SUMMARY BASIS OF REGULATORY ACTION
CROSS DISCIPLINE TEAM LEADER REVIEW
PRIMARY CLINICAL REVIEW

Application Type	Supplemental NDA
Application Number(s)	NDAs 202293/S-031, 205649/S-022 \\CDSESUB1\evsprod\NDA202293\1346
Priority or Standard	Priority
Submit Date(s)	December 12, 2023
Received Date(s)	December 12, 2023
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Division/Office	Division of Diabetes, Lipid Disorders and Obesity (DDLO)/ Office of Cardiology, Hematology, Endocrinology and Nephrology (OCHEN)
Clinical Reviewer	Dolly Misra, MD
Clinical Team Lead	Justin Penzenstadler, PharmD
Signatory Authority	Patrick Archdeacon, MD
Review Completion Date	See Electronic Stamp
Established/Proper Name	dapagliflozin; dapagliflozin and metformin hydrochloride extended release
Trade Name	Farxiga; Xigduo XR
Applicant	AstraZeneca Pharmaceuticals LP
Dosage Form(s)	tablet
Applicant Proposed Dosing Regimen(s)	Farxiga: 5 mg and 10 mg once daily Xigduo XR: 2.5/1000 mg, 5/500 mg, 5/1000 mg, 10/500 mg, 10/1000 mg dose is individualized based on the patient's current treatment (daily doses not to exceed 10 mg dapagliflozin / 2000 mg metformin HCl extended-release)
Applicant Proposed Indication(s)/Population(s)	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 for new indication for Farxiga and Xigduo XR PMR 3199-1 fulfilled; grant pediatric exclusivity
Recommended Indication(s)/Population(s) (if applicable)	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

A1C	hemoglobin A1c
AC	advisory committee
AE	adverse event
AEoSI	adverse event of special interest
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AR	adverse reaction
AST	aspartate aminotransferase
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBC	complete blood count
CBER	Center for Biologics Evaluation and Research
CEC	clinical event committee
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
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
CSS	Controlled Substance Staff
DBP	diastolic blood pressure
DKA	diabetic ketoacidosis
DMC	data monitoring committee
DSMB	data safety monitoring board
DPP-4	dipeptidyl peptidase-4
ECG	electrocardiogram
eCTD	electronic common technical document
eGFR	estimated glomerular filtration rate
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007

FDASIA	Food and Drug Administration Safety and Innovation Act
FPG	fasting plasma glucose
GCP	good clinical practice
GIP	gastric inhibitory polypeptide
GLP-1	glucagon-like peptide-1
GRMP	good review management practice
ICH	International Council for Harmonization
IGF-1	insulin-like growth factor 1
IGFBP-3	insulin-like growth factor binding protein 3
IMP	investigational medical product
IND	Investigational New Drug Application
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
IR	immediate release
ITT	intent to treat
LDL	low density lipoprotein
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NGSP	National Glycohemoglobin Standardization Program
NME	new molecular entity
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
PeRC	Pediatric Review Committee
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
popPK	population pharmacokinetic
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
SGE	special government employee
sNDA	supplemental new drug application
SOC	standard of care
T2D	type 2 diabetes mellitus
Tcon	teleconference
TEAE	treatment emergent adverse event
TSAP	trial statistical analysis plan
TSH	thyroid stimulating hormone
ULN	upper limit of normal
US	United States
USPI	US prescribing information
WBC	white blood cells
WR	written request
XR	extended release

1. Executive Summary

This document summarizes clinical and cross-disciplinary review of sNDA 202293 (Supplement-31) and sNDA 205649 (Supplement-22) and provides the basis for regulatory action. The subject matter of this review is a single adequate and well controlled (A&WC) safety and efficacy pediatric study, D1680C00019, which is referred to as Study 19 throughout this document. The Sponsor initiated Study 19 to fulfill a Pediatric Research Equity Act (PREA) - mandated post-marketing requirement (PMR 3199-1). Based upon the submission of Study 19, the Applicant is seeking to fulfill the PMR, and to expand the glycemic control indication for Farxiga and Xigduo XR to adult and pediatric patients with type 2 diabetes (T2D) aged 10 years and older.

Study 19 demonstrated a statistically significant and clinically meaningful reduction in the placebo-adjusted change from baseline hemoglobin A1c (A1C) in the pediatric population at Week 26. The review team concluded substantial evidence of efficacy was met, by way of one adequate and well controlled investigation (Study 19) and confirmatory evidence (trials in adults previously conducted and reviewed). There were no clinical observations related to safety which warrant labeling changes or change the benefit-risk calculus specific to the pediatric population. These findings are supported by comparative pharmacokinetic (PK) and pharmacodynamic (PD) assessments between adults and pediatric patients, which were similar.

In consultation with the Pediatric Review Committee (PeRC), the Pediatric Exclusivity Board, and the review team, the signatory authority concluded that Study 19 fulfills PMR-3199-1, pediatric exclusivity should be granted, and the proposed indication be approved.

Table 1: Materials consulted for this Summary Review

Office of New Drugs (OND) Action Package Material Reviewed/Consulted	**Names of Discipline Reviewer(s) [Dates of Review in DARRTS or Panorama]**	**Sections Referencing**
Office of Scientific Investigation	Ling Yang, Min Lu, Jenn Sellers [4/29/2024]	**4.1**
Office of Pharmaceutical Quality Review	Sarah Zimmerman [5/21/2024]	**4.2**
Office of Clinical Pharmacology	Dong Guo, Justin Earp, Edwin Chow [5/29/2024]	**4.5**
Office of Biostatistics	Sunghee Kim [5/17/2024]	**6**
Patient Labeling Review, Division of Medical Policy Programs (DMPP) and Office	Mary Carroll, Ankur Kalola, Marcia Williams, Lashawn Griffiths [5/17/2024]	**10**

of Prescription Drug Promotion (OPDP)		
Pediatric Review Committee (PeRC) minutes from the 5-14-2024 meeting	Yvette Macklin [6/3/2024]	**1**
Pediatric Exclusivity Determination	Niquiche Guity, Mary Thanh Hai [5/30/2024]	**1**

1.1. Product Introduction

Dapagliflozin is a once daily, orally active, competitive, reversible inhibitor of the sodium-glucose co-transporter-2 (SGLT2). SGLT-2 inhibitors lower blood sugar levels by blocking the reabsorption of filtered glucose in proximal tubules of the kidney while concomitantly reducing sodium reabsorption, resulting in urinary excretion of glucose and osmotic diuresis. The original new drug application (NDA) for dapagliflozin was approved on January 8, 2014, as an adjunct to diet and exercise to improve glycemic control in adults with T2D (Farxiga, NDA 202293). Following its initial approval, the label for Farxiga has been expanded to include the following cardiorenal indications:

- to reduce the risk of hospitalization for heart failure in adults with T2D and either established cardiovascular disease or multiple cardiovascular risk factors,
- to reduce the risk of cardiovascular death and hospitalization for heart failure, and urgent heart failure visits in adults with heart failure,
- to reduce the risk of sustained estimated glomerular filtration rate decline, end stage kidney disease, cardiovascular death, and hospitalization for heart failure in adults with chronic kidney disease at risk of progression.

Xigduo XR (dapagliflozin and metformin HCl extended release) is a once daily, oral, fixed-dose combination (FDC) product consisting of dapagliflozin and an extended release biguanide. Metformin HCl improves glycemic control through several mechanisms including improved glucose tolerance, decreased hepatic glucose production, and enhanced peripheral insulin sensitivity. NDA 205649 for Xigduo XR was approved on October 29, 2014, as an adjunct to diet and exercise to improve glycemic control in adults with T2D when treatment with both dapagliflozin and metformin are appropriate. Xigduo XR is approved for the same indications as dapagliflozin; however, because of the metformin component, the use of Xigduo XR is limited to adults with T2D for all indications.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The effectiveness of dapagliflozin to improve glycemic control in pediatric patients with T2D was established based on the results of a single adequate and well-controlled trial plus confirmatory evidence[1].

Study 19 was a 26-week randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of dapagliflozin for the treatment of pediatric patients ages 10 to <18 years with T2D, followed by a 26-week site- and subject-blinded safety extension period (weeks 26 to 52). Eligible subjects had A1C ≥ 6.5% and ≤ 10.5% on a diet and exercise program and stable background therapy of metformin (minimum dose 1000 mg), or insulin, or both.

Study 19 demonstrated statistically significant superiority of dapagliflozin (pooled dosages of 5 mg and 10 mg) compared to placebo for A1C change from baseline at Week 26: the placebo-adjusted treatment difference was -1.03% (95% CI -1.57 to -0.49; $p < 0.001$). The result of this primary analysis was robust to sensitivity analyses using alternative missing data assumptions. Confirmatory evidence is derived from the previous finding of effectiveness of dapagliflozin 5 and 10 mg in adult patients with T2D based upon demonstration of durable and clinically meaningful reductions A1C in ten multi-center, multinational, randomized, double-blind, well-controlled trials (7 placebo-controlled, 3 active-controlled) as monotherapy and as add-on therapy to maximally effective doses of metformin, sulfonylurea, insulin, thiazolidinedione (TZD), and sitagliptin[2].

The efficacy and safety of the metformin XR component of Xigduo XR in pediatric patients is supported by its demonstration of bioequivalence to Glucophage XR[3] and the Applicant's scientific justification that Glucophage XR is safe and efficacious in pediatric patients aged 10 years and older with T2D.

1.3. Benefit-Risk Assessment

T2D in the pediatric population has been increasing in incidence and prevalence globally and has been paralleling the rising rates of obesity in children and adolescents over the past 3 decades. Epidemiological data also suggest that youths from racial and ethnic minorities appear to be disproportionately afflicted with T2D. In addition, pediatric patients with this condition appear to be a more vulnerable than adults to rapid glycemic deterioration and the development of disease-related complications and comorbidities. Together, these factors elevate concerns about the burden of this chronic condition on global public health.

[1] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/demonstrating-substantial-evidence-effectiveness-human-drug-and-biological-products
[2] https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af8030dd87
[3] NDA 205649 Summary Review of Regulatory Action

The primary objective of Study 19 was to demonstrate that treatment with dapagliflozin provides superior glycemic control compared to placebo. Study 19 was a randomized, placebo-controlled, double-blind, parallel-group study evaluating the safety and efficacy of dapagliflozin (5 mg and 10 mg), and, separately, saxagliptin (2.5 mg and 5 mg) in pediatric patients with T2D. Eligible subjects were aged between 10 and < 18 years with A1C ≥ 6.5% and ≤ 10.5% on a diet and exercise program and stable background therapy of metformin (minimum dose 1000 mg), or insulin, or both.

Subjects on study Day 1 were randomized (1:1:1) to receive low-dose treatment with dapagliflozin 5 mg, saxagliptin 2.5 mg, or placebo. A blinded A1C assessment occurred at Week 12, and subjects with values ≥ 7% ("non-responders") underwent a 2nd randomization (1:1) to either continue low dose (dapagliflozin 5 mg or saxagliptin 2.5 mg) or up-titrate to a higher dose (dapagliflozin 10 mg or saxagliptin 5 mg) beginning Week 14. The primary efficacy endpoint was change in A1C from baseline at Week 26 for the pooled dapagliflozin dose groups vs placebo (i.e., responders on 5 mg, non-responders remaining on 5 mg, and non-responders up-titrated to 10 mg). Following the primary efficacy assessment after completing the short-term (ST) treatment period at Week 26, subjects entered a long-term (LT), double-blind, 26-week treatment extension period. In the LT period, subjects on dapagliflozin receiving background therapy with metformin alone and achieving A1C values <7.5 underwent a 3rd randomization (1:1)[4] to either continue current therapy or undergo withdrawal of metformin to assess the efficacy of monotherapy with dapagliflozin through Week 52. For eligible subjects randomized to withdrawal of metformin, those on dapagliflozin 5 mg were up-titrated to dapagliflozin 10 mg, and those on dapagliflozin 10 mg remained on the 10 mg dose. Subjects on placebo receiving background therapy with metformin alone and achieving A1C values < 7.5% were randomized (1:1:1) to remain on placebo with metformin, or withdraw metformin and begin dapagliflozin 10 mg, or withdraw metformin and begin saxagliptin 5 mg.

A total of 245 subjects were treated with either dapagliflozin (5 mg or 10 mg; N=81), saxagliptin (N=88), or placebo (N=76). Background therapies included metformin alone (51.4%), a combination of metformin and insulin (36.3%), or insulin alone (12.2%). The mean A1C at baseline was 8.0% and the mean duration of T2D was 2.5 years. The mean age of randomized subjects was 14.5 years (range: 10-17 years) and 52.7% were aged 15 years and older. Approximately 60% of subjects were female. Approximately 50% of study subjects were White, 27% were Asian, 6% were Black or African American, 12% were American Indian or Alaska Native, and 50% were of Hispanic or Latino ethnicity. The mean BMI was 29.6 kg/m^2 and mean BMI Z-score was 1.67.

[4] Subjects were assessed for eligibility for the third randomization at week 26 or week 32, and if eligible, underwent the third randomization on week 32 or week 40, respectively

For Study 19, the primary efficacy analysis of the primary endpoint was met, demonstrating superiority of the pooled dapagliflozin group compared to placebo for A1C change from baseline at Week 26: the placebo-adjusted treatment difference was -1.03% (95% CI -1.57 to -0.49; p < 0.001). These results were corroborated by the FDA statistical reviewer and the results of the sensitivity analyses were similar to the primary analysis. The efficacy of the other dapagliflozin regimens also demonstrated superiority vs placebo for this endpoint: [responders + non-responders up-titrated to 10 mg: placebo-adjusted treatment difference = -0.86 (95% CI -1.44 to -0.27; p=0.004)] and [responders + non-responders continuing 5 mg: placebo-adjusted treatment difference = -1.19 (95% CI -1.76 to -0.62; p < 0.001)]. The results of the multiplicity adjusted secondary endpoint analyses also provide supportive evidence for the efficacy of dapagliflozin for glycemic control in the pediatric population with T2D. A significant difference favoring the dapagliflozin pooled group vs the placebo group was noted for the fasting plasma glucose (FPG) change from baseline at Week 26: placebo-adjusted treatment difference = -19.5 (95% CI -36.4 to -2.5). In addition, although not achieving statistical significance, the proportion of subjects achieving A1C target of < 7% at Week 26 favored the pooled dapagliflozin group compared to placebo with an odds ratio of 2.16 (95% CI 0.98 to 4.73). The secondary hypothesis testing for the last subgroup, comparing the A1C reduction from baseline at Week 26 of the non-responders up-titrated to 10 mg to the non-responders remaining on 5 mg, did not demonstrate a difference in treatment effect between doses [treatment difference 10 mg vs 5 mg of the non-responders: -0.03 (95% CI -1.00 to 0.94)].

The review of the safety data from Study 19 did not reveal any clinically significant imbalances in safety endpoints between dapagliflozin and placebo treatment arms. During the ST period, the dapagliflozin treatment group, compared to placebo, had a lower incidence of treatment emergent adverse events (TEAEs) (54.3% vs 61.8%) and numerically fewer events (97 vs 135). The proportion of patients reporting hypoglycemia was comparable between treatment groups. The incidence of Level 2 and Level 3 events was similar between treatment arms (dapagliflozin 12.3% vs placebo 13.2%). Level 3 events were rare (dapagliflozin 3 subjects with 3 events vs placebo 4 subjects with 4 events). The number of serious adverse events (SAEs) occurring during Study 19 was low but numerically higher in the dapagliflozin arm than placebo arm with 7 subjects experiencing 9 events vs 5 subjects experiencing 5 events, respectively. No SAEs involved hypoglycemia or resulted in study treatment discontinuation. Diabetic ketoacidosis, which is noted in the warnings and precautions of the dapagliflozin label, was reported in 1 subject in each treatment arm. Other adverse events of special interest (AEoSIs) similarly did not reveal any unfavorable imbalances for dapagliflozin: 20 subjects with 34 events for dapagliflozin vs 28 subjects with 53 events for placebo. No clinically significant differences were noted in vital signs or laboratory measures between dapagliflozin and placebo groups.

The data from Study 19 support the efficacy for dapagliflozin for glycemic control in the pediatric population with T2D. The primary outcome analysis demonstrated superiority of dapagliflozin (pooled doses) to placebo on change in A1C from baseline at Week 26. The result

of the primary analysis was robust to sensitivity analyses using alternative missing data assumptions. Efficacy analyses of the other dapagliflozin dosing regimens also demonstrated statistically significant change in A1C from baseline at Week 26 compared to placebo. A1C is a well-validated surrogate for the long-term microvascular complications of diabetes mellitus. The results of the Diabetes Control and Complications Trial (DCCT)[5] in patients with T1D and the Kumamoto Study[6] in patients with T2D showed that intensive therapy, resulting in better glycemic control (A1C < 7.1%), prevents the progression of microvascular complications.

No difference in treatment effect was noted for change in A1C from baseline to Week 26 when comparing dapagliflozin 10 mg vs 5 mg in non-responders; however, the small number of subjects in each treatment arm (N=21) was inadequate to power an analysis of dose-response. Despite this limitation, the labeling for both the 5 mg and 10 mg dose in the pediatric population, is supported the efficacy and the dose-response of dapagliflozin 5 mg and 10 mg previously been demonstrated in phase 3 trials in the adult population with T2D. Also, PK and PD similarity for dapagliflozin is noted between the adult and the pediatric populations, including a demonstration of similarity of dose-response. Together, these data support the labeling for 5 mg and 10 mg for dapagliflozin in the pediatric population with T2D. Study 19 also confirmed that the safety profile of dapagliflozin in pediatric subjects is similar to that established in adults and is appropriately outlined in the current label.

For Xigduo XR, the Applicant amended its submission for NDA 205649/S-022 from a 505(b)(1) to a 505(b)(2) supplement, proposing to rely on the Agency's previous findings of safety and effectiveness of Glucophage IR (metformin HCL immediate release) tablets (NDA 020357) available in the Glucophage IR/Glucophage XR prescribing information to support the approval of Xigduo XR broadening the patient population for the glycemic control indication by adding pediatric patients aged 10 years and older. A scientific bridge based upon PK similarity data from the following sources was provided by the Applicant:

- PK similarity of Glucophage IR between adults and pediatric patients in Glucophage IR label
- PK similarity between Glucophage XR and Glucophage IR in adults in Glucophage IR label
- bioequivalence of metformin XR component of Xigduo XR with Glucophage XR from original Xigduo XR submission.

This scientific bridge provided by the Applicant is considered appropriate to justify the Applicant's proposal to rely on the Agency's previous findings of safety and effectiveness for

[5] Orchard TJ, Nathan DM, Zinman B, Cleary P, Brillon D, Backlund JY and Lachin JM. Association between 7 years of intensive treatment of type 1 diabetes and long-term mortality. Writing Group for the DCCT/EDIC Research Group, JAMA. 2015;313:45-53.

[6] Ohkubo Y, Kishikawa H, Araki E, Miyata T, Isami S, Motoyoshi S, Kojima Y, Furuyoshi N and Shichiri M. Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: a randomized prospective 6-year study. Diabetes Res Clin Pract. 1995;28:103-17

Glucophage IR to broaden the glycemic control indication for Xigduo XR to include pediatric patients aged 10 and greater with T2D.

In summary, the review team recommends approval of both supplements, The favorable benefit-risk assessment of the data from Study 19 submitted by the Applicant for Farxiga (NDA 202293/S-31) and the scientific bridge justifying the Applicant's proposal to rely on the Agency's previous findings of safety and effectiveness of Glucophage IR for Xigduo XR (NDA 205649/S-22) provide support to broaden the indication "as adjunct to diet and exercise to improve glycemic control in adults and pediatric patients aged 10 years and older with type 2 diabetes mellitus" for both products.

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 incidence of T2D is increasing in the pediatric population in the US and worldwide and appears to disproportionately affect racial minorities. • The clinical course of glycemic deterioration and development of complications and comorbidities in the pediatric population appears to be more aggressive than in the adult population.	T2D in the pediatric population is a serious chronic condition which is rising in prevalence and is associated with a more aggressive clinical disease progression than 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. • Currently, one SGLT-2 inhibitor (empagliflozin) and three GLP-1 receptor agonists (liraglutide, exenatide, and dulaglutide) are FDA 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 19 provides evidence of efficacy for dapagliflozin in improving glycemic control in the pediatric population with a statistically significant reduction in A1C from baseline for pooled dapagliflozin doses vs placebo at Week 26: the placebo adjusted treatment difference was -1.03% (95% CI -1.57 to -0.49; $p < 0.001$). Similarly, statistically significant treatment differences for change in A1C from baseline vs placebo were noted for the 5 mg and 10 mg treatment subgroups. • Secondary efficacy analyses showed supportive evidence of efficacy	Data from Study 19 supports the effectiveness for dapagliflozin in the pediatric population with T2D by demonstrating a reduction in A1C from baseline which was both clinically significant and statistically persuasive.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	for dapagliflozin with a statistically significant reduction in FPG from baseline vs placebo at week 26 and greater proportion of subjects achieving A1C target with dapagliflozin compared to placebo. • Xigduo XR provides additional potential benefits of convenience of once daily dosing and simplification of treatment regimens by decreasing pill burden, which may improve compliance. • Dapagliflozin has been demonstrated in adults to have other therapeutic benefits such as cardiorenal protection which will also likely benefit the pediatric population.	
Risk and Risk Management	• No deaths occurred in Study 19. • SAEs were infrequent and did not result in treatment discontinuation. • No unfavorable imbalances in hypoglycemia or DKA noted for dapagliflozin treated subjects compared to placebo. • No new safety signals were noted from the safety analyses. • The safety profile of dapagliflozin in the pediatric population appears to be similar to that established in adults and is appropriately reflected in the proposed label.	Dapagliflozin was well-tolerated in the pediatric population with T2D with a safety profile similar to what is noted in adults and reflected in the current label.

1.4. Patient Experience Data

□	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)	
X	Patient experience data was not submitted as part of this application.	

2. Therapeutic Context

2.1. Analysis of Condition

T2D is characterized by hyperglycemia, insulin resistance, and relative impairment in insulin secretion secondary to progressive pancreatic β-cell failure. The incidence of T2D among youth is increasing in many countries, coinciding with increasing prevalence of childhood obesity. As an example, in the US, there was a sharp rise in T2D from 9.0 cases per 100,000 in 2002-2003 to 13.8 cases per 100,000 in 2014-2015, with an adjusted annual increase of T2D of 4.8%, based on data from the SEARCH for Diabetes in Youth study[7]. In addition, youths from racial and ethnic minorities appear to be disproportionately afflicted with T2D. The highest annual percentage increase in T2D incidence in the SEARCH database from 2002 to 2015 was among Asians and Pacific Islanders (7.7% per year), followed by Hispanic patients (6.5% per year), non-Hispanic African Americans (6.0% per year), and Native Americans (3.7% per year). The American Diabetes Association currently recommends screening for T2D in asymptomatic youths with body mass index (BMI) ≥ 85th percentile for age and gender with one or more risk factors for T2D beginning at age 10 years or at onset of puberty if this occurs before 10 years of age[8]. The diagnostic criteria for diabetes and prediabetes in children are the same as for adults.

Although T2D in adults and pediatrics share some similarity in that there is insulin resistance and loss of β-cell function, evidence suggests that glycemic control and β-cell function declines more rapidly in adolescents. The rate of loss of glycemic control on either metformin monotherapy or combination therapy with rosiglitazone in the TODAY study appears to be three- to fourfold higher than published rates in adults, via cross-study comparisons with ADOPT and UKPDS[9]. In addition, the onset of T2D at a younger age equates to a longer duration of disease and thus, increased potential for disease-associated complications. Youth with T2D also appear to have accelerated development of diabetes complications and co-morbidities, including high prevalence of hyperfiltration (predicting rapid GFR decline), diabetic retinopathy, and echocardiographic changes associated with major cardiovascular risk. Data from the SEARCH study estimate that 72% of youth with T2D experience at least one comorbidity or complication by early adulthood[10].

The rising prevalence, faster rate of glycemic deterioration, and higher life-long risk of complications with pediatric T2D emphasize the fact that therapeutic options for pediatric patients with T2D is a significant unmet need.

[7] Nadeau KJ, Anderson BJ, Berg EG, et al. Youth-Onset Type 2 Diabetes Consensus Report: Current Status, Challenges, and Priorities. Diabetes Care. 2016;39(9):1635-1642. doi:10.2337/dc16-1066
[8]American Diabetes Association. Standards of Medical Care in Diabetes-2019. Diabetes Care. 2019; 42: S1-S193.
[9] Nadeau et al 2016 https://care.diabetesjournals.org/content/39/9/1635
[10] Pyle and Kelsey 2021: https://pubmed.ncbi.nlm.nih.gov/34075436/

2.2. Analysis of Current Treatment Options

There is an unmet need for additional treatment options for the management of T2D in pediatric patients.

At the time of this review, there are 13 unique pharmacological classes of medications approved in the US to treat adult-onset T2D. However, until as recently as 2019, approved therapies for pediatric patients were limited to biguanides and insulin. Since 2019, three products from the glucagon like peptide-1 (GLP-1) receptor agonist class have expanded indications for use in the pediatric population: liraglutide (Victoza NDA 022341, approved 2019), exenatide (Bydureon Bcise NDA 209210, approved 2021) and dulaglutide (Trulicity BLA 125469, approved 2022). In 2023, empagliflozin (Jardiance, NDA 204629; Synjardy, NDA 206111) became the first SGLT-2 inhibitor, and only the second oral agent, to be approved for use in the pediatric population with T2D to improve glycemic control.

A summary non-insulin therapies approved for pediatric use is provided in **Table 2**.

Table 2. Summary of Approved Non-Insulin Therapies for T2D in Pediatric Patients

Product (s) Name	Year of Approval	Currently Marketed (Yes/No)	Dosage and Route 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).	Common AEs: diarrhea, nausea, vomiting, flatulence, asthenia, indigestion, abdominal discomfort, and headache. Warning/Precaution: 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 NDA 022341	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% confidence interval 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 NDA 209210	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% confidence interval of -1.42% to 0%, p<0.05)	Common AEs: nausea, diarrhea, vomiting, constipation, headache, dyspepsia, injection- 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 BLA 125469	SC injection, once weekly Dosage: 0.75 mg once weekly, may to 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 1.5 mg) versus placebo was -1.4% (95% confidence interval of -1.9% to -0.8%).	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 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) Synjardy (empagliflozin/ metformin hydrochloride)	2023	Yes NDA 204629 NDA 206111	Oral, once daily 10 mg or 25 mg Oral, twice daily	In a 26-week double-blind, placebo-controlled trial of 157 pediatric T2D patients aged 10 to 17 years, estimated treatment difference in HbA1c reduction from baseline between pooled empagliflozin arms (10 mg and 25 mg) versus placebo was -0.84% (95% confidence interval of -1.5% to - 0.19%).	Common AEs: urinary tract infections and female genital mycotic infections, and hypoglycemia with or without insulin or insulin secretagogues (in pediatric patients only). Warnings/Precautions: diabetic ketoacidosis in patients with T1D and other ketoacidosis, volume depletion, urosepsis and pyelonephritis, hypoglycemia risk increased when used in combination with insulin secretagogues or insulin (risk higher in pediatric patients regardless of concomitant insulin use),

					necrotizing fasciitis of the perineum (Fournier's gangrene), genital mycotic infections, lower limb amputation, hypersensitivity reactions.

Source: Adapted from Table 1 in Clinical Review for NDA 204629 S-15 (authored by Kim Shimy, MD)
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 treated with liraglutide, increased risk of hypoglycemia was seen only with concomitant insulin or insulin secretagogue therapy

3. Regulatory Background

3.1. US Regulatory Actions and Marketing History

The following are the various indications for Farxiga and Xigduo XR:

Trade Name/NDA Number	Indication	Approval Date
Farxiga/ NDA 202293	as an adjunct to diet and exercise to improve glycemic control in adults with T2D	January 8, 2014
	to reduce the risk of hospitalization for heart failure (HF) in adults with T2D and either established cardiovascular (CV) disease or multiple CV risk factors	October 18, 2019
	to reduce the risk of CV death, hospitalization for HF, or urgent HF visits in adults with HF with reduced ejection fraction	May 5, 2020
	to reduce the risk of CV death and hospitalization for HF, and urgent HF visits in adults with HF (b) (4)	May 8, 2023
	to reduce the risk of sustained estimated glomerular filtration rate (eGFR) decline, end stage kidney disease, CV death, and hospitalization for HF in adults with chronic kidney disease at risk of progression	April 30, 2021
Xigduo XR/ NDA 205649	as an adjunct to diet and exercise to improve glycemic control in adults with T2D	October 29, 2014
	to reduce the risk of hospitalization for HF in adults with T2D and either established CV disease or multiple CV risk factors	October 18, 2019
	to reduce the risk of CV death and hospitalization for HF in adults with HF (NYHA class II-IV) with reduced ejection fraction	February 3, 2022
	to reduce the risk of sustained eGFR decline, end stage kidney disease, CV death, and hospitalization for HF in adults with chronic kidney disease at risk of progression	April 11, 2022
	(b) (4)	

3.2. Summary of Presubmission/Submission Regulatory Activity

Regulatory History Pertaining to PREA PMRs

January 8, 2014: Approval letter issued for Farxiga (NDA 202293) stated that under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), the pediatric study requirement for ages 0 through 9 years (inclusive) was waived because the product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this age group and is not likely to be used in a substantial number of pediatric patients in this group. The following pediatric assessments were required:

> **PMR 2121-1**: A randomized, multicenter, parallel, single-dose group study to explore pharmacokinetics (PK)/pharmacodynamics (PD) of dapagliflozin in pediatric T2DM patients aged 10 to 17 years, receiving one of three dose levels of dapagliflozin over the range of 2.5 mg to 10 mg. At least 30% of randomized subjects in each dose group will be 10 to 15 years of age.
>
> Final Protocol Submission: April 2012
> Study Completion: August 2014
> Final Report Submission: February 2015
>
> **PMR 2121-2**[11]: A 26-week randomized, double-blind, placebo-controlled study to evaluate the efficacy, safety, and tolerability of dapagliflozin for the treatment of pediatric subjects 10 to <18 years of age with T2D, as add-on to metformin or as monotherapy, followed by a 26-week double-blind, placebo- or active-controlled extension period (Week 26 to Week 52). At least 30% of randomized subjects will be 10 to 14 years of age and at least one-third and not more than two-thirds of subjects in both age subsets (10 to 14 years and 15 to <18 years) will be female. Secondary safety endpoints should include the effect of dapagliflozin on mineral and bone metabolism, and the effect of dapagliflozin on growth.
>
> Final Protocol Submission: August 2015
> Study Completion: February 2020
> Final Report Submission: August 2020

May 30, 2014: Applicant submitted a request for deferral of Final Report Submission of PMR 2121-1 because of study enrollment difficulties with study D1690C00016, particularly for male subjects. Study D1690C00016 was designed to meet the requirements of PMR 2121-1, and FDA had previously reached agreement for this study protocol on October 6, 2011.

[11] On March 31, 2015, the Applicant sent the Final Report Submission of study D1690C00016 to fulfill PMR 2121-1. The clinical pharmacology review was completed February 16, 2016. FDA issued a Fulfillment of Postmarketing Requirement letter on March 21, 2016, for PMR 2121-1.

July 10, 2014: FDA granted a deferral extension for Final Report Submission of PMR 2121-1 with the following revision:

Final Report Submission: February 2016

October 29, 2014: Approval letter for Xigduo XR (NDA 205649) stated that under PREA, that the pediatric study requirement for ages 0 through 9 years (inclusive) was waived because necessary studies are impossible or highly impracticable because there are too few children in this age range with T2D to study. The studies required for NDA 202293 for Farxiga (dapagliflozin) tablets, dated January 8, 2014, also apply to NDA 205649. In addition, the following pediatric assessment were required:

(b) (4)

***June 30, 2015:** FDA issued letter to the Applicant releasing PMR (b) (4) FDA determined that an evaluation (b) (4) was no longer necessary based on the rationale that there is a lack of clarity regarding the design and interpretation such a study, and that there is no prospect of benefit for study participants.

July 14, 2015: Applicant proposed a revised milestone for PMR 2121-2 for the Final Protocol Submission from August 2015 to February 2016 because of ongoing discussions with FDA regarding the study design[12].

January 21, 2016: FDA issued to the Applicant Acknowledge Revised Postmarketing Requirement Milestone letter for PMR 2121-2 and agreed that there was adequate justification for failure to comply with the Final Protocol Submission milestone. The following dates were revised:

[12] On July 2, 2015, the Applicant requested a meeting with FDA (b) (4) to discuss their proposal of a multi-arm clinical study that would address the PREA PMRs for three products: saxagliptin (Onglyza, NDA 022350), saxagliptin and metformin HCL extended-release (Kombiglyze XR, NDA 200678) and dapagliflozin (Farxiga, NDA 202093). In Written Responses issued on September 15, 2015, the Division agreed, in concept, that the efficacy and safety of saxagliptin and dapagliflozin could be evaluated in one study using a shared placebo-control arm.

Final Protocol Submission:	**February 2016**
Study Completion:	February 2020
Final Report Submission:	August 2020

February 8, 2016: Applicant requested a deferral extension request for PMR 2121-2 for the Final Protocol Submission because of ongoing discussion with FDA regarding the study design. The Applicant also requested deferral extension on the Study Completion and Final Report Submission dates, proposing to revise the milestone dates as follows:

Final Protocol Submission:	August 2016 (from February 2016)
Study Completion:	August 2020 (from February 2020)
Final Report Submission:	February 2021 (from August 2020)

March 18, 2016: FDA issued to the Applicant a Deferral Extension Denied letter for the Final Report Submission date of August 2020 because it was considered premature to agree on the Final Report Submission date based on the currently available information. The milestone date remained:

Final Report Submission:	August 2020.

March 24, 2016: Applicant submitted the initial protocol for Study 19[13] titled, "A 26 Week, Multicenter, Randomized, Placebo-Controlled, Double-Blind, Parallel Group, Phase 3 Trial with a 26 Week Safety Extension Period Evaluating the Safety and Efficacy of Dapagliflozin 5 and 10 mg, and Saxagliptin 2.5 and 5 mg in Pediatric Patients with Type 2 Diabetes Mellitus who are between 10 and below 18 years of age".

March 26, 2016: FDA issued Acknowledge Revised Postmarketing Requirement Milestone letter to the Applicant for PMR 2121-2. The following were the revised dates:

Final Protocol Submission:	**August 2016**
Study Completion:	**August 2020**
Final Report Submission:	August 2020

April 24, 2017: Following the November 9, 2016, submission of protocol Study 19 Amendment 3, FDA agreed that this single clinical protocol could satisfy the PREA-required pediatric assessments for Farxiga and Xigduo XR, as well as Onglyza (NDA 022350, saxagliptin) and Kombiglyze XR (NDA 200678 saxagliptin/ metformin XR) and issued a letter to the Applicant to Acknowledge Final

[13] Collaborative discussions between FDA and Applicant occurred as well as between the Applicant and the European Medicines Agency (EMA), resulting in several revisions to the protocol for study D1680C00019. With the submission of Amendment 3 for D1680C00019 on November 9, 2016, FDA agreed that this single clinical protocol could satisfy the PREA-required pediatric assessments for Onglyza, Kombiglyze XR, and Farxiga, and Xigduo XR.

Protocol for Postmarketing Requirements for the aforementioned applications. However, because the protocol for Study 19 differed in several substantive ways from the original PMRs, FDA issued a Release for Postmarketing Requirements for PMR- 2121-2, PMR-1493-1 (NDA 022350, saxagliptin) and PMR-1703-3 (NDA 200678 saxagliptin/ metformin XR). A New Postmarketing Requirement was reissued for all four applications as follows:

> **PMR 3199-1:** Conduct a 26-week randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of the monotherapies saxagliptin and dapagliflozin for the treatment of pediatric patients ages 10 to <18 years with T2D, followed by a 26-week site- and subject-blinded safety extension period (weeks 26 to 52). Background therapy will consist of either metformin, insulin, or metformin plus insulin. A second randomization will take place at week 14, with up-titration of dose (saxagliptin may be increased from 2.5 mg to 5 mg; dapagliflozin from 5 mg to 10 mg) for approximately half of the subjects with a hemoglobin A1C greater than or equal to 7%.
>
> Study Completion: December 2021
> Final Report Submission: April 2022

June 28, 2021: Applicant requested a deferral extension of the timeline to complete the study to fulfill PMR 3199-1.

July 28, 2021: FDA issued to the Applicant a letter for Deferral Extension Granted and Acknowledged Revised Postmarketing Requirement Milestones for PMR 3199-1. FDA agreed to the Applicant's request and the milestone dates were adjusted as follows:

> Study Completion: **January 2024** (revised date)
> Final Report Submission: **July 2024** (deferral extension date)

Regulatory History Related to Written Request:
March 4, 2019: FDA issued a Written Request (WR) for Farxiga (dapagliflozin) and Onglyza (saxagliptin), in response to the November 8, 2018, Proposed Pediatric Study Request (PPSR) submission from the Applicant. The Applicant acknowledged receipt and agreed to the terms outlined in the WR for pediatric study D168C00019.

March 26, 2019: FDA reissued the WR letter to update the statistical information section of the WR to clarify the treatment regimens to be considered for analysis.

May 18, 2021: Applicant submitted request for advice from FDA for Study 19 regarding study site 4910 located in Mexico. This site enrolled 11 subjects; however, because of an ongoing legal dispute, the Applicant was not able to access the site and the subjects' records. Because of the

timeline to fulfill the WR and PMR, the Applicant expressed concern with difficulty being able to replace the 11 subjects and requested a reduction in study sample size from 240 to 229 subjects.

June 4, 2021: FDA issued a General Advice letter to the Applicant advising that Applicant submit an amendment to the WR for FDA to review any proposed changes to the Study 19.

July 2, 2021: Applicant submitted Amendment 1 to the WR with the following proposed changes:

1. broaden the eligibility criterion for A1C from 6.5-10% to 6.5 to 10.5%
2. update timelines for study visits to allow greater flexibility due to the COVID-19 pandemic
3. because of issues obtaining the data from Site 4910, the Applicant proposed to adjust the study size minimum requirement to (b) (4) and minimum US enrolment to 11% (from 15%) (the Applicant stated that given the statistical assumptions, these changes would still result in a power of approximately 78%)
4. eliminate the requirement of a pre-dose assessment of plasma DPP-4 from the protocol

October 29, 2021: FDA issued WR-Amendment 1 to the Applicant. The key modifications to the WR included the following:

- broaden of the A1C inclusion criterion to 6.5% to 10.5%
- adjust timelines of assessments to allow for flexibility
- removal of the assessment of monotherapy of dapagliflozin following the randomized withdrawal of background metformin in subjects achieving A1C< 7.5% at week 26 or 32
- FDA did not agree with a reduction in the study size. The total number of subjects to be studied in Study 19 remained 243[14].

November 17, 2021: Teleconference (Tcon) was held between the Applicant and the FDA clinical and statistical teams to discuss the power re-estimation requested by FDA for Study 19. During the Tcon, the Applicant shared the cumulative blinded data from Study 19 as well as results from pediatric trial T2GO2, which investigated dapagliflozin in pediatric/young adults with T2D (conducted satisfy the pediatric investigational plan for EMA). Study 19 was noted to have an SD of 1.71 (higher than the assumed SD of 0.9 used for study sample size estimation). The results of the

[14] During the review of the Applicant's WR Amendment, additional discussions were held between DDLO, the Division of Pediatrics and Maternal Health (DPMH), and the statistical team. Review of recent study data from pediatric trials with non-insulin antihyperglycemic product programs show that the SDs of the treatment effects appear to be consistently larger in pediatric studies than those observed from corresponding adult studies. These underestimations of SDs could result in underpowered studies. Based on insights gleaned from these completed pediatric trials, the Applicant was informed of the Division's concern that study D1680C00019 may be underpowered; therefore, the Applicant was advised to not lock the database and unblind the study data until a power re-estimation is performed. Should the power be less than predicted, further discussion with the Division would be necessary to determine how to proceed to amend the WR (i.e., revise the statistical analysis plan [SAP] or sample size). FDA recommended a teleconference discussion to review this information and requested that the Applicant was calculate the observed SD for the primary endpoint based on the cumulative blinded data for study D1680C00019 prior to the scheduled meeting.

T2GO2 study also found an SD of 1.7; however, a higher-than-expected effect size was noted with a A1C reduction of -0.75% (the assumed effect size of 0.5 was used for study sample size estimation). Based upon review and discussion of these data, the following additional protocol related proposals were agreed upon by the FDA during the meeting:

- The pediatric effect size assumption will be increased to 0.75 (instead of 0.5) based on the data from the Applicant's pediatric study T2GO2, conducted for EMA.
- The SD assumption increased to 1.7 (instead of 0.9)
- The primary analysis will be changed to all dapagliflozin (5 mg and 10 mg doses combined) versus placebo treatment arm, and all saxagliptin doses (2.5 mg and 5 mg combined) versus placebo treatment arm (instead of subgroup analysis based on titration doses).
- The full alpha (0.05) will be used for each primary comparison (instead of a split alpha of 0.025 previously proposed), to align with FDA's guidance for industry *COVID-19: Master Protocols Evaluating Drugs and Biological Products for Treatment or Prevention* (May 2021), which states, "[…] Applicants do not need to perform multiplicity adjustments for the multiple comparisons of different investigational drugs to the comparator group to ensure control of the overall familywise type I error rate."
- FDA agreed that the percentage of US patients required in the study may be reduced to 11% (instead of 15%).

The Applicant was advised that all changes discussed should be incorporated into the study protocol and SAP prior to data base lock/unblinding.

February 21, 2022: Applicant notified FDA that they no longer plan to pursue the saxagliptin WR.

June 22, 2022: FDA issued WR- Amendment 2 letter to the Applicant. Key modifications to the WR include the following:

- primary efficacy analysis changed to include 5 mg and 10 mg dapagliflozin doses combined
- statistical information adjusted based on data discussed during teleconference held 11/17/2021: "If 243 pediatric subjects are randomized and analyzed, and each treatment analyzed compared to placebo at a two-sided alpha = 0.05 level, this will provide approximately 80% power for each comparison to detect a 0.75% reduction in A1C change from baseline assuming a standard deviation of 1.7%."

October 21, 2022: Applicant submitted a Type B pre-sNDA submission meeting request.

December 20, 2022: FDA issued Written Responses Only (WRO) for Type B pre-sNDA meeting request. The following key topics were discussed:

- In general, FDA considered Applicant's proposals for planned submission of sNDA acceptable.
- The Applicant claimed that the adverse events of special interest for dapagliflozin captured during the study are no longer considered to be of special interest. FDA advised the

Applicant to still provide safety narratives of these events for review as a separate category "Other Adverse Events of Interest."

- FDA added advice that, based on accumulating experiences reviewing completed pediatric trials of antihyperglycemic agents in patients with T2D, FDA recommended that the WR should be amended to remove the requirement for Week 104 data for growth, maturity, Tanner staging, and markers of bone health[15]. Accordingly, this change should occur in the WR for Study 19.

January 27, 2023: FDA issued Advice Letter to the Applicant as a follow-up to December 20, 2022, WRO letter. FDA clarified that, with respect to Good Clinical Practice concern for site 4910 (data unavailable for audit and inspection), FDA agreed with the Applicant's proposal to exclude the 11 subjects from site 4910 from the main efficacy and safety analyses and to conduct sensitivity analyses that include these subjects' data.

February 6, 2023: Applicant inquired via email correspondence whether, to be comprehensive of all potential categories, "other" could be added as an option as a designation for race in addition to those listed, i.e., American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander or White. On February 8, 2023, the FDA replied to this email inquiry and confirmed that the proposed change would not negatively affect the Applicant's ability to fulfill the WR as written.

February 15, 2023: FDA issued WR- Amendment 3 to the Applicant with removal of Week 104 data requirement for the WR.

April 25, 2023: Tcon was held between FDA review team and the Applicant to review the top-level results of Study 19. Dapagliflozin results showed a clinically meaningful improvement in glycemic control in the pediatric patients with T2D. The Applicant also stated that the safety results were consistent with the established safety profile for dapagliflozin in adults and there were no new safety concerns.

July 7, 2023: Applicant submitted Type D meeting request to discuss contents of the 4-month safety update (4MSU) for the planned sNDA submissions. On July 12, 2023, FDA granted the meeting request as WRO.

[15] FDA has determined that data for effects on growth, maturity, Tanner staging, and markers of bone health have proven uninterpretable in previously reviewed pediatric T2D studies, as most pediatric patients with T2D enrolled have already completed puberty. Further, saxagliptin and dapagliflozin are the only DPP-4 and SGLT2 products, respectively, for which this 104-week requirement was included in the WR (e.g., it does not appear in the WR for empagliflozin or canagliflozin). Also, keeping this requirement would require patients to come back one year later to complete a single study visit and delay submission of the NDA, potentially depriving children of an additional oral treatment other than metformin for an additional year. Thus, FDA recommended removal of Week 104 data from the terms of the WR.

August 22, 2023: FDA issued WRO to the Applicant for the Type D meeting request and concurred with the Applicant's plan to submit annual periodic benefit-risk evaluation report for Farxiga and Xigduo XR in lieu of a separate document for the 4MSU.

3.3. Foreign Regulatory Actions and Marketing History

As of August 18, 2023, dapagliflozin is approved for the treatment of T2D in adult patients in 122 countries and is approved for the treatment of T2D in pediatric patients aged 10 years and above in 49 countries (not including the US). The pediatric indication for the treatment of T2D was first approved in the European Union (EU) based on pediatric study D1690C00017 (MB102138) which fulfilled the pediatric requirements in the EU for dapagliflozin. However, this study did not adequately fulfill US pediatric requirements due to its modified extrapolation design; thus, Study 19 was designed by the Applicant in discussion with FDA to fulfill the US pediatric requirements (see **Section 3.2** for details). The other indications for dapagliflozin beyond glycemic control are limited to the adult population (see **Section 3.1** for list of indications).

As of August 18, 2023, dapagliflozin/metformin HCl FDC is approved for the treatment of T2D in adult patients in 97 countries (as immediate release [IR] in 37 countries and extended release [XR] in 61 countries, including the US). The dapagliflozin/metformin HCl FDC is currently not approved for use in pediatric patients with T2D.

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

4.1. Office of Scientific Investigations (OSI)

The Office of Scientific Investigations (OSI) was consulted to conduct a routine[16] inspection of the clinical investigators for this study, given that the results from this study support expansion of the labeled population. The multidisciplinary team (including the clinical and statistical review team, and OSI reviewer) identified three clinical sites[17] for a detailed inspection, based upon the large enrollment numbers of study subjects, high proportion of treatment responders, and lack of an inspection history. Based on the overall inspection results of these three clinical sites and the regulatory assessments, the OSI review concluded that data generated by these clinical investigator sites are verifiable. The primary efficacy endpoint of the change from

[16] The biostatistics reviewer and the clinical reviewer did not identify any data quality or integrity issues that would prompt a for-cause inspection

[17] one domestic clinical site (Dr. Audre Lee Jones [Site #7852, Texas] enrolled 7 subjects) and two international clinical sites (Dr. Raymundo Garcia-Reza [Site # 4904, Mexico] enrolled 12 subjects; Dr. Rosa Isela Luna Ceballos [Site # 4905, Mexico] enrolled 13 subjects)

baseline in A1C at Week 26 was verified using the source records with no notable discrepancies. Safety data including AEs and SAEs were appropriately documented. Study 19 appears to have been conducted adequately and the clinical data submitted by the Applicant appear to be acceptable. For additional details of these audits, see the Clinical Inspection Summary by Dr. Ling Yang dated April 29, 2024.

4.2. Product Quality

No new product quality information was submitted with these supplements. The CMC review team recommends approval.

4.3. Clinical Microbiology

Not applicable. No new microbiology data were submitted with these supplements.

4.4. Nonclinical Pharmacology/Toxicology

Not applicable. No new nonclinical data were submitted with these supplements.

4.5. Clinical Pharmacology

This review references the primary review authored by Dr. Dong Guo and concurred by team leaders Dr. Edwin Chow and Dr. Justin Earp from the Office of Clinical Pharmacology. The clinical pharmacology package to support this indication included a dedicated PK/PD study (Study D168C0016) and a population PK model, including rich PK samples from Study D168C0016, sparse PK samples from Study 19, and PK samples from adult patients.

Study D168C0016 was an open label, single dose, PK and PD study in pediatric patients aged 10 to 17 years with T2D. This study was conducted to fulfill PMR 2121-1 and supported dose selection for the efficacy trial. The clinical study report for D168C0016 was submitted March 31, 2015, reviewed by OCP (OCP review dated 2/16/2016), and PMR 2121-1 was considered fulfilled in March 2016 (refer to PMR fulfill letter dated 3/21/2016 in DARRTS). At that time, FDA agreed that the study supported using the approved doses for adults in the Study 19.

The key clinical pharmacology questions are (1) is the PK and PD in pediatric patients similar to adults (as supportive evidence of efficacy), and (2) is the dose and dose regimen studied in the confirmatory trial appropriate for approval.

PK/PD Similarity: The clinical pharmacology review team noted that the mean-level PK (Cmax and AUCinf) and PD (24-hour urine glucose excretion) in pediatric subjects was “within the range” of adult patients. The clinical pharmacology team noted that the point estimate for urine glucose excretion, a measurement directly related to the primary mechanism of action for

the product, was nominally higher in the pediatric population than in adults. Although this difference did not meet traditional statistical significance thresholds (potentially due to small sample size), there was a notable difference in kidney function between adults and pediatric subjects which likely drove the changes. This difference may also explain, to some degree, the increased efficacy (based on point estimates) in pediatric patients as compared to adults, for both empagliflozin and dapagliflozin. The clinical pharmacology team recommended a minor modifying statement in section 12 of the labeling to the Sponsor's proposed language (the PK/PD was similar *in adults and pediatric patients with the same renal function).*

Dose-response relationship for efficacy: The Applicant proposed an oral dapagliflozin dose of 5 mg once daily, and for additional glycemic control, a dose increase to 10 mg, as the recommended dosing regimen. The clinical pharmacology team noted that the evidence of efficacy for the 10 mg dose was derived from a sub-study in Study 19, whereby patients randomized to 5 mg dapagliflozin, who did not achieve A1C of less than 7% at week 12, were re-randomized to stay on 5 mg or up titrate to 10 mg. The difference in A1C at 26 weeks between those who stayed on 5 mg and up-titrated to 10 mg was essentially 0 (-0.03% 95%CI: -1 – 0.94). In alignment with the clinical team, the clinical pharmacology team noted that the small sample size (n=41), and restriction of the analysis to "non-responders" were likely contributing factors to the failure to demonstrate a dose-response relationship. The clinical team noted imbalances in baseline metabolic characteristics between the treatment arms, as well as rather remarkable treatment emergent imbalances in glycemic control (e.g., A1C at week 12) between treatment arms contributed to the lack of dose-response. See **Section 6.1.2** Assessment of Dose-Response Relationship for Efficacy for additional details.

Overall, the clinical pharmacology reviewers recommend approval of Farxiga in pediatric patients 10 years and older. The clinical pharmacology reviewers consider the proposed starting dose (5 mg) to be acceptable. The clinical pharmacology team deferred to the clinical review team for approval of the 10 mg dose for additional glycemic control. The clinical review team recommends approval of the 10 mg dose, in general alignment with the dosing and administration instructions in adult labeling. See **Section 7.1** for an integrated discussion of this issue.

4.6. Devices and Companion Diagnostic Issues

Not applicable to these submissions.

4.7. Consumer Study Reviews

Not applicable. No consumer study was submitted with these supplements.

5. Sources of Clinical Data and Review Strategy

5.1. Clinical Review Strategy

The analyses used to formulate conclusions of efficacy (benefit) and to determine the information to include in the product labeling are those which were conducted and/or corroborated by Dr. Sung Hee Kim, the FDA Statistical Reviewer for Biometrics Division II (DB II) in the Office of Biostatistics. Efficacy analyses were conducted on the modified intent-to-treat (mITT) population, defined as all randomized subjects who received at least one dose of study drug, regardless of treatment adherence or rescue medication. Key tables summarizing the analyses of the primary and multiplicity adjusted endpoints are presented in **Section 6.1.2.** Refer to the Office of Biometrics Division DBII Review for more detailed discussion of efficacy analyses by Dr. Kim dated May 17, 2024, in DARRTS. Refer to **Section 8.1** for safety review approach.

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. Study 19

6.1.1. Study Design

The study under review is also known as "T2NOW" and has a National Clinical Trial ID of NCT03199053. The results of this trial, as analyzed and summarized by the Applicant or the Applicant's designees, are available to the public (Digital Object Identifier (DOI: 10.1056/EVIDoa2300210).

Overview and Objectives

Study Title: A 26-Week, Multicenter, Randomized, Placebo-Controlled, Double-Blind, Parallel Group, Phase 3 Trial with a 26-Week Safety Extension Period Evaluating the Safety and Efficacy of Dapagliflozin 5 and 10 mg, and Saxagliptin 2.5 and 5 mg in Pediatric Patients with Type 2 Diabetes Mellitus Who Are Between 10 and Below 18 Years of Age.

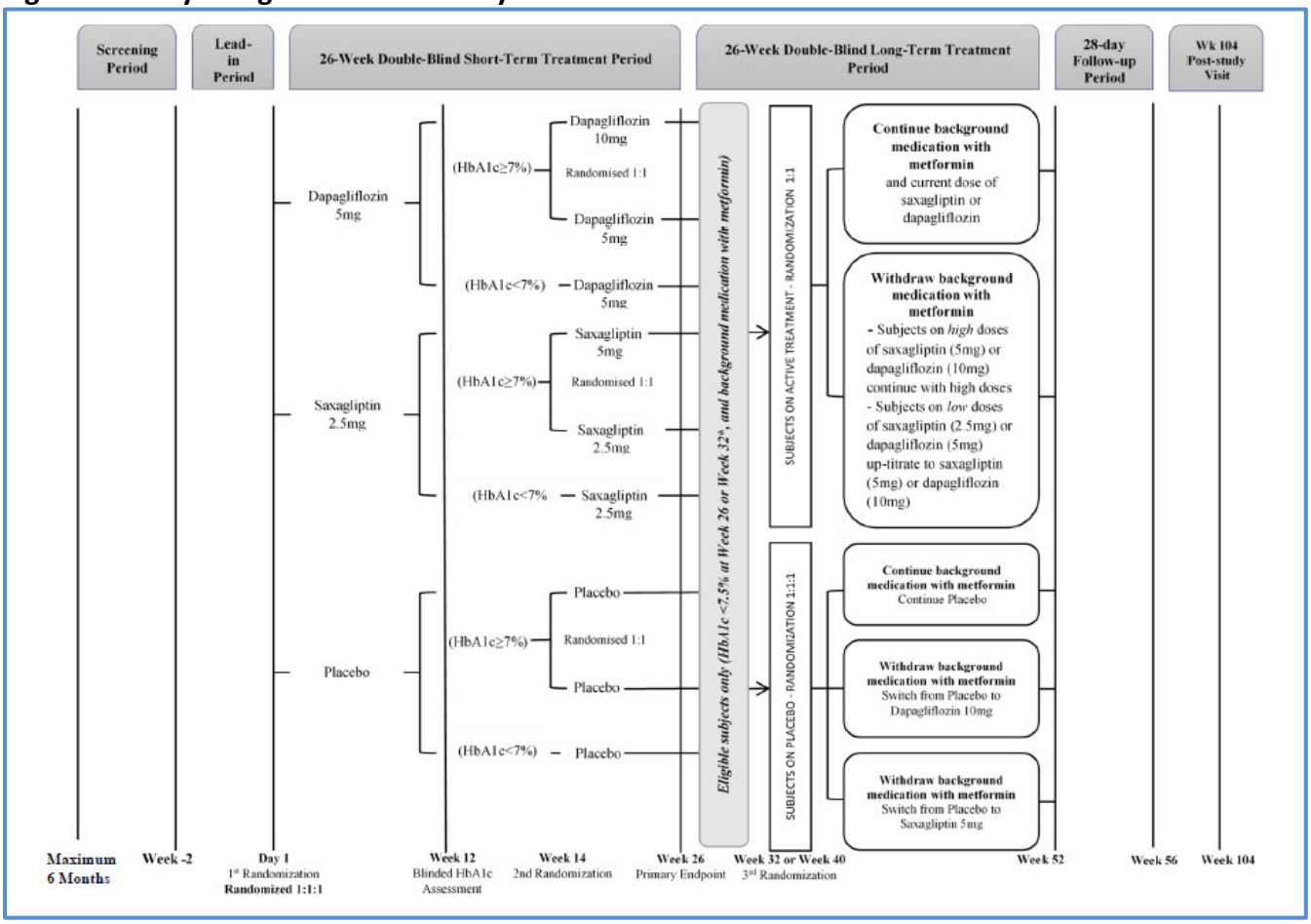
Primary Objective: To determine if there will be a greater mean reduction from baseline in A1C achieved after 26 weeks of dapagliflozin (5 mg or 10 mg [all doses and regimens combined]) or saxagliptin (2.5 mg or 5 mg [all doses and regimens combined]) compared to a common placebo group in pediatric subjects with T2D.

Study Design

Study 19 was a global phase 3 umbrella study designed to investigate the efficacy and safety dapagliflozin and saxagliptin as add on to standard of care (metformin, insulin, or both) compared to a shared placebo group for the treatment of pediatric patients with T2D (**Figure 1**). Study 19 included a 26-week randomized, double-blind, placebo-controlled, parallel-group short-term (ST) treatment period. The ST period was followed by a 26-week site and subject-blind long-term (LT) extension (Weeks 26 to 52). Eligible subjects had A1C ≥ 6.5% and ≤ 10.5% on a diet and exercise program and stable background therapy of metformin (minimum dose 1000 mg of immediate release [IR] or extended release [XR]), insulin, or metformin (IR or XR) plus insulin.

The study was conducted at 123 clinical sites in 23 countries (Argentina, Australia, Brazil, Canada, Chile, Columbia, England, Finland, India, Israel, Italy, Malaysia, Mexico, New Zealand, Philippines, Poland, Russia, South Korea, Taiwan, Thailand, Turkey, Ukraine, and United States).

Figure 1. Study Design Schematic Study 19



Source: Clinical Study Protocol Figure 3

Study Procedures

Following the 2-week lead-in period, subjects who meet the eligibility criteria were randomly assigned by the Interactive Web/Voice Response System (IXRS) at the Day 1 Randomization visit, to one of the following three double-blind treatment arms in a 1:1:1 ratio: low-dose treatment with dapagliflozin 5 mg, saxagliptin 2.5 mg, or placebo. Randomization was stratified based on baseline antidiabetic medication (metformin vs insulin vs metformin + insulin), sex (male vs female), and age (10 to below 15 years vs 15 to below 18 years). All subjects were given two identical tablets (their assigned treatment and a placebo tablet).

A blinded A1C assessment occurred at Week 12, and subjects with values ≥ 7% ("non-responders") underwent a 2nd randomization (1:1) to either continue low dose (dapagliflozin 5 mg or saxagliptin 2.5 mg) or up-titrate to a higher dose (dapagliflozin 10 mg or saxagliptin 5 mg) beginning Week 14. Non-responders assigned to the placebo group continued placebo. To maintain blinding of treatments and A1C results, all placebo subjects and all responders at Week 12 underwent a dummy second randomization process indistinguishable from the actual 2nd randomization and at Week 14, and all subjects were instructed to take **3** tablets daily (their assigned treatment and 2 placebo tablets). The primary efficacy endpoint was change in A1C from baseline at Week 26 for the pooled dapagliflozin dose groups (i.e., responders on 5 mg, non-responders remaining on 5 mg, and non-responders up-titrated to 10 mg) vs placebo.

***Reviewer comment**: The blinded A1C assessment and subsequent secondary randomization introduces interpretability issues for the 26- week pooled treatment comparison, for those who were randomized to dapagliflozin 5 mg or placebo at baseline. The 26- week treatment comparison includes a mix of subjects who were (1) controlled at week 12 and remained on 5 mg, (2) subjects who were uncontrolled at week 12 and were randomly and anonymously assigned to remain on 5 mg or (3) the same subjects, but were randomly assigned to up-titrate to 10 mg. All relevant clinical scenarios involving an up-titration event would include an "unblinded" assessment. Including uncontrolled subjects in the estimand (of unknown proportion) with an average dapagliflozin dose of 7.5 mg q.d. is not relevant. Hence, the pooled treatment intervention itself (including titration and post-randomization procedures) does not represent a relevant therapeutic experiment.*

Following the primary efficacy assessment after completing the ST treatment period at Week 26, subjects entered the double-blind, 26-week LT treatment extension period. In the LT period, subjects on dapagliflozin and receiving background therapy with metformin alone and achieving A1C values <7.5% underwent a 3rd randomization (1:1) [18], to either continue current therapy or undergo withdrawal of metformin to assess the efficacy of monotherapy with

[18] Subjects were assessed for eligibility for the third randomization at week 26 or week 32, and if eligible, underwent the third randomization on week 32 or week 40, respectively

dapagliflozin through Week 52. For eligible subjects randomized to withdrawal of metformin, those on dapagliflozin 5 mg were up titrated to dapagliflozin 10 mg, and those on dapagliflozin 10 mg remained on the 10 mg dose. Subjects on placebo receiving background therapy with metformin alone and achieving A1C values < 7.5% were randomized (1:1:1) to remain on placebo with metformin, or withdraw metformin and begin dapagliflozin 10 mg, or withdraw metformin and begin saxagliptin 5 mg. Subjects who were receiving background medication with insulin only or insulin and metformin (and therefore not eligible for the 3rd randomization) continued with their randomized study drug assigned after the 12-week assessment during the double-blind LT treatment period. Following Week 52 assessments, investigational products were discontinued, and study subjects were placed on standard of care therapy to maintain glycemic control. Subjects returned for a 28-day safety follow-up visit. A final post-treatment safety follow-up visit will occur at Week 104.

Reviewer comment: *As outlined in the presubmission history, Study 19 was designed and modified via multiple communications with FDA as part of the Written Request. The study duration and design, including 3 separate randomizations, were all agreed upon by FDA prior to study initiation. The incorporation of 2nd randomization at week 14 for subjects who did not achieve A1C target of < 7% was intended to investigate the effect of continued treatment with dapagliflozin 5mg vs up-titration to dapagliflozin 10 mg in the subset of non-responders. The planned 3rd randomization for withdrawal of metformin in the subset of subjects who achieved A1C < 7.5% during the LT treatment period was intended to assess the treatment effect of monotherapy with dapagliflozin. This design element during the LT period complicated the evaluation of safety during this extension period and is discussed further in* ***Section 8.1.***

Key Inclusion Criteria

- T2D by World Health Organization/American Diabetes Association (ADA) criteria[19]
- A1C ≥ 6.5% and ≤ 10.5% obtained during the 6-month screening period
- Treated with diet and exercise on a stable dose of at least 1000 mg/day metformin (IR or XR), or stable dose of insulin, or a stable combination of at least 1000 mg/day metformin (IR or XR) and insulin for a minimum of 8 weeks prior to Day 1
- Male and female aged 10 to <17 years with at least 30% between 10-14 years and one-third but no more than two-thirds female
- Women of childbearing potential using highly effective birth control methods

Key Exclusion Criteria

- Pre-existing diagnosis of T1D
- Positive at screening for autoantibodies to glutamic acid decarboxylase (GAD) or islet cell

[19] American Diabetes Association Professional Practice Committee; 2. Diagnosis and Classification of Diabetes: *Standards of Care in Diabetes—2024*. *Diabetes Care* 1 January 2024; 47 (Supplement_1): S20–S42. https://doi.org/10.2337/dc24-S002

antigen (IA-2) AND abnormally low levels of C-peptide
- Previous diagnosis of monogenic etiology of T2D
- Diabetic ketoacidosis within 6 months of screening
- Current use of anti-diabetes medications other than metformin and/or insulin or use within 16 weeks of screening
- Initiation or discontinuation of prescription or non-prescription weight loss drugs within 8 weeks of screening (use of weight loss drugs required to be stable during the study)
- Medical history and concurrent diseases:
    - Pregnancy or planned pregnancy or lactation during the trial
    - Unstable or rapidly progressive renal disease
    - Unresolved vesico-ureteral reflux
    - Acute or chronic pancreatitis
    - Recurrent hemolysis or hemoglobinopathy with exception of sickle trait or thalassemia
    - Malignancy within 5 years of screening except treated basal cell or squamous cell carcinoma
    - Immunosuppression or current treatment for cancer
    - Replacement or chronic systemic corticosteroid therapy (i.e., > 4 weeks within 3 months of Day 1 study visit)
- Physical and lab findings:
    - Estimated glomerular filtration rate (eGFR) calculated by the Schwartz Formula < 80 mL/min/1.73 m^2 (1.33 mL/s)
    - Abnormal TSH with abnormal free T4
    - Hematuria
    - Alanine transaminase (ALT) or aspartate transaminase (AST) or alkaline phosphatase > 2 x upper limit of normal (ULN) or clinically significant hepatic disease including active infectious hepatitis
    - Anemia (hemoglobin < 10.7 g/dL for females, < 11.3 g/dL for males)
    - Volume depletion
    - Abnormal electrocardiogram (ECG)
- Known allergies or adverse drug reactions to study drug or excipients
- Other exclusion criteria:
    - Alcohol or substance abuse within 6 months of screening
    - Prisoners or involuntary incardinated patients
    - Patients who were compulsorily detained for treatment of psychiatric or physical illness
    - Participants in other clinical study within 3 months

***Reviewer comment**: In general, the eligibility requirements appear to be reasonable.*

SGLT-2 inhibitors have been associated with an increased risk of diabetic ketoacidosis (DKA), so subjects with T1D or T2D with a history of DKA within 6 months of screening were appropriately excluded. The study included a broad range for A1C eligibility of 6.5% to 10.5%. It is more difficult to demonstrate a treatment effect with a baseline A1C closer to the normal range. However, to ease recruitment challenges that have been historically associated with pediatric trials for T2D, this broad range of A1C has typically been accepted. The rate of disease progression and resulting glycemic deterioration has been noted to be more rapid in pediatric patients with T2D compared to adults; therefore, it can be anticipated that the need for rescue for hyperglycemia will be greater for subjects assigned to placebo, particularly with A1C levels at the higher range of eligibility. The study was designed to compare treatment with dapagliflozin vs placebo, and all study subjects were required to be receiving standard of care background therapy with metformin and/or insulin. Although trials with placebo comparator for 6 months duration have generally been considered acceptable for pediatric subjects with T2D, provided that acceptable rescue criteria are in place for the safety of study subjects, T2D trials being initiated today in this population vulnerable to rapid glycemic deterioration are more likely to incorporate an active comparator such as an approved GLP-1 agonist. It is unclear why subjects with eGFR below 80 mL/min/1.73 m^2 were excluded from study participation. The label for dapagliflozin states that patients with diabetes and renal impairment using dapagliflozin may be more likely to experience hypotension and may be at higher risk for acute kidney injury secondary to volume depletion; however, the eGFR threshold for which use of dapagliflozin is not recommended for glycemic control is less than 45 mL/min/1.73 m^2. It is also notable that subjects with transaminase levels above 2 x ULN were prohibited from the study. Because metabolic dysfunction-associated steatotic liver disease (MASLD) is highly prevalent in the population of patients with obesity and/or T2D, subjects with transaminase levels up to 5 x ULN are permitted into adult trials for T2D. Therefore, it may be reasonable to consider liberalizing the upper limit level of the exclusion criterion and the lower limit of eGFR criterion for future diabetes studies in the pediatric population.

Administrative Structure

Data Monitoring Committee (DMC):

An independent DMC comprised of pediatric and endocrine therapeutic area specialists and a statistician convened on a regular basis to review trial data. The DMC was responsible for safeguarding the interests of the patients in the trial by assessing the safety and efficacy of the interventions during the trial and for reviewing the overall conduct of the clinical trial.

Adjudication Committees:

Independent adjudication committees blinded to study treatment were in place if needed for the following safety findings:

- Cardiovascular Adjudication Committee - to adjudicate all potential events CHF requiring hospitalization.
- Hepatic Adjudication Committee - to determine the probability that all potential events

of drug induced liver injury (DILI) were the cause of liver-related abnormalities.

- DKA Adjudication Committee - to adjudicate all potential events of DKA.

Investigational Drug Dosing

Doses of dapagliflozin (5 mg and 10 mg) and saxagliptin (2.5 mg and 5 mg), which are approved for the glycemic control indication for adults with T2D, were administered once daily. All study subjects were given two identical tablets (i.e., their assigned treatment and a matching placebo tablet). To maintain blinding with the 2nd randomization, eligible subject underwent randomization and ineligible subjects underwent dummy randomization. All subjects were then instructed to take 3 tablets daily (their assigned treatment and 2 placebo tablets).

Down-titration of blinded study drug and/or background metformin was not allowed at any time during the study. Patients on background insulin treatment who experienced multiple or severe episodes of hypoglycemia could down-titrate insulin treatment during the study at the Investigator's discretion.

Concomitant Medications

Once consented, subjects were:

- not to receive any prescription antihyperglycemic medication other than study drug, metformin and/or insulin
- not to begin treatment with any systemic corticosteroid therapy lasting > 5 days (subjects who require systemic corticosteroid therapy were to be discussed with the medical monitor prior to starting therapy whenever possible)
- not to commence or modify therapy with any prescription or over-the-counter weight loss medications
- not to undergo any bariatric surgery
- to comply with their prescribed dosing regimen to preserve study integrity and ensure subject safety

Discontinuation of Investigational Product

Subjects who discontinued study drug before the end of the study treatment period were to enter a non-treatment, follow-up phase, in which subjects followed their visit schedules with modified assessments until study completion. Subjects are to also attend a post-study visit at Week 104, for assessment of measures of growth and maturity.

Rescue Medication

During the trial, subjects were eligible for the addition of open-label rescue medication to their blinded treatment regimen to treat ongoing hyperglycemia. Insulin could be used as rescue, at the Investigator's discretion. Subjects who were already taking insulin at the start of the study could be switched to a flexible insulin dose following a Rescue Visit. For subjects on baseline insulin, persistently increased doses of insulin 20% or more above baseline dose, despite advice and counsel to keep the insulin dose stable, could be considered another potential

manifestation of poor glycemic control, and such subjects were to be evaluated for rescue. Only insulin could be used as rescue medication, but subjects could be rescued without the use of medication.

The criteria for initiation of glycemic rescue are summarized in **Table 3**. Subjects who met rescue criteria were to first complete the Rescue Visit procedures before receiving open-label rescue medication to ensure that important trial endpoint measurements were collected. Rescued subjects were to then continue in the study according to their original visit schedule.

Table 3. Glycemic Criteria for Initiation of Rescue Medication

Study week	Rescue criterion
Week 6 visit up to and not including Week 26 visit	FPG > 240 mg/dL based on 3 consecutive fasting SMBG values followed by a confirmatory central laboratory FPG or Single central laboratory FPG followed by a confirmatory central laboratory FPG
Week 26 visit up to and not including Week 52 visit	FPG >180 mg/dL based on SMBG for 3 consecutive days followed by a confirmatory central laboratory FPG or Single central laboratory FPG followed by a confirmatory central laboratory FPG or A1C >8.0% (while A1C values will remain blinded throughout the study, sites will be notified to allow rescue if values exceed this threshold)

Abbreviations: FPG= fasting plasma glucose, SMBG= self-monitored blood glucose
Source: Clinical Protocol Table 3.5.2-1

***Reviewer comment**: In general, the study blinding procedures related to investigational drug products appear to have been acceptable to minimize bias. The criteria for initiation of glycemic rescue were also reasonable to maintain subject safety when persistent hyperglycemia occurred.*

Study Endpoints

Primary Endpoint

- Change from baseline in A1C (%) at Week 26

Secondary Efficacy Endpoints

- Change from baseline in FPG at Week 26
- Incidence of A1C < 7.0% at Week 26

Safety Endpoints

- Incidence of AEs, SAEs, discontinuations due to AEs
- Hypoglycemic events
- Marked clinical laboratory abnormalities
- Vital signs
- Tanner staging, measures of growth and maturation
- DKA events

Study Assessments: See schedule in **Section 13.3**.

Reviewer comment*: The primary efficacy endpoint for Study 19 is change from baseline in A1C at Week 26. A1C is a well-validated surrogate marker for the risk of long-term microvascular complications of diabetes mellitus and is therefore an acceptable surrogate clinical endpoint. The timing of this assessment is also appropriate because it allows 12 weeks of exposure at a stable dapagliflozin dose following the 2nd randomization (dose adjustment) for non-responders at Week 14. A1C is derived from the average of the blood glucose fluctuation in the preceding 3 months and therefore, approximately 12 weeks of exposure to a new dose is necessary to demonstrate the treatment effect.*

Statistical Analysis Plan

Sample Size Estimation
Assuming a -0.75% treatment effect difference between the active treatment group (dapagliflozin) and the placebo group and a 1.7% standard deviation (SD), a sample size of 81 subjects per initial randomized treatment arm (162 subjects in total) would provide 80% power at a two-sided alpha level of 0.05. In the study, 81 subjects on dapagliflozin and 76 subjects on placebo were randomized and treated. From study results, the pooled SD for the dapagliflozin and the placebo groups was 1.64%, and the estimated placebo-adjusted treatment effect was -1.03% for dapagliflozin. The study was adequately powered.

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

Population & Analysis Set:
The primary population for analysis was the modified intent-to-treat (mITT) population, defined as all randomized subjects who received at least one dose of study drug, regardless of treatment adherence or rescue medication.

Handling of Missing Data:

Missing data was handled by multiple imputation based on placebo washout. Specifically, missing data from the placebo arm were imputed with a sequential linear regression constructed based on observed A1C values from the placebo arm, measured at baseline, Week 6, 12, 20 and 26. Missing data from the treatment arm were imputed with a sequential linear regression constructed based on the observed A1C values from the placebo arm, measured at baseline and Week 26. Two hundred imputed datasets were created, and Rubin's Rule was used to combine the analysis results.

Weighting Scheme:
The secondary hypotheses intended to explore the question of whether non-responders to dapagliflozin 5 mg would benefit from a dose up-titration to dapagliflozin 10 mg. Each hypothesis test from the secondary hypotheses was performed based on the same ANCOVA as for the primary hypothesis test, but with the application of the inverse probability weighting (IPW) technique.

To explain how IPW works, consider comparing dapagliflozin 5 mg (without dose up-titration) vs placebo as an example. At the beginning of the study, a weight variable ω was created for each subject. All subjects started with $\omega = 1$. At Week 14, non-responders (A1C at Week 12 $\geq$ 7.0%) were randomized to either dapagliflozin non-responders up-titrated to dapagliflozin 10 mg (TITR10) or dapagliflozin non-responders continued with dapagliflozin 5 mg (TITR5). The dapagliflozin non-responders who were up-titrated to dapagliflozin 10 mg (TITR10) would have their weights transferred to the dapagliflozin non-responders who were randomized to continue with dapagliflozin 5 mg (TITR5) (i.e., the TITR5 group had $\omega = 2$, and the TITR10 group had $\omega = 0$). This way, the TITR10 group were represented by the TITR5 group. All other subjects not involved in the second randomization had $\omega = 1$.

A similar weighting scheme was applied for the comparison of dapagliflozin up-titration to 10 mg vs placebo, where the transfer of weight was from TITR5 to TITR10. Since the two hypothesis tests from the secondary hypothesis share the same subset of dapagliflozin responders, the comparisons of TITR5 and TITR10 to placebo are highly correlated.

Multiplicity Adjustment
Hierarchical testing at a 2-sided alpha level of 0.05 of the primary and secondary efficacy endpoints was presented. The primary hypothesis testing was to determine if there would be a greater mean reduction from baseline in A1C achieved after 26 weeks of the pooled dapagliflozin regimens compared to placebo. After having obtained statistically significant result for the primary hypothesis, secondary hypotheses that compare different dapagliflozin regimen groups against placebo were tested formally in the order listed as follows:

- Mean reduction in A1C from baseline at Week 26

  - of low-dose/high-dose treatment regimen (dapagliflozin responders + TITR10) vs Placebo
  - of low-dose treatment regimen (dapagliflozin responders + TITR5) vs Placebo
- Mean reduction in FPG from baseline at Week 26
  - of pooled dapagliflozin vs Placebo
  - of low-dose/high-dose treatment regimen vs Placebo
  - of low-dose treatment regimen vs Placebo
- Percentage of subjects with A1C < 7% at Week 26
  - of pooled dapagliflozin vs Placebo
  - of high-dose/low-dose treatment regimen vs Placebo
  - of low-dose treatment regimen vs Placebo
- For the TITR10 vs the TITR5
  - Mean reduction in A1C from baseline at Week 26
  - Mean reduction in FPG from baseline at Week 26
  - Percentage of subjects with A1C < 7% at Week 26

Primary Efficacy Analysis

The primary hypothesis test was performed based on an ANCOVA, with A1C change from baseline at Week 26 as the response variable, and treatment, baseline A1C, sex, baseline age stratum (<15 years vs 15 to <18 years), and background antidiabetic medication (metformin only vs insulin ± metformin) as covariates.

Sensitivity Analysis

To assess the robustness of the primary analysis result, return-to-baseline (RTB) approach to handle missing data was performed as a sensitivity analysis. The same ANCOVA model as the primary efficacy analysis was fitted to 200 imputed datasets, and Rubin's Rule was applied to combine the analysis results.

A 2-way tipping point analysis for the treatment policy estimand was also performed to assess the robustness of the primary analysis with respect to missing data assumptions. The analysis is performed by adding positive (detrimental) penalties to dapagliflozin and negative (beneficial) penalties to the placebo and considering when results tip from superiority of dapagliflozin to non-superiority.

Protocol Amendments

All amendments to the study protocol were discussed and agreed upon with FDA. **Table 4** provides a summary of key modifications. Additional details of the discussions between the Applicant and FDA pertaining to the protocol are recorded in the presubmission history in **Section 3.2**.

Table 4. Protocol Amendments Related to Changes in Study Conduct

Number	Date	Key Changes
1	10/11/2016	• The original study design was entirely revised in accordance with FDA-specified preferred study objectives and design.
2	4/4/2017	• Protocol revised to reflect cessation of Bristol-Myers Squibb's involvement in the study • Specified preferred objectives and procedures following EMA and FDA discussions. • A post-treatment visit was added at Week 104 to assess growth and maturity.
3	10/4/2018	• Per recommendations from FDA: o addition of randomized withdrawal of background medication in a subset of eligible patients from the active treatment groups, o randomized withdrawal of background medication or switch to active treatment in a subset of eligible patients in the placebo group. • Collection of vital status removed.
4	4/27/2019	• Revised to reflect modifications in study design: o extension of the screening period and change in the screening/retesting design, o update of safety concerns and monitoring of AEs of interest o revision of fasting blood glucose, growth, bone and maturation marker measurements, as well as Tanner staging schedules in patients who discontinued study drug early o clarification of initiation or up-titration of insulin at the Rescue Visit o AE/SAE collection until study completion o correction of the study drug dispensation schedule
5	9/24/2020	• Because of some study delays related to the COVID-19 pandemic: o flexibility was granted in the timing of scheduled assessments to maintain an interval of at least 12 weeks between the Week 14 and Week 26 visits and between the third randomization visit and the Week 52 visit. o Short- and long-term period study visits could be delayed by a maximum of 11 months in total. o If the duration of study drug administration was longer than 5 fety follow-up period was to be

		shortened such that the complete study duration did not exceed 104 weeks.
6	2/7/2022	• To allow for flexibility in scheduling, the window period for the Week 104 post-dose visit was modified from "± 7 days" to "-28 days to +7 days" from the original scheduled date. • Based on discussions with FDA: o the primary objective was modified to assess the effect of all doses and regimens combined for each drug vs placebo o accordingly, the primary and secondary objectives were reordered and updated to make overall analysis (all doses for each treatment) as the primary objective o corresponding to the change in primary objective, the primary analysis was updated as: "The primary analysis will be performed using an analysis of covariance (ANCOVA)" o the analyses were updated to use a fully alpha of 0.05 to test each drug vs placebo rather than the current split into 0.025 o for power analysis, the assumption of an effect size of 0.75% rather than 0.5% was used.

Source: Reviewer generated from CSR Table 10

6.1.2. Study Results

Compliance with Good Clinical Practices

The Applicant attested that Study 19 was performed in accordance with the ethical principles of the Declaration of Helsinki, in accordance with International Council of Harmonization (ICH) /Good Clinical Practice (GCP) guideline, and in accordance with applicable regulatory requirements and the AstraZeneca policy on Bioethics.

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

There were 509 subjects screened. 234 (46%) subjects failed to meet enrollment criteria, and 11 subjects were excluded due to being part of site 4910 (site in Mexico, legal issues precluded access to source trial data).

A total of 245 subjects were randomized from 94 sites in 21 countries: 81 to the dapagliflozin group, 88 to the saxagliptin group, and 76 to the placebo group and all randomized subjects received at least one dose of study drug. A summary of subject disposition is presented in **Table 5** for the randomized subjects who received dapagliflozin or placebo. Two subjects treated with placebo were discontinued from study visit up to Week 26 but were measured for A1C value at Week 26 (denoted with an asterisk in the table).

Of the 81 subjects who were initially randomized to dapagliflozin 5 mg group, 4 prematurely discontinued study drug or study before Week 14, 1 missed the week 12 A1C assessment. and 34 of subjects achieved a A1C < 7%. This left 42 "non-responder" subjects (52% of the ITT) who underwent a second randomization to either dapagliflozin 10 mg (TITR10, N=21) or dapagliflozin 5 mg (TITR5, N=21).

Table 5. Subject Disposition and Data Capture (A1C and FPG at Week 26)
Randomized Population

	Dapa pooled [5 mg & 10 mg] QD N=81	Placebo N=76	Total
Randomized [n]	81	76	157
Randomized and treated with at least 1 dose [n (%)]	81 (100)	76 (100)	157 (100)
Discontinuation from study treatment up to Week 26 [n (%)]	8 (9)	11 (13)	19 (12)
Lost to follow-up [n]	2	0	2
Withdrawal by subject [n]	3	7	10
Non-compliance [n]	3	4	7
Discontinuation from study visits up to Week 26 [n (%)]	5 (6.2)	8* (10.5)	13 (8.3)
Lost to follow-up [n]	2	1	3
Withdrawal by subject/guardian [n]	3	7	10
Completed 26-week A1C [n (%)]	75 (92.6)	70 (92.1)	145 (92.4)
On Treatment [n]	73	66	139
Off Treatment (Retrieved Drop-outs) [n]	2	4	6
Missing in 26-week A1C [n (%)]	6 (7.4)	6* (7.9)	12 (7.6)
On Treatment [n]	0	0	0
Off Treatment [n]	6	6	12
Discontinuation from study treatment up to Week 52 [n (%)]	10 (12.3)	20 (26.3)	30 (19.1)
Lost to follow-up [n]	2	1	3
Withdrawal by subject [n]	4	9	13
Others [n]	4	10	14

Discontinuation from study visits up to Week 52 [n (%)]	7 (8.6)	17 (22.4)	24 (15.3)
Lost to follow-up [n]	1	3	4
Withdrawal by subject [n]	5	12	17
Others [n]	1	2	3
Affected by Covid-19 pandemic [n (%)]	14 (17.3)	18 (23.7)	32 (20.4)

* Two subjects treated with placebo were discontinued from study visit up to Week 26 but were measured for A1C value at Week 26
Abbreviations: Dapa = dapagliflozin, mITT = modified intent to treat, QD = once daily
Source: Statistical Review Table 3

Reviewer comment*: Compared to other contemporary pediatric glycemic control studies, there was good study retention and treatment compliance. There were very few missing data for the primary efficacy analysis, with a high proportion of subjects on study continuing to receive treatment (142 of 157, 88%) and staying on the study (144 of 157, 92%) at Week 26. The disposition was relatively balanced between treatment arms, but it is notable that nominally fewer subjects in the dapagliflozin arm discontinued study treatment or study participation than the placebo arm at both the 26 and 52 week timepoints.*

Protocol Violations/Deviations

Relevant protocol deviations were defined as deviations that could potentially affect the interpretability of the study results and are summarized in **Table 6**. Over the ST period, of the 245 subjects randomized, 59 (24.1%) had at least one relevant protocol deviation: 18 (22.2%) in the dapagliflozin group, 15 (17.0%) in the saxagliptin group, and 26 (34.2%) in the placebo group. The most common reason for relevant protocol deviation was treatment compliance < 80% or > 120% during the ST treatment period (11 [13.6%] dapagliflozin group, and 9 [11.8%] in the placebo group).

Table 6. Relevant Protocol Deviations During the ST Period Randomized Population

Relevant protocol deviation	**Total dapagliflozin (N = 81)**	**Placebo (N = 76)**	**Total (N = 245)**
Number of patients with at least 1 relevant deviation	18 (22.2)	26 (34.2)	59 (24.1)
Randomized patients not meeting baseline antihyperglycemic requirement (metformin, insulin, or both)	5 (6.2)	3 (3.9)	11 (4.5)
Randomized patients with randomization strata error - age, sex, background medication	1 (1.2)	2 (2.6)	3 (1.2)

Randomized patients who used antihyperglycemic medication (other than protocol allowed medication) for 7 or more consecutive days during the ST period	0	3 (3.9)	3 (1.2)
Randomized patients who were treated with any systemic corticosteroid therapy for ≥ 5 consecutive days initiated or changed during ST period, or within 5 days prior to randomization	1 (1.2)	0	2 (0.8)
Randomized patients whose background metformin dose was not stable and/or background insulin dose increases or decreases 20% or more above baseline dose and/or there is a gap of greater than 14 days of background metformin or insulin during the ST treatment period	3 (3.7)	11 (14.5)	15 (6.1)
Randomized patients with treatment compliance < 80% or > 120% during the ST treatment period	11 (13.6)	9 (11.8)	28 (11.4)
Randomized patients who received no double-blind medication for 14 or more consecutive days during the ST treatment period	3 (3.7)	2 (2.6)	8 (3.3)
Randomized patients who received incorrect study drug for 14 or more consecutive days during the ST treatment period	0	1 (1.3)	1 (0.4)

Source: Clinical Reviewer. Curated from Table 12 in the clinical study report

Reviewer comment: *Glycemic rescue was considered a protocol deviation (7th row from the top of the table). This imbalance would favor placebo. All other protocol deviations were balanced between treatment groups and do not raise concerns about the overall conduct of the study.*

Demographic and Baseline Characteristics

Table 7 provides a summary of subject demographic and baseline disease characteristics of the dapagliflozin and placebo groups.

Table 7. Demographics and Baseline Characteristics Randomized Population

	Dapagliflozin N=81	Placebo N=76	Total N=157
Sex, n (%)			
Female	49 (60.5)	44 (57.9)	93 (59.2)
Male	32 (39.5)	32 (42.1)	64 (40.8)
Age, years			
Mean (SD)	14.4 (2.00)	14.7 (1.64)	14.5 (1.83)
Median	15.0	15.0	15.0
IQR	13.0, 16.0	14.0, 16.0	13.0, 16.0
Min, Max	10.0, 17.0	11.0, 17.0	10.0, 17.0

	Dapagliflozin N=81	Placebo N=76	Total N=157
Age categories, n (%)			
>=10 and <15	38 (46.9)	35 (46.1)	73 (46.5)
>=15 and <18	43 (53.1)	41 (53.9)	84 (53.5)
Race, n (%)			
American Indian or Alaska Native	11 (13.6)	12 (15.8)	23 (14.6)
Asian	18 (22.2)	24 (31.6)	42 (26.8)
Black or African American	7 (8.6)	3 (3.9)	10 (6.4)
Native Hawaiian or Other Pacific Islander	0	3 (3.9)	3 (1.9)
Other	3 (3.7)	2 (2.6)	5 (3.2)
White	42 (51.9)	32 (42.1)	74 (47.1)
Ethnicity, n (%)			
Hispanic or Latino	45 (55.6)	34 (44.7)	79 (50.3)
Not Hispanic or Latino	36 (44.4)	42 (55.3)	78 (49.7)
Geographic Region 1, n (%)			
Asia/Pacific	19 (23.5)	23 (30.3)	42 (26.8)
Europe	11 (13.6)	17 (22.4)	28 (17.8)
Latin America	39 (48.1)	23 (30.3)	62 (39.5)
North America (United States)	12 (14.8)	13 (17.1)	25 (15.9)
Baseline BMI Z-score			
Mean (SD)	1.7 (0.72)	1.5 (0.83)	1.6 (0.79)
Median	1.8	1.6	1.7
IQR	1.5, 2.2	1.0, 2.1	1.2, 2.1
Min, Max	-1.8, 2.9	-1.7, 3.0	-1.8, 3.0
A1C at Baseline (%)			
Mean (SD)	8.2 (1.46)	8.0 (1.63)	8.1 (1.54)
Median	8.4	7.7	7.9
IQR	7.1, 9.3	6.6, 9.1	6.8, 9.2
Min, Max	5.1, 11.1	5.2, 12.0	5.1, 12.0
eGFR at Baseline (%)			
Mean (SD)	115 (21)	113 (21)	114 (21)
Median	114	111	112
IQR	97-130	95-127	96-129
Min, Max	68, 174	67, 166	67, 174
Background Diabetes Medication, n (%)			
Insulin	10 (12.3)	8 (10.5)	18 (11.5)
Metformin	42 (51.9)	39 (51.3)	81 (51.6)
Metformin and Insulin	29 (35.8)	29 (38.2)	58 (36.9)

Abbreviations: IQR = interquartile range, SD = standard deviation
No information was collected for "Other" category in race
Source: Statistical Review Table 4, Clinical Review Team (adsl.xpt)

Reviewer comment:
All subjects enrolled in Study 19 had A1C (%) values during screening between 6.5-10.5, inclusive. Subjects were not assessed for eligibility based on A1C criteria at the randomization visit. It is notable, but not unexpected, that both dapagliflozin and placebo groups reported minimum and maximum values for A1C at baseline outside of the eligibility thresholds (the screening visit could occur up to 6 months prior to randomization). Both treatment arms were

comprised of a sizable proportion of subjects with baseline A1C values below 6.5 (dapagliflozin 13.6% vs placebo 17.1%), and above 10.5 (dapagliflozin 3.7% vs placebo 9.2%). Notably, the median A1C was higher for the dapagliflozin group (dapagliflozin 8.4 vs placebo 7.7), and the standard deviation was greater for the placebo group (dapagliflozin 1.46 vs placebo 1.63). The resulting mean A1C (%) values were similar between treatment groups (dapagliflozin 8.2 and placebo 8.0). Of note, per the study protocol, A1C was not a stratification factor.

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 anti-diabetic therapy). The "typical" patient studied was a white, obese[20], 14 to 15 year-old, female, moderately uncontrolled (A1C ~ 8.0%) on metformin alone. There is also good representation of male and female subjects using basal insulin with or without metformin. The study population was diverse in terms of ethnicity (50% Hispanic or Latino) and inclusion of subjects of Asian (~27%) and American Indian or Alaskan Native (~15%) descent. However, Black or African American subjects, despite being the race with the highest prevalence of pediatric T2D in 2017[21], were under-represented in this study (~7% of the study population). Importantly, only 15% of enrolled subjects were from the US. Despite these important differences, the enrolled population is generally like enrolled populations of other pediatric T2D studies, including those with a higher US enrollment.

A weakness of the study is that it enrolled relatively few US and African American subjects. The Applicant cites that the patient population from the US was generally comparable with the non-US population in terms of patient disposition, demographics, characteristics, and baseline disease characteristics. Although the Applicant concludes that any imbalances observed were possibly due to the low numbers in the US population subgroup, and/or differences due to the ethnic make-up of the two populations, some concerns remain about the generalizability of the results to the US patient population. On the other hand, the subgroup analyses for the primary endpoint, particularly those involving geographical location or race, were generally consistent with the marginal estimate. We also note that other placebo-controlled trials of both adult and pediatric patients treated with an SGLT2 inhibitor did not identify potentially meaningful heterogeneity in the primary endpoint for geography or race. These observations provide some reassurance that the results of Study 19 are generalizable to the US population.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment Compliance

During the trial, subjects were considered compliant with their investigational treatment regimen if their adherence rates, based on tablet counts, were between 80 and 120%. During

[20] The mean BMI Z-score was 1.67, corresponding to the 90th percentile for BMI based on age and gender matched controls

[21] Lawrence 2021 - https://pubmed.ncbi.nlm.nih.gov/34427600/

the ST period, 87.8% of enrolled subjects met this definition and this was similar between treatment arms (84.0% with dapagliflozin vs 88.2% placebo). Comparable compliance was noted during the LT period.

Concomitant Medications

As expected for an otherwise healthy pediatric population, treatment emergent use of new concomitant medications was not particularly common. The most common treatment emergent non-diabetes medications used by subjects during the ST period included paracetamol (15.9%) and vitamin D and analogues (8.6%). There were no notable imbalances between treatment arms that might be reasonably considered to contribute to any between-arm differences in safety or efficacy.

Rescue Medications

The proportion of subjects who required glycemic rescue medication or discontinued study drug due to lack of efficacy was lower in the dapagliflozin group than the placebo group during the ST period: dapagliflozin 2.5% (2/81) vs placebo 14.5% (11/76). During the ST+LT period, this proportion continued to be lower for the dapagliflozin group: dapagliflozin 28.4% vs placebo 46.1%.

Reviewer Comment: *The primary efficacy analysis was based on the change in A1C, regardless of rescue (i.e., treatment policy estimand), which doesn't penalize the placebo arm for glycemic rescue. Rescued subjects, no matter how "potent" the rescue therapy, are still considered to be on the placebo regimen. An estimand strategy which focused on a "true" placebo control (i.e., a hypothetical estimand where rescue therapy did not occur) would likely reveal a larger treatment effect. This is not particularly worrisome for a positive trial with a potent investigational product.*

Efficacy Results – Pooled Treatment Comparisons (Primary and Secondary Endpoints)

The primary endpoint for Study 19 was change in A1C from baseline at Week 26 regardless of rescue, and the results of the primary efficacy analysis are presented in Change from baseline in FPG at Week 26 was a secondary efficacy endpoint of Study 19. As summarized in **Table 8**, a significant difference was noted between the dapagliflozin pooled group and the placebo group with respect to FPG change from baseline with the placebo-adjusted treatment effect (95% CI) of -19.5 (-36.4, -2.5). This result further supports the finding of efficacy of dapagliflozin demonstrated in the primary analysis. Comparable differences for reduction in FPG from baseline at Week 26 favoring dapagliflozin over placebo were noted for the low-dose/high-dose and low-dose/low-dose treatment groups.

Table 8. The FDA analyses conducted by Dr. Kim replicated the Applicant's results presented in the submission. The primary efficacy analysis demonstrated a statistically superior and clinically

important treatment difference favoring dapagliflozin. The mean difference (95% CI) in A1C change from baseline at Week 26 was -1.03 (-1.57, -0.49) for dapagliflozin pooled vs placebo, with a two-sided p-value less than 0.001.

The degree of missing endpoint data was very low (7-8%) and balanced between treatment arms. Nonetheless, Dr. Kim performed a sensitivity analysis (assuming a return-to-baseline imputation model rather than a placebo washout imputation model) and a 2-way tipping point analysis. The findings of these analyses confirmed the robustness of the primary analysis with respect to missing data assumptions. For additional details of this analysis, see the Clinical Statistical Review by Dr. Kim.

Change from baseline in FPG at Week 26 was a secondary efficacy endpoint of Study 19. As summarized in **Table 8**, a significant difference was noted between the dapagliflozin pooled group and the placebo group with respect to FPG change from baseline with the placebo-adjusted treatment effect (95% CI) of -19.5 (-36.4, -2.5). This result further supports the finding of efficacy of dapagliflozin demonstrated in the primary analysis. Comparable differences for reduction in FPG from baseline at Week 26 favoring dapagliflozin over placebo were noted for the low-dose/high-dose and low-dose/low-dose treatment groups.

Table 8. Pooled Treatment Comparison: Primary and Secondary Analysis of A1C and FPG Change from Baseline at Week 26

	Dapagliflozin pooled [5 mg & 10 mg] QD N=81	Placebo N=76
Primary Efficacy Analysis (Change from Baseline in A1C)		
Baseline, Mean (SD)	8.22 (1.46)	7.96 (1.63)
Week 26 Missing, n (%)	6 (7.4)	6 (7.9)
Change from baseline to Week 26[1], LS Mean (SE)	-0.62 (0.22)	0.41 (0.22)
Comparison to Placebo[1] LS Mean difference (95% CI) Two-sided P-value		 -1.03 (-1.57, -0.49) <0.001
Secondary Analysis (Change from Baseline in Fasting Plasma Glucose)		
Baseline, Mean (SD)	162.24 (64.54)	152.01 (57.18)
Week 26 Missing, n (%)	6 (7.4)	8 (10.5)
Change from baseline to Week 26, LS Mean (SE)	-10.27 (6.73)	9.23 (6.91)
Comparison to Placebo LS Mean difference (95% CI)		 -19.49 (-36.42, -2.56)

Source: Statistical Review Table 1 and Table 12Abbreviations: CI = confidence interval, LS = least square, SD = standard deviation, SE = standard error, QD = 1 daily

[1]The LS mean estimate is based on an ANCOVA model adjusted for baseline A1C (or baseline FPG), baseline age stratum (<15 years vs 15 to <18 years), sex, background antidiabetic medication (metformin only vs insulin ± metformin), and treatment after imputing missing endpoint using placebo washout method.

The analysis was performed in the mITT using all observed data.
Source: Statistical Review Table 1 and Table 12

Proportion of Subjects Achieving an A1C below 7% at 26 Weeks

Secondary efficacy assessments also included the proportion of subjects achieving A1C < 7.0% (i.e., responders) at Week 26. The Applicant assessed this endpoint for the pooled dapagliflozin group vs placebo in the subset of subjects who had A1C ≥7% at baseline, as presented in **Table 9**. The adjusted odds ratio (95% CI) of achieving this glycemic target was 3.82 (1.24, 11.70) for the pooled dapagliflozin group compared to placebo. For the purposes of clinical trial data to be placed into Section 14 of the prescribing information (PI), the statistical team prefers that the assessment include all randomized subjects rather than a subset, as presented in **Table 10.** With the inclusion of the additional 17 subjects in the dapagliflozin group and 26 in the placebo group having A1C <7% at baseline, the adjusted odds achieving A1C < 7% at Week 26 ratio was 2.16 (0.98, 4.73) for the pooled dapagliflozin group compared to placebo. The odds ratio was no longer statistically significant because the confidence interval included 1; however, the proportion of subjects achieving this glycemic target remained numerically higher for the dapagliflozin group (dapagliflozin 34.6% vs placebo 25.0%) and continues to support the efficacy of dapagliflozin.

Table 9. Proportion of Subjects Achieving A1C < 7.0% at Week 26 in the Subset of Subjects with Baseline A1C ≥ 7.0%

	Dapagliflozin pooled [5 mg & 10 mg] QD N=64	Placebo N=50
# known responders (A1C < 7.0%) at Week 26, n (%)	17 (26.6)	5 (10.0)
Average # of responders across imputed datasets, n (%)	18.5 (37.0)	5.12 (8.0)
Comparison to Placebo Adjusted Odds Ratio (95% CI)		3.82 (1.24, 11.70)

Abbreviations: CI = confidence interval, QD = 1 daily
Secondary efficacy analysis is based on multiple imputations using placebo wash-out model. 200 datasets were generated, and each dataset was analyzed with logistic regression, adjusted for treatment, sex, age group (10-14/15-<18), background antidiabetic medication (metformin only vs insulin ± metformin), baseline A1C. The analysis was performed in the mITT using all observed data.
Source: Statistical Review Table 13

Table 10. Proportion of Subjects Achieving A1C < 7.0% at Week 26 in all Randomized Subjects

	Dapagliflozin pooled [5 mg & 10 mg] QD N=81	Placebo N=76
Subjects with A1C < 7.0% at baseline, n (%)	17 (21.0)	26 (34.2)

# known responders (A1C < 7.0%) at Week 26, n (%)	28 (34.6)	19 (25.0)
Average # of responders across imputed datasets, n (%)	29.6 (36.6)	20.1 (26.5)
Comparison to Placebo Adjusted Odds Ratio (95% CI)		2.16 (0.98, 4.73)

Abbreviations: CI = confidence interval, QD = once daily
Secondary efficacy analysis is based on multiple imputations using placebo wash-out model. 200 datasets were generated, and each dataset was analyzed with logistic regression, adjusted for treatment, sex, age group (10-14/15-<18), background antidiabetic medication (metformin only/insulin ± metformin), baseline A1C. The analysis was performed in the mITT using all observed data.
Source: Statistical Review Table 14

Reviewer comment: *The most likely treatment effect on A1C based on the data (point estimate) and a conservative estimate of effect (lower bound of the 95% confidence interval) are clinically meaningful by a large margin.*

The results of the secondary endpoint efficacy analyses provide additional supportive evidence for the efficacy of dapagliflozin for glycemic control in the pediatric population with T2D. A significant difference favoring the dapagliflozin pooled group vs the placebo group was noted for the FPG change from baseline at Week 26. In addition, the odds ratio for the proportion of subjects achieving A1C target of < 7% at Week 26 was greater for the pooled dapagliflozin group compared to placebo.

Of note, there is a baseline treatment imbalance in A1C (approximately 0.28%) and FPG not favoring the placebo group.

Assessment of Dose-Response Relationship for Efficacy

The hierarchical testing of TITR10 vs TITR5 for change from baseline in A1C at Week 26 occurred after the assessments for the pooled dapa, low-dose/high-dose, and low-dose/low-dose treatment groups for the primary and secondary endpoints. This dose-response assessment only occurs in subjects randomized to dapagliflozin 5mg, who are deemed non-responders (i.e., did not achieve A1C of < 7% after 12 weeks of treatment with dapagliflozin 5 mg). These subjects underwent a 2nd randomization to either remain on the dose of dapagliflozin 5 mg or up-titrate to dapagliflozin 10 mg. As summarized in **Table 11**, the treatment difference of dapagliflozin 10 mg vs dapagliflozin 5 mg in A1C at Week 26 in subset of non-responders was negligible at -0.03 (95% CI -1.00 to 0.94). Note the sample size is 21 subjects per arm, approximately one-quarter of the sample size needed for an adequately powered comparison to placebo in the primary endpoint (e.g., 81 vs 76).

Table 11. A1C (%) Change from Baseline at Week 26, Subset of Dapagliflozin Non-responders

	TITR10 N=21	**TITR5 N=21**
Baseline, Mean (SD)	8.74 (1.33)	9.00 (0.90)

Week 26 Missing, n (%)	2 (9.5)	0
Change from baseline to Week 26, LS Mean (SE)	-0.78 (0.34)	-0.76 (0.32)
LS Mean difference (95% CI)		-0.03 (-1.00, 0.94)

Abbreviations: CI = confidence interval, LS = least square, SD = standard deviation, SE = standard error
Primary efficacy analysis is based on multiple imputations using placebo washout. 200 datasets were generated, and each dataset was analyzed with ANCOVA, adjusted for treatment, sex, age group (10-14/15-<18), background antidiabetic medication (metformin only/insulin ± metformin), baseline A1C. The analysis was performed in the mITT using all observed data.
Source: Statistical Review Table 9

Table 12 summarizes the change in A1C that occurred between Week 12 and Week 26 for the non-responders. To explore potential factors that may have contributed to the "null" dose-response findings, the baseline demographic and metabolic parameters for TITR10 and TITR5 groups were investigated. Notably, the mean reduction in A1C from baseline at Week 12, prior to the second randomization, differed between TITR10 and TITR5 groups. TITR10 had Week 12 A1C of 8.40%, with a change from baseline in A1C of -0.34%, and TITR5 had a Week 12 A1C of 7.73%, with a change from baseline in A1C of -1.27%. This chance imbalance likely contributed to the lack of dose-response relationship observed at 26 weeks.

Table 12. Baseline Demographic and Disease Characteristics for TITR10 vs TITR5 and A1C (%) Change from Week 12 at Week 26, Subset Dapagliflozin Non-responders

	TITR10 N=21	TITR5* N=20
Baseline Characteristics		
Baseline A1C % (mean (SD))	8.74 (1.3)	9.00 (0.9)
Fasting Plasma Glucose, mg/dL (mean (SD))	165 (70)	196 (68)
eGFR mL/min/1.73m^2 (mean (SD))	112.8 (20.9)	116.5 (21.9)
Body Weight kg (SD)	73.9 (14.9)	82.1 (22.1)
Body Mass Index, kg/1.73 m^2(mean (SD))	29.2 (4.5)	30.9 (6.2)
Baseline Antidiabetic Medication (%)		
Insulin	3 (14.3)	2 (10.0)
Metformin	7 (33.3)	13 (65.0)
Metformin + Insulin	11 (52.4)	5 (25.0)
Duration of Diabetes, years (mean (SD))	2.8 (1.8)	2.8 (2.2)
Age years (SD)	14.3 (2.1)	14.2 (2.1)
Sex (% Male)	9 (42.9)	6 (30.0)
Race (%)		
AMERICAN INDIAN OR ALASKA NATIVE	3 (14.3)	3 (15.0)
ASIAN	1 (4.8)	6 (30.0)
BLACK OR AFRICAN AMERICAN	2 (9.5)	1 (5.0)
OTHER	1 (4.8)	1 (5.0)
WHITE	14 (66.7)	9 (45.0)
Region (%)		
Asia/Pacific	1 (4.8)	7 (35.0)
Europe	3 (14.3)	5 (25.0)

Latin America	14 (66.7)	5 (25.0)
North America	3 (14.3)	3 (15.0)
Treatment Emergent A1C		
Week 12, Mean (SD)	8.40 (1.17)	7.73 (0.73)
Week 26 Missing, n (%)	2 (9.5)	0
Change from Week 12 to Week 26, LS Mean (SE)	0.11 (0.31)	-0.03 (0.31)
LS Mean difference (95% CI)	0.14 (-0.78, 1.06)	

Source: Clinical Review Team (adsl.xpt) and Statistical Review Table 10
Abbreviations: CI = confidence interval, LS = least square, SD = standard deviation, SE = standard error
Primary efficacy analysis is based on multiple imputations using placebo washout. 200 datasets were generated, and each dataset was analyzed with ANCOVA, adjusted for treatment, sex, age group (10-14/15-<18), background antidiabetic medication (metformin only/insulin ± metformin), A1C at Week 12. The analysis was performed in the mITT using all observed data.
*One subject in the safety population randomized to dapa, and rerandomized to stay on dapagliflozin 5mg did not have a week 12 A1C measurement and thus was omitted from this analysis.

***Reviewer comment**: **Table 12** highlights some baseline imbalances that could explain the discrepant dose-related A1C findings. The TITR5 group was significantly heavier than TITR10, with mean baseline weight of 82.1 kg vs 73.9 kg, respectively. The majority (52%) of subjects were treated with insulin + metformin in the TITR10 group, whereas 25% of the TITR5 group received insulin + metformin. The greater proportion of subjects in the TITR10 group requiring dual therapy is suggestive of a group with more advanced disease. Overall, there are several baseline imbalances noted in both prognostic and treatment-predictive factors between TITR5 and TITR10.*

There are multiple limitations with the design of Study 19 which do not allow for a proper assessment of dose-response relationship for dapagliflozin 5 mg vs dapagliflozin 10 mg. First, the potential for exposure to dapagliflozin 10 mg was limited to only a subset of the total study population namely, non-responders to the 5 mg dose at Week 12. In addition, by virtue of the 2nd randomization, the dose-response comparison equates to an analysis from a small, nested, sub-study of strictly the non-responder population which is not a clinically meaningful therapeutic experiment. Further, the resulting sub-groups of TITR5 and TITR10 include only 21 subjects each, and these small samples increase the liability of baseline imbalances (and associated variability in treatment differences), as evidenced in **Table** 12 *and discussed above. There were several imbalances, some potentially favoring the TITR10 arm, some potentially favoring the TITR5 arm, but all imbalances had unclear clinical significance. Most importantly, the sample size of this sub-study is insufficiently powered for a placebo-controlled comparison, let alone a dose-response analysis.*

Nevertheless, the inclusion of the 10 mg dose of dapagliflozin in labeling for the pediatric population is supported by the robust demonstration of dose-response relationship in adults with T2D. We also note a dose-response for urine glucose excretion, a key pharmacodynamic

endpoint directly related to the mechanism of action. Also, PK similarity for dapagliflozin is noted in the adult and the pediatric populations. Together, these data support the labeling for 5 mg and 10 mg for dapagliflozin in the pediatric population with T2D.

Assessment of Durability of Response for Efficacy

The difference in change in A1C from baseline at Week 52 (**Table 13**) demonstrated greater effect treatment of the pooled dapagliflozin group vs placebo: the placebo adjusted treatment effect was -1.13 (-1.90, -0.36). Although this finding is suggestive of durability efficacy of dapa, the data required weighted analyses by exclusion of subjects who were randomized to undergo withdrawal of metformin and, therefore, the results are considered exploratory.

Table 13. A1C Change from Baseline at Week 52, Exploratory Analysis

	Dapagliflozin pooled [5 mg & 10 mg] QD N=81	Placebo N=76
Baseline, Mean (SD)	8.22 (1.46)	7.96 (1.63)
Week 52 Missing, n (%)	10 (12.3)	15 (19.7)
Change from baseline to Week 52, LS Mean (SE)	-0.20 (0.32)	0.94 (0.32)
Comparison to Placebo LS Mean difference (95% CI)		-1.13 (-1.90, -0.36)

Abbreviations: CI = confidence interval, LS = least square, SD = standard deviation, SE = standard error
Exploratory efficacy analysis is based on multiple imputations using placebo washout. 200 datasets were generated, and each dataset was analyzed with ANCOVA, adjusted for treatment, sex, age group (10-14/15-<18), background antidiabetic medication (metformin only/insulin + metformin), baseline A1C. The analysis was performed in the mITT using all observed data.
Source: Statistical Review Table 8

Additional Analyses Conducted on the Individual Trial

Low-dose/High-dose Regimen (dapagliflozin responders + TITR10) vs Placebo

The low-dose/high-dose treatment regimen group included 39 dapagliflozin responders (includes the 34 responders and the subjects who discontinued study drug/study before Week 14 [n=4] and the subjects on study drug but missed Week 14 visit [n=1]) and 21 dapagliflozin non-responders up-titrated to dapagliflozin 10 mg (TITR10) after 2nd randomization. Results comparing the change in A1C from baseline at Week 26 for this group vs placebo is presented in **Table** 14**.** The placebo-adjusted treatment effect (95% CI) was -0.86 (-1.44, -0.27) for the low-dose/high-dose group.

Table 14. A1C (%) Change from Baseline at Week 26, Low-dose/High-dose vs Placebo

	TITR10 + Responders N=60	Placebo N=76
Baseline, Mean (SD)	7.94 (1.52)	7.96 (1.63)
Week 26 Missing, n (%)	6 (10)	6 (7.9)
Change from baseline to Week 26, LS Mean (SE)	-0.42 (0.21)	0.43 (0.21)
Comparison to Placebo LS Mean difference (95% CI)		-0.86 (-1.44, -0.27)

Abbreviations: CI = confidence interval, LS = least square, SD = standard deviation, SE = standard error
Primary efficacy analysis is based on multiple imputations using placebo washout. 200 datasets were generated, and each dataset was analyzed with ANCOVA, with the application of inverse probability weighting, adjusted for treatment, sex, age group (10-14/15-<18), background antidiabetic medication (metformin only/insulin ± metformin), baseline A1C. The analysis was performed in the mITT using all observed data.
Source: Statistical Review Table 7

Low-dose/Low-dose Regimen (dapagliflozin responders + TITR5) vs Placebo

The low-dose/low-dose treatment regimen group included 39 dapagliflozin responders and 21 dapagliflozin non-responders remaining on dapagliflozin 5 mg (TITR5) after 2nd randomization. Results comparing the change in A1C from baseline at Week 26 for this group vs placebo is presented in **Table 15.** The placebo-adjusted treatment effect (95% CI) was -1.19 (-1.76, -0.62) for low-dose/low-dose group.

Table 15. A1C (%) Change from Baseline at Week 26, Low-dose/Low-dose vs Placebo

	TITR5 + Responders N=60	Placebo N=76
Baseline, Mean (SD)	8.03 (1.47)	7.96 (1.63)
Week 26 Missing, n (%)	4 (6.7)	6 (7.9)
Change from baseline to Week 26, LS Mean (SE)	-0.79 (0.20)	0.43 (0.21)
Comparison to Placebo LS Mean difference (95% CI)		-1.19 (-1.76, -0.62)

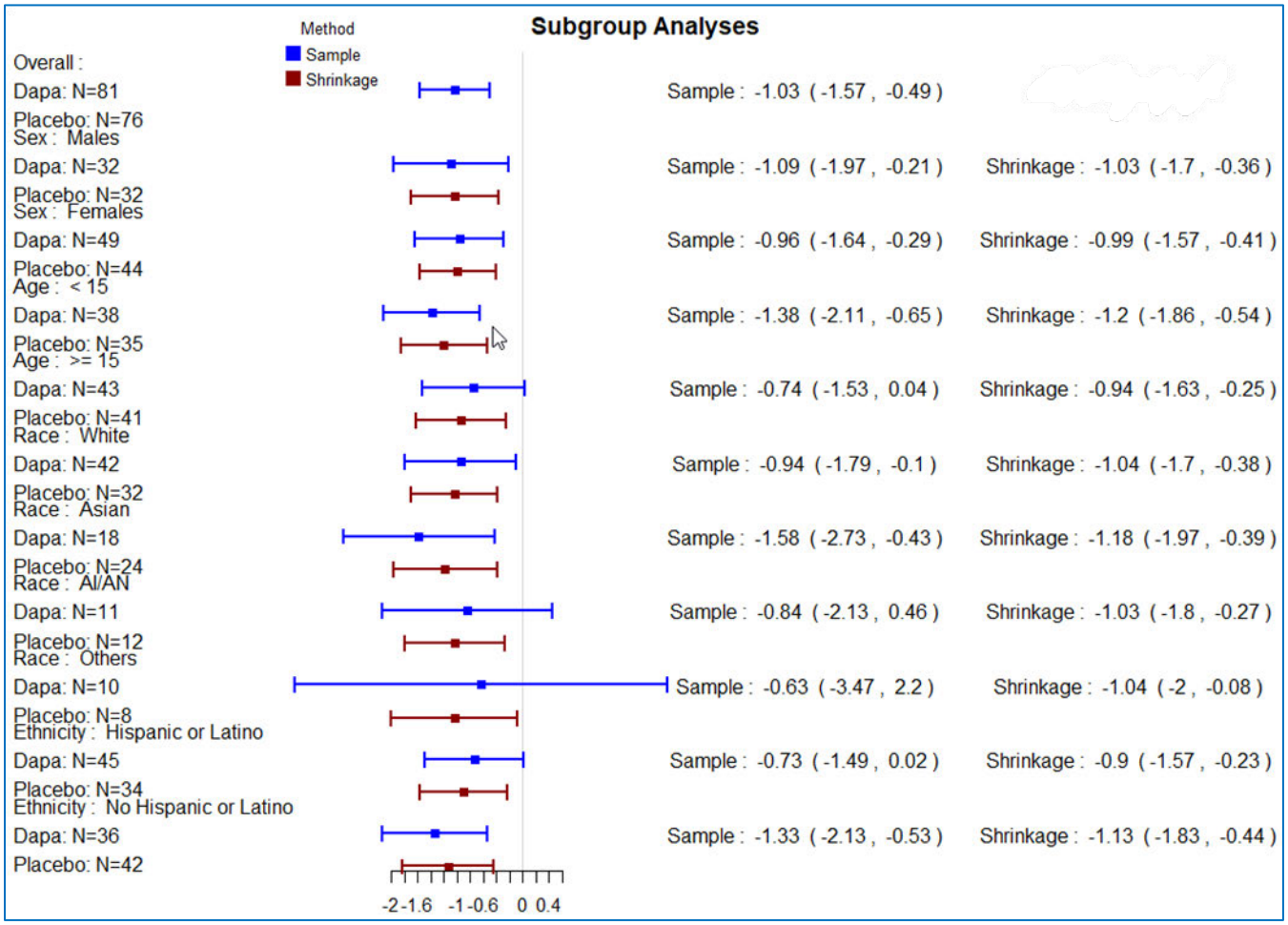
Abbreviations: CI = confidence interval, LS = least square, SD = standard deviation, SE = standard error
Primary efficacy analysis is based on multiple imputations using placebo washout. 200 datasets were generated, and each dataset was analyzed with ANCOVA, with the application of inverse probability weighting, adjusted for treatment, sex, age group (10-14/15-<18), background antidiabetic medication (metformin only/insulin ± metformin), baseline A1C. The analysis was performed in the mITT using all observed data.
Source: Statistical Review Table 8

Reviewer comment: *Both low-dose/low-dose and low-dose/high-dose dapagliflozin treatment regimens demonstrated statistically significant reductions in A1C compared to placebo, providing further support for the efficacy of dapagliflozin for glycemic control in the pediatric population with T2D. It is notable that the mean A1C reduction from baseline at Week 26 demonstrated an inverse dose-response relationship: A1C reduction was greater for the group continuing the lower dose of dapagliflozin 5 mg than the group up-titrated to dapagliflozin 10 mg. The various issues contributing to this aberrant finding have already been reviewed above in the Assessment of Dose-Response Relationship for Efficacy subsection of* ***Section 6.1.2****.*

Subpopulations

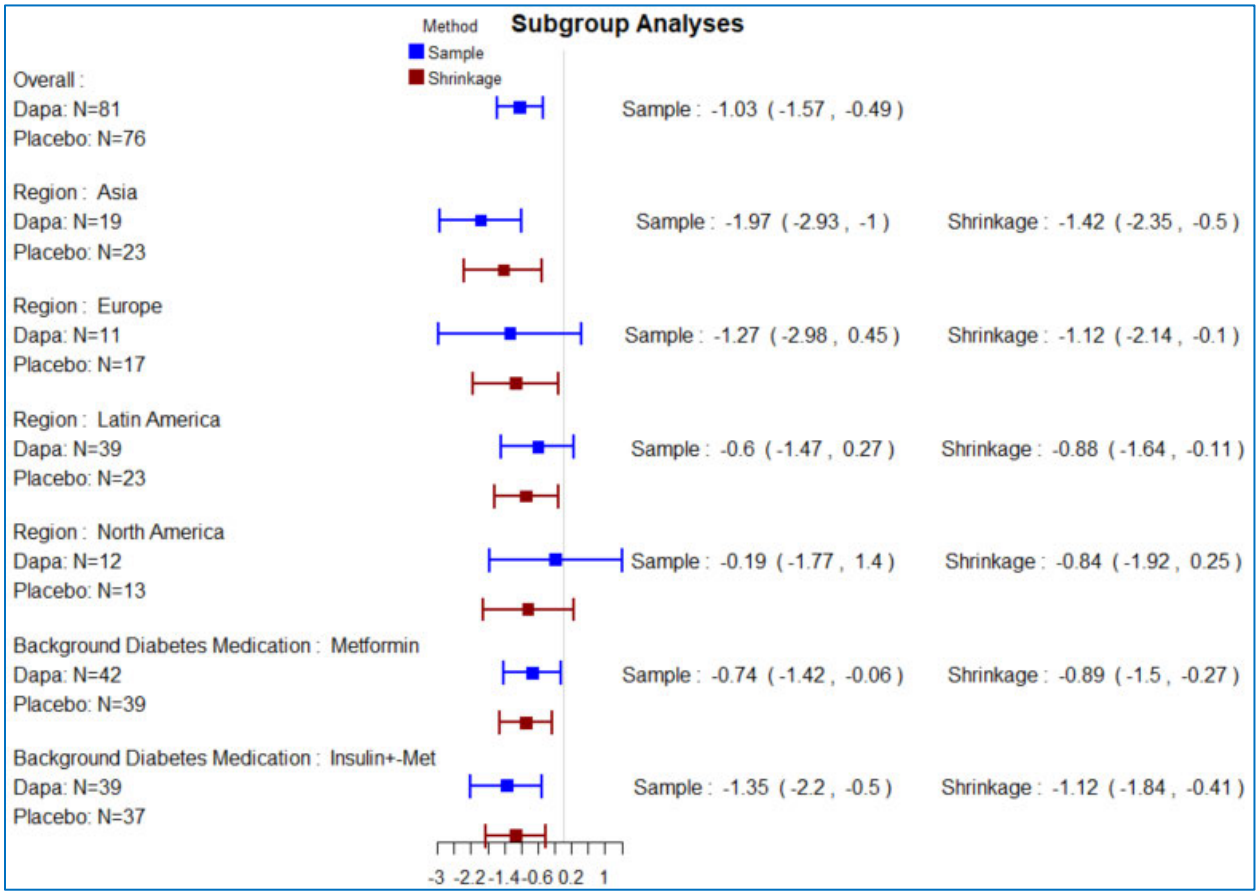
Dr. Kim conducted subgroup analyses on the primary efficacy endpoint. The sample estimates and the shrinkage estimates of the treatment difference with respect to A1C change from baseline at Week 26 are presented for subgroup levels defined by sex, age, race, ethnicity (**Figure 2.**), and region and background antidiabetic medication (**Figure 3**). The plots include the corresponding 95% confidence and credible intervals for the sample and shrinkage estimates, respectively. Compared to the sample estimate, the shrinkage estimate had less variability and a magnitude closer to the overall estimate. Subgroup analyses are consistent with primary analysis results which shows homogeneous treatment effects of dapagliflozin across different subpopulations. No significant interactions were found between subgroups and treatment.

Figure 2. Forest Plot of Subgroup Analyses for Sex, Age, Race, and Ethnicity: Placebo-Adjusted A1C (%) Change from Baseline at Week 26



Abbreviations: AI/AN = American Indian or Alaska Native
Values on the negative side favor dapagliflozin, values on the positive side favor placebo.
Source: Statistical Review Figure 3

Figure 3. Forest Plot of Subgroup Analyses for Region and Background Antidiabetic Medication: Placebo-adjusted A1C (%) Change from Baseline at Week 26



Values on the negative side favor dapa, values on the positive side favor placebo. North America indicates US. Background diabetes medication group of Insulin ± Metformin include Insulin only (n=18) or Insulin with Metformin (n=58). For the Insulin only group, the mean baseline A1C was 7.84 and 7.46 for dapagliflozin (n=10) and placebo (n=8) arms, respectively. The mean change from baseline to Week 26 in A1C was -0.88 and 1.07 for dapagliflozin and placebo arms, respectively. For the Insulin with Metformin group, the mean baseline A1C was 8.79 and 8.48 for dapagliflozin (n=29) and placebo (n=29) arms, respectively. The mean change from baseline to Week 26 in A1C was -1.23 and 0.57 for dapagliflozin and placebo arms, respectively.
Source: Statistical Review Table 4

Background Metformin

Subgroup analysis was performed to examine the treatment effect of dapagliflozin in combination with metformin. A total of 139 subjects (71 dapagliflozin pooled and 68 placebo) were treated with background metformin ± insulin in the cohort. Dr. Kim's analysis confirmed that the estimated treatment effect for the subset of subjects receiving concomitant metformin was consistent with that of the overall population: the placebo-adjusted treatment effect for dapagliflozin with respect to A1C change from baseline at Week 26 was -1.01% (95% CI -1.57 to

-0.45).

The Applicant conducted an additional post-hoc subgroup analysis comparing efficacy of pooled dapagliflozin group by the background metformin formulation (IR vs XR). Background metformin IR resulted in a treatment difference of -0.87% (95% CI -1.57 to -0.16) and background metformin XR resulted in a difference of -1.23% (95% CI -2.27 to -0.18).

These exploratory efficacy analyses were consistent with the results of the primary efficacy analysis, supporting the efficacy of dapagliflozin in combination with all formulations of metformin in the pediatric population with T2D.

7. Integrated Review of Effectiveness

This application includes an adequate demonstration of substantial evidence of effectiveness of Farxiga for glycemic control in the pediatric population with T2D. This is provided by the efficacy analyses from Study 19 (an adequate and well-controlled study) along with confirmatory evidence derived from the previous finding of effectiveness of dapagliflozin 5 and 10 mg in adult patients with T2D from the adult phase 3 program.

The scientific bridge provided by the Applicant adequately justifies the proposal to rely on the Agency's previous findings of safety and effectiveness of Glucophage IR for Xigduo XR to broaden the glycemic control indication with the addition of pediatric patients. Together, the submitted data and information support the broadened indication "as an adjunct to diet and exercise to improve glycemic control in adults and pediatric patients aged 10 years and older with type 2 diabetes mellitus" for both Farxiga and Xigduo XR.

7.1. Integrated Assessment of Effectiveness: Dapagliflozin Component

The primary objective of Study 19 was to demonstrate that treatment with dapagliflozin provides superior glycemic control compared to placebo, as measured by the change from baseline A1C 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 is a validated surrogate clinical endpoint, study procedures reasonably approximated routine clinical practice, and the enrolled population reasonably represented the US pT2DM population. The Agency was appraised of changes throughout the planning and execution of this protocol and did not note any objectionable design elements.

In Study 19, the primary efficacy analysis of the primary endpoint was met, demonstrating superiority of the pooled dapagliflozin group compared to placebo for A1C change from

baseline at Week 26: the placebo-adjusted treatment difference was -1.03% (95% CI -1.57 to -0.49; $p < 0.001$). The results of the primary analysis were robust to sensitivity analyses using alternative missing data assumptions. These results are statistically persuasive (even a pessimistic statistical view of the results, such as the lower 95% confidence interval, are clinically relevant). The primary endpoint was supported by statistically significant differences in secondary endpoints that were consistent the results of the primary endpoint (e.g., FPG and responder analyses). Although a cross-study comparison, the PK and PD (UGE) is similar to adults. These findings, along with the robust clinical efficacy findings in adults, constituted substantial evidence of effectiveness for dapagliflozin.

One key shortcoming of Study 19 is that it was not adequately designed to rigorously establish a dose-response relationship. Based on the data that was observed, one might reasonably be concerned that up titration to 10 mg does not provide additional benefits. The comparison of A1C reduction from baseline at Week 26 of the non-responders up-titrated to 10 mg to the non-responders remaining on 5 mg, did not demonstrate a difference in treatment effect between doses [treatment difference 10 mg vs 5 mg of the non-responders: -0.03 (95% CI -1.00 to 0.94)]. Of note, the clinical pharmacology review team did not provide a recommendation for the 10 mg dose but deferred to the clinical team. The clinical review team recommends approval of both the 5 mg and 10 mg doses in the pediatric population. The efficacy of 10 mg is supported by the robust demonstration of dose-response relationship in adults with T2D. We also note a dose-response for urine glucose excretion, a key pharmacodynamic endpoint directly related to the mechanism of action.

In addition to improving glycemic control in adults with T2D, dapagliflozin has demonstrated efficacy in improving various cardiorenal outcomes in adults with heart failure and chronic kidney disease at risk for progression in both diabetic and non-diabetic populations. It is thus highly likely that treatment with dapagliflozin will confer these protective benefits to pediatric patients with T2D as well. The approval of dapagliflozin will provide a second SGLT-2 inhibitor to the armamentarium of anti-diabetes therapeutics. An additional benefit with the approval of Xigduo XR will be the availability of the first FCD product with once-daily dosing for the pediatric population with T2D. Patient compliance with medications is known to be improved by reducing the frequency of dosing[22] and FDC products have the additional advantage of reducing pill burden and simplifying medication regimens which can also lead to improved adherence to pharmacological therapy[23]and therefore, potentially better clinical outcomes.

[22] Paes AH, Bakker A, Soe-Agnie CJ. Impact of dosage frequency on patient compliance. Diabetes Care. 1997 Oct;20(10):1512-7. doi: 10.2337/diacare.20.10.1512. PMID: 9314626.
[23] Böhm AK, Schneider U, Aberle J, Stargardt T. Regimen simplification and medication adherence: Fixed-dose versus loose-dose combination therapy for type 2 diabetes. PLoS One. 2021 May 4;16(5):e0250993. doi: 10.1371/journal.pone.0250993. PMID: 33945556; PMCID: PMC8096115.

7.2 Integrated Assessment of Effectiveness: Xigduo XR

The original approval of Xigduo XR was based on the demonstration of bioequivalence of 5/500 mg and 10/1000 mg dapagliflozin/metformin XR FDC formulations to their individual components administered together in the fasted state[24]. Clinical efficacy and safety of the individual components of dapagliflozin and metformin XR in the adult population with T2D were previously demonstrated in the Farxiga and Glucophage XR (metformin HCl extended release, NDA 021202) programs, respectively. The efficacy and safety of these components administered in combination were based upon the review of data from twelve previously conducted phase 3 studies from the Farxiga clinical program[25]. Importantly, no pediatric efficacy studies have been conducted using Xigduo XR, and Glucophage XR (to which Xigduo XR has demonstrated bioequivalence to) does not have a pediatric indication for which to "bridge".

During this review, the review team determined there was insufficient information submitted in NDA 205649/S-022 to support the proposed pediatric indication for Xigduo XR. FDA sent an information request (IR) to the Applicant requesting a scientific justification and/or supporting information (i.e., a scientific bridge) to support the efficacy of Xigduo XR (n.b., the metformin XR component of Xigduo XR) for the pediatric population with T2D.

The Applicant responded with an amendment to NDA 205649/S-022 (Xigduo XR) from a 505(b)(1) to a 505(b)(2) supplement, proposing to rely on the Agency's previous findings of safety and effectiveness of Glucophage (metformin HCL immediate release; NDA 020357) and Glucophage XR (available in the Glucophage IR/Glucophage XR US prescribing information (USPI) to support broadening the population for the glycemic control indication for Xigduo XR to include pediatric patients aged 10 years and older. The USPI for Glucophage IR (NDA 020357, approved 1998) and Glucophage XR (approved 2000) is provided in a joint label[26]. Glucophage IR is indicated to improve glycemic control in both adults and pediatric patients with T2D age 10 and above while Glucophage XR does not have the pediatric indication[27]. However, there is data and information within the joint label to support the efficacy and safety of Glucophage XR in the pediatric population with T2D and the relevant information is excerpted:

[24] The dapagliflozin/metformin XR FDC program consisted of five biopharmaceutical studies (three relative bioavailability [BA] and two bioequivalence [BE] studies).
[25] See primary clinical review for Xigduo XR by Dr. Kaveeta Vasisht under NDA 205649.
[26] NDA 020357 Glucophage IR & NDA 021202 Glucophage XR label
[27] Glucophage XR was approved in October 2000, prior to PREA enactment in 2003, and was retroactively subject to PREA. From review of the administrative record, in 2004, a deferral was issued for two deferred pediatric studies for Glucophage XR: a pediatric PK study and a 24-week active controlled trial (Glucophage IR vs Glucophage XR). In 2006, a pediatric waiver was granted based on the application holder's argument that adult utilization of Glucophage XR was low and that the product was not anticipated to be used substantially by pediatric patients.

Safety and efficacy in pediatric population with T2D are established for Glucophage IR.

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 in Table 9.

Table 9: Mean Change in Fasting Plasma Glucose at Week 16 Comparing GLUCOPHAGE vs Placebo in Pediatric Patients with Type 2 Diabetes Mellitus

	GLUCOPHAGE	***Placebo***	***p-Value***
FPG (mg/dL)	***(n=37)***	***(n=36)***	
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.

PK similarity for Glucophage IR is noted between the pediatric patients and adults.

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.
Section 14.1 Clinical Studies - GLUCOPHAGE
Efficacy similar to that observed in the pediatric T2DM study (mean change in fasting plasma glucose (FPG) -42.9 mg/dL from baseline to Week 16; Table 9 in the USPI) was

seen in an adult T2DM study (mean change in FPG -53.0 mg/dL from baseline to Week 29; Table 7 in the USPI)

Safety, efficacy, & exposure are similar between Glucophage IR and Glucophage XR in adults

Section 2.1 Dosage and Administration – Adult Dosage
Patients receiving GLUCOPHAGE may be switched to GLUCOPHAGE XR once daily at the same total daily dose, up to 2000 mg once daily.
Section 12.3 Pharmacokinetics
The extent of metformin absorption (as measured by AUC) from GLUCOPHAGE XR at a 2000 mg once-daily dose is similar to the same total daily dose administered as GLUCOPHAGE tablets 1000 mg twice daily.
Section 14 Clinical Studies
The results from adult studies with Glucophage and Glucophage XR showed similar efficacy with respect to change in FPG and glycated hemoglobin (HbA1c) (Table 7 and Table 10 in the USPI), although it is noted that the studies were not identical with respect to dosing regimen and treatment duration.
A 24-week, double-blind, randomized study of Glucophage XR, taken once daily with the evening meal, and Glucophage, taken twice daily (with breakfast and evening meal), was conducted in patients with type 2 diabetes mellitus who had been treated with Glucophage 500 mg twice daily for at least 8 weeks prior to study entry. The results showed that both formulations maintained HbA1c control (Table 11 in the USPI).

In summary, the USPI for Glucophage IR states that Glucophage IR is indicated as an adjunct to diet and exercise to improve glycemic control in adults and pediatric patients 10 years of age and older with T2D. The clinical data show similar efficacy and safety profile for both adults and pediatric populations with Glucophage IR treatment and PK data from the label show that Glucophage IR exposure (AUC) is similar between adults and pediatric patients. The clinical and PK data in adults also show that the exposure of a given dose of Glucophage XR administered once daily is comparable to the same total dose of Glucophage IR administered twice a day such that dosing for patients receiving Glucophage IR may be switched to Glucophage XR and expect the same efficacy. This PK bridge (i.e., Glucophage IR in pediatric patients similar to Glucophage IR in adults, and Glucophage IR in adults similar to Glucophage XR in adults, and Xigduo XR metformin component bioequivalent to Glucophage XR) supports the Applicant's proposal to rely on FDA's previous findings of efficacy and safety of Glucophage IR to broaden the glycemic control indication for Xigduo XR to include pediatric patients aged 10 and greater with T2D.

This scientific bridge provided by the Applicant is considered appropriate to justify the Applicant's proposal to rely on the Agency's previous findings of safety and effectiveness for Glucophage IR to and Glucophage XR to broaden the glycemic control indication for Glucophage XR by adding pediatric patients aged 10 and older. Because the Applicant conducted a bioequivalence study to bridge Xigduo XR to Glucophage XR, this also supports broadening the

glycemic control indication for Xigduo XR by adding pediatric patients aged 10 and older.

8. Review of Safety

8.1. Safety Review Approach

With a premarket clinical safety database that includes several cardiovascular outcomes trials, and subsequently, over a decade of clinical experience for glycemic control and cardiorenal indications in *adult* populations with and without T2D, the safety profile for dapagliflozin has been well characterized. In the USPI, the most common adverse reactions with an incidence ≥ 5% in adults include female genital mycotic infections, nasopharyngitis, and urinary tract infections.

The labeling also cites the following risks under Warnings and Precautions: diabetic ketoacidosis in patients with T2D and other ketoacidosis, volume depletion, urosepsis and pyelonephritis, hypoglycemia with concomitant use with insulin and insulin secretagogues, necrotizing fasciitis of the perineum (Fournier's Gangrene), and genital mycotic infections.

Unless otherwise specified, the FDA safety review focused on the set of observations for subjects who received at least one dose of study drug (e.g., a modified intention to treat population), and considered data after rescue or treatment discontinuation (e.g., an on-study analysis). This dataset may be referred to as the Safety Analysis Data Set or the Treated Patients Data Set.

The FDA primary review of safety pooled the events that occurred from both dapagliflozin 5 mg and 10 mg exposures. Safety was not analyzed separately by dapagliflozin dose because subjects were treated with 10 mg only for a subset of their time on trial, and this was conditioned on a post-randomization observation based on A1C results for the 2nd randomization (i.e., non-responders with A1C > 7.0%) and 3rd randomization (i.e., subjects on placebo or on active treatment with dapagliflozin 5 mg with A1C < 7.5% and metformin only as background for randomized withdrawal of metformin). In contrast, subjects in the dapagliflozin 5 mg group included all who continued active treatment beginning at the 1st randomization on Day 1. The biases resulting from these differences in group construction as well as the potential for chance variation due to the small numbers of patients preclude the ability to draw meaningful comparisons between dapagliflozin doses.

The primary review of safety involved AEs that occurred during the fixed-duration 26-week ST period. There was excellent disposition of trial participants during the ST period (73 of 81 patients randomized to dapagliflozin, and 66 of 76 patients randomized to placebo completed

the 26-week primary treatment period on treatment) which permitted adequate interpretation of incidence-based landmark adverse event analyses for the 26-week ST period. For this reason, more sophisticated analysis methods were not warranted. The FDA safety analyses for various categories of AEs for the pooled dapagliflozin group vs placebo group generally corroborated the results of the Applicant presented in the CSR.

In contrast, analysis and interpretation of the ST+LT treatment period is challenged by a tertiary randomization at week 26. Subjects who had poor glycemic control were not randomized (and hence contribute interpretable safety data). Subjects who had good glycemic control were randomized to either continue Week 26 treatment (and hence contribute interpretable safety data) or receive a new treatment. Hence, the continued treatment from Weeks 26 to 52 is conditioned on a post-randomization variable. Due to confounding, subjects who were randomized to receive a new treatment (i.e., patients re-randomized to withdraw from metformin) should not contribute to longitudinal AE analyses.

To allow for an unbiased assessment of 52-week safety data, the Applicant weighted incident AEs in subjects who were randomized to continue Week 0 to Week 26 treatment by counting them twice or thrice (depending on the randomization ratio to continue Week 26 treatment), then applying a weighting factor such that the trial population comprising the denominator of the 26 to 52-week data was the same as before selective censoring of “non responders” and “responders.” For this reason, safety analyses were focused on the 26-week ST period and the results are presented in the tables in the corresponding subsections. The Applicant’s analyses for ST+ LT period were reviewed to inspect for any significant differences from the ST period that warranted further investigation or discussion.

All AEs which were considered serious or lead to withdrawal of treatment were scrutinized regardless of their occurrence in the 26 or 52-week period.

The FDA reviewer tools Analysis Studio and MAED were used to analyze the datasets for safety signals and select case narratives were reviewed to gather additional AE details when warranted.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

Treatment exposure between study arms is displayed for the ST period (**Table 16**) and the ST+LT period (**Table 17**). The median duration of exposure to study drug was the same for the total dapagliflozin and placebo groups during the 26-wek ST period (182.0 days) and for the 52-

week ST+LT period (~364.0 days). Most patients took study drug for > 270 days in both treatment groups.

Table 16. Duration of Exposure to Dapagliflozin Pooled vs Placebo Regardless of Rescue for ST Period Based on Actual Dose and Treatment Taken (Safety Analysis Data Set)

	Placebo (N=76)	Total Dapagliflozin (N=81)
Duration of Exposure (days)		
Mean (SD)	177.3 (40.61)	181.8 (31.63)
Median (Min, Max)	182.0 (6, 290)	182.0 (50, 344)
Duration of Exposure (patient-years)		
Total patient years	36.9	40.3

Source: Reviewer generated using Analysis Studio, Custom Table Tool.
Columns - Dataset: Demographics; Filter: SAFFL = 'Y'.
ST Period Duration of Exposure (days) - Dataset: Demographics; Filter: EXPDYTO1' - '6' - '365'.
SD = Standard Deviation.

Table 17. Duration of Exposure to Study Drug Regardless of Rescue for Dapagliflozin & Placebo During the ST + LT Period Based on Actual Dose and Treatment Taken (Safety Analysis Data Set)

Characteristic	Statistic	Dapagliflozin 5mg (N = 81)	Dapagliflozin 10mg (N = 31)	Total dapagliflozin (N = 84)	Placebo (N = 76)
Duration of exposure (days)	n	81	31	84	76
	Mean	264.5	210.2	332.6	320.6
	SD	122.76	77.52	88.25	100.02
	Min	50	24	50	6
	1st Quartile	103.0	140.0	359.0	265.5
	Median	359.0	259.0	364.0	363.0
	3rd Quartile	364.0	273.0	369.0	367.0
	Max	392	281	526	475
	Total treatment days	21422	6515	27937	24365
Duration of exposure (patient-years)	Total patient-years	58.7	17.8	76.5	66.7
Duration of exposure category (days) n (%)	1-90	2 (2.5)	3 (9.7)	3 (3.6)	3 (3.9)
	91-180	23 (28.4)	9 (29.0)	5 (6.0)	4 (5.3)
	181-270	10 (12.3)	9 (29.0)	5 (6.0)	12 (15.8)
	271-365	31 (38.3)	10 (32.3)	46 (54.8)	34 (44.7)

	> 365	15 (18.5)	0	25 (29.8)	23 (30.3)

Duration of exposure is defined as the date of last dose - date of first dose + 1.

Patient years is calculated as the sum of exposure duration (days) for each patient divided by 365.25. Percentages are based on the total number of patients in the treatment group (N).

Patients are included in each treatment column for which they took actual treatment. Patients who were third randomized to dapagliflozin 10 mg monotherapy (randomized metformin withdrawal) are included in the dapagliflozin 10 mg column.

Total dapagliflozin patients may be included in both dapagliflozin 5 mg and 10 mg with duration of exposure calculated separately for each dose. The Ns for the dapagliflozin 10 mg and Total dapagliflozin group includes patients who switched treatments at the third randomization.

Max, maximum; Min, minimum; N, number of patients in the treatment group or regimen in the analysis set; n, number of patients included in the analysis; SD, standard deviation; ST + LT, short-term + long-term

Source: CSR Table 39

8.2.2. Relevant characteristics of the safety population:

This submission contains a single clinical study. Because all randomized subjects received at least one dose of study treatment, the clinical characteristics of the safety and efficacy analysis set are the same. The characteristics are presented in **Table 7** and discussed in **Section 6.1.2**.

8.2.3. Adequacy of the safety database:

In general, pediatric T2D programs are designed to demonstrate efficacy, rather than constitute a rigorous, stand-alone assessment of safety. The sample size and total treatment exposure in this study is similar to other pediatric T2D programs. Because the safety profile for dapagliflozin has been extensively evaluated from previous clinical trials in adults, the exposure and size of the safety database for dapagliflozin in the pediatric population is generally considered adequate and 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

Overall, the submission quality was found to be adequate; no issues were identified related to data quality or integrity affecting the review of safety. The key safety findings presented in this sNDA were reproducible and confirmed using the submitted datasets. In addition, the findings from OSI inspections of two clinical sites from the trial, selected based on higher subject enrollment and site risk rankings, supported the validity of the data.

8.3.2. Categorization of Adverse Events

The definition of seriousness and severity for adverse events were consistent with standard practice. Adverse events were classified according to Medical Dictionary for Regulatory Activities (MedDRA) Version 25.1. There were 452 adverse events reported, 370 (82%) verbatim terms did not have a one-to-one MedDRA preferred term. The clinical review team inspected all verbatim-preferred term pairs (n=208) and did not identify verbatim-preferred term pairs that were unreasonable or inconsistent (i.e., potentially splitting or diluting an adverse event concept) or that required further scrutiny.

8.3.3. Routine Clinical Tests

Relevant timed assessments of safety included the following:

		Baseline	6w	12w	20w	26w	32w	40w	46w	52w
ECG	-	X				X				X
Clinical Laboratory*	(CBC), biochemistry, urinalysis (with microscopy, creatinine albumin, glucose)	X	X	X	X	X		X		X
Urine HCG		X	X	X	X	X	X	X	X	X
Clinical Exam	Targeted physical exam, height, body weight, orthostatic blood pressure and heart rate	X	X	X	X	X	X	X		X
Growth, Bone, Maturation Markers	TSH, FT4, LH, FSH, estradiol, total testosterone, IGF-1, IGFBP-3, calcitonin, 25-hydroxy vitamin D, bone alkaline phosphatase, osteocalcin, PTH and CTX-1	X				X				X
Tanner Staging		X				X				X

Source: Curated by the Clinical Reviewer from the CSR.
*estimated glomerular filtration rate according to the Schwartz formula

See also **Appendix 13.3** for detailed Schedule of Assessments.

8.4. Safety Results

8.4.1. Overall Adverse Events

An overview of all categories of AEs that occurred during the ST + LT periods for Study 19 is presented **Table 18** (Applicant analysis). Each category of AE is discussed in greater detail in the respective subsections.

During the ST + LT period, the percentage of patients reporting any AE was similar in the total dapagliflozin group and placebo groups (72.8% vs 71.1%). The number of AEs and the reported exposure-adjusted incidence rate per 100 patient years were lower in the total dapagliflozin group than in the placebo group (160.00 vs 182.69 per 100 patient years). Overall, the incidence of the broad categories of AEs that occurred over the 52-week ST-LT period was generally balanced between dapagliflozin and placebo groups.

Table 18: Overview of all Categories of AEs for Dapagliflozin and Placebo During ST + LT Period

	Total dapagliflozin (N = 81)			**Placebo (N = 76)**		
AE category	Number (%) of patients [a]	Number of events	Incidence rate adjusted for exposure time (per 100 patient years) [b]	Number (%) of patients [a]	Number of events	Incidence rate adjusted for exposure time (per 100 patient years) [b]
Any AE	59 (72.8)	170	160.00	54 (71.1)	218	182.69
Any hypoglycemia event	24 (29.6)	118	40.91	22 (28.9)	161	41.49
Any SAE	7 (8.6)	9	9.50	5 (6.6)	5	7.46
Any hypoglycemia SAE	0	0	0	0	0	0
Any adjudicated DKA SAE	1 (1.2)	1	1.33	1 (1.3)	1	1.47
Any AE leading to d/c of study drug	1 (1.2)	1	1.32	1 (1.3)	1	1.45
Any SAE leading to d/c of study drug	0	0	0	0	0	0
Deaths	0	0	0	0	0	0
Any AEoSI	20 (24.7)	34	31.67	28 (36.8)	53	56.25

[a] Subjects with multiple events in the same category are counted only once in that category. Subjects with events in more than 1 category are counted once in each of those categories.

[b] Number of subjects with AEs divided by the sum of the minimum of exposure time or time to event per subject across all subjects multiplied by 100.

Includes AEs with an onset date on or after the date of first dose of ST study drug and up to and including 4 days (30 days in case of SAEs) following the date of last dose of ST + LT study drug, regardless of rescue medication initiation.

Percentages are based on the total number of patients in the treatment group (N).

AE, adverse event; AEoSI, adverse event of special interest; d/c, discontinuation; DKA, diabetic ketoacidosis; N, number of patients in the treatment group or regimen in the analysis set; SAE, serious adverse event; ST + LT, short-term + long- term

Source: Modified from CSR Table 40

8.4.2. Deaths, Serious Adverse Events, Significant Adverse Events, and Dropouts and/or Discontinuations due to Adverse Events

Deaths

No fatal outcomes were reported in Study 19.

Serious Adverse Events

All SAEs that occurred from randomization to the safety follow up for Study 19 were reviewed in depth. As expected, the incidence of SAEs was infrequent in both treatment arms; numerically, the number of observed SAEs was higher in the dapagliflozin treatment arm compared to placebo (7 subjects experienced 9 SAEs for dapagliflozin vs 5 subjects reporting 5 events for placebo). During the ST period, one SAE of occurred in the dapagliflozin group (ovarian cyst) and two SAEs in the placebo group (diabetic ketoacidosis and hyperglycemia in different subjects).

No SAEs were related to an organ system or clinical concept, except for SAEs related to hyperglycemia. Serious hyperglycemia was reported in two subjects in the placebo group, and 'glycosylated hemoglobin increased' was reported in one subject in the dapagliflozin group. There were two adjudicated events of DKA, one in each treatment group. 'Euglycemic diabetic ketoacidosis' was reported in the dapagliflozin arm (concomitant SAE of 'urinary tract infection') and a case of 'diabetic ketoacidosis' was reported in the placebo arm. A comprehensive summary of each individual case narrative for dapagliflozin-related SAES is provided in **Section 13.4.**

Discontinuations of Due to AEs

There were only two subjects who discontinued study treatment due to AE, one in each treatment arm. One *Wolff-Parkinson-White syndrome* event was reported for subject on dapagliflozin. The finding was noted on ECG and the subject discontinued study treatment. A *urinary tract infection* event was reported for subject receiving placebo. The event was non-serious, and patient discontinued study treatment.

8.4.3. Treatment Emergent Adverse Events, Adverse Events of Special Interest

The incidence of TEAEs occurring during the ST period was lower in the dapagliflozin group than placebo (dapagliflozin 54% vs placebo 62%). The most common TEAEs that occurred in greater than 5% of subjects in any treatment arm during the ST period are summarized by SOC and PT in descending order for dapagliflozin in **Table 19**.

Table 19. Summary of TEAEs by SOC and PT Occurring in > 5% of Subjects in the ST Period

System Organ Class Preferred Term	DAPA Pooled N = 81 n (%)	PLACEBO N = 76 n (%)	Risk Difference RD (95% CI)	Forest Plot
Any AE	44 (54.3)	47 (61.8)	-7.52 (-22.91, 7.87)	
Infections and infestations	**20 (24.7)**	**27 (35.5)**	-10.83 (-25.12, 3.45)	
Urinary tract infection	3 (3.7)	4 (5.3)	-1.56 (-8.05, 4.93)	
Influenza	2 (2.5)	4 (5.3)	-2.79 (-8.85, 3.26)	
Upper respiratory tract infection	1 (1.2)	4 (5.3)	-4.03 (-9.60, 1.54)	
Gastrointestinal disorders	**11 (13.6)**	**9 (11.8)**	1.74 (-8.67, 12.15)	
Diarrhea	4 (4.9)	4 (5.3)	-0.32 (-7.21, 6.56)	
Abdominal pain	3 (3.7)	4 (5.3)	-1.56 (-8.05, 4.93)	
Nervous system disorders	**10 (12.3)**	**4 (5.3)**	7.08 (-1.67, 15.83)	
Headache	10 (12.3)	3 (3.9)	8.40 (0.00, 16.79)	
Metabolism	**9 (11.1)**	**16 (21.1)**	-9.94 (-21.38, 1.50)	
Hypertriglyceridemia	5 (6.2)	3 (3.9)	2.23 (-4.60, 9.05)	
Vitamin D deficiency	3 (3.7)	6 (7.9)	-4.19 (-11.52, 3.13)	

Source: Reviewer generated using OCS Analysis Studio, Safety Explorer.
Filters: TRT01A = "DAPA5_5" or "DAPA5_10" or "DAPA5_5*" or "DAPA5" and SAFFL = "Y" (ALL DAPA); TRT01A = "PLAC" or "PLACPLAC" and SAFFL = "Y" (ALL PLACEBO); TRTEMFL = "Y" and APERIOD = 1 to 1 (Adverse Events).
Percent Threshold: Any Column ≥ 5%.
Risk Difference calculated by comparing the left column (Group 1) to the right column (Group 2).
mITT population; those who received at least 1 dose of study drug based on actual treatment received regardless of any intercurrent events
patients who reported at least one event (if one patient had two events it was only counted once)

The SOC of Infections and Infestations was the SOC with the greatest number of AEs for both dapagliflozin and placebo groups. The most common PTs in this SOC were *urinary tract infection* and *influenza* with both having similar number of subjects reporting these events. SOC of Gastrointestinal disorders contained the next most events with *diarrhea* and *abdominal pain* being the most common PTs and also reporting similar number of subjects with these events. It is notable that the PT *headache* was the only PT showing an unfavorable imbalance for the

dapagliflozin group, compared to placebo group, with and incidence of 12.3% vs 3.9%. respectively. All other common TEAEs were balanced between treatment arms.

The reason for the unfavorable imbalance for headache is unclear. The AE of headache is discussed in greater detail in **Section 8.5.1**. Treatment differences for the most commonly occurring adverse events during the ST+LT period were generally consistent to the ST period alone (**Table 20**).

Table 20. Summary of TEAEs by SOC and PT Occurring in > 5% of Subjects in the ST+LT Period

	Total dapagliflozin (N = 81)		Placebo (N = 76)	
Preferred term	**Number (%) of patients [a]**	**Number of events**	**Number (%) of patients [a]**	**Number of events**
Patients with any AE	59 (72.8)	170	54 (71.1)	218
Headache	12 (14.8)	17	4 (5.3)	7
Hypertriglyceridemia	6 (7.4)	6	3 (3.9)	3
Influenza	5 (6.2)	5	6 (7.9)	6
Urinary tract infection	5 (6.2)	5	7 (9.2)	11
Vitamin D deficiency	5 (6.2)	5	9 (11.8)	9
Diarrhea	4 (4.9)	5	6 (7.9)	6
Nasopharyngitis	4 (4.9)	5	6 (7.9)	7
Abdominal pain	3 (3.7)	3	4 (5.3)	5
Upper respiratory tract infection	2 (2.5)	2	5 (6.6)	6
Alanine aminotransferase increased	0	0	4 (5.3)	4
COVID-19	0	0	4 (5.3)	4
Cough	0	0	4 (5.3)	4

a Number (%) of patients with AE, sorted by decreasing frequency by PT according to the total dapagliflozin treatment group.

Source: CSR Table 41

Patients with multiple events in the same PT are counted only once in that PT. Patients with events in more than 1 PT are counted once in each of those PTs.

Includes AEs with an onset date on or after the date of first dose of ST study drug and up to and including 4 days (30 days in case of SAEs) following the date of last dose of ST + LT study drug, regardless of rescue medication initiation.

Percentages are based on the total number of patients in the treatment group (N).

MedDRA version 25.1

AE, adverse event; COVID-19, coronavirus disease 2019; MedDRA, Medical Dictionary for Regulatory Activities; N, number of patients in the treatment group or regimen in the analysis set; PT, preferred term; SAE, serious adverse event; ST, short-term; ST + LT, short-term + long-term

*mITT population; those who received at least 1 dose of study drug based on actual treatment received

*regardless of any intercurrent events
*patients who reported at least one event (if one patient had two events it was only counted once)

8.4.4. Vital Signs and Laboratory Findings

Vital Signs

No clinically meaningful mean changes were observed in vital signs.

- Heart rate and blood pressure was stable during the treatment period.
- As expected in a pediatric population, small increase in measured height was observed over the course of 52-weeks, which was similar between treatment groups.
- Small reductions in weight and BMI were observed in the dapagliflozin treatment group, which is consistent with observations form adult trials in T2D. Weight was found to be stable in the placebo group over the course of the study.

Clinical Laboratory Evaluations

There were no clinically notable mean changes observed in clinical chemistry or hematology parameters.

- There were few elevated liver tests or hepatic AEs reported during Study 19, and the proportion of subjects with these events was lower in the dapagliflozin group compared with the placebo group (dapagliflozin 6.2% vs placebo 11.8%).
- Of the 4 reported hepatic AEs for dapagliflozin subjects, the PT included 'transaminitis', 'hepatic steatosis', and 'transaminases increased'. All events were mild in intensity, and none resulted in interruption of study treatment.
- No cases in either the dapagliflozin or placebo groups were suspicious for DILI or required independent adjudication.
- Slight mean increases in hematocrit and hemoglobin were observed in the dapagliflozin group, comparable to changes noted in the adult trials. Most subjects had baseline hematology values within normal pediatric reference ranges and remained within those ranges over time during the ST and ST + LT periods.
- Four subjects in the dapagliflozin group were flagged with having serum hemoglobin levels above the alert threshold of 18 g/dL during the treatment period, and two of these subjects had corresponding increases in hematocrit levels to above the alert threshold of 55%.
- Three subjects were male, one female; all were White with ages between 14 and 17 years.
- All subjects had baseline hemoglobin values above the upper limit of normal age and sex based reference ranges. One subject (17 year old male) had both hemoglobin and hematocrit levels above the *alert* thresholds before beginning treatment.
- Peak values were recorded between 12 and 26 weeks and all values gradually declined to near baseline levels after during weeks 26 to 52.

Reviewer comment*: All SGLT-2 labels list increase in hematocrit and/or increase hemoglobin under lab changes noted in clinical trials adverse reactions. The label for dapagliflozin additionally states hematocrit levels > 55% were reported in 1.3% of adults taking dapagliflozin 10 mg vs 0.4% of placebo-treated subjects in the pooled studies of glycemic control. Although the incidence for this lab change is higher in this study, it is unsurprising and does not increase clinical concern given that all subjects who experienced this event had levels above the normal reference range at baseline. The current label for dapagliflozin adequately relays this laboratory risk.*

8.4.5. Electrocardiograms (ECGs) and QT

Thorough QT study was assessed in original review.

8.4.6. Immunogenicity

No immunogenicity assessments occurred during this study.

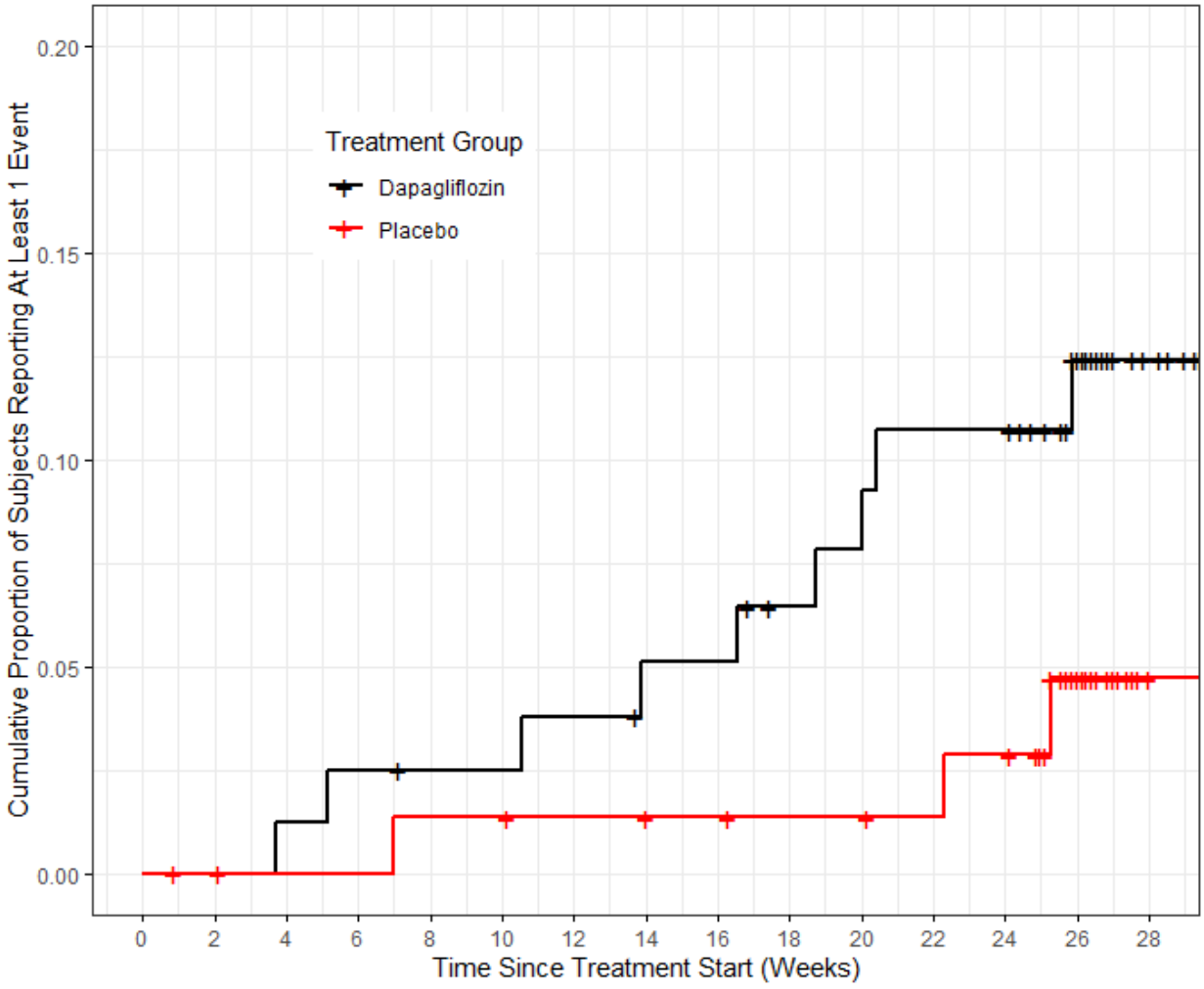
8.5. Analysis of Submission-Specific Safety Issues

8.5.1. Headache

During the ST period, 10 subjects experienced 12 events of headache in the dapagliflozin group, and 3 subjects experienced 6 events in the placebo group. During the LT period, 2 additional subjects reported AE of headache (total of 12) in the dapagliflozin group, and 1 additional subject (total of 4) and reported headache in the placebo group. Headache is not listed in the current label for dapagliflozin as a common adverse reaction. To further investigate the unexpected imbalance in the incidence of this TEAE between the dapagliflozin group and placebo, the timing of events, characteristics of the events, and the profiles of the subjects reporting headache events were examined.

Focusing on the ST period, **Figure 4** shows a Kaplan-Meier plot with time in weeks on the x-axis and proportion of subjects reporting the event of headache on the y-axis. The first event for the dapagliflozin group occurs between weeks 3 and 4, and events appear to accrue steadily from week 14 to 20 and then appear to slow down. The placebo arm has the first event occurring at week 7 and additional events at weeks 22 and 25. The headache events for dapagliflozin tend to accumulate throughout the treatment period.

Figure 4. Time to Event Analysis for Treatment Emergent Events of Headache ST period (Safety Analysis Set)



Source: Clinical Review Team, ADAE.xpt and ADSL.xpt. R version 3.4.
Modified intention to treat population; This analysis considers only adverse events which occurred in the Short Term (ST) period. One AE was not counted in the dapagliflozin arm because it did not have a start date of the AE but was considered treatment emergent.

Table 21 summarizes the characteristics of the headache events in the dapagliflozin and placebo groups. It is notable that all events resolved in both treatment groups and none of the events resulted in interruption or change to the dosing regimen. Additionally, 75% of the events for dapagliflozin were mild in intensity and 25% were moderate. The placebo group also had 83% mild events and 16.7% moderate. No events were rated severe in either treatment group. Despite similar ratings for intensity, more events in the dapagliflozin group were treated with medication (acetaminophen or nonsteroidal anti-inflammatory drugs) compared placebo (dapagliflozin 83% vs placebo 16.7%). The majority of events resolved within 24 to 48 hours in

both groups (dapagliflozin 75% vs placebo 83.3%). Longer lasting events were the ones most likely to receive treatment and events ranged 3 days, 6, days, 18 days, and 31 days for dapagliflozin and 10 days for placebo. The majority of events presented as the singular AE of headache; however, in the dapagliflozin group 2 of the 12 events had additional associated events at the time of presentation (discussed in greater detail below).

Upon examination of the subjects who reported the AE of headache (**Table 22**), the majority of subjects in both treatment arms were female (dapagliflozin 70% vs placebo 100%) and were aged 15 years or greater (dapagliflozin 70% vs placebo 100%). The dapagliflozin group had 20% of subjects with a past medical history significant for headaches while the placebo group had none. Most subjects experienced a single event of headache (dapagliflozin 80% vs placebo 33.3%) compared to recurrent events (dapagliflozin 20% vs placebo 66.6%).

Because headache can be a presenting symptom of hypoglycemia, and recent pediatric labeling for empagliflozin following review of DINAMO data suggested an unfavorable imbalance vs placebo, I closely examined the details provided for each event in the study groups. Appropriately, none of the reported TEAEs for headache were associated with a low blood glucose reading or were reported as a hypoglycemic symptom by the subjects. It is notable that for two of the subjects in the dapagliflozin arm, the past medical history was significant for recurrent headaches which required regular pharmacologic intervention. In addition, headache events for two additional subjects occurred with concomitant symptoms during presentation that suggest the headache could possibly have been secondary to the associated events rather than an independent primary event (e.g., one subject presented with erythema and pruritis of the head/scalp and another with gastroenteritis/vomiting). The cephalgia occurring under these circumstances makes It is difficult to draw a causal inference between the study treatment and event of headache when confounders such as medical history of recurrent headaches or concomitant symptoms that may predispose to the event of headache are present. For this reason, I looked at subject and event characteristics after removing these subjects from the analysis (**Table 23)**

After excluding the event scenarios that preclude the ability to attribute an independent effect of the study drug to the AE of headache, the incidence of headache (dapagliflozin 7.4% vs placebo 3.9%) and number of events (dapagliflozin 7 vs placebo 6) are more balanced between treatment arms and appear less suggestive of a new safety signal.

Table 21. Characteristics of Headache Events during ST Period

	dapagliflozin	placebo
n	12	6
Recovered/Resolved (%)	12 (100.0)	6 (100.0)
Severity (%)		
Mild	9 (75)	5 (83.3)

Moderate	3 (25.0)	1 (16.7)
Concomitant symptoms reported with event		
No	10 (83.3))	6 (16.7)
Yes	2 (16.6)	0
Duration of event - days (median [IQR])	2.00 [1.00, 5.00]	1.00 [1.00, 1.75]
Events Receiving Treatment	10 (83.3)	1 (16.7)
Treatment Dosage Not Changed (%)	12 (100.0)	6 (100.0)

Source: Clinical Review Team using adae.xpt in R Ver 3.4 and Tidyverse
AEs decoded as PT "Headache" (searched all other AEs -nothing that would be miscoded/tangentially coded as HA)
Safety Pop, treatment emergent, ST period only.

Table 22. Characteristics of Subjects with Headache during ST Period

	dapagliflozin	**placebo**
Subjects with Event n	10	3
Events n	12	6
Subjects with recorded past history of headaches	2 (20.0)	0 (0)
Subjects (%) experiencing single vs multiple events		
1	8 (80.0)	1 (33.3)
2	2 (20.0)	1 (33.3)
3	0	1 (33.3)
Sex		
Female	7 (70.0)	3 (100)
Male	3 (30.0)	0

Source: Clinical Review Team using adae.xpt and adsl.xpt and admh.xpt
AEs decoded as PT "Headache" (searched all other AEs -nothing that would be miscoded/tangentially coded as HA)
Safety Pop, treatment emergent, ST period only.

Table 23. Characteristics of Subjects with New Events of Primary Headache during ST Period

	dapagliflozin N = 81	**placebo** N = 76
Incidence of events n (%)	6 (7.4)	3 (3.9)
Events n	7	6
Severity of events (%)		
Mild	6 (85.7)	5 (83.3)
Moderate	1 (14.3)	1 (16.7)
Duration of events (%) of subjects		
≤ 48 hours	4 (66.6)	2 (66.6)
> 48 hours	2 (33.3)	1 (33.3)

Subjects (%) experiencing single vs multiple events		
1	4 (66.6)	1 (33.3)
2	2 (33.3)	1 (33.3)
3	0	1 (33.3)

Source: Clinical Review Team using adae.xpt and adsl.xpt and admh.xpt
AEs decoded as PT "Headache" (searched all other AEs -nothing that would be miscoded/tangentially coded as HA)
Safety Pop, treatment emergent, ST period only.

***Reviewer comment**: The SAEs, discontinuations due to AEs, hypoglycemia, and AEoSI that occurred during this pediatric trial were either balanced with placebo or favorable for dapagliflozin with the exception of the incidence for the TEAE of headache (dapagliflozin 13.3% vs placebo 3.9%). This was an unexpected imbalance because the labels for other approved SGLT-2 inhibitors (empagliflozin, canagliflozin, ertugliflozin and bexagliflozin) do not list headache as a commonly occurring AE for the class. Further, the recent review of pediatric T2D trial DINAMO did not reveal this finding; however, the incidence of headache for pediatric subjects on empagliflozin and on placebo from DINAMO (~14%) was comparable to that observed in Study 19 and higher than that observed in adult T2D studies. Discerning causality with dapagliflozin was difficult because dosage adjustment or interruption did not occur with any of the cases to assess for exposure outcome. The Kaplan-Meier plot did not suggest a temporal pattern to the occurrence of events. In reviewing the laboratory patterns over time for these cases, I did not appreciate any significant shifts in hematocrit or electrolytes that could explain a potential biological or mechanistic explanation for headache in these subjects. Also, headaches in children are not uncommon. A recently published meta-analysis cites that the pooled prevalence of overall primary headache in children and adolescents was 62% with a slightly higher prevalence in females (38%) vs males (27%)[28]. Reassuringly, when the cases of headache were analyzed with the removal of subjects with a known past history of recurrent headaches or in which concomitant symptoms preclude the determination of a primary headache, the comparison of subjects and events between dapagliflozin and placebo were more balanced. Finally, as previously stated, the small size of this study precludes a robust assessment of safety. Given these facts and analysis of safety findings, it is my opinion that the proposed labeling for dapagliflozin adequately relays the relevant safety profile and the inclusion of headache to the AE profile for pediatric subjects is not needed.*

8.5.2. Major Hypoglycemic Events

During Study 19, subjects were provided study blood glucose meters and were advised to SMBG and record at least once per day and during times when experiencing symptoms of

[28] Onofri, A., Pensato, U., Rosignoli, C. et al. Primary headache epidemiology in children and adolescents: a systematic review and meta-analysis. J Headache Pain 24, 8 (2023). https://doi.org/10.1186/s10194-023-01541-0

hypoglycemia or hyperglycemia. The ADA classification of hypoglycemia was used to categorize events occurring during the study:

- Level 1 - Glucose <70 mg/dL and ≥54 mg/dL
- Level 2 - Glucose <54 mg/dL
- Level 3 - A severe event characterized by altered mental and/or physical status requiring assistance for treatment of hypoglycemia, irrespective of glucose level.

Table 24 provides a summary of events of hypoglycemia that occurred during the ST period. The proportion of patients reporting hypoglycemia was comparable between treatment groups, with the frequency of events numerically slightly higher for the placebo group (dapagliflozin 20 subjects with 59 events vs placebo 20 subjects with 81 events). Most reported events were ADA level 1. Clinically meaningful events of hypoglycemia (Level 2 and Level 3) were similar between treatment arms: dapagliflozin 10 subjects with 10 events vs placebo 10 subjects with 11 events. Level 3 events were rare: dapagliflozin 3 subjects with 3 events vs placebo 4 subjects with 4 events.

Table 24. Summary of Hypoglycemia Subjects Pooled Dapagliflozin vs Placebo During the ST Period, Regardless of Rescue (Safety Analysis Data Set)

	Total dapagliflozin (N = 81)		**Placebo (N = 76)**	
ADA Classification	Number (%) of patients [a]	Number of events	Number (%) of patients [a]	Number of events
Any hypoglycemia event	20 (24.7)	59	20 (26.3)	81
Level 1	17 (21.0)	49	15(19.7)	70
Level 2	7 (8.6)	7	6 (7.9)	9
Level 3	3 (3.7)	3	4 (5.3)	4

[a] Subjects with multiple events in the same category are counted only once in that category. Subjects with events in more than 1 category are counted once in each of those categories. Percentages are based on the total number of patients in the treatment group (N).

Source: Modified from Week 56 CSR Table 14.3.2.7.2.a

***Reviewer comment**: Hypoglycemia is a common AE occurring with anti-diabetes medications. During Study 19, treatment with dapagliflozin did not adversely affect the incidence or rate of hypoglycemia compared to placebo. Upon review of the cases of dapagliflozin Level 2 and 3 events, 3/3 of Level 3 events and 5/7 of the Level 2 events occurred in subjects receiving concomitant insulin therapy. The current label already states in the Warnings and Precautions that FARXIGA may increase the risk of hypoglycemia when combined with insulin or an insulin secretagogue; therefore, a lower dose of insulin or insulin secretagogue may be required to*

minimize the risk of hypoglycemia when these agents are used in combination with FARXIGA.

8.5.3. Diabetic Ketoacidosis Events

Subjects were advised to self-monitor blood ketones and record at least once daily when experiencing potential symptoms of DKA (e.g., excessive thirst, nausea and vomiting, frequent urination, weakness or fatigue, fever, fruity scented breath, confusion, and/or consistently elevated blood glucose). There was one adjudicated event of DKA reported in each treatment group. See further discussion in **Section 8.4.2.**

8.5.4. Other Adverse Events of Special Interest

As a term of the Written Request, AEoSI were tabulated during ST+LT period (**Table 25**). Because Study 19 was an umbrella trial that included saxagliptin with a shared placebo arm, the list of PTs for this category of AEs included events related to both the SGLT-2 inhibitor class as well as the dipeptidyl-peptidase-4 (DPP4) class. Remarkably, there were no unfavorable imbalances of these AEs for the dapagliflozin group vs placebo. The most frequently occurring AEoSI for the dapagliflozin group had similar incidence in the placebo group:

- Hypertriglyceridemia: dapagliflozin 6 vs placebo 5
- Urinary tract infection: dapagliflozin 5 vs placebo 8
- Hypersensitivity: dapagliflozin 5 vs placebo 6

Table 25. Incidence of AEoSIs for Dapagliflozin and Placebo During the ST + LT Period, Regardless of Rescue (Safety Analysis Data Set)

	Total dapagliflozin (N = 81)		Placebo (N = 76)	
AEoSI category	Number (%) of patients	Number of events	Number (%) of patients	Number of events
Genital mycotic infections/ balanitis/ vulvovaginal mycotic	2 (2.5)	3	2 (2.6)	2
Urinary tract infections	5 (6.2)	5	8 (10.5)	12
Ketoacidosis	1 (1.2)	1	1 (1.3)	2
Amputations/ peripheral revascularizations/ wound complications	1 (1.2)	1	1 (1.3)	2
Bone fractures/ radius	0	0	1 (1.3)	1
Volume depletion/ syncope	0	0	1 (1.3)	1
Marked hepatic lab abnormalities hepatic steatosis, hypertransaminasemia/	3 (3.7)	4	7 (9.2)	11

transaminases increased				
Hypersensitivity reactions/ conjunctivitis /dermatitis /eczema/ erythema/ pruritis/ rhinitis/ swelling face	5 (6.2)	9	6 (7.9)	7
Severe cutaneous adverse reactions / conjunctivitis	0	0	1 (1.3)	1
Hyperlipidemia	3 (3.4)	3	4 (5.3)	4
Arthralgia/ joint swelling	0	0	3 (3.9)	4
Hyperglycemia	3 (3.4)	5	6 (7.9)	8
Hypoglycemia	1 (1.2)	1	0	0
Hypertriglyceridemia	6 (7.4)	6	5 (6.5)	5
Oropharyngeal soft tissue pain	0	0	1	1
Conjunctivitis	0	0	1	1
Changes in growth	No AEoSIs			
Acute kidney injury	No AEoSIs			
Fournier's gangrene	No AEoSIs			
Pancreatitis	No AEoSIs			
Malignancies (including bladder cancer)	No AEoSIs			
Cardiac failure	No AEoSIs			
Decreased lymphocyte count	No AEoSIs			
Opportunistic infections	No AEoSIs			

Source: Modified from Week 56 CSR Table 14.3.2.7.2.a

8.6. Safety Analyses by Demographic Subgroups

The Applicant analyzed the incidence of any AE by race, ethnicity, sex, age group, region, background antidiabetic medication, baseline A1C, and baseline BMI. Although there were small imbalances in the percentage of patients (< 14%) reporting AEs between the dapagliflozin and placebo groups for some of the subgroups, these were not considered meaningful. Imbalances were seen by region, race, and ethnicity, which reflected the smaller number of patients in some subgroups, and possible random variation.

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.

8.6.1. Human Carcinogenicity or Tumor Development

Not applicable to this submission.

8.6.2. Human Reproduction and Pregnancy

Not applicable to this submission. No reports of pregnancy occurred during the conduct of Study 19.

8.6.3. Pediatrics and Assessment of Effects on Growth

The Applicant's CSR summary for the markers of growth, maturation, and bone health, including Tanner scores and puberty status during the ST + LT period, reports that no safety concerns were raised with dapagliflozin treatment. The design of Study 19 includes a post-treatment visit at Week 104 for a final assessment of measures of growth and maturity. Although the requirement of this final study visit was removed as a term of the Written Request, the Applicant agreed to submit an addendum to the CSR with the full analyses of these measures once all study subjects complete the final visit.

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

Not applicable to this submission.

8.7. Safety in the Postmarket Setting

8.7.1. Safety Concerns Identified Through Postmarket Experience

As agreed per FDA WRO issued August 22, 2023, the Applicant submitted annual periodic benefit-risk evaluation report (PBRER) for Farxiga and Xigduo XR in lieu of a separate document for the 4MSU.

The most recent dapagliflozin PBRER submission to the Agency was on November 23, 2023, (Reporting Period: 05 October 2022 to 04 October 2023). In total, 56,395 patients and/or healthy volunteers have been enrolled into the clinical development programs, of which approximately 31,735 have received dapagliflozin. The cumulative worldwide post-approval patient exposure since launch is estimated to be 43,413,338 patient-years. No significant actions related to safety were taken or proposed during the reporting period. No safety-related changes were made to the Core Data Sheet (CDS) during the reporting period.

The most recent dapagliflozin/metformin FDC PBRER submission to the Agency was on March 7, 2024, (Reporting Period: 16 January 2023 to 15 January 2024). In total, 979 healthy subjects have been included in the dapagliflozin/metformin FDC clinical trials with cross-over designs. There were 13 subjects who did not receive dapagliflozin/metformin FDC. The cumulative world-wide post-approval patient exposure since launch is estimated to be 10,363,717 patient-years. The CDS update dated 17 April 2023 included the following safety related changes:

- An addition was made to section 4.4 Special Warnings and Special Precautions of the CDS on Vitamin B12 decrease/deficiency.
- The adverse drug reaction 'Vitamin B12 deficiency' was re-defined as 'Vitamin B12 decrease/deficiency' and the frequency category was updated from 'very rare' to 'common' and the related footnote was deleted in section 4.8 of the CDS.

The CDS update dated 10 October 2023 included the following safety related changes:

- Section 4.1 (Therapeutic indications) - Indication expanded to include the treatment of T2D in pediatric patients aged 10 years and above.
- Section 4.2 (Posology and method of administration) – Statement added confirming that the dose recommendations for XIGDUO in pediatric patients aged 10 years and above are the same as in adults.
- Section 5.1 (Pharmacodynamic properties) – Inclusion of the T2GO and T2NOW (Study 19) studies, presenting efficacy and safety data for the pediatric population.

In summary, there is no new safety information presented in the PBRERs for Farxiga or Xigduo XR which affects the information proposed in the current draft labeling.

8.7.2. Expectations on Safety in the Postmarket Setting

During Study 19, dapagliflozin was well-tolerated in study subjects. Upon review of the AEs, the safety profile for dapagliflozin in the pediatric population appears to be consistent with what is noted in the adult population and in the current label. I do not foresee a reason to expect any greater safety concerns in the postmarket setting for pediatric population.

8.7.3. Additional Safety Issues From Other Disciplines

No additional safety issues were identified from other disciplines.

8.8. Integrated Assessment of Safety

No deaths occurred during the study, only two AEs lead to a treatment discontinuation (one in each group). The sole AE leading to discontinuation from the dapagliflozin group was unrelated to treatment and was due to an ECG finding of WPW syndrome. As expected for a young and otherwise healthy population, serious adverse events were infrequent. The number of SAEs occurring during Study 19 was low but numerically higher in the dapagliflozin arm than placebo arm with 7 subjects experiencing 9 events vs 5 subjects experiencing 5 events, respectively. The

SAEs in the dapagliflozin arm were either related to diabetes (e.g., A1C increased), unlikely to be related to randomized treatment based upon experience in adults or background incidence in children (e.g., gastroenteritis, accidental OD, lymphadenitis, ovarian cyst), due to a clear alternative etiology (e.g., trauma-related splenic rupture), or already included in labeling (euglycemic DKA, UTI,). Apart from SAEs related to hyperglycemia, review of the individual case narratives did not reveal a common organ system, clinical concept, or pattern meriting further work up. These SAEs do not suggest that there is a unique serious risk to the pediatric population. The observed serious adverse events are already included in labeling (i.e., the Warnings and Precautions include DKA and euglycemic DKA; UTI is listed as a common adverse reaction).

During the ST period, the dapagliflozin treatment group, compared to placebo, had a lower incidence of TEAEs (dapagliflozin 54.3% vs placebo 61.8%) and numerically fewer events (dapagliflozin 97 vs placebo 135). The proportion of patients reporting hypoglycemia was comparable between treatment groups (dapagliflozin 24.7% vs placebo 26.3%). The majority of reported events were ADA level 1. Level 2 and Level 3 events were similar between treatment arms (dapagliflozin 10 subjects with 10 events vs placebo 10 subjects with 11 events). Level 3 events were rare (dapagliflozin 3 subjects with 3 events vs placebo 4 subjects with 4 events). No Hypoglycemia events were considered serious. Diabetic ketoacidosis, a risk which is noted in the Warnings and Precautions of the dapagliflozin label, was reported in 1 subject in each treatment arm. Other AEoSIs similarly did not reveal any unfavorable imbalances (dapagliflozin 20 subjects with 34 events vs placebo 28 subjects with 53 events). No clinically significant differences were noted in vital signs or laboratory measures between dapagliflozin and placebo groups.

Overall, dapagliflozin was well tolerated in pediatric patients. The review of the safety data from Study 19 did not reveal any clinically significant imbalances in safety endpoints between dapagliflozin and placebo treatment arms. No new knowledge of AEs was accumulated (which could be contributed to study size) that should be labeled. To this end, the observed safety results from the pediatric study suggest a similar risk profile to that of adults; at this time, the labeled safety information based on adults is an appropriate summary for the pediatric indication. The safety findings observed in this study do not raise considerations that would bear significantly on the benefit-risk assessment of the drug for the pediatric population with T2D.

9. Advisory Committee Meeting and Other External Consultations

No advisory committee meeting was held. No new safety or efficacy issues arose during the review which required the input of an advisory committee.

10. Labeling Recommendations

During the course of this review, some edits were affected related to the structure and format of the label to align with updated guidance or labeling practices (either requested by DDLO or by the Applicant). The clinical review team carefully reviewed all edits to the labeling for consistency of the medical content. Edits which did not add, modify, or remove a medical concept are not discussed in this review, but the changes are archived DARRTs as labeling negotiations.

The information contained in this supplement, and subsequent review conclusions were labelled according to typical Division practice. There were no remarkable or precedent setting review issues that require a thorough discussion and justification for approach to labeling. All medically important changes are summarized in **Table 26**.

Table 26: Summary of Changes to the Full Prescribing Information

Section	Medical Concept Added, Modified, or Removed	Section in review
Section 1 Indications and Usage	Addition of pediatric indication (aged 10 and above) for glycemic control in type 2 diabetes.	1 (Executive Summary)
Section 2 Dosage and Admin.	Addition of recommended dose for pediatric patients (same as adults - The recommended starting dose is 5 mg orally once daily. Dose can be increased to 10 mg orally once daily for additional glycemic control)	1 (Executive Summary), 7 (Integrated Summary of Effectiveness)
Section 6.1 Adverse Reactions	Statement that the safety observed in Study 19 was similar to that observed in adults	8 (Safety)
Section 8.4 Special Populations	Statement of indication, description of Study 19, and cross references to relevant sections	1, 7, 8
Section 12.3 Pharmacokinetics	Statement that the PK and PD (glucosuria) were similar between adults and pediatric patients	4.5 (Clinical Pharmacology)
Section 14.2 Clinical Studies	Description of the primary efficacy results of the Study 19.	6 (Efficacy)

11. Risk Evaluation and Mitigation Strategies (REMS)

No REMS are considered necessary.

12. Postmarketing Requirements and Commitments

This application is in response to a PREA PMR 3199-1. The Division met with the PeRC and recommended the PMR be fulfilled. The PeRC agreed (PeRC Meeting Minutes, 5/24/2024).

13. Appendices

13.1. References

References have been provided as footnotes.

13.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): 1

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 394		
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) 1		
Is an attachment provided with the reason:	Yes ☒ *	No ☐ (Request explanation from Applicant)

*Dr. Luisa Teixeira worked as a sub-investigator on Study 19 at Site 2808 in London, England, UK, from September 21, 2021- September 9, 2022. The Applicant reports that Dr. Teixeira, in error, did not complete a financial disclosure form during her time on the study and was therefore not added to the FDA 1572 equivalent. The Applicant's attempts to contact Dr. Teixeira via her study site email or phone number or via social media (LinkedIn and Twitter on June 6, 2023) were also unsuccessful. The site enrolled 3 subjects and randomized 1 subject. The absence of financial disclosure for this investigator does not raise concerns as it is unlikely that the data from a single subject would affect the validity of study results.

13.3. Schedule of Assessments

Table 5.1-1: Screening Procedural Outline (CV181375 [D1680C00019])

Procedure	Screening Maximum 6 months[a]	Lead-in Wk –2[b]	Notes
Eligibility Assessments			
Informed Consent	X		
Obtain written Assent (If applicable)	X		
Inclusion/Exclusion Criteria	X		
Medical History	X		
Review Concomitant Medication	X	X	
ECG		X	
Safety Assessments			
Physical Examination		X	
Targeted Physical Examination	X		
Tanner Staging (Investigator determined/Self-reported)		X	See Appendix 3
Vital Signs	X	X	
Height	X		
Body Weight	X		
BMI	X		
Serious Adverse Events Assessment	X	X	
Adverse Events Assessment		X	
Laboratory Tests			
Standard Safety Laboratory Panel (Blood/Urine)	X		See Appendix 1
GAD/IA2 Autoantibodies	X		

Table 5.1-1: Screening Procedural Outline (CV181375 [D1680C00019])

Procedure	Screening Maximum 6 months[a]	Lead-in Wk –2[b]	Notes
C-peptide	X		C-peptide will only be performed in otherwise eligible GAD and IA2 antibody-positive subjects
HbA1c	X		
Pregnancy Test (WOCBP only)	X		For WOCBP only urine test with reflex serum test, if positive
TSH	X		An abnormal TSH value at enrollment will be further evaluated by free T4
Hepatitis Screening Panel	X		Includes Hepatitis Screen Panel (anti-HAV [IgM], HBsAg, and anti-HCV)
Study Drug / IXRS			
Contact IXRS	X	X	
General			
Provide Dietary and Exercise Counseling		X	
Provide glucose meter and supplies / instructions		X	
Provide logs / instructions		X	
Assessment of signs and symptoms of hypoglycemia episodes		X	

[a] The screening period lasts a maximum of 6 months. Any screening procedures and assessments can be retested as determined by the Investigators during the 6-month screening period if subjects fail to meet the eligibility criteria at the first attempt and the Investigators believe that subjects may meet the eligibility criteria within 6 months. Any additional tests should be recorded as unscheduled assessments in the EDC system.

[b] The lead-in period should start within 6 weeks after completion of the screening visit, and may start as early as 2 weeks after completion of the screening visit if all laboratory results have been received.

Table 5.1-2: Short-term Procedural Outline (CV181375 [D1680C00019])

Procedure	Day 1[a]	Wk 2[a,b]	Wk 6[a]	Wk 12[a]	Wk 14[a,c]	Wk 20[a]	Wk 26/ETD (early discontinuation of IP)/Rescue[a,c]	Notes
Eligibility Assessments								
Inclusion/Exclusion Criteria	X							
Review concomitant medications / procedures	X	X*	X	X	X	X	X	*Assessed by phone
Safety Assessments								
Physical Examination							X	
Targeted Physical Examination	X		X	X		X		
Tanner Staging (Investigator determined/Self-reported)							X	See Appendix 3
Vital Signs	X		X	X	X	X	X	
Height	X		X	X		X	X	
Body Weight	X		X	X		X	X	
ECG							X	
Assessment of signs and symptoms of hypoglycemia episodes	X	X*	X	X	X	X	X	*Assessed by Phone
Serious Adverse Event Assessment	X	X*	X	X	X	X	X	*Assessed by Phone
Adverse Events Assessment	X	X*	X	X	X	X	X	*Assessed by Phone
Laboratory Tests								
Standard Safety Laboratory Panel (Blood/Urine)	X		X	X		X	X	See Appendix 1
Fasting Lipid panel	X						X	Total cholesterol, triglycerides, HDL, and LDL

Table 5.1-2: Short-term Procedural Outline (CV181375 [D1680C00019])

Procedure	Day 1[a]	Wk 2[a,b]	Wk 6[a]	Wk 12[a]	Wk 14[a,c]	Wk 20[a]	Wk 26/ETD (early discontinuation of IP)/Rescue[a,c]	Notes
Fasting Plasma Glucose (FPG)[d]	X		X	X		X	X	On Day 1, the FPG sample will be collected pre-dose only. At the Wk 6, 12, 20 and 26 visits FPG samples will be collected pre-dose and approximately 2 hours post-dose (± 1 hour) All samples will be drawn in the fasting condition.
HbA1c	X		X	X		X	X	Results masked following IP administration on Day 1 until after study completion
Pregnancy Test (WOCBP only)	X		X	X	X	X	X	WOCBP must have a negative serum or urine pregnancy test within 24 hours prior to the start of study drug. Home pregnancy kits will be provided.

Table 5.1-2: Short-term Procedural Outline (CV181375 [D1680C00019])

Procedure	Day 1[a]	Wk 2[a,b]	Wk 6[a]	Wk 12[a]	Wk 14[a,c]	Wk 20[a]	Wk 26/ETD (early discontinuation of IP)/Rescue[a,c]	Notes
Spot Urine Glucose	X		X	X		X	X	Results blinded to the Sponsor, Investigator, site, and subject for the duration of the study following IP administration on Day 1 until after study completion
Growth, bone and maturation markers	X						X	Thyroid-stimulating hormone (TSH), free thyroxine, luteinizing hormone (LH), follicle-stimulating hormone (FSH), estradiol, total testosterone, insulin-like growth factor-1 (IGF-1), insulin-like growth factor binding protein-3 (IGFBP-3), calcitonin, 25-hydroxy vitamin D, bone alkaline phosphatase, osteocalcin, parathyroid hormone (PTH) and carboxyterminal cross-linked telopeptide of Type 1 collagen (CTX-1)
Plasma samples for analysis of dapagliflozin, saxagliptin and 5-OH-saxagliptin[d]			X	X		X	X#	Samples will be collected pre-dose and approximately 2 hours post-dose (± 1 hour) Samples will be drawn in the fasting condition. # No samples will be drawn at the Rescue Visit or the Week 26 Visit following Early Treatment Discontinuation Visit
Plasma samples for DPP-4 activity[d]	X		X	X		X	X	On Day 1 plasma samples for DPP-4 activity will be drawn pre-dose only. At the Weeks 6, 12, 20 and 26 visits, plasma samples for DPP-4 activity will be drawn at 2 hours (± 1 hour) post-dose only. Samples will be drawn in the fasting condition.

Table 5.1-2: Short-term Procedural Outline (CV181375 [D1680C00019])

Procedure	Day 1[a]	Wk 2[a,b]	Wk 6[a]	Wk 12[a]	Wk 14[a,c]	Wk 20[a]	Wk 26/ETD (early discontinuation of IP)/Rescue[a,c]	Notes
Study Drug / IXRS								
Contact IXRS	X		X		X	X	X	
First randomization	X							
Second randomization					X			
Dispense Study Drug	X		X		X	X	X*	* No study drug dispensed during ETD or Rescue Visit. Rescued subjects will continue with their current assigned IP regimen.
Study Drug Compliance Review			X		X	X	X	
General								
Provide diet and exercise counseling	X	X*	X	X	X	X	X	*Assessed by Phone
Dispense meter supplies	X		X	X		X	X	
Review daily diary of finger-stick glucose values	X	X*	X	X	X	X	X	*Assessed by Phone
Provide logs / instructions	X		X	X		X	X	
Assess Rescue			X	X	X	X	X	

[a] Visits may be scheduled ± 7 days (of original schedule) to allow flexibility of scheduling. Week 12 and Week 14 visits should be scheduled at least 7 days apart. The visit window for the Rescue Visit assessments starts at the site's receipt of the HbA1c alert or FPG confirmation.

[b] Phone assessments

[c] In case the Week 14 visit is delayed, subsequent visits should be delayed to maintain an interval of at least 12 weeks between the Week-14 and Week-26 visits. Short- and long-term period study visits can be delayed by a maximum of 11 months in total.. If the duration of IP administration is longer than 52 (+1) weeks, the safety follow-up period should be shortened such that the complete study duration does not exceed 104 weeks (+7 days).

[d] Samples will be drawn at the times shown in Table 5.5-1 Sampling Schedule

Table 5.1-3: Long-term Procedural Outline (CV181375 [D1680C00019])

Procedure	Wk 32[a,c]	Wk 36 [a,b]	Wk 40[a,c]	Wk 46[a,b]	Wk 52 / early discontinuation of IP)/Rescue[a]	Wk 56[a,c]	Quarterly between Wk 56 and Wk 104	Wk 104 Post-study Visit[d]	Notes
Eligibility Assessments									
Review concomitant medications/procedures	X	X*	X	X*	X				*Assessed by Phone
Safety Assessments									
Physical Examination					X				
Targeted Physical Examination	X		X						
Tanner Staging (Investigator determined/Self-reported)					X			X	Appendix 3
Vital Signs	X		X		X				
Height	X		X		X			X	
Body Weight	X		X		X			X	
ECG					X				
Assessment of signs and symptoms of hypoglycemia episodes	X	X*	X	X*	X				*Assessed by Phone
Serious Adverse Event Assessment	X	X*	X	X*	X	X*	X*	X	*Assessed by Phone
Adverse Events Assessment	X	X*	X	X*	X	X*	X*	X	*Assessed by Phone
Laboratory Tests									
Standard Safety Laboratory Panel (Blood/Urine)	X		X		X				Appendix 1

Table 5.1-3: Long-term Procedural Outline (CV181375 [D1680C00019])

Procedure	Wk 32[a,c]	Wk 36 [a,b]	Wk 40[a,c]	Wk 46[a,b]	Wk 52 / early discontinuation of IP)/Rescue[a]	Wk 56[a,c]	Quarterly between Wk 56 and Wk 104	Wk 104 Post-study Visit[d]	Notes
Fasting Lipid panel					X				Total cholesterol, triglycerides, HDL, and LDL
Fasting Plasma Glucose (FPG)	X		X		X				
HbA1c	X		X		X				Results masked following IP administration on Day 1 until after study completion
Pregnancy Test (WOCBP only)	X	X*	X	X*	X				*Parent will provide result over the phone. Home pregnancy kits will be provided.
Growth, bone and maturation markers					X			X	Thyroid-stimulating hormone (TSH), free thyroxine, luteinizing hormone (LH), follicle-stimulating hormone (FSH), estradiol, total testosterone, insulin-like growth factor-1 (IGF-1), insulin-like growth factor binding protein-3 (IGFBP-3), calcitonin, 25-hydroxy vitamin D, bone alkaline phosphatase, osteocalcin, parathyroid hormone (PTH) and carboxyterminal cross-linked telopeptide of Type 1 collagen (CTX-1)
Study Drug/IXRS									
Contact IXRS	X		X		X				

Table 5.1-3: Long-term Procedural Outline (CV181375 [D1680C00019])

Procedure	Wk 32[a,c]	Wk 36 [a,b]	Wk 40[a,c]	Wk 46[a,b]	Wk 52 / early discontinuation of IP)/Rescue[a]	Wk 56[a,c]	Quarterly between Wk 56 and Wk 104	Wk 104 Post-study Visit[d]	Notes
Third randomization	X		X*						The third randomization will apply only to subjects who are eligible for randomized withdrawal of background medication (i.e., subjects who have background medication with metformin only and HbA1c < 7.5% at Week 26 or Week 32 ***Randomization at Week 40 only for eligible subjects not randomized at Week 32**
Instruction regarding metformin withdrawal	X		X*						Subjects withdrawn from background medication with metformin following the third randomization will be reminded to stop taking metformin. ***Only subjects randomized at Week 40**
Dispense Study Drug	X		X						No drug dispensed during ETD or Rescue Visit. Rescued subjects will continue with their current assigned IP regimen.
Study Drug Compliance Review	X		X		X				

Table 5.1-3: Long-term Procedural Outline (CV181375 [D1680C00019])

Procedure	Wk 32[a,c]	Wk 36 [a,b]	Wk 40[a,c]	Wk 46[a,b]	Wk 52 / early discontinuation of IP)/Rescue[a]	Wk 56[a,c]	Quarterly between Wk 56 and Wk 104	Wk 104 Post-study Visit[d]	Notes
General									
Provide diet and exercise counseling	X	X*	X	X*					*Assessed by Phone
Dispense Meter Supplies	X		X						
Review daily diary of finger-stick glucose values	X	X*	X	X*	X				*Assessed by Phone
Provide logs / instructions	X		X						
Assess Rescue	X	X*	X	X*					*Assessed by Phone
Telephone contact with subject/parent (reminder calls)							X		

[a] Visits may be scheduled ± 7 days (of original schedule) to allow flexibility of scheduling. The visit window for the Rescue Visit assessments starts at the site's receipt of the HbA1c alert or FPG confirmation.

[b] Phone assessments.

[c] In case the third randomization visit (at Week 32 or Week 40) is delayed, subsequent visits should be delayed to maintain an interval of at least 12 weeks between this visit and the Week 52 visit. Short- and long-term study period visits can be delayed by a maximum of 11 months in total. If the duration of IP administration is longer than 52 (+1) weeks, the safety follow-up period should be shortened such that the complete study duration does not exceed 104 weeks (+7 days).

[d] Visit may be scheduled at any time between Day -28 to +7 days of the original scheduled date to allow flexibility of scheduling.

CSP, clinical study protocol; CTX-1, carboxyterminal cross-linked telopeptide of Type 1 collagen; ECG, electrocardiogram; ETD, early treatment discontinuation; FPG, fasting plasma glucose; FSH, follicle-stimulating hormone; HbA1c, glycated haemoglobin; HDL, high-density lipoprotein; IGF-1, insulin-like growth factor-1; IGFBP-3, insulin-like growth factor binding protein-3; IXRS, interactive web/voice response system; LDL, low-density lipoprotein; LH, luteinising hormone; PTH, parathyroid hormone, TSH, thyroid-stimulating hormone; Wk, Week; WOCBP, women of childbearing potential

13.4. Summary of SAE Narratives for Subjects Receiving Dapagliflozin

SUBJID: (b) (6) **– *glycosylated A1C increased***

The subject is a 16-year-old Black female from the UK with a history of T2D on background therapy with metformin 1000 mg b.i.d. Her past medical history was significant for polycystic ovarian syndrome (PCOS), dysmenorrhea, non-alcoholic fatty liver disease (NAFLD) and obesity. On (b) (6) she was randomized to treatment with dapagliflozin 5 mg. On (b) (6) (study day 235), she was noted on laboratories to have elevated A1C and FPG. The results of these labs prompted the initiation of rescue therapy with insulin glargine 20u q.d. on (b) (6) Treatment with investigational medical product (IMP) remained uninterrupted. She completed the study on (b) (6)

> ***Reviewer comment**: The A1C and FPG values that necessitated rescue therapy were not provided in the case narrative. Based on the available information, the increase in A1C was a result of uncontrolled or progressive DM. The SAE is unrelated to IMP.*

SUBJID: (b) (6) **– *hematuria***

The subject is a 17-year-old White, non-Hispanic male from Italy with a history of T2D on background therapy with metformin 1000 mg b.i.d. and insulin glargine 24u q.d. On (b) (6) he was randomized to dapagliflozin 5 mg and on (b) (6) the dose was titrated to dapagliflozin 10 mg. On (b) (6) (study day 339) the reported asymptomatic hematuria. The subject had no pain or fever at the time of the event. Repeat labs on (b) (6) showed hematuria on urinalysis and the subject was hospitalized. Abdominal ultrasound, blood count, and other labs were reportedly normal. On (b) (6) urinalysis was normal, and patient was discharged from hospital on (b) (6) Treatment with IMP was uninterrupted. Subject completed the study on (b) (6)

> ***Reviewer comment**: The details of the narrative are scant. It appears that the subject was hospitalized only to facilitate the diagnostic studies, not for therapeutic intervention. The event of hematuria appears to have been asymptomatic with no abnormalities in serum chemistries, evidence of urinary tract infection, or nephrolithiasis by ultrasound. The subject continued IMP until the end of the study without recurrence of hematuria. This event only qualifies as an SAE by virtue of hospitalization. There is insufficient data to draw a definitive conclusion, but the event is unlikely to be related to the IMP.*

SUBJID: (b) (6) **- *splenic rupture***

The subject is a 17-year-old White, non-Hispanic male from Italy with a history of T2D on background insulin glargine 14u q.d. and regular insulin 20u q.d. On (b) (6) he was randomized to dapagliflozin 5 mg. The subject stopped the IMP on (b) (6) (study day 230) with reason for discontinuation listed as 'withdrawal by subject.' On (b) (6) (study day 235) the narrative states that the subject was reported to have rib contusions. The following day,

(b) (6) the subject was reported to be hospitalized with splenic rupture. The subject underwent surgery and was discharged from the hospital on (b) (6) The narrative states that on (b) (6) he was diagnosed with pancreatitis and was hospitalized from (b) (6) through (b) (6)

Reviewer comment: *From the scant information in the narrative, the SAE of splenic rupture appears to have been the result of some form of trauma, with report of rib contusion the day prior. The event appears to be mechanical in nature and unrelated to IMP. Notably, treatment was discontinued 5 days prior to the event because of withdrawal by subject.*

SUBJID: (b) (6) - ***euglycemic DKA, UTI***

The subject is a 15-year-old non-Hispanic Asian female from Malaysia with a history of T2D on background therapy with metformin 1500mg q.d. On (b) (6) she was randomized to dapagliflozin 5 mg. On (b) (6) rescue treatment with insulin glargine was initiated at 10u daily. The dose was titrated to a dose of 18u daily. On (b) (6) (study day 328) the subject presented to the emergency room with fever, rigors, and vomiting for 24 hours. She reported intermittent myalgias for previous 3 days and symptoms of dysuria and urinary frequency. She skipped her insulin dose because of little intake of food by mouth. Labs revealed serum HCO3=18, pH=7.3, ketones=4.2, urine nitrate negative, urine culture with mixed growth. The subject was hospitalized with a diagnosis of euglycemic DKA secondary to UTI. She received treatment with intravenous antibiotics, diclofenac, oral potassium supplement, and paracetamol. During the hospitalization, metformin and IMP were withheld and insulin glargine dose was increased. On (b) (6) metformin was resumed. The subject was discharged (b) (6) on insulin glargine 40u daily. On (b) (6) IMP was resumed. The subject completed the study and stopped IMP on (b) (6) (day 364 of study).

Reviewer comment: *This case also lacked details such as the full lab panel from the ER visit (including the glucose level). The data provided did not include units or reference ranges for. The subject's history of decreased food intake and missing insulin dose is consistent with events that increase risk of euglycemic DKA while taking SGLT-2 inhibitors and is outlined in the current label in the Warning and Precautions.*

SUBJID: (b) (6) - ***Gastroenteritis, Lymphadenitis***

The subject is a 10-year-old non-Hispanic Asian female from Malaysia with T2D on background therapy of metformin 1000 mg bid and insulin glargine 12u daily. On (b) (6) she was randomized to dapagliflozin 5 mg. On (b) (6) (study day 214) she presented with pain in the right iliac fossa, vomiting, diarrhea and abdominal pain. She was diagnosed with acute gastroenteritis and mesenteric adenitis and was hospitalized. She received intravenous hydration, antidiarrheal therapy, probiotic supplementation in addition to ampicillin and sulbactam. She remained in the hospital through (b) (6) and was reported to recover from

this SAE on [redacted] (study day 231). Treatment with IMP was uninterrupted. Subject completed the study on [redacted] (study day 363).

Reviewer comment: *The narrative does not provide details as to how the diagnosis of mesenteric lymphadenitis was made (e.g., abdominal ultrasound) and does not provide any laboratory data. Nevertheless, gastroenteritis is not an uncommon occurrence in children and this SAE was unlikely related to the IMP.*

SUBJID: [redacted] ***ovarian cyst***

The subject is a 14-year-old White Hispanic female from Mexico with T2D on background therapy with metformin 1275 mg daily and insulin glargine 26u q.d. She has a PMH of ovarian cyst. On [redacted] she was randomized to dapagliflozin 5 mg. On [redacted] (study day 43) she presented to the ER with abdominal pain of 4 days duration. She had been treated with ibuprofen by her primary physician. She began vomiting in the ER and had labs and pelvic US which revealed normal uterus and a left ovarian cyst with thin partitions measuring 10.9x8.9 cm with no pelvic fluid. She underwent an exploratory laparotomy and had excision of the cyst. The pathology report was pending at the time of the hospital report and was not amended in the case narrative. The subject's pain resolved, and she was treated with oral amoxicillin and acetaminophen. She was discharged from the hospital on [redacted] She remained off of IMP from [redacted] and resumed on [redacted] She remained off of metformin and insulin glargine from [redacted] and resumed on [redacted] Subject completed the study on [redacted] (study day 364)

Reviewer comment: *The subject had a prior history of ovarian cyst. The investigator assessed the SAE to not be related to the IMP and I concur with this assessment. The subject resumed treatment with dapagliflozin and completed the study.*

SUBJID: [redacted] ***accidental overdose***

The subject is a 16-year-old White Hispanic female from the US with T2D on background of metformin 1000 mg b.i.d. Her PMH is also significant for hepatic steatosis and vitamin D deficiency. On [redacted] the subject was randomized to dapagliflozin 5 mg. On [redacted] (study day 344) the subject experienced symptoms of dizziness, lightheadedness, hunger, shaking and sweating. She did not require external assistance. The IMP was withheld for one day then resumed. Subject completed the study on [redacted] (study day 392)

Reviewer comment: *From the narrative, it appears the subject had symptoms suggestive of hypoglycemia but did not have a documented glucose measurement and was able to treat herself. The narrative suggests that the subject self-reported this adverse event as an accidental overdosage of IMP. No additional details are available in the narrative. The apparent hypoglycemic event was not severe given that the subject was able to treat herself, and it is rare for hypoglycemia to occur with SGLT-2 inhibitors without concurrent insulin or insulin secretagogue therapy, however it is possible that symptoms occurring with the episode was related to accidental ingestion of extra doses of IMP .*

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/s/

DOLLY MISRA
06/12/2024 10:01:20 AM

JUSTIN A PENZENSTADLER
06/12/2024 10:03:22 AM

PATRICK ARCHDEACON
06/12/2024 10:55:44 AM