CLINICAL REVIEW

Application Type	Supplemental NDA
Application Number(s)	NDA 204629/S-042, NDA 206111/S-038, NDA 208658/S-026
Priority or Standard	Priority
Submit Date(s)	December 20, 2022 (NDA 204629/S-042 Jardiance) January 31, 2023 (NDA 206111/S-038 Synjardy) April 25, 2023 (NDA 208658/S-026 Synjardy XR)
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PDUFA Goal Date	June 20, 2023
Division/Office	Division of Diabetes, Lipid Disorders and Obesity (DDLO)/ Office of Cardiology, Hematology, Endocrinology and Nephrology (OCHEN)
Reviewer Name(s)	Kim Shimy, MD
Review Completion Date	May 26, 2023
Established/Proper Name	Empagliflozin, empagliflozin and metformin hydrochloride, empagliflozin and metformin hydrochloride extended-release
(Proposed) Trade Name	Jardiance, Synjardy, Synjardy XR
Applicant	Boehringer Ingelheim Pharmaceuticals, Inc
Dosage Form(s)	tablet
Applicant Proposed Dosing Regimen(s)	Jardiance: 10 mg and 25 mg once daily Synjardy: twice daily, 10 to 25 mg total daily dose of empagliflozin; 1000 to 2000 mg total daily dose of metformin Synjardy XR: once daily, 10 to 25 mg total daily dose of empagliflozin; 1000 to 2000 mg total daily dose of metformin
Applicant Proposed Indication(s)/Population(s)	Jardiance and Synjardy: Adjunct to diet and exercise to improve glycemic control in patients 10 years and older with type 2 diabetes mellitus Synjardy XR: Not Applicable
Recommendation on Regulatory Action	Approval of proposed new indication; PMR 3300-1 Fulfilled; grant pediatric exclusivity
Recommended Indication(s)/Population(s) (if applicable)	Jardiance and Synjardy: Adjunct to diet and exercise to improve glycemic control in patients 10 years and older with type 2 diabetes mellitus Synjardy XR: Not Applicable

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Glossary

AC	advisory committee
AE	adverse event
AESI	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
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
CMQ	custom MedDRA query
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
DINAMO	A double-blind, randomized, placebo-controlled, parallel group trial to evaluate the efficacy and safety of empagliflozin and linagliptin over 26 weeks, with a double-blind active treatment safety extension period up to 52 weeks, in children and adolescents with type 2 diabetes mellitus
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
HbA1c	hemoglobin A1c
HDL	high density lipoprotein
HHF	hospitalization for heart failure
ICH	International Council for Harmonization
IGF-1	insulin-like growth factor 1
IGFBP-3	insulin-like growth factor binding protein 3
IND	Investigational New Drug Application
IR	information request
IRT	interactive response technology
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
LDL	low density lipoprotein
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed models for repeated measures
MI	myocardial infarction
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
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act

PRO	patient reported outcome
PSUR	Periodic Safety Update report
RBC	red blood cells
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SE	standard error
SD	standard deviation
SGE	special government employee
SMQ	standardized MedDRA query
sNDA	supplemental new drug application
SOC	standard of care
T2D	type 2 diabetes
TEAE	treatment emergent adverse event
TSAP	trial statistical analysis plan
TSH	thyroid stimulating hormone
ULN	upper limit of normal
USPI	U.S. prescribing information
WBC	white blood cells
WR	written request

1. Executive Summary

1.1. Product Introduction

Empagliflozin is a sodium-glucose cotransporter 2 (SGLT2) inhibitor. SGLT2 inhibitors have been used as treatments for type 2 diabetes (T2D), based on a mechanism of action in which plasma glucose levels are lowered by blocking reabsorption of filtered glucose in the proximal kidney tubules. Empagliflozin is available as Jardiance tablets (empagliflozin, NDA 204629), Synjardy tablets (empagliflozin and metformin hydrochloride, NDA 206111) and Synjardy XR tablets (empagliflozin and metformin hydrochloride extended release, NDA 208658)[1]. These products are indicated as an adjunct to diet and exercise to improve glycemic control in adults with T2D. Jardiance, and the empagliflozin component of Synjardy and Synjardy XR are also indicated reduce the risk of cardiovascular death (CVD) in adult patients with T2D and established cardiovascular disease, and to reduce the risk of CVD and hospitalization for heart failure (HHF) in adults with heart failure. Pursuant to the Pediatric Research Equity Act (PREA), and in response to a Written Request (WR), the Applicant has conducted a pediatric postmarketing study ("DINAMO") to assess the safety and efficacy of empagliflozin for the glycemic control indication in pediatric patients with type 2 diabetes aged 10 years and older. Based on the results of the DINAMO study, the Applicant requests expansion of the glycemic control indication for Jardiance and Synjardy to adult and pediatric patients aged 10 years and older. The Applicant is not seeking any change to the indication for Synjardy XR due to the absence of a labeled pediatric indication for the metformin hydrochloride extended-release component of this fixed-dose combination product (FDCP); however, the Applicant has submitted proposed labeling to combine the U.S. Prescribing Information (USPI) for Synjardy and Synjardy XR. The description of the pediatric study results in this combined label will also fulfill the requirements under PREA for Synjardy XR.

1.2. Conclusions on the Substantial Evidence of Effectiveness

Effectiveness of empagliflozin to improve glycemic control in pediatric patients with T2D was established based on results from one adequate and well-controlled study plus confirmatory evidence[2]. After 26 weeks, treatment with empagliflozin was superior to placebo in reducing hemoglobin A1c (HbA1c) compared to baseline [placebo-adjusted treatment difference – 0.84% (95% confidence interval -1.50 to -0.19, p=0.0116)]. Confirmatory evidence is derived from phase 3 studies of empagliflozin in the adult T2D population, in which the efficacy of

[1] Empagliflozin is also available as Glyxambi tablets (linagliptin and empagliflozin, NDA 206073) and Trijardy tablets (linagliptin and empagliflozin and metformin hydrochloride extended-release, NDA 212614); the pediatric study requirement under PREA was waived for these products.
[2] See FDA's December 2019 Draft Guidance for Industry, "Demonstrating Substantial Evidence of effectiveness for Human Drug and Biological Products"

empagliflozin to reduce HbA1c when administered as monotherapy and as add-on therapy to metformin and other background anti-diabetic agents, was demonstrated[3].

The efficacy of Jardiance and the empagliflozin component of Synjardy in pediatric patients aged 10 years and older is demonstrated by the results of the DINAMO study. The efficacy of the metformin component of Synjardy in pediatric patients has been previously established.

In addition, the DINAMO study fulfills the Pediatric Research Equity Act Postmarketing Requirement (PMR) 3300-1.

The Pediatric Exclusivity Board agreed that DINAMO fulfilled the Written Request, issued on July 30, 2019 and amended on August 11, 2022, in accordance with the Best Pharmaceuticals for Children Act (BPCA). Pediatric Exclusivity has been granted for studies conducted on empagliflozin, and empagliflozin and metformin hydrochloride, effective June 9, 2023, under section 505A of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355a).

1.3. Benefit-Risk Assessment

[3] See primary clinical review by Dr. Bill Chong under NDA 204629.

Benefit-Risk Integrated Assessment

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

Boehringer Ingelheim Pharmaceuticals, Inc ("the Applicant") has submitted supplemental new drug applications (sNDAs) for Jardiance (empagliflozin) and Synjardy (metformin immediate release and empagliflozin fixed dose combination product), proposing an indication to improve glycemic control in pediatric patients with T2D aged 10 to 17 years, based on the results of a single adequate and well-controlled pediatric phase 3 study, "DINAMO" (Study 1218.91) plus confirmatory evidence derived from phase 3 studies of empagliflozin in the adult T2D population. The DINAMO study a was a 26-week, double-blind, randomized, placebo-controlled study with a safety extension period of an additional 26 weeks in 157 pediatric T2D subjects aged 10 to 17 years. Subjects were randomized 1:1:1 to empagliflozin 10 mg, linagliptin 5 mg, or placebo over 26 weeks. Subjects in the empagliflozin 10 mg group who failed to achieve HbA1c <7.0% at week 12 underwent a second randomization at Week 14 to remain on the 10 mg dose or increase to 25 mg. Subjects in the placebo group were re-randomized at week 26 to either linagliptin or one of the empagliflozin doses (10 mg or 25 mg). The average age was 14.5 years, the average duration of T2D was 2.1 years, and the mean hemoglobin A1c (HbA1c) was 8.0%. The majority of subjects (91.1%) were treated with background metformin and 43.3% were treated with insulin. Approximately, 50% were White, 6% were Asian, 31% were Black or African American, and 38% were of Hispanic or Latino ethnicity. The majority were obese (mean body mass index (BMI) 36.0 kg/m^2).

The primary efficacy endpoint of the DINAMO study was change from baseline in HbA1c at 26 weeks, tested simultaneously for the pooled empagliflozin dosing group (including all subjects who received empagliflozin at any dose) versus placebo and for linagliptin versus placebo. Based on the primary efficacy analysis (which was adjusted for treatment, baseline HbA1c, and baseline age group), empagliflozin was superior to placebo in reducing HbA1c from baseline to week 26 [placebo-adjusted treatment difference – 0.84% (95% confidence interval -1.50 to -0.19, p=0.0116)]. Treatment with linagliptin did not result in a statistically significant improvement in HbA1c compared to placebo [placebo-adjusted treatment difference -0.34% (95% CI -0.99 to 0.30; p=0.2935). Subgroup analyses for age, sex, BMI, race, geographical region and background antidiabetic therapy were generally consistent with results in the overall study population. As agreed to under the pediatric

Written Request, the Applicant also conducted supportive Bayesian analyses which were consistent with the primary efficacy analysis results for empagliflozin.

Dose-response analyses of empagliflozin during the placebo-controlled period are limited by the small number of subjects receiving empagliflozin 25 mg (N=13), presence of several outliers, and differences in baseline characteristics among these subjects. However, efficacy of the empagliflozin 25 mg dose is supported based on the primary outcome analysis (which included data from subjects who received both empagliflozin 10 mg and 25 mg). Additionally, a numerically greater change in HbA1c from week 26 to week 52 in placebo subjects re-randomized to empagliflozin 25 mg vs 10 mg during the safety extension period provides supportive evidence regarding dose-response.

Substantial evidence of effectiveness of empagliflozin to improve glycemic control in pediatric patients with T2D was based on a single, adequate and well-controlled study (DINAMO) demonstrating the efficacy of empagliflozin to reduce HbA1c in pediatric T2D subjects when administered as monotherapy or as add-on therapy to metformin and/or insulin, plus confirmatory evidence derived from phase 3 studies of empagliflozin in the adult T2D population demonstrating the efficacy of empagliflozin to reduce HbA1c when administered as monotherapy and as add-on therapy to metformin and other background antidiabetic agents. The observed reduction in HbA1c from baseline in the DINAMO study (-0.84%) is clinically meaningful, and of similar magnitude to the HbA1c reduction observed in adult studies (-0.6 to -0.9%). Although there are differences in disease progression between the adult and pediatric T2D populations, the use of adult data as confirmatory evidence for the substantial evidence of effectiveness determination is appropriate considering the similar underlying disease pathophysiology and similar exposure-response to empagliflozin between adult and pediatric T2D subjects as demonstrated in the DINAMO study. HbA1c is a validated surrogate endpoint for regulatory decision-making; improved glycemic control, as measured by HbA1c reduction, has clearly demonstrable benefits in improving microvascular outcomes and may also improve macrovascular outcomes. Therefore, the improved glycemic control from empagliflozin treatment as demonstrated in the DINAMO study is expected to result in a reduced risk of microvascular disease.

The risks of empagliflozin in adult T2D subjects are well characterized and include diabetic ketoacidosis, volume depletion, hypoglycemia with concomitant use of insulin and/or sulfonylureas, infections (including urinary tract infections, genital mycotic infections and necrotizing fasciitis) and hypersensitivity reactions The safety profile of empagliflozin in pediatric subjects with T2D in the DINAMO study was similar to the known and labeled safety profile in adults with T2D, with the exception of hypoglycemia. In adult empagliflozin studies, the risk of hypoglycemia was higher when empagliflozin was used concomitantly with insulin and/or sulfonylureas. In the DINAMO study, the risk of hypoglycemia was higher in pediatric subjects treated with empagliflozin compared with placebo, regardless of concomitant insulin use. Among patients on background insulin, American Diabetes Association/EASD Level 2 hypoglycemia[3] (blood glucose < 54 mg/dL), occurred in 6 out of 25

patients (24%) in the empagliflozin treatment arm and in 3 out of 21 subjects (14.3%) in the placebo treatment arm. Among subjects not on background insulin, Level 2 hypoglycemia occurred in 4 out of 27 subjects (14.8%) in the empagliflozin treatment arm and in 1 out of 32 subjects (3.1%) in the placebo treatment arm. Overall, Level 2 hypoglycemia occurred in 10 out of 52 (19.2%) subjects in the empagliflozin treatment arm and in 4 out of 52 (7.5%) subjects in the placebo treatment arm. No severe hypoglycemia events occurred in the study. Several exploratory analyses supported the conclusion that the risk of hypoglycemia was higher in empagliflozin-treated subjects compared with placebo-treated subjects regardless of background insulin therapy.

During the placebo-controlled period, serious adverse events (SAEs) occurred in 2 (3.8%) subjects treated with empagliflozin and in 2 (3.8%) subjects treated with placebo; during the safety extension period SAEs occurred in 1 subject (2.1%) treated with empagliflozin 10 mg and in no subjects treated with empagliflozin 25 mg. All SAEs and adverse events of special interest (AESIs) assessed as treatment-related reflect known and labeled safety issues in adults (e.g., genital mycotic infections, urinary tract infections, hypersensitivity reactions, tubulointerstitial nephritis). No episodes of diabetic ketoacidosis occurred in pediatric T2D subjects treated with empagliflozin. Small decreases in estimated glomerular filtration rate (eGFR) and small increases in hematocrit occurred from baseline to week 26, consistent with findings in adult studies. No clinically significant changes in heart rate or blood pressure were observed. The ability to draw conclusions regarding the impact of empagliflozin on pubertal progression and growth was limited by the small number of subjects in early stages of pubertal development, absence of relevant pre-study information regarding growth patterns and growth potential, and possible misclassification of pubertal stage during the study. Finally, no dose-related safety signals were observed during the safety extension period during treatment with empagliflozin 25 mg versus 10 mg.

In summary, the data submitted from the DINAMO study plus confirmatory evidence from adult studies of empagliflozin support the benefit of empagliflozin to improve glycemic control in pediatric T2D patients. Apart from an increased risk of hypoglycemia regardless of concomitant insulin use in pediatric T2D subjects, no new safety signals relating to empagliflozin treatment were identified in the DINAMO study as compared to the established safety signals based on adult studies. The safety risks identified in adult studies of empagliflozin are described in the current product labeling; the risk of hypoglycemia pediatric T2D subjects regardless of concomitant insulin therapy will be added to product labeling along with instructions for mitigating this risk. The overall evidence from the DINAMO study supports a favorable benefit-risk profile of empagliflozin in pediatric subjects aged 10 years and older with T2D, and all review disciplines support approval of this supplement.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• The prevalence of pediatric type 2 diabetes (T2D) is increasing in the U.S., with racial and ethnic groups that have historically experienced healthcare disparities disproportionately affected • Although the pathophysiology of T2D is similar to adults, pediatric patients may experience more rapid disease progression and earlier beta-cell dysfunction compared with adults with T2D • Pediatric patients also appear to have accelerated development of diabetes complications and comorbidities as compared to adults with T2D	T2D in the pediatric population is a serious, chronic condition with increasing prevalence that disproportionately affects minority racial and ethnic groups. Pediatric T2D is characterized by more rapid disease progression, accelerated beta cell function decline, and accelerated development of diabetes complications, compared to adults with T2D. Given these differences in disease process between adults and children with T2D, full extrapolation of efficacy from adults is not appropriate.
Current Treatment Options	• Metformin, liraglutide, exenatide-extended release, dulaglutide and insulin are currently labeled therapeutic options for pediatric T2D. Metformin is the only available oral therapy.	There are limited treatment options for pediatric patients with T2D and only one labeled oral therapy (metformin).
Benefit	• In the DINAMO study, at week 26 the HbA1c placebo-adjusted treatment difference for empagliflozin-placebo was - 0.84% (95% confidence interval -1.50 to -0.19, p=0.0116)]. • The following pre-specified hierarchical tested endpoints also demonstrated nominal superiority as compared to placebo at Week 26: Change in fasting plasma glucose (FPG). • Subgroup analyses for the treatment effect based on age (including subjects aged <15 years), sex, race, region and background medication were generally consistent with the overall population. • No differences in blood pressure or body weight were observed.	Empagliflozin (at doses of 10 mg or 25 mg) with or without baseline metformin and/or baseline insulin therapy showed superior glycemic lowering at 26 weeks compared to placebo. Similar glycemic findings were observed in the hierarchical endpoint of FPG.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• The results of a prespecified exploratory Bayesian analysis were consistent with the primary efficacy results. • Dose-response analyses of empagliflozin during the placebo-controlled period are limited by the small number of subjects receiving the higher dose of empagliflozin 25 mg (N=13), presence of several outliers, and differences in baseline characteristics among these subjects. A numerically greater change in HbA1c from week 26 to week 52 in placebo subjects re-randomized to empagliflozin 25 mg versus 10 mg during the safety extension period provides additional evidence for dose response.	
Risk and Risk Management	• No deaths occurred in the DINAMO study • SAEs occurred in 3.8% of empagliflozin-treated subjects; SAEs and AESIs were consistent with the known safety profile in adults, and included genital mycotic infections, urinary tract infections, hypersensitivity reactions, tubulointerstitial nephritis. No events of diabetic ketoacidosis occurred in empagliflozin-treated subjects. • Among patients on background insulin, Level 2 hypoglycemia (blood glucose < 54 mg/dL) occurred in 24% of empagliflozin-treated subjects and in 14.3% of placebo-treated subjects. Among subjects not on background insulin, hypoglycemia occurred in 14.8% of subjects treated with empagliflozin and in 3.1% of subjects treated with placebo. • No severe hypoglycemia events occurred in the study. • No clinically significant changes in heart rate or blood pressure were noted. • There were no detected differences in pubertal progression and growth between treatment arms; the study data were limited due to	In pediatric subjects, there was a higher rate of Level 2 hypoglycemic events among empagliflozin-treated subjects compared to placebo-treated subjects regardless of concomitant insulin use; there were no events of severe hypoglycemia. Although it is unclear whether this risk would be generalizable to the postmarketing setting, this information will be included in labeling.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	small number of patients in early stages of pubertal development, absence of relevant pre-study information regarding growth patterns and growth potential, and possible misclassification of pubertal stage. • No differences were observed in the safety profile of empagliflozin 10 mg versus 25 mg in this study.	

1.4. Patient Experience Data

This section is not relevant to the submission.

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

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

2. Therapeutic Context

2.1. Analysis of Condition

The incidence of pediatric type 2 diabetes mellitus (T2D) has been increasing over the past 2 decades[1]. As of 2017, the U.S. prevalence of pediatric T2D was estimated at 28,000, however, if current trends continue, the prevalence is projected to reach 220,000 by 2060[4]. The prevalence of pediatric T2D appears to be higher in certain racial and ethnic groups (including Non-Hispanic Blacks, Hispanics, Asians/Pacific Islanders and American Indians) and in adolescent girls (with a 60% higher prevalence rate than boys)[5]. Nearly 80 to 90% of youth with T2D have overweight and obesity. The onset of pediatric T2D often coincides with pubertal insulin resistance and it is rarely diagnosed in patients below 10 years of age.

The pathophysiology of pediatric T2D is similar to that in adults, involving non-autoimmune pancreatic β-cell failure occurring on a background of insulin resistance. However, there are several differences in disease process and progression in pediatric versus adult T2D. The degree of insulin resistance in pediatric T2D appears to be more profound than in adults, even at the same degree of adiposity[6,7]. According to the TODAY study, nearly 50% of pediatric patients on metformin monotherapy failed glycemic control over a 4-year follow up with a median time to insulin of 11 months, far greater than the rates of glycemic failure reported in adults on metformin monotherapy[8]. Data from the TODAY study also suggest that some youth with T2D may experience more rapid deterioration of β-cell function as compared to adults[9], while others may exhibit more durable glycemic control on metformin monotherapy[10]. The predictors of treatment response in pediatric T2D are not fully understood and currently under study. TODAY study participants who failed to maintain glycemic control had significantly lower β-cell function, higher fasting glucose concentration, higher HbA1c at randomization, and higher HbA1c after a short course of metformin compared to those who did not fail[9,11,12]. Diabetic ketoacidosis at the time of diagnosis of pediatric T2D also appears to predict greater β-cell decline over time[13].

Youth with T2D also have accelerated development of diabetes complications and co-morbidities. Based U.S. and Canadian registry studies, there is a higher prevalence of diabetic kidney disease, hypertension, retinal disease, and peripheral nerve disease in youth with T2D as compared to type 1 diabetes[2],[14]. Compared to adults with T2D, diabetes-related complications appear early in youth with T2D and accumulate more rapidly. According to a longitudinal follow up study of youths with T2D[2], at a mean time of 13.3 years since diagnosis (and mean age of 26.4 years), the incidence of diabetic kidney disease was 54.8%, the incidence of nerve disease was 32.4%, and the prevalence of retinal disease (including more advanced stages) was as high as 51% within a 1-year period. At least 1 diabetes-related complication occurred in 60.1% of participants, at least two complications occurred in 28.4% of participants, and serious cardiovascular events occurred despite the young age of participants. The higher incidence of complications in youth-onset T2D may relate to more rapid disease progression, sub-optimal response to currently approved treatments, and additional age and socioeconomic-related challenges[2].

2.2. Analysis of Current Treatment Options

There is an unmet need for additional treatment options for pediatric T2D. Current treatment options (other than insulin) approved for pediatric T2D are listed in Table 1. Glucophage (metformin hydrochloride) was approved for use in pediatric patients aged 10 years and older in 2000[4]. A metformin extended-release product, Riomet ER (metformin hydrochloride extended-release oral suspension) was also approved in 2019 but is no longer marketed. In the past several years, 3 injectable glucagon-like peptide-1 (GLP-1) receptor agonist products have been approved for use in pediatric T2D: liraglutide (pediatric approval in 2019), exenatide (pediatric approval in 2021) and dulaglutide (pediatric approval in 2022. Currently, metformin hydrochloride is the only oral antihyperglycemic agent approved for use in pediatric type 2 diabetes. Many oral antihyperglycemic agents available to adults with T2D (including the commonly used drug classes of sulfonylureas, dipeptidyl peptidase 4 (DPP-4) inhibitors, SGLT2 inhibitors and thiazolidinediones) are not approved for use in children. Recent pediatric trials of DPP-4 inhibitors have failed to demonstrate efficacy in pediatric T2D patients, despite the established efficacy in adults. The difference in pediatric versus adult efficacy for DPP-4 inhibitors may relate to the comparatively weaker glycemic lowering of DPP-4 inhibitors (as compared to GLP-1 receptor agonists) in the setting of a more progressive underlying disease. Some of the insulin products that have an indication "to improve glycemic control in adults and children with diabetes mellitus" are Humulin R (insulin human), Novolin R (insulin human), Humulin N (isophane insulin human), Novolin N (isophane insulin human), Novolin 70/30 (isophane insulin human and insulin human), Humulin R U-500 (insulin human), Apidra (insulin glulisine), Fiasp (insulin aspart), Humalog (insulin lispro), Levemir (insulin detemir), Novolog (insulin aspart), Ryzodeg (insulin degludec and insulin aspart), Toujeo (insulin glargine), Tresiba (insulin degludec), and Lyumjev (insulin lispro-aabc). No insulin product labels include any pediatric T2D efficacy trial data.

[4] Glucophage is no longer marketed; however, generic hydrochloride products are available for use in pediatric T2D patients.

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

Product (s) Name	Year of Approval	Currently Marketed (Yes/No)	Route and Frequency of Administration	Efficacy Information	Important Safety and Tolerability Issues
Glucophage (metformin hydrochloride)	2000	No* (several ANDAs available)	Oral, twice daily Dosage: 500 mg twice daily to be increased in 500 mg increments to a maximum of 2000 mg per day in divided doses	In a double-blind placebo-controlled study in pediatric patients, FPG change of -42.9 mg/dL in metformin group compared to + 21.4 mg/dL in placebo group (p<0.0001).	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	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	SC injection, weekly	In a 24-week double-blind, placebo-controlled trial in 82	Common AEs: nausea, diarrhea, vomiting, constipation, headache, dyspepsia, injection-

			Dosage: 2 mg once weekly	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)	site nodule, injection site pruritis. Warnings/Precautions: thyroid C-cell tumors (contraindicated in patients with a personal or family history of MTC or MEN2), acute pancreatitis, acute kidney injury, gastrointestinal disease, hypersensitivity reactions, drug-induced immune mediated thrombocytopenia, serious injection site reactions, immunogenicity-associated decreased glycemic control, acute gallbladder disease, hypoglycemia with concomitant use of insulin secretagogues or insulin.
Trulicity (dulaglutide)	2022	Yes	SC injection, once weekly Dosage: 0.75 mg once weekly, may 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

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

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Jardiance tablets (empagliflozin, NDA 204629) was approved on August 1, 2014 and is indicated as an adjunct to diet and exercise to improve glycemic control in adults with T2D and to reduce the reduce the risk of cardiovascular death (CVD) in adult patients with T2D and established cardiovascular disease. A new indication to reduce the risk of CVD and hospitalization for heart failure (HHF) in adults with heart failure and reduced ejection fraction was approved on August 18, 2021. This indication was broadened to reduce the combined risk of CVD or HHF in patients with heart failure on February 22, 2022.

Synjardy tablets (empagliflozin and metformin hydrochloride, NDA 206111) and Synjardy XR tablets (empagliflozin and metformin hydrochloride extended release, NDA 208658) were approved on August 26, 2015, and December 9, 2019, respectively, and are both indicated as an adjunct to diet and exercise to improve glycemic control in adults with T2D. The approval of Synjardy tablets (NDA 206111) was based on a 505 (b)(2) application that relied upon the Agency's finding of safety and effectiveness for NDA 020357 Glucophage (metformin hydrochloride tablets) as the listed drug (LD). The approval of Synjardy XR tablets (NDA 208658) was based on a 505 (b)(1) application that relied upon the Agency's finding of safety and effectiveness for Glumetza tablets (metformin hydrochloride extended release, NDA 021748), for which the Sponsor (Boehringer Ingelheim Pharmaceuticals, Inc) had obtained a right to reference. On December 23, 2016, the prescribing information (PI) for these products was updated to state that when used as a component of Synjardy or Synjardy XR, empagliflozin is indicated to reduce the risk of CVD in adults with T2D and established cardiovascular disease. On February 6, 2023, this indication was broadened to reduce the risk of CVD in adults with established cardiovascular disease; additionally, a new indication to reduce the risk of CVD and HHF in adults with heart failure was added for the empagliflozin component of Synjardy and Synjardy XR.

(b) (4)

3.2. Summary of Presubmission/Submission Regulatory Activity

Regulatory History relating to Pediatric PMRs

- According to the approval letters for Jardiance (NDA 204629) and Synjardy (NDA 206111), the pediatric study requirement for ages 0 to 9 years (inclusive) was waived because the necessary studies were impossible or highly impracticable due to too few children in this age range with T2D, and the following deferred pediatric studies were required under the following Pediatric Research Equity Act (PREA) post-marketing requirements (PMRs):
    - PMR 2755-1 A single-dose pharmacokinetic and pharmacodynamics trial of empagliflozin in pediatric patients 10 to 17 years (inclusive) with type 2 diabetes mellitus.
    - PMR 2755-2: A 24-week, randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of empagliflozin for the treatment of pediatric patients 10 to 17 years (inclusive) with type 2 diabetes mellitus as an add-on to metformin, followed by a 28-week double-blind, placebo-or active-controlled extension period. The efficacy and safety study should have at least 30% of randomized subjects 10 to 14 years (inclusive) of age and at least one-third (but not more than two-thirds) of subjects in both age subsets (10 to 14 years [inclusive] and 15 to 17 [inclusive]) will be female. Secondary safety endpoints should include the effect of empagliflozin on mineral and bone metabolism, and the effect of empagliflozin on growth. This trial should not be initiated until after the data from the juvenile animal study have been submitted to and reviewed by the Agency.
    - PMR 2755-3: A study to evaluate empagliflozin toxicity in juvenile rats.
- On February 2, 2016, following the submission of a 10-week juvenile rat toxicology study, PMR 2755-3 was fulfilled.
- On December 9, 2016, Synjardy XR (empagliflozin and metformin hydrochloride extended-release tablets, NDA 208658) was approved. The approval letter stated that PMRs 2755-1 and 2755-2 apply to Synjardy XR (NDA 208658) in addition to Jardiance (NDA 204629) and Synjardy (NDA 20611).
- On June 16, 2016, the Applicant submitted a draft protocol for a new pediatric Study 1218.91, in which both linagliptin and empagliflozin were proposed to be studied with a common placebo arm. In response, the Agency issued Advice letters dated March 1, 2017, August 9, 2017, as well as FDA Written Responses dated June 27, 2017, related to the protocol for Study 1218.91. Following these communications, the sponsor agreed to

a 3-arm, 2-stage randomization design, with a re-randomization in patients treated with empagliflozin 10 mg not achieving HbA1c <7% at week 12, which will allow obtaining information on safety and efficacy of linagliptin 5 mg, empagliflozin 10 and 25 mg, as well as evaluating whether increasing the dose of empagliflozin from 10 mg to 25 mg is beneficial to pediatric patients.

- On February 24, 2017, following the submission of the final report for Study 1245.97, entitled “An open-label, randomized, multicenter, single-dose, parallel group trial to evaluate pharmacokinetics and pharmacodynamics of empagliflozin in children and adolescents from 10 to less than 18 years of age with type 2 diabetes mellitus,” PMR 2755-1 was fulfilled (see Section 4.5 for details).
- On September 27, 2017, the Applicant submitted the final protocol for Study 1218.91 entitled "A double-blind, randomized, placebo-controlled, parallel group trial to evaluate the efficacy and safety of empagliflozin and linagliptin over 26 weeks, with a double-blind active treatment safety extension period up to 52 weeks, in children and adolescents with type 2 diabetes mellitus (DINAMO) ". The Sponsor proposed to conduct this study to address PREA PMRs applicable to both empagliflozin-containing and linagliptin-containing products, specifically PMR 2755-1 (NDA 204629 (Jardiance), NDA 206111 (Synjardy), and NDA 208658 (Synjardy XR)) and PMR 1776-2 (NDA 201280 (Tradjenta [linagliptin]), NDA 201281 (Jentadueto [linagliptin and metformin hydrochloride]), and NDA 208026 (Jentadueto XR [linagliptin and metformin hydrochloride extended-release])). As discussed above, the design of study 1218.91 was developed in consultation with the Division to address significant enrollment difficulties in pediatric T2D trials, by evaluating empagliflozin and linagliptin in a single trial with a shared placebo comparator. The Division also discussed this updated study plan with the PeRC on December 13, 2017, and the PeRC was in agreement (see Memorandum to File dated 12/22/2017 under IND 102145).
- Following non-hold comments issued on December 4, 2017, the Agency accepted Study 1218.91 as the final pediatric protocol on December 22, 2017. On the same date, given substantive differences in Study 1218.91 from the original study described for PMR 2755-2 and PMR 1766-2 (as a result of changes made through collaborative discussion with FDA), the Agency released the Sponsor from PMR 2755-2 and from PMR 1776-2 and issued a new PMR (3300-1) applicable to NDA 204629 (Jardiance), NDA 206111 (Synjardy), NDA 208658 (Synjardy XR), NDA 201280 (Tradjenta), NDA 201281 (Jentadueto), and NDA 208026 (Jentadueto XR), as follows:
    - PMR 3300-1 Conduct a 26-week randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of linagliptin and empagliflozin for the treatment of pediatric patients ages 10 to < 18 years with type 2 diabetes mellitus, followed by a 26-week site- and subject-blinded safety extension period (weeks 26 to 52). Background therapy will consist of metformin, insulin, or metformin plus insulin. A second randomization will take place at week 12, with up-titration of empagliflozin dose (from 10 mg to 25 mg) for approximately half of the subjects with a hemoglobin A1C greater than or equal to 7%.

See Section 6.1.1 for review of protocol amendments for the DINAMO study.

Regulatory History relating to the Written Request

- On July 30, 2019 a Written Request (WR) was issued to all products containing the active moiety of empagliflozin and to all products containing the active moiety of linagliptin. In addition to the DINAMO study, this WR also required an additional clinical study to evaluate the efficacy and safety of linagliptin and empagliflozin as a monotherapy (DINAMO-Mono).
- On August 5, 2019, a corrected WR letter was issued with changes to the statistical information, including power of the study(ies) and statistical assessments: Study 1(DINAMO) with updated power estimates of 85% (0.05 alpha) and 78% (0.025 alpha).
- On November 9, 2021, the Applicant submitted a WR Amendment to reword the study endpoints for DINAMO and DINAMO Mono, reword statistical assessment provisions, and correct a typographical error.
- On November 15, 2021, the Agency provided a written response to the Applicant's September 3, 2021 Type-C meeting request. The purpose of the meeting request was to discuss the technical aspects of the planned supplemental new drug applications (sNDAs) to support a new indication of linagliptin and empagliflozin as an adjunct to diet and exercise to improve glycemic control in patients 10 years and older with T2D.
- On February 4, 2022, the Agency recommended the Applicant withdraw the November 9, 2021 amendment and resubmit a revised WR amendment to address a sample size concern with Study 1218.91, incorporating a proposal to provide Bayesian borrowing analysis as additional supporting evidence in the DINAMO study.
- On March 22, 2022, the Agency provided an Inadequate Proposed Amendment Letter, recommending to remove DINAMO-Mono from WR, citing changing standards of care and recruitment difficulties with subjects with T2D who are treatment naïve.
- On August 11, 2022, the Agency issued a Revised Written Request – Amendment 1 letter incorporating Bayesian borrowing analysis and removal of DINAMO-Mono. Of note, the 20 subjects already enrolled in the DINAMO-Mono study will complete the study as planned, but ongoing recruitment was halted.

Regulatory History relating to labeling updates for Synjardy XR:

- On July 26, 2022, the Applicant proposed not to update the label for Synjardy XR regardless of the DINAMO study results (i.e., positive, negative, or inconclusive), but noted that labeling updates would be submitted if the DINAMO study identifies any pediatric safety issues.
- On August 25, 2022, the Agency agreed with the Applicant's July 26, 2022 proposal not to update the labeling for Synjardy XR with positive, negative or inconclusive efficacy information, but recommended labeling updates if data from pediatric studies suggest clinically significant differences in adverse reactions in pediatric patients.

- On January 31, 2023, the Applicant submitted the DINAMO clinical study report to NDA 208658 (Synjardy XR) to satisfy PREA PMR 3300-1.
- On April 4, 2023, the Agency updated prior advice regarding labeling updates for Synjardy XR, noting that since Synjardy XR is subject to PREA PMR 3300-1, results of pediatric studies conducted under PREA (i.e., the DINAMO study) must be described in the label (whether positive, negative or inconclusive data) as a condition of fulfillment of PMR 3300-1.
- On April 12, 2023, the Applicant agreed to the Agency's request to combine the PIs for Synjardy and Synjardy XR and stated that the proposed combined labeling will include description of results for the DINAMO study conducted under PREA and will be submitted to NDA 208658 Synjardy XR by April 25, 2023.
- In an April 13, 2023 amendment to the supplemental NDA for Synjardy currently under review (S-038) and in an April 25, 2023 new supplemental NDA for Synjardy XR (S-025), the Applicant proposed a combined label for Synjardy and Synjardy XR. In this proposed combined label, the glycemic control indication for Synjardy is expanded to pediatric patients 10 years and older, however, the glycemic control indication for Synjardy XR is unchanged (i.e., indicated only for adults with type 2 diabetes), and corresponding labeling updates to support the pediatric indication for Synjardy are proposed to Sections 2.3, 6, 8.4, 12.3 and 14.

3.3. Foreign Regulatory Actions and Marketing History

As of April 17, 2022, Jardiance is authorized in 110 countries and Synjardy is authorized in 84 countries[5]. Synjardy XR is not marketed outside of the U.S.

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

4.1. Office of Scientific Investigations (OSI)

OSI conducted inspections for two domestic clinical investigators (CIs): Drs. Ruth Weinstock (Site #1218-0091-USA101) and Risa Wolf (Site #1218-0091-USA105). These sites were selected based on enrolling a relatively higher number of subjects as compared to other domestic sites (5 subjects enrolled from site USA101, 6 subjects enrolled from site USA105) that may have had an impact on the clinical decision-making process. In general, the inspection verified adequate source data for the inspected study subjects with no reported deficiencies or discussion items. The primary efficacy endpoint, change in HbA1c (%) from baseline to the end of 26 weeks, was

[5] Periodic Benefit-Risk Evaluation Report, April 18, 2021 through April 17, 2022, submitted to NDAs for Jardiance, Synjardy and Synjardy XR.

verified using the sources records with no discrepancies noted. Safety data including adverse events and serious adverse events were appropriately reported. FDA form 483 was not issued. Based on the overall inspection results of the two CIs and the regulatory assessments, the OSI reviewers concluded that Study 1218.91 appears to have been conducted adequately and that the clinical data submitted by the Applicant appear to be acceptable[6].

4.2. Product Quality

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

4.3. Clinical Microbiology

There are no new data with regard to microbiology information in the submission.

4.4. Nonclinical Pharmacology/Toxicology

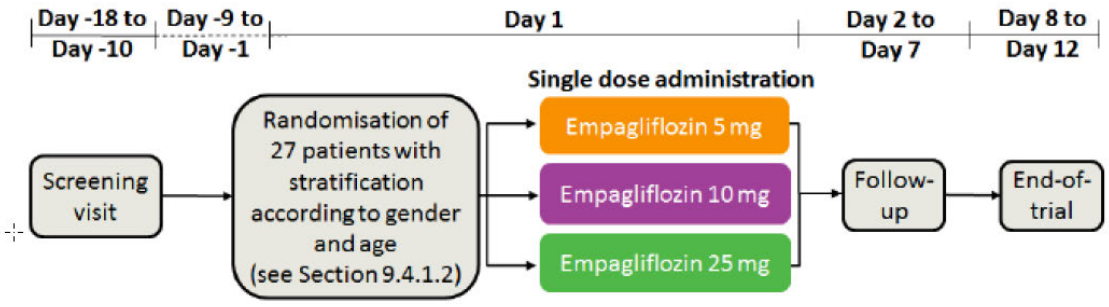
There are no new data with regard to pharmacology/toxicology information in the submission.

4.5. Clinical Pharmacology

Study 1245.87

Study 1245.87 was an open-label, parallel group study conducted in 27 children and adolescents aged 10 to 18 years to evaluate the PK and PD of empagliflozin after a single dose of 5 mg, 10 mg or 25 mg (Figure 1). Pediatric patients with inadequately controlled T2D (eligible HbA1c ≤10.5%) despite treatment with diet and exercise and/or stable metformin and/or stable basal or multiple daily injection insulin therapy were enrolled. Eligible subjects were randomized to receive single doses of empagliflozin 5 mg, 10 mg or 25 mg under fasting conditions. Background antidiabetic therapy doses were to remain unchanged throughout the study. PK and PD (via urinary glucose excretion (UGE)) were evaluated for 48-hours post-dose.

Figure 1: Study 1245.87 Design



Source: Study 1245.77 CSR

[6] See Clinical Inspection Summary by Dr. Ling Yang submitted on 5/19/2023 under NDAs 204529 and 201280.

The results of study 1246.87 were submitted on October 12, 2016. Treated subjects had a mean age of 14.1 years, with 48.1% below 15 years of age. The mean HbA1c was 7.0%, and background therapies included diet and exercise (22.2%), metformin alone (51.9%), or metformin in combination with basal insulin (25.9%). The mean eGFR (Schwartz equation) was 165.8 mL/min/1.73m^2

Comparative PK parameters in pediatric and adult patients are described in Table 2. With regard to PD, both pediatric and adult T2D patients experienced a dose-dependent increase in UGE in the 24 hours following administration of single doses of empagliflozin. In pediatric patients, the adjusted mean (SE) change from baseline in in UGE was 53.1 (10.2) g/24 hr, 73.0 (10.1) g/24 hr, 87.4 (9.4) g/24 hr for the 5 mg, 10 mg, and 25 mg doses, respectively. In adult patients (from study 1245.4) the mean, the adjusted mean (SE) change in UGE from baseline was 70.0 g/24 hr, 91.0 g/24 hr for the 10 mg and 25 mg dose, respectively.

Table 2: Comparison of PK parameters[1] of empagliflozin in pediatric and adult patients with T2D following the administration of single doses of empagliflozin

Population/ trial	Empagliflozin dose [mg]	$AUC_{0-\infty}$ [nmol·h/L]	AUC_{0-24} [nmol·h/L]	C_{max} [nmol/L]	t_{max} [h]	$t_{1/2}$ [h]	Weight [kg]
Paediatrics/ 1245.87 (n=8)	10	1450 (17.2)	1310 (18.9)	211 (59.1)	1.25 (0.97-4.17)	7.61 (27.0)	111 (21.3)
Adults/ 1245.4 (n=16)	10	1740 (16.4)	1550 (16.2)	309 (45.2)	1.50 (1.00-2.50)	8.76 (13.0)	91.7 (12.3)
Adults/ Pop PK analysis[2]		2300 (955-13600)					
Paediatrics/ 1245.87 (n=10)	25	5250 (27.6)	4720 (27.4)	692 (57.3)	1.78 (0.50-4.00)	8.09 (26.8)	91.1 (25.7)
Adults/ 1245.4 (n=16)	25	4340 (23.1)	3930 (22.9)	722 (20.0)	1.50 (0.75-2.00)	8.24 (14.9)	93.6 (16.0)
Adults/ Pop PK analysis[2]		5750 (2390-34 000)					

[1] For $AUC_{0-\infty}$, AUC_{0-24}, C_{max}, and $t_{1/2}$, the mean and %CV are given. For t_{max} and AUC of the PopPK analysis, the median and range are given. For the weight, mean and SD are listed.
[2] AUC at steady state as determined by population pharmacokinetic modelling of empagliflozin in adult patients with T2DM [c02090424-03].

Source: Study 1245.87 CSR

According to the OCP review,[7] no clinically meaningful difference in empagliflozin PK or PD was observed between pediatric patients and adult patients with T2D, a finding that supported the use of adult empagliflozin doses (10 mg and 25 mg) in the pediatric phase 3 study (study 1218-

[7] See review by Dr. Shalini Wickramaratne Senarath Yapa submitted on 1/20/2017 under NDA 20469

91).

PK data from Study 1218.91

In Study 1218.91, PK samples for empagliflozin were obtained at pre-dose (approximately 24 hours after dosing on the prior day) and at 1.5 hours post-dose at week 26 and week 52. According to the clinical pharmacology review by Dr. Thanukrishnan, the mean empagliflozin concentrations were similar between week 26 and 52 which indicates that steady-state exposure was obtained. No influence of age (i.e., < 15 years and ≥15 years) was observed on empagliflozin exposure; however, higher concentrations were observed in subjects with lower body weight (below 70 kg) and in female subjects. The plasma concentrations of empagliflozin at steady state in pediatric subjects enrolled in Study 1218.91 were generally comparable to those observed in an adult phase 2 study (Study 1245.33).

Population PK Model: The PK results from Study 1218.91 (DINAMO) were also compared to data previously obtained in adult T2D patients via both a descriptive analysis and based on a population PK model. The population PK model included data from both pediatric studies (Studies 1245.87 and 1218.91) as well as several adult studies. Based on the Applicant's descriptive analysis, plasma concentrations of empagliflozin in children and adolescents with T2D observed in Study 1218.91 were generally comparable to those previously observed in adult T2D patients. Results of the population PK analyses were also generally comparable to the results from the descriptive analysis. The Applicant's population PK analyses were verified by the OCP review team and considered acceptable; see clinical pharmacology review by Dr. Thanukrishnan for additional comments.

Exposure-Response Analysis: The Applicant also conducted an exposure-response (E-R) analysis based on data from Study 1218.91. The E-R analysis re-estimated based on information from a prior E-R model that had been developed for longitudinal HbA1c using adult data. Overall, the placebo-adjusted change from baseline in the pediatric population decreased with a higher magnitude than in the adult population, likely reflecting progression of T2D over time. The administration of 10 mg empagliflozin also resulted in a larger decrease of HbA1c from baseline in pediatric as compared to adult patients, a finding that the Applicant is attributing to higher renal function in pediatric patients rather than suggesting any underlying differences in exposure-response. The E-R analysis also suggested that concomitant insulin therapy was associated with a larger simulated magnitude of placebo-adjusted change from baseline in pediatric patients, a finding that the Applicant concluded was driven by a combination of higher baseline HbA1c values in patients on background insulin along with disease progression of HbA1c over time. The Applicant's proposed E-R model was overall acceptable to the OCP review team. See Section 6.1.2 for additional details regarding internal exposure-response analyses conducted by the OCP review team.

Reviewer Comment: Overall, the clinical pharmacology data suggests that PK, PD and exposure-response for empagliflozin is similar in adult and pediatric patients with T2D. Slight

differences that were observed between adult and pediatric patients likely reflect more rapid disease progression and higher baseline renal function in pediatric patients as compared to adults. Based on the exposure-response analysis, concomitant insulin therapy was also associated with a larger simulated magnitude of placebo-adjusted change from baseline in pediatric patients. As displayed in Table 10, subjects on background insulin therapy were more likely to have a higher baseline HbA1c; and response to treatment (as measured by change from baseline in HbA1c) may be impacted by baseline HbA1c. Based on subgroup analyses conducted by the Applicant and the statistical review team, there did not appear to be any difference in treatment response based on background insulin therapy (see Section 6.1.2).

4.6. Devices and Companion Diagnostic Issues

This section is not applicable to the submission.

4.7. Consumer Study Reviews

This section is not applicable to the submission.

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

The primary efficacy and safety data to substantiate the proposed labeling claims and updates are based on a single adequate and well-controlled phase 3 study, Study 1218.91 (DINAMO).

5.2. Review Strategy

The primary documents reviewed were submitted under NDA 204629/S-042. The review of efficacy focused on the Applicant's analyses and confirmatory analyses conducted by the statistician, Dr. Wenda Tu. I also performed exploratory efficacy analyses to evaluate dose-response based on information submitted in the datasets.

The primary safety analysis is based on the 26-week placebo-controlled assessment period of study 1218.91. Safety data from weeks 26 to 52 weeks were reviewed to evaluate for any differences in safety signals between subjects who received empagliflozin 10 mg versus empagliflozin 25 mg from weeks 26 to 52. Where applicable, I reviewed the safety data using the submitted datasets and also reviewed safety analyses completed by the Applicant.

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. DINAMO (Study 1218.91)

6.1.1. Study Design

Overview and Objective

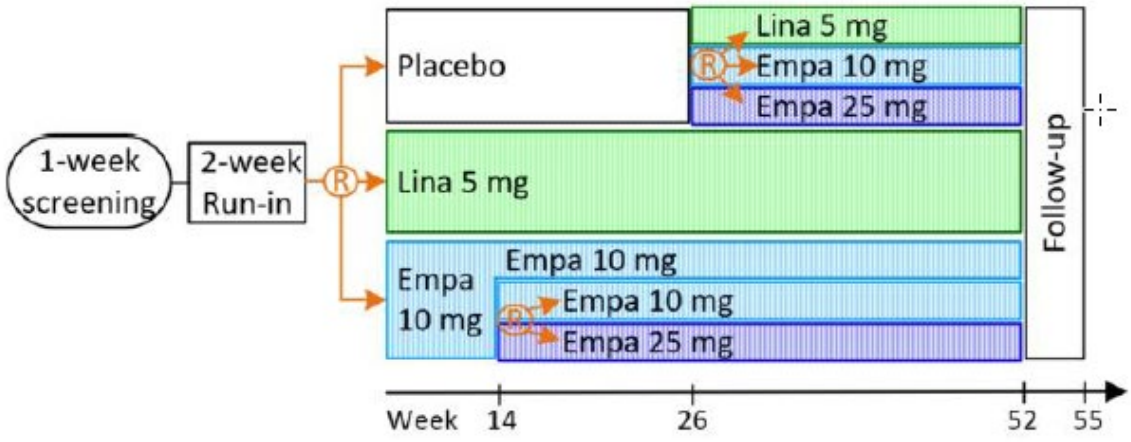
Study Title: A double-blind, randomized, placebo-controlled, parallel group rial to evaluate the efficacy and safety of empagliflozin and linagliptin over 26 weeks, with a double-blind active treatment safety extension period up to 52 weeks, in children and adolescents with type 2 diabetes mellitus (DINAMO)

Primary Objective: The objective of DINAMO was to assess the efficacy and safety of 1 dose of linagliptin and an empagliflozin dosing regimen versus placebo after 26 weeks of treatment in children and adolescents with T2D treated with metformin and/or insulin or who were not tolerating metformin.

Study Design

The DINAMO study (Figure 2) was a randomized, placebo-controlled, double-blind, and parallel group trial with 3 treatment arms (placebo, linagliptin 5 mg, empagliflozin) lasting 26 weeks in T2D patients from 10 to ≤17 years of age who were treated with a background of metformin and/or insulin therapy. All patients in the empagliflozin arm received a dose of 10 mg empagliflozin initially, but those who did not achieve HbA1c <7.0% at Week 12 (i.e., "non-responders") were re-randomized at Week 14 to either continue with 10 mg empagliflozin or increase to 25 mg empagliflozin through week 26. After the primary outcome measurement at week 26, patients on placebo were re-randomized to receive either 5 mg linagliptin or empagliflozin (10 mg or 25 mg) to allow for a double-blind active treatment safety extension period through 52 weeks.

Figure 2: DINAMO Study Design



Source: Study 1218.91 CSR

Reviewer Comment: The study was designed to evaluate the efficacy of the pooled doses (10 mg and 25 mg) of empagliflozin[8]. Because only subjects who were non-responders to empagliflozin 10 mg were eligible for re-randomization a higher dose of empagliflozin through week 26, caution must be taken when interpreting efficacy information in this subgroup who may have had more rapid disease progression than responders. Exploratory analyses of data from week 26 to week 52 in subjects initially in placebo arm and re-randomized to empagliflozin 10 mg versus 25 mg provided additional information regarding dose response to empagliflozin.

The initial randomization was stratified by age (<15 years; ≥15 to <18 years) to ensure that at least 30% but no more than 70% of randomized patients were < 15 years of age as required by the Written Request. The re-randomizations at week 14 (for those in the empagliflozin 10 mg arm with HbA1c ≥ 7% at week 12) and at week 26 (for those in the placebo arm) was also stratified by the same age criteria and occurred via IRT (interactive response technology) to maintain double blind conditions.

Reviewer Comment: Use of the IRT along with a double blind, double dummy approach to study treatment (see Table 3) appear adequate to maintain the double-blind condition.

Trial Location and Administrative Structure: DINAMO was a multinational study conducted in 78 sites in 13 countries in Asia, Europe, North and South America. The study included a steering committee (SC), a data monitoring committee (DMC) and a clinical event committee (CEC). The SC, comprising 6 physicians with expertise in pediatric T2D and clinical trials and 3 sponsor representatives, provided scientific and clinical advice in the design, planning, conduct, analysis, interpretation and reporting of study results. An independent DMC, composed of 2 physicians and 1 statistician, regularly monitored patient safety including review of unblinded data. A blinded CEC, consisting of 17 members across 4 sub-committees (cardiology, neurology, endocrinology, and hepatology/gastroenterology) adjudicated whether prespecified criteria for investigator-reported events and laboratory abnormalities were met (see section 8.3.2). Clinical research organizations (CROs) were used to provide trial services including statistics, programming, trial training, interactive response system, management of adjudication by CEC, management of DMC, supply of study medication and laboratory analyses.

Key Inclusion Criteria:

- Aged 10 to ≤17 years
- Male or female patients

[8] An earlier draft version of the protocol had included a separate arm for empagliflozin 25 mg; however, in the final version of the protocol accepted by the Agency, the empagliflozin 25 mg arm had been removed and replaced with the re-randomization approach at week 14.

- Women of childbearing potential using highly effective birth control methods
- T2D diagnosis for at least 8 weeks
- HbA1c ≥6.5% and ≤ 10.5%
- Treated with diet and exercise and metformin (at least 1000 mg/day or maximally tolerated dose[9]) and/or stable basal or multiple daily injection insulin therapy (weekly average variation of basal insulin dose < 0.1 IU/kg over 8 weeks prior to randomization)
- BMI > 85th percentile for age and sex
- Non-fasting[10] serum C-peptide > 0.6 ng/mL or > 0.199 nmol/L
- Compliance > 75% with trial medication during the open-label run-in period
- Use of highly effective birth control for females of childbearing potential

Key Exclusion Criteria

- Positive for islet cell antigen auto-antibodies (IA-2) and glutamic acid decarboxylase (GADA) autoantibodies
- History of ketoacidosis within 8 weeks
- Monogenic diabetes
- History of pancreatitis
- Diagnosis of metabolic bone disease
- Gastrointestinal disorders that may interfere with study drug absorption
- Any antidiabetic medication (with the exception of metformin and/or insulin background) within 8 weeks
- Treatment with weight-reduction medications within 3 months
- History of weight-loss surgery or current aggressive diet regimen
- > 1 week treatment with systemic corticosteroids within 4 weeks
- Change in dose of thyroid medications within 6 weeks
- Estimated glomerular filtration rate (eGFR)[11] < 60 ml/min/1.72 m^2
- Alanine transaminase (ALT) or aspartate transaminase (AST) or alkaline phosphatase > 3 x upper limit of normal (ULN)
- Active or suspected malignancy or history of malignancy within 5 years except appropriately treated basal cell skin carcinoma or in situ carcinoma of uterine cervix
- Blood dyscrasias or any disorders causing hemolysis or unstable red blood cells
- Medical contraindications to metformin (for patients on metformin background therapy)

[9] Subjects "not tolerating metformin" (defined as patients who were on metformin treatment for at least 1 week and had to discontinue metformin due to metformin-related side effects as assessed by the investigator) were also enrolled.
[10] Non-fasting C-peptide was used for screening purposes, however fasting C-peptide was monitored as an exploratory efficacy endpoint.
[11] The DINAMO protocol specified that eGFR would be calculated using the Zappitelli formula (Zappitelli et la, Am J. Kidney Dis, 2006). According to DPMH consultants, the bedside Schwartz formula (eGFR = 0.413 x height (cm) / Serum creatinine (mg/dL) is preferred for estimating eGFR in a pediatric population > 1 year of age.

- Chronic alcohol or drug abuse within 3 months
- Female patients who are pregnant, nursing or plan to become pregnant

Reviewer Comment: It is unclear why pediatric subjects with eGFR < 60 mL/min/1.73m^2 were excluded from the DINAMO study; however, most other pediatric studies of antihyperglycemic agents have employed a similar exclusion criterion. The exclusion of subjects with moderate or severe renal impairment is relevant considering the mechanism of action of empagliflozin (glucosuria). In adults, the glycemic lowering efficacy of empagliflozin appears to decrease with worsening renal function; current labeling recommends that empagliflozin not be used for glycemic control in adults with eGFR < 30 mL/min/1.73m2. Despite the plan to enroll subjects with eGFR as low as 60 mL/min/1.73m^2, as discussed in Section 6.1.2, very few subjects with mild renal impairment (eGFR between 60 to < 90 mL/min/1.73m^2) were actually enrolled in the study and the majority of the study population had normal or elevated eGFR at baseline, likely reflecting the phenomenon of hyperfiltration which may be seen in up to 50% of pediatric T2D patients (see Section 6.1.2). In addition, the occurrence of moderate to severe renal impairment in pediatric T2D patients appears to be infrequent, such that it is unclear whether the study would have enrolled an adequate number of subjects to evaluate the impact of renal impairment, even if the exclusion criterion relating to eGFR had been broadened.

Dose Selection: The doses of empagliflozin and linagliptin used in the DINAMO study were the same doses approved for use in adults with T2D. The selection of the empagliflozin 10 mg and 25 mg doses was based on results of a single dose PK/PD study (Study 1245.87) showing similar exposure-response relationship among adult and pediatric patients with T2D (see Section 4.5). The selection of the linagliptin 5 mg dose (same dose approved for use in adults with T2D) was based on results of a pediatric dose finding study (Study 1218.56) comparing linagliptin 1 mg, linagliptin 5 mg and placebo. A protocol-defined interim analysis revealed superiority of the linagliptin 5 mg dose over the linagliptin 1 mg dose regarding DPP-4 inhibition at trough at steady state (see clinical review for NDA 201280/S-027).

Study Treatments:
Possible study treatments included empagliflozin 10 mg tablets, empagliflozin 25 mg tablets, linagliptin 5 mg tablets, placebo to empagliflozin 10 mg tablets, placebo to empagliflozin 25 mg tablets and placebo to linagliptin 5 mg tablets. During the course of the study, all subjects received a total of 3 tablets of study treatment, as indicated in Table 3.

Table 3: Study Treatments in Study 1218.91

Treatment Groups	Study Weeks	Study Treatments (tablets)					
		Pbo to lina 5 mg	Pbo to empa 10 mg	Pbo to empa 25 mg	Lina 5 mg	Empa 10 mg	Empa 25 mg
Placebo arm	Through	X	X	X			

	week 26						
Placebo arm re-randomized to lina 5 mg	week 26-52		X	X	X		
Placebo arm re-randomized to empa 10 mg	week 26-52	X		X		X	
Placebo arm Re-randomized to empa 25 mg	week 26-52	X	X				X
Empagliflozin 10 mg arm	Through week 14	X		X		X	
Empagliflozin 10 mg responders	week 14-52	X		X		X	
Empagliflozin 10 mg non-responders re-randomized to empa 10 mg	week 14-52	X		X		X	
Empagliflozin 10 mg non-responders re-randomized to empa 25 mg	week 14-52	X	X				X
Linagliptin arm	Through week 52		X	X	X		

Source: reviewer created. Abbreviations: Pbo: placebo, empa: empagliflozin, lina: linagliptin

Discontinuation criteria:
Criteria to discontinue study treatment for individual subjects included:
- the necessity to initiate a restricted concomitant medication therapy
-medical reasons preventing continued treatment with study medications (e.g., surgery, adverse events, other diseases, pregnancy)
- repeated non-compliance
- based on patient or parent choice.

Subjects who prematurely discontinued study drug were asked to attend an early end-of-termination visit and encouraged to attend all subsequent planned visits and study procedures except pharmacokinetic sampling. In the event that the subject does not agree to come to future visits, attempts were made to get information on vital status at week 55 post-randomization.

Treatment Compliance:
Treatment compliance was assessed based on pill counts evaluated at all study visits (treatment compliance % was defined as number of pills actually taken x 100 divided by number of pills which should have been taken).

Background therapy: Dose and dosing frequency of background antidiabetic therapy (metformin and/or insulin) were to remain unchanged unless medically appropriate. Weekly average variation of basal insulin dose was targeted to remain <0.1 IU/kg however changes to insulin dose were allowed to avoid hypoglycemia or hyperglycemia and to ensure that the

patient is achieving the best standard of care.

Rescue Treatment:
Glycemic rescue criteria were as follows:

- At any point in the study:
  - Acute metabolic compensation accompanied by significant symptoms (e.g., vomiting, dehydration, lethargy) and/or repeatedly elevated blood ketone values > 1.5 mmol/L irrespective of glucose value
  - Rescue therapy should also be considered for sustained hyperglycemia (80% non-fasting glucose > 300 mg/dL or fasting > 200 mg/dL for 1 week
- From week 12 onwards: two successive HbA1c > 9.0% and absolute increase of HbA1c > 1% compared to baseline

In general, insulin (or increased insulin doses for subjects on background insulin therapy) were to be used for rescue therapy. However, any new antidiabetic therapy and any dose increase of basal insulin of more than 0.1 IU/kg above the baseline prescribed dose for more than 21 consecutive days was considered rescue therapy.

Reviewer Comment: Rescue treatment in the first 12 weeks of the study was predominantly limited to situations involving acute metabolic decompensation, to avoid interference with evaluation of response to empagliflozin 10 mg at week 12 (leading to re-randomization for non-responders at week 14 to empagliflozin 10 mg or 25 mg).

Study Procedures: Subject monitoring was conducted as per the following schedule of events:

Trial Periods	**Screening**	**Placebo Run-in[1]**	**Randomised treatment period[4]**								**Follow-up**
Visit	**1A**	**1B**	**2[2]**	**3**	**4A**	**4B[3]**	**5[2]**	**6**	**7**	**8[2] EOT[5]**	**9[13]**
Days calculated from the day of first (randomised) treatment	**-21 to -14**	**-14**	**Day 1**	**29**	**85**	**99**	**183**	**211**	**295**	**365**	**386**
Weeks from date of first randomised treatment			**(**)**	**4**	**12**	**14**	**26**	**30**	**42**	**52**	**55**
Time window for visits	+7 days[1]	+7 days[1]	none	±7 days	±7 days	±7 days	±7 days	±7 days	±7 days	±7 days	+7 days
Informed consent and assent (*)	X										
Demographics	X										
Medical history	X										
Physical examination		X	X				X			X	X
Tanner staging (modified)[6]			X				X			X	
Vital signs (seated)[14]		X	X	X	X		X	X	X	X	X
12 lead-ECG		X					X			X	
Safety Laboratory tests[14]	X[7]		X[2]	X	X		X[2]	X	X	X[2]	X
HbA_{1c} [14]	X		X	X	X		X	X	X	X	
PK blood sampling							X[8]			X[8]	
Fasting plasma glucose			X[2]				X[2]			X[2]	
IGF-1, IGF-BP3 and markers of bone turnover[14]			X	X[9]			X	X[9]		X	X
DPP-4 activity			X[10]								
Pregnancy test[14]	X		X	X	X		X	X	X	X	
Auto-antibodies for diabetes (IA-2 and GADA)	X										
Serum C-peptide	X		X[2]				X[2]			X[2]	
Height	X						X			X	
Weight[14]		X	X	X	X		X	X	X	X	X
BMI		X					X			X	
Review of in-/exclusion criteria	X	X	X								
Dispense open-label trial drugs		X									
Administer open-label trial drugs		X									
Randomisation			X			X	X				
Dispense double-blind trial drugs[16]			X	X	X	X	X	X	X		
Administer trial drugs[16]			X	X	X	X	X	X	X	X	
Instructions/reminder on blood ketone measurements[15]			X	X	X		X	X	X	X	
Self-blood ketone monitoring[11]			X	X	X	X	X	X	X	X	X
Instructions/reminder on glucometer use[15]		X	X	X	X		X	X	X	X	
Self-blood glucose monitoring		X	X	X	X	X	X	X	X	X	X

Trial Periods	Screening	Placebo Run-in[1]	Randomised treatment period[4]								Follow-up
Visit	1A	1B	2[2]	3	4A	4B[3]	5[2]	6	7	8[2] EOT[5]	9[13]
Days calculated from the day of first (randomised) treatment	-21 to -14	-14	Day 1	29	85	99	183	211	295	365	386
Weeks from date of first randomised treatment			(**)	4	12	14	26	30	42	52	55
Adverse events[15]	X	X	X	X	X	X	X	X	X	X	X
Compliance check[15]			X	X	X	X	X	X	X	X	
Concomitant therapy[15]	X	X	X	X	X	X	X	X	X	X	X
Completion of patient participation (***)											X
Vital status collection[12]											X

1 Visit 1B could be performed on the same day as Visit 1A. Visit 1A could occur -28 days before Visit 2 per allowed out of window. Visit 1B could occur -21 days before Visit 2 per allowed out of window.

2 Visits to be performed in a fasted state (overnight fast for at least 8 h).

3 This visit could be either on-site visit or ambulatory visit (nurse/health care professional/validated courier to be assigned for delivering the trial medications at home and retrieving the previous ones dispensed at Visit 4A) as per the investigator's decision. In case of ambulatory visit not performed by a site representative, a phone contact by the investigator or a site staff representative was required to check any new adverse event or concomitant therapy.

4 Additional interactions (phone contact, text messaging or emails, as deemed appropriate) with the patient was performed a day or two after randomised treatment started and then after 2, 8, 18, 22, 34, 38, 46 and 50 weeks of treatment. Visits 3, 4A, 6, 7, 9 could be done remotely/by telephone/telemedicine under exceptional circumstances due to the COVID-19 pandemic. Reasons a remote/telephone/telemedicine visit may have been performed included confirmed or suspected COVID-19 infection or unwillingness to return to the investigator site due to concerns of COVID-19 exposure.

5 If a patient discontinued treatment early, an immediate End of Treatment (EOT) visit was to be conducted.

6 For patients with Tanner stage V at Visit 2, further assessment was not required at the subsequent visits.

7 Laboratory tests at Visit 1A included TSH, liver enzymes, alkaline phosphatase, serum creatinine, cystatine C, haemoglobin and haematocrit only in addition to HbA_{1c} and C-peptide and did not need to be collected in a fasted state.

8 Blood samples for pharmacokinetic analysis was to be collected within 30 min prior to drug administration at site (and preferably approximately 24 h after drug administration on the previous day) and 1.5h ±15 min after drug administration.

9 IGF-1 and IGF-BP3 were not to be measured at this Visit.

10 Blood sample for DPP-4 activity measurement was to be collected within 30 min prior to trial drug administration.

11 Daily blood ketone measurements in the first 4 weeks of treatment and the 4 subsequent weeks after Visit 5; otherwise at least 3 times per week and in case of intercurrent illness/stress or if deemed necessary by the investigator. In addition, blood ketone levels were to be checked by using the meter at clinic visits.

12 Patients who completed an early End of Treatment visit and did not accept to attend all remaining planned visits were to be contacted for vital status collection at Week 55. This could be done by phone.

13 Patients who discontinued treatment early were to attend Visit 9 at Week 55 in person or by telephone if agreed. At minimum, data on adverse events, concomitant therapies, and vital status were to be collected at Visit 9 at Week 55.

14 Vital signs, weight, and local laboratory testing was allowed for Visits 3, 4A, 6, 7, 9 under exceptional circumstances due to the COVID-19 pandemic.

15 Study procedure for Visits 3, 4A, 6, 7, 9 could be done remotely/by telephone/telemedicine/in-home visits under exceptional circumstances due to the COVID-19 pandemic.

16 Shipment/dispensing/administration of study medication to/at the patient's home was allowed for Visits 3, 4A, 6, 7 under exceptional circumstances due to the COVID-19 pandemic and requires discussion with the sponsor first using a sponsor-approved shipment provider. Prior to shipment of study medication to the patient's home, the investigator was to first conduct a remote/telephone/telemedicine/in-home visit to discuss adverse events, concomitant therapies, glucose/ketone monitoring, and study medication compliance. The review of local laboratory results could occur after shipment of study medication but within the protocol defined window of the visit. Reasons for shipment of study medication to a patient's home may have included unwillingness to return to the investigator site due to concerns of COVID-19 exposure or suspected COVID-19 infection.

(*) All patients' legal representative(s) had to sign an informed consent consistent with ICH-GCP guidelines prior to participation in the trial. Re-consenting may have been necessary when new relevant information became available and was to be conducted according to the sponsor's instructions. Re-consent could have been done remotely/by telephone/telemedicine/in-home visit under exceptional circumstances due to the COVID-19 pandemic. The initial informed consent and assent at Visit 1A had to be done in the clinic.

(**) Day of Randomisation / Day of first intake of randomised medication.

(***) Completion of patient participation also had to be completed if the patient withdrew prematurely following randomisation.

Source: Study 1218.91 Protocol

Subjects were provided a blood ketone meter and were recommended to obtain daily ketone measurements before breakfast during the first 4 weeks of treatment period and from weeks 26 to 30 (reflecting the time when subjects randomized to the placebo were re-randomized to active treatment), and measurements 2 to 3 times per week at all other times. Subjects were advised to contact the study site for any ketone measurements > 0.6 mmol/L, and to contact an emergency physician for any ketone measurements > 1.5 mmol/L. Ketone measurements > 1.5 mmol/L were to be reported as an adverse event.

Reviewer Comment: The requirement for frequent ketone monitoring was appropriate considering that euglycemic ketoacidosis is a known safety issue with SGLT2 inhibitors.

Study Endpoints

Primary efficacy endpoint:

- Change from baseline in HbA1c (%) after 26 weeks

Secondary efficacy endpoints:

- Change from baseline in fasting plasma glucose (FPG) (mg/dl) after 26 weeks
- Change from baseline in body weight (kg) after 26 weeks
- Change from baseline in systolic blood pressure (SBP) after 26 weeks
- Change from baseline in diastolic blood pressure (DBP) after 26 weeks

Exploratory efficacy endpoints:

Change from baseline in HbA1c (%) after 12 and 52 weeks

- Change from baseline in FPG (mg/dl) after 52 weeks
- Change from baseline in body weight (kg) after 12 and 52 weeks
- Change from baseline in SBP and DBP after 12 and 52 weeks
- Percentage of patients achieving HbA1c goals (<6.5% and <7%) after 26 and 52 weeks
- Percentage of patients initiating glycemic rescue therapy up to 26 and 52 weeks
- Change from baseline in fasting serum C-peptide after 26 and 52 weeks
- Change from baseline in urine albumin creatinine ratio (UACR) (mg/mmol) after 26 and 52 weeks
- Change from baseline in eGFR (mL/min/1.73m^2) after 26 and 52 weeks
- Change from week 12 to week 26 in HbA1c (%) in patients randomized to empagliflozin 10 mg due to not being at glycemic target at week 12

Safety endpoints:

- Adverse events (AE) including genital tract infections, urinary tract infections and ketone measurements reported as AE
- Percentage of patients with reported hypoglycemia after 26 and 52 weeks
- Change from baseline in Tanner staging after 26 and 52 weeks
- Change from baseline in serum electrolytes, lipids, IGF-1 and IGFBP-3 and markers of
- mineral and bone metabolism after 26 and 52 weeks
- Change from baseline in height (cm) and BMI (kg/m^2) after 26 and 52 weeks
- Growth velocity (cm/year) after 26 and 52 weeks

PK endpoints:

- Empagliflozin and linagliptin trough levels in plasma after 26 and 52 weeks

Per protocol, HbA1c was to be assessed by a National Glycohemoglobin Standardization Program (NGSP)-certified assay in a Central laboratory. However, due to the COVID-19 pandemic, a local instead of central laboratory could have been used. For HbA1c analyses, both NGSP-certified and non-NGSP certified HbA1c values were used, with order of preference being 1) NGSP-certified central laboratory values, (2) local laboratory values, and (3) non-NGSP certified local laboratory values. A sensitivity analysis was added excluding non-NGSP certified assay values for HbA1c in a global protocol amendment#4 (see below).

Statistical Analysis Plan

Treatment groupings: The following treatment groupings were used by the Applicant for efficacy analyses that are discussed in the context of this review[12]:

Treatment Grouping (TG)	Study Weeks	Treatment Groups included
TG1	Day 1-Week 26	1. Placebo 2. Linagliptin 5 mg 3. Empagliflozin Pooled*
TG2	Day 1-Week 26	1. Placebo 2. Empagliflozin 10 mg (E10) and empagliflozin 10 mg non-responders titrated to 25 mg at week 14 (E10NR-25)
TG3	Day 1-Week 26	1. Placebo 2. Empagliflozin 10 mg (E10) and empagliflozin 10 mg non-responders titrated to 10 mg at week 14 (E10NR-10)
TG4	Week 14 through Week 26/Week 52	1. Empagliflozin 10 mg non-responders titrated to 10 mg at week 14 (E10NR-10) 2. Empagliflozin 10 mg non-responders titrated to 25 mg at week 14 (E10NR-25)
TG7	Week 26 to Week 52	3. Linagliptin 5 mg after initial placebo (P/L5) 4. Empagliflozin 10 mg after initial placebo (P/E10) 5. Empagliflozin 25 mg after initial placebo (P/E25)

**all subjects treated with empagliflozin from Day 1 through Week 26*
Source: reviewer created based on review of TSAP

[12] Additional treatment groupings described by the Applicant (TG5, TG6, TG8 and TG9) were not considered relevant to the clinical review.

Hypothesis Testing:

The primary hypothesis testing included two hypotheses for TG1, to be tested simultaneously with an overall 2-sided alpha = 0.05 using the Hochberg procedure to account for multiple testing:

- TG1: Mean change in HbA1c (%) from baseline to the end of 26 weeks in the pooled empagliflozin group versus the placebo group
- TG1: Mean change in HbA1c (%) from baseline to the end of 26 weeks in the linagliptin 5 mg group versus the placebo group

If statistically significant results were obtained for both primary hypotheses, the following two secondary hypotheses for TG2 and TG3, respectively were to be tested in hierarchical order at the significance level alpha =0.05 (two-sided):

1. TG2: Mean change in HbA1c (%) from baseline to the end of 26 weeks in subjects treated with empagliflozin 10 mg (E10) and subjects initially treated with empagliflozin 10 mg and titrated to 25 mg (E10NR-25) versus the placebo group.
2. TG3: Mean change in HbA1c (%) from baseline to the end of 26 weeks in subjects treated with empagliflozin 10 mg (E10) and subjects initially treated with empagliflozin and titrated to 10 mg (E10NR-10) versus the placebo group.

Reviewer Comment: As discussed earlier, the study was not designed to directly evaluate efficacy of the empagliflozin 25 mg dose versus placebo. The empagliflozin groups specified in TG2 and TG3 differed based on the inclusion of "non-responder" subjects (i.e., TG2 includes non-responders who were titrated to 25 mg at week 14, while TG3 includes non-responders who were titrated to 10 mg at week 14); however, both groups also included "responder" subjects who were maintained on empagliflozin 10 mg through week 26. Because the titration of empagliflozin to 25 mg occurred at week 14, a comparison of HbA1c change from week 14 to week 26 may be more informative to evaluate dose response in the subgroup of non-responders who were re-randomized to 10 mg versus 25 mg.

Analysis methods: The primary efficacy endpoint analysis used analysis of covariance (ANCOVA) with "washout" approach. Additional sensitivity analyses for the primary endpoint used mixed models for repeated measures (MMRM). Key secondary efficacy endpoints were analyzed using ANCOVA (change in FPG), MMRM (change in body weight, SBP and DBP) and exact confidence interval (proportion of patients achieving HbA1c goals).

Populations:
The modified intention-to-treat set (mITT) was defined as a patient set including all randomized patients who were treated with at least one dose of the study medication and have a baseline HbA1c measurement. The primary efficacy endpoint analyses (including sensitivity analyses using MMRM, sensitivity analyses based on NGSP status of HBA1c, sensitivity analyses relating to COVID-19, and subgroup analyses), and analyses of secondary/additional efficacy endpoints

were all performed on the mITT.

The per protocol set (PPS) was defined as all patients in the mITT set who do not have any important protocol deviation through week 26 that may be expected to influence the assessment for the primary endpoint. Important protocol deviations occurring after week 26 did not to exclusion from the PPS. Additional analyses of the primary endpoint were performed on the PPS.

The following subgroups were considered in the primary efficacy analysis:

- Age group at randomization (< 15 years, and ≥ 15 to < 18 years)
- Baseline HbA1c (< 8.0%, 8.0 to 9.0% and > 9.0%)
- Baseline BMI (<34.65 kg/m2 and ≥34.65 kg/m2) and BMI Z-score (>2 to ≤3, and > 3)
- Baseline FPG (<126 mg/dL, 140 to < 200 mg/dL, and ≥ 200 mg/dL)
- Geographical Region (US or non-US)
- Sex (male or female)
- Time since diagnosis of diabetes (< 1 year, 1 year to 3 years, and > 3 years)
- Background antidiabetic medication (metformin only, metformin and insulin)
- Baseline eGFR (mL/min/1.72m^2) (<120, 120 to < 150 and ≥150)
- Race (Black of African American, White)

Approach for missing data: Multiple imputations (MI) approach was considered to impute missing data.

Protocol Amendments

In total, 6 global protocol amendments were issued, as summarized below in Table 4.

Table 4: Summary of Implemented Global Protocol Amendments for Study 1218-0091

Amendment #	Date	Key Changes
1	10/3/2019	• Statistical methods for the primary endpoint changed from MMRM to pattern mixture model (jump to placebo and inverse probability weighting approach). Prior MMRM became a sensitivity analysis. • Sample size increased • Addition of ancillary study (DINAMO Mono) • Updated exclusion criterion to specify acute metabolic decompensation • Addition of further efficacy endpoint (proportion of patients who achieve HbA1c reduction of >0.5% at the end of 26 and 52 weeks)

		• Addition of AESIs for arthralgia, bullous pemphigoid and AEs relating to reduced intravascular volume • Frequency for blood ketone bodies measurement adapted • Removal of hospitalization for unstable angina and of pancreatic events from adjudication process • Addition of BMI as a new subgroup
2	9/28/2020	• Updated inclusion criteria: reduction in length of diagnosis of T2DM from 12 to 8 weeks and addition of minimum daily metformin dosage • Change in primary endpoint analysis from pattern mixture model ('jump-to-placebo' and 'inverse probability weighting' approach) to 'wash-out' and 'inverse probability weighting' approach for primary and secondary hypotheses • Addition of measures relating to the COVID-19 pandemic (including remote visits, guidance for premature discontinuations, use of local instead of central laboratory testing, direct shipment of study medications to patients, possibility to replace patients to maintain sample size, addition of sensitivity analysis for the primary endpoint)
3	12/14/2020	• Further measures relating to COVID-19 pandemic (remote option for reconsent, local laboratory for serum pregnancy test)
4	7/14/2021	• Time between rescreening visits reduced from 12 to 8 weeks to allow earlier inclusion of patients • Clarification of maintaining blinded conditions relating to migration of data between main and ancillary study • Use of HbA1c from local laboratory acceptable if centrally analyzed NGSP-certified HbA1c assay unavailable (e.g., due to COVID-19 pandemic), with corresponding sensitivity analysis • Clarification of secondary hypotheses for ANCOVA • Addition of alternative means to measure blood glucose concentration
5	9/28/2021	• Clarification that patients with a CGM device may use relevant readings to avoid additional fingerpicks • Further clarification of secondary hypotheses for the ANCOVA

6	5/23/2022	• Addition of bone fracture as a further safety endpoint (already present in the TSAP)

Source: Reviewer created based on summary provided in the DINAMO CSR. Note that the dates correspond to the protocol version date, not the date of submission to the FDA. Specific changes relevant to DINAMO Mono ancillary trial not described.
Abbreviations: MMRM: Mixed model for repeated measures, AE: adverse event, AESI: adverse event of special interest, HbA1c: hemoglobin A1c, BMI: body mass index, ANCOVA: Analysis of covariance, CGM: continuous glucose monitoring, TSAP: Trial statistical analysis plan

Changes to the original Trial Statistical Analysis Plan (TSAP) mirrored the changes in the global amendments, and included:

- Changes relating to the primary endpoint analyses (Global Amendments 1, 2, 4, and 5)
- Addition of new further safety endpoints: arthralgia, bullous pemphigoid, volume depletion
- AEs related to ketone measurements, vital signs (including height, heart rate and BMI), endpoints related to hematology and biochemistry
- Specification of PK analyses
- Addition of analyses related to COVID-19
- Addition of AESIs relating to hepatic injury and lower limb amputation

6.1.2. Study Results

Compliance with Good Clinical Practices

The Applicant attested that the study was carried out in accordance with the principles of the Declaration of Helsinki, in accordance with the International Council for Harmonization (ICH)/ Good Clinical Practice (GCP) guideline, and in accordance with applicable regulatory requirements and Boehringer Ingelheim (BI) standard operating procedures (SOPs). For matters in which the CROs were involved in study conduct, the CRO's SOPs were followed as the SOP content was consistent with BI standards, GCP requirements, and requirements of local law.

Financial Disclosure

In the initial submission, the Applicant provided a completed form FDA 3454 certifying that each listed clinical investigator required to disclose to the Sponsor whether the investigator had any propriety interest in this product or a significant equity in the Sponsor as defined in 21 CFR 54.2 (b) did not disclose such interests (i.e., box 1 was selected). However, attached to form FDA 3454 (in Table "C"), the Applicant also included a listing of principal investigators/sub investigators who did not provide a certification of financial interests. On January 24, 2023, an IR was issued to the Applicant requesting clarification regarding the number of investigators/sub-investigators without completed financial disclosure and inquiring as to whether the Applicant had acted with due diligence to obtain all financial disclosures as required under 21 CFR 54.4. On February 7, 2023, the Applicant submitted a revised Table C

(attached to form FDA 3454) to eliminate investigators from sites that were not initiated and to eliminate investigators who did not participate in the study. The Applicant clarified that out of a total of 437 investigators/sub investigators, 415 had certified regarding the absence of financial interest and/or arrangements. The Applicant also clarified that despite due diligence, they were unable to obtain the information for 21 investigators. 15 of these investigators had incomplete financial disclosures (1 signed an incomplete form but did not participate in the study, 14 were considered incomplete because they only reported financial disclosures for the Applicant and did not include Eli Lilly as a co-sponsor, and 6 were not collected). The Applicant also indicated ongoing attempts to obtain corrected/completed financial disclosures.

FDA Form 3455 was completed for an Investigator at study site (b) (6) who received > $25,000 in payments from the Applicant for consulting services from (b) (6) through (b) (6)
(b) (6)

Reviewer Comment: Overall, the Applicant has adequately disclosed financial interests/arrangements with clinical investigators. With respect to the investigator at study site (b) (6) for whom FDA form 3455 was completed, given the relatively small proportion of subjects enrolled by this Investigator ((b) (6) total treated subjects) and considering the objective nature of the primary endpoint (HbA1c), I conclude that the financial interest of this Investigator would not have introduced any significant bias that would affect the study results or their interpretation.

Patient Disposition

Subject disposition within the DINAMO study is summarized in **Table 5**. Almost 40% of subjects who were screened were not randomized, most commonly due to HbA1c between outside of the acceptable range of 6.5 to 10.5% (56.7%) or due to having a positive islet cell antigen or glutamic acid decarboxylase auto-antibody (11.5%). A total of 158 subjects were randomized to study treatment, but only 157 subjects were treated (1 subject randomized to the linagliptin arm withdrew prior to receiving study treatment). Among treated subjects, 89.2% continued study treatment through week 26 and 82.8% continued study treatment through 52 respectively. The majority of treated subjects (89.2%) completed the planned study procedures through week 55.

Table 5: Subject Disposition in Study 1218.91

	Empagliflozin pooled n (%)[1]	**Linagliptin 5 mg**	**Placebo n (%)[1]**	**Total n(%)[1]**

				n (%)[1]			
Screened							262
Randomized	52			53	53		158
Treated (treated set)	52			52	53		157
Week 14 on study drug	**Responders***	**Non-responders***		49 (94.2)	49 (92.5)		145 (92.4)
	23 (44.2)	24 (46.2)					
		E10NR/10*	**E10NR/25***				
		11 (21.2)	13 (25.0)				
	Total: 47 (90.3)						
Week 26 on study drug (PPS)	44 (84.6)			49 (4.2)	47 (88.7)		140 (89.2)
Week 26 re-randomization					Lina 5 mg	16	
					Empa 10 mg	15	
					Empa 25 mg	16	
Week 52 on study drug	44			44	42		130 (82.8)
Study drug discontinuations through week 26	8 (15.4)[2]			3 (5.8)[3]	6 (11.3)[4]		17 (10.8)
Study drug discontinuations through week 52	8 (15.4)[2]			8 (15.4)[5]	11 (20.8)[6]		27 (17.2)

Source: reviewer created based on review of DINAMO CSR
*empa= empagliflozin, PPS= per protocol set. * responders were subjects initially randomized to empagliflozin 10 mg who had an HbA1c ≤7% at week 12 and were continued on empagliflozin 10 mg, non-responders were subjects initially randomized to empagliflozin 10 mg who had an HbA1c > 7% at week 12 and who were re-randomized at week 14 to empagliflozin 10 mg (E10NR/10) or 25 mg (E10NR/25).*

[1] Percentage of treated
[2] 4 patient withdrawals, 4 "other".
[3] 1 lost to follow up, 2 patient withdrawals by patient
[4] 1 lost to follow up, 4 patient withdrawals, 1 due to adverse event
[5] 1 lost to follow up, 5 patient withdrawals, 2 "other".
[6] 1 lost to follow up, 7 patient withdrawals, 1 "other".

Reviewer Comment:
It is notable that ~51% of subjects in empagliflozin arm were re-randomized at week 14 due to being non-responders (i.e., HbA1c >7%) at week 12. See below for further discussion regarding differences in demographic and baseline characteristics between empagliflozin non-responders versus empagliflozin responders. Through week 26, discontinuations were

lowest in the linagliptin arm and highest in empagliflozin arms. The majority of discontinuations were due to patient withdrawals/loss to follow up. No discontinuations due to an adverse event occurred in subjects treated with empagliflozin or linagliptin.

Protocol Violations/Deviations

According to the TSAP, Protocol deviations (PDs) were defined as important if they affected the rights or safety or the study patients, of if they could potentially influence the primary outcome measurement for the respective patients in a way that is neither negligible nor in accordance with the study objectives. The Applicant reported all important protocol deviations, and all non-important protocol deviations relating to the COVID-19 pandemic; this information is summarized in Table 6. Overall, important protocol deviations occurred in 26.4% of subjects in the placebo arm and in 23.1% of subjects in the empagliflozin arm. The majority of important protocol deviations involved non-compliance with study medication (occurring with greatest frequency in the placebo arm prior to week 26) and treatment interruption (occurring at slightly greater incidence in the empagliflozin arm versus placebo). Protocol deviations involving non-compliance with study medication prior to week 26 occurred with greatest frequency in the placebo arm (13.2% of subjects) as compared to the empagliflozin and linagliptin treatment arms (5.8% and 3.8% of subjects, respectively). The incidence of protocol deviations relating to treatment interruption for more than 7 days prior to week 26 was slightly greater in the empagliflozin and linagliptin arms (5.8% and 5.7% of subjects, respectively) as compared to the placebo arms (3.8% of subjects). A greater percentage of subjects within the empagliflozin arm appeared to have important protocol deviations relating to the study entrance criteria (7.7% of subjects), as compared to 1.9% of subjects in the linagliptin arm and 3.8% of subjects in the placebo arm). Protocol deviations relating to entrance criteria in the empagliflozin arm occurred in 1 subject (1840059001) who was negative for glutamic acid decarboxylase antibodies but had an initial detectable IA2 antibody (1.5 U/mL, reference range < 1.0 U/mL) at screening that was undetectable (<1.0 U/mL) on repeat testing on Day 1, and in 1 subject (1376001007) for whom the initial non-fasting C-peptide level was below the eligibility criteria of > 0.199 nmol/L, however a repeat value during the screening period was within the eligible range (0.759 nmol/L). Relatively few important protocol deviations relating to the COVID-19 pandemic occurred.

Table 6: Important Protocol Deviations in all Randomized Subjects in Study 1218.91

	Empagliflozin Pooled (N=52)	Linagliptin (N=53)	Placebo (N=53)	Total (N=158)
Subjects with at least 1 IPD	12 (23.1)	8 (15.1)	14 (26.4)	34 (21.5)
Subjects with at least 1 IPD leading to exclusion from PPS*	7 (13.5)	4 (7.5)	9 (17.0)	20 (12.7)
IPDs *(* indicates exclusion from PPS)*				
Entrance criteria not met	4 (7.7)	1 (1.9)	2 (3.8)	7 (4.4)

	Empagliflozin Pooled (N=52)	Linagliptin (N=53)	Placebo (N=53)	Total (N=158)
BMI out of range	0	0	1 (1.9)	1 (0.6)
Compliance during placebo run-in period	1 (1.9)	1 (1.9)	0	2 (1.3)
**Negative for IA-2 and GADA autoantibodies*	1 (1.9)	0	0	1 (0.6)
**Non-fasting C-peptide level out of range*	1 (1.9)	0	0	1 (0.6)
Prior antidiabetic treatment is not stable within timeframe prior to Visit 2 (DINAMO only)	1 (1.9)	0	1 (1.9)	2 (1.3)
Informed consent	1 (1.9)	0	0	1 (0.6)
Re-informed consent/assent (child or adolescent) during study not available, too late or not done.	1 (1.9)	0	0	1 (0.6)
Trial medication and randomization	7 (13.5)	7 (13.2)	11 (20.8)	25 (15.8)
**Non-compliance with study drug intake (Before or at Week 26)*	3 (5.8)	2 (3.8)	7 (13.2)	12 (7.6)
**Patient randomized but not treated*	0	1 (1.9)	0	1 (0.6)
Patient re-screened > 5 times within the protocol and/or < 12 weeks between each screening visit.	0	0	1 (1.9)	1 (0.6)
Treatment interruption for more than 7 consecutive days (After Week 26)	3 (5.8)	3 (5.7)	2 (3.8)	8 (5.1)
**Treatment interruption for more than 7 consecutive days (Before or at Week 26)*	3 (5.8)	1 (1.9)	2 (3.8)	6 (3.8)
Concomitant medication	1 (1.9)	0	1 (1.9)	2 (1.3)
**Use of prohibited medication during treatment period (Before or at Week 26)*	1 (1.9)	0	1 (1.9)	2 (1.3)
Inclusion Exclusion Criteria	3 (5.8)	0	2 (3.8)	5 (3.2)
BMI greater or equals 85th percentile for age and sex according to WHO references at Visit 1B	0	0	1 (1.9)	1 (0.6)
Compliance with trial medication intake must be between 75% and 125% during the open-label placebo run-in period	1 (1.9)	0	0	1 (0.6)
Patients treated with diet and exercise plus metformin at a stable dose for 8 weeks prior to Visit 2 AND/OR diet and exercise plus stable basal or MDI insulin therapy	1 (1.9)	0	0	1 (0.6)
Patients treated with diet and exercise plus metformin at a stable dose of at least 1000 mg daily or at the maximal tolerated dose for 8 weeks prior to V2 AND/OR diet and exercise	0	0	1 (1.9)	1 (0.6)
Positive for islet cell antigen auto-antibodies (IA-2) and glutamic acid decarboxylase (GADA) autoantibodies as measured by the central laboratory at Visit 1A	1 (1.9)	0	0	1 (0.6)
Protocol Deviations relating to COVID-19				
IPDs	0	1 (1.9)	1 (1.9)	2 (1.3)
Non-important PDs	5 (9.6)	2 (3.8)	7 (13.2)	14 (8.9)

PPS: per protocol set, PD: protocol deviation, IPD, important protocol deviations,
Source: Reviewer generated using OCS Analysis Studio, Custom Table Tool.
Columns - Dataset: Demographics; Filter: RANDFL = 'Y'.
Subjects with at least 1 IPD - Dataset: Other 1; Filter: ACAT = 'IMP-COV19' or ''.
Subjects with at least 1 IPD leading to exclusion from PPS - Dataset: Other 1; Filter: ACAT = 'IMP-COV19' or '', PARCAT3 = 'PPS, TS, TSactive, mITT set' or 'PPS'. IPDs - Dataset: Other 1; Filter: ACAT = 'IMP-COV19' or ''. Protocol Deviations relating to COVID-19 - Dataset: Other 1; Filter: ACAT = 'NONIMP-COV19' or 'IMP-COV19'.

The Applicant did not provide any information regarding non-important protocol deviations unrelated to the COVID-19 pandemic in the submission. Following an IR from the Agency, the Applicant stated that collation of non-important PDs was not required based on the TSAP and although non-important PDs may be documented in multiple internal data systems and were reviewed by the study team during the course of the study, a validated listing was unavailable.

Only 1 subject ((b) (6) in the placebo arm) was included as having an important protocol deviation relating to BMI out of range. However, upon review of the baseline characteristics of the treated study population (see Table 8 below), 2 additional subjects were enrolled who did not meet eligibility criteria relating to BMI ((b) (6) in the empagliflozin arm and (b) (6) in the placebo arm). Characteristics of these 3 subjects are detailed in Table 7 below. Given that all three subjects had negative pancreatic autoantibodies and preserved beta cell function (i.e., C-peptide >0.199 nmol/L), misdiagnosis of type 1 diabetes seems unlikely. According to the American Diabetes association a diagnosis of monogenic diabetes (MODY) should be considered in children when there are atypical features (including negative diabetes-associated autoantibodies, nonobese, lacking other metabolic features, strong family history of diabetes)[13]. Although the protocol specified exclusion of subjects with a known diagnosis of MODY, all 3 subjects had relatively recent onset of diabetes therefore it is unclear whether a diagnosis of MODY (and associated genetic testing) would have been considered prior to study enrollment. Following an IR, the Applicant stated that the BMI was not calculated at the inclusion visit for these subjects due to a technical issue with the case report forms that was later corrected. The Applicant was unable to confirm whether a diagnosis of MODY had been ruled out in these subjects. As displayed in Table 6 above, protocol deviations relating to BMI being out of range did not lead to exclusion from the PPS. Even if these subjects were misdiagnosed as having T2D, the overall study conclusions are unlikely to have been impacted due to the small numbers of subjects involved.

Table 7: Baseline characteristics of 3 enrolled subjects with normal BMI

	Subject		
	(b) (6)	(b) (6)	(b) (6)
Treatment arm based on initial randomization	Empagliflozin	Placebo	Placebo
Baseline BMI (kg/m2)	21.1	23.6	19.6
Baseline BMI Z-score	0.1	0.7	0.8
Duration of T2D (years)	0.4	1.1	0.4
Background antidiabetic medication	Metformin and insulin	Metformin	Metformin
HbA1c	6.6%	6.0%	7.9%
Baseline Fasting C-	0.802	0.921	0.439

[13] American Diabetes Association; 2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes—2021. Diabetes Care 1 January 2021; 44 (Supplement_1): S15–S33

peptide (nmol/L)			
Glutamic acid decarboxylase antibody	Negative*	Negative*	Negative*
Islet cell antibody*	Negative*	Negative*	Negative*
Noted to have protocol deviation relating to BMI inclusion criterion	No	No	Yes

Source: Reviewer created based on review of adlb.xpt and adsl.xpt datasets
**Reference range varied, all reported below lower limit*

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

Table of Demographic Characteristics

A summary of the demographic and baseline characteristics of the study population is provided in Table 8. The mean age was 14.5 years and the majority (61.8%) of the study population was female. 24.2% of subjects had a race and ethnicity designation of "white" and "Not Hispanic or Latino", and 31.2% of subjects were "black of African American". The majority of subjects (66.2%) were enrolled from the United States, followed by Mexico (14%) and the Russian Federation (5.1%), with additional subjects enrolled from Argentina, Brazil, Canada, Columbia, Germany, Israel, Korea, Thailand and the United Kingdom. The mean BMI was 36 kg/m2, mean BMI Z-score was +3.0, and 98.1% of the study population had a BMI Z-score > 1 (indicative of overweight or obese).

Table 8: Demographic and Baseline Characteristics of Treated Subjects in Study 1218.91

	Empagliflozin (N=52)	Linagliptin (N=52)	Placebo (N=53)	Total (N=157)
Age (years)				
Mean (SD)	14.4 (1.94)	14.6 (1.94)	14.6 (1.76)	14.5 (1.87)
Median (Min, Max)	15.0 (10, 17)	14.5 (10, 17)	14.0 (11, 17)	14.0 (10, 17)
Age groups, n (%)				
10-14	25 (48.1)	25 (48.1)	26 (49.1)	76 (48.4)
≥15 to <18	27 (51.9)	27 (51.9)	27 (50.9)	81 (51.6)
Sex, n (%)				
Female	33 (63.5)	30 (57.7)	34 (64.2)	97 (61.8)
Male	19 (36.5)	22 (42.3)	19 (35.8)	60 (38.2)
Race				
AMERICAN INDIAN OR ALASKA NATIVE	4 (7.7)	3 (5.8)	1 (1.9)	8 (5.1)
ASIAN	2 (3.8)	4 (7.7)	3 (5.7)	9 (5.7)
BLACK OR AFRICAN AMERICAN	19 (36.5)	13 (25.0)	17 (32.1)	49 (31.2)
DID NOT REPORT	0	2 (3.8)	1 (1.9)	3 (1.9)
MULTIPLE	4 (7.7)	2 (3.8)	1 (1.9)	7 (4.5)
NATIVE HAWAIIAN OR OTHER PACIFIC ISLANDER	0	2 (3.8)	1 (1.9)	3 (1.9)

	Empagliflozin (N=52)	Linagliptin (N=52)	Placebo (N=53)	Total (N=157)
WHITE	23 (44.2)	26 (50.0)	29 (54.7)	78 (49.7)
Ethnicity				
HISPANIC OR LATINO	17 (32.7)	22 (42.3)	21 (39.6)	60 (38.2)
NOT HISPANIC OR LATINO	35 (67.3)	30 (57.7)	32 (60.4)	97 (61.8)
Race and Ethnicity				
WHITE AND HISPANIC OR LATINO	8 (15.4)	16 (30.8)	16 (30.2)	40 (25.5)
WHITE AND NOT HISPANIC OR LATINO	15 (28.8)	10 (19.2)	13 (24.5)	38 (24.2)
Geographic Region				
Asia	1 (1.9)	3 (5.8)	1 (1.9)	5 (3.2)
Europe	6 (11.5)	5 (9.6)	7 (13.2)	18 (11.5)
North America	36 (69.2)	37 (71.2)	34 (64.2)	107 (68.2)
South America	9 (17.3)	7 (13.5)	11 (20.8)	27 (17.2)
Population				
Non-US	16 (30.8)	17 (32.7)	20 (37.7)	53 (33.8)
US	36 (69.2)	35 (67.3)	33 (62.3)	104 (66.2)
Height (cm)				
Mean (SD)	166.0 (10.4)	167.2 (10.4)	164.8 (10.4)	166.0 (10.4)
Median (Min, Max)	165.5 (142, 191)	168.5 (143, 184)	164.0 (144, 192)	165.0 (142, 192)
Weight (kg)				
Mean (SD)	98.7 (24.4)	102.8 (26.4)	98.4 (29.6)	99.9 (26.8)
Median (Min, Max)	94.0 (42.5, 157)	97.6 (43.2, 171)	94.0 (50.7, 168)	94.1 (42.5, 171)
Body Mass Index Z-score				
Mean (SD)	2.9 (0.8)	3.1 (0.7)	2.9 (1.0)	3.0 (0.9)
Median (Min, Max)	3.0 (0.1, 4.4)	3.1 (1.5, 4.3)	3.0 (0.7, 4.8)	3.1 (0.1, 4.8)
Body Mass Index Z-score Groups				
>=-2 to 1 (Normal)	1 (1.9)	0	2 (3.8)	3 (1.9)
>1 to 2 (Overweight)	4 (7.7)	4 (7.7)	7 (13.2)	15 (9.6)
>2 (Obese)	47 (90.4)	48 (92.3)	44 (83.0)	139 (88.5)
Body Mass Index (kg/m2)				
Mean (SD)	35.5 (7.17)	36.5 (7.6)	36.1 (10.1)	36.0 (8.3)
Median (Min, Max)	34.5 (21.1, 56.2)	34.8 (20.6, 55.2)	34.6 (19.6, 65.1)	34.7 (19.6, 65.1)

Source: Reviewer created using OCS Analysis Studio, Custom Table Tool.
SD = Standard Deviation. Columns - Dataset: Demographics; Filter: TRTFL = 'Y'.

Reviewer Comment: The demographics (i.e., mean age of around 14 years and majority female) are generally similar to other recently completed pediatric trials of antihyperglycemic therapies. In terms of race and ethnicity, 38.2% of subjects were Hispanic or Latino and 31.2% were Black or African American. A minority of subjects (24.2%) were non-Hispanic White. Based on U.S. prevalence estimates from 2001 to 2017, the representation of ethnic and racial minorities among youths with T2D has increased rapidly, particularly among non-Hispanic black and Hispanic youths[14]. However, the racial/ethnic distributions of the study

[14] Lawrence JM et al. Trends in Prevalence of Type 1 and Type 2 Diabetes in Children and Adolescents in the US, 2001-2017. JAMA. 2021;326(8):717–727. Per Supplementary eTable 2, estimated prevalence of T2D per 1000 youth aged 10-14 years in 2017 was 0.10 (white females), 0.03 (white males), 1.36 (black females), 0.60 (black males), 0.51 (Hispanic females), 0.26 (Hispanic males), 0.37 (Asian/pacific islander females), 0.26 (Asian/pacific

population may have also been influenced by enrollment of a third of subjects from non-US sites. In general, the majority (88.5%) of the study population had a BMI in the obese range. Notably, a total of 3 subjects with normal BMI were enrolled (1 in the empagliflozin arm and 2 in the placebo arm) despite the requirement for BMI > 85th percentile for age and sex (see discussion of protocol deviations above).

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

Table 9 displays the baseline characteristics relating to T2D. The mean HbA1c was 8.0% and 66.2% of the study population had a baseline HbA1c of < 8.5%. The mean duration of T2D was 2.1 years. The vast majority of patients (91%) were on background metformin, and 40% were on background metformin and insulin. 5.7% of subjects were on no background antidiabetic therapy, and 3.2% of subjects were treated with insulin alone. The proportion of subjects receiving background metformin and insulin was highest in subjects with baseline HbA1c > 9%, as compared to subjects with baseline HbA1c 8 to 9% and those with baseline HbA1c < 8% (61.8% vs. 42.5% vs. 25.3%, respectively) (Table 10). The mean total daily dose of metformin was 1661.5 mg, with the majority (76.2%) of subjects receiving a daily dose of > 1500 mg. Among insulin users, the mean basal insulin total daily dose was 54.3 IU/day. In terms of diabetes complications and related comorbidities, the mean eGFR (based on the bedside Schwartz calculation)[15] was 115.3 mL/min/1.73m^2. Nearly a quarter of subjects had evidence of either microalbuminuria (21.0%) and/or macroalbuminuria (3.8%). The majority of subjects were normotensive at baseline, but 15.9% had hypertension. No enrolled subjects had diabetic retinopathy.

islander males), 0.70 (American Indian females), 0.57 (American Indian males). Estimated prevalence of T2D per 1000 youth aged 15 -19 years in 2017 was 0.33 (white females), 0.31 (white males), 3.48 (black females), 1.81 (black males), 1.94 (Hispanic females), 1.44 (Hispanic males), 1.09 (Asian/pacific islander females), 0.65 (Asian/pacific islander males), 3.52 (American Indian females), 1.78 (American Indian males).

[15] Bedside Schwartz formula for eGFR = 0.413 x height (cm) / Serum creatinine (mg/dL). The DINAMO protocol specified that eGFR would be calculated using the Zappitelli formula (Zappitelli et la, Am J. Kidney Dis, 2006). According to DPMH consultants, the bedside Schwartz formula is preferred for estimating eGFR in a pediatric population > 1 year of age; therefore, eGFR calculated with the bedside Schwartz formula has been used in this clinical review.

Table 9: Baseline characteristics relating to T2D, all treated subjects, Study 1218.91

	Empagliflozin (N=52)	Linagliptin (N=52)	Placebo (N=53)	Total (N=157)
HbA1c (%)				
Mean (SD)	8.0 (1.29)	8.0 (1.11)	8.1 (1.23)	8.0 (1.20)
Median (Min, Max)	7.9 (6.2, 10.6)	8.0 (6.1, 10.6)	7.6 (6, 10.7)	7.9 (6, 10.7)
HbA1c Ranges				
<8.5%	36 (69.2)	31 (59.6)	37 (69.8)	104 (66.2)
>=8.5%	16 (30.8)	21 (40.4)	16 (30.2)	53 (33.8)
Duration of T2D (years)				
Mean (SD)	2.0 (1.68)	2.2 (1.61)	2.2 (2.30)	2.1 (1.88)
Median (Min, Max)	1.3 (0.2, 8.6)	1.6 (0.3, 6.2)	1.7 (0.2, 13.7)	1.6 (0.2, 13.7)
Background Antidiabetic Medication				
Insulin only	3 (5.8)	0	2 (3.8)	5 (3.2)
Metformin and Insulin	22 (42.3)	22 (42.3)	19 (35.8)	63 (40.1)
Metformin only	26 (50.0)	26 (50.0)	28 (52.8)	80 (51.0)
None	1 (1.9)	4 (7.7)	4 (7.5)	9 (5.7)
Basal insulin total daily dose among insulin users[1]	N=25	N=22	N=21	N=68
Mean (SD)	59.6 (38.9)	50.3 (27.3)	52.3 (36.4)	54.3 (34.5)
Median (Min, Max)	50.0 (10, 195)	37.5 (12, 112)	46.0 (10, 195)	48.5 (10, 195)
Metformin total daily dose (N, %)[1]				
< 1500 mg	13 (25.0)	10 (19.2)	11 (20.8)	34 (21.7)
>1500 mg	35 (67.3)	38 (73.1)	36 (67.9)	109 (69.4)
No metformin	4 (7.7)	4 (7.7)	6 (11.3)	14 (8.9)
Fasting C-peptide (nmol/L)				
Mean (SD)	1.0 (0.5)	1.1 (0.6)	0.9 (0.4)	1.0 (0.5)
Median (Min, Max)	0.8 (0.1, 3.1)	1.0 (0.2, 3.0)	0.8 (0.04, 1.7)	0.9 (0.04, 3.1)
Fasting Plasma Glucose (mg/dL)				
Mean (SD)	154.4 (57.8)	162.8 (56.01)	158.6 (53.8)	158.7 (55.6)
Median (Min, Max)	143.0 (44.0, 331.2)	157.1 (84.0, 314.1)	151.5 (50.1, 293.0)	150.1 (44.0, 331.2)
eGFR (Schwartz Calculation, mL/min/1.73m2)				
Mean (SD)	115.2 (25.2)	120.0 (34.8)	110.8 (22.3)	115.3 (28.0)
Median (Min, Max)	109.6 (72.6, 220.7)	114.2 (77.7, 255.5)	106.0 (67.0, 162.2)	109.9 (67.0, 255.5)
eGFR (Schwartz Calculation, mL/min/1.73m2) Ranges				
>=150	4 (7.7)	7 (13.5)	4 (7.5)	15 (9.6)
120 to <150	12 (23.1)	15 (28.8)	13 (24.5)	40 (25.5)
60 to <90	3 (5.8)	9 (17.3)	8 (15.1)	20 (12.7)
90 to <120	33 (63.5)	21 (40.4)	28 (52.8)	82 (52.2)
Urine Albumin/Creatinine Ratio (mg/g) Ranges				
<30 (Normal)	40 (76.9)	36 (69.2)	40 (75.5)	116 (73.9)
<NO DATA>	1 (1.9)	0	1 (1.9)	2 (1.3)
>300 (Macroa buminuria)	1 (1.9)	2 (3.8)	3 (5.7)	6 (3.8)
30 to 300 (Microalbuminuria)	10 (19.2)	14 (26.9)	9 (17.0)	33 (21.0)
Hypertension				
N	46 (88.5)	42 (80.8)	44 (83.0)	132 (84.1)

	Empagliflozin (N=52)	Linagliptin (N=52)	Placebo (N=53)	Total (N=157)
HbA1c (%)				
Mean (SD)	8.0 (1.29)	8.0 (1.11)	8.1 (1.23)	8.0 (1.20)
Median (Min, Max)	7.9 (6.2, 10.6)	8.0 (6.1, 10.6)	7.6 (6, 10.7)	7.9 (6, 10.7)
HbA1c Ranges				
<8.5%	36 (69.2)	31 (59.6)	37 (69.8)	104 (66.2)
>=8.5%	16 (30.8)	21 (40.4)	16 (30.2)	53 (33.8)
Duration of T2D (years)				
Mean (SD)	2.0 (1.68)	2.2 (1.61)	2.2 (2.30)	2.1 (1.88)
Median (Min, Max)	1.3 (0.2, 8.6)	1.6 (0.3, 6.2)	1.7 (0.2, 13.7)	1.6 (0.2, 13.7)
Background Antidiabetic Medication				
Insulin only	3 (5.8)	0	2 (3.8)	5 (3.2)
Y	6 (11.5)	10 (19.2)	9 (17.0)	25 (15.9)

Source: Reviewer generated using OCS Analysis Studio, Custom Table Tool. Columns - Dataset: Demographics; Filter: TRTFL = 'Y'. SD= Standard Deviation.
[1]Basal insulin total daily dose and metformin total daily dose data were taken from CSR Table 15.1.4:3 and is based on dosing at the start of study drug

Table 10: Background Antidiabetic Medication Use according to Baseline HbA1c, Study 1218.91

	Empagliflozin Pooled	Linagliptin	Placebo	Total
Baseline HbA1c > 9.0%	**N=12**	**N=10**	**N=12**	**N=34**
Insulin only	0	0	1 (8.3)	1 (2.9)
Metformin and Insulin	7 (58.3)	6 (60.0)	8 (66.7)	21 (61.8)
Metformin only	5 (41.7)	2 (20.0)	3 (25.0)	10 (29.4)
None	0	2 (20.0)	0	2 (5.9)
Baseline HbA1c 8 to 9%	**N=12**	**N=16**	**N=12**	**N=40**
Metformin and Insulin	7 (58.3)	8 (50.0)	6 (50.0)	21 (52.5)
Metformin only	4 (33.3)	7 (43.8)	6 (50.0)	17 (42.5)
None	1 (8.3)	1 (6.2)	0	2 (5.0)
Baseline HbA1c <8.0%	**N=28**	**N=26**	**N=29**	**N=83**
Insulin only	3 (10.7)	0	1 (3.4)	4 (4.8)
Metformin and Insulin	8 (28.6)	8 (30.8)	5 (17.2)	21 (25.3)
Metformin only	17 (60.7)	17 (65.4)	19 (65.5)	53 (63.9)
None	0	1 (3.8)	4 (13.8)	5 (6.0)

Source: Reviewer created in OCS Analysis Studio, Custom Table Tool.
Columns - Dataset: Demographics; Filter: TRTFL = 'Y', HBA1CB2 = '>9.0'.
Columns - Dataset: Demographics; Filter: TRTFL = 'Y', HBA1CB2 = '8.0 to 9.0'.
Columns - Dataset: Demographics; Filter: TRTFL = 'Y', HBA1CB2 = '<8.0'.
Dataset: Demographics; Filter: None.

Reviewer Comment: The mean HbA1c in this study (8.0%) was similar to that observed in other recently completed pediatric trials of antihyperglycemic agents. It is notable that 9% of enrolled subjects were not treated with metformin at baseline. This finding is likely related to the provision in the eligibility criteria that allowed for enrollment of patients with documented intolerance to metformin due to metformin-related side effects. The vast majority of subjects (91.1%) received background metformin therapy. The specific metformin

formulation (i.e., metformin immediate release versus metformin extended-release product) was not systematically collected during the study, however, in response to an IR, the Applicant confirmed that at least 9 subjects (i.e., 6.3% of subjects who received background metformin) received a metformin extended-release formulation based on the reported drug names.

As discussed previously, subjects with eGFR < 60 mL/min/1.73m^2 were excluded. In addition, a small proportion of enrolled subjects had mild renal impairment (eGFR between 60 to 90 mL/min/1.73m^2), and the overall mean eGFR of the study population (115.3 mL/min/1.73m^2) was elevated as compared to studies of empagliflozin in adults (mean eGFR was 86.8 mL/min/1.73m^2). This is consistent with published reports that 24 to 50% of pediatric patients with T2D can experience hyperfiltration as a predictor of progressive diabetic kidney disease[16]. Nearly a quarter of the DINAMO study population had early evidence of diabetic kidney disease at baseline (i.e., microalbuminuria or macroalbuminuria), despite a mean duration of T2D of only around 2 years. This finding is consistent with the early-onset of diabetes-related complications that has been reported in children with T2D (as discussed above in Section 2).

Baseline/demographic characteristics among subjects treated with empagliflozin

As discussed previously, subjects treated with empagliflozin 10 mg who did not achieve a week 12 HbA1c > 7% were considered "non-responders" and underwent a second randomization at week 14 to either continue empagliflozin 10 mg or to titrate to empagliflozin 25 mg. Subjects treated with empagliflozin 10 mg who achieved a week 12 HbA1c $\leq$ 7% were not offered the option for a second randomization and continued receiving empagliflozin 10 mg. The baseline/demographic characteristics for the empagliflozin non-responders who underwent the second randomization at week 14 versus the empagliflozin responders who did not undergo a second randomization is displayed in Table 11. The baseline/demographic characteristics of empagliflozin non-responders who were continued on 10 mg versus those who were titrated to 25 mg are described in Table 12.

[16] Bjornstad P, Cherney DZ. Renal Hyperfiltration in Adolescents with Type 2 Diabetes: Physiology, Sex Differences, and Implications for Diabetic Kidney Disease. Curr Diab Rep. 2018 Mar 19;18(5):22.

Table 11: Baseline/Demographic Characteristics of Subjects treated with Empagliflozin 10 mg at week 14

	Non-responders re-randomized at week 14 (N=24)	Responders not re-randomized at week 14 (N=23)
Age		
Mean (SD)	14.2 (1.94)	14.6 (1.95)
Median (Min, Max)	14.0 (10, 17)	15.0 (11, 17)
Sex		
F	16 (66.7)	14 (60.9)
M	8 (33.3)	9 (39.1)
Ethnicity		
HISPANIC OR LATINO	10 (41.7)	6 (26.1)
NOT HISPANIC OR LATINO	14 (58.3)	17 (73.9)
Race		
AMERICAN INDIAN OR ALASKA NATIVE	0	3 (13.0)
ASIAN	1 (4.2)	1 (4.3)
BLACK OR AFRICAN AMERICAN	10 (41.7)	8 (34.8)
MULTIPLE	3 (12.5)	1 (4.3)
WHITE	10 (41.7)	10 (43.5)
BMI Z-score		
>=-2 to 1 (Normal)	1 (4.2)	0
>1 to 2 (Overweight)	1 (4.2)	3 (13.0)
>2 (Obese)	22 (91.7)	20 (87.0)
Duration of T2D		
<1 year	9 (37.5)	7 (30.4)
>3 years	4 (16.7)	7 (30.4)
1 year - 3 years	11 (45.8)	9 (39.1)
Background Anti-diabetic Medication		
Insulin only	0	3 (13.0)
Metformin and Insulin	14 (58.3)	5 (21.7)
Metformin only	10 (41.7)	15 (65.2)
HbA1c (%)		
Mean (SD)	8.5 (1.12)	7.2 (0.91)
Median (Min, Max)	8.2 (6.6, 10.6)	6.9 (6.2, 9.9)
HbA1c ranges		
<8.5	13 (54.2)	21 (91.3)
>=8.5	11 (45.8)	2 (8.7)
C-peptide		
Mean (SD)	1.0 (0.68)	1.0 (0.33)
Median (Min, Max)	0.8 (0.24, 3.1)	0.9 (0.16, 1.46)

Source: OCS Analysis Studio, Custom Table Tool. Columns - Dataset: Demographics; Filter: RAND14FL = 'Y'.

Table 12: Baseline Characteristics of Empagliflozin 10 mg Non-Responders continued on Empagliflozin 10 mg (E10NR/10) versus those titrated to Empagliflozin 25 mg (E10NR/25) at Week 14

	E10NR/10 (N=11)	E10NR/25 (N=13)
HbA1c (%)		
Mean (SD)	8.8 (1.15)	8.2 (1.08)
Median (Min, Max)	9.0 (6.6, 10.6)	8.1 (6.9, 10.6)
HbA1c Range		
<8.5	5 (45.5)	8 (61.5)
>=8.5	6 (54.5)	5 (38.5)
Age		
Mean (SD)	14.6 (1.63)	13.9 (2.18)
Median (Min, Max)	14.0 (11, 17)	14.0 (10, 17)
Duration of T2D (years)		
<1 year	5 (45.5)	4 (30.8)
>3 years	1 (9.1)	3 (23.1)
1 year - 3 years	5 (45.5)	6 (46.2)
Background ADA		
Metformin and Insulin	8 (72.7)	6 (46.2)
Metformin only	3 (27.3)	7 (53.8)

E10NR/10= empagliflozin 10 mg non-responders randomized at week 14 to remain on empagliflozin 10 mg; E10NR/25= empagliflozin 10 mg non-responders randomized at week 14 to titrate to empagliflozin 25 mg.
Source: Reviewer Created in OCS Analysis Studio, Custom Table Tool. Columns - Dataset: Demographics; Filter: RAND14FL = 'Y'. HbA1c (%) - Dataset: Demographics; Filter: None. HbA1c Range - Dataset: Demographics; Filter: None. Age - Dataset: Demographics; Filter: None. Duration of T2D (years) - Dataset: Demographics; Filter: None. Ethnicity - Dataset: Demographics; Filter: None. Background ADA - Dataset: Demographics; Filter: None. SD = Standard Devia ion.

Reviewer Comment: Compared to empagliflozin-treated subjects who were not re-randomized at week 14, subjects who were re-randomized at week 14 due to being identified as "non-responders" at week 12 had higher baseline HbA1c (8.5% vs 7.2%) and a higher frequency of background treatment with both metformin and insulin (58.3% vs. 21.7%). These findings suggest that the empagliflozin 10 mg non-responders may have had comparatively more advanced disease at baseline or were more rapid progressors than responders. A greater percentage of non-responders were also Hispanic or Latino or Black or African American. In the TODAY study, the treatment failure (defined as HbA1c >8% for 6 months or inability to wean from temporary insulin therapy within 3 months of an acute metabolic decompensation) was found to be greatest in minority racial/ethnic groups[8].

Due to differences in treatment response (see discussion regarding dose/dose-response below), an analysis of baseline characteristics relating to T2D between subgroups of non-responder subjects who were continued on empagliflozin 10 mg (E10NR/10) as compared to those who were titrated to empagliflozin 25 mg at week 14 (E10NR/25) was also pursued. Compared to the subgroup E10NR/25, the subgroup of E10NR/10 had a slightly higher baseline HbA1c (8.8% vs. 8.2%) and a greater proportion of subjects on background metformin and insulin (72.7% vs. 46.2%). However, these differences are not as pronounced as those seen in the non-responders vs. responders.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment Compliance: Mean treatment compliance during the placebo-controlled period (average of compliance measured at weeks 4, 12, 14 and 26) was 95% in the empagliflozin arm, 96% in the linagliptin arm and 92% in the placebo arm (Table 13) A minority of subjects had < 75% compliance over the course of the placebo-controlled period (data not shown) and at week 26. Based on an Applicant conducted analysis comparing compliance with study medication before and after the start of COVID-19 disruption, there was no significant impact of COVID-19 on the overall compliance of patients. Mean treatment compliance during the safety extension period (measured at weeks 30, 42 and 52) was 94.1% in subjects who received empagliflozin 10 mg or 25 mg and 90.8% in subjects who received linagliptin.

Table 13: Treatment Compliance* through Week 26, Study 1218.91

	E Pooled (N=52)	Linagliptin (N=52)	Placebo (N=53)
Treatment Compliance* at Weeks 4, 12, 14, and 26			
Mean (SD)	95.0 (14.04)	96.0 (12.36)	92.0 (17.23)
Median (Min, Max)	100.0 (1, 125)	100.0 (20, 114)	99.5 (0, 126)
Treatment Compliance* Categories at Week 26 for Subjects on Active Treatment			
N	44 (84.6)	47 (90.4)	47 (88.7)
<75%	5 (9.6)	5 (9.6)	7 (13.2)
>125%	0	0	1 (1.9)
75% to 125%	39 (75.0)	41 (78.8)	38 (71.7)
Incalculable	0	1 (1.9)	1 (1.9)

Source: Reviewer created in OCS Analysis Studio, Custom Table Tool. Columns - Dataset: Demographics; Filter: TRTFL = 'Y'. Treatment Compliance at Weeks 4, 12, 14, and 26 - Dataset: Exposure; Filter: PARAM = 'Reported compliance up to week 26 [%]', AVISIT = 'Week 4' or 'Week 12' or 'Week 14' or 'Week 26'. Treatment Compliance Categories at Week 26 for Subjects on Active Treatment - Dataset: Exposure; Filter: PARAM = 'Reported compliance up to week 26 [%]', AVISIT = 'Week 26'. Treatment Compliance Categories at Week 26 for Subjects on Active Treatment - Dataset: Exposure; Filter: PARAM = 'Reported compliance up to week 26 [%]', AVISIT = 'Week 26'. SD = Standard Devia ion.

· *Treatment compliance % was defined as number of pills actually taken x 100 divided by number of pills which should have been taken).*

Reviewer Comment: Treatment compliance with study drug was reasonable.

Concomitant Medications:

Background antidiabetic medication at baseline was previously reported in Table 9. Table 14 displays information regarding the initiation of new antidiabetic concomitant medications from baseline to week 26. The rate of initiation of new antidiabetic medications was overall low across treatment arms. New antidiabetic agents were typically insulin products, however, 1 subject in the empagliflozin arm was initiated on metformin (dose of 500 mg daily), and 1

subject in the placebo arm was initiated on a sulfonylurea[17].

Table 14: New Antidiabetic Concomitant Medication through Week 26

	Empagliflozin Pooled (N=52)	Linagliptin (N=52)	Placebo (N=53)
Subjects with New Antidiabetic Concomitant Medication	3 (5.8)	1 (1.9)	3 (5.7)
Insulin	2 (3.8)	1 (1.9)	2 (3.8)
Metformin	1 (1.9)	0	0
Sulfonylurea	0	0	1 (1.9)

Source: Reviewer created in OCS Analysis Studio, Custom Table Tool. Columns - Dataset: Demographics; Filter: TRTFL = 'Y'. Subjects with New An idiabetic Concomitant Medication - Dataset: Concomitant Medications; Filter: APERIOD = '1' - '2', CRIT1FL = 'Y'. Insulin - Dataset: Concomitant Medications; Filter: APERIOD = '1' - '2', CRIT1FL = 'Y', BMEDGRM = 'Y'. Metformin - Dataset: Concomitant Medications; Filter: APERIOD = '1' - '2', BMEDGRI = 'Y', CRIT1FL = 'Y'. Sulfonylurea - Dataset: Concomitant Medications; Filter: APERIOD = '1' - '2', CRIT1FL = 'Y', BMEDGRI = '', BMEDGRM = ''.

From weeks 26 to 52, a new antidiabetic agent (insulin) was introduced in 1 subject (1.3%) receiving empagliflozin, and in 5 subjects (7.7%) receiving linagliptin.

The most commonly used non-antidiabetic medications through week 26 included vitamin D supplementation[18] (20.3%), paracetamol (14.0%), amoxicillin (12.7%) and ibuprofen (7.6%).

Rescue Therapy

As discussed previously, rescue therapy was defined as any new addition of antidiabetic therapy introduced after the first dose of study treatment or any total daily dose increase of basal insulin of more than 0.1 IU/kg above the baseline prescribed dose for more than 21 consecutive days.

From baseline to (and including) Week 26, 6 patients (11.3%) in the placebo group, 4 patients (7.7%) in the linagliptin 5 mg group, and 5 patients (9.6%) in the empagliflozin pooled group initiated glycemic rescue therapy. Through week 26, insulin was predominantly used as rescue therapy (either new initiation of insulin therapy as described in Table 14 above, or increase in insulin dose > 0.1 IU/kg for more than 21 days).

From week 26 to 52, 4 patients (6.1%) in the linagliptin 5 mg group and 3 patients (4%) in the empagliflozin pooled group initiated glycemic rescue therapy. For all of these subjects, rescue therapy was an increase in insulin dose > 0.1 IU/kg for more than 21 days.

Efficacy Results – Primary Endpoint

The primary endpoint was the change in HbA1c (%) from baseline to the end of 26 weeks. As

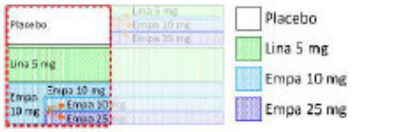
[17] Subject (b) (6) in the placebo arm was initiated on glipizide on study day 173. Upon secondary review, this subject did not experience any hypoglycemic events associated with BG <54 mg/dL (see Section 8.4.4).
[18] Ergocalciferol, cholecalciferol and vitamin D not otherwise specified

discussed above, hierarchical hypothesis testing was applied to the primary endpoint first testing the primary hypotheses followed by the secondary hypotheses. For the primary hypotheses, the effect of linagliptin and of pooled empagliflozin were simultaneously compared with placebo at an overall alpha of 0.05 (two-sided) using the Hochberg method to account for multiple testing. The primary analysis was performed with an ANCOVA adjusted for treatment, baseline HbA1c, and baseline age group.

Figure 3 below was taken from the Applicant's analysis of the primary efficacy endpoint. The efficacy of empagliflozin versus placebo was established, with a placebo-adjusted treatment effect of -0.84% change in HbA1c from baseline (95% confidence interval of -1.50 to -0.19, with p value of 0.0116). The efficacy of linagliptin versus placebo was not established, with a non-significant placebo-adjusted treatment effect of -0.34% change in HbA1c from baseline (95% confidence interval of -0.99 to 0.30 with p value of 0.2935). The Applicant's primary endpoint analysis for empagliflozin was confirmed by the statistical review team (Dr. Tu), with no major statistical issues identified[19]. The overall missing data rate was 9.6% for empagliflozin and 5.7% for placebo.

Figure 3: Primary endpoint analysis: HbA1c (%) Change from Baseline at Week 26, ANCOVA-mITT

Treatment	N analysed	Baseline Mean	Baseline SD	Change from baseline Adjusted mean	Change from baseline 95% CI		Comparison vs placebo Adjusted mean	Comparison vs placebo 95% CI		p-value
Primary hypotheses based on TG1, multiple imputation with wash-out approach										
Placebo	53	8.05	1.23	0.68	0.23	1.13				
Lina 5	52	8.05	1.11	0.33	−0.13	0.79	−0.34	−0.99	0.30	0.2935
Empa pooled	52	8.00	1.29	−0.17	−0.64	0.31	−0.84	−1.50	−0.19	0.0116



Source: DINAMO CSR

The Applicant conducted a sensitivity analysis for the primary hypothesis family using a mixed model for repeated measure (MMRM) based on the mITT population; these results were consistent with the results of the primary efficacy analysis. According to Dr. Tu, this sensitivity analysis is considered insufficient from a regulatory perspective, as MMRM assumes that data are missing at random which is unlikely in the clinical trial setting. Dr. Tu conducted an additional sensitivity analysis to account for the impact of missing data on the primary analysis result using the same ANCOVA model in the primary analysis but by imputing missing primary endpoints based on a return-to-baseline approach (Table 15). This analysis confirmed the results of the primary efficacy analysis.

[19] See primary statistical review by Dr. Wenda Tu under NDA 204629

Table 15: HbA1c Change from Baseline at Week 26, Sensitivity Analysis

	Empa pooled N=52	Placebo N=53
Baseline, mean (SD)	8.00 (1.29)	8.05 (1.23)
Change from baseline, LSMean[1] (SE)	-0.25 (0.23)	0.66 (0.22)
Difference from Placebo, LSMean[1] (CI)	-0.90 (-1.53, -0.27)	
Two-sided p-value (unadjusted)	0.01	

Abbreviations: CI = confidence interval, SD = standard deviation, SE = standard error.
[1] The LSMean estimate is based on an ANCOVA model adjusted for baseline HbA1c, baseline age stratum (< 15 years vs 15 to <18 years), and treatment. Missing data was multiply imputed based on the method of the method of return to baseline. Inference results were combined with Rubin's Rule.
Source: Dr. Tu's Analysis from the Primary Statistical Review; ada1c.xpt, adsl.xpt

Due to the failure of the primary hypothesis testing for the linagliptin vs. placebo comparison, formal statistical testing for the secondary hypotheses was not performed by the Applicant. Results of the Applicant's exploratory analyses for the secondary hypotheses are displayed in Table 16. As discussed previously, TG2 compares the primary endpoint in empagliflozin 10 mg responders + non-responders who were titrated to 25 mg versus placebo; whereas TG3 compares the primary endpoint in empagliflozin 10 mg responders + non-responders who were continued on 10 mg versus placebo. A larger treatment difference (-1.18%) was observed in TG3 as compared to TG2 (-0.52%). Sensitivity analyses for the secondary hypotheses conducted by the Applicant (Table 17) revealed a slightly larger treatment effect in TG2 (-0.87% and -0.81%), however the magnitude remained comparatively smaller as compared to TG3/

According to Dr. Tu, since the primary hypothesis testing concerned two independent tests of distinct drugs versus placebo, there was no need to control for multiplicity adjustment using the Hochberg procedure; i.e., testing of the primary hypotheses for both linagliptin versus placebo and empagliflozin versus placebo could have been performed each at a two-sided alpha of 0.05. Further, the failure of the primary hypothesis testing on linagliptin versus placebo should not preclude the formal testing of the secondary hypothesis family. Given that, a more efficient testing structure for the DINAMO study could have involved two testing sequences, the first involving a single test of linagliptin versus placebo, and the second sequence involving a sequential testing procedure of the pooled empagliflozin group versus placebo, followed by the two secondary hypothesis tests on the empagliflozin subgroups versus placebo. However, even if this more efficient structure had been utilized, it would have yielded the same conclusions as the current testing structure, as the secondary hypothesis testing for TG2 would have failed, precluding testing of the secondary hypothesis for TG3.

Table 16: Secondary Hypotheses Testing (Exploratory) for the Primary Endpoint; HbA1c (%) Change from Baseline at Week 26, ANCOVA-mITT

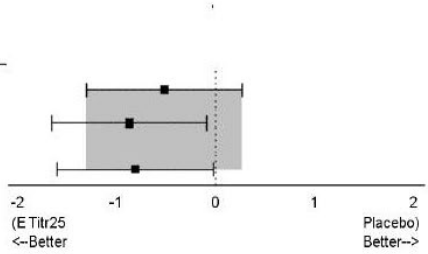
Treatment	N analysed	Baseline Mean	Baseline SD	Change from baseline Adjusted mean	Change from baseline 95% CI		Comparison vs placebo Adjusted mean	Comparison vs placebo 95% CI		p-value
Secondary hypothesis based on TG2, multiple imputation with wash-out and inverse probability weighting approach										
Placebo	53	8.05	1.23	0.66	0.12	1.21				
Empa 10+titr 25	41	7.80	1.26	0.14	−0.42	0.71	−0.52	−1.31	0.27	0.1943 (nominal)
Secondary hypothesis based on TG3, multiple imputation with wash-out and inverse probability weighting approach										
Placebo	53	8.05	1.23	0.68	0.19	1.17				
Empa 10+titr 10	39	7.92	1.36	−0.49	−1.03	0.04	−1.18	−1.90	−0.45	0.0015 (nominal)

Source: DINAMO CSR

Table 17: Sensitivity Analyses for the Primary Endpoint, HbA1c (%) Change from Baseline at Week 26, in TG2 and TG3

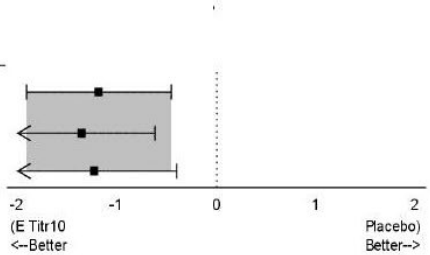
Empagliflozin (10 mg + titration to 25 mg) vs placebo (TG2)

Analysis – Analysis set (Data type)	E Titr25 (N)	Pbo (N)	Adjusted mean (95%-CI) Comparison vs. Placebo	p-value
Primary analysis: MI and IPW – mITT (OC-AD)	41	53	-0.52 (-1.31 0.27)	0.1943
Sensitivity analysis: MMRM at Wk 26 – mITT (OC-AD)	37	50	-0.87 (-1.65 -0.09)	0.0298
Sensitivity analysis: MI and IPW – PPS (OC-AD)	34	44	-0.81 (-1.60 -0.02)	0.0458



Empagliflozin (10 mg + titration to 10 mg) vs placebo (TG3)

Analysis – Analysis se: (Data type)	E Titr10 (N)	Pbo (N)	Adjusted mean (95%-CI) Comparison vs. Placebo	p-value
Primary analysis: MI and IPW – mITT (OC-AD)	39	53	-1.18 (-1.90 -0.45)	0.0015
Sensitivity analysis: MMRM at Wk 26 – mITT (OC-AD)	35	50	-1.35 (-2.09 -0.62)	0.0004
Sensitivity analysis: MI and IPW – PPS (OC-AD)	34	44	-1.22 (-2.04 -0.40)	0.0037



Source: DINAMO CSR

Reviewer Comment: The smaller treatment difference in TG2 as compared to TG3 is unexpected, considering that TG2 included some subjects that received a higher dose of empagliflozin (i.e., 25 mg) as compared to TG3 (in which the maximal dose of empagliflozin

was 10 mg). This finding raises question as to the dose-response of empagliflozin in pediatric subjects. This issue is discussed in further detail in the section on dose-response, below.

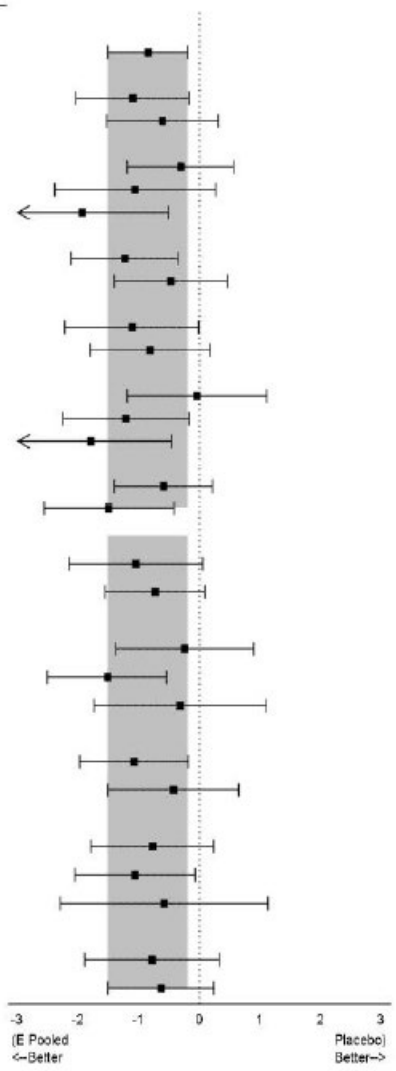
Subgroup Analyses for the Primary Efficacy Endpoint

The Applicant's subgroup analyses for the primary efficacy endpoint for the pooled empagliflozin treatment group versus placebo (TG1) included age at randomization (<15 years, >15 years), baseline HbA1c (<8.0%, 8.0 to 9.0%, > 9%), BMI (<34.65 kg/m2, >34.65 kg/m2), BMI Z-score (>2 to <3, >3), baseline fasting plasma glucose (< 126 mg/dL, 140 to < 200 mg/dL, >200 mg/dL), geographical region (US, non-US), sex (male, female), time since diagnosis of T2D (< 1 year, 1-3 years, > 3 years), background antidiabetic medication at baseline (metformin only, metformin and insulin), eGFR (<120, 120 to < 150, >150 mL/min/1.73m2) and race (Black or African American, White) (Figure 4). The estimated treatment effect was generally consistent across all subgroups, with the exception of subgroups with higher baseline HbA1c and FPG in which a trend towards a larger treatment effect was observed. Some slight differences in treatment response based on duration of T2D diagnosis were also seen (slightly larger treatment effect in subjects with T2D for 1 to 3 years as compared to those with T2D duration < 1 year or > 3 years), however this likely represents a chance finding based on the small numbers of subjects involved. No clear differences were seen in treatment response based on background antidiabetic medication at baseline (i.e., metformin only versus metformin and insulin), although the adjusted mean difference appeared to be numerically higher in those who received metformin only as compared to those who received dual therapy with metformin and insulin.

Figure 4: Subgroup Analyses for the Primary Endpoint for TG1, mITT, study 1218.91

Empagliflozin pooled vs placebo (TG1)

Subgroup \Category	E Pooled (N)	Pbo (N)	Adjusted mean (95%-CI) Comparison vs. Placebo	p-value
Overall	52	53	-0.84 (-1.50 -0.19)	0.0116
Age [years] at randomisation				
<15	25	26	-1.10 (-2.03 -0.16)	0.0212
>=15 to <18	27	27	-0.61 (-1.53 0.32)	0.1976
HbA1c [%] at baseline				
<8.0	28	29	-0.30 (-1.18 0.58)	0.5001
8.0 to 9.0	12	12	-1.05 (-2.38 0.27)	0.1185
>9.0	12	12	-1.93 (-3.35 -0.50)	0.0080
BMI [kg/m²]				
<34.65 [4]	26	27	-1.23 (-2.12 -0.35)	0.0065
>=34.65 [4]	26	26	-0.46 (-1.40 0.48)	0.3342
BMI z-score				
>2 to <=3 (Class 1 obesity)	21	17	-1.11 (-2.21 -0.01)	0.0487
>3 (Class 2 or 3 obesity)	26	27	-0.81 (-1.80 0.18)	0.1093
FPG [mg/dL] at baseline				
<126	19	13	-0.03 (-1.18 1.12)	0.9565
140 to <200	15	23	-1.21 (-2.24 -0.17)	0.0227
>=200	11	10	-1.79 (-3.13 -0.45)	0.0086
Geographical region				
US	36	33	-0.59 (-1.40 0.22)	0.1555
Non-US	16	20	-1.48 (-2.66 -0.42)	0.0066
Sex				
Male	19	19	-1.04 (-2.14 0.06)	0.0641
Female	33	34	-0.73 (-1.55 0.09)	0.0819
Time since diagnosis of T2DM				
<1 year	17	18	-0.23 (-1.37 0.90)	0.6847
1 year - 3 years	21	24	-1.52 (-2.50 -0.53)	0.0025
>3 years	14	11	-0.31 (-1.73 1.10)	0.6636
Background antidiabetic medication at baseline				
Metformin only	26	28	-1.07 (-1.97 -0.18)	0.0190
Metformin and Insulin	22	19	-0.42 (-1.50 0.66)	0.4473
eGFR [mL/min/1.73m2] (Zappitelli) at baseline				
<120	21	24	-0.77 (-1.79 0.24)	0.1360
120 to <150	19	23	-1.06 (-2.06 -0.06)	0.0373
>=150	12	6	-0.58 (-2.29 1.13)	0.5092
Race				
Black or African American	19	17	-0.78 (-1.89 0.33)	0.1666
White	23	29	-0.83 (-1.50 0.24)	0.1583

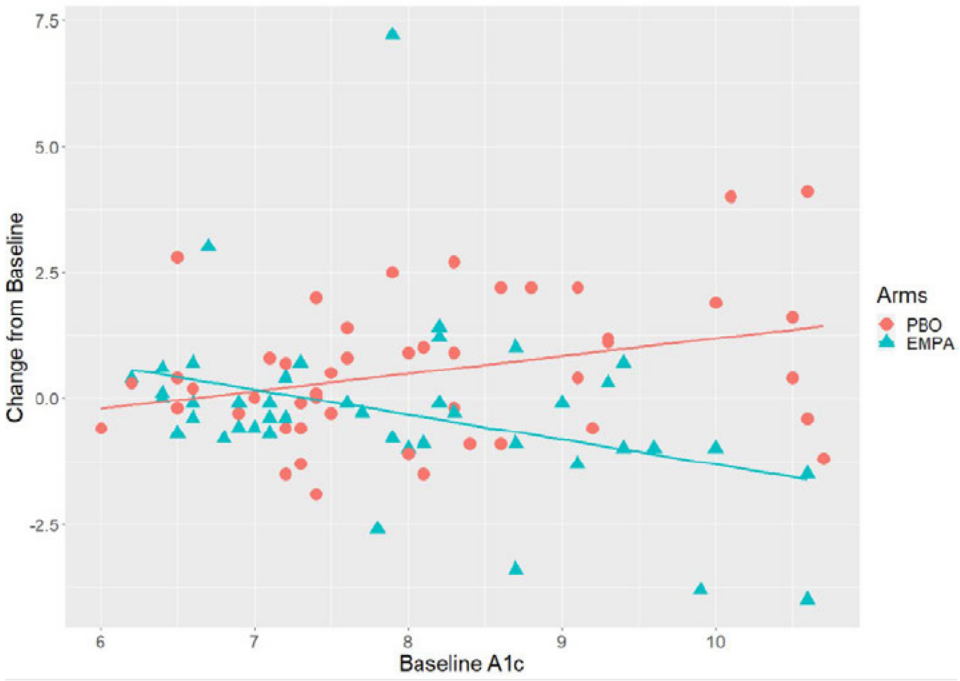


Source: DINAMO CSR

Dr. Tu also conducted subgroup analyses for the primary efficacy endpoint for the pooled empagliflozin treatment group versus placebo based on sex, race, age, geographic location, and background antidiabetic therapies. Subgroup analyses for background therapies included three groupings: 1) metformin only, metformin + insulin, and or other; 2) metformin or no metformin; 3) metformin monotherapy or other. Subgroup analyses for race included Black, White and "Other" (which combined race categories for American Indian/Alaska Native, Asian, Multiple, Native Hawaiian/Other Pacific Islander and included a subject with missing race). According to Dr. Tu's analyses, the estimated treatment effects for all subgroups were generally

consistent with the overall population, with the exception of an uncommonly large treatment effect difference in the "Other" race category that appeared to have been driven by outliers in both the empagliflozin and placebo arms[20]. Dr. Tu also conducted an analysis of baseline HbA1c as an effect modifier (Figure 5). Based on the difference in slopes of the regression lines for empagliflozin versus placebo (0.84), for every 1% increase in baseline HbA1c, the placebo-adjusted treatment effect measured by Hb1c change from baseline increases by 0.84%. Dr. Tu notes that in the primary analysis, baseline HbA1c was included in the ANCOVA model to adjust for this modification effect.

Figure 5: Scatterplot of Baseline HbA1c vs. Change from Baseline



Source: Dr. Tu's Statistical Review, Figure 6; ada1c,xpt, adsl.xpt

Reviewer Comment: Based on the Applicant's subgroup analyses, a trend towards a larger treatment effect of empagliflozin was observed within the subgroup of subjects with worse glycemic control at baseline, including those with baseline HbA1c > 9.0% and those with FPG ≥ 200 mg/dL. However, this finding is not unexpected, since the measured treatment effect may depend on the baseline HbA1c. Baseline HbA1c was included in the ANCOVA model for the primary efficacy analysis to account for this effect modification.

Data Quality and Integrity

[20] See Section 4.1 and Figure 3 of Dr. Tu's Primary Statistical Review

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

Efficacy Results – Secondary and other relevant endpoints

The Applicant's analysis of secondary endpoints relating to fasting plasma glucose (FPG), body weight, systolic blood pressure (SBP) and diastolic blood pressure (DBP) are displayed in

Table **18**. Compared with placebo, the adjusted mean change from baseline at Week 26 in FPG for empagliflozin pooled was −35.18 mg/dL (95% CI: −58.61 to −11.74, nominal p=0.0035). This analysis, while exploratory, is supportive of the primary endpoint analysis. No clinically significant changes in body weight, SBP or DBP were seen.

Table 18: Secondary endpoints based on FPG, body weight, SBP and DBP: change from baseline at Week 26

Treatment (TG1)	N analysed	Baseline		Change from baseline			Comparison vs placebo			
		Mean	SD	Adjusted mean	95% CI		Adjusted mean	95% CI		Nominal p-value
Fasting plasma glucose (FPG) [mg/dL], ANCOVA (OC-AD-BOCF)										
Placebo	52	158.62	53.80	15.70	−0.53	31.93				
Empa pooled	48	154.43	57.78	−19.48	−36.39	−2.57	−35.18	−58.61	−11.74	0.0035
Body weight [kg], MMRM (OC-AD)										
Placebo	52	98.87	29.62	−0.04	−1.40	1.32				
Empa pooled	52	98.66	24.35	−0.79	−2.17	0.59	−0.75	−2.68	1.19	0.4476
Systolic blood pressure (SBP) [mmHg], MMRM (OC-AD)										
Placebo	52	118.34	11.87	1.30	−1.01	3.61				
Empa pooled	52	120.23	9.97	−0.12	−2.47	2.24	−1.42	−4.72	1.88	0.3967
Diastolic blood pressure (DBP) [mmHg], MMRM (OC-AD)										
Placebo	52	72.60	8.94	0.76	−1.01	2.53				
Empa pooled	52	72.03	8.38	0.78	−1.04	2.60	0.02	−2.52	2.56	0.9878

Although not shown in this table, the linagliptin 5 mg group was included in the models.

Source: DINAMO CSR

Reviewer Comment: In adult studies of empagliflozin, small but statistically significant decreases in systolic blood pressure (placebo-adjusted decrease ranging from around 2 to 4 mmHg) and body weight (placebo-adjusted % change from baseline around 2% for 24-week studies) were observed with empagliflozin treatment versus placebo. In the DINAMO study, pediatric subjects treated with empagliflozin appear to have had small numeric reductions in body weight and systolic blood pressure compared to placebo, suggesting a similar response to adults despite failure to reach statistical significance.

Other endpoints relating to HbA1c response:

A numerically greater percentage of subjects treated with empagliflozin achieved HbA1c < 6.5% and HbA1c < 7.0% at week 26 as compared to the other treatment arms; however, this difference was non-significant compared to placebo (For HbA1c < 6.5% and < 7.0%, the rate difference for empagliflozin vs. placebo was 11.7% [95% CI -2.4 to 26.3] and 10.1% [95% CI -7.7 to 28.1], respectively). A numerically higher proportion of empagliflozin-treated subjects achieved a reduction in HbA1c from baseline of > 0.5% by week 26 as compared to the other treatment arms (34.6% for empagliflozin, 21.2% for linagliptin, 18.9% for placebo)[21]. As discussed previously, the proportion of patients who initiated glycemic rescue therapy by Week 26 was also lower in the empagliflozin group as compared to placebo.

Reviewer Comment: Although no significant differences were observed in the additional endpoints relating to HbA1c response, the overall trends are consistent with the results of the primary endpoint analysis and support the glycemic efficacy of empagliflozin as compared to placebo.

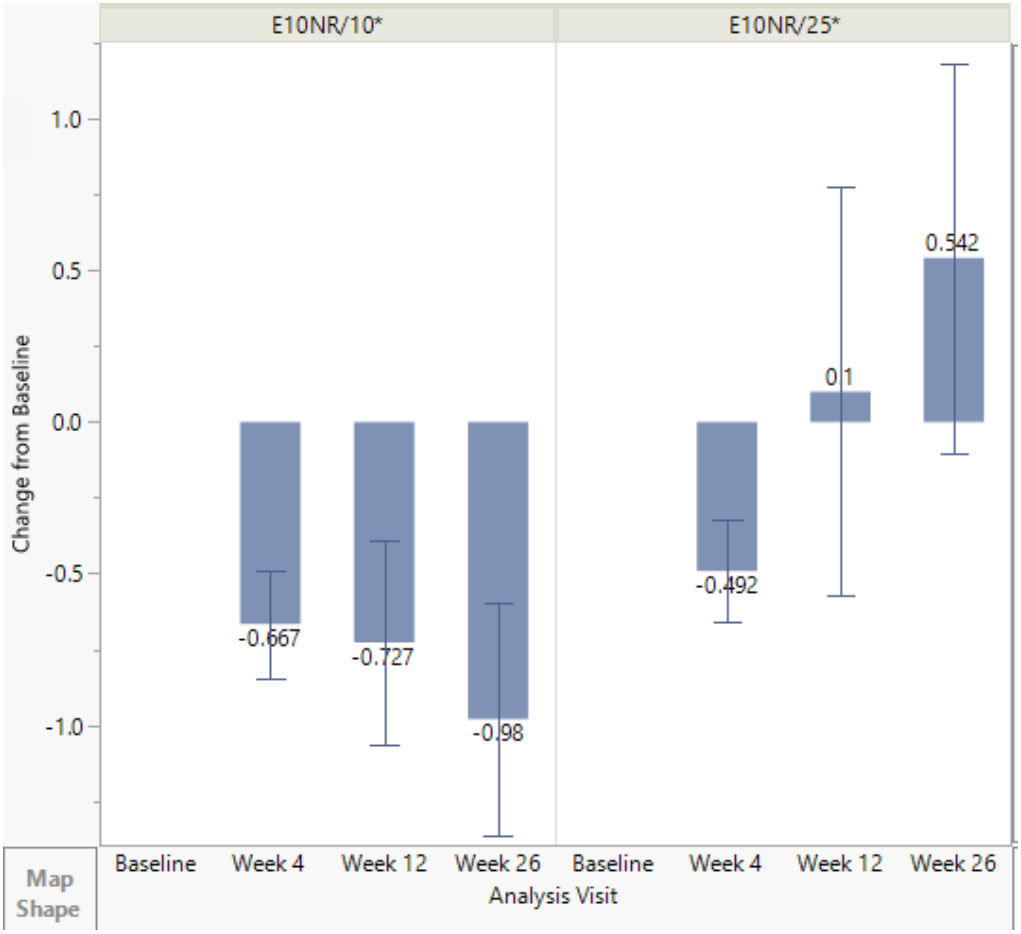
Dose/Dose Response

As discussed earlier, the treatment effect of empagliflozin when including non-responder subjects randomized to 25 mg (TG2) was numerically lower than the treatment effect of empagliflozin when including non-responder subjects who were continued on 10 mg (TG3); this finding is unexpected and raises questions as to the efficacy of the 25 mg dose.

To better evaluate the dose-response of empagliflozin, an exploratory analysis was conducted to evaluate HbA1c change within the subgroup of non-responder subjects who underwent the second randomization to either empagliflozin 10 mg or 25 mg. This exploratory analysis included evaluation of the mean HbA1c change over time (Figure 6) and median HbA1c change over time (Figure 7) in non-responder subjects who were continued on empagliflozin 10 mg (E10NR/10) versus non-responder subjects who were titrated to empagliflozin 25 mg (E10NR/25). When evaluating mean HbA1c change, differences in the treatment response were evident even prior to the second randomization (i.e., mean HbA1c change at week 12 was -0.727% in E10NR/10 versus +0.1% in E10NR/25). However, when evaluating the median HbA1c change, the treatment response appeared similar up until week 12 (i.e., median HbA1c change at week 12 was -0.7% in E10NR/10 versus -0.6% in E10NR/25).

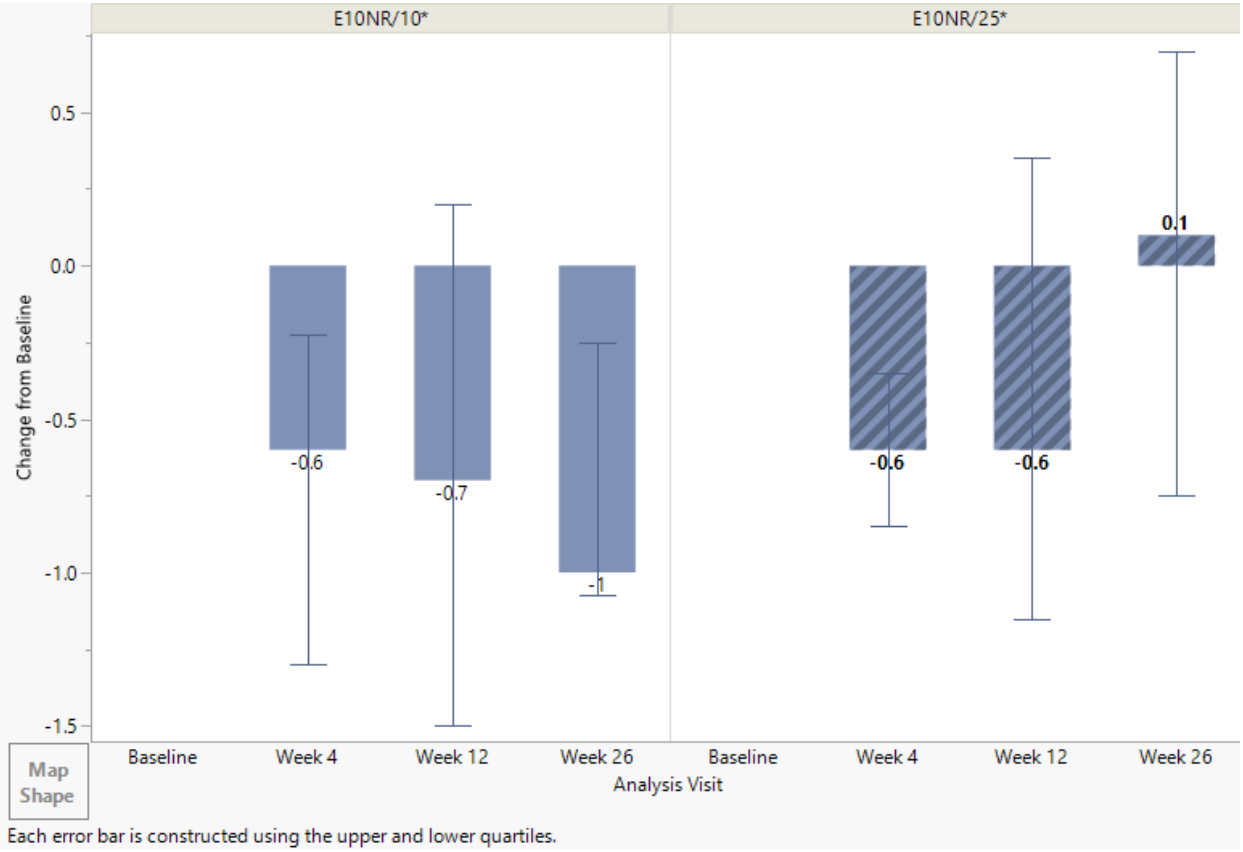
[21] As the proportion of subjects achieving HbA1c reduction from baseline > 0.5% was a "further endpoint", results were summarized descriptively.

Figure 6: Mean Change from Baseline in HbA1c by Study Week in Non-Responder Subjects Randomized at Week 14 to Empagliflozin 10 mg (E10NR/10) or Empagliflozin 25 mg (E10NR/25), Study 1218.91



Source: Reviewer generated in JMP using adhba1c.xpt dataset. Mean and standard error. E10NR/10= empagliflozin 10 mg non-responders randomized at week 14 to remain on empagliflozin 10 mg; E10NR/25= empagliflozin 10 mg non-responders randomized at week 14 to titrate up to empagliflozin 25 mg.

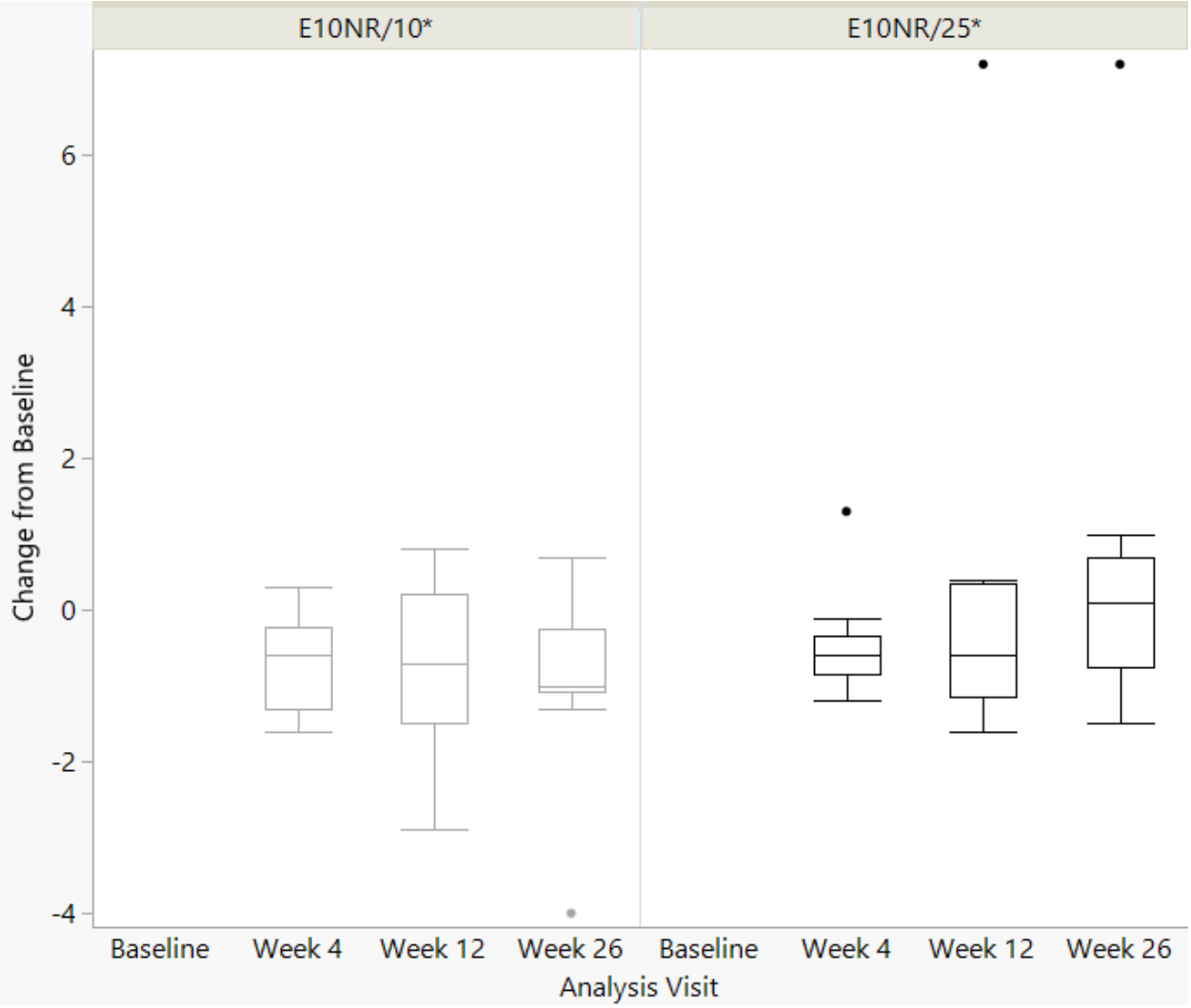
Figure 7: Median Change from Baseline in HbA1c by Study Week in Non-responder Subjects Randomized at Week 14 to Empagliflozin 10 mg (E10NR/10) or Empagliflozin 25 mg (EN10NR/25), Study 1218.91



Source: Reviewer generated in JMP using adhba1c.xpt dataset. Median and interquartile range. E10NR/10= empagliflozin 10 mg non-responders randomized at week 14 to remain on empagliflozin 10 mg; E10NR/25= empagliflozin 10 mg non-responders randomized at week 14 to titrate to empagliflozin 25 mg.

This pattern may reflect the influence of outliers, as is demonstrated in a box-plot analysis (Figure 8). Within the E10NR/25 group, one outlier subject (subject # (b) (6)) treated with background therapies of metformin and insulin had an HbA1c of 7.9%, 9.2%, 15.1% and 15.1% at baseline, Weeks 4, 12 and 26, respectively. These individual Week 12 and 26 values represented a 7.2% increase from baseline, contributing +0.6% (7.2% / 12) to the mean HbA1c at Weeks 12 and 26 in this group. This subject was also known to have low treatment compliance (39% compliance from Day 1 to Week 4, 1% compliance from Week 14 to Week 26, 20% compliance from Week 26 to Week 30) which was reported as an important protocol deviation, and had longer treatment interruptions due to the COVID-19 pandemic.

Figure 8: Box Plot showing Change from Baseline in HbA1c by Study Week in Non-responder Subjects Randomized to Empagliflozin 10 mg (left) or Empagliflozin 25 mg (right) at Week 14



Source: Reviewer generated in JMP using adhba1c.xpt dataset. E10NR/10= empagliflozin 10 mg non-responders randomized at week 14 to remain on empagliflozin 10 mg; E10NR/25= empagliflozin 10 mg non-responders randomized at week 14 to titrate to empagliflozin 25 mg.

Reviewer Comment: Overall, observed differences in mean HbA1c from baseline to week 26 between the non-responders who were continued on 10 mg (E10NR/10) versus those who were titrated to 25 mg (E10NR/25) are difficult to interpret, due to small sample size and the influence of outlier subjects.

An additional exploratory analysis conducted by Dr. Tu to evaluate the change in HbA1c from week 12 to week 26 demonstrates that non-responder subjects who were continued on 10 mg did not achieve much further change in HbA1c, while non-responder subjects who were titrated

to 25 mg exhibited a rise in HbA1c from week 12 to week 26. These results are unlikely impacted by the outlier subject described above, since that subject had no interval change in HbA1c from week 12 to week 26 (HbA1c was 15.1% on weeks 12 and week 26).

Table 19: Mean HbA1c Change from Week 12 to Week 26 in Empagliflozin 10 mg non-Responder subjects continued on 10 mg (E10NR/10) or titrated to 25 mg (E10NR/25)*.

Treatment	N	HbA1c (%) Change from Week 12 to Week 26	Difference (95% CI)
E10NR/10	13	-0.14	
E10NR/25	11	0.41	0.54 (-0.28, 1.37)

*Source: Dr. Wenda Tu, Statistical Reviewer. *The result was generated based on an ANCOVA adjusted for age group and treatment group. Missing data (one subject from each treatment group) were imputed in the same manner as for the primary efficacy analysis.*

The Applicant provided an additional descriptive analysis regarding change in HbA1c from week 12 to weeks 30, 42 and 52 in E10NR/10 and E10NR/25 subjects (Table 20). Beyond week 26, subjects in the E10NR/25 group had continued rise in HbA1c above what was measured at Week 12. However, subjects in the E10NR/10 group also had a progressive rise in HbA1c as compared to week 12.

Table 20: Mean HbA1c % change from Week 12 to Week 30, 42 and 52 in Empagliflozin 10 mg non-Responder subjects continued on 10 mg (E10NR/10) or titrated to 25 mg (E10NR/25)

Treatment	N	HbA1c (%) Change from Week 12 to Week 30	HbA1c (%) Change from Week 12 to Week 42	HbA1c (%) Change from Week 12 to Week 52
E10NR/10	11	-0.05	0.56	0.62
E10NR/25	12	0.41	0.75	0.83

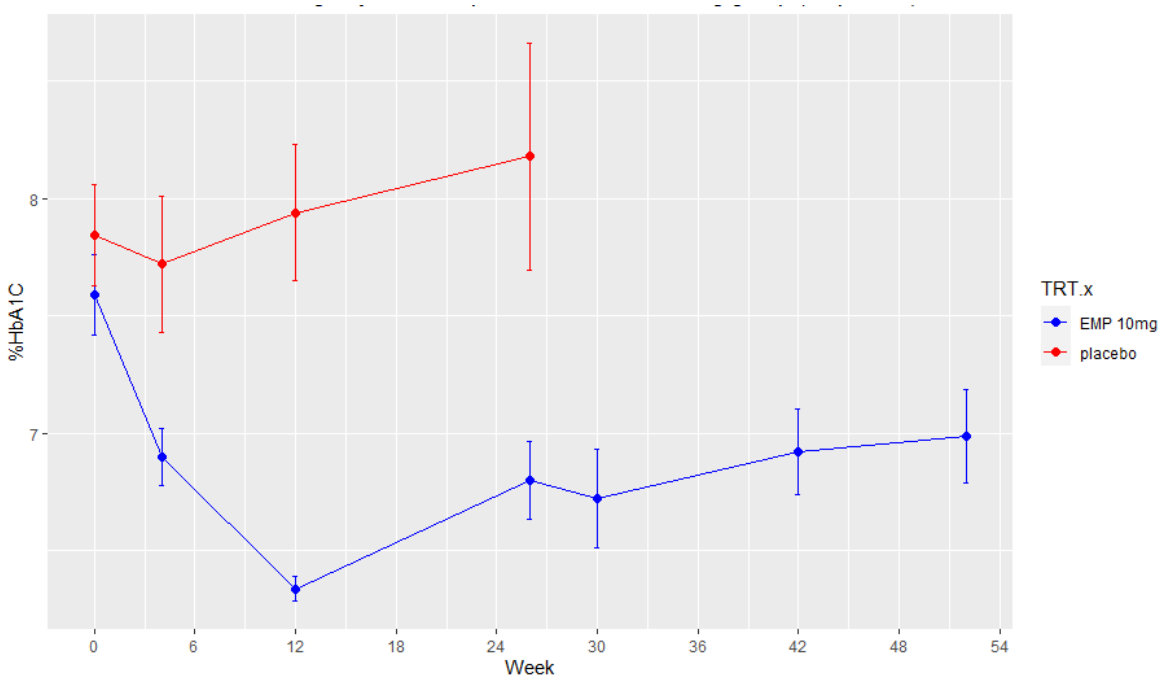
Source: Adapted from the Applicants Table 15.2.3:9 in the DINAMO CSR, providing descriptive statistics of HbA1c [%] over time from Wk12 up to Wk52 − mITT (TG4) (OC−AD)

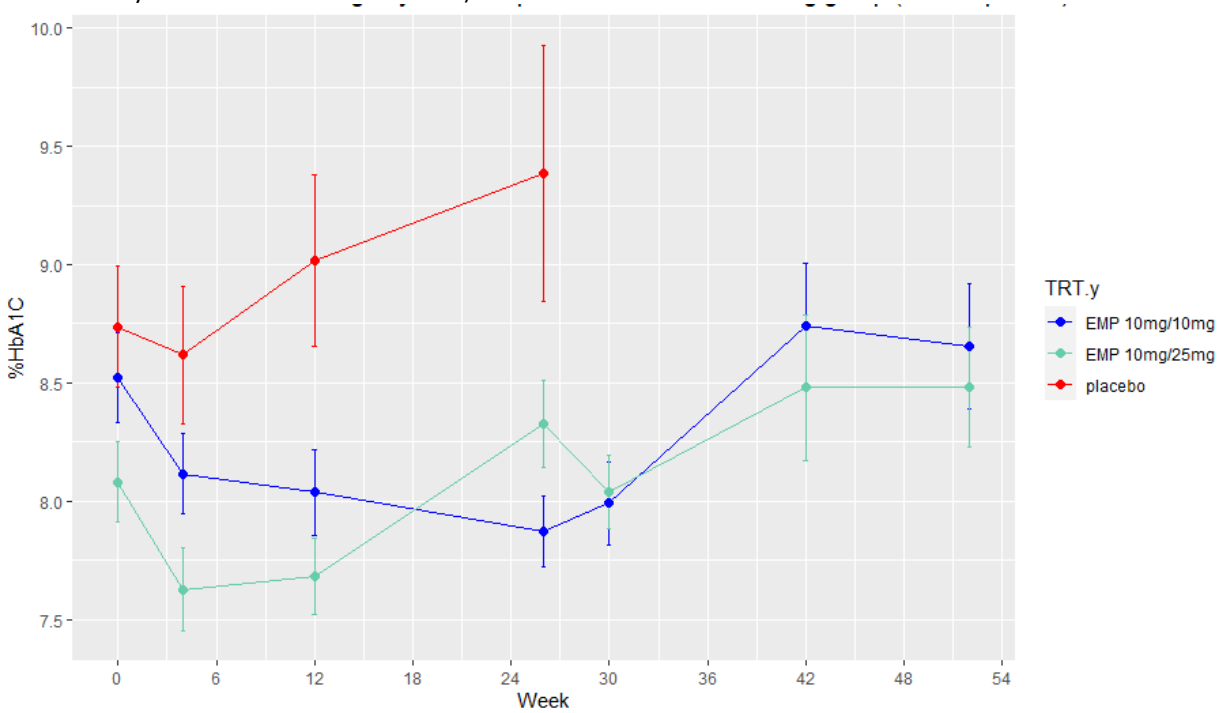
Reviewer Comment: After the second randomization at Week 14, subjects non-responsive to empagliflozin who were continued on empagliflozin 10 mg (E10NR/10) exhibited a minimal decrease in HbA1c at week 26, followed by a progressive rise in HbA1c throughout the safety extension period. Subjects non-responsive to empagliflozin who were titrated to the 25 mg dose (E10NR/25) also had progressive rise continuing through week 52. Compared to week

12, HbA1c rose by 0.6% in the E10NR/10 group and by 0.4% in the E10NR/25 group by week 52. These findings suggests that any differences in treatment response at week 26 between the E10NR/10 and E10NR/25 group were un-sustained.

The OCP review team conducted additional analyses on exposure-response (see clinical pharmacology review by Dr. Thanukrishnan for additional details). Based on these analyses, the OCP review team concluded that pediatric subjects with a baseline HbA1c ≥ 7.5 % and/or concomitant insulin use were more likely to have more rapid disease progression rate and to be "non-responders", whereas pediatric subjects with a baseline HbA1c < 7.5 % and/or without concomitant insulin use were more likely to have slower disease progression rate and to be responders. Due to these differences in disease progression rate between responders and non-responders, propensity score matching was used to find corresponding subjects within the placebo group matched for baseline HbA1c and baseline insulin use. After propensity score matching and removal of an outlier subject (Subject # (b) (6) discussed above), a significant treatment effect was observed for both empagliflozin responders and non-responders (see Figure 9 below). Dr. Thanukrishnan also concluded that there is limited additional treatment effect by increasing the dose from 10 mg to 25 mg among the non-responder subjects, and that the advantage of titrating the dose from 10 mg to 25 mg in responders is unknown based on the available data.

Figure 9: HbA1c (%) Change in Empagliflozin 10 mg Responders (top panel) and Non-responders* (bottom panel) and Matched-Placebo by Study Week, Study 1218.91





Source: Figures 28 and 29 in Dr. Thanukrishnan's OCP Review
**outlier subject in EMP 10mg/25 mg removed*

Additional evidence for efficacy of the empagliflozin 25 mg dose is based on a descriptive analysis of the change in HbA1c from week 26 to week 52 among placebo subjects who were re-randomized to empagliflozin, conducted by the Applicant (Table 21), in which subjects re-randomized to empagliflozin 25 mg exhibited a numerically higher HbA1c change as compared to subjects re-randomized to empagliflozin 10 mg.

Table 21: Mean HbA1c (%) Change from Week 26 to Week 52 Among Subjects Initially Randomized to Placebo and Re-Randomized to Active Treatment

Treatment Group	N	HbA1c (%) at Week 26	HbA1c (%) Change from Week 26 to Week 30	HbA1c (%) Change from Week 26 to Week 42	HbA1c (%) Change from Week 26 to Week 52
Placebo-Linagliptin	16	9.01 (1.8)	-0.22 (0.52)	0.53 (2.76)	0.59 (1.95)
Placebo-Empagliflozin 10 mg	15	8.43 (2.38)	-0.48 (0.65)	0.12 (1.41)	-0.35 (1.5)
Placebo -Empagliflozin 25 mg	16	8.53 (2.37)	-0.60 (0.85)	-0.57 (1.05)	-0.53 (1.13)

Source: Adapted from Applicant's Table 11.4 from the DINAMO CSR, showing Descriptive statistics of HbA1c (%) change from Week 26 to 52 by treatment-grouping 7.

Reviewer Comment: Overall, the evaluation of dose-response of empagliflozin in the DINAMO study is limited by the study design, because the efficacy of empagliflozin 25 mg was only assessed in a small subgroup of 13 subjects who were non-responsive to empagliflozin 10 mg. Although the treatment effect at week 26 for non-responder subjects who received empagliflozin 25 mg was numerically lower than for non-responder subjects who received empagliflozin 10 mg, conclusions are limited by the small sample size and the presence of outlier subjects. Results of OCP's exploratory analyses using propensity score matching and after removal of an outlier subject suggested similar treatment effects of the 10 mg and 25 mg dose in the non-responder subjects (i.e., no added benefit to titrating from 10 mg to 25 mg). However, differences in the baseline characteristics of the non-responder subjects raise questions as to the applicability of these findings to the broader pediatric T2D population because these non-responder subjects appear to have had more advanced disease at baseline. The advantage of titrating empagliflozin from 10 mg to 25 mg in responder subjects was not formally evaluated in the DINAMO study. However, additional evidence for the efficacy of the 25 mg dose is provided by the numerically greater change in HbA1c from week 26 to week 52 in placebo subjects who were re-randomized to empagliflozin 25 mg as compared to empagliflozin 10 mg (HbA1c change of -0.6% as compared to -0.46%, respectively). Given these data, and the absence of any dose-related safety signals (see Section 8.10), the Division concludes it is reasonable to label both the 10 mg and 25 mg dose for use in pediatric patients.

Durability of Response

Interpretation of data beyond week 26 is limited by the absence of a placebo-control arm. Within the empagliflozin arm, mean HbA1c reduction from baseline gradually decreased during the safety-extension period, with mean HbA1c returning to just above baseline levels by week 52 (Table 22). By comparison, within the linagliptin arm, mean HbA1c reached above-baseline values by week 26 and continued to increase reaching 0.81% above baseline by week 52.

Table 22: HbA1c (%) through Week 52, Study 1218.91

		E Pooled						
	N	Mean	SD	Min	Q1	Median	Q3	Max
OC-AD								
Baseline	52	8.00	1.29	6.2	6.90	7.90	8.85	10.6
Week 4	50	7.39	1.05	5.9	6.60	7.15	8.00	9.8
Week 12	48	7.24	1.50	5.4	6.45	6.85	7.50	15.1
Week 26	47	7.58	1.69	5.2	6.40	7.10	8.40	15.1
Week 30	46	7.60	1.90	5.1	6.60	7.10	8.40	16.0
Week 42	45	7.92	2.10	5.3	6.50	7.40	8.30	16.2
Week 52	46	7.96	2.17	5.2	6.50	7.30	9.00	17.2
Change at Week 4	50	-0.58	0.52	-1.6	-0.90	-0.50	-0.30	1.3
Change at Week 12	48	-0.66	1.52	-3.7	-1.25	-0.65	-0.15	7.2
Change at Week 26	47	-0.29	1.70	-4.0	-1.00	-0.30	0.40	7.2
Change at Week 30	46	-0.28	2.01	-4.0	-0.80	-0.35	0.20	8.1
Change at Week 42	45	0.05	2.00	-4.3	-0.90	-0.10	0.70	8.3
Change at Week 52	46	0.09	2.07	-4.0	-0.90	-0.05	0.80	9.3

	Pbo							L5						
	N	Mean	SD	Min	Q1	Median	Q3	Max	N	Mean	SD	Min	Q1	Median	Q3	Max
OC-AD																
Baseline	53	8.05	1.23	6.0	7.20	7.60	8.80	10.7	52	8.05	1.11	6.1	7.10	7.95	8.85	10.6
Week 4	50	8.17	1.56	5.6	7.00	8.05	9.10	12.0	48	7.83	1.37	5.9	6.80	7.50	8.75	11.2
Week 12	52	8.40	1.96	4.7	7.00	8.10	9.40	14.4	49	7.92	1.68	5.0	6.70	7.80	9.10	12.8
Week 26	50	8.77	2.41	5.4	6.90	8.25	10.40	16.7	49	8.33	1.79	5.0	6.90	8.30	9.90	11.6
Week 30									48	8.41	1.77	4.9	6.85	8.55	9.65	12.5
Week 42									48	9.03	2.21	5.3	7.15	8.90	10.30	15.6
Week 52									46	8.85	2.32	5.1	7.20	8.60	10.00	16.7
Change at Week 4	50	0.08	0.50	-1.2	-0.20	0.00	0.30	1.8	48	-0.25	0.61	-1.3	-0.50	-0.30	-0.05	2.7
Change at Week 12	52	0.33	1.16	-2.1	-0.30	0.20	1.00	3.8	49	-0.17	1.21	-2.0	-0.80	-0.40	0.20	4.3
Change at Week 26	50	0.69	1.80	-1.9	-0.40	0.40	1.40	8.8	49	0.31	1.20	-1.8	-0.40	0.10	0.80	4.0
Change at Week 30									48	0.40	1.25	-1.9	-0.40	0.30	1.10	4.6
Change at Week 42									48	1.03	1.86	-1.5	-0.20	0.70	1.75	6.9
Change at Week 52									46	0.81	2.09	-2.4	-0.30	0.40	1.50	9.9

Source: Adapted from the Applicant's Table 15.2.3:1 from the DINAMO CSR, showing descriptive statistics of HbA1c [%] over time up to Wk52 – mITT. Abbreviations: E pooled= empagliflozin pooled, L5= linagliptin, Pbo= placebo. OC-AD= observed cases all data.

Reviewer Comment: Several completed pediatric type 2 diabetes trials (e.g., liraglutide, extended-release exenatide, dulaglutide) demonstrated a similar increase from baseline in HbA1c among subjects randomized to placebo that contributed to the overall treatment effect for the primary efficacy endpoint (measured at weeks 24 to 26). In the liraglutide pediatric T2D study at week 52 subjects randomized to the placebo arm experienced a 0.8% increase in HbA1c from baseline, reflecting the rapid disease progression of pediatric T2D patients. In the DINAMO study, given the absence of a placebo comparator beyond week 26, it is unknown whether an interval decrease in HbA1c reduction from baseline between weeks 26 and 52 among empagliflozin-treated subjects reflects a lack of durability of treatment response or rapid disease progression in the study population. The finding that by week 52, HbA1c was increased by 0.8% above baseline in the linagliptin arm, as compared to 0.1% above baseline in the empagliflozin arm, suggests that some treatment effect in the empagliflozin arm was preserved through week 52. Notably, similar findings of a decrease in the HbA1c change from baseline by Week 52 were seen in pediatric subjects treated with extended-release exenatide and dulaglutide in their respective phase 3 trials[22] which further supports the conclusion that these trends may be related to underlying rapid disease progression.

Persistence of Effect

Persistence of effect was not assessed in Study 1218.91.

Additional Analyses Conducted on the Individual Trial

As agreed to under the pediatric Written Request, prespecified Bayesian borrowing analyses were conducted to compensate for an expected reduced statistical power in study 1218.91, due

[22] See primary clinical reviews by Dr. Suchitra Balakrishnan based on the AWARD-PEDS study of Trulicity in pediatric T2D subjects (BLA 125469/S-51) and by Dr. Mahtab Niyyati based on Study BCB114 of Bydureon in pediatric T2D subjects (NDA 022200/S-03 and NDA 209210/S-017).

to a greater than expected variability in the primary endpoint that was observed in a blinded interim assessment (see Section 3.2).

Results from Bayesian borrowing analyses using two different priors were provided. In the first approach, the informative component of the Bayesian prior distributions was derived from previously fitted PK and exposure-response models for empagliflozin based on available historical data in adult and pediatric patients with T2D. The pre-specified weight of 0.65 for the informative component ensured the prior effective sample size (ESS) of 51 to be less than total number (105) of enrolled pediatric subjects in the empagliflozin and placebo arm. The exposure response-based Bayesian borrowing analysis confirmed evidence for superior efficacy with posterior mean (SD) of −0.95% (0.21%) and a 95% credible interval of (−1.35%, −0.53%).

In the second approach, the informative component of the Bayesian prior distributions was derived from the pediatric efficacy of other SGLT2 inhibitors. The pre-specified weight for the informative component of the prior was 0.75 and the prior ESS was 14. The posterior mean (SD) placebo-corrected treatment effect was −0.80% (0.28%), with a 95% credible interval (-1.35%, −0.26%), consistent with superior efficacy compared to placebo.

Tipping point sensitivity analyses were also conducted using a full range of alternative weights for each of the Bayesian borrowing analyses and superior efficacy of empagliflozin was observed for any choice of prior weight.

7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

This section is not applicable to the review.

7.1.1. Primary Endpoints

This section is not applicable to the review.

7.1.2. Secondary and Other Endpoints

This section is not applicable to the review.

7.1.3. Subpopulations

This section is not applicable to the review.

7.1.4. Dose and Dose-Response

This section is not applicable to the review.

7.1.5. Onset, Duration, and Durability of Efficacy Effects

This section is not applicable to the review.

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Postmarket Setting

As discussed in Section 6.1.1, subjects with moderate or severe renal impairment (eGFR < 60 mL/min/1.73m^2) were excluded from study 1218.91, and despite the intention to enroll some pediatric patients with mild renal impairment, too few subjects with eGFR between 60 to < 90 mL/min/1.73m^2 were actually enrolled in the study to draw any conclusions regarding the impact of renal impairment on the efficacy of empagliflozin in pediatric patients.

Although pediatric T2D patients are at risk for the development diabetic kidney disease over time, 24 to 50% of patients may experience elevated eGFR relating to hyperfiltration. Therefore, the occurrence of eGFR < 60 mL/min/1.73m^2 would unlikely be related to diabetic nephropathy in a pediatric T2D patient aged < 18 years; however, a reduced eGFR could occur in the setting of a concomitant diagnosis of chronic kidney disease (CKD). Pediatric patients with CKD may also develop diabetes relating to treatments for CKD and/or post-renal transplantation. Other than glycemic control, empagliflozin has established benefits for heart failure and cardiovascular disease in adults (b) (4) (b) (4)

In the adult program, the efficacy of empagliflozin was evaluated in adults with renal impairment in Study 1245.36. Although a significant treatment effect with respect to HbA1c was observed in both mild (eGFR 60 to < 90 mL/min/1.73m2) and moderate (eGFR 30 to 60 mL/min/1.73m2) renal impairment, the magnitude of the treatment effect of empagliflozin 25 mg in subjects with moderate renal impairment was attenuated (treatment effect of -0.42%, compared to -0.68% in subjects with mild renal impairment). A post-hoc analysis showed reduced efficacy in subjects with eGFR between 30 to <45 mL/min/1.73m^2, and that the treatment effect in this subgroup had been driven by a worsening of glycemic control in the placebo group. Given that several risks of empagliflozin (e.g., acute kidney injury, volume depletion adverse events, and urinary tract infection) were known to be worsened with renal impairment, empagliflozin was not recommended for use for glycemic control for patients with eGFR < 45 mL/min/1.73m^2 in the original approval in August 2014[23]. In June 2021, the product label was updated to reflect a limitation of use for glycemic control in type 2 diabetes patients with eGFR < 30 mL/min/1.73m^2. The rationale to support expanding the glycemic control

[23] See primary clinical review by Dr. Chong and primary clinical pharmacology review by Dr. Manoj Khurana under NDA 204629.

indication to subjects with eGFR as low as 30 mL/min/1.73m^2 was based on a re-evaluation of the benefit-risk assessment in the renal impairment population, based on updated safety analyses from the EMPA-REG study along with accumulated evidence of renal-related benefits with empagliflozin and other SGLT2 inhibitors[24].

The current limitation of use for glycemic control will be applied to both adult and pediatric patients with eGFR < 30 mL/min/1.73m^2. See Section 10.1 for further discussion of the labeling approach.

7.2.2. Other Relevant Benefits

Currently, metformin is the only approved oral antihyperglycemic agent for pediatric T2D. Other therapeutic options (liraglutide, extended-release exenatide, dulaglutide and insulin) involve subcutaneous injection, which can be a less convenient route of administration in pediatric patients. As new oral antihyperglycemic agents, Jardiance and Synjardy would offer an additional once daily oral therapy to pediatric T2D patients.

7.3. Integrated Assessment of Effectiveness

The Applicant submitted results from a single, adequate and well-controlled study (DINAMO) to support the effectiveness of empagliflozin in pediatric T2D subjects; efficacy results from the adult T2D program provide confirmatory evidence to establish substantial evidence of effectiveness in the pediatric T2D population. DINAMO was a 26-week, double-blind, randomized, placebo-controlled, parallel group study, with a double-blind active treatment safety extension of an additional 26 weeks. The study enrolled pediatric subjects aged 10 to 17 years with inadequately controlled type 2 diabetes mellitus (HbA1c 6.5 to 10.5%) including those treated with metformin (or with documented intolerance to metformin), with or without insulin therapy. Subjects were randomized 1:1:1 to receive empagliflozin 10 mg, linagliptin 5 mg, or placebo over 26 weeks. Subjects in the empagliflozin 10 mg group who failed to achieve HbA1c <7.0% at Week 12 ("non-responders") underwent a second randomization at Week 14 to remain on the 10 mg dose or increase to 25 mg; subjects in the empagliflozin 10 mg group who achieved an HbA1c < 7.0% ("responders") at week 12 did not undergo a second randomization. Subjects on placebo were re-randomized at Week 26 to either linagliptin or one of the empagliflozin doses (10 mg or 25 mg). The primary efficacy endpoint was the change from baseline in HbA1c at 26 weeks, tested simultaneously for the pooled empagliflozin dosing group vs placebo and for linagliptin vs. placebo. Secondary hypothesis testing evaluated change from baseline in HbA1c at week 26 in two empagliflozin subgroups versus placebo; the first subgroup included empagliflozin responders and non-responders who were increased to 25 mg, and the second subgroup included empagliflozin responders and non-responders who were continued on 10 mg. Key secondary efficacy endpoints included changes in fasting plasma glucose, systolic

[24] See memorandum to file by Dr. Lungu for NDA 204629/S-029 and 029.

blood pressure, diastolic blood pressure, body weight, and proportion of subjects achieving HbA1c < 6.5% and < 7.0% by week 26.

A total of 157 subjects were treated with either empagliflozin (10 mg or 25 mg; N=52), linagliptin (N=52), or placebo (N=53). Background therapies included metformin (51%), a combination of metformin and insulin (40.1%), insulin (3.2%), or none (5.7%). The mean HbA1c at baseline was 8.0% and the mean duration of type 2 diabetes mellitus was 2.1 years. The mean age was 14.5 years (range: 10-17 years) and 51.6% were aged 15 years and older. Approximately, 50% were White, 6% were Asian, 31% were Black or African American, and 38% were of Hispanic or Latino ethnicity. The mean BMI was 36.0 kg/m2 and mean BMI Z-score was 3.0. Subjects with an eGFR less than 60 mL/min/1.73 m2 were not enrolled in the study. Approximately 25% of the study population had microalbuminuria or macroalbuminuria.

The primary analysis was performed with an ANCOVA adjusted for treatment, baseline HbA1c, and baseline age group. At week 26, treatment with empagliflozin was superior to placebo in reducing HbA1c from baseline [placebo-adjusted treatment difference – 0.84% (95% confidence interval -1.50 to -0.19, p=0.0116)]. Treatment with linagliptin did not provide a significant improvement in HbA1c compared to placebo [placebo-adjusted treatment difference -0.34% (95% CI -0.99 to 0.30; p=0.2935). Nominal secondary hypothesis testing for the empagliflozin subgroup including non-responder subjects titrated to 25 mg and for the empagliflozin subgroup including non-responder subjects who remained on 10 mg revealed placebo-adjusted HbA1c treatment effects of -0.52% (95% confidence interval -1.31 to 0.27) and -1.18% (95% confidence interval -1.9 to -0.45), respectively. With regard to key secondary endpoints, nominally significant treatment differences in fasting plasma glucose and numerical trends in proportion of subjects achieving HbA1c targets were observed favoring empagliflozin over placebo. No differences in blood pressure or body weight were observed. The results of a prespecified supplemental Bayesian analysis confirmed the primary efficacy results.

Dose-response analyses of empagliflozin during the placebo-controlled period are limited by the small number of subjects receiving empagliflozin 25 mg (N=13), presence of several outliers, and apparent differences in baseline characteristics of the non-responder subjects. However, efficacy of the empagliflozin 25 mg dose is supported based on the primary outcome analysis (which included subjects who received both empagliflozin 10 mg and 25 mg). Additionally, a numerically greater change in HbA1c from week 26 to week 52 in placebo subjects re-randomized to empagliflozin 25 mg vs 10 mg provides supportive evidence regarding dose-response.

In subjects randomized to empagliflozin, the Applicant's descriptive analysis shows that the mean HbA1c reduction from baseline diminished over the safety extension period and that HbA1c rose slightly above baseline (+0.1%) by 52 weeks. However, subjects randomized to linagliptin experienced an even more prominent rise in HbA1c reaching 0.8% above baseline by 52 weeks. Based on similar findings in recent pediatric type 2 diabetes trials for agents with

established pediatric efficacy, this finding more likely represents rapid disease progression rather than lack of durability.

Overall, the evidence from DINAMO study supports the efficacy of empagliflozin compared to placebo when administered as monotherapy or as add-on therapy to metformin and/or insulin in pediatric patients aged 10 years and older with type 2 diabetes. The magnitude of HbA1c reduction in pediatric patients (-0.84%) is similar to that described in adult studies of empagliflozin (placebo-adjusted treatment effect ranging from -0.6 to -0.9% across phase 3 studies). Substantial evidence of effectiveness to support expanding the glycemic control indication to pediatric patients aged 10 years and older is based on the results of a single, adequate and well-controlled study (DINAMO), plus confirmatory evidence derived from phase 3 studies demonstrating the efficacy of empagliflozin in adult T2D subjects. Although there are differences in disease progression among the adult and pediatric T2D populations, the use of adult data as confirmatory evidence for the substantial evidence of effectiveness determination is appropriate considering the similar underlying disease pathophysiology and similar exposure-response to empagliflozin as demonstrated in the DINAMO study.

8. Review of Safety

8.1. Safety Review Approach

The safety of empagliflozin has been well-characterized in adult subjects with T2D and other diagnoses. In adult studies of empagliflozin, the most common adverse events (AEs with > 5% incidence) were female genital mycotic infections and urinary tract infections (UTIs). The USPI for empagliflozin-containing products also describes Warnings and Precautions regarding the risks of ketoacidosis, volume depletion, urosepsis and pyelonephritis, hypoglycemia with concomitant use of sulfonylureas and insulin, necrotizing fasciitis of the perineum (Fournier's gangrene), genital mycotic infections, and hypersensitivity reactions.

The safety review focused primarily on previously identified risks of empagliflozin observed in adult studies, but also evaluated any potential risks that may be specific to pediatric patients. For the DINAMO study, the Applicant prespecified several AESIs and other specific AEs based on the known safety profile of empagliflozin, and pediatric-specific safety issues including effects on growth, bone development and puberty. These safety issues were also specified in the pediatric WR. The DINAMO study also included AESIs and specific AEs relevant to the known safety profile of linagliptin; these data are presented for completeness, but the results are discussed in more detail in the clinical review for NDA 201280/S-027.

The primary safety analysis is based on the 26-week placebo-controlled assessment period of study 1218.91. Safety data for this period is reported for the pooled empagliflozin arm (i.e., all

subjects who received empagliflozin at any dose from baseline to week 26), linagliptin arm and placebo arm.

Supportive safety analyses were also conducted based on safety data obtained during the safety extension period. Safety data for this period are generally reported based on treatment assignment from weeks 26 to 52 (i.e., empagliflozin 25 mg, empagliflozin 10 mg or linagliptin 5 mg), with the exception of the exposure analysis (see Section 8.2.1 for details). In general, subject numbers for each treatment arm were calculated based on the total number of subjects initially randomized to empagliflozin and linagliptin who remained on study drug at week 26 and the total number of subjects initially randomized to placebo who were re-randomized to empagliflozin 10 mg, empagliflozin 25 mg or linagliptin 5 mg at week 26 [i.e., empagliflozin 10 mg (N=47), empagliflozin 25 mg (N=28) and linagliptin 5 mg (N=65)]. This approach was taken due to inherent limitations in interpreting safety data from baseline to week 52, considering that subjects who received placebo from baseline to week 26 were re-randomized to active therapy from week 26 to 52. This approach also allows for evaluation of potential differences in safety signals between subjects who received empagliflozin 10 mg versus empagliflozin 25 mg from weeks 26 to 52. Note that the Applicant utilized a different approach in reporting safety data from baseline through week 52 by pooling safety data for subjects who received linagliptin or empagliflozin at any time during the study[25].

For safety review of adverse events and hypoglycemia, I conducted my own analysis of the submitted tabulations/datasets using OCS Analysis Studio or JMP 16.0, followed by a review of the Applicant's safety data presented in the DINAMO CSR to verify the findings in my analyses. For other safety data, I reviewed the Applicants safety data in the CSR and conducted my own analyses from the datasets when appropriate. Some additional analyses were also requested from the Applicant.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

The duration of exposure through Week 26 is described in Table 23. The mean duration of exposure to empagliflozin during the placebo-controlled treatment period was 23.8 weeks.

[25] The Applicant conducted analyses based on treatment-grouping 6 (TG6) consisting of subjects who received linagliptin active treatment (including those who received linagliptin 5 mg from the initial randomization and those who received linagliptin 5 mg after initial placebo), and subjects who received empagliflozin pooled active (including those who received empagliflozin after initial randomization, and those who received empagliflozin 10 mg or 25 mg after initial placebo).

Table 23: Exposure through Week 26 (placebo-controlled period)

	Empagliflozin Pooled (N=52)	Linagliptin (N=52)	Placebo (N=53)
Duration of Exposure (days)			
Mean (SD)	166.8 (42.82)	173.5 (37.16)	172.1 (37.53)
Median (Min, Max)	182.0 (12, 199)	182.0 (1, 195)	182.0 (12, 196)

Source: Reviewer generated using OCS Analysis Studio, Custom Table Tool.
Columns - Dataset: Demographics; Filter: TRTFL = 'Y'.
Duration of Exposure (days) - Dataset: Exposure; Filter: PARAM = 'Treatment exposure up to week 26 [days]'.
SD = Standard Deviation.

The duration of active exposure from baseline through week 52 is described in Table 24. Note that this analysis differs from the general approach to safety analyses described in Section 8.1, in order to describe the overall exposure to active treatment for all subjects who received empagliflozin or linagliptin at any time point during the study, but excludes periods of placebo treatment for subjects who were initially randomized to placebo and re-randomized to active treatment at week 26. When considering the placebo-controlled period and the safety extension, the mean duration of exposure to empagliflozin was 38.1 weeks.

Table 24: Active exposure through Week 52

	Empagliflozin active* (N=83)	Linagliptin active* (N=68)
Duration of Exposure (days)		
Mean (SD)	266.6 (113.44)	297.6 (102.85)
Median (Min, Max)	357.0 (12, 393)	363.0 (1, 378)

Source: Reviewer generated using OCS Analysis Studio, Custom Table Tool.
Columns - Dataset: Demographics; Filter: TRTFL = 'Y'.
Duration of Exposure (days) - Dataset: Exposure; Filter: PARAM = 'Active treatment exposure up to week 52 [days]'.
SD = Standard Deviation. *excludes duration of exposure to placebo for subjects initially randomized to placebo and re-randomized to active treatment at week 26.

8.2.2. Relevant characteristics of the safety population:

The characteristics of the safety population for the primary safety analysis (i.e., the placebo-controlled treatment period through weeks 26) have already been described in Section 6.1.2 (see Table 8 and Table 9).

As discussed above, safety was also evaluated from weeks 26 to 52 to obtain information regarding dose-related safety events in subjects who received empagliflozin 10 mg versus empagliflozin 25 mg and to evaluate for rare safety events. As subjects initially randomized to placebo were re-randomized at week 26 the empagliflozin 10 mg, empagliflozin 25 mg or linagliptin 5 mg, an additional analysis was conducted to determine any differences in baseline characteristics based on treatment assignment from weeks 26 to 52 (see Table 25) below. Baseline and demographic characteristics among treatment arms during the safety extension period were generally comparable with a few exceptions. Compared to the other treatment

arms in the safety extension, a higher proportion of subjects receiving empagliflozin 25 mg were of Hispanic or Latino ethnicity (42.9%) and were receiving background antidiabetic medication with both metformin and insulin at baseline (42.9%). Subjects receiving empagliflozin 25 mg also had a higher baseline HbA1c as compared to subjects who received empagliflozin 10 mg (8.2% vs. 7.8%) and had a slightly longer mean duration of T2D (2.5 years versus 1.5 years).

Table 25: Demographic and Baseline Characteristics of Subjects based on Treatment Assignment in Safety Extension Period (week 26 to 52)

	Empagliflozin 10 mg (N=47)	Empagliflozin 25 mg (N=28)	Linagliptin 5 mg (N=65)
Age (years)			
Mean (SD)	14.4 (1.86)	14.5 (1.97)	14.5 (1.86)
Median (Min, Max)	14.0 (11, 17)	14.5 (10, 17)	14.0 (10, 17)
Sex			
Female	31 (66.0)	15 (53.6)	39 (60.0)
Male	16 (34.0)	13 (46.4)	26 (40.0)
Race			
DID NOT REPORT	1 (2.1)	0	1 (1.5)
AMERICAN INDIAN OR ALASKA NATIVE	3 (6.4)	0	4 (6.2)
ASIAN	3 (6.4)	1 (3.6)	5 (7.7)
BLACK OR AFRICAN AMERICAN	16 (34.0)	9 (32.1)	16 (24.6)
MULTIPLE	2 (4.3)	2 (7.1)	2 (3.1)
NATIVE HAWAIIAN OR OTHER PACIFIC ISLANDER	1 (2.1)	0	2 (3.1)
WHITE	21 (44.7)	16 (57.1)	35 (53.8)
Ethnicity			
HISPANIC OR LATINO	15 (31.9)	12 (42.9)	28 (43.1)
NOT HISPANIC OR LATINO	32 (68.1)	16 (57.1)	37 (56.9)
HbA1c (%)			
Mean (SD)	7.8 (1.27)	8.2 (1.10)	8.1 (1.17)
Median (Min, Max)	7.4 (6.2, 10.6)	8.1 (6, 10.7)	7.8 (6.1, 10.6)
BMI Z-score			
Mean (SD)	2.9 (1.0)	2.8 (0.9)	3.0 (0.8)
Median (Min, Max)	3.0 (0.1, 4.8)	3.1 (0.7, 4.1)	3.0 (1.2, 4.8)
Duration of T2D (years)			
Mean (SD)	1.5 (1.22)	2.5 (2.69)	2.2 (1.73)
Median (Min, Max)	1.3 (0.2, 4.8)	1.3 (0.2, 13.7)	1.7 (0.2, 6.6)
Background Antidiabetic Medication			
Insulin only	3 (6.4)	1 (3.6)	1 (1.5)
Metformin and Insulin	16 (34.0)	12 (42.9)	27 (41.5)
Metformin only	26 (55.3)	15 (53.6)	32 (49.2)
None	2 (4.3)	0	5 (7.7)

Source: Reviewer generated using OCS Analysis Studio, Custom Table Tool. Columns - Dataset: Demographics; Filter: TRTFL = 'Y'. Age (years) - Dataset: Demographics; Filter: None. Sex - Dataset: Demographics; Filter: None. Race - Dataset: Demographics; Filter: None. Ethnicity - Dataset: Demographics; Filter: None. HbA1c (%) - Dataset: Demographics; Filter: None.
BMI Z-score - Dataset: Demographics; Filter: None. Dura ion of T2D (years) - Dataset: Demographics; Filter: None. Background Antidiabetic Medication - Dataset: Demographics; Filter: None. SD = Standard Deviation.

Review Comment: Differences in baseline and demographic characteristics for subjects who received empagliflozin 25 mg during the safety extension likely reflect the comparatively smaller size (N=28) of this treatment arm and comparatively greater proportion of subjects with more advanced disease at baseline, given the inclusion of 12 subjects (42.8%) who received empagliflozin 25 mg due to being non-responders to empagliflozin 10 mg during the placebo-controlled period (see 6.1.2 and Table 11 for discussion of differences in baseline characteristics among non-responder subjects).

8.2.3. Adequacy of the safety database:

Because the safety profile of empagliflozin has been previously evaluated in adults, the exposure and size of the safety database in the DINAMO study is considered generally adequate and is similar to exposures for other recently completed pediatric trials (e.g., liraglutide, extended-release exenatide, dulaglutide) that supported expanding the indication of these products to pediatric T2D patients aged 10 years and older. The exposure and size of the safety database is also consistent with that specified in the pediatric WR.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

The overall quality of the data submitted was acceptable. Based on clinical inspections conducted at two study sites (see Section 4.1), no discrepancies were noted in the source records for any of the safety data including adverse events, serious adverse events, laboratory tests and physical exam results.

8.3.2. Categorization of Adverse Events

Protocol definitions for AEs, SAEs, and intensity of AEs were acceptable. AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 25.0. All AEs and AESIs were collected from the period of informed consent through the end of the study. After completion of the study, only related SAEs and related AESIs which the investigator subsequently became aware of were collected.

Treatment-emergent adverse events (TEAEs) were defined as all AEs occurring between start of treatment and until 7 days after the last dose of study medication, and all AEs that started before first drug intake and deteriorated under treatment. Pre-treatment events were defined as AEs occurring before the first dose of study medications; post-treatment events were defined as AEs occurring 7 days after the last dose of study medication.

Table 26 below describes all AESIs and specific AEs that were identified for the DINAMO study, definitions for each AESI, and whether the AESI or specific AE was selected evaluate known or

potential safety signals associated with treatment of empagliflozin, linagliptin or both.

Table 26: AESIs and Specific AEs in the DINAMO study

	Definition(s)	Relevant product
AESI		
Hypersensitivity reactions such as angioedema, angioedema-like events, and anaphylaxis	• Narrow SMQ for hypersensitivity	Linagliptin and empagliflozin
Skin lesions such as exfoliative rash, skin necrosis, bullous dermatitis	• Narrow SMQ for severe cutaneous adverse reactions	Linagliptin
Pancreatitis	• PT for chronic pancreatitis AND narrow SMQ for acute pancreatitis	Linagliptin
Pancreatic cancer	• Narrow BIcMQ[26] for pancreatic neoplasms	Linagliptin
Hepatic Injury	• Narrow SMQs for 1) cholestasis and jaundice of hepatic origin, 2) hepatic failure, fibrosis, cirrhosis and other liver-damage related conditions, 3) hepatitis, non-infections, 4) liver related investigations, signs and symptoms • AST and/or ALT ≥3xULN and total bilirubin >2x ULN measured in the same blood draw sample • Isolated ALT and/or AST ≥ 5xULN	Linagliptin and empagliflozin
Decreased renal function	• Narrow SMQ for acute renal failure • ≥ 2x increase in creatinine from baseline and above the ULN.	Empagliflozin
Diabetic ketoacidosis (DKA)	• Narrow BIcMQ for ketoacidosis[27] • Investigator assessment, based on ADA diagnostic criteria	Empagliflozin
Events involving lower limb amputation	• Investigator determined, including amputation, disarticulation, and auto-amputations[28].	Empagliflozin
Specific AEs		

[26] Complete listing of preferred terms provided in Listing 10 within document "1218-0091-17027-adverse-event-listings"
[27] PTs included diabetic hyperglycemic coma, diabetic ketoacidosis, diabetic ketoacidotic hyperglycemic coma, ketoacidosis, euglycemic diabetic ketoacidosis
[28] Not including debridement (removal of callus or dead tissue), procedures on a stump (like stump revision, drainage of an abscess, wound revision etc.) and other procedures (e.g., nail resection or removal) without a concomitant resection of a limb (amputation or disarticulation).

Genital infections	• Narrow sub BIcMQ for genital tract infections predisposed by glucosuria[26] • Investigator assessment	Empagliflozin
Urinary tract infections (UTI)	• Narrow sub BIcMQ for UTI predisposed by glucosuria • Investigator assessment[26]	Empagliflozin
Acute pyelonephritis or urosepsis	• Narrow BIcMQ for renal infections predisposed by glucosuria[26] AND PT of urosepsis	Empagliflozin
Bone fractures	• Narrow BIcMQ for bone fractures[26]	Empagliflozin
Arthralgia	• HLGT (primary path) for joint disorders	Linagliptin
Pemphigoid in bullous conditions	• HLT (primary path) for bullous conditions	Linagliptin
Volume depletion	• Narrow BIcMQ for volume depletion and hypotension due to dehydration[26]	Empagliflozin
Ketone measurement reported as an AE	• Narrow BIcMQ for increased ketones excluding acidosis and ketoacidosis[29]	Empagliflozin

Source: reviewer created based on DINAMO CSR, TSAP and adverse event listing file
Abbreviations: AESI= adverse event of special interest, SMQ= standardized MedDRA query, BIcMQ= Applicant custom MedDRA query, ULN= upper limit of normal, ADA= American diabetes association, HLGT= high level group term, HLT= high level term, PT= preferred term

Hypoglycemia AEs were defined as follows:

- Symptomatic and asymptomatic hypoglycemia AEs with documented glucose < 70 mg/dL
- Hypoglycemia AEs with glucose < 54 mg/dL
- Severe hypoglycemia AEs, defined as an event requiring the assistance of another person to actively administer carbohydrates, glucagon or take other corrective actions. Plasma glucose concentrations may not be available during an event, but neurological recovery following the return of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration

Events adjudicated by the CEC:

As discussed in Section 6.1.1, an independent CEC with 4 sub-committees was established to adjudicate centrally and in a blinded fashion the following AESIs and laboratory abnormalities:

- Ketoacidosis (CEC Endocrinology)
- Hepatic events (CEC Hepatology/Gastroenterology)

[29] PTs included acetonemia, diabetic ketosis, ketonuria, ketosis, blood ketone body increased, urine ketone body present, blood ketone body present, acetonemic vomiting

- Cardiovascular events, including myocardial ischemia, myocardial infarction, cardiovascular death, hospitalization for heart failure, and all fatal events (CEC Cardiology)
- Stroke (fatal and non-fatal stroke and transient ischemic attacks) (CEC Neurology)

Events triggering CEC adjudication for Ketoacidosis:

According to the CEC charter, the following events would trigger adjudication for ketoacidosis.

- Any adverse event flagged as "metabolic acidosis event" in the CRF
- Any blood ketone level > 3.8 mmol/L in subjects ≥16 years or > 3 mmol/L for subjects < 16 years
- Selected MedDRA preferred terms indicative of ketoacidosis and/or diabetic ketoacidosis (Figure 10)

Figure 10: MedDRA preferred terms triggering CEC adjudication for ketoacidosis

MedDRA preferred terms	
Acidosis	Diabetic encephalopathy
Acid base balance abnormal	Diabetic hyperglycaemic coma
Acid-base balance disorder mixed	Diabetic ketoacidosis
Alcoholic ketoacidosis	Diabetic ketoacidotic hyperglycaemic coma
Anion gap abnormal	Diabetic ketosis
Anion gap increased	Diabetic metabolic decompensation
Blood pH abnormal	Euglycaemic diabetic ketoacidosis
Blood pH decreased	Ketoacidosis
Coma acidotic	Kussmaul respiration
Diabetic coma	Metabolic acidosis

Source: DINAMO CEC charter

- MedDRA preferred terms indicative of acetonemia[30] if combined with a reported symptom[31] suggestive of ketoacidosis, hospitalization or if reported as a serious adverse event.
- All serum ketone readings > 1.5 and < 3.8 mmol/L for subjects ≥16 years of > 1.5 and < 3.0 mmol/L for subjects < 16 years if accompanied by a reported symptom[31] suggestive of ketoacidosis, hospitalization or if reported as a serious adverse event.

Case definitions used for DKA adjudication by the CEC are displayed below:

[30] acetonemia, ketonuria, blood ketone body, blood ketone body increased, blood ketone body present, ketosis, urine ketone body, urine ketone body present)

[31] Various MedDRA terms indicating confusion, nausea/vomiting, drowsiness/reduced state or loss of consciousness, dehydration/hypotension, tachypnea/Kussmaul respiration, tachycardia, hypothermia, abdominal pain.

Figure 11: Case definitions for ketoacidosis adjudication by Clinical Event Committee

	Certain Ketoacidosis		Potential Ketoacidosis					Unlikely Ketoacidosis	Unlikely KA but ketosis	Unclassifiable
pH	≤7.3	N/A	≤7.3	N/A	N/A	N/A	N/A	Blood BHB ≤1.5 (if blood BHB N/A, then urine ketones <++) *AND/OR* pH >7.3 (if pH N/A, then Bicarbonate >18)	Blood BHB >1.5 to < 3.8 (if blood BHB N/A, then urine ketones ≥++) *AND ONE OF THE BELOW* • pH > 7.3 • Bicarb. >18 (if pH N/A) • No history/ symptoms reported	*IF ONLY ONE OF THE BELOW IS AVAILABLE* • pH <7.3 • Bicarbonate ≤18 • Suggestive history • Typical symptoms
Bicarbonate (mEq/l)		<15		≤18	15 to ≤18	N/A	N/A			
Blood BHB (mmol/l)	>1.5	>1.5			>1.5	>1.5	≥ 3.8*			
Urine ketones when blood BHB N/A	≥ ++	≥ ++			≥++	≥++	++++			
Suggestive history or Typical KA symptoms reported			Y	Y		Y				
CEC assessment of case category	X	X	X	X	X	X	X	X	X	X

*Source: DINAMO CEC Charter. Legend: BHB: ß-hydroxybutyrate; Y: Yes, evidence or history or typical symptoms reported; N/A: Data not available; Suggestive history: Pump failure, insulin dose omission, illness, improper sick day plan etc.; Bicarb.: Bicarbonate; Typical KA symptoms: Neurological (confusion, drowsiness, loss of consciousness, etc.) and non-neurological symptoms (dehydration, nausea/vomiting, abdominal pain, Kussmaul breathing, etc.); Urine ketones: "++/+++" equivalent to "moderate/ large", translates to 1.5-2.9 mmol/l blood BHB; "++++" equivalent to "very large", translates to ≥3 mmol/l blood BHB (Metzger D. BCMJ 2010; Brink S, Laffel L. Pediatric Diabetes 2009); *Blood BHB cut-off for patients below 16 years of age is ≥ 3 mmol/l; value for blood BHB selected per Sheikh-Ali et al. Diabetes Care 2008 (7). For potential KA blood BHB reading ≥ 3.8 mmol/l should be confirmed by an additional measurement ≥ 3.8 mmol/l within 24 hours. Single BHB reading ≥ 3.8 mmol/l without symptoms/suggestive history should be regarded as unlikely KA but ketosis. The occurrence of two BHB readings ≥ 3.8 mmol/L (Blood BHB cut-off for patients below 16 years of age is ≥ 3 mmol/l) within 60 mins constitutes clinically the same reading and as such it is required that two BHB values ≥ 3.8 mmol/L within 24 hours be separated by more than 60 min (in absence of any other parameters) to fulfil the criterion needed for the classification of such an event as Potential ketoacidosis; * with the understanding that CECE assessment of case category would still apply.*

Reviewer Comment: Use of adjudication for DKA is appropriate in this setting, particularly given the occurrence of euglycemic DKA associated with SGLT2 inhibitor therapy. The criteria to trigger CEC evaluation for ketoacidosis and the case definitions used for adjudication appear reasonable.

<u>Events triggering CEC adjudication for hepatic event:</u>
According to the CEC charter, the following events would trigger evaluation for adjudication for a hepatic event:

- ALT and/or AST elevation ≥ 3x ULN with concomitant or subsequent total bilirubin (TB) ≥ 2x ULN in a 30-day period after ALT and/or AST elevation (either identified via lab (central lab) or AESI (as hepatic injury)
- ALT and/or AST elevation ≥ 5x ULN

- Serious adverse events with preferred terms including hepatitis fulminant, acute hepatic failure, hepatic failure, hepatic necrosis, hepatorenal failure, drug-induced liver injury
- Cases with fatal hepatic events as captured by various liver-related SMQs[32]

Detailed definitions regarding events triggering CEC cardiology adjudication (i.e., cardiovascular death, non-cardiovascular death, hospitalization for heart failure, non-fatal myocardial infarction) and those triggering CEC neurology adjudication (i.e., TIA and stroke) are available in the CEC charter.

8.3.3. Routine Clinical Test

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

Specific clinical laboratory tests are further described below:

Laboratory Category	Specific measurements
Hematology	hematocrit, hemoglobin (reticulocyte count if hemoglobin abnormal), red blood cell count (RBC), white blood cell count (WBC), platelet count, and automatic differential counts (neutrophils, eosinophils, basophils, monocytes, lymphocytes)
Clinical Chemistry	albumin, alkaline phosphatase, γ-glutamyl transferase (reflex test triggered by elevated alkaline phosphatase on 2 sequential measures), ALT, AST, total bilirubin (fractionated if increased), beta-hydroxy-butyrate, bicarbonate, calcium, chloride, C-peptide, creatinine, Cystatin C, creatinine kinase (troponin I if creatinine kinase was increased), lactate dehydrogenase, lipase, magnesium, phosphate, potassium, total protein, sodium, TSH (at screening only), blood urea nitrogen, and uric acid
Lipids	total cholesterol, high-density lipoprotein (HDL) cholesterol, calculated low density lipoprotein (LDL) cholesterol, and triglycerides
Urine	Urine dipstick for nitrite, protein, ketones, urine pH, leukocyte esterase (for WBC) with microscopic and urine culture as reflex tests[33] Quantitative analysis for albumin, creatinine, human chorionic

[32] SMQ 20000098 for Liver related investigations, signs and symptoms, 20000009 for Cholestasis and jaundice of hepatic origin, 20000010 for Hepatitis, non-infectious, 20000013 for Hepatic failure, fibrosis, and cirrhosis and other liver damage-related conditions

[33] Microscopic urinalysis performed as a reflex test if any of urine dipstick tests except for ketones were abnormal, urine culture triggered by positive leukocyte esterase and/or nitrite

	gonadotrophin (albumin/creatinine ratio calculated in spot urine)
Growth factors and markers of bone turnover	IGF-1, IGFBP-3, Calcium, phosphate, alkaline phosphatase, 25-OH vitamin D, intact parathyroid hormone, Serum Procollagen type I N-terminal propeptide (for bone formation), Serum N-terminal cross-linked telopeptide (for bone resorption)

Source: DINAMO protocol

8.4. Safety Results

8.4.1. Deaths

No deaths occurred in the study.

8.4.2. Serious Adverse Events

SAEs that occurred during the placebo-controlled period (through week 26) and during the safety extension period (from week 26 to 52) are described in Table 27 and Table 28, respectively. From week 0 to 26, overall, there were a total of 13 SAEs in 6 subjects, including 3 SAEs in 2 subjects treated with empagliflozin (1 subject who received empagliflozin 10 mg, and another subject who received empagliflozin 10 mg through week 14 followed by empagliflozin 25 mg), 2 SAEs in 2 subjects treated with linagliptin, and 8 SAEs in 2 subjects treated with placebo. From week 26 to 52, a total of 8 SAEs occurred in 7 subjects, including 2 SAEs in a single subject treated with empagliflozin 10 mg, and 6 SAEs in 6 subjects treated with Linagliptin. No SAEs occurred in subjects treated with empagliflozin 25 mg from week 26 to 52.

Table 27: Serious Adverse Events through Week 26, Study 1218.91

Preferred Term	Empagliflozin Pooled (N=52) n (%)	Linagliptin (N=52) n (%)	Placebo (N=53) n (%)
Acute kidney injury	0 (0.0)	0 (0.0)	1 (1.9)
Acute respiratory failure	0 (0.0)	0 (0.0)	1 (1.9)
Breast abscess	0 (0.0)	1 (1.9)	0 (0.0)
Diabetic ketoacidosis	0 (0.0)	0 (0.0)	1 (1.9)
Hyperglycemia	0 (0.0)	0 (0.0)	1 (1.9)
Hypovolemic shock	0 (0.0)	0 (0.0)	1 (1.9)
Pancreatitis acute	0 (0.0)	0 (0.0)	1 (1.9)
Pneumomediastinum	0 (0.0)	1 (1.9)	0 (0.0)
Road traffic accident	1 (1.9)	0 (0.0)	0 (0.0)
Skin candida	1 (1.9)	0 (0.0)	0 (0.0)
Splenic vein thrombosis	0 (0.0)	0 (0.0)	1 (1.9)
Suicidal ideation	1 (1.9)	0 (0.0)	0 (0.0)
Systemic inflammatory response syndrome	0 (0.0)	0 (0.0)	1 (1.9)

Source: Reviewer generated using OCS Analysis Studio, Safety Explorer.
Filters: TRT01A = "E10" and TRTFL = "Y" (Empagliflozin Pooled); TRT01A = "L5" and TRTFL = "Y" (Linagliptin); TRT01A = "Pbo" and TRTFL = "Y" (Placebo); TRTEMFL = "Y" and APERIODC = "Up to Week 14 (on-trt" or "Week 14 to Week 26 (on-trt" and AESER = "Y" (Adverse Events).

Table 28: Serious Adverse Events from Week 26 to Week 52, Study 1218.91

Preferred Term	Empagliflozin 10 mg (N=47) n (%)	Empagliflozin 25 mg (N=28) n (%)	Linagliptin (N=65) n (%)
Asthma	0 (0.0)	0 (0.0)	1 (1.5)
Blood glucose increased	0 (0.0)	0 (0.0)	1 (1.5)
Chorioretinitis	0 (0.0)	0 (0.0)	1 (1.5)
Colitis	1 (2.1)	0 (0.0)	0 (0.0)
Diabetic ketoacidosis	0 (0.0)	0 (0.0)	2 (3.1)
Hyperglycemia	0 (0.0)	0 (0.0)	1 (1.5)
Tubulointerstitial nephritis	1 (2.1)	0 (0.0)	0 (0.0)

Source: Reviewer generated using OCS Analysis Studio, Safety Explorer.
Filters: TRT03A = "E10" and TRTFL = "Y" (Empagliflozin 10 mg); TRT03A = "E25" and TRTFL = "Y" (Empagliflozin 25 mg); TRT03A = "L5" and TRTFL = "Y" (Linagliptin); TRTEMFL = "Y" and APERIODC = "Week 26 to EOT (on-trt" and AESER = "Y" (Adverse Events).

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

SAEs associated with empagliflozin treatment	Clinical Reviewer Assessment of Relatedness to Study Treatment /Comments

The SAEs of suicidal ideation and road traffic accident occurred on study days 148 and 149 a 17-year-old female subject who was treated with empagliflozin 10 mg and re-randomized to continue on empagliflozin 10 mg at week 14. The subject had stayed away from home for several days prior to the event without medication, and was eventually hospitalized and received citalopram as therapy. The SAE of road traffic accident occurred when the patient and father were enroute to a planned appointment with a diabetic specialist and psychologist. Workup including CT scan, spinal and shoulder x-rays were performed (results not reported). Study medication was not interrupted for either of these SAEs. According to the Applicant, this subject had a history of suicidal ideation for > 5 years at study entry.	Not related
The SAE of skin candida occurred on day 111 of treatment with empagliflozin in a 12-year-old female who was treated initially with empagliflozin 10 mg and re-randomized to empagliflozin 25 mg after week 14. The subject presented with a rash on the groin, thigh an armpits and history of low-grade fever, sore throat and conjunctivitis for 3 days. She was admitted due to concerns for possible systemic candida infection versus bacterial superinfection, but had no signs of bacterial infection on subsequent testing and was afebrile following admission. She was treated with fluconazole, clindamycin, clotrimazole, nystatin, diphenhydramine and ketorolac and the event resolved within 2 days. The subject permanently discontinued study medication upon discharge from the hospital.	The risk of genital mycotic infections is known to be increased with empagliflozin therapy. It is unclear whether this event involved a genital infection; however, the rash is described as appearing on the “groin” (in addition to other areas); therefore, this SAE was likely elated to empagliflozin therapy.
The SAEs of colitis and tubulointerstitial nephritis (TIN) occurred on day 207 and 211, respectively of empagliflozin 10 mg treatment in a 14-year-old female subject who was initially randomized to empagliflozin 10 mg and remained on empagliflozin 10 mg during the safety extension. According to the narrative, the subject presented on day 207 with abdominal pain, severe diarrhea and vomiting. An abdominal CT scan confirmed colitis (no prior history of colitis or Crohn’s disease) and she was started on treatment with metronidazole and ciprofloxacin on day 210. On day 211, the subject presented with abdominal pain, diarrhea, vomiting, loss of appetite and dehydration and was found to have acute kidney injury (BUN/Creatinine 19/2.7 on presentation, rising to 23/3.4). Urinalysis was negative for bilirubin, ketone, protein, nitrite, leukocyte esterase, bacteria, and blood trace. An MRI showed inflammatory fluid along retroperitoneum, lower poles of kidney and duodenum and mild retroperitoneal adenopathy. The subject was treated with pain medications, anti-emetics and ceftriaxone and subsequently discharged on day 216 at which time both SAEs of colitis and TIN were considered resolved. The narrative does not report any biopsy being conducted to confirm the diagnosis of TIN. Study drug was	TIN is defined as acute kidney injury (AKI) accompanied by specific histological findings; extra-renal manifestations may include fever rash and eosinophilia, but the presentation may be highly variable therefore diagnosis may require renal biopsy. Given the absence of a renal biopsy or description of other characteristic manifestations of TIN in the narrative, it is uncertain whether this subject experienced TIN or AKI of another cause. The presentation with abdominal pain, severe

temporarily discontinued for 2 months but then resumed and the subject completed the study.	diarrhea and vomiting along with elevated BUN to creatinine ratio could suggest volume depletion as an alternative cause for AKI. The subject was initiated on ciprofloxacin the day prior to the event; treatment was discontinued upon presentation with the TIN/AKI. Ciprofloxacin has also been associated with TIN, which introduces further uncertainty as to the relationship of the event with empagliflozin treatment. A possible increased risk of TIN associated with empagliflozin therapy has been identified in post-marketing reports; this risk is currently described in the product label. However, based on the narrative, there is insufficient information to conclude whether this event was truly TIN or related to treatment of empagliflozin.
SAEs associated with linagliptin treatment	
The SAE of pneumomediastinum occurred in a 16-year-old male subject 5 days after the first intake of linagliptin and was resolved in a follow up chest Xray performed 3 days later. The subject had a history of diarrhea and orthostatic dizziness and was treated with metformin at baseline. 1 day prior to the SAE, the subject experienced elevated ketones (2.3 mmol/L) which had since resolved; however, the narrative does not describe any vomiting or other potential precipitating factors for a spontaneous pneumomediastinum.	Not related
The SAE of breast abscess occurred on day 84 of treatment with linagliptin in a 12-year-old female subject. She presented to the emergency room with breast pain, an ultrasound was performed (results not reported) and she was treated with cephalexin and	Not related

discharged that same day. Study medication was not interrupted. This subject had a medical history of "other genital infections".	
The SAE of "blood glucose increased" occurred on day 260 of linagliptin treatment in a subject who was initially randomized to linagliptin and continued on linagliptin during the safety extension period. On day 210, the subject had chronic gastritis and Helicobacter pylori infection. In the month prior to the SAE, the subject was also noted to have had a glucose of 267 mg/dL on laboratory findings and was reportedly hospitalized (date unknown) for "eradication therapy and diabetes therapy" and also started on metformin (date unknown). It is unclear whether the subject experienced a separate hospitalization at the time of the SAE or whether the initial hospitalization was prolonged; no further details are provided in the narrative.	Not related
The SAE of chorioretinitis occurred on day 63 days of linagliptin treatment in a 16-year-old male subject initially randomized to placebo and re-randomized to linagliptin at week 26. An SAE was reported because the subject was hospitalized due to decreased visual acuity. However, upon review of the narrative, the subject appears to have had symptoms of decreased visual acuity with initial onset during treatment with placebo, prior to initiating linagliptin.	Not related
The SAE of diabetic ketoacidosis occurred on day 26 of linagliptin treatment in a 15-year-old male subject initially randomized to placebo and re-randomized to linagliptin at week 26. Upon review of the narrative, the subject was asymptomatic and reportedly had "positive urine ketones and elevated beta-hydroxybutyrate; however, the highest blood ketone value was 0.2 mmol/L and there was no evidence of hyperglycemia or acidosis (bicarbonate > 18 meq/L and glucose 193 mg/dL).	Not related. Based on my review, this event does not appear consistent with DKA; this event was also not confirmed as DKA after adjudication.
The SAE of hyperglycemia occurred on day 183 of linagliptin therapy in a 14-year-old male subject initially randomized to linagliptin and continued on linagliptin during the safety extension. The subject presented with very high blood sugar levels and elevated HbA1c (values not reported) and was hospitalized and treated with insulin. Study medication was not interrupted.	Not related
The SAE of diabetic ketoacidosis occurred on day 274 of linagliptin therapy in a 16-year-old male subject initially randomized to linagliptin and continued on linagliptin during the safety extension. After not taking background insulin and metformin for a week (though reportedly continuing study medication), the subject presented to the emergency room with vomiting, hyperglycemia (glucose 331 mg/dL), elevated ketones (4.9 mmol/L) and acidosis (bicarbonate 10 to < 15 meq/L). Diabetic ketoacidosis resolved in 2	Not related

days after treatment with insulin and other therapies. Study medication was not interrupted.	
The SAE of asthma exacerbation requiring hospitalization occurred on day 253 of linagliptin therapy in a 13-year-old female subject initially randomized to linagliptin and continued on linagliptin during the safety extension. The subject had a pre-existing history of asthma, atopic dermatitis and seasonal allergies and also experienced another asthma exacerbation on day 228 of the study. Due to respiratory symptoms, the subject was seen in the emergency room, initially discharged with a prednisone course but subsequently hospitalized that same day due to worsening symptoms and received magnesium sulfate. The asthma exacerbation resolved after 3 days. Study medication was not interrupted	Not related.

Source: reviewer created

As displayed in Table 27, a high frequency of SAEs occurred in the placebo arm, however, 7 of these SAEs occurred in a single subject who presented with acute pancreatitis on day 24, followed by related SAEs of systemic inflammatory response syndrome, diabetic ketoacidosis, acute kidney injury, acute respiratory failure and hypovolemic shock the following day. This subject experienced a prolonged hospitalization during which time an SAE of splenic vein thrombosis also occurred.

Reviewer Comment: Overall, SAEs occurred in 2(3.8%) empagliflozin-treated subjects during the placebo-controlled period, and in 1 subject (2.1%) treated with empagliflozin 10 mg during the safety extension . Based on review of the subject narratives, SAEs of skin candida (involving the groin) and tubulointerstitial nephritis (TIN) were likely related to treatment with empagliflozin, though there was insufficient information provided in both narratives to draw definitive conclusions regarding the relationship of the SAE to study treatment. Genital mycotic infections and tubulointerstitial nephritis are both known safety issues associated with empagliflozin treatment that are described in the product label.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

During the placebo-controlled treatment period through week 26, no TEAEs led to discontinuation in subjects treated with empagliflozin or linagliptin (see Table 29).

During the safety extension period (Table 30), an SAE of tubulointerstitial nephritis (discussed above in Section 8.4.2) led to temporary discontinuation of study treatment in a subject treated with empagliflozin 10 mg, however, treatment was subsequently resumed after 2 months. Several gastrointestinal-related TEAEs all occurring 15-days after initiating linagliptin and lasting for a total of 27 days led to study drug discontinuation in a single subject (16-year-old female) who was initially randomized to placebo and re-randomized to linagliptin during the safety

extension. No discontinuations due to TEAEs occurred in subjects treated with empagliflozin 25 mg.

Table 29: TEAEs leading to Discontinuation through Week 26, Study 1218.91

Preferred Term	Empagliflozin Pooled (N=52) n (%)	Linagliptin (N=52) n (%)	Placebo (N=53) n (%)
Menstruation irregular	0 (0.0)	0 (0.0)	1 (1.9)
Pancreatitis acute	0 (0.0)	0 (0.0)	1 (1.9)
Polyuria	0 (0.0)	0 (0.0)	1 (1.9)

Source: Reviewer generated using OCS Analysis Studio, Safety Explorer.
Filters: TRT01A = "E10" and TRTFL = "Y" (Empagliflozin Pooled); TRT01A = "L5" and TRTFL = "Y" (Linagliptin); TRT01A = "Pbo" and TRTFL = "Y" (Placebo); TRTEMFL = "Y" and APERIOD = 1 to 2 and AEACN = "DRUG WITHDRAWN" (Adverse Events).

Table 30: TEAEs leading to Discontinuation, Week 26 to Week 52, Study 1218.91

Preferred Term	Empagliflozin 10 mg (N=47) n (%)	Empagliflozin 25 mg (N=28) n (%)	Linagliptin (N=65) n (%)
Abdominal discomfort	0 (0.0)	0 (0.0)	1 (1.5)
Abdominal pain	0 (0.0)	0 (0.0)	1 (1.5)
Decreased appetite	0 (0.0)	0 (0.0)	1 (1.5)
Diarrhea	0 (0.0)	0 (0.0)	1 (1.5)
Tubulointerstitial nephritis	1 (2.1)	0 (0.0)	0 (0.0)

Source: Reviewer generated using OCS Analysis Studio, Safety Explorer.
Filters: TRT03A = "E10" and TRTFL = "Y" (Empagliflozin 10 mg); TRT03A = "E25" and TRTFL = "Y" (Empagliflozin 25 mg); TRT03A = "L5" and TRTFL = "Y" (Linagliptin); TRTEMFL = "Y" and APERIOD = 3 to 3 and AEACN = "DRUG WITHDRAWN" (Adverse Events).

8.4.4. Significant Adverse Events

Hypoglycemia events, AESIs and specific AEs (as defined in Table 26), and events adjudicated by the CEC are discussed in this section.

Hypoglycemia events:
The Applicant reported hypoglycemia events within two separate datasets as described below:

Hypoglycemia events captured in the ADAE dataset:
-all symptomatic hypoglycemic events
-all asymptomatic hypoglycemia events with glucose levels < 54 mg/dL
-all asymptomatic hypoglycemic events that were considered as adverse events by the investigator

Hypoglycemia events captured in the ADHYPO dataset:
- asymptomatic hypoglycemia events not considered to be adverse events with glucose values

between 54 mg/dL to 70 mg/dL

For the purposes of the hypoglycemia safety review, hypoglycemia events were categorized in the following manner:

- All hypoglycemia events: included all hypoglycemia events reported within the ADAE and ADHYPO datasets (i.e., all events associated with glucose value ≤70 mg/dL)
- Hypoglycemia AEs with BG < 70 mg/dL: included all hypoglycemia events reported within the ADAE dataset associated with a glucose value ≤ 70 mg/dL (i.e., all events associated with glucose < 70 mg/dL that were considered as adverse events by the investigator).
- Hypoglycemia AEs with BG < 54 mg/dL: included all hypoglycemia events reported in within the ADAE dataset associated with a glucose value <54 mg/dL (i.e., both asymptomatic and symptomatic events associated with glucose < 54 mg/dL). **This category of hypoglycemia events is consistent with the American Diabetes Association (ADA) Level 2 hypoglycemia definition[3], and is pertinent for labeling.**

Reviewer Comment: The Applicant did not classify hypoglycemia events according to the ADA Level 1 hypoglycemia definition (i.e., events associated with a glucose ≥54 but <70 mg/dL) [3].

No severe hypoglycemia events occurred in the study; therefore, the category of severe hypoglycemia events does not appear in the subsequent analyses.

An increased risk of hypoglycemia has been reported in adult studies of empagliflozin and in adult studies of linagliptin, but only when used concomitantly with insulin and/or sulfonylureas. As previously discussed, around 43% of the study population received background insulin at baseline. For this reason, the hypoglycemia safety review also evaluated the impact of background insulin use at baseline on the incidence and frequency of hypoglycemia.

Table 31 below displays the incidence and count of hypoglycemia events by treatment arm through week 26 in all subjects and for subjects according to insulin use at baseline. Level 2 hypoglycemia, defined as blood glucose < 54 mg/dL, occurred in 19.2% of subjects treated with empagliflozin versus 7.5% of subjects treated with placebo. Among subjects treated with insulin at baseline, the incidence of Level 2 hypoglycemia was 24.0% with empagliflozin versus 14.3% with placebo. Among subjects not treated with insulin at baseline, the incidence of Level 2 hypoglycemia was 14.8% with empagliflozin versus 3.1% with placebo. The incidence of hypoglycemia events within all other hypoglycemia categories (i.e., all hypoglycemia events, and hypoglycemia AEs with BG < 70 mg/dL) was also higher with empagliflozin versus placebo treatment in all subjects, in subjects with insulin use at baseline, and in subjects without insulin use at baseline. The frequency of hypoglycemia events was also greater with empagliflozin treatment as compared to placebo among all categories of hypoglycemia, even in subjects who were not treated with insulin at baseline.

Table 31: Hypoglycemia Incidence and Frequency through Week 26

Hypoglycemia Category	Empagliflozin Pooled			Linagliptin			Placebo		
	N	Incidence n (%)	Episodes (count)	N	Incidence n (%)	Episodes (count)	N	Incidence n (%)	Episodes (count)
All subjects	52			52			53		
All hypoglycemia events		15 (28.9)	69		15 (28.9)	89		7 (13.2)	42
Hypoglycemia AE with BG ≤70		12 (23.1)	46		10 (19.2)	34		5 (9.4)	16
Hypoglycemia AE with BG < 54		10 (19.2)	21		8 (15.4)	30		4 (7.5)	8
Subjects with insulin use at baseline	25			22			21		
All hypoglycemia events		10 (40.0)	53		9 (40.9)	49		5 (23.8)	28
Hypoglycemia AE with BG ≤70		8 (32.0)	33		7 (31.8)	26		3 (14.3)	11
Hypoglycemia AE with BG < 54		6 (24.0)	11		5 (22.7)	23		3 (14.3)	4
Subjects with no insulin use at baseline	27			30			32		
All hypoglycemia with BG ≤ 70		5 (18.5)	16		6 (20.0)	40*		2 (6.3)	14
Hypoglycemia AE with BG ≤70		4 (14.8)	13		3 (10.0)	8		2 (6.3)	5
Hypoglycemia AE with BG < 54		4 (14.8)	10		3 (10.0)	7		1 (3.1)	4

** Of these 40 events occurring in the linagliptin arm, 20 occurred in 1 subject (17 of which were asymptomatic hypoglycemia events with BG between 54 to 70 mg/dL) and 13 occurred in another subject (10 of which were asymptomatic hypoglycemia events with BG between 54 to 70 mg/dL).*
Source: Reviewer created based on review of adae.xpt and adhypo.xpt datasets.

Reviewer Comment:
Through week 26, a higher percentage of subjects in the empagliflozin arm experienced one or more hypoglycemia events, both with and without concomitant insulin use, as compared

to the placebo arm. Additionally, a higher number of hypoglycemia events occurred in subjects treated with empagliflozin as compared to placebo, both with and without concomitant insulin use. These findings suggest that in pediatric patients, treatment with empagliflozin may be associated with a higher risk of hypoglycemia regardless of background insulin therapy.

As discussed above, the analysis presented in Table 31 categorized subjects according to background insulin use at baseline. Subjects who received rescue therapy (i.e., insulin) during the study were not excluded. Given that, a secondary review was conducted to determine whether any subjects in Table 31 represented as not receiving insulin at baseline had received rescue therapy with insulin through week 26[34]. Based on this review, only 1 subject with hypoglycemia AEs was identified who was not on background insulin at baseline but received rescue therapy prior to Week 26[35]. This subject (subject (b) (6)) was initially randomized to empagliflozin 10 mg (followed by a second randomization to empagliflozin 25 mg at week 14), and experienced a hypoglycemia AE with BG <54 mg/dL on (b) (6) and a hypoglycemia AE with BG ≤ 70 mg/dL on (b) (6) Upon review of the antidiabetic therapy concomitant medications dataset, this subject is reported as having been initiated on insulin at a dose of 0.01 IU on (b) (6) 3 days after initiating study treatment. Following an IR, the Applicant provided source data suggesting that the subject initiated insulin lispro (admelog) at a dose of 1 unit on (b) (6) however a frequency was not reported[36]. This subject was also subsequently started on insulin glargine at 25 units daily on (b) (6) however, this occurred after the hypoglycemia events described above.

Reviewer Comment: Based on the source data, it is possible that this subject had been initiated on insulin lispro as part of a sliding scale for mealtime coverage on study day 3, however, there is no record of any AEs (e.g., hyperglycemia or elevated ketones) that would have prompted the initiation of insulin therapy. Even if this subject is excluded from the analysis of subjects who were not on insulin therapy at baseline, there remains an imbalance in hypoglycemia risk between the empagliflozin and placebo arms.

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[34] This secondary review focused on hypoglycemia data within the ADAE datasets, and did not consider asymptomatic hypoglycemia events associated with BG between 54 to 70 mg/dL that were included in the ADHYPO dataset, since these events would not be described in product labeling.

[35] In the Applicant's 5/23/2023 response to the Agency's IR of 5/18/2023 regarding subgroup analyses for commonly reported TEAEs including hypoglycemia, the Applicant stated that among subjects in the empagliflozin group who had hypoglycemia at week 26, 2 subjects (subject (b) (6) discussed above, and subject (b) (6)) had received additional antidiabetic therapy as rescue. Upon further review, it appears that subject (b) (6) received insulin at baseline and was initiated on treatment with metformin as rescue therapy during the study; this subject experienced several Level 1 hypoglycemia AEs and hypoglycemia events, but none were associated with a blood glucose of < 54 mg/dL. Given that an increased risk of hypoglycemia with concomitant insulin therapy is already recognized as a safety signal for empagliflozin in adult studies, and since this subject did not experience any Level 2 hypoglycemia events during the study, the addition of metformin therapy in this patient is unlikely to change any conclusions regarding the hypoglycemia risk in pediatric patients.

[36] According to the analysis datasets plan, if no daily dose is available in the source data, the dose was imputed as 0.01 units for the datasets to allow further calculations.

During the review cycle, the statistical team requested that the Applicant conduct additional safety analyses based on the number of hypoglycemia events through Week 26, the results of which are displayed below. The Applicant's analysis of any hypoglycemia event with BG ≤ 70 mg/dL (including hypoglycemia AEs with BG ≤ 70 mg/dL and asymptomatic hypoglycemia events with BG ≥ 54 and ≤70 mg/dL) is displayed in Table 32. The Applicant's analysis of hypoglycemia AEs with BG < 54 mg/dL is displayed in Table 33. Overall, subjects treated with empagliflozin had an increased risk for all types of hypoglycemic events compared to those treated with placebo, however, these differences did not reach statistical significance.

Table 32: Analysis of Any Hypoglycemia Events* with BG <=70 mg/dL up to Week 26, Study 1218.91

	Empa pooled N = 52	Placebo N = 53
Incidence (%)	15 (28.8)	7 (13.2)
Number of events	69	42
Total time at risk (patient year)	23.90	25.08
Unadjusted event rate, events per patient year	2.89	1.67
Adjusted event rate[1], events per patient year (95% CI)	2.86 (1.23, 6.61)	1.51 (0.64, 3.53)
Comparison vs. placebo Adjusted event rate ratio[1] (95% CI)		1.89 (0.57, 6.33)
Nominal p-value (two-sided)		0.30

Abbreviations: CI = confidence interval
[1] The adjusted event rate and rate ratio were based on a negative binomial regression, adjusted for treatment and age stratum (< 15 years vs 15 to <18 years), and offset by time of exposure to treatment.

** including hypoglycemia adverse events with BG < 70 mg/dL and asymptomatic hypoglycemia events with BG > 54 and <70 mg/dL.*
Source: Table 15 from Dr. Tu's Statistical Review, based on Applicant's analysis, submitted 4/27/2023 (SDN 3655).

Table 33: Analysis of Hypoglycemia AEs with BG <54 mg/dL up to Week 26, Study 1218.91

	Empa pooled N = 52	Placebo N = 53
Incidence (%)	10 (19.2)	4 (7.5)
Number of events	21	8
Total time at risk (patient year)	23.90	25.08
Unadjusted event rate	0.88	0.32
Adjusted event rate[1], events per patient year (95% CI)	0.86 (0.34, 2.18)	0.31 (0.11, 0.91)
Comparison vs. placebo Adjusted event rate ratio[1] (95% CI)		2.73 (0.67, 11.20)
Nominal p-value (two-sided)		0.16

Abbreviations: CI = confidence interval
[1] The adjusted event rate and rate ratio were based on a negative binomial regression, adjusted for treatment and age stratum (< 15 years vs 15 to <18 years), and offset by time of exposure to treatment.

Source: Table 14 from Dr. Tu's Statistical Review, based on Applicant's analysis, submitted 4/27/2023 (SDN 3655).

Reviewer Comment: In both this reviewer's and the Applicant's hypoglycemia safety analyses, based on data from all treated pediatric subjects in the DINAMO study, there appears to be an increased risk of Level 2 hypoglycemia associated with empagliflozin therapy versus placebo. This finding was not observed in the hypoglycemia analyses for adult studies of empagliflozin. According to the primary clinical review by Dr. Chong for the original NDA submission for empagliflozin, an imbalance in hypoglycemia events was primarily seen in analyses of adults who received background insulin and/or sulfonylureas; however, this hypoglycemia imbalance was not seen in the safety analyses that considered data from all treated adult subjects. This difference may reflect an overall higher risk of hypoglycemia in pediatric patients versus adults, or may relate to higher frequency of background insulin use in the pediatric study versus adult studies.

Dr. Tu also conducted separate analyses regarding the hypoglycemia event count in subjects who received background insulin at baseline and in subjects who did not receive background insulin at baseline (Table 34, Table **35**, Table 36, Table 37). Although the results were not significant, an elevated risk of hypoglycemia is observed with empagliflozin treatment as compared to placebo regardless of background insulin use at baseline. With respect to hypoglycemia AEs with BG < 54 mg/dL, the magnitude of the adjusted event rate ratio versus placebo was 3.9 in subjects on background insulin and 4.3 in subjects not on background insulin. For hypoglycemia AEs with BG < 70 mg/dL, the magnitude of the adjusted event rate ratio versus placebo was 4.5 in subjects on background insulin and 3.3 in subjects not on background insulin.

Table 34: Analysis of Hypoglycemia AEs with BG < 54 mg/dL through Week 26 in Subjects on Background Insulin at Baseline, Study 1218.91

	Empa pooled (N = 25)	Placebo (N = 21)
Incidence (%)	6 (24.0)	3 (14.3)
Number of events	11	4
Total time at risk (patient year)	11.35	9.74
Unadjusted event rate	0.97	0.41
Adjusted event rate[1], events per patient year (95% CI)	1.07 (0.36, 3.16)	0.27 (0.06, 1.18)
Comparison vs. placebo Adjusted event rate ratio[1] (95% CI)		3.89 (0.59, 25.57)
nominal p-value (two-sided)		0.16

Abbreviations: CI = confidence interval
[1] The adjusted event rate and rate ratio were based on a negative binomial regression, adjusted for treatment and age stratum (< 15 years vs 15 to <18 years), and offset by time of exposure to treatment.

Source: Table 16 of Dr. Tu's Statistical Review.

Table 35: Analysis of Hypoglycemia AEs with BG < 54 mg/dL through Week 26 in Subjects Not on Background Insulin at Baseline, Study 1218.91

	Empa pooled (N = 27)	Placebo (N = 32)
Incidence (%)	4 (14.8)	1 (3.1)
Number of events	10	4
Total time at risk (patient year)	12.55	15.35
Unadjusted event rate	0.80	0.26
Adjusted event rate[1], events per patient year (95% CI)	0.65 (0.14, 3.04)	0.15 (0.03, 0.89)
Comparison vs. placebo Adjusted event rate ratio[1] (95% CI)		4.25 (0.41, 43.62)
p-value (two-sided)		0.22

Abbreviations: CI = confidence interval
[1] The adjusted event rate and rate ratio were based on a negative binomial regression, adjusted for treatment and age stratum (< 15 years vs 15 to <18 years), and offset by time of exposure to treatment.
Source: Table 17 of Dr. Tu's statistical review

Table 36: Analysis of Hypoglycemia AEs with BG < 70 mg/dL through Week 26 in Subjects on Background Insulin at Baseline, Study 1218.91

	Empa pooled (N = 25)	Placebo (N = 21)
Incidence (%)	8 (32.0)	3 (14.3)
Number of events	33	11
Total time at risk (patient year)	11.35	9.74
Unadjusted event rate	2.91	1.13
Adjusted event rate[1], events per patient year (95% CI)	3.27 (1.15, 9.36)	0.74 (0.20, 2.71)
Comparison vs. placebo Adjusted event rate ratio[1] (95% CI)		4.45 (0.74, 26.64)
nominal p-value (two-sided)		0.10

[1] The adjusted event rate and rate ratio were based on a negative binomial regression, adjusted for treatment and age stratum (< 15 years vs 15 to <18 years), and offset by time of exposure to treatment.
Source: Dr. Wenda Tu's analysis based on adsl.xpt, adae.xpt, and adhypo.xpt

Table 37: Analysis of Hypoglycemia AEs with BG < 70 mg/dL through Week 26 in Subjects Not on Background Insulin at Baseline, Study 1218.91

	Empa pooled (N = 27)	Placebo (N = 32)
Incidence (%)	4 (14.8)	2 (6.3)
Number of events	13	5
Total time at risk (patient year)	12.55	15.35

Unadjusted event rate	1.04	0.33
Adjusted event rate[1], events per patient year (95% CI)	0.89 (0.20, 3.94)	0.27 (0.05, 1.31)
Comparison vs. placebo Adjusted event rate ratio[1] (95% CI)		3.34 (0.39, 28.93)
p-value (two-sided)		0.27

[1] The adjusted event rate and rate ratio were based on a negative binomial regression, adjusted for treatment and age stratum (< 15 years vs 15 to <18 years), and offset by time of exposure to treatment.
Source: Dr. Wenda Tu's analysis based on adsl.xpt, adae.xpt, and adhypo.xpt

Reviewer Comment: Although the results of Dr. Tu's hypoglycemia analyses were not statistically significant, which is expected given the study power estimates were calculated based on the HbA1c primary efficacy endpoint, the magnitude of the point estimates of the relative risk of hypoglycemia with empagliflozin versus placebo were all > 3, including that observed in analyses of subjects who did not receive background insulin at baseline. This suggests that the safety signal for hypoglycemia in subjects not on background insulin at baseline is less likely to be a chance finding. The results of these exploratory analyses support the conclusion that the hypoglycemia risk in pediatric patients may be increased with empagliflozin therapy regardless of concomitant insulin use.

An analysis of hypoglycemia events was also conducted during the safety extension period[37]. Table 38 displays the incidence and count of hypoglycemia events by treatment arm from weeks 26 to 52 in all subjects, and for subjects according to insulin use at baseline. Subjects who received rescue therapy were not excluded from this analysis. From week 26 to 52, Level 2 hypoglycemia events (i.e., hypoglycemia AEs with <54 mg/dL) occurred in 3 subjects (2 of which were not on background insulin at baseline) treated with empagliflozin 10 mg and in 1 subject (7.7%) on background insulin at baseline who was treated with empagliflozin 25 mg.

Table 38: Hypoglycemia Incidence and Frequency Week 26 to Week 52, Study 1218.91

Hypoglycemia Category	Empagliflozin 10 mg			Empagliflozin 25 mg			Linagliptin 5 mg		
	N	Incidence n (%)	Episodes (count)	N	Incidence n (%)	Episodes (count)	N	Incidence n (%)	Episodes (count)
All subjects	47			28			65		
Hypoglycemia AE with BG ≤70		6 (12.8)	21		3 (10.7)	49		8 (12.3)	39
Hypoglycemia AE with BG < 54		3 (12.8)	10		1 (7.7)	19		5 (7.7)	34

[37] Hypoglycemia data from the ADHYPO dataset (i.e., asymptomatic hypoglycemia events with BG between 54 to 70 mg/dL not associated with an AE) were not included in this analysis.

Subjects with insulin use at baseline	19			13			28		
Hypoglycemia AE with BG ≤70		4 (21.1)	17		2 (15.4)	48*		4 (14.3)	35*
Hypoglycemia AE with BG < 54		1 (5.3)	6		2 (7.1)	18		3 (10.7)	32*
Subjects with no insulin use at baseline	28			15			37		
Hypoglycemia AE with BG ≤70		2 (7.1)	4		1 (6.7)	1		4 (10.8)	4
Hypoglycemia AE with BG < 54		2 (7.1)	4		0 (0)	1		2 (5.4)	2

** Of the events among insulin users who received empagliflozin 25 mg, 46 out of 48 events with BG ≤ 70 mg/dL occurred in a single subject* (b) (6) *Of the events for insulin users who received linagliptin, 10 events of BG ≤ 70 mg/dL and BG <54 mg/dL occurred in 1 subject* (b) (6) *and 22 events of BG ≤ 70 mg/dL and 21 events of BG <54 mg/dL occurred in another subject* (b) (6).
Source: Reviewer created based on adae.xpt and adhypo.xpt datasets

The Applicant also conducted an analysis of the relationship of hypoglycemia to empagliflozin exposure based on pre (-0.5 hour) and post-dose (1.5 hour) PK samples obtained at Week 52 for subjects treated with empagliflozin 10 mg versus 25 mg. In subjects treated with empagliflozin 10 mg, the geometric mean (gMean) post-dose plasma concentrations were only slightly higher in subjects who had hypoglycemia compared to those who did not, whereas the gMean pre-dose plasma concentrations were lower in subjects who had hypoglycemia as compared to those who did not. In subjects treated with empagliflozin 25 mg, the gMean post-dose plasma concentrations were higher in subjects with hypoglycemia; however, data was unavailable regarding the pre-dose plasma concentrations in these subjects. Overall, it is difficult to draw conclusions regarding the relationship of hypoglycemia to empagliflozin exposure given the limited numbers of subjects involved and missing data.

Table 39: Pooled drug plasma concentrations of empagliflozin after multiple oral administration of 10 mg or 25 mg empagliflozin once daily at week 52 by hypoglycemia

Plasma concentration of empagliflozin	Patients without hypoglycaemia		Patients with hypoglycaemia	
	N	gMean (gCV %)	N	gMean (gCV %)
Empagliflozin 10 mg				
At Week 52/-0.5 h [nmol/L]	20	29.9 (211)	5	16.7 (56.2)
At Week 52/1.5 h [nmol/L]	25	294 (72.5)	9	350 (18.4)
Empagliflozin 25 mg				
At Week 52/-0.5 h [nmol/L]	16	60.5 (144)	2	-
At Week 52/1.5 h [nmol/L]	19	492 (189)	4	713 (37.8)

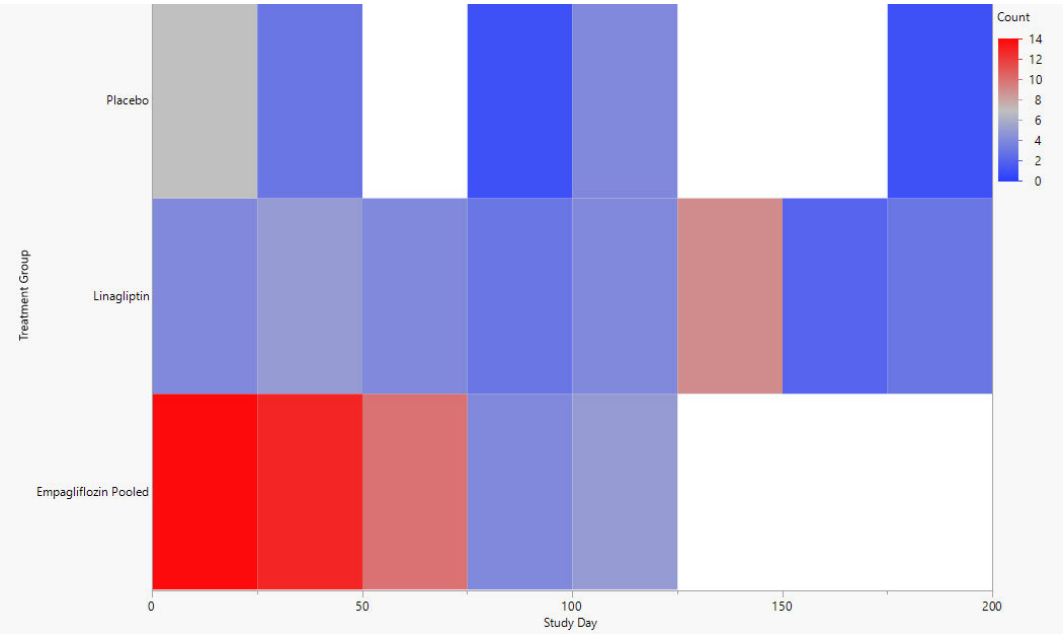
Source: Applicant's 5/31/2023 submission, in response to the Agency's IR issued on 5/18/2023.

Reviewer Comment: From weeks 26 to 52, fewer subjects experienced one or more hypoglycemia events, limiting the interpretation of data. The majority of hypoglycemia events occurred among insulin-users, with a few subjects experiencing multiple events. Based on these limited data, there does not appear to be any evidence of increased risk of hypoglycemia events with the empagliflozin 25 mg dose as compared to the 10 mg dose, both with and without concomitant insulin therapy.

Timeframe of Hypoglycemia Events:
To evaluate the timeframe of hypoglycemia events, a heatmap distribution analysis was performed for hypoglycemia AEs associated with blood glucose ≤ 70 mg/dL by study day through week 26. In all subjects treated with empagliflozin (Figure 12), the greatest proportion of hypoglycemia events (as indicated by the red shaded boxes) occurred within the first few weeks of the study- a distinct pattern that was not seen in subjects treated with placebo or linagliptin.

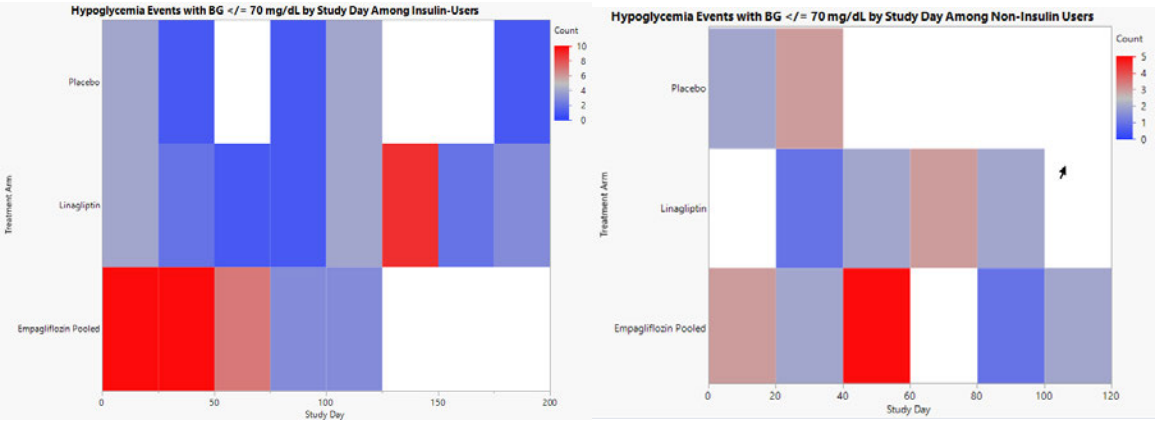
Upon conducting a separate heatmap distribution for subjects who were treated with background insulin therapy versus those who were not (Figure 13), it appears that insulin users treated with empagliflozin (Figure 13, left) had the greatest frequency of hypoglycemia events immediately after initiation of therapy. However, this pattern was not seen among non-insulin users treated with empagliflozin in which the timeframe of hypoglycemia events was more variable throughout the study (Figure 13, right). Of note, the rates of study treatment discontinuation through week 26 in the empagliflozin arm were overall similar between insulin users and non-insulin users [discontinuations in 4/25 subjects (16%) treated with background insulin versus 4/27 (14.8%) not treated with background insulin]; therefore, the timing of hypoglycemia events does not appear to be related to differential subject drop-outs.

Figure 12: Hypoglycemia AEs (blood glucose ≤ 70 mg/dL) by Study Day, Week 0 to Week 26, Study 1218.91



Source: Reviewer Created in JMP

Figure 13: Hypoglycemia AEs (blood glucose ≤70 mg/dL) by Study Day Among Subjects on Insulin at baseline (left) and Subjects not on insulin at baseline (right), Week 0 to Week 26, Study 1218.91



Source: Reviewer Created in JMP

To further explore this finding, an additional analysis was conducted to determine the proportion of subjects experiencing one or more hypoglycemia events within the first 30 days of treatment (Table 40). Among subjects treated with empagliflozin, 15.4% experienced

hypoglycemia events associated with blood glucose ≤ 70 mg/dL and 11.5% experienced hypoglycemia events associated with blood glucose < 54 mg/dL within the first 30 days. Additionally, the vast majority of subjects experiencing hypoglycemia events within the first 30 days of the study were treated with background insulin.

Table 40: Subjects with one or more Hypoglycemia AEs within the first 30 days, Study 1218.91

	Empagliflozin Pooled (N=52)	Linagliptin (N=53)	Placebo (N=53)
Hypoglycemia AE with BG </= 70 mg/dL	8 (15.4	5 (9.4)	2 (3.8)
Subjects on background insulin at baseline*	6 (11.5)	5 (9.4)	1 (1.9)
Subjects not on background insulin at baseline*	2 (3.8)	0	1 (1.9)
Hypoglycemia AE with BG < 54 mg/dL	6 (11.5)	3 (5.7)	1 (1.9)
Subjects on background insulin at baseline*	4 (7.7)	3 (5.7)	0
Subjects not on background insulin at baseline*	2 (3.8)	0	1 (1.9)
Severe Hypoglycemia Events	0	0	0

Source: Reviewer generated using OCS Analysis Studio, Custom Table Tool.
*percentage calculated based on all treated subjects

Reviewer Comment: In subjects treated with empagliflozin, hypoglycemia AEs occurred with greatest frequency at the beginning of the study (i.e., upon initiation of treatment). These early hypoglycemia events predominantly occurred in subjects who were treated with background insulin at baseline, a finding that may reflect the absence of any pre-specified adjustment in background insulin dose at randomization. Among non-insulin users, the occurrence of hypoglycemia was not substantially higher immediately after treatment initiation but occurred with variable frequency throughout the study. These findings suggest that for pediatric patients treated with background insulin, an insulin dose reduction may be warranted upon initiation of empagliflozin to prevent hypoglycemia. Additionally, all pediatric patients should be informed about the risk of hypoglycemia upon initiation of empagliflozin and should be educated regarding the signs and symptoms of hypoglycemia. These recommendations have been incorporated into the proposed labeling (see Section 10.1).

AESIS and Specific AEs

AESIs that did not occur during active treatment included skin lesions, pancreatitis, pancreatic cancer and events involving lower limb amputation.

Subjects experiencing 1 or more AESIs occurring during the placebo-controlled period through week 26 are described in Table 41 below. Overall, there appeared to be an imbalance in hypersensitivity reactions in pediatric subjects treated with empagliflozin versus placebo.

No AESIs of pancreatitis, decreased renal function or diabetic ketoacidosis occurred in any subjects treated with empagliflozin. AESIs of pancreatitis, decreased renal function and diabetic ketoacidosis occurred in a single subject (b) (6) treated with placebo, previously reviewed in Section 8.4.2. The AESI of diabetic ketoacidosis that occurred in a subject (b) (6) treated with linagliptin was based on investigator assessment but was not confirmed by the adjudication group (see further details below in section regarding CEC adjudication).

Table 41: Summary of AESIs occurring through Week 26, Study 1218.91

	Empagliflozin Pooled (N=52)	Linagliptin (N=52)	Placebo (N=53)
Hypersensitivity Reactions	**4 (7.7)**	**2 (3.8)**	**1 (1.9)**
Dermatitis	0	1 (1.9)	0
Dermatitis allergic	1 (1.9)	0	0
Eczema	1 (1.9)	0	0
Rash	3 (5.8)	1 (1.9)	0
Rhinitis allergic	0	0	1 (1.9)
Pancreatitis	0	0	1 (1.9)
Pancreatitis acute	0	0	1 (1.9)
Hepatic Injury	**2 (3.8)**	**2 (3.8)**	**1 (1.9)**
Alanine aminotransferase increased	1 (1.9)	1 (1.9)	1 (1.9)
Aspartate aminotransferase increased	1 (1.9)	0	0
Gamma-glutamyltransferase increased	0	0	1 (1.9)
Hepatic steatosis	0	1 (1.9)	0
Transaminases increased	1 (1.9)	0	0
Decreased Renal Function	**0**	**0**	**1 (1.9)**
Acute kidney injury	0	0	1 (1.9)
Diabetic Ketoacidosis	**0**	**0**	**1 (1.9)**
Diabetic ketoacidosis	0	1 (1.9)	1 (1.9)

Source: Reviewer generated using OCS Analysis Studio, Custom Table Tool.
Columns - Dataset: Demographics; Filter: TRTFL = 'Y'.
Hypersensitivity Reactions - Dataset: Adverse Events; Filter: TRTEMFL = 'Y', APERIODC = 'Up to Week 14 (on-trt)' or 'Week 14 to Week 26 (on-trt)', CRIT03FL = 'Y'. Hepatic Injury - Dataset: Adverse Events; Filter: TRTEMFL = 'Y', APERIODC = 'Up to Week 14 (on-trt)' or 'Week 14 to Week 26 (on-trt)', CRIT07FL = 'Y'. Decreased Renal Function - Dataset: Adverse Events; Filter: TRTEMFL = 'Y', APERIODC = 'Up to Week 14 (on-trt)' or 'Week 14 to Week 26 (on-trt)', CRIT08FL = 'Y'. Diabetic Ketoacidosis - Dataset: Adverse Events; Filter: TRTEMFL = 'Y', APERIODC = 'Up to Week 14 (on-trt)' or 'Week 14 to Week 26 (on-trt)', CRIT09FL = 'Y' and AEKETTYP = 'DIABETIC KETOACIDOSIS'

Narratives for the hepatic injury AESIs occurring in subjects treated with empagliflozin and linagliptin through Week 26 were reviewed with key findings summarized below:

Empagliflozin

- The AEs of ALT increased and AST increased occurred after 30 days of treatment with empagliflozin in a 16-year-old male subject (b) (6) Upon review of the narrative, this subject had baseline hepatic steatosis with a baseline ALT of 126 U/L (reference 6-43) and baseline AST of 43 U/L (reference 10-40). ALT measured on Visit 3 increased to 150 U/L but declined over the course of the study to below baseline

values. AST also increased at Visit 3 to 59 U/L and subsequently declined to below baseline values. No action was taken with the study medication.

- The AE of transaminase increased occurred in after 84 days of treatment with empagliflozin in an 11-year-old female subject (b) (6) who had a baseline elevated ALT of 86 U/L and a baseline elevated AST of 74 U/L. The highest ALT and AST measured during the study were 98 U/L and 83 U/L on Visit 2, however, ALT and AST values generally declined over the course of the study to below baseline values. No action was taken with the study medication.

Linagliptin

- The AE of ALT increased occurred on the same day as the first intake of the study medication in a 13-year-old female subject (b) (6) treated with linagliptin. Upon review of the laboratory values, the baseline ALT was 31 U/L. The highest ALT measured during the study was 42 U/L (at Visit 5) and ALT was 38 U/L at the end of treatment visit. AST values were all normal.
- The AE of hepatic steatosis occurred on day 134 of treatment with linagliptin in an 18-year-old male subject (b) (6) with baseline conditions that included elevated ALT and AST and hypertriglyceridemia. ALT and AST at baseline were 72 U/L and 42 U/L respectively. The highest values of ALT and AST were measured at Visit 04A (111 U/L and 70 U/L, respectively) but both values were near baseline at the end of treatment visit.

Reviewer Comment: Based on review of subject narratives, none of the hepatic event AESIs occurring during the placebo-controlled period appeared related to active study treatment (i.e., empagliflozin or linagliptin).

A summary of AESIs occurring during the safety extension period is described in Table 42. Relatively few AESIs occurred during this period. Narratives for all AESIs during this period were reviewed. Hepatic injury AESIs generally occurred in subjects with baseline abnormalities of AST and/or ALT and appear to have resolved without any action relating to the study medication. Details regarding the AESI of liver injury that occurred in a subject (b) (6) treated with linagliptin are presented in the review of hepatic events that were adjudicated by the CEC; however, this event was assessed as unlikely related to study treatment.

The AESI of renal impairment occurred in a 14-year-old female subject (b) (6) treated after 296 days of treatment with linagliptin. The event was noted on laboratory screening due to an elevated creatinine of 1.02 mg/dL, two-fold greater than the baseline value (0.49 mg/dL). There were no associated symptoms, signs of dehydration/hypovolemia. A concomitantly measured BUN value was normal (11 mg/dL). No action was taken with the study medication, and a follow up creatinine level measured on day 371 was 0.43 mg/dL.

Based on review of the AESIs of DKA occurring in subjects treated with linagliptin during the safety extension period, these events appeared related to omission of antidiabetic medication. Further details are available in the section regarding CEC adjudication of DKA event.

Table 42: Summary of AESIs occurring from Week 26 to Week 52, Study 1218.91

	Empagliflozin 10 mg (N=47)	Empagliflozin 25 mg (N=28)	Linagliptin (N=65)
Hypersensitivity Reactions	**1 (2.1)**	**0**	**1 (1.5)**
Eczema	1 (2.1)	0	0
Hypersensitivity	0	0	1 (1.5)
Hepatic Injury	**1 (2.1)**	**0**	**3 (4.6)**
Alanine aminotransferase increased	1 (2.1)	0	0
Aspartate aminotransferase increased	1 (2.1)	0	0
Hepatic enzyme increased	0	0	1 (1.5)
Hypertransaminasemia	0	0	1 (1.5)
Liver injury	0	0	1 (1.5)
Non-alcoholic fatty liver	0	0	1 (1.5)
Decreased Renal Function	**0**	**0**	**1 (1.5)**
Renal impairment	0	0	1 (1.5)
Diabetic Ketoacidosis	**0**	**0**	**2 (3.1)**
Diabetic ketoacidosis	0	0	2 (3.1)

Source: Reviewer generated using OCS Analysis Studio, Custom Table Tool.
Columns - Dataset: Demographics; Filter: TRTFL = 'Y'.
Hypersensitivity Reactions - Dataset: Adverse Events; Filter: TRTEMFL = 'Y', APERIODC = 'Week 26 to EOT (on-trt)', CRIT03FL = 'Y'.
Hepatic Injury - Dataset: Adverse Events; Filter: TRTEMFL = 'Y', APERIODC = 'Week 26 to EOT (on-trt)', CRIT07FL = 'Y'.
Decreased Renal Func ion - Dataset: Adverse Events; Filter: TRTEMFL = 'Y', APERIODC = 'Week 26 to EOT (on-trt)', CRIT08FL = 'Y'.
Diabetic Ketoacidosis - Dataset: Adverse Events; Filter: TRTEMFL = 'Y', APERIODC = 'Week 26 to EOT (on-trt)', CRIT09FL = 'Y'.

An FDA Medical Query (narrow and broad) for DKA was also conducted and did not reveal any risk difference for empagliflozin vs. placebo[38].

[38] This analysis was limited by an inability to filter for duration of events (i.e., week 0 to 26 vs week 26 to 52), considering that subjects in the placebo arm were re-randomized to active therapy (i.e., empagliflozin or linagliptin) during the safety extension. However, when using the initial assigned treatment (i.e., empagliflozin vs linagliptin vs placebo), no difference in DKA was seen through the 5-week period.

Narrow FDA Medical Queries and Terms

FDA Medical Query	L5 (N = 53)	E10 (N = 52)	Pbo (N = 53)	Risk Difference for L5 over Pbo	Risk Difference for E10 over Pbo
Diabetic Ketoacidosis	1 (1.9%)	0 (0%)	2 (3.8%)	-0.02 (-0.08, 0.04)	-0.04 (-0.09, 0.01)
Diabetic ketoacidosis	1 (1.9%)	0 (0%)	2 (3.8%)	-0.02 (-0.08, 0.04)	-0.04 (-0.09, 0.01)

Broad FDA Medical Queries and Terms

FDA Medical Query	L5 (N = 53)	E10 (N = 52)	Pbo (N = 53)	Risk Difference for L5 over Pbo	Risk Difference for E10 over Pbo
Diabetic Ketoacidosis	8 (15.1%)	4 (7.7%)	8 (15.1%)	0 (-0.14, 0.14)	-0.07 (-0.19, 0.05)
Blood ketone body increased	8 (15.1%)	4 (7.7%)	5 (9.4%)	0.06 (-0.07, 0.18)	-0.02 (-0.12, 0.09)
Blood bicarbonate decreased	0 (0%)	1 (1.9%)	0 (0%)		0.02 (-0.02, 0.06)
Acetonaemia	0 (0%)	0 (0%)	1 (1.9%)	-0.02 (-0.06, 0.02)	-0.02 (-0.06, 0.02)
Ketosis	0 (0%)	0 (0%)	1 (1.9%)	-0.02 (-0.06, 0.02)	-0.02 (-0.06, 0.02)
Diabetic ketoacidosis	1 (1.9%)	0 (0%)	2 (3.8%)	-0.02 (-0.08, 0.04)	-0.04 (-0.09, 0.01)

Source: Reviewer generated using JMP clinical

Specific AEs of interest:

Specific AEs of interest that did not occur during active treatment included bullous pemphigoid, bone fracture events, and acute pyelonephritis.

A summary of specific AEs of interest from during the placebo-controlled treatment period is shown in Table 43 Genital infections and urinary tract infections occurred with greater frequency in subjects treated with empagliflozin versus placebo. Increase in ketone bodies was noted in subjects in all three treatment arms, with a slightly higher incidence in the linagliptin arm compared to the other arms. However, 1 subject with blood ketone body increased in linagliptin arm was considered to have DKA as assessed by investigator, but this was not confirmed by the CEC (see discussion below).

Table 43: Specific AEs of Interest through Week 26, Study 1218.91

	Empagliflozin pooled (N=52)	Linagliptin (N=52)	Placebo (N=53)
Genital Infections	**3 (5.8)**	**2 (3.8)**	**2 (3.8)**
Fungal infection	2 (3.8)	0	0
Fungal skin infection	0	0	1 (1.9)
Genital infection fungal	1 (1.9)	0	1 (1.9)
Vulvovaginal mycotic infection	0	2 (3.8)	0
Urinary Tract Infections	**4 (7.7)**	**1 (1.9)**	**1 (1.9)**
Pyuria	1 (1.9)	0	0
Urinary tract infection	3 (5.8)	1 (1.9)	1 (1.9)
Arthralgia	**1 (1.9)**	**2 (3.8)**	**1 (1.9)**
Arthralgia	1 (1.9)	1 (1.9)	1 (1.9)
Joint swelling	0	1 (1.9)	0
Volume Depletion	**0**	**0**	**1 (1.9)**

	Empagliflozin pooled (N=52)	Linagliptin (N=52)	Placebo (N=53)
Hypovolemic shock	0	0	1 (1.9)
Ketone Measurements	**2 (3.8)**	**4 (7.7) ***	**2 (3.8)**
Blood ketone body increased	2 (3.8)	4 (7.7) *	2 (3.8)

Source: Reviewer created in OCS Analysis Studio, Custom Table Tool.
Columns - Dataset: Demographics; Filter: TRTFL = 'Y'.
Genital Infections - Dataset: Adverse Events; Filter: TRTEMFL = 'Y', APERIODC = 'Up to Week 14 (on-trt)' or 'Week 14 to Week 26 (on-trt)', CRIT01FL = 'Y' and Filter: APERIOD = '1' - '2', GENINFAE = 'Y'. Urinary Tract Infections - Dataset: Adverse Events; Filter: TRTEMFL = 'Y', APERIODC = 'Up to Week 14 (on-trt)' or 'Week 14 to Week 26 (on-trt)', CRIT02FL = 'Y'. AND Filter: APERIOD = '1' - '2', UTIAE = 'Y'.
Arthralgia - Dataset: Adverse Events; Filter: TRTEMFL = 'Y', APERIODC = 'Up to Week 14 (on-trt)' or 'Week 14 to Week 26 (on-trt)', CRIT10FL = 'Y'.
Volume Depletion - Dataset: Adverse Events; Filter: TRTEMFL = 'Y', APERIODC = 'Up to Week 14 (on-trt)' or 'Week 14 to Week 26 (on-trt)', CRIT12FL = 'Y'. Ketone Measurements - Dataset: Adverse Events; Filter: TRTEMFL = 'Y', APERIODC = 'Up to Week 14 (on-trt)' or 'Week 14 to Week 26 (on-trt)', CRIT15FL = 'Y'.

A summary of specific AEs of interest from during the safety extension period is displayed in Table 44. Overall, there was no evidence of increased risk of specific AEs in subjects treated with empagliflozin 25 mg as compared to empagliflozin 10 mg; however, the interpretation may have been limited by the small number of events.

Table 44: Specific AEs of interest from Week 26 to Week 52, Study 1218.91

	Empagliflozin 10 mg (N=47)	Empagliflozin 25 mg (N=28)	Linagliptin (N=65)
Genital Infections	**1 (2.1)**	**0**	**4 (6.2)**
Anogenital warts	0	0	1 (1.5)
Fungal infection	1 (2.1)	0	0
Cervicitis	0	0	1 (1.5)
Vulvovaginal mycotic infection	0	0	1 (1.5)
Vulvovaginitis	0	0	1 (1.5)
Urinary Tract Infections	**3 (6.4)**	**1 (3.6)**	**0**
Pyuria	1 (2.1)	0	0
Urinary tract infection	2 (4.3)	1 (3.6)	0
Arthralgia	**1 (2.1)**	**0**	**3 (4.6)**
Arthralgia	1 (2.1)	0	3 (4.6)
Volume Depletion	**0**	**0**	**2 (3.1)**
Dehydration	0	0	1 (1.5)
Syncope	0	0	1 (1.5)
Ketone Measurements	**4 (8.5)**	**3 (10.7)**	**4 (6.2)**
Acetonemia	1 (2.1)	0	0
Blood ketone body increased	3 (6.4)	3 (10.7)	4 (6.2)
Ketosis	0	1 (3.6)	0

Source: Reviewer generated using OCS Analysis Studio, Custom Table Tool.
Columns - Dataset: Demographics; Filter: TRTFL = 'Y'.
Genital Infections - Dataset: Adverse Events; Filter: TRTEMFL = 'Y', CRIT01FL = 'Y', APERIODC = 'Week 26 to EOT (on-trt)'. And Filter: GENINFAE = 'Y', Urinary Tract Infections - Dataset: Adverse Events; Filter: TRTEMFL = 'Y', CRIT02FL = 'Y', APERIODC = 'Week 26 to EOT (on-trt)'. And Filter: UTIAE = 'Y' Arthralgia - Dataset: Adverse Events; Filter: TRTEMFL = 'Y', CRIT10FL = 'Y', APERIODC = 'Week 26 to EOT (on-trt)'.
Volume Depletion - Dataset: Adverse Events; Filter: TRTEMFL = 'Y', CRIT12FL = 'Y', APERIODC = 'Week 26 to EOT (on-trt)'.
Ketone Measurements - Dataset: Adverse Events; Filter: TRTEMFL = 'Y', CRIT15FL = 'Y', APERIODC = 'Week 26 to EOT (on-trt)'.

Reviewer Comment: Compared to placebo, a higher proportion of AEs relating to genital injections, urinary tract infections, and hypersensitivity reactions occurred with empagliflozin

treatment; these safety signals are consistent with those identified in adult studies of empagliflozin and are already described in the product label. Based on these limited data, no differences in the safety profile of empagliflozin were observed as compared to those described in adults.

AEs adjudicated by CEC

A summary of ketoacidosis events that were adjudicated by the CEC is displayed below in Table 45. During the placebo-controlled period, there was only 1 event of DKA that was confirmed by the CEC; this was an SAE of DKA that occurred in subject (b) (6) who was treated with placebo. During the safety extension period, 2 events were confirmed as DKA by the CEC. These include an SAE of DKA that occurred in subject (b) (6) who was treated with linagliptin, and a lab-related event (elevated beta-hydroxybutyrate) in subject (b) (6) who was treated with linagliptin. Based on my review of the narrative for this lab-related event, there appears to be inadequate information to draw any certain conclusions regarding ketoacidosis (see reviewer comments below). There were no CEC confirmed events of DKA in subjects treated with empagliflozin.

Table 45: Ketoacidosis Events adjudicated by the CEC

Subject ID	AEs	Actual Treatment at time of AE	Study Day	Ketoacidosis Confirmed by CEC (Y/N)	Reviewer Comments
(b) (6)	**Diabetic Ketoacidosis**	**Placebo**	**25**	**Y**	**See Section 8.4.2**
(b) (6)	Blood Ketone Body increased (2 events); Investigator-assessed diabetic ketoacidosis	Linagliptin 5 mg	11	N	Subject had elevated ketones (max 2.1 mmol/L) 11 days after initiating linagliptin, with normal blood glucoses. Ketones resolved with no additional therapy and no change in study medication.
(b) (6)	Blood ketone body increased	Linagliptin 5 mg	254	N	No trigger
(b) (6)	**Diabetic ketoacidosis**	**Linagliptin 5 mg**	**274**	**Y**	**Subject presented with vomiting, glucose of 284 mg/dL, blood ketones of 4.9 mmol/L, abdominal pain and was seen in the emergency room and diagnosed with DKA, admitted to the ICU. Lab tests included bicarbonate 10 to < 15 mEq/L, anion gap > 12 mEq/L, glucose 331 mg/dL. Subject admitted to missing a week of insulin and metformin treatment prior to DKA event.**
(b) (6)	Diabetic ketoacidosis	Linagliptin	208	N	Subject was asymptomatic, bicarbonate was > 18 mEq/L, glucose

					193 ng/dL, with highest blood ketone 0.2 mmol/L though narrative also states that the subject had positive urine ketones and elevated beta hydroxybutyrate. There were no precipitating factors and the patient had taken 42 units of bolus insulin and 36 units of basal insulin within the 24 hours prior to the event. No therapy documented for the event and the patient was advised to present to the emergency room only if symptoms became present. Study medication was discontinued for around 3 weeks, and resumed after a repeat test showed normal beta hydroxybutyrate and improvement in average fasting glucose.
(b) (6)	Ketonemia	Empagliflozin 10 mg	272	N	Likely ketosis not ketoacidosis
(b) (6)	Blood ketone body increased (4 events)	Empagliflozin 25 mg	269, 312, 315	N	Likely ketosis not ketoacidosis
(b) (6)	**Lab-event (beta hydroxybutyrate 4.8 mol/L)**	**Linagliptin 5 mg**	**295**	**Y**	**No corresponding AE was reported, no investigator assessment for the lab-related event was available in the eCRF and no further details including laboratory results, therapy or action taken with study medication were available. While the ketone value is quite elevated and could have been associated with acidosis, there appears to be insufficient information to conclude that this was a certain ketoacidosis event.**
(b) (6)	Blood ketone body increased (3 events)	Linagliptin 5 mg	4, 27, 13	N	Likely ketosis not ketoacidosis
(b) (6)	Blood ketone body increased (2 events)	Linagliptin 5 mg	7, 15	N	Likely ketosis not ketoacidosis

Source: Reviewer created

Reviewer Comment: No AEs of diabetic ketoacidosis occurred in the empagliflozin arm. Two (2) events involving increased ketones in subjects treated with empagliflozin were referred to the CEC for adjudication; neither were adjudicated as being confirmed ketoacidosis events.

Subjects with events that met the criteria for adjudication for myocardial infarction (MI) and

hospitalization for heart failure (HHF) are displayed in Table 46. None of these events were confirmed as MI or HHF by the CEC.

Table 46: Cardiovascular Events Adjudicated by the CEC

Subject ID	Treatment at onset of AE	PT	CEC Outcome
(b) (6)	Placebo	CK increased	Not confirmed as MI
(b) (6)	Linagliptin	Electrocardiogram ST segment elevation	Not confirmed as MI
(b) (6)	Linagliptin	CK increased	Not confirmed as MI
(b) (6)	Empagliflozin 10 mg	CK increased	Not confirmed as MI
(b) (6)	Placebo	AKI	Not confirmed as HHF—non-cardiac cause (pancreatic)
(b) (6)	Placebo	Hypertension aggravated (3 episodes)	Not confirmed as HHF
(b) (6)	Linagliptin	Syncope vasovagal	Not confirmed as HHF
(b) (6)	Empagliflozin 10 mg	Interstitial nephritis	Not confirmed as HHF—non cardiac cause (renal)

Source: Reviewer created. Abbreviations: CK= creatine kinase, AKI= acute kidney injury, MI= myocardial infarction, HHF= hospitalization for heart failure

1 event met CEC criteria for adjudication for hepatic injury. This event was an AESI of liver injury that occurred in a 12-year-old female subject (b) (6) who received linagliptin from week 26 to 52. The event occurred 217 days after the first intake of linagliptin, and was also reported as an AESI of hypertransaminasemia. The subject had elevated AST and ALT at baseline (92 U/L and 69 U/L) and a pre-existing history of non-alcoholic fatty liver disease. AST and ALT values during the study are summarized in Table 47 and also displayed in Figure 14 . All measured bilirubin and alkaline phosphatase levels were normal. The study medication was temporarily discontinued from (b) (6) (after the elevated values were noted from labs measured on (b) (6) /Visit 06) through (b) (6) but then resumed until (b) (6) after which the subject permanently discontinued the study medication (this discontinuation was classified as relating to withdrawal by patient). This event was confirmed by the CEC as mild to moderate hepatic injury though causality to study drug was felt to be unlikely.

Table 47: AST and ALT values for Subject (b) (6)

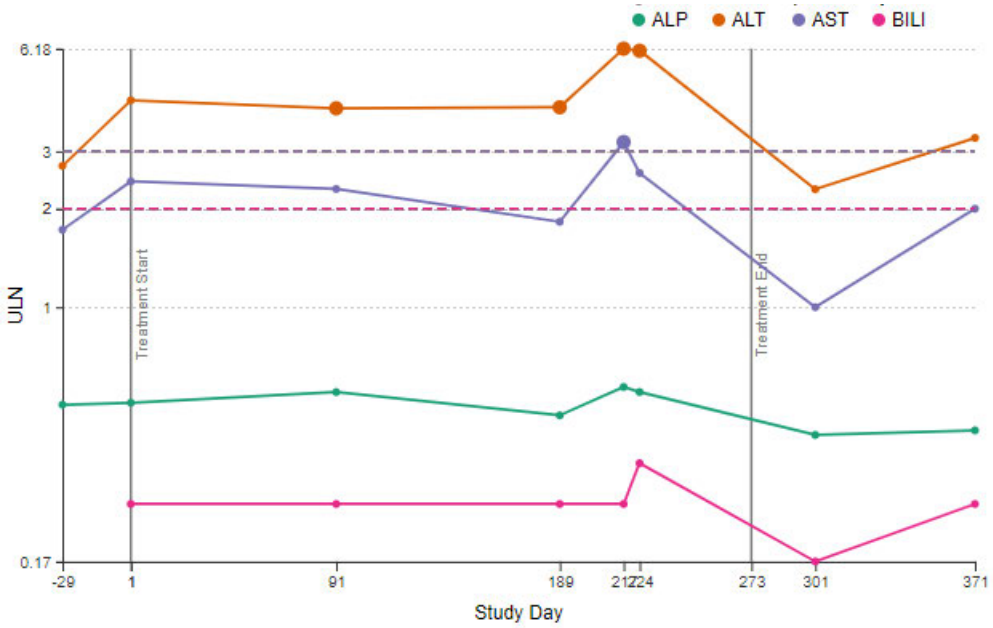
	ALT (U/L), reference 6-34	AST (U/L), reference 10-40
Screening (Visit 01A)	92	69
Visit 02	146	97
Visit 04A	138	92
Visit 05	139	73
Visit 06 (b) (6)	210	128
Unscheduled visit (b) (6) (b) (6)	207*	103*

Visit 08 (end of treatment, [redacted])	78*	40*
Visit 09 (follow up)	112*	80*

*measured off treatment

Source: Reviewer created based on review of narrative

Figure 14: Hepatic Function Tests in Subject [redacted] over time



Source: Reviewer created using OCS Analysis Studio, Hepatic Explorer

No events met the CEC criteria for adjudication for stroke or TIA, death.

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

A summary of TEAEs by system organ class (SOC) and by preferred term (PT) occurring in > 2% of subjects treated with empagliflozin and with risk difference > 1% as compared to placebo through Week 26 is displayed in Table 48. A greater percentage of TEAEs occurred in the SOCs of metabolism and nutrition disorders, skin and subcutaneous tissue disorders, infections and infestations and gastrointestinal disorders in subjects treated with empagliflozin as compared to placebo. Hypoglycemia was the most common PT in subjects treated with empagliflozin, with the greatest risk difference as compared to placebo.

Table 48: TEAEs by SOCs and by PTs occurring in > 2% of subjects treated with empagliflozin through Week 26 and with risk difference > 1%, Study 1218.91

System Organ Class	Empagliflozin (N=52) n (%)	Placebo (N=53) n (%)	Risk Difference RD (95% CI)	Forest Plot
Eye disorders	1 (1.9)	0 (0.0)	1.92 (-1.81, 5.66)	
Gastrointestinal disorders	12 (23.1)	10 (18.9)	4.21 (-11.35, 19.77)	
Immune system disorders	4 (7.7)	0 (0.0)	7.69 (0.45, 14.94)	
Infections and infestations	18 (34.6)	13 (24.5)	10.09 (-7.27, 27.45)	
Metabolism and nutrition disorders	16 (30.8)	12 (22.6)	8.13 (-8.73, 24.99)	
Reproductive system and breast disorders	2 (3.8)	1 (1.9)	1.96 (-4.42, 8.34)	
Skin and subcutaneous tissue disorders	5 (9.6)	1 (1.9)	7.73 (-1.08, 16.54)	

Preferred Term	Empagliflozin (N=52) n (%)	Placebo (N=53) n (%)	Risk Difference RD (95% CI)	Forest Plot
Dysmenorrhea	2 (3.8)	0 (0.0)	3.85 (-1.38, 9.07)	
Fungal infection	2 (3.8)	0 (0.0)	3.85 (-1.38, 9.07)	
Headache	8 (15.4)	7 (13.2)	2.18 (-11.21, 15.57)	
Hypoglycemia	11 (21.2)	5 (9.4)	11.72 (-1.89, 25.33)	
Limb injury	2 (3.8)	1 (1.9)	1.96 (-4.42, 8.34)	
Oropharyngeal pain	2 (3.8)	1 (1.9)	1.96 (-4.42, 8.34)	
Rash	3 (5.8)	0 (0.0)	5.77 (-0.57, 12.11)	
Seasonal allergy	4 (7.7)	0 (0.0)	7.69 (0.45, 14.94)	
Upper respiratory tract infection	2 (3.8)	0 (0.0)	3.85 (-1.38, 9.07)	
Urinary tract infection	3 (5.8)	1 (1.9)	3.88 (-3.44, 11.20)	

System Organ Class	Empagliflozin (N=52) n (%)	Placebo (N=53) n (%)	Risk Difference RD (95% CI)	Forest Plot
Vomiting	3 (5.8)	2 (3.8)	2.00 (-6.16, 10.15)	

Source: Reviewer created using OCS Analysis Studio, Safety Explorer.
Filters: TRT01A = "E10" and TRTFL = "Y" (Empagliflozin); TRT01A = "Pbo" and TRTFL = "Y" (Placebo); TRTEMFL = "Y" and APERIODC = "Up to Week 14 (on-trt" or "Week 14 to Week 26 (on-trt" (Adverse Events).
Percent Threshold: Empagliflozin ≥ 2%.
Risk Difference calculated by comparing the left column (Group 1) to the right column (Group 2).

A summary of TEAEs by SOC and PT occurring in > 5% of subjects treated with empagliflozin 10 mg or empagliflozin 25 mg during the safety extension period is provided in Table 49. The incidence of gastrointestinal related AEs was higher in subjects treated with empagliflozin 25 mg as compared to empagliflozin 10 mg.

Table 49: TEAEs by SOC and PT occurring in >5% of subjects treated with Empagliflozin 10 mg or Empagliflozin 25 mg from Week 26 to Week 52, Study 1218.91

System Organ Class - Preferred Term	Empagliflozin 10 mg (N=47) n (%)	Empagliflozin 25 mg (N=28) n (%)
Blood and lymphatic system disorders	**3 (6.4)**	**1 (3.6)**
Gastrointestinal disorders	**5 (10.6)**	**6 (21.4)**
Abdominal pain upper	1 (2.1)	2 (7.1)
Diarrhea	1 (2.1)	2 (7.1)
Vomiting	2 (4.3)	2 (7.1)
Infections and infestations	**14 (29.8)**	**7 (25.0)**
Influenza	3 (6.4)	0 (0.0)
Investigations	**9 (19.1)**	**4 (14.3)**
Blood ketone body increased	3 (6.4)	3 (10.7)
Metabolism and nutrition disorders	**15 (31.9)**	**6 (21.4)**
Hyperglycemia	3 (6.4)	0 (0.0)
Hypoglycemia	6 (12.8)	3 (10.7)
Vitamin d deficiency	3 (6.4)	2 (7.1)
Musculoskeletal and connective tissue disorders	**5 (10.6)**	**0 (0.0)**
Nervous system disorders	**8 (17.0)**	**3 (10.7)**
Headache	7 (14.9)	3 (10.7)
Psychiatric disorders	**3 (6.4)**	**0 (0.0)**
Reproductive system and breast disorders	**4 (8.5)**	**2 (7.1)**
Dysmenorrhea	4 (8.5)	1 (3.6)
Respiratory, thoracic and mediastinal disorders	**6 (12.8)**	**1 (3.6)**
Cough	4 (8.5)	1 (3.6)
Nasal congestion	3 (6.4)	0 (0.0)
Oropharyngeal pain	3 (6.4)	0 (0.0)
Skin and subcutaneous tissue disorders	**4 (8.5)**	**0 (0.0)**

Source: Reviewer created using OCS Analysis Studio, Safety Explorer.
Filters: TRT03A = "E10" and TRTFL = "Y" (Empagliflozin 10 mg); TRT03A = "E25" and TRTFL = "Y" (Empagliflozin 25 mg); TRTEMFL = "Y" and APERIOD = 3 to 3 (Adverse Events).

System Organ Class - Preferred Term	Empagliflozin 10 mg (N=47) n (%)	Empagliflozin 25 mg (N=28) n (%)

Percent Threshold: Any Column ≥ 5%.

Reviewer Comment: Based on an analysis of TEAEs, the safety profile of empagliflozin in pediatric patients appears generally similar to adults. The incidence of gastrointestinal TEAEs appeared to be increased with empagliflozin 25 mg as compared to empagliflozin 10 mg during the safety extension period, however, no other dose-related changes in safety findings were apparent.

8.4.6. Laboratory Findings

The safety review focused on laboratory-related safety issues that have been reported in adult studies of empagliflozin, and specific laboratory studies relevant to pediatric patients. The laboratory review was based on analyses of the laboratory datasets focused on the placebo-controlled period (through week 26).

Renal Function Parameters:

Mean change from baseline in urine albumin/creatinine ratio, serum creatinine, and estimated GFR through week 26 is displayed in Table 50. A mean decrease of 2.15 mL/min/1.72 m3 eGFR occurred in subjects treated with empagliflozin from baseline to week 26. A small decrease in mean eGFR and small increase in mean serum creatinine was notable as early as week 4 in subjects treated with empagliflozin (Figure 15), suggesting that these changes occurred upon initiation of treatment. A shift table for renal impairment based on eGFR is displayed in Table 52. A small percentage of subjects with normal renal function at baseline developed mild renal impairment by week 26 in all three treatment arms, though with numerically greater frequency in the empagliflozin arm (8 subjects) versus linagliptin and placebo arms (2 and 4 subjects respectively). Among the 8 subjects treated with empagliflozin who shifted from normal to mild renal impairment category, the mean baseline eGFR was 96.5 mL/min/1.73m2, mean eGFR at week 26 was 86.0 mL/min/1.73m2, and mean change in eGFR was 12.4 mL/min/1.72m2. However, when looking at the entire group of subjects treated with empagliflozin, a smaller proportion of subjects experienced at 10% or more rise in eGFR from baseline to week 26, as compared to the other treatment arms (Table 53). No subjects within any treatment arm developed moderate or severe renal impairment or had a rise in serum creatinine > 0.25 mg/dL by week 26. According to a shift table for urine albumin/creatinine ratio (Table 51) a small percentage of subjects shifted from baseline normoalbuminuria to microalbuminuria, or from baseline microalbuminuria to macroalbuminuria by week 26 within all three treatment arms, a pattern that most likely reflects underlying disease progression. A small percentage of subjects in all treatment arms who had microalbuminuria at baseline reverted back to

normoalbuminuria by week 26, a phenomenon that has been previously reported[39].

Table 50: Renal Function Parameter Difference from Baseline to Week 26 Summary Table

Parameter	Statistic	Empagliflozin Pooled	Linagliptin	Placebo
Urine Albumin/Creatinine Ratio (mg/g)	Subject Count	47	48	49
	Baseline	43.97 ± 140.79, 12.17	52.02 ± 105.26, 10.82	52.57 ± 137.36, 9.37
	Week 26	31.26 ± 67.23, 13.16	68.68 ± 235.57, 11.08	69.78 ± 215.26, 11.51
	Difference	-12.71 ± 78.51, 1.40	16.67 ± 189.27, -0.42	17.22 ± 233.54, 2.49
Serum Creatinine (mg/dL)	Subject Count	48	49	50
	Baseline	0.63 ± 0.13	0.61 ± 0.16	0.63 ± 0.13
	Week 26	0.63 ± 0.13	0.61 ± 0.15	0.63 ± 0.14
	Difference	0.1 ± 0.10	0.00 ± 0.07	0.00 ± 0.07
Estimated GFR (Schwartz calculation, mL/min/1.73m2)	Subject Count	48	49	50
	Baseline	114.20 ± 25.22	120.99 ± 35.31	112.47 ± 21.74
	Week 26	112.06 ± 22.34	120.68 ± 28.50	114.19 ± 24.67
	Difference	-2.15 ± 18.12	-0.31 ± 17.39	1.72 ± 12.55

Source: Reviewer created using OCS Analysis Studio, Kidney Function Tool.
Subject Count: All subjects with test results for both baseline and end of treatment were included.
Mean ± standard deviation, median.
End of Treatment: AVISIT = 'Week 26'.

Table 51: Urine Albumin/Creatinine Shift Table from Baseline to Week 26

		Final Albuminuria		
Treatment Arm	**Baseline Albuminuria**	**Normoalbuminuria**	**Microalbuminuria**	**Macroalbuminuria**
Empagliflozin Pooled (N = 47)	Normoalbuminuria	34 (72.3%)	4 (8.5%)	0
	Microalbuminuria	2 (4.3%)	6 (12.8%)	0
	Macroalbuminuria	0	0	1 (2.1%)

[39] de Boer IH, et al (2011) Long-term renal outcomes of patients with type 1 diabetes mellitus and microalbuminuria: an analysis of the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications cohort. Arch Intern Med 171:412–420

		Final Albuminuria		
Treatment Arm	**Baseline Albuminuria**	**Normoalbuminuria**	**Microalbuminuria**	**Macroalbuminuria**
Linagliptin (N = 48)	Normoalbuminuria	30 (62.5%)	4 (8.3%)	0
	Microalbuminuria	4 (8.3%)	8 (16.7%)	0
	Macroalbuminuria	0	0	2 (4.2%)
Placebo (N = 49)	Normoalbuminuria	35 (71.4%)	2 (4.1%)	0
	Microalbuminuria	1 (2.0%)	6 (12.2%)	2 (4.1%)
	Macroalbuminuria	0	3 (6.1%)	0

Source: Reviewer created using OCS Analysis Studio, Kidney Function Tool.
Normoa buminuria: <=30 mg/g; Microalbuminuria: 30-300 mg/g; Macroalbuminuria: >=300 mg/g.
Percentage based on population of a given treatment arm.
End of Treatment: AVISIT = 'Week 26'.

Table 52: Renal Impairment (based on eGFR) Shift Table from Baseline to Week 26

		Final Renal Impairment		
Treatment Arm	**Baseline Renal Impairment**	**None**	**Mild**	**Moderate**
Empagliflozin Pooled (N = 48)	None	37 (77.1%)	8 (16.7%)*	0
	Mild	2 (4.2%)	1 (2.1%)	0
	Moderate	0	0	0
Linagliptin (N = 49)	None	39 (79.6%)	2 (4.1%)	0
	Mild	4 (8.2%)	4 (8.2%)	0
	Moderate	0	0	0
Placebo (N = 50)	None	39 (78.0%)	4 (8.0%)	0
	Mild	3 (6.0%)	4 (8.0%)	0
	Moderate	0	0	0

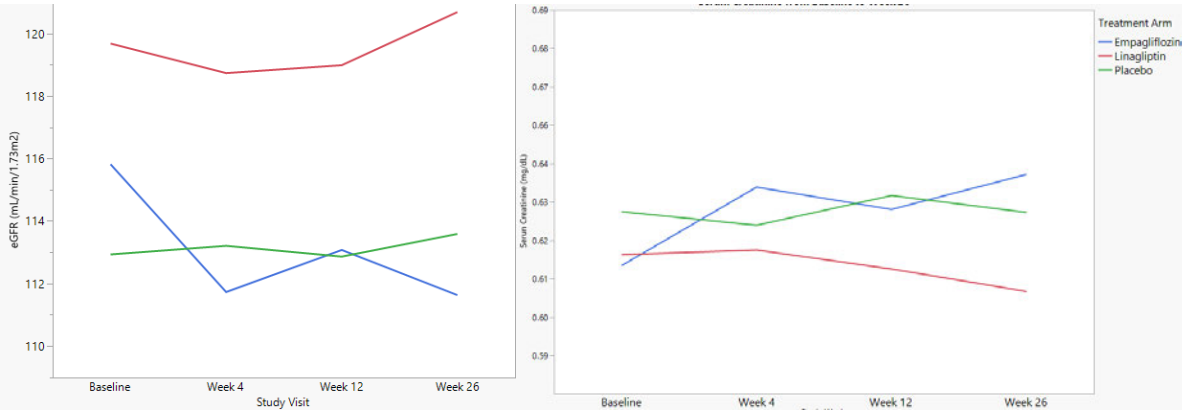
Source: Reviewer created using OCS Analysis Studio, Kidney Function Tool.
None: >=90 mL/min/1.73 m^2; Mild: 90-60 mL/min/1.73 m^2; Moderate: <=60 mL/min/1.73 m^2.
Percentage based on population of a given treatment arm.
End of Treatment: AVISIT = 'Week 26'.
* Among the 8 subjects treated with empagliflozin who shifted from normal to mild renal impairment category, the mean baseline eGFR was 96.5 mL/min/1.73m2, mean eGFR at week 26 was 86.0 mL/min/1.73m2, and mean change in eGFR was 12.4 mL/min/1.72m2.

Table 53: Subjects with >10% increase in eGFR from baseline to week 26

	Empagliflozin Pooled (N=52)	Linagliptin (N=52)	Placebo (N=53)
Subjects with >10% increase in eGFR from baseline to week 26	9 (17.3)	14 (26.9)	14 (26.4)

Source: Reviewer generated using OCS Analysis Studio, Custom Table Tool.
Columns - Dataset: Demographics; Filter: TRTFL = 'Y'.
Table Section 1 - Dataset: Laboratory; Filter: PARAMCD = 'EGFRSZ', AVISIT = 'Week 26', CHG, ≥10%.

Figure 15: Mean eGFR (left) and mean serum creatinine (right) from Baseline to week 26



Source: reviewer created in JMP using adlb.xpt dataset. eGFR based on Schwartz calculation

Reviewer Comment: Similar to findings in adult studies, a small decrease in eGFR was noted upon initiation of treatment with empagliflozin in pediatric T2D patients. Since the vast majority of the study population had normal to elevated renal function at baseline (with baseline mild renal impairment in only 3 subjects treated with empagliflozin), there were insufficient data to evaluate the effects of empagliflozin in pediatric patients with renal impairment.

Growth-hormone dependent factors, markers of mineral and bone metabolism.

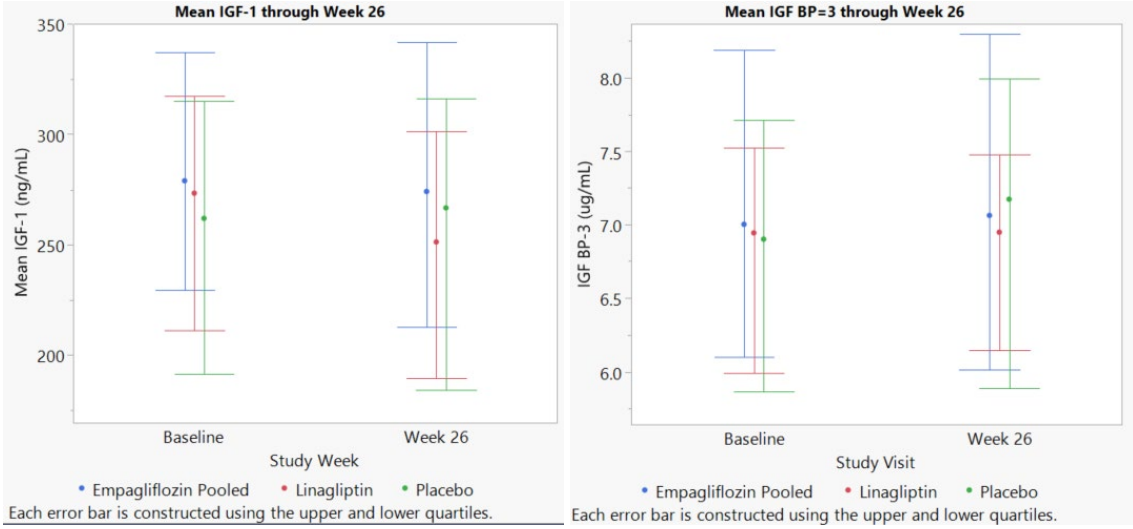
There were no clinically significant treatment-related differences in mean IGFBP-3 or IGF-1 (Figure 16), alkaline phosphatase (Figure 17), calcium, phosphorus, intact PTH, N-telopeptide, procollagen 1 N-Terminal Propeptide[40], vitamin D[41] (data not shown).

An additional analysis of change in IGF-1 and IGFBP-3 was conducted excluding subjects who were Tanner stage 5 at baseline, as these subjects may have been expected to have already

[40] Baseline differences in procollagen 1 N-terminal propeptide between the treatment arms (mean value 1.5 x greater at baseline in the empagliflozin pooled arm versus the placebo arm) limited the interpretation of treatment-related effects.
[41] The mean vitamin D levels measured at baseline, week 4 and week 26 in all three treatment arms was < 20 ng/mL, consistent with the reported high prevalence of vitamin D deficiency in obesity and related conditions.

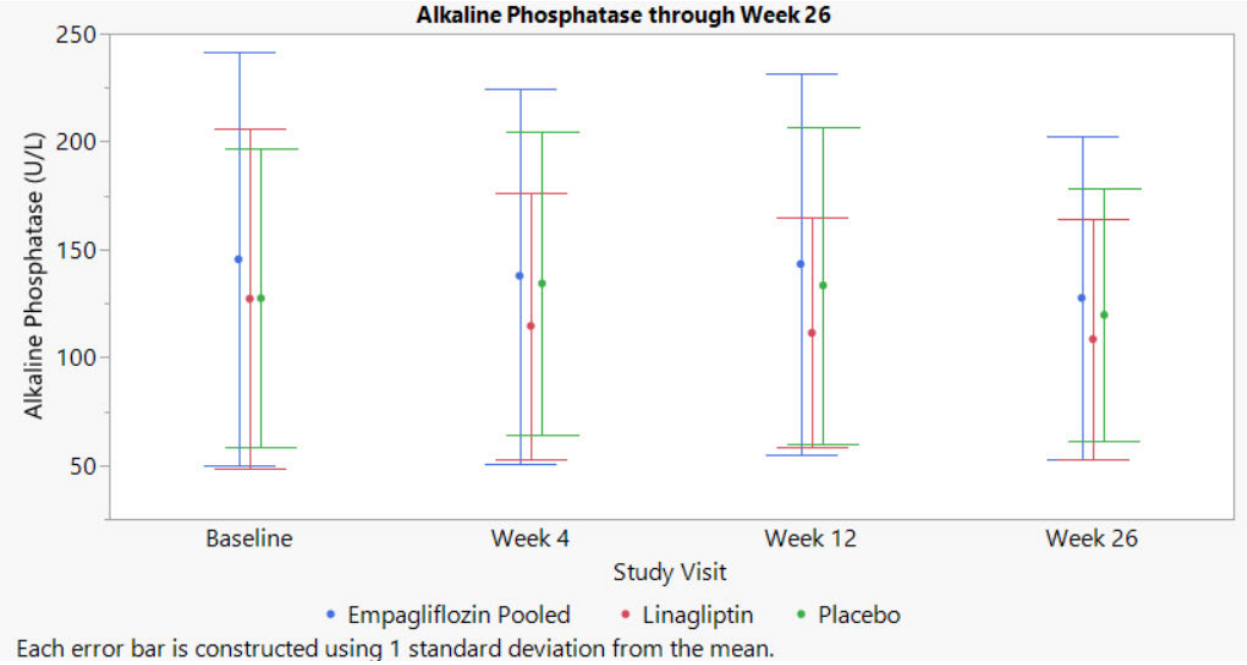
completed linear growth (Table 54). Subjects who were Tanner stage 2 to 4 at baseline who were treated with linagliptin had a mean decrease in IGF-1 of 40.3 ng/dL from baseline to Week 26; whereas IGF-1 was minimally changed in the other treatment arms. In all three treatment arms, there appear to have been subjects who had a marked (e.g., ≥ 100 ng/dL) decrease in IGF-1 from baseline to Week 26; this finding is unexpected as typically IGF-1 would be expected to increase over time in pubertal children. In the empagliflozin and placebo treatment arms, there were also subjects who exhibited a marked increase in IGF-1 from baseline to Week 26 (maximum change from baseline of 137.6 ng/dL in the empagliflozin arm and 248.5 in the placebo arm); increases also occurred in some subjects in the linagliptin arm though to a lesser extent (maximum change from baseline of 78 ng/dL). Given the overall variability in IGF-1 measurements during the study, it is difficult to draw any conclusions. The fact that the mean change in IGFBP-3 was not decreased from baseline in pubertal subjects treated with empagliflozin is reassuring against any treatment-related impact on the growth-hormone axis. See Section 8.8.3 regarding safety analyses for growth and puberty.

Figure 16: Mean IGF-1 and IGFBP-3 through Week 26



Source: Reviewer created in JMP

Figure 17: Mean Alkaline Phosphatase through Week 26



Source: Reviewer created in JMP

Table 54: Change from Baseline to Week 26 in IGF-1 and IGFBP-3 among subjects with Baseline Tanner Stage 2 through 4

	Empagliflozin Pooled (N=24)	Linagliptin (N=19)	Placebo (N=21)
IGF-1 (ng/mL)			
Mean (SD)	2.8 (64.2)	-40.3 (59.0)	-6.4 (90.9)
Median (Min, Max)	5.0 (-129.3, 137.6)	-41.3 (-167.5, 78.1)	2.6 (-224.9, 248.5)
IGFBP-3 (ug/mL)			
Mean (SD)	0.2 (1.75)	0.1 (1.05)	0.1 (1.22)
Median (Min, Max)	0.3 (-6.4, 2.8)	0.2 (-2.5, 2.2)	-0.1 (-2.0, 2.2)

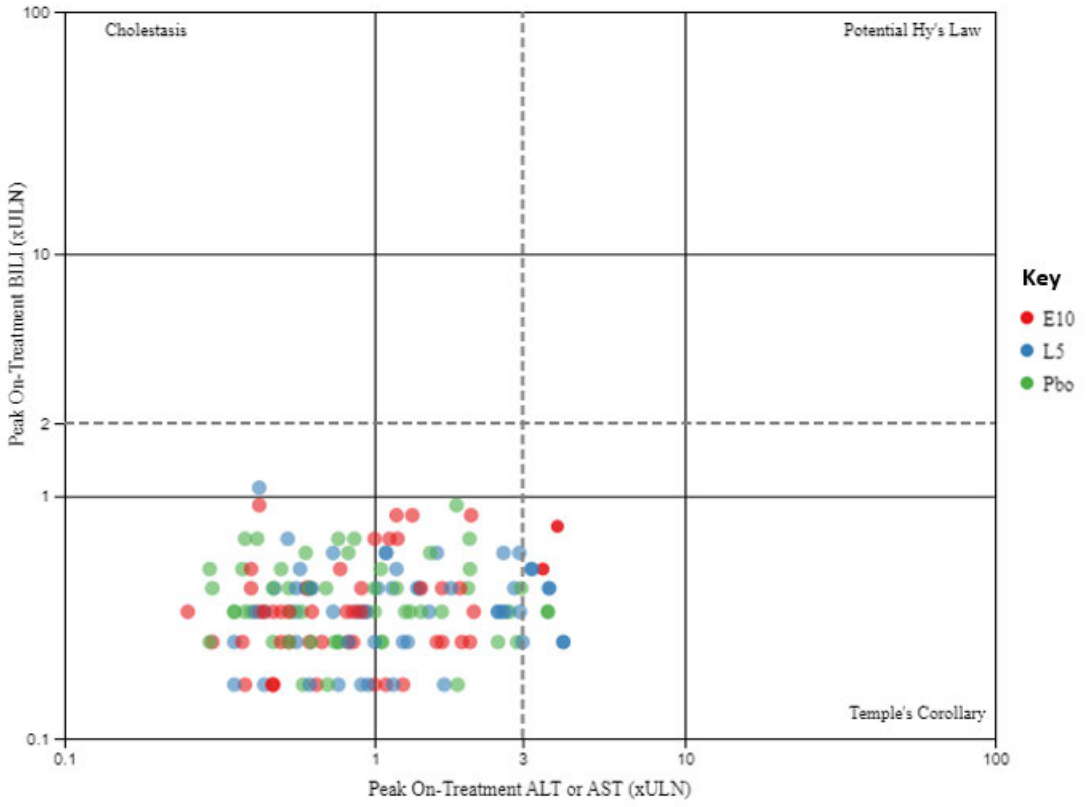
Source: Reviewer generated using OCS Analysis Studio, Custom Table Tool.
Columns - Dataset: Demographics; Filter: TRTFL = 'Y', TANSTGBL = '2' - '4'.
IGF-1 (ng/mL) - Dataset: Laboratory; Filter: AVISIT = 'Week 26', PARAM = 'Insulin-like Growth Factor-1 [ng/mL]'.
IGFBP-3 (ug/mL) - Dataset: Laboratory; Filter: AVISIT = 'Week 26', PARAM = 'Insulin-like Growth Factor Binding Prot3 [ug/mL]'.
SD = Standard Deviation.

Hepatic Function Parameters

A hepatocellular DILI plot analysis was conducted for the placebo-controlled treatment period (Figure 18) and including the safety extension (not shown). No hepatic event fulfilled Hy's Law criteria (i.e., AST or ALT ≥ 3 x ULN and total bilirubin ≥ 2 x ULN) during the placebo-controlled treatment period or safety extension. 2 subjects in the Empagliflozin pooled arm, 3 subjects in the Linagliptin arm, and 1 subject in the placebo arm were in the right lower quadrant for Temple's corollary through Week 26 (Table 55). Hepatic function data for these subjects over

the course of the entire study were individually reviewed. All of these subjects had elevation in baseline AST and/or ALT. As previously discussed, subject [redacted] (b) (6) who was treated with linagliptin had a liver injury AESI that was adjudicated by the CEC as consistent with mild to moderate hepatic injury though was felt unlikely to be related to drug treatment (see Figure 14). For the 2 subjects treated with empagliflozin, hepatic function changes over the course of the study are displayed in Figure 19 (subject [redacted] (b) (6)) and Figure 20 (subject [redacted] (b) (6)). Subject [redacted] (b) (6) was noted to have an AE of fatty liver after discontinuation of study treatment on study day 393; and subject [redacted] (b) (6) was noted to have AEs of alanine aminotransferase increase and aspartate aminotransferase increase on study day 30.

Figure 18: Hepatocellular DILI Screening Plot through Week 26, Study 1218.91



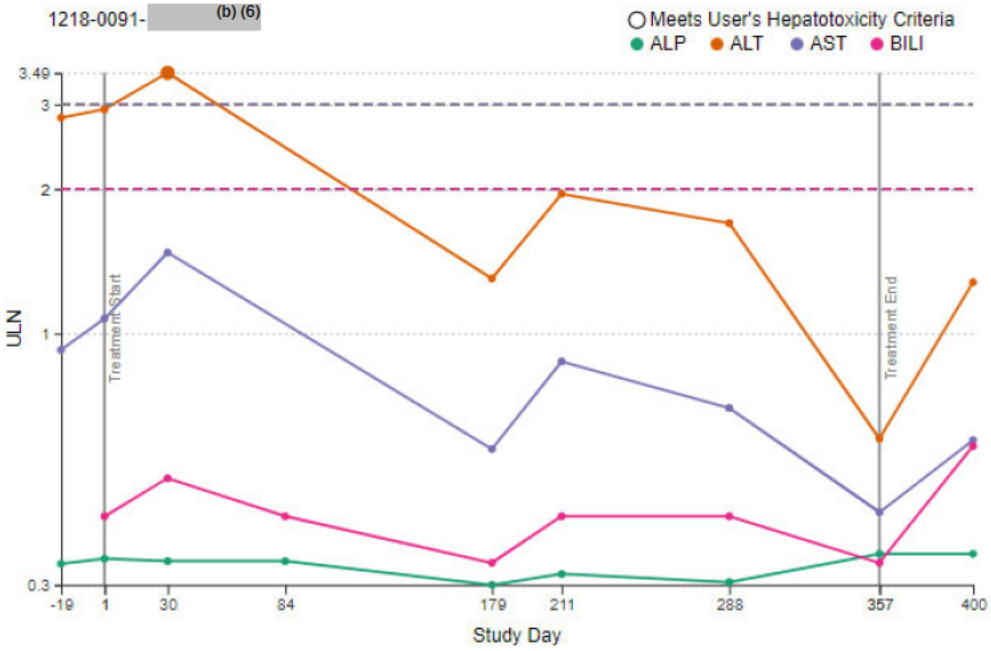
Source: Reviewer created in OCS Analysis Studio, Hepatic Explorer.
Filters: TRTFL = "Y"; APERIOD = 1 to 2.
**Hepatotoxicity Candidates: ALT or AST >= 3*ULN; BILI >= 2*ULN (0-30 days forward); ALP < 2*ULN (0-999 days backward).*
**Results missing ULN values were imputed using the weighted mean of the lab code.*
Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BILI, bilirubin;
DILI, drug-induced liver injury; ULN, upper limit of normal.

Table 55: Listing of Subjects in Temple's Corollary through Week 26

Subject	TRT01A	Peak ALT or AST (xULN)	Peak BILI (x ULN)	Baseline ALT or AST > ULN	Follow up (off-treatment) ALT or AST > ULN
(b) (6)	E10	3.4884	0.5	Y	Y
	E10	3.8837	0.75	Y	Y
	Pbo	3.6176	0.3333	Y	n/a
	L5	3.2093	0.5	Y	Y
	L5	4.0588	0.25	Y	Y
	L5	3.6512	0.4167	Y	Y

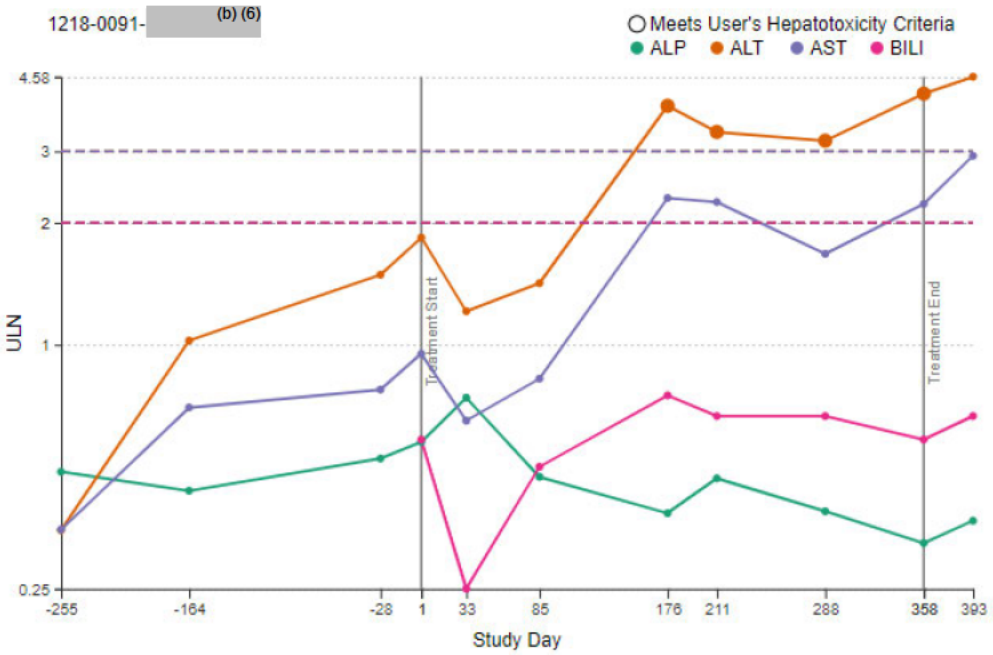
Source: Reviewer created in OCS Analysis Studio, Hepatic Explorer

Figure 19: Hepatic Function Tests for Subject (b) (6) treated with Empagliflozin



Source: Reviewer created in OCS Analysis Studio, Hepatic Explorer

Figure 20: Hepatic Function Tests for Subject (b) (6) treated with Empagliflozin.



Source: Reviewer created in OCS Analysis Studio, Hepatic Explorer

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

Lipids

There were no clinically significant changes in mean total cholesterol, HDL cholesterol, LDL cholesterol or triglyceride values from baseline to Week 26 in any of the treatment groups (data not shown).

Other laboratory parameters

According to the Applicant, differences in mean change from baseline to week 26 were observed for hematocrit, hemoglobin, creatine kinase, and lipase in empagliflozin treated subjects versus placebo. Mean changes in these laboratory parameters are displayed below in Table 56. Overall, subjects treated with empagliflozin had small mean increases in hemoglobin and hematocrit from baseline to Week 26 as compared to subjects in the other treatment arms. This finding is consistent with adult studies in which a small increase in hematocrit was also observed with empagliflozin as compared to placebo. Mean creatine kinase decreased from baseline to Week 26 in all treatment arms; though the difference was more pronounced in the empagliflozin arm. This finding appears to have been driven by an outlier (subject (b) (6)) who had a baseline CK level recorded as 4363 U/L, followed by CK levels measured at 52 U/L at week 3, 52 U/L at week 12 and 56 U/L at week 26. After excluding this subject, the mean change from baseline to Week 26 in the empagliflozin arm was + 15.9 U/L. A small increase in

mean lipase was observed from baseline to week 26 in subjects treated with empagliflozin and linagliptin; however, the magnitude of change is not clinically significant. As discussed previously, no episodes of pancreatitis occurred in subjects treated with empagliflozin and linagliptin.

Table 56: Change from Baseline to Week 26 in hemoglobin, hematocrit, creatine kinase, and lipase; Study 1218.91.

	Empagliflozin Pooled (N=52)	Linagliptin (N=52)	Placebo (N=53)
Hemoglobin (g/dL)			
Mean (SD)	0.5 (1.29)	0.1 (0.83)	0.1 (1.03)
Median (Min, Max)	0.4 (-1.9, 6.4)	0.1 (-2.5, 1.4)	0.1 (-3.3, 4.2)
Hematocrit (%)			
Mean (SD)	1.8 (4.24)	-0.2 (2.74)	0.4 (3.23)
Median (Min, Max)	1.0 (-7, 18)	0.0 (-9, 5)	0.5 (-8, 13)
Creatine kinase (U/L)			
Mean (SD)	-72.3 (625.18)	-2.5 (58.77)	-22.7 (117.81)
Median (Min, Max)	6.0 (-4307, 446)	1.0 (-213, 176)	-0.5 (-705, 276)
Creatine Kinase (U/L) excluding outlier in empagliflozin arm			
Mean (SD)	15.9 (98.32)	-2.5 (58.77)	-22.7 (117.81)
Median (Min, Max)	6.0 (-284, 446)	1.0 (-213, 176)	-0.5 (-705, 276)
Lipase (U/L)			
Mean (SD)	3.3 (13.07)	3.7 (8.96)	0.1 (3.98)
Median (Min, Max)	1.0 (-14, 67)	2.0 (-12, 36)	0.0 (-9, 14)

Source: Reviewer generated using OCS Analysis Studio, Custom Table Tool.
Columns - Dataset: Demographics; Filter: TRTFL = 'Y'.
Hemoglobin (g/dL) - Dataset: Laboratory; Filter: PARAM = 'Hemoglobin [g/dL]', AVISIT = 'Week 26'.
Hematocrit (%) - Dataset: Laboratory; Filter: AVISIT = 'Week 26', PARAM = 'Hematocrit [%]'.
Creatine kinase (U/L) - Dataset: Laboratory; Filter: AVISIT = 'Week 26', PARAM = 'Creatine Kinase [U/L]'.
Lipase (U/L) - Dataset: Laboratory; Filter: AVISIT = 'Week 26', PARAM = 'Lipase [U/L]'.
SD = Standard Deviation.

According to the Applicant, no differences were observed for other safety laboratory parameters with empagliflozin treatment[42]. This finding was confirmed in an analysis of change from baseline in all other laboratory parameters through Week 26 (laboratory data explored via OCS Analysis Studio, data not shown), in which no clinically relevant changes were noted.

Reviewer Comment: Overall, the safety analysis based on laboratory parameters suggests that treatment with empagliflozin may be associated with small increases in hematocrit and small decreases in eGFR in pediatric patients, similar to findings previously described in adults. No new safety signals in pediatric patients were observed based on the laboratory analysis.

8.4.7. Vital Signs

[42] For linagliptin versus placebo, the Applicant conducted a pooled analysis of safety laboratory data that was limited to possibly clinically significant laboratory abnormalities, based on predefined criteria

Changes in systolic blood pressure (SBP) and diastolic blood pressure (DBP) from baseline to Week 26 are displayed in Table 57. No clinically meaningful changes in blood pressure occurred in any treatment arm. Change in SBP and DBP were also considered secondary endpoints in the DINAMO protocol (see 6.1.2 for details); exploratory analyses did not reveal any treatment-related changes from baseline to Week 26.

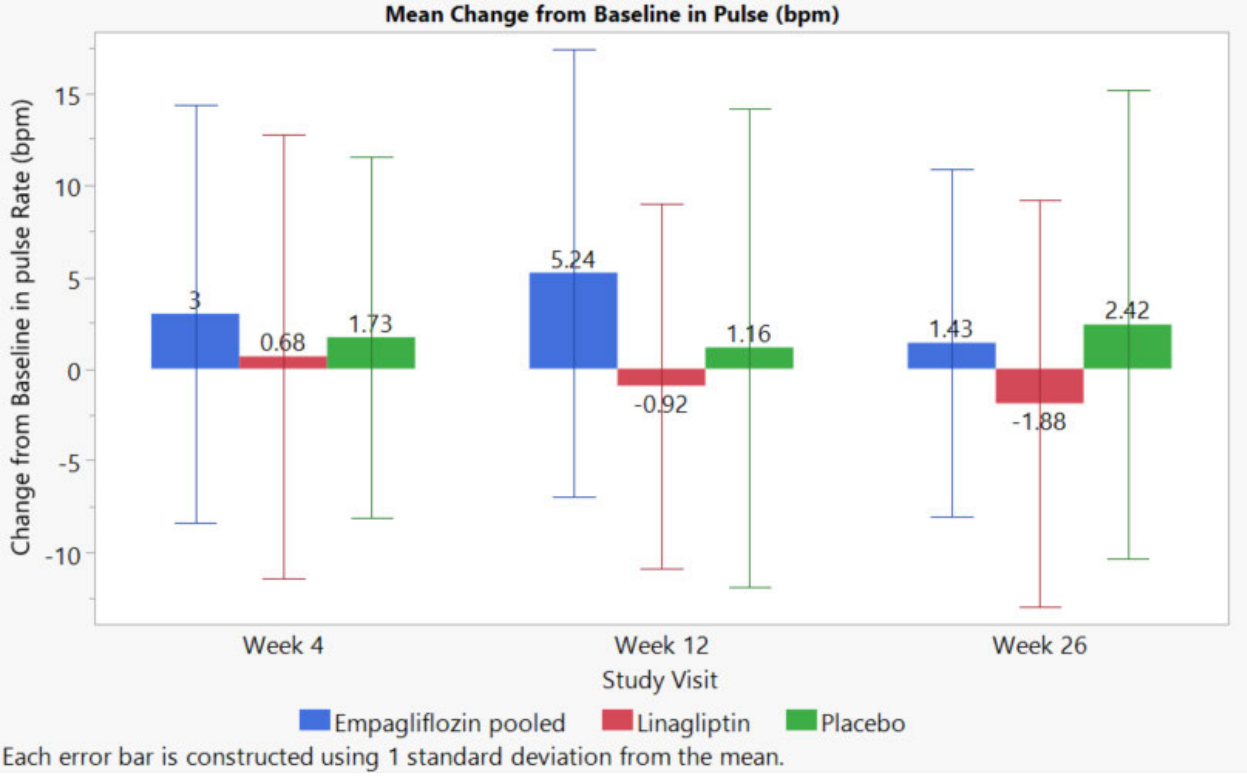
Table 57: Change from Baseline to Week 26 in Blood Pressure, Study 1218.91

	Empagliflozin Pooled (N=52)	Linagliptin (N=52)	Placebo (N=53)
SBP at Baseline (N)	52 (100.0)	52 (100.0)	53 (100.0)
SBP at Baseline (mmHg)			
Mean (SD)	120.2 (9.9)	122.3 (10.9)	119.2 (11.8)
Median (Min, Max)	120.0 (99, 140.7)	120.7 (106. 7, 147.3)	118.2 (95, 149)
SBP at Week 26 (N)	48 (92.3)	49 (94.2)	50 (94.3)
SBP at Week 26 (mmHg)			
Mean (SD)	119.8 (8.9)	123.3 (11.4)	120.1 (11.7)
Median (Min, Max)	120.0 (99, 139)	123.5 (100.3, 150)	120.0 (100.7, 149)
DBP at baseline (N)	52 (100.0)	52 (100.0)	53 (100.0)
DBP at baseline (mmHg)			
Mean (SD)	72.0 (8.34)	73.8 (8.04)	72.8 (8.08)
Median (Min, Max)	71.2 (53.7, 89)	74.3 (53.3, 94.3)	71.7 (52.7, 95.3)
DBP at Week 26 (N)	48 (92.3)	49 (94.2)	50 (94.3)
DBP at Week 26 (mmHg)			
Mean (SD)	73.1 (7.48)	75.5 (8.7)	73.6 (6.3)
Median (Min, Max)	72.3 (59, 87)	75.2 (57.7, 93)	72.7 (61.7, 87.7)

Source: Reviewer generated using OCS Analysis Studio, Custom Table Tool.
Columns - Dataset: Demographics; Filter: TRTFL = 'Y'.
SBP at Baseline (N) - Dataset: Vital Signs; Filter: ABLFL = 'Y', PARAM = 'Systolic Blood Pressure [mmHg] - Mean'. SBP at Baseline (mmHg) - Dataset: Vital Signs; Filter: ABLFL = 'Y', PARAM = 'Systolic Blood Pressure [mmHg] - Mean'. SBP at Week 26 (N) - Dataset: Vital Signs; Filter: AVISIT = 'Week 26', PARAM = 'Systolic Blood Pressure [mmHg] - Mean'. SBP at Week 26 (mmHg) - Dataset: Vital Signs; Filter: AVISIT = 'Week 26', PARAM = 'Systolic Blood Pressure [mmHg] - Mean'. DBP at baseline (N) - Dataset: Vital Signs; Filter: ABLFL = 'Y', PARAM = 'Diastolic Blood Pressure [mmHg] - Mean'. DBP at baseline (mmHg) - Dataset: Vital Signs; Filter: ABLFL = 'Y', PARAM = 'Diastolic Blood Pressure [mmHg] - Mean'. DBP at Week 26 (N) - Dataset: Vital Signs; Filter: AVISIT = 'Week 26', PARAM = 'Diastolic Blood Pressure [mmHg] - Mean'. DBP at Week 26 (mmHg) - Dataset: Vital Signs; Filter: AVISIT = 'Week 26', PARAM = 'Diastolic Blood Pressure [mmHg] - Mean'. SD = Standard Deviation.
SBP= systolic blood pressure, DBP= diastolic blood pressure

Mean change from baseline in heart rate from baseline through Week 26 is shown in Figure 21. Subjects treated with empagliflozin experienced small increases in heart rate compared to baseline starting week 4, peaking at week 12 and then declining to close to baseline by week 26.

Figure 21: Change from Baseline in Heart Rate by Study Visit through Week 26, Study 1218.19



Source: Reviewer created in JMP

In adult studies of empagliflozin, small decreases in blood pressure were seen in clinical trials; however, no changes in heart rate were noted. As discussed above, AEs relating to volume depletion were prespecified as a special AE of interest in the DINAMO study; however, no AEs relating to volume depletion occurred in empagliflozin treated subjects.

Reviewer Comment: Overall, no significant safety findings relating to vital signs were observed. In the DINAMO study, treatment with empagliflozin may have been associated with very small transient increases in heart rate but no changes in blood pressure were evident.

8.4.8. Electrocardiograms (ECGs)

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

8.4.9. QT

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

8.4.10. Immunogenicity

Immunogenicity was not assessed in the study.

8.5. Analysis of Submission-Specific Safety Issues

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

8.6. Safety Analyses by Demographic Subgroups

An analysis of the impact of background antidiabetic medication on hypoglycemia risk was conducted and previously described (see Section 8.4.4).

The CSR of the DINAMO study did not contain specific safety analyses by demographic subgroups, as this was not prespecified in the TSAP. For this safety review, I performed analyses of TEAEs by SOC and PT occurring during the placebo-controlled period within several demographic subgroups, including subjects of Hispanic or Latino ethnicity, subjects of non-white race, male subjects and subjects aged > 15 years (see Appendix 13.3). Several numerical imbalances were seen with empagliflozin treatment as compared to placebo, including a higher incidence of the PT "headache" among subjects of Hispanic and Latino ethnicity, a higher incidence of the PT "upper respiratory tract infection" among subjects of non-White race, and a higher incidence of the PT "seasonal allergy" in male subjects. These imbalances are most likely due to chance, considering the small number of subjects within these subgroups.

Following an IR, the Applicant conducted key demographic subgroup analyses of the most frequently reported TEAEs (occurring in > 5% of subjects) based on age (<15 years versus $\geq$ 15 years), sex (male versus female), race (white versus all other race classifications), and ethnicity (Hispanic or Latino versus not Hispanic or Latino). The results of the Applicant's subgroup analyses for commonly reported TEAEs were consistent with the conclusions from the reviewer-conducted analyses described above.

8.7. Specific Safety Studies/Clinical Trials

No additional specific safety studies are being conducted.

8.8. Additional Safety Explorations

8.8.1. Human Carcinogenicity or Tumor Development

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

8.8.2. Human Reproduction and Pregnancy

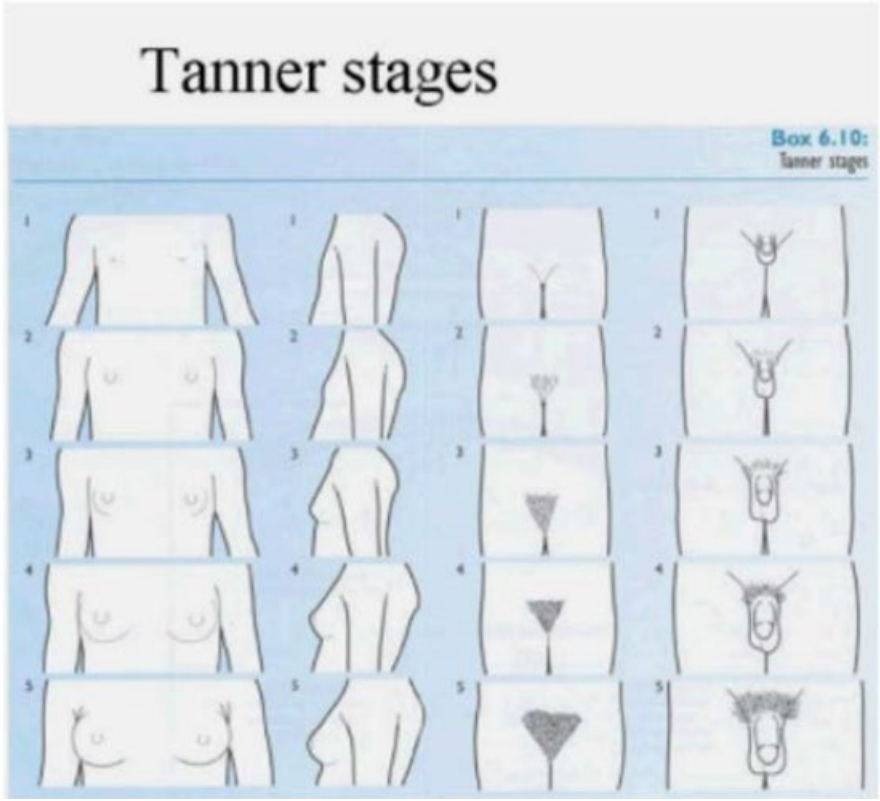
There is no information relevant to this section of the review in the submission. No pregnancies occurred in the DINAMO study.

8.8.3. Pediatrics and Assessment of Effects on Growth

Sexual Maturation:

In clinical practice, Tanner staging is performed separately for genitals (in boys), for breast development (in girls) and for pubic hair development (in both boys and girls). However, in the DINAMO study, a "modified" Tanner stage scale was used that combined elements of Tanner staging for genitals/breast and Tanner stating for pubic hair (see below), to allow for a single Tanner stage assessment to be provided by the Investigator. Based on the protocol, it appears that investigators were instructed to document the "most advanced" pubertal stage based on visual examination.

Figure 22: "Modified" Tanner Stage Scale utilized in Study 1218.91



Source: DINAMO protocol

Reviewer Comment: The approach used for Tanner staging in the DINAMO study was suboptimal, as a single Tanner stage was assigned based on the most advanced genital, breast or pubic hair development, rather than reporting separate Tanner stage for genitals (in boys), breasts (in girls) and pubic hair (in boys and girls). Changes in puberty are reflected by genital development in boys, and by breast development in girls. Pubic hair development is primarily the result of adrenarche in girls; and may reflect both adrenarche and puberty in boys. The timing of puberty and adrenarche does not always coincide; and staging for each

may be discrepant. For example, a girl may have Tanner stage 3 breast development but Tanner stage 1 pubic hair, and a boy may have Tanner stage 1 genital development but Tanner stage 2 pubic hair. In some cases, children may have very advanced adrenarche (e.g., Tanner stage 4-5 pubic hair) but may not have entered puberty. Given that puberty, rather than adrenarche, drives the development of secondary sex characteristics and linear growth, the absence of a specific measurement for puberty (i.e., Tanner stage for genitals in boys and breast for girls) in the DINAMO study limits the interpretation of any safety findings relating to puberty.

The baseline characteristics of the study population with respect to this "modified" Tanner stage displayed in Table 58. No subjects with baseline Tanner stage 1 were enrolled. Overall, more than half of the study subjects were at Tanner Stage 5 at baseline. Among female subjects, 87.6% were at Tanner Stage 4 or 5 at baseline, and only 2.1% were at Tanner stage 2. Among male subjects, 71.7% were at Tanner Stage 4 or 5 at baseline and 10% were at Tanner Stage 2.

In subjects who were below Tanner stage 5 at baseline, Tanner staging was re-evaluated at week 26 and again at week 52.

Table 58: Baseline Tanner Stage, Study 1218.91

Baseline Tanner Stage in All Treated Subjects

	Empagliflozin Pooled (N=52)	Linagliptin (N=52)	Placebo (N=53)	Total (N=157)
Tanner Stage 2	5 (9.6)	0	3 (5.7)	8 (5.1)
Tanner Stage 3	7 (13.5)	6 (11.5)	8 (15.1)	21 (13.4)
Tanner Stage 4	12 (23.1)	13 (25.0)	10 (18.9)	35 (22.3)
Tanner Stage 5	28 (53.8)	33 (63.5)	32 (60.4)	93 (59.2)

Source: Reviewer generated using OCS Analysis Studio, Custom Table Tool. Columns - Dataset: Demographics; Filter: TRTFL = 'Y', SEX = 'F' or 'M'. Tanner Stage 2 - Dataset: Demographics; Filter: TANSTGBL = '2' - '2'. Tanner Stage 3 - Dataset: Demographics; Filter: TANSTGBL = '3' - '3'. Tanner Stage 4 -Dataset: Demographics; Filter: TANSTGBL = '4' - '4'.Tanner Stage 5 - Dataset: Demographics; Filter: TANSTGBL = '5' - '5'.

Baseline Tanner Stage in Female Subjects

	Empagliflozin Pooled (N=33)	Linagliptin (N=30)	Placebo (N=34)	Total (N=97)
Tanner Stage 2	1 (3.0)	0	1 (2.9)	2 (2.1)
Tanner Stage 3	3 (9.1)	3 (10.0)	4 (11.8)	10 (10.3)
Tanner Stage 4	8 (24.2)	7 (23.3)	6 (17.6)	21 (21.6)
Tanner Stage 5	21 (63.6)	20 (66.7)	23 (67.6)	64 (66.0)

Source: Reviewer generated using OCS Analysis Studio, Custom Table Tool. Columns - Dataset: Demographics; Filter: TRTFL = 'Y', SEX = 'F'. Tanner Stage 2 - Dataset: Demographics; Filter: TANSTGBL = '2' - '2'. Tanner Stage 3 - Dataset: Demographics; Filter: TANSTGBL = '3' - '3'. Tanner Stage 4 - Dataset: Demographics; Filter: TANSTGBL = '4' - '4'. Tanner Stage 5 - Dataset: Demographics; Filter: TANSTGBL = '5' - '5'.

Baseline Tanner Stage in Male Subjects

	Empagliflozin Pooled (N=19)	Linagliptin (N=22)	Placebo (N=19)	Total (N=60)
Tanner Stage 2	4 (21.1)	0	2 (10.5)	6 (10.0)

Baseline Tanner Stage in All Treated Subjects

	Empagliflozin Pooled (N=52)	Linagliptin (N=52)	Placebo (N=53)	Total (N=157)
Tanner Stage 3	4 (21.1)	3 (13.6)	4 (21.1)	11 (18.3)
Tanner Stage 4	4 (21.1)	6 (27.3)	4 (21.1)	14 (23.3)
Tanner Stage 5	7 (36.8)	13 (59.1)	9 (47.4)	29 (48.3)

Source: Reviewer generated using OCS Analysis Studio, Custom Table Tool. Columns - Dataset: Demographics; Filter: TRTFL = 'Y', SEX = 'M'. Tanner Stage 2 - Dataset: Demographics; Filter: TANSTGBL = '2' - '2'. Tanner Stage 3 - Dataset: Demographics; Filter: TANSTGBL = '3' - '3'. Tanner Stage 4 - Dataset: Demographics; Filter: TANSTGBL = '4' - '4'. Tanner Stage 5 - Dataset: Demographics; Filter: TANSTGBL = '5' - '5'.

Reviewer Comment: Most subjects who were enrolled were reported to be at baseline Tanner stage 4 or 5. The enrollment of a study population with baseline advanced pubertal development is consistent with other recently completed pediatric type 2 diabetes trials. No subjects enrolled in the DINAMO study were Tanner stage 1 at baseline. However, given the limitations in the Tanner staging approach that was used, it is possible that some subjects who were prepubertal (i.e., with baseline Tanner stage 1 for genitals or breasts) could have been enrolled but were classified as having more advanced sexual maturation based on pubic hair development.

The Applicant performed a shift-table analysis for Tanner staging from baseline to Week 26 (Table 59). The Applicant concluded that there were no relevant differences between empagliflozin versus placebo, or between linagliptin versus placebo with regard to shifts in Tanner staging score.

Table 59: Frequency of patients with shifts in Tanner staging score from baseline to Week 26, Study 1218.91

Treatment/ Tanner staging score at Wk26	Baseline 1 N	1 %	2 N	2 %	3 N	3 %	4 N	4 %	5[1] N	5[1] %	Total N	Total %
Pbo												
1	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
2	0	0.0	2	3.8	0	0.0	0	0.0	0	0.0	2	3.8
3	0	0.0	1	1.9	5	9.4	0	0.0	0	0.0	6	11.3
4	0	0.0	0	0.0	0	0.0	6	11.3	0	0.0	6	11.3
5	0	0.0	0	0.0	3	5.7	3	5.7	20	37.7	26	49.1
Missing	0	0.0	0	0.0	0	0.0	1	1.9	12	22.6	13	24.5
Total	0	0.0	3	5.7	8	15.1	10	18.9	32	60.4	53	100.0
L5												
1	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
2	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
3	0	0.0	0	0.0	4	7.7	0	0.0	0	0.0	4	7.7
4	0	0.0	0	0.0	1	1.9	8	15.4	0	0.0	9	17.3
5	0	0.0	0	0.0	1	1.9	4	7.7	20	38.5	25	48.1
Missing	0	0.0	0	0.0	0	0.0	1	1.9	13	25.0	14	26.9
Total	0	0.0	0	0.0	6	11.5	13	25.0	33	63.5	52	100.0
E Pooled												
1	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
2	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
3	0	0.0	1	1.9	2	3.8	0	0.0	0	0.0	3	5.8
4	0	0.0	2	3.8	5	9.6	5	9.6	0	0.0	12	23.1
5	0	0.0	1	1.9	0	0.0	6	11.5	18	34.6	25	48.1
Missing	0	0.0	1	1.9	0	0.0	1	1.9	10	19.2	12	23.1
Total	0	0.0	5	9.6	7	13.5	12	23.1	28	53.8	52	100.0

Pbo = Placebo, L5 = Linagliptin 5 mg, E Pooled = Empagliflozin pooled.
Baseline is the study baseline (last observed measurement on or prior to administration of any initially randomised study medication at Day 1).
[1] Further Tanner stage scoring was not required for patients who scored Tanner stage 5 at baseline.

Source: table 15.3.4:1 DINAMO CSR

Reviewer Comment: The interpretation of shifts in Tanner staging during the study is limited by the deficiencies in the Tanner staging approach, previously discussed. It is unclear whether shifts represent changes in adrenarche, puberty or both. A few subjects in the empagliflozin arm appear to have shifted multiple stages over the 26-week period (i.e.., 2 subjects with baseline Tanner stage 2 shifted to Tanner stage 4 and 5, respectively by week 26); this also appears to have occurred in the placebo arm (3 subjects shifted from Tanner stage 3 to Tanner stage 5). Additionally, some subjects in the placebo and empagliflozin arms appear to have shifted to a lower Tanner stage by Week 26; which may be related to the subjective nature of Tanner staging in general (based on visual examination), or due to variations in the investigator's determination of the "overall" Tanner stage in the setting of significant discordance between the Tanner staging of genitals or breasts versus pubic hair. Given the limitations in the data, and overall small numbers of subjects involved, no conclusions can be drawn regarding the impact of empagliflozin therapy as compared to placebo on pubertal development.

Height:

Height was measured at screening (baseline measurement), Week 26, and at Week 52. Height

Z-score was calculated using the World Health Organization (WHO) age and sex-specific references. Changes in height and height Z-score in all treated subjects during the placebo-controlled period are displayed in Table 60. In all treatment arms, a minimal increase (≤1 cm) in mean height was observed from baseline to week 26 in all treatment arms. Height Z-score was also minimally changed (mean increase of +0.1 in all three treatment arms).

As subjects who have completed puberty and linear growth would not be expected to have further changes in height, a separate analysis of height was conducted for the subgroup subjects who were characterized as having baseline Tanner stage 2 through 4 (Table 61). Within this subgroup, slightly larger increases in mean height and mean height Z-score were observed in all three treatment arms; though the magnitude of mean change in height remains far below what would normally be expected in pubertal subjects over a 6-month period.

Due to re-randomization of subjects in the placebo arm from week 26 to 52, it is difficult to determine treatment-related effects on growth beyond week 26. However, to further investigate this finding of lower-than-expected interval linear growth through week 26, an analysis of height change from baseline through week 52 was conducted in subjects with baseline Tanner stage < 5 (Table 62). Overall, this subgroup continued to experience lower than expected change in height over a 52-week period, with a mean increase in height of 2.3 cm. However, there appeared to be significant variability based on the range of values observed.

Table 60: Height in All Treated Subjects through Week 26, Study 1218.91

	Empagliflozin Pooled (N=52)	Linagliptin (N=52)	Placebo (N=53)
Baseline Height Z-score	N=52	N=52	N=53
Mean (SD)	0.7 (1.6)	0.6 (1.07)	0.5 (1.3)
Median (Min, Max)	0.8 (-3.1, 6.3)	0.7 (-2.8, 3.2)	0.4 (-2.5, 3.3)
Height Z-score at week 26	N=48	N=50	N=52
Mean (SD)	0.8 (1.7)	0.7 (1.1)	0.4 (1.4)
Median (Min, Max)	0.8 (-3.1, 6.5)	0.8 (-2.8, 3.5)	0.4 (-2.5, 3.3)
Change in Height Z-score from Baseline to Week 26			
Mean (SD)	0.1 (0.2)	0.1 (0.2)	0.1 (0.2)
Median (Min, Max)	0.1 (0, 0.8)	0.1 (-0.3, 0.9)	0.0 (-0.4, 1.2)
Change in Height (cm) from Baseline to Week 26			
Mean (SD)	1.0 (1.39)	0.9 (1.38)	0.8 (1.46)
Median (Min, Max)	0.5 (0, 6)	1.0 (-2, 7)	0.0 (-3, 8)

Source: Reviewer generated using OCS Analysis Studio, Custom Table Tool.
Columns - Dataset: Demographics; Filter: TRTFL = 'Y'.
Baseline Height - Dataset: Vital Signs; Filter: PARAM = 'Height SDS', ABLFL = 'Y'.
Height at week 26 - Dataset: Vital Signs; Filter: AVISIT = 'Week 26', PARAM = 'Height SDS'.
Change in Height from Baseline to Week 26 - Dataset: Vital Signs; Filter: AVISIT = 'Week 26', PARAM = 'Height SDS'.
SD = Standard Deviation.

Table 61: Change in Height in Subjects with Baseline Tanner Stage < 5 through Week 26, Study 1218.91

	Empagliflozin Pooled (N=24)	Linagliptin (N=19)	Placebo (N=21)
Change in Height Z-score from Baseline to Week 26			
Mean (SD)	0.2 (0.2)	0.1 (0.3)	0.2 (0.3)
Median (Min, Max)	0.1 (0, 0.8)	0.1 (-0.3, 0.9)	0.1 (0, 1.2)
Change in Height (cm) from Baseline to Week 26			
Mean (SD)	1.3 (1.62)	1.1 (1.94)	1.5 (1.91)
Median (Min, Max)	1.0 (0, 6)	1.0 (-2, 7)	1.0 (0, 8)

Source: Reviewer generated using OCS Analysis Studio, Custom Table Tool.
Columns - Dataset: Demographics; Filter: TRTFL = 'Y', TANSTGBL = '2' - '4'.
Change in Height from Baseline to Week 26 - Dataset: Vital Signs; Filter: AVISIT = 'Week 26', PARAM = 'Height SDS'.
Change in Height from Baseline to Week 26 - Dataset: Vital Signs; Filter: AVISIT = 'Week 26', PARAM = 'Height [cm]'.
SD = Standard Deviation

Table 62: Change in Height in Subjects with Baseline Tanner Stage < 5 through Week 52, based on initial randomization, Study 1218.91

	Empagliflozin Pooled (N=24)	Linagliptin (N=19)	Placebo* (N=21)	Total (N=64)
Change in Height (cm) from baseline to Week 52				
Mean (SD)	2.7 (2.44)	1.7 (2.43)	2.3 (2.64)	2.3 (2.50)
Median (Min, Max)	2.0 (0, 9)	2.0 (-2, 7)	1.5 (0, 10)	2.0 (-2, 10)

Source: Reviewer generated using OCS Analysis Studio, Custom Table Tool.
Columns - Dataset: Demographics; Filter: TANSTGBL = '2' - '4', TRTFL = 'Y'.
Table Section 1 - Dataset: Vital Signs; Filter: PARAM = 'Height [cm]', AVISIT = 'Week 52'.
SD = Standard Deviation.
**Subjects in the placebo arm received empagliflozin or linagliptin from week 26 to 52.*

Reviewer Comment: Because adolescents who have completed linear growth would not be expected to exhibit further changes in height, a safety evaluation for any treatment-related effects on growth should be focused on subjects who have remaining growth potential. Remaining growth potential would have been best assessed either by evaluation of pre-study growth velocity, bone age assessment, and/or information regarding mid-parental height; however, none of this information was collected systematically. Because the end of puberty (i.e., Tanner stage 5) typically correlates with near completion of linear growth, changes in height in the subgroup of subjects who were below Tanner stage 5 at baseline were explored. However, even within this subgroup, minimal changes in height were observed through week 26 and through week 52, with an overall change in height of ~ 2.3 cm/year. This represents an abnormally low growth velocity for subjects undergoing puberty. Most likely, this finding is the result of misclassification of Tanner staging, leading to the inclusion of subjects who had completed linear growth within the subgroup of subjects who were classified as having Tanner stage < 5 at baseline. As these findings were consistent across treatment arms, there is no obvious evidence of any treatment-related impact on growth; however, it is difficult to draw any conclusions given the limitations in the data.

Growth velocity:
Growth velocity (cm/year) was calculated based on changes in measured height in cm over the measured interval in years. The growth velocity results through week 26 and through week 52 were consistent with changes in height described above.

BMI:
No changes from baseline in BMI Z-score were observed at week 26 or week 52 in any treatment arm (data not shown).

Reviewer Comment: Conclusions regarding treatment-related effects on pubertal progression and growth are limited due to several issues, including small number of subjects in early stages of pubertal development, absence of relevant information including mid-parental target height and pre-trial growth pattern, and possible misclassification of Tanner stage. Similar challenges were noted in the review of recently completed pediatric T2D trials for other products (e.g., liraglutide, sitagliptin, extended-release exenatide, dulaglutide).

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

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

8.9. Safety in the Postmarket Setting

8.9.1. Safety Concerns Identified Through Postmarket Experience

The Applicant states that the cumulative global post-marketing adult patient exposure to Jardiance from April 2014 through April 2022 is estimated to be 22,181,610 patient years. The cumulative global post-marketing adult patient exposure to Synjardy and Synjardy XR from July 2015 through April 2022 is estimated to be 3,697,300 patient years.

Following the initial approval of Jardiance, important safety issues identified either in the postmarket setting or in clinical trials of empagliflozin and/or other SGLT2-inhibitors include increased risks of ketoacidosis (particularly in patients with type 1 diabetes), serious hypersensitivity reactions (e.g., angioedema), necrotizing fasciitis of the perineum (Fournier's gangrene), urosepsis and pyelonephritis, acute kidney injury, constipation and tubulointerstitial nephritis. These safety issues are described in the PI for all empagliflozin-containing products. A drug-drug interaction between empagliflozin and lithium[43] was also recently identified and is described in the product label.

[43] According to the PI, concomitant use of an SGLT2 inhibitor with lithium may decrease serum lithium concentrations

(b) (4)

a Citizen Petition dated June 24, 2020 that requested a boxed warning for all SGLT2 inhibitor drugs contraindicating their use in patients with type 1 diabetes. The PI for empagliflozin-containing products currently includes the following limitation of use: "not recommended in patients with type 1 diabetes mellitus. It may increase the risk of diabetic ketoacidosis in these patients".

(b) (4)

No new safety issues other than those already described in the label were identified in a review of the most recent periodic Benefit-Risk Evaluation Report for Jardiance, Synjardy and Synjardy XR (reporting period from April 18, 2020 to April 17, 2022) or the safety updates submitted by the Applicant on March 13, 2022 (to NDA 204629, covering the period from April 18, 2022 through December 31, 2022)[44] and on May 15, 2023 (to NDA 206111, covering the period from April 1, 2022 through December 31, 2022).

In the summary of clinical safety included in this submission, the Applicant stated that off-label use of empagliflozin and empagliflozin/metformin (fixed-dose combination product) has been documented in 138 and 8 pediatric patients, respectively, but that no relevant difference in the safety profile was observed between adults and off-label use in pediatric patients below 18 years of age. Following an IR, on May 24, 2023, the Applicant provided the following summary regarding these cases:

Jardiance (138 cases)

11 serious cases

- *6 DKA/Euglycemic DKA*
  - *1 case with simultaneous pancreatitis in a patient with type 1 diabetes*
  - *1 patient with T2D using insulin and liraglutide but no information concerning insulin adherence.*
  - *1 case in a patient with 4-year-old receiving insulin.*
  - *3 cases were flagged as child cases however, the age was not provided, and the medical history described in the narrative is compatible to adult patients.*
- *1 case with the events of Blood glucose increased and Loss of consciousness; however, the medical history described in the narrative is compatible with an adult patient;*
- *1 case in a reported 5-year-old patient with the event of Toe amputation and history of smoking and cocaine addiction; the patient's status as a child cannot be confirmed; most*

[44] On January 30, 2023, the Agency agreed with the Applicants request to submit a 3-month safety update for Jardiance/NDA 204629

(b) (4)

likely the case is involving an adult patient;

- *1 case of suicidal intention derived from a 15-year-old patient who ingested 125mg of Jardiance as suicidal intention and experienced hypertension of 135/92 and urinary incontinence as simultaneous events reported;*
- *1 case with the event of Myocardial infarction with very limited information precluding any causality assessment;*
- *1 case with event Death reported without any specific AE or without any information concerning the cause of death in a 16-year-old female. Very limited information provided.*

For the non-serious cases, most cases had reported off-label use/ product administered to patient of inappropriate age without any further events or cases with AEs which are part of the known safety profile of empagliflozin without any specific trend.

Synjardy (8 Cases)
1 serious case, reported as DKA (described above – patient treated with insulin and liraglutide). The other 7 cases were non-serious cases and most cases had reported off-label use/ product administered to patients of inappropriate age, without any further events or cases with AEs which are part of the known safety profile of empagliflozin, without any specific trend.

Reviewer Comment: Among the serious postmarketing reports regarding off-label use of Jardiance and Synjardy in pediatric patients, there appear to have been several events of DKA occurring in pediatric subjects who had type 1 diabetes or likely had type 1 diabetes (based on age < 10 years and concomitant treatment with insulin). The risk of ketoacidosis in patients with type 1 diabetes who are treated with empagliflozin is described in the product label; information regarding this risk in Section 5 has been recently revised and these changes have been incorporated into the labels for Jardiance, Synjardy and Synjardy XR.

8.9.2. Expectations on Safety in the Postmarket Setting

The postmarket safety of empagliflozin in pediatric patients is expected to be no worse than what is currently labeled. As discussed in Sections 6.1.1 and 7.2.1, the DINAMO study did not enroll subjects with eGFR < 60 mL/min/1.73m^2, and the occurrence of renal impairment relating to diabetic nephropathy is likely to be infrequent in pediatric T2D patients < 18 years. In the postmarket setting, empagliflozin may be used for glycemic control in pediatric T2D patients with concomitant CKD, or by pediatric patients with diabetes relating to treatment of CKD (e.g., steroid-induced or renal-transplantation-related diabetes). Based on adult studies of empagliflozin, there appears to be an increased risk for adverse reactions such as volume depletion-related AEs, urinary tract infections and acute changes in renal function in patients with worse renal function; these risks are currently described in the product label and as discussed earlier (see Section 7.2.1) the overall benefit risk assessment was considered favorable for use for glycemic control in adult patients with eGFR$\geq$30 mL/min/1.73m^2.

According to the primary clinical pharmacology review at the time of the Jardiance approval, there was also a concern for higher susceptibility for hypoglycemia among patients with moderate or severe renal impairment[45] though it is unclear whether this risk was also related to higher use of concomitant insulin in this subgroup. The product label currently details an increased risk of hypoglycemia with concomitant use of insulin and/or insulin secretagogues based on findings in adult studies. Based on the findings of this safety review, a higher risk of hypoglycemia was observed pediatric patients regardless of concomitant insulin use, which will be described in the product labeling.

8.9.3. Additional Safety Issues From Other Disciplines

No additional safety issues were identified from other disciplines.

8.10. Integrated Assessment of Safety

The risks of empagliflozin in adults with T2D are well characterized, and include diabetic ketoacidosis, volume depletion, hypoglycemia with concomitant use of insulin and/or sulfonylureas, infections (including urinary tract infections, genital mycotic infections and necrotizing fasciitis) and hypersensitivity reactions.

In the DINAMO study, the overall safety profile of empagliflozin was generally similar to the known and labeled risks in adults with T2D with the exception of hypoglycemia.

In adult studies of empagliflozin therapy, the risk of hypoglycemia was higher only with concomitant use of insulin and/or sulfonylureas. In the DINAMO study, the risk of hypoglycemia was higher in pediatric subjects treated with empagliflozin regardless of concomitant insulin use. Among subjects on background insulin, Level 2 hypoglycemia (blood glucose < 54 mg/dL), occurred in 6 out of 25 subjects (24%) treated with empagliflozin and in 3 out of 21 subjects (14.3%) treated with placebo. Among subjects not on background insulin, Level 2 hypoglycemia occurred in 4 out of 27 subjects (14.8%) treated with empagliflozin and in 1 out of 32 subjects (3.1%) treated with placebo. Overall, Level 2 hypoglycemia occurred in 10 out of 52 (19.2%) of subjects treated with empagliflozin and in 4 out of 52 (7.5%) of subjects treated with placebo. No severe hypoglycemia events occurred. Although the overall numbers of subjects experiencing hypoglycemic events in the DINAMO study were small, based on several exploratory analyses conducted as part of the safety review and by the statistical review team, I believe the evidence suggests an overall higher risk of hypoglycemia in pediatric subjects as compared to adult subjects, including evidence of an increased risk in pediatric subjects who are not treated with background insulin.

The reason for the increased risk in hypoglycemia in subjects who are not receiving background insulin is unclear. However, a similar safety finding was also observed in the pediatric study for

[45] See Figure 4 of the primary clinical pharmacology review by Dr. Manoj Khurana under NDA 204629

liraglutide; this led to changes in the product label to describe the increased risk of hypoglycemia in pediatric subjects regardless of concomitant insulin use in the Warnings and Precautions section. Notably, this finding was not observed in the pediatric trials for extended-release exenatide or dulaglutide; however, the overall occurrence of hypoglycemia was generally lower in those trials.

No deaths occurred in the study. SAEs and AESIs were consistent with known safety issues of empagliflozin that are already described in the product label. During the placebo-controlled period, SAEs occurred in 2 (3.8%) of subjects treated with empagliflozin and in 2 (3.8%) of subjects treated with placebo; during the safety extension period SAEs occurred in 1 subject (2.1%) treated with empagliflozin 10 mg and in no subjects treated with empagliflozin 25 mg. Based on a review of subject narratives, SAEs of skin candida (involving the groin) and tubulointerstitial nephritis were likely related to empagliflozin treatment. Compared to placebo, a higher proportion of AEs relating to genital mycotic injections, urinary tract infections, and hypersensitivity reactions occurred with empagliflozin treatment. No AESIs of decreased renal function or diabetic ketoacidosis occurred in any subjects treated with empagliflozin. Two (2) events involving increased ketones in subjects treated with empagliflozin were referred to the CEC for adjudication; neither were confirmed as being confirmed ketoacidosis events. No events involving bone fracture, acute pancreatitis or lower limb amputation occurred in the study. Common TEAEs appeared generally consistent with the reported safety profile of empagliflozin in adults. With respect to laboratory parameters, small decreases in eGFR (mean change of 2.15 mL/min/1.72 m3 from baseline to week 26) and small increases in hematocrit (mean change of 1.8% from baseline to week 26) were noted in pediatric subjects, similar to findings previously described in adults. No clinically significant changes in heart rate or blood pressure were noted. Conclusions regarding the impact of empagliflozin on pubertal progression and growth were limited due to small number of subjects in early stages of pubertal development, absence of relevant information regarding mid-parental target height and pre-study growth pattern, and possible misclassification of Tanner stage. Based on limited data obtained during the safety extension period, there was no evidence of any increased safety risk associated with empagliflozin 25 mg versus 10 mg.

Based on the submitted data from the DINAMO study, apart from an increased risk of hypoglycemia in pediatric T2D subjects treated with empagliflozin regardless of concomitant insulin use, no new safety signals were identified in pediatric T2D subjects as compared to those described in adult studies. The safety risks identified in adult studies of empagliflozin are described in the current product labeling and may be managed and mitigated in clinical practice; the risk of hypoglycemia pediatric T2D subjects regardless of concomitant insulin therapy will be added to product labeling along with instructions for mitigating this risk (i.e., considering reductions in the insulin dose, and educating patients or caregivers on the signs and symptoms of hypoglycemia).

9. Advisory Committee Meeting and Other External Consultations

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

10. Labeling Recommendations

10.1. Prescription Drug Labeling

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

Section 1
- The glycemic control indication was expanded to include adult and pediatric patients aged 10 years and older with type 2 diabetes.

Section 2 (Dosage and Administration)
- Use for glycemic control is not recommended in adults and pediatric patients with eGFR less than 30 mL/min/1.72m^2
- The recommended dosage of empagliflozin in pediatric patients aged 10 years and older for glycemic control is 10 mg orally once daily in the morning, taken with or without food. For additional glycemic control, may increase to 25 mg orally once daily in patients tolerating 10 mg once daily.
- Recommendations regarding missed dose were added (if a dose is missed, instruct patients to administer the dose as soon as possible, do not double up on the next dose).

Section 5.4:
- Revision to describe the risk of hypoglycemia as being higher in pediatric patients regardless of concomitant insulin use, and to incorporate mitigating strategies including a reduction in the dose of insulin and to inform pediatric patients regarding the risk of hypoglycemia and educate them on the signs and symptoms of hypoglycemia.

Section 6.0
- Description of safety findings in the DINAMO study including demographics and baseline characteristics of the study population, and rates of hypoglycemia events.

Section 8.4 (pediatric use)
- Description of the DINAMO study with cross references to relevant sections.

Section 8.6 (renal impairment)

- A statement was added to indicate that pediatric patients with eGFR less than 60 mL/min/1.73m2 were not studied.

Section 12.3

- Revision to describe similar exposures of empagliflozin in pediatric patients versus adults.

Section 14.2

- Description of the primary efficacy results of the DINAMO study.

A labeling review conducted by the Division of Medication Error Prevention and Analysis 1 (DMEPA 1) did not identify areas of vulnerability [46]that may lead to medication errors.

10.2. Nonprescription Drug Labeling

This section is not applicable to this application.

11. Risk Evaluation and Mitigation Strategies (REMS)

No REMS are recommended.

12. Postmarketing Requirements and Commitments

No postmarketing requirements or commitments are applicable to this supplement.

13. Appendices

13.1. References

See references at the end of this document.

[46] See labeling review submitted on 4/24/2023 under NDA 204629

13.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): 1218-0091

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 437		
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): 1		
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: 0 Significant payments of other sorts: 1 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Sponsor of covered study: 0		
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) 21		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

13.3. Safety Analyses by Demographic Subgroups

Table 63: Summary of TEAEs by SOC in Subjects of Hispanic or Latino Ethnicity, occurring in > 1 Subject Treated with Empagliflozin and with Risk Difference > 1% through Week 26

System Organ Class	Empagliflozin Pooled Hispanic Latino (N=17) n (%)	placebo-Hispanic Latino (N=21) n (%)	Risk Difference RD (95% CI)	Forest Plot
Gastrointestinal disorders	7 (41.2)	4 (19.0)	22.13 (-6.67, 50.93)	
General disorders and administration site conditions	3 (17.6)	0 (0.0)	17.65 (-0.47, 35.77)	
Infections and infestations	9 (52.9)	10 (47.6)	5.32 (-26.60, 37.25)	
Investigations	3 (17.6)	2 (9.5)	8.12 (-13.92, 30.17)	
Metabolism and nutrition disorders	5 (29.4)	4 (19.0)	10.36 (-17.04, 37.77)	
Musculoskeletal and connective tissue disorders	2 (11.8)	0 (0.0)	11.76 (-3.55, 27.08)	
Nervous system disorders	9 (52.9)	4 (19.0)	33.89 (4.82, 62.96)	
Psychiatric disorders	2 (11.8)	0 (0.0)	11.76 (-3.55, 27.08)	
Reproductive system and breast disorders	3 (17.6)	0 (0.0)	17.65 (-0.47, 35.77)	
Respiratory, thoracic and mediastinal disorders	4 (23.5)	1 (4.8)	18.77 (-3.36, 40.89)	
Skin and subcutaneous tissue disorders	4 (23.5)	0 (0.0)	23.53 (3.37, 43.69)	

Source: OCS Analysis Studio, Safety Explorer.
Filters: TRT01A = "E10" and ETHNIC = "HISPANIC OR LATINO" and TRTFL = "Y" (E10- Hispanic Latino); TRT01A = "Pbo" and ETHNIC = "HISPANIC OR LATINO" and TRTFL = "Y" (placebo- Hispanic Latino); TRTEMFL = "Y" (Adverse Events).
Percent Threshold: E10- Hispanic Latino ≥ 2%.
Risk Difference calculated by comparing the left column (Group 1) to the right column (Group 2).

Table 64: Summary of TEAEs by PT occurring in >1 Subject Treated with Empagliflozin of Hispanic or Latino Ethnicity and with Risk Difference > 1% through Week 26

Preferred Term	Empagliflozin Pooled Hispanic Latino (N=17) n (%)	Placebo-Hispanic Latino (N=21) n (%)	Risk Difference RD (95% CI)	Forest Plot
Cough	3 (17.6)	0 (0.0)	17.65 (-0.47, 35.77)	

Preferred Term	Empagliflozin Pooled Hispanic Latino (N=17) n (%)	Placebo-Hispanic Latino (N=21) n (%)	Risk Difference RD (95% CI)	Forest Plot
Dizziness	2 (11.8)	3 (14.3)	-2.52 (-23.94, 18.89)	
Dysmenorrhea	3 (17.6)	0 (0.0)	17.65 (-0.47, 35.77)	
Fatigue	2 (11.8)	0 (0.0)	11.76 (-3.55, 27.08)	
Headache	6 (35.3)	1 (4.8)	30.53 (6.06, 55.01)	
Hypoglycemia	2 (11.8)	0 (0.0)	11.76 (-3.55, 27.08)	
Nasal congestion	2 (11.8)	0 (0.0)	11.76 (-3.55, 27.08)	
Nausea	2 (11.8)	1 (4.8)	7.00 (-10.82, 24.82)	
Oropharyngeal pain	3 (17.6)	0 (0.0)	17.65 (-0.47, 35.77)	
Pain	2 (11.8)	0 (0.0)	11.76 (-3.55, 27.08)	
Rash	2 (11.8)	0 (0.0)	11.76 (-3.55, 27.08)	
Urinary tract infection	3 (17.6)	0 (0.0)	17.65 (-0.47, 35.77)	
Vomiting	2 (11.8)	0 (0.0)	11.76 (-3.55, 27.08)	

Source: OCS Analysis Studio, Safety Explorer.
Filters: TRT01A = "E10" and ETHNIC = "HISPANIC OR LATINO" and TRTFL = "Y" (E10- Hispanic Latino); TRT01A = "Pbo" and ETHNIC = "HISPANIC OR LATINO" and TRTFL = "Y" (placebo- Hispanic Latino); TRTEMFL = "Y" (Adverse Events).
Percent Threshold: E10- Hispanic Latino ≥ 2%.
Risk Difference calculated by comparing the left column (Group 1) to the right column (Group 2).

Table 65: Summary of TEAEs by SOC in Subjects of Non-White Race, occurring in >5% of Subjects Treated with Empagliflozin and Risk Difference > 1% through Week 26

System Organ Class	Empagliflozin Pooled-Non-White (N=29) n (%)	Placebo- Non-White (N=24) n (%)	Risk Difference RD (95% CI)	Forest Plot
Blood and lymphatic system disorders	2 (6.9)	1 (4.2)	2.73 (-9.48, 14.94)	
Gastrointestinal disorders	10 (34.5)	8 (33.3)	1.15 (-24.44, 26.74)	

System Organ Class	Empagliflozin Pooled- Non-White (N=29) n (%)	Placebo- Non-White (N=24) n (%)	Risk Difference RD (95% CI)	Forest Plot
Immune system disorders	3 (10.3)	0 (0.0)	10.34 (-0.74, 21.43)	
Infections and infestations	12 (41.4)	7 (29.2)	12.21 (-13.32, 37.75)	
Metabolism and nutrition disorders	14 (48.3)	9 (37.5)	10.78 (-15.79, 37.35)	
Nervous system disorders	9 (31.0)	7 (29.2)	1.87 (-22.92, 26.65)	
Skin and subcutaneous tissue disorders	4 (13.8)	1 (4.2)	9.63 (-5.25, 24.51)	

Source: OCS Analysis Studio, Safety Explorer.

Filters: TRT01A = "E10" and RACEGR3 = "Black or African American" or "American Indian or Alaska Native" or "Asian" or "All other respondents (Multiple/missing race respondent" or "Native Hawaiian or Other Pacific Islander" and TRTFL = "Y" (Empagliflozin Pooled- Non White); TRT01A = "Pbo" and RACEGR3 = "Black or African American" or "American Indian or Alaska Native" or "Asian" or "All other respondents (Multiple/missing race respondent" or "Native Hawaiian or Other Pacific Islander" and TRTFL = "Y" (Placebo- Non White); TRTEMFL = "Y" (Adverse Events).

Percent Threshold: Empagliflozin Pooled- Non-White ≥ 5%.

Risk Difference calculated by comparing the left column (Group 1) to the right column (Group 2).

Table 66: Summary of TEAEs by PT in Subjects of Non-White Race, occurring in > 5% of Subjects Treated with Empagliflozin and with Risk Difference > 1%, through Week 26

Preferred Term	Empagliflozin Pooled- Non-White (N=29) n (%)	Placebo- Non-White (N=23) n (%)	Risk Difference RD (95% CI)	Forest Plot
Dysmenorrhea	2 (6.9)	1 (4.3)	2.55 (-9.88, 14.98)	
Headache	8 (27.6)	5 (21.7)	5.85 (-17.58, 29.27)	
Hypertriglyceridemia	2 (6.9)	0 (0.0)	6.90 (-2.33, 16.12)	
Hypoglycemia	9 (31.0)	3 (13.0)	17.99 (-3.76, 39.74)	
Nausea	3 (10.3)	0 (0.0)	10.34 (-0.74, 21.43)	
Oropharyngeal pain	2 (6.9)	1 (4.3)	2.55 (-9.88, 14.98)	
Pyuria	2 (6.9)	0 (0.0)	6.90 (-2.33, 16.12)	
Rash	3 (10.3)	0 (0.0)	10.34 (-0.74, 21.43)	

Preferred Term	Empagliflozin Pooled- Non-White (N=29) n (%)	Placebo- Non-White (N=23) n (%)	Risk Difference RD (95% CI)	Forest Plot
Seasonal allergy	3 (10.3)	0 (0.0)	10.34 (-0.74, 21.43)	
Upper respiratory tract infection	4 (13.8)	0 (0.0)	13.79 (1.24, 26.34)	
Urinary tract infection	2 (6.9)	1 (4.3)	2.55 (-9.88, 14.98)	
Vitamin d deficiency	5 (17.2)	3 (13.0)	4.20 (-15.26, 23.65)	
Vomiting	3 (10.3)	2 (8.7)	1.65 (-14.33, 17.63)	

Source: OCS Analysis Studio, Safety Explorer.

Filters: TRT01A = "E10" and RACEGR3 = "Black or African American" or "American Indian or Alaska Native" or "Asian" or "All other respondents (Multiple/missing race respondent" or "Native Hawaiian or Other Pacific Islander" and TRTFL = "Y" (Empagliflozin Pooled- Non-White); TRT01A = "Pbo" and RACE = "BLACK OR AFRICAN AMERICAN" or "AMERICAN INDIAN OR ALASKA NATIVE" or "ASIAN" or "MULTIPLE" or "NATIVE HAWAIIAN OR OTHER PACIFIC ISLANDER" and TRTFL = "Y" (Placebo- Non-White); TRTEMFL = "Y" (Adverse Events).

Percent Threshold: Empagliflozin Pooled- Non-White ≥ 5%.

Risk Difference calculated by comparing the left column (Group 1) to the right column (Group 2).

Table 67: Summary of TEAEs by SOC in Male Subjects, for TEAEs occurring in > 1 Subject Treated with Empagliflozin and Risk Difference > 1% through Week 26

System Organ Class	Empagliflozin Pooled- Male (N=19) n (%)	Placebo- Male (N=19) n (%)	Risk Difference RD (95% CI)	Forest Plot
Gastrointestinal disorders	6 (31.6)	6 (31.6)	0.00 (-29.56, 29.56)	
General disorders and administration site conditions	2 (10.5)	1 (5.3)	5.26 (-11.80, 22.33)	
Immune system disorders	4 (21.1)	0 (0.0)	21.05 (2.72, 39.38)	
Metabolism and nutrition disorders	8 (42.1)	7 (36.8)	5.26 (-25.77, 36.30)	
Psychiatric disorders	2 (10.5)	1 (5.3)	5.26 (-11.80, 22.33)	
Renal and urinary disorders	2 (10.5)	1 (5.3)	5.26 (-11.80, 22.33)	
Skin and subcutaneous tissue disorders	2 (10.5)	1 (5.3)	5.26 (-11.80, 22.33)	

Source: OCS Analysis Studio, Safety Explorer.

Filters: TRT01A = "E10" and SEX = "M" and TRTFL = "Y" (Empagliflozin Pooled- Male); TRT01A = "Pbo" and SEX = "M" and TRTFL = "Y" (Placebo- Male); TRTEMFL = "Y" (Adverse Events).

Percent Threshold: Empagliflozin Pooled- Male ≥ 5%.

Risk Difference calculated by comparing the left column (Group 1) to the right column (Group 2).

Table 68: Summary of TEAEs in Male Subjects, for TEAEs occurring in > 1 Subject Treated with Empagliflozin and Risk Difference > 1%, through Week 26

Preferred Term	Empagliflozin Pooled- Male (N=19) n (%)	Placebo- Male (N=19) n (%)	Risk Difference RD (95% CI)	Forest Plot
Hypoglycemia	5 (26.3)	1 (5.3)	21.05 (-1.15, 43.25)	
Seasonal allergy	4 (21.1)	0 (0.0)	21.05 (2.72, 39.38)	

Source: OCS Analysis Studio, Safety Explorer.
Filters: TRT01A = "E10" and SEX = "M" and TRTFL = "Y" (Empagliflozin Pooled- Male); TRT01A = "Pbo" and SEX = "M" and TRTFL = "Y" (Placebo-Male); TRTEMFL = "Y" (Adverse Events).
Percent Threshold: Empagliflozin Pooled- Male ≥ 10%.
Risk Difference calculated by comparing the left column (Group 1) to the right column (Group 2).

Table 69: Summary of TEAEs by SOC in Subjects < 15 years of Age, for TEAEs occurring in > 5% of Subjects Treated with Empagliflozin and with Risk Difference > 1%, through Week 26

System Organ Class	Empagliflozin Pooled- Age < 15 years (N=25) n (%)	Placebo- Age < 15 years (N=26) n (%)	Risk Difference RD (95% CI)	Forest Plot
Blood and lymphatic system disorders	2 (8.0)	1 (3.8)	4.15 (-8.80, 17.11)	
Gastrointestinal disorders	9 (36.0)	7 (26.9)	9.08 (-16.31, 34.47)	
Immune system disorders	2 (8.0)	0 (0.0)	8.00 (-2.63, 18.63)	
Metabolism and nutrition disorders	12 (48.0)	6 (23.1)	24.92 (-0.49, 50.34)	
Musculoskeletal and connective tissue disorders	3 (12.0)	2 (7.7)	4.31 (-12.04, 20.65)	
Nervous system disorders	7 (28.0)	3 (11.5)	16.46 (-5.00, 37.92)	
Reproductive system and breast disorders	2 (8.0)	0 (0.0)	8.00 (-2.63, 18.63)	
Skin and subcutaneous tissue disorders	3 (12.0)	0 (0.0)	12.00 (-0.74, 24.74)	
Vascular disorders	2 (8.0)	1 (3.8)	4.15 (-8.80, 17.11)	

Source: OCS Analysis Studio, Safety Explorer.

System Organ Class	Empagliflozin Pooled- Age < 15 years (N=25) n (%)	Placebo- Age < 15 years (N=26) n (%)	Risk Difference RD (95% CI)	Forest Plot

Filters: TRT01A = "E10" and AGEGR1 = "<15" and TRTFL = "Y" (Empagliflozin Pooled- Age < 15 years); TRT01A = "Pbo" and AGEGR1 = "<15" and TRTFL = "Y" (Placebo- Age < 15 years); TRTEMFL = "Y" (Adverse Events).
Percent Threshold: Empagliflozin Pooled- Age < 15 years ≥ 5%.
Risk Difference calculated by comparing the left column (Group 1) to the right column (Group 2).

Table 70: Summary of TEAEs by PT in Subjects < 15 years of Age, for TEAEs occurring in > 5% of Subjects Treated with Empagliflozin and with Risk Difference > 1%, through Week 26

Preferred Term	Empagliflozin Pooled- Age < 15 years (N=25) n (%)	Placebo- Age < 15 years (N=26) n (%)	Risk Difference RD (95% CI)	Forest Plot
Acne	2 (8.0)	0 (0.0)	8.00 (-2.63, 18.63)	
Blood ketone body increased	3 (12.0)	2 (7.7)	4.31 (-12.04, 20.65)	
Dysmenorrhea	2 (8.0)	0 (0.0)	8.00 (-2.63, 18.63)	
Headache	6 (24.0)	2 (7.7)	16.31 (-3.32, 35.93)	
Hypertriglyceridemia	2 (8.0)	0 (0.0)	8.00 (-2.63, 18.63)	
Hypoglycemia	6 (24.0)	4 (15.4)	8.62 (-13.12, 30.36)	
Nausea	2 (8.0)	0 (0.0)	8.00 (-2.63, 18.63)	
Neck pain	2 (8.0)	0 (0.0)	8.00 (-2.63, 18.63)	
Pyuria	2 (8.0)	0 (0.0)	8.00 (-2.63, 18.63)	
Seasonal allergy	2 (8.0)	0 (0.0)	8.00 (-2.63, 18.63)	
Upper respiratory tract infection	2 (8.0)	0 (0.0)	8.00 (-2.63, 18.63)	
Urinary tract infection	3 (12.0)	1 (3.8)	8.15 (-6.57, 22.88)	
Vitamin d deficiency	4 (16.0)	1 (3.8)	12.15 (-4.01, 28.31)	

Source: OCS Analysis Studio, Safety Explorer.
Filters: TRT01A = "E10" and AGEGR1 = "<15" and TRTFL = "Y" (Empagliflozin Pooled- Age < 15 years); TRT01A = "Pbo" and AGEGR1 = "<15" and TRTFL = "Y" (Placebo- Age < 15 years); TRTEMFL = "Y" (Adverse Events).
Percent Threshold: Empagliflozin Pooled- Age < 15 years ≥ 5%.
Risk Difference calculated by comparing the left column (Group 1) to the right column (Group 2).

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