, not number of episodes.
*Subjects with any biochemically documented hypoglycemia episodes; Results of LOW are included in all the three glucose categories (i.e., = 70, <56, and/or <36 mg/dL).
A subject may be counted in each of the three glucose categories.
[TSFAE17.RTF] [JNJ-28431754B/DIA3018/DBR_FINAL_RE2/RE_CSR/PROD/TSFAE17.SAS] 28DEC2023, 17:43

Source: Study DIA2018 CSR p. 495

Table 22 shows an analysis of treatment-emergent hypoglycemia in the subset of study subjects who were not on concomitant insulin therapy. There was no imbalance in treatment-emergent hypoglycemia events in this subgroup.

Table 22. Biochemically-Documented Treatment-Emergent Hypoglycemia Prior to Rescue Medication - Diet and Exercise Only or Metformin Monotherapy

		Canagliflozin		
	Placebo	100 mg	300 mg	Combined
Analysis set: Safety	50	41	11	52
Subjects with episodes*	8 (16.0%)	7 (17.1%)	0	7 (13.5%)
<=70 mg/dL (3.9 mmol/L)	8 (16.0%)	7 (17.1%)	0	7 (13.5%)
< 56 mg/dL (3.1 mmol/L)	2 (4.0%)	1 (2.4%)	0	1 (1.9%)
< 36 mg/dL (2.0 mmol/L)	0	0	0	0
Total number of episodes	58	36	0	36
Subjects with numbers of biochemically documented hypoglycemia	8 (16.0%)	7 (17.1%)	0	7 (13.5%)
1 episode	2 (4.0%)	3 (7.3%)	0	3 (5.8%)
2 episodes	3 (6.0%)	2 (4.9%)	0	2 (3.8%)
>= 3 episodes	3 (6.0%)	2 (4.9%)	0	2 (3.8%)
Event rate per subject-year exposure	0.98	0.62	-	0.5

Note: Count (%) is based on Number of Subjects, Not Number of Episodes.
*Subjects with any treatment-emergent biochemically documented hypoglycemia episodes;
A subject may be counted in each of the three glucose categories listed below;
Results of LOW is included in all the three glucose categories (i.e., ≤ 70, <56, and/or <36 mg/dL).
Glucose data could be reported in either mg/dL or mmol/L units. No conversion between the two units was made. The comparison between the reported glucose values and the cutoffs was based on the units in which the glucose values were reported.
[TSFAE15A.RTF] [JNJ-28431754B/DIA3018/DBR_FINAL_RE2/RE_CSR/PROD/TSFAE15A.SAS] 28DEC2023, 17:49

Source: Study DIA3018 CSR p. 101

Table 23 shows an analysis of treatment-emergent hypoglycemia in the subgroup of study subjects who were treated with concomitant insulin therapy. There was an increased rate of hypoglycemia events associated with canagliflozin treatment as compared to placebo treatment in the subgroup of insulin-treated subjects.

Table 23. Biochemically Documented Treatment-Emergent Hypoglycemia Prior to Rescue Medication–On Insulin (with or without Metformin)

	Placebo	Canagliflozin 100 mg	Canagliflozin 300 mg	Combined
Analysis set: Safety	37	26	6	32
Subjects with episodes*	6 (16.2%)	7 (26.9%)	1 (16.7%)	8 (25.0%)
<=70 mg/dL (3.9 mmol/L)	6 (16.2%)	7 (26.9%)	1 (16.7%)	8 (25.0%)
< 56 mg/dL (3.1 mmol/L)	5 (13.5%)	5 (19.2%)	0	5 (15.6%)
< 36 mg/dL (2.0 mmol/L)	2 (5.4%)	0	0	0
Total number of episodes	16	21	1	22
Subjects with numbers of biochemically documented hypoglycemia	6 (16.2%)	7 (26.9%)	1 (16.7%)	8 (25.0%)
1 episode	2 (5.4%)	2 (7.7%)	1 (16.7%)	3 (9.4%)
2 episodes	3 (8.1%)	1 (3.8%)	0	1 (3.1%)
>= 3 episodes	1 (2.7%)	4 (15.4%)	0	4 (12.5%)
Event rate per subject-year exposure	0.27	0.36	0.07	0.3

Note: Count (%) is based on Number of Subjects, Not Number of Episodes.
*Subjects with any treatment-emergent biochemically documented hypoglycemia episodes;
A subject may be counted in each of the three glucose categories listed below;
Results of LOW is included in all the three glucose categories (i.e., ≤ 70, <56, and/or <36 mg/dL).
Glucose data could be reported in either mg/dL or mmol/L units. No conversion between the two units was made. The comparison between the reported glucose values and the cutoffs was based on the units in which the glucose values were reported.

Source: Study DIA3018 CSR p. 102

Reviewer's Comment: An increased risk of hypoglycemia has been reported in adult studies of canagliflozin but only when used concomitantly with insulin and/or sulfonylureas; this risk is described as a Warning and Precaution in the USPI. In Study DIA3018, an imbalance in hypoglycemia events was observed with canagliflozin treatment as compared to placebo only among subjects treated with background insulin; however, this imbalance was not observed in the subgroup of subjects who were not treated with insulin or in the overall study population. These findings suggest that the hypoglycemia risk in pediatric T2D subjects is comparable to that described in adults as reflected in the current USPI.

Adverse Events of Special Interest (AESIs)

The AESIs prespecified by the Applicant were diabetic ketoacidosis, fractures, and pancreatitis, as required in the pediatric WR. Subjects experiencing 1 or more AESIs occurring during Study DIA3018 are described in Table 24 below.

Table 24. Summary of AESIs occurring through Week 52, Study DIA3018

	Canagliflozin (N=84)	Placebo (N=87)	Total (N=171)
Ketoacidosis Events, n (%)	5 (6.0)	5 (5.7)	10 (5.8)
Preferred Term			
Blood ketone body increased	2 (2.4)	2 (2.3)	4 (2.3)
Diabetic ketoacidosis	1 (1.2)	1 (1.1)	2 (1.2)
Ketonuria	1 (1.2)	0	1 (0.6)

	Canagliflozin (N=84)	Placebo (N=87)	Total (N=171)
Ketosis	2 (2.4)	1 (1.1)	3 (1.8)
Metabolic acidosis	0	1 (1.1)	1 (0.6)
Fractures, n (%)	1 (1.2)	2 (2.3)	3 (1.8)
Preferred Term			
Ankle fracture	0	1 (1.1)	1 (0.6)
Hand fracture	1 (1.2)	1 (1.1)	2 (1.2)
Pancreatitis, n (%)			
Pancreatitis acute	1 (1.2)	0	1 (0.6)

Source: OCS Analysis Studio, Custom Table Tool.
Columns - Dataset: Demographics; Filter: SAFFL = 'Y'.
Ketoacidosis Events - Dataset: Adverse Events; Filter: CQ36NAM = 'Diabetic Ketoacidosis'.
Preferred Term - Dataset: Adverse Events; Filter: CQ36NAM = 'Diabetic Ketoacidosis'.
Fractures - Dataset: Adverse Events; Filter: CQ03NAM = 'Fracture'.
Preferred Term - Dataset: Adverse Events; Filter: CQ03NAM = 'Fracture'.
Pancreatitis - Dataset: Adverse Events; Filter: CQ31NAM = 'Pancreatitis (Select)'.

- Diabetic Ketoacidosis (DKA)

The adjudication committee determined that 3 of the 10 ketoacidosis events were DKA events, and all were considered mild in severity. Only 1 DKA event occurred in the canagliflozin group, in a subject receiving the 100 mg dose, and it was also reported as a SAE. The narrative was described in Section 8.4.2. The 2 other DKA events were in the placebo group.

Reviewer's comment: The incidence of ketoacidosis events was balanced in the canagliflozin and placebo groups. Of these events, only 3 were adjudicated to be DKA events, of which only 1 was in the canagliflozin group, and was attributed to a missed dose of insulin the night before, as well as inconsistent compliance with metformin and diabetic diet (see discussion in Section 8.4.2). Nevertheless, canagliflozin is known to increase the risk of diabetic ketoacidosis, so the possibility remains that canagliflozin therapy may have contributed to this DKA event.

- Fractures

Of the three subjects who experienced bone fractures during the study, only 1 was on canagliflozin (100 mg). The two others were on placebo. The subject on canagliflozin 100 mg reported a thumb fracture, which could not be confirmed by external adjudication. The event was non-serious, mild in severity, and not considered by the investigator to be related to canagliflozin.

Reviewer's comment: Fractures are common in the pediatric population, and this one isolated case of fracture in the canagliflozin group does not by itself increase concern for fracture risk beyond what is already established for the adult population.

- Pancreatitis

There was 1 case of acute pancreatitis in Study DIA3018, in a participant who at the time was

on canagliflozin 100mg. This was reported as an SAE. As discussed in Section 8.4.2, this participant had a prior history of acute pancreatitis prior to enrollment and experienced another episode of acute pancreatitis during the study. The study drug was temporarily withdrawn until the acute pancreatitis resolved, and was subsequently re-randomized to canagliflozin 300 mg. The participant completed the study without any recurrence of pancreatitis.

Reviewer's comment: Based on the fact that the subject had a pre-existing history of acute pancreatitis and risk factors for acute pancreatitis, including hypertriglyceridemia and recently-initiated treatment with a GLP-1 agonist (liraglutide), as well as the fact that after resolution, the subject resumed canagliflozin, had a dose increase to 300 mg, and went on to complete the study, without a recurrence of acute pancreatitis, it seems unlikely that this participant's case of acute pancreatitis was related to canagliflozin treatment. An increased risk of pancreatitis has not been described in adult studies of canagliflozin.

Specific AEs of Clinical Interest

Selected AEs for additional analysis were vulvovaginal candidiasis, balanitis or balanoposthitis, urinary tract infections, volume depletion, hepatic injury, renal impairment/renal failure, hypersensitivity, venous thromboembolic event, photosensitivity, malignancy, and lower extremity amputation. The AEs that occurred within these categories are presented in Table 25. There were no AEs related to renal impairment/renal failure, venous thromboembolic events, photosensitivity, malignancies, or lower extremity amputation. Hepatic & renal analyses will be presented separately in Section 8.4.6.

Table 25. Specific AEs of Clinical Interest, Study DIA3018

	Canagliflozin (N=84)	Placebo (N=87)	Total (N=171)
Genital Mycotic Infections	5 (6.0)	0	5 (2.9)
Genital infection fungal	1 (1.2)	0	1 (0.6)
Vaginal infection	1 (1.2)	0	1 (0.6)
Vulvitis	1 (1.2)	0	1 (0.6)
Vulvovaginal candidiasis	2 (2.4)	0	2 (1.2)
Male Genital Infections	2 (2.4)	0	2 (1.2)
Balanitis candida	2 (2.4)	0	2 (1.2)
Balanoposthitis	1 (1.2)	0	1 (0.6)
Urinary Tract Infections	6 (7.1)	4 (4.6)	10 (5.8)
Urinary tract infection	6 (7.1)	4 (4.6)	10 (5.8)
Urinary tract infection bacterial	1 (1.2)	0	1 (0.6)
Volume Depletion	1 (1.2)	2 (2.3)	3 (1.8)
Dehydration	1 (1.2)	1 (1.1)	2 (1.2)
Syncope	0	1 (1.1)	1 (0.6)

	Canagliflozin (N=84)	Placebo (N=87)	Total (N=171)
Hepatic Injury			
Hepatic steatosis	1 (1.2)	1 (1.1)	2 (1.2)
Hypersensitivity	2 (2.4)	0	2 (1.2)
Anaphylactic reaction	1 (1.2)	0	1 (0.6)
Urticaria	1 (1.2)	0	1 (0.6)

Source: OCS Analysis Studio, Custom Table Tool.
Columns - Dataset: Demographics; Filter: SAFFL = 'Y'.
Genital Mycotic Infections - Dataset: Adverse Events; Filter: CQ07NAM = 'Mycotic Genital (Narrow)'.
Table Section 2 - Dataset: Adverse Events; Filter: CQ07NAM = 'Mycotic Genital (Narrow)'.
Male Genital Infections - Dataset: Adverse Events; Filter: CQ04NAM = 'Male Genital Infections'.
Table Section 4 - Dataset: Adverse Events; Filter: CQ04NAM = 'Male Genital Infections'.
Urinary Tract Infections - Dataset: Adverse Events; Filter: CQ15NAM = 'UTI'.
Table Section 6 - Dataset: Adverse Events; Filter: CQ15NAM = 'UTI'.
Volume Depletion - Dataset: Adverse Events; Filter: CQ17NAM = 'Volume Depletion'.
Table Section 8 - Dataset: Adverse Events; Filter: CQ17NAM = 'Volume Depletion'.
Hepatic Injury - Dataset: Adverse Events; Filter: CQ27NAM = 'Hepatic Injury'.
Hypersensitivity - Dataset: Adverse Events; Filter: CQ34NAM = 'Sev Hypsens and Sev Cut AEs'.
Table Section 11 - Dataset: Adverse Events; Filter: CQ34NAM = 'Sev Hypsens and Sev Cut AEs'.

Reviewer's Comment: There was a clear imbalance in genital mycotic infections (female, as well as male), as all such AEs occurred in the canagliflozin group and none occurred in the placebo group. The 8% of pediatric subjects affected by genital mycotic infections is consistent with the current adult labeling for Invokana which cites a 5% or greater incidence of genital mycotic infections. Volume depletion/dehydration was balanced between the two groups with 1 case in each group, as was hepatic steatosis. There were two hypersensitivity reactions in the canagliflozin group. As discussed in Section 8.4.2, it is unlikely that the anaphylactic reaction was related to canagliflozin, as there was a clear temporal association of the anaphylactic reaction to a flying insect bite, and the participant did not re-experience anaphylaxis or other hypersensitivity reactions to subsequent re-exposures to canagliflozin for 222 days afterwards until she withdrew from the study due to her college schedule. There was also a higher percentage of UTIs in the canagliflozin group compared to the placebo group, which is also consistent with UTI already being a labeled adverse reaction to canagliflozin in the adult population.

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

A summary of TEAEs by preferred term (PT) occurring in > 3% of subjects treated with canagliflozin and with risk difference > 1% as compared to placebo through Week 26 is displayed in Table 26. Headache (10.7%), nasopharyngitis (9.5%), UTI (7.1%), and vomiting (6.0%) were the most common PTs affecting the canagliflozin group. While formal statistical conclusions cannot be drawn from these data, overall, the 95% confidence intervals calculated for the risk difference between canagliflozin and placebo for these TEAEs contain values which include 0, suggesting that there is no difference between treatment arms.

Table 26. TEAEs by PT occurring in >3% of Subjects Treated with Canagliflozin through Week 52, Study DIA3018

Preferred Term	Canagliflozin Pooled (100 mg & 300 mg) N = 84 n (%)	Placebo N = 87 n (%)	Risk Difference RD (95% CI)	Forest Plot
Any AE	65 (77.4)	65 (74.7)	2.67 (-10.12, 15.45)	
Abdominal pain	3 (3.6)	0 (0.0)	3.57 (-0.40, 7.54)	
Diarrhea	4 (4.8)	5 (5.7)	-0.99 (-7.67, 5.70)	
Dizziness	3 (3.6)	1 (1.1)	2.42 (-2.14, 6.98)	
Headache	9 (10.7)	3 (3.4)	7.27 (-0.38, 14.91)	
Hyperglycemia	3 (3.6)	5 (5.7)	-2.18 (-8.47, 4.12)	
Hypoglycemia	3 (3.6)	8 (9.2)	-5.62 (-12.88, 1.63)	
Influenza	3 (3.6)	4 (4.6)	-1.03 (-6.95, 4.90)	
Nasopharyngitis	8 (9.5)	5 (5.7)	3.78 (-4.18, 11.73)	
Nausea	4 (4.8)	1 (1.1)	3.61 (-1.46, 8.69)	
Pain in extremity	3 (3.6)	0 (0.0)	3.57 (-0.40, 7.54)	
Pyrexia	4 (4.8)	3 (3.4)	1.31 (-4.64, 7.27)	
Rhinitis	4 (4.8)	2 (2.3)	2.46 (-3.07, 8.00)	
Upper respiratory tract infection	4 (4.8)	11 (12.6)	-7.88 (-16.22, 0.46)	
Urinary tract infection	6 (7.1)	4 (4.6)	2.55 (-4.50, 9.60)	
Viral upper respiratory tract infection	3 (3.6)	1 (1.1)	2.42 (-2.14, 6.98)	
Vitamin D deficiency	4 (4.8)	6 (6.9)	-2.13 (-9.14, 4.87)	
Vomiting	5 (6.0)	2 (2.3)	3.65 (-2.31, 9.61)	

Source: OCS Analysis Studio, Safety Explorer.
Filters: TRTCA = "Cana" and SAFFL = "Y" (Canagliflozin Pooled (100 mg & 300 mg)); TRTCA = "Placebo" and SAFFL = "Y" (Placebo); TRTEMFL = "Y" (Adverse Events).
Percent Threshold: Canagliflozin Pooled (100 mg & 300 mg) ≥ 3%.
Risk Difference calculated by comparing the left column (Group 1) to the right column (Group 2).

8.4.6. Laboratory Findings

Renal Function Parameters

Mean change from baseline in urine albumin/creatinine ratio, serum creatinine, and estimated GFR through week 52 is displayed in Table 27. A mean decrease of eGFR of 4.48 mL/min/1.72

m^2 occurred in subjects treated with canagliflozin from baseline to Week 52. A shift table for renal impairment based on eGFR is displayed in Table 28. Of the subjects with available eGFR measurements (canagliflozin N=69, placebo N=72) only 1 subject in Study DIA3018 (canagliflozin group) with normal renal function at baseline developed mild renal impairment by Week 52. Additionally, baseline mild renal impairment in another subject in the canagliflozin group resolved to the normal range during the study. All subjects with available eGFR measurements in the placebo group had eGFRs $\geq$90 mL/min/1.72 m^2 throughout the 52 weeks of the study. According to a shift table for urine albumin/creatinine ratio (Table 29) a small percentage of subjects shifted from baseline normoalbuminuria to microalbuminuria by Week 52 within both treatment arms. A small percentage of subjects in all treatment arms who had microalbuminuria at baseline reverted back to normoalbuminuria by Week 52, a phenomenon that has been previously reported.[17]

Table 27. Renal Function Parameter Difference from Baseline to Week 52 Summary Table, Study DIA3018

Parameter	Statistic	Canagliflozin Pooled	Placebo
Serum Creatinine (mg/dL)	Subject Count	70	75
	Baseline	0.60 ± 0.14, 0.60	0.63 ± 0.12, 0.60
	End of Treatment	0.62 ± 0.13, 0.60	0.63 ± 0.13, 0.60
	Difference	0.02 ± 0.12, 0.00	0.00 ± 0.09, 0.00
Estimated GFR (Schwartz calculation, mL/min/1.73m^2)	Subject Count	69	72
	Baseline	166.41 ± 34.70, 168.00	151.97 ± 29.22, 147.00
	End of Treatment	161.93 ± 34.10, 157.00	152.32 ± 28.87, 145.00
	Difference	-4.48 ± 29.68, 1.00	0.35 ± 22.53, 0.75
Urine Albumin/Creatinine Ratio (mg/g)	Subject Count	58	65
	Baseline	42.93 ± 133.05, 9.33	39.63 ± 162.92, 8.31
	End of Treatment	59.59 ± 199.40, 10.81	46.83 ± 137.34, 10.00
	Difference	16.66 ± 75.97, 0.49	7.20 ± 58.39, 1.00

Source: OCS Analysis Studio, Kidney Function Tool.
Subject Count: All subjects with test results for both baseline and end of treatment were included.
Mean ± standard deviation, median.
End of Treatment: AVISIT = 'WEEK 52'.

Table 28. Shift Table of Renal Impairment (based on eGFR) from Baseline to Week 52, Study DIA3018

		Final Renal Impairment		
Treatment Arm	**Baseline Renal Impairment**	**None**	**Mild**	**Moderate-Severe**
Canagliflozin (N = 69)	None	67 (97.1%)	1 (1.4%)	0
	Mild	1 (1.4%)	0	0
	Moderate-Severe	0	0	0
Placebo (N = 72)	None	72 (100.0%)	0	0
	Mild	0	0	0
	Moderate-Severe	0	0	0

Source: OCS Analysis Studio, Kidney Function Tool.
None: >=90 mL/min/1.73 m^2; Mild: 90-60 mL/min/1.73 m^2; Moderate-Severe: <=60 mL/min/1.73 m^2.
Percentage based on population of a given treatment arm.
End of Treatment: AVISIT = 'WEEK 52'.

Table 29. Urine Albumin/Creatinine Shift Table from Baseline to Week 52, Study DIA3018

		Final Albuminuria		
Treatment Arm	**Baseline Albuminuria**	**Normoalbuminuria**	**Microalbuminuria**	**Macroalbuminuria**
Cana (N = 58)	Normoalbuminuria	46 (79.3%)	5 (8.6%)	0
	Microalbuminuria	3 (5.2%)	1 (1.7%)	0
	Macroalbuminuria	0	0	3 (5.2%)
Placebo (N = 65)	Normoalbuminuria	50 (76.9%)	6 (9.2%)	0
	Microalbuminuria	3 (4.6%)	4 (6.2%)	1 (1.5%)
	Macroalbuminuria	0	0	1 (1.5%)

Source: OCS Analysis Studio, Kidney Function Tool.
Normoalbuminuria: <=30 mg/g; Microalbuminuria: 30-300 mg/g; Macroalbuminuria: >=300 mg/g.
Percentage based on population of a given treatment arm.
End of Treatment: AVISIT = 'WEEK 52'.

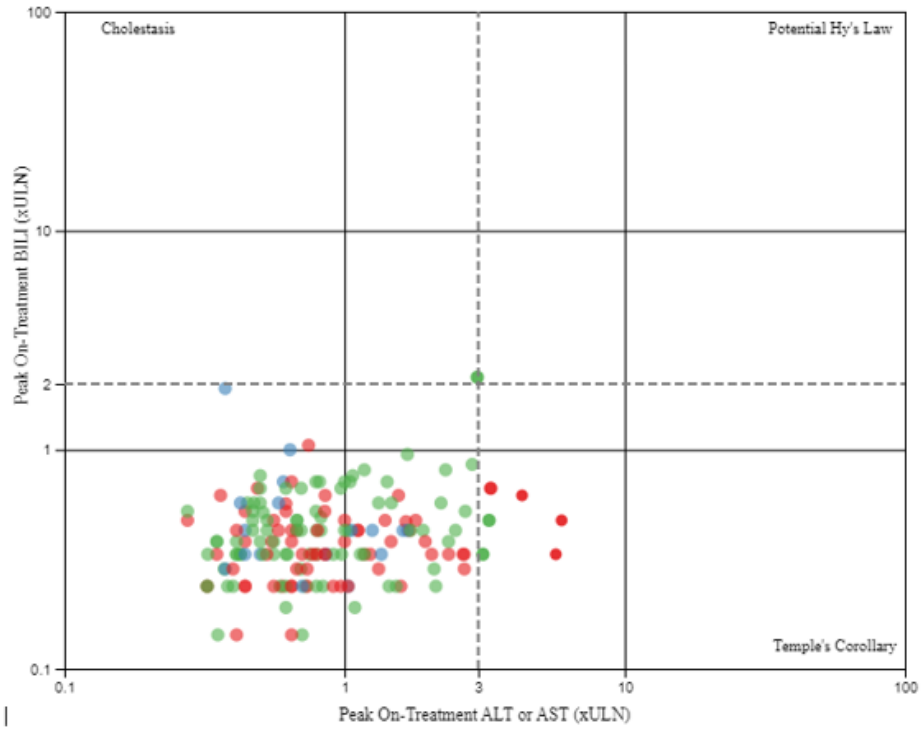
Reviewer's comment: As discussed in Section 6.1.2, the mean baseline eGFR in both treatment arms was in the hyperfiltration range. Since renal function in the vast majority of subjects in both treatment arms remained at a normal to hyperfiltrating range (eGFR of ≥90), and renal impairment was only present in only 2 subjects in the canagliflozin group (one at baseline which resolved, and one that progressed to the mild range during the study), there were insufficient data to evaluate the effects of canagliflozin in pediatric patients with renal impairment.

Hepatic Function Parameters

A hepatocellular DILI plot analysis was conducted for the period through Week 52 of Study DIA3018 (Figure 4). No hepatic event fulfilled Hy's Law criteria (i.e., AST or ALT ≥ 3 x ULN and

total bilirubin ≥ 2 x ULN) during the study. Four subjects in the canagliflozin arm and 2 subjects in the placebo arm were in the right lower quadrant for Temple's corollary through Week 52 (Table 30). Two of 85 participants (2.4%) receiving placebo exhibited ALT values >3xULN, compared to 4 of 84 participants (4.8%) receiving canagliflozin. In addition, 2 of 67 participants (3.0%) on canagliflozin 100 mg had ALT values >5xULN, compared to none receiving the higher dose. Hepatic function data for these subjects over the course of the entire study were individually reviewed. For the 4 subjects treated with canagliflozin, hepatic function changes over the course of the study are displayed in Figure 5, Figure 6, Figure 7, and Figure 8. All of these subjects had elevation in baseline AST and/or ALT. Subject (b) (6) had a pre-existing history of hepatic steatosis. ALT and AST for Subjects (b) (6) improved from baseline over the course of the study.

Figure 4. Hepatocellular DILI Screening Plot through Week 52, Study DIA3018



Source: OCS Analysis Studio, Hepatic Explorer.
Filters: None.
*Hepatotoxicity Candidates: ALT or AST >= 3*ULN; BILI >= 2*ULN (0-30 days forward); ALP < 2*ULN (0-999 days backward).
*Results missing ULN values were imputed using the weighted mean of the lab code.
Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BILI, bilirubin;
DILI, drug-induced liver injury; ULN, upper limit of normal.

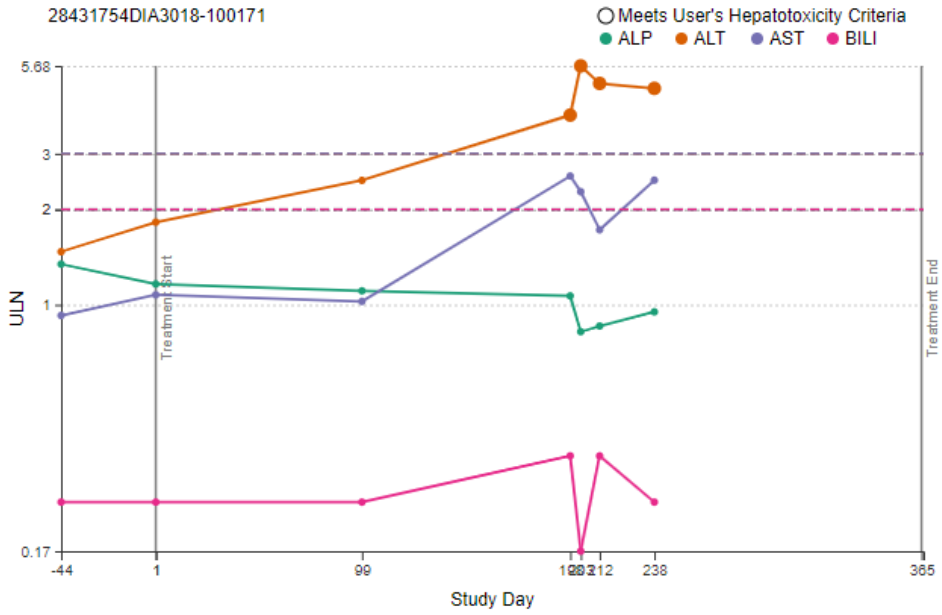
Key
- Hepatotoxicity Candidate Based on User's Criteria
- Cana 100 mg
- Cana 300 mg
- Placebo

Table 30. Listing of Subjects in Temple's Corollary through Week 52, Study DIA3018

Subject	TRT01A	Peak ALT or AST	Peak BILI
(b) (6)	Placebo	3.1176	0.3333
	Cana 100 mg	5.6786	0.3333
	Cana 100 mg	4.3023	0.619
	Placebo	3.2791	0.4762
	Cana 100 mg	3.3235	0.6667
	Cana 100 mg	5.9535	0.4762

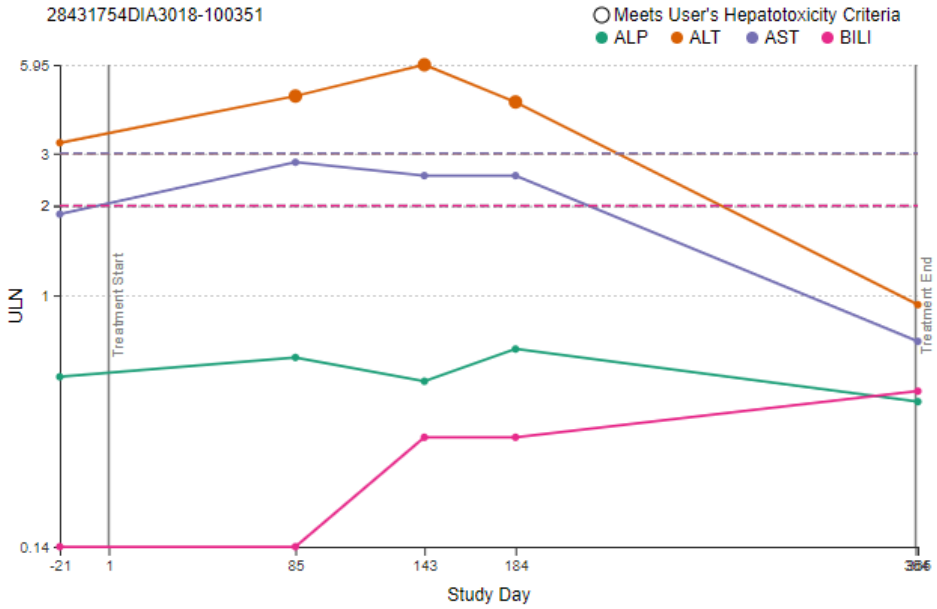
Source: Reviewer created in OCS Analysis Studio, Hepatic Explorer

Figure 5. Hepatic Function Tests for Subject (b) (6) treated with Canagliflozin



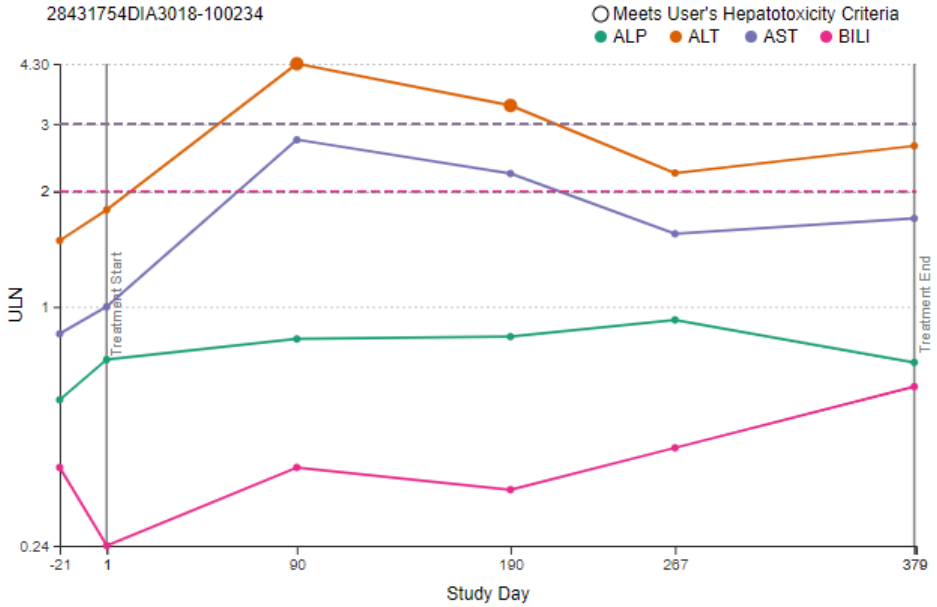
Source: Reviewer created using OCS Analysis Studio, Hepatic Explorer

Figure 6. Hepatic Function Tests for Subject (b) (6) treated with Canagliflozin



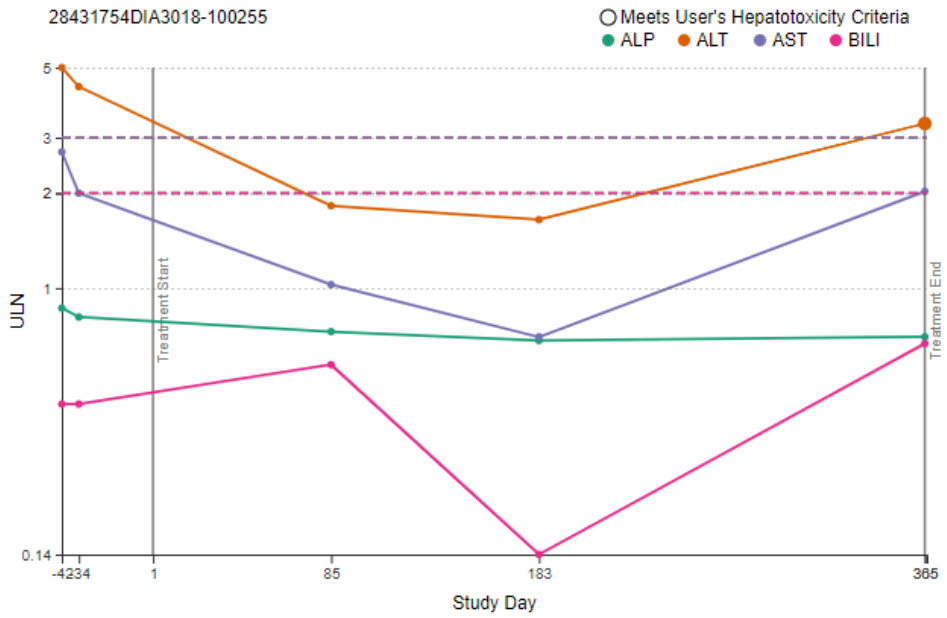
Source: Reviewer created using OCS Analysis Studio, Hepatic Explorer

Figure 7. Hepatic Function Tests for Subject (b) (6) treated with Canagliflozin



Source: Reviewer created using OCS Analysis Studio, Hepatic Explorer

Figure 8. Hepatic Function Tests for Subject (b) (6) treated with Canagliflozin



Source: Reviewer created using OCS Analysis Studio, Hepatic Explorer

Reviewer's Comment: Based on review of hepatic function, there does not appear to be any evidence for drug-induced liver injury among pediatric T2D subjects treated with canagliflozin.

Lipids

According to the Applicant's analyses, canagliflozin treatment was associated with a small reduction in baseline HDL cholesterol (HDL-C) as compared to placebo over 52 weeks (Table 31).

Table 31. LS Mean Percent Change from Baseline in HDL-C Over Time; Full Analysis Set, Study DIA3018

	Placebo (N=87)		Cana (N=84)		Difference (Cana-Placebo)		
	N[a]	LS Mean (SE)	N[a]	LS Mean (SE)	LS Mean (SE)	CI[b]	p-value[b]
WEEK 6			2	-3.2 (11.94)			
WEEK 12			3	12.1 (8.69)			
WEEK 20	1	-0.4 (20.47)	2	-13.8 (13.83)	-13.4 (27.83)	(-68.6, 41.7)	0.630
WEEK 26	67	0.6 (2.45)	66	5.0 (2.42)	4.4 (3.25)	(-2.0, 10.8)	0.178
WEEK 34	3	-1.4 (10.01)	2	2.2 (8.97)	3.6 (14.94)	(-26.0, 33.2)	0.810
WEEK 42			2	16.8 (12.06)			
WEEK 52	68	1.0 (2.43)	60	8.2 (2.50)	7.2 (3.30)	(0.7, 13.8)	0.031

[a]: Number of subjects with non-missing value of change from baseline.
[b]: CIs (confidence interval) and p-values are based on a mixed model for repeated measures including the fixed effects of treatment, stratification factors (i.e., background AHA and age group), visit, and treatment-by-visit interaction, as well as the fixed, continuous covariates of baseline and baseline-by-visit interaction. An AR(1) covariance structure was used to model within subject errors since the model did not converge using the unstructured covariance.
[tefhdlc02.rtf] [PROD/jnj-28431754b/dia3018/dbr_final_re2/re_csr/tefhdlc02.sas] 28DEC2023, 17:49

Source: Study DIA3018 CSR, p. 354

In addition, canagliflozin treatment was associated with a greater reduction in triglyceride levels as compared to placebo (Table 32) over 52 weeks.

Table 32. LS Mean Percent Change from Baseline in Triglycerides Over Time; Full Analysis Set, Study DIA3018

	Placebo (N=87)		Cana (N=84)		Difference (Cana-Placebo)		
	N[a]	LS Mean (SE)	N[a]	LS Mean (SE)	LS Mean (SE)	CI[b]	p-value[b]
WEEK 6	5	18.3 (23.80)	2	2.7 (38.39)	-15.6 (45.73)	(-106.0, 74.9)	0.734
WEEK 12			2	-21.3 (50.64)			
WEEK 20	1	-482.1 (1779.15)	2	-195.0 (664.90)	287.1 (1116.3)	(-1922, 2496.1)	0.797
WEEK 26	74	10.7 (6.40)	70	5.8 (6.49)	-4.9 (8.75)	(-22.2, 12.5)	0.579
WEEK 34	3	32.2 (74.51)	2	6.2 (41.04)	-25.9 (69.21)	(-162.9, 111.0)	0.708
WEEK 42			2	4.6 (41.89)			
WEEK 52	71	21.6 (6.53)	62	-6.4 (6.89)	-28.0 (9.15)	(-46.1, -9.9)	0.003

[a]: Number of subjects with non-missing value of change from baseline.
[b]: CIs (confidence interval) and p-values are based on a mixed model for repeated measures including the fixed effects of treatment, stratification factors (i.e., background AHA and age group), visit, and treatment-by-visit interaction, as well as the fixed, continuous covariates of baseline and baseline-by-visit interaction. An AR(1) covariance structure was used to model within subject errors since the model did not converge using the unstructured covariance.
[teftrig02.rtf] [PROD/jnj-28431754b/dia3018/dbr_final_re2/re_csr/teftrig02.sas] 28DEC2023, 17:49

Source: Study DIA3018 CSR, p. 382

There were no clinically significant changes in mean LDL cholesterol (LDL-C) or non-HDL-C from

baseline to Week 52 in either of the treatment groups (data not shown).

Hemoglobin
A possible imbalance of hemoglobin values with a >2 g/dL (>20 g/L) increase from baseline was noted between the treatment groups, with a higher percentage occurring in the canagliflozin group (11.3%) versus placebo (3.8%). However, the 95% CI of the treatment difference (canagliflozin vs placebo) was wide and included zero (95% CI -1.8 to 16.8).

Reviewer's comment: All SGLT2 labels report an increase in hematocrit and/or increase hemoglobin in subsections of Section 6.1 regarding lab changes in clinical trials. The adult Invokana trials showed a small mean percent increase from baseline in hemoglobin levels, but these changes were not associated with an increase in potentially related events such as thromboembolic events (original Invokana NDA 204042 clinical review by Dr. Kwon dated February 8, 2013). Data from the pediatric trials for other SGLT2 inhibitors (empagliflozin and dapagliflozin) also suggested slightly higher rates of mild hemoglobin increases with SGLT-2 inhibitor treatment versus placebo. This finding in Study DIA3018 for canagliflozin is consistent with these previous observations for the SGLT-2 inhibitor class.

Bone Turnover Markers
Bone turnover marker data (osteocalcin, Type 1 collagen C-telopeptides) did not suggest any apparent clinically meaningful differences from placebo, given the wide standard deviations on osteocalcin measurements, and the relatively low number of subjects who had serum Type 1 collagen C-telopeptide measurements.

Other labs
The incidence of laboratory values outside pre-defined limits for magnesium was higher in participants receiving canagliflozin. Five of 84 (6.0%) participants on canagliflozin (versus none in the placebo group) had magnesium values above the upper limit of normal and with a >25% increase from baseline, however the 95% confidence interval was wide and included zero (95% CI -0.3 to 12.2).

Reviewer's comment: Overall, there were no clinically notable mean changes observed in clinical chemistry or hematology parameters.

8.4.7. Vital Signs

Change in heart rate (HR), systolic blood pressure (SBP), and diastolic blood pressure (DBP) from baseline to Week 52 in Study DIA3018 are displayed in Table 33, Table 34, and Table 35, respectively. No clinically meaningful changes in HR, SBP, or DBP occurred in any treatment arm.

Table 33. Heart Rate (HR) at Baseline and at Week 52 , Study DIA3018

	Canagliflozin Pooled (100 mg & 300 mg) N=84	Placebo N=87
HR at Baseline (N)	84 (100.0)	87 (100.0)
HR at Baseline (bpm)		
Mean (SD)	84.1 (11.19)	82.8 (12.90)
Median (Min, Max)	84.5 (60, 111)	83.0 (55, 131)
HR at Week 52 (N)	74 (88.1)	75 (86.2)
HR at Week 52 (bpm)		
Mean (SD)	82.6 (9.66)	84.0 (10.95)
Median (Min, Max)	83.5 (63, 113)	83.0 (62, 113)

Source: OCS Analysis Studio, Custom Table Tool.
Columns - Dataset: Demographics; Filter: SAFFL = 'Y'.
HR at Baseline (N) - Dataset: Vital Signs; Filter: ABLFL = 'Y', PARAM = 'Pulse Rate (BEATS/MIN)'.
HR at Baseline (bpm) - Dataset: Vital Signs; Filter: ABLFL = 'Y', PARAM = 'Pulse Rate (BEATS/MIN)'.
HR at Week 52 (N) - Dataset: Vital Signs; Filter: AVISIT = 'WEEK 52', PARAM = 'Pulse Rate (BEATS/MIN)'.
HR at Week 52 (bpm) - Dataset: Vital Signs; Filter: AVISIT = 'WEEK 52', PARAM = 'Pulse Rate (BEATS/MIN)'.
SD = Standard Deviation.

Table 34. Systolic Blood Pressure (SBP) at Baseline and at Week 52, Study DIA3018

	Canagliflozin Pooled (100 mg & 300 mg) N=84	Placebo N=87
SBP at Baseline (N)	84 (100.0)	87 (100.0)
SBP at Baseline (mmHg)		
Mean (SD)	115.5 (13.19)	114.9 (12.34)
Median (Min, Max)	114.5 (91, 152)	114.3 (80, 149)
SBP at Week 52 (N)	74 (88.1)	75 (86.2)
SBP at Week 52 (mmHg)		
Mean (SD)	115.1 (14.32)	115.6 (11.80)
Median (Min, Max)	113.8 (82, 153)	115.5 (85, 149)

Source: OCS Analysis Studio, Custom Table Tool.
Columns - Dataset: Demographics; Filter: SAFFL = 'Y'.
SBP at Baseline (N) - Dataset: Vital Signs; Filter: ABLFL = 'Y', PARAM = 'Systolic Blood Pressure (mmHg)'.
SBP at Baseline (mmHg) - Dataset: Vital Signs; Filter: ABLFL = 'Y', PARAM = 'Systolic Blood Pressure (mmHg)'.
SBP at Week 52 (N) - Dataset: Vital Signs; Filter: AVISIT = 'WEEK 52', PARAM = 'Systolic Blood Pressure (mmHg)'.
SBP at Week 52 (mmHg) - Dataset: Vital Signs; Filter: AVISIT = 'WEEK 52', PARAM = 'Systolic Blood Pressure (mmHg)'.
SD = Standard Deviation.

Table 35. Diastolic Blood Pressure (DBP) at Baseline and at Week 52, Study DIA3018

	Canagliflozin Pooled (100 mg & 300 mg) N=84	Placebo N=87
DBP at Baseline (N)	84 (100.0)	87 (100.0)
DBP at Baseline (mmHg)		
Mean (SD)	73.0 (8.63)	72.0 (8.07)
Median (Min, Max)	72.7 (55, 96)	72.3 (51, 94)
DBP at Week 52 (N)	74 (88.1)	75 (86.2)
DBP at Week 52 (mmHg)		
Mean (SD)	72.2 (9.03)	72.4 (8.41)
Median (Min, Max)	71.0 (50, 97)	72.0 (52, 98)

Table 35. Diastolic Blood Pressure (DBP) at Baseline and at Week 52, Study DIA3018

	Canagliflozin Pooled (100 mg & 300 mg) N=84	Placebo N=87

Source: OCS Analysis Studio, Custom Table Tool.
Columns - Dataset: Demographics; Filter: SAFFL = 'Y'.
DBP at Baseline (N) - Dataset: Vital Signs; Filter: ABLFL = 'Y', PARAM = 'Diastolic Blood Pressure (mmHg)'.
DBP at Baseline (mmHg) - Dataset: Vital Signs; Filter: ABLFL = 'Y', PARAM = 'Diastolic Blood Pressure (mmHg)'.
DBP at Week 52 (N) - Dataset: Vital Signs; Filter: AVISIT = 'WEEK 52', PARAM = 'Diastolic Blood Pressure (mmHg)'.
DBP at Week 52 (mmHg) - Dataset: Vital Signs; Filter: AVISIT = 'WEEK 52', PARAM = 'Diastolic Blood Pressure (mmHg)'.
SD = Standard Deviation.

Reviewer's comment: Adult studies showed small but statistically significant decreases in SBP (approximately -3 to -6 mmHg) with canagliflozin (Section 14.1 of the Invokana label), but did not show changes in HR. No changes in HR, SBP, or DBP were evident in the pediatric population of Study DIA3018.

8.4.8. Electrocardiograms (ECGs)

No clinically relevant findings with regards to ECG recordings were reported as adverse events.

8.4.9. QT

This section was evaluated as part of the original NDA review.

8.4.10. Immunogenicity

Immunogenicity was not assessed in the study.

8.5. Analysis of Submission-Specific Safety Issues

Submission-specific safety issues are discussed throughout Section 8.4 of this review, with the exception of puberty and growth assessments which are described in Section 8.8.3.

8.6. Safety Analyses by Demographic Subgroups

The CSR of Study DIA3018 did not contain specific safety analyses by demographic subgroups, as this was not prespecified in the Statistical Analysis Plan.

The clinical review team did not explore drug safety by demographic subgroups because (a) the safety profile observed in the pediatric study is broadly consistent with the safety profile in adults, (b) The original NDA medical reviews of the large, adult, premarket databases did not identify a meaningful treatment interaction with demographic subgroups, despite being adequately powered and (c) the pediatric safety database is generally inadequate to identify

marginal treatment differences in adverse events, let alone treatment interactions by patient subgroups such as race, gender, or age.

8.7. Specific Safety Studies/Clinical Trials

No additional specific safety studies are being conducted.

8.8. Additional Safety Explorations

8.8.1. Human Carcinogenicity or Tumor Development

There is no information relevant to this section of the review in the submission.

8.8.2. Human Reproduction and Pregnancy

There is no information relevant to this section of the review in the submission. There was only 1 pregnancy that occurred in Study DIA3018, and it was in the placebo group.

8.8.3. Pediatrics and Assessment of Effects on Growth

The Applicant's CSR summary for the markers of growth, maturation, and bone health, including height, height velocity, and Tanner scores during the 52-week treatment period of Study DIA3018 reports that no safety concerns were raised with canagliflozin treatment. The study duration of only 1 year and participants being at different stages of growth at study entry are limitations to the information this study can provide about effects of canagliflozin on growth and puberty.

8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

This section was evaluated as part of the original NDA review. There are no unique considerations for pediatrics that warrant discussion.

8.9. Safety in the Postmarket Setting

8.9.1. Safety Concerns Identified Through Postmarket Experience

The Applicant states that the cumulative global post-marketing adult patient exposure to Invokana, Invokamet and Invokamet XR is (b) (4) person-years, respectively, from launch to March 31, 2024.

Following the initial approval of Invokana, important safety issues identified either in the post-market setting or in clinical trials of canagliflozin and/or other SGLT2-inhibitors include increased risks of ketoacidosis (particularly in patients with type 1 diabetes), serious hypersensitivity reactions (e.g., angioedema), necrotizing fasciitis of the perineum (Fournier's

gangrene), urosepsis and pyelonephritis, acute kidney injury, constipation, tubulointerstitial nephritis, lower limb amputation, and a drug-drug interaction between canagliflozin and lithium that may decrease serum lithium concentrations when taken concomitantly. These safety issues are all described in USPI for canagliflozin-containing products.

No new safety issues other than those already described in the label were identified in a review of the most recent Periodic Benefit-Risk Evaluation Report for Invokana, Invokamet, and Invokamet XR submitted on May 21, 2024, covering the reporting period of March 29, 2023 to March 28, 2024 or the 4-month safety update submitted on September 30, 2024 covering the period March 29, 2024 through August 23, 2024.

8.9.1. Expectations on Safety in the Postmarket Setting

The post-market safety of canagliflozin in pediatric patients is expected to be similar to what is currently labeled for adults. As discussed in Sections 6.1.1 and 7.2.1, Study DIA3018 did not enroll subjects with eGFR < 60 mL/min/1.73m^2, and the occurrence of renal impairment due to diabetic nephropathy is likely to be infrequent in pediatric T2D patients < 18 years. In the post-market setting, canagliflozin may be used for glycemic control in pediatric T2D patients with concomitant CKD, or by pediatric patients with diabetes relating to treatment of CKD (e.g., steroid-induced or renal-transplantation-related diabetes). Based on adult studies of canagliflozin, there appears to be an increased risk for adverse reactions such as volume depletion-related AEs, urinary tract infections and acute changes in renal function in patients with worse renal function; these risks are currently described in the product label and as discussed earlier (see Section 7.2.1) the overall benefit risk assessment was considered favorable for use for glycemic control in pediatric patients with eGFR>30 mL/min/1.73m^2.

8.9.2. Additional Safety Issues From Other Disciplines

No additional safety issues were identified from other disciplines.

8.10. Integrated Assessment of Safety

The risks of canagliflozin in adults with T2D are well characterized, and include diabetic ketoacidosis, volume depletion, hypoglycemia with concomitant use of insulin and/or sulfonylureas, infections (including urinary tract infections, genital mycotic infections and necrotizing fasciitis), hypersensitivity reactions, and bone fractures. In Study DIA3018, the overall safety profile of canagliflozin was generally similar to the known and labeled risks in adults with T2D.

No deaths occurred in the study. Only two AEs led to a treatment discontinuation (one in each group). The sole AE leading to discontinuation from the canagliflozin group was unrelated to

treatment and was due to a tonic-clonic seizure in a subject with a pre-existing history of epilepsy who had been off of anti-epileptic medication for about 6 months. Canagliflozin is not known to lower seizure threshold, so this participant's pre-existing history of epilepsy and history of discontinuing anti-convulsant medications are more likely explanations for this AE. The overall number of SAEs occurring during Study DIA3018 was low but numerically higher in the canagliflozin arm (8 subjects experiencing 8 events) versus the placebo arm (5 subjects experiencing 5 events), however only two SAEs in the canagliflozin arm were determined to be possibly related to treatment, including a case of mild DKA and a case of hyperglycemia that responded to hydration suggesting it was due to volume depletion. Both of these safety signals (i.e., DKA and volume depletion) are currently described in the product labeling for canagliflozin. Review of other SAEs did not reveal a common organ system, clinical concept, or pattern meriting further work up for a pediatric-specific safety signal.

Most hypoglycemia events that occurred in the study were consistent with ADA Level 1 events (i.e., <70 mg/dL), with few events associated with glucose < 54 mg/dL and only 1 severe hypoglycemia event in placebo-treated subject on background insulin. However, an increased incidence of hypoglycemia events was observed with canagliflozin as compared to placebo in the subgroup of patients treated with background insulin (25% vs. 16.2%), whereas a similar imbalance was not observed in the subgroup of subjects who were not treated with background insulin, or in the overall study population. These findings suggest that the hypoglycemia risk in pediatric T2D subjects is comparable to that described in adults in the current USPI and that it is expected to occur in the setting of concomitant treatment with insulin or insulin secretagogues.

During the 52-week study period, the canagliflozin group had a similar incidence of TEAEs as the placebo group. Among the AESIs, ketoacidosis events and fractures were evenly distributed between the canagliflozin and placebo groups. There was only 1 case of acute pancreatitis occurring in a canagliflozin-treated subject but was considered unlikely related to treatment. Among the specific AEs of clinical interest, genital mycotic infections and UTI were more common in the canagliflozin group than in the placebo group; these are already described in the USPI. No clinically significant differences were noted in vital signs or laboratory measures between canagliflozin and placebo groups.

Overall, canagliflozin was well tolerated in pediatric patients aged 10 to <18 years. The SAEs considered related to treatment and as well as the hypoglycemia risk and reported AESIs were consistent with known safety issues of canagliflozin that are already described in the product label. There were no new pediatric-specific safety signals or AEs that became apparent that are not already included in the product labeling. To this end, the observed safety results from the pediatric study suggest a similar risk profile of canagliflozin to that of adults. The safety findings observed in this study do not raise considerations that would significantly alter the benefit-risk assessment of canagliflozin for the pediatric population with T2D.

9. Advisory Committee Meeting and Other External Consultations

No new efficacy or safety issue rose to the level of requiring the input of an advisory committee. Therefore, these sNDAs were not discussed at an advisory committee meeting.

10. Labeling Recommendations

10.1. Prescription Drug Labeling

Based on the results of this review, the following recommendations were incorporated into labeling updates for Invokana, Invokamet and Invokamet XR (at the time of this review filing, labeling negotiations were ongoing):

Invokana Label
Section 1
--changed indication "as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus" to "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"

--changed statement under Limitations of Use from
"INVOKANA is not recommended for use to improve glycemic control in adults with type 2 diabetes mellitus with an eGFR less than 30 mL/min/1.73 m^2" to "INVOKANA is not recommended for use to improve glycemic control in patients with type 2 diabetes mellitus with an eGFR less than 30 mL/min/1.73 m^2."

Section 2.2
--Updated heading to "Recommended Dosage for Glycemic Control in Adults and Pediatric Patients Aged 10 years and Older"
--Added separate heading for the two indications only for adults (CVD and ESKD)

Section 2.3
Updated to add "pediatric patients aged 10 years and older" to the section title, text, and table for dosage in renal impairment.

Section 6.1
The following paragraph was added:

"INVOKANA has been evaluated in clinical trials in adults and pediatric patients aged 10 years and older with type 2 diabetes mellitus. Additionally, INVOKANA has been studied in clinical trials in adult patients with type 2 diabetes mellitus who also have heart failure or chronic kidney disease. The overall safety profile of INVOKANA was consistent across the studied indications."

Updated headings, table titles, and text summaries about studies pertaining to adults to clarify that those studies were in adults.
Added summary of the DIA3018 pediatric clinical trial.

Section 8.4
Updated with summary of the DIA3018 pediatric clinical trial.
Statement added that the safety and effectiveness of Invokana have not been established in pediatric patients to reduce the risk of CVD or ESKD.

Section 12.3
The following paragraph was added under Specific Populations:
"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."

Section 14
--Section 14.1
Text and Table/Figure titles were updated to clarify that the information is about adults.

--Section 14.2 was replaced with a summary of the DIA3018 pediatric clinical trial. Following an IR, the mean baseline BMI z-score was provided by the Applicant and added into this section.

--Subsequent subsection numbering within Section 14 were updated to account for the insertion of the DIA3018 pediatric clinical trial information in Section 14.2. Subsection headings were updated to clarify they pertain to adults.

Medication Guide
--Updated with "and children aged 10 years and older" under "What is Invokana?"

Invokamet/Invokamet XR Label
Section 1
Invokamet and Invokamet XR separated into two distinct statements, which both include

Section 2.2 – Dosage Overview
Heading added: "Adults and Pediatric Patients Aged 10 Years and Older"

Section 2.3 – Dosage and Administration
Table heading and text updated to add "Pediatric Patients Aged 10 Years and Older" where applicable.

(b) (4)

Section 6.1
The following paragraph was added:
"Canagliflozin has been evaluated in clinical trials in adults and pediatric patients aged 10 years and older with type 2 diabetes mellitus. Additionally, canagliflozin has been studied in clinical trials in adult patients with type 2 diabetes mellitus who also have heart failure or chronic kidney disease. The overall safety profile of canagliflozin was consistent across the studied indications."

Updated headings, table titles, and text summaries about studies pertaining to adults to clarify that those studies were in adults.

Added summary of the DIA3018 pediatric clinical trial.

Added statement about metformin in pediatric patients with type 2 diabetes mellitus:
"In clinical trials with metformin HCl immediate-release tablets in pediatric patients with type 2 diabetes mellitus, the profile of adverse reactions was similar to that observed in adults."

Section 8.4
Updated with summary of the DIA3018 pediatric clinical trial.
Statement added that the safety and effectiveness of Invokana have not been established in pediatric patients to reduce the risk of CVD or ESKD.

Section 10
Updated with more specific instructions on what to do in the event of an overdose.

Section 11
Updated with alphanumeric codes corresponding to excipient ingredients

Section 12.3
The following two paragraphs was added under Specific Populations:

"Pediatric Patients
Canagliflozin
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.

Metformin HCl
After administration of a single oral metformin 500 mg immediate-release tablet with food, geometric mean metformin Cmax and AUC differed less than 5% between pediatric type 2 diabetic patients (12-16 years of age) and gender-and weight-matched healthy adults (20-45 years of age), all with normal renal function."

Section 14
--Section 14.1
Text and Table/Figure titles were updated to clarify that the information is about adults.

--Section 14.2 was replaced with a summary of the DIA3018 canagliflozin pediatric clinical trial, and the glycemic control trial of metformin HCl in pediatric patients. Following an IR, the mean baseline BMI z-score was provided by the Applicant and added into this section.

--Subsequent subsection numbering within Section 14 were updated to account for the insertion of the DIA3018 pediatric clinical trial information in Section 14.2. Subsection headings were updated to clarify they pertain to adults.

Medication Guide
--Updated with "and children aged 10 years and older" under "What is Invokamet or Invokamet XR?"

10.2. Nonprescription Drug Labeling

This section is not applicable to this application.

11. Risk Evaluation and Mitigation Strategies (REMS)

No REMS are recommended.

12. Postmarketing Requirements and Commitments

No postmarketing requirements or commitments are applicable to this supplement.

13. Appendices

13.1. References

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13.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): 28431754DIA3018

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from

		Applicant)
Total number of investigators identified: 321		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

13.3. Summaries of Studies Supporting the 505(b)2 Bridge for Invokamet XR

Because Glucophage has a pediatric indication, but Glumetza does not, the Sponsor provided the following published literature in support of the bridge of Invokamet XR (canagliflozin/metformin XR) to the listed drug Glucophage (metformin), to demonstrate that metformin XR has demonstrated safety and effectiveness in pediatric patients:

Meyers et al 2021[18] – This was a retrospective chart review used a cross-sectional analysis to evaluate adolescents with T2D or prediabetes who received either the XR or IR formulations of

metformin or were not treated with metformin at the most recent visit to a tertiary care clinic (from 2016 to 2019). There were 103 adolescents in the XR group, 202 adolescents in the IR group, and 183 adolescents not treated with either. Most adolescents treated with the IR formulation were prescribed a total daily dose of 2,000 mg (50%) or 1,000 mg (31%), whereas most adolescents prescribed the XR formulation were treated with ≥1,500 mg/day (59.4%). There was no significant difference in the rate of gastrointestinal (GI) symptoms between the IR (18.3%) and XR (14.6%) groups (p=0.41), nor between the XR (14.5%) and the control (9.8%) groups (p=0.23). Among the 58 adolescents who switched from IR to XR, there was no significant change in the prevalence of GI symptoms (IR: 17% vs XR: 14%, p=0.6).

Clarson et al 2014[19] – This was a randomized, placebo-controlled trial of 69 obese adolescents to evaluate varying degrees of exercise intensity (moderate vs vigorous), in combination with metformin XR or placebo, on BMI, risk factors for T2D, and cardiovascular disease over 24 months. Subjects were randomized to 1 of 4 groups: metformin XR (n=33) 2,000 mg daily or placebo, with either moderate or vigorous intensity exercise for the first 3 months. Subsequently the exercise intervention was the same for all 4 groups. The metformin XR dose was initiated at 500 mg/day and increased by 500 mg/day every 7 days to a maximum tolerated dose of 2,000 mg/day. A high subject attrition rate (58%) occurred by 24 months. There were no severe medication related AEs reported. There were 2 expected, nonserious AEs related to metformin XR: 1 adolescent had transient elevation of transaminases at 1 year, which resolved 1 month after discontinuing metformin XR, and another temporarily discontinued the metformin XR for 2 weeks at 1 year, due to persistent diarrhea. The diarrhea continued off metformin XR, and therefore it was resumed. Six adolescents were unable to tolerate the 2,000 mg/day dose of metformin XR, so it was reduced to 1,500 mg/day in 4 adolescents (metformin XR: n=2, placebo: n=2) and to 1,000 mg in 2 adolescents (both were on metformin XR). BMI and % body fat decreased in the metformin XR groups, but not the placebo groups, at 6 (-0.88, -3.16) and 12 months (-0.56, -2.34) ($P < 0.05$). Insulin resistance, fasting blood glucose, and leptin improved in all groups at 6 and 12 months. The authors concluded that a comprehensive, intensive lifestyle intervention combined with metformin XR led to a decline in BMI and % body fat at 1 year, independent of initial exercise intensity.

Wilson et al (2010)[20] - This was a 48-week (with a 48-week follow-up) randomized, double-blind, placebo-controlled clinical study that evaluated the safety and efficacy of metformin XR for the treatment of obesity in adolescents. Obese (BMI > or = 95th percentile) adolescents (aged 13-18 years) were randomly assigned to the intervention (n = 39) or placebo groups. Following a 1-month run-in period, subjects following a lifestyle intervention program were randomized 1:1 to 48 weeks' treatment with metformin XR, 2000 mg once daily, or an identical placebo. Subjects were monitored for an additional 48 weeks. After 48 weeks, mean (SE) adjusted BMI increased 0.2 (0.5) in the placebo group and decreased 0.9 (0.5) in the metformin XR group ($P = .03$). This difference persisted for 12 to 24 weeks after cessation of treatment. No significant effects of metformin on body composition, abdominal fat, or insulin indices were

observed. There was no statistically significant difference between the metformin XR and placebo groups in the incidence of any particular class of AEs.

Jalaludin et al (2022)[21] – Data were pooled from 2 companion, randomized, double-blind, placebo-controlled studies that evaluated the safety and efficacy of adding sitagliptin or placebo to a treatment regimen for adolescents with T2D and inadequate glycemic control on metformin (XR or IR) without or with insulin. The first study evaluated the safety and efficacy of sitagliptin (50 mg twice daily) or placebo + metformin IR (500 mg twice daily, 850 mg twice daily, or 1000 mg twice daily). The second study evaluated the safety and efficacy of sitagliptin (100 mg once daily) or placebo + metformin XR (1000 mg once daily, 1500 mg once daily, or 2000 mg once daily. In the first study, 125 adolescents were randomized to sitagliptin + metformin IR (n=63) or placebo + metformin IR (n=62). In the second study, 98 adolescents were randomized to sitagliptin + metformin XR (n=47) or placebo + metformin XR (n=51). An analysis of the pooled safety data showed that the AEs reported were similar between the treatment groups, both of which included both metformin XR and metformin IR, through Week 54.

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