CLINICAL REVIEW

Application Type	Supplemental NDA
Application Number(s)	NDA 201280/S-027, NDA 201281/S-035, 208206/S-024
Priority or Standard	Priority
Submit Date(s)	December 20, 2022 (NDA 201280/S-027 Tradjenta) January 31, 2023 (NDA 201281/S-035 Jentadueto) April 25, 2023 (NDA 208026/S-024 Jentadueto 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	Linagliptin, linagliptin and metformin hydrochloride, linagliptin and metformin hydrochloride extended-release
(Proposed) Trade Name	Tradjenta, Jentadueto, Jentadueto XR
Applicant	Boehringer Ingelheim Pharmaceuticals, Inc
Dosage Form(s)	tablet
Applicant Proposed Dosing Regimen(s)	Tradjenta: 5 mg once daily Jentadueto: twice daily, not to exceed 2.5 mg linagliptin/1000 mg metformin hydrochloride twice daily. Jentadueto XR: once daily, not to exceed 5 mg linagliptin/2000 mg metformin hydrochloride extended-release once daily.
Applicant Proposed Indication(s)/Population(s)	Not Applicable
Recommendation on Regulatory Action	Approval; PMR 3300-1 Fulfilled; grant pediatric exclusivity
Recommended Indication(s)/Population(s) (if applicable)	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

Linagliptin is a dipeptidyl-peptidase-4 (DPP-4) inhibitor. DPP-4 inhibitors lower blood glucose in adults with type 2 diabetes (T2D) by preventing the enzymatic breakdown of the incretin hormones, glucagon-like peptide-1 (GLP-1) and gastric inhibitory polypeptide (GIP), leading to enhancement of incretin-stimulated insulin-release and glucagon suppression. Linagliptin is available as Tradjenta tablets (linagliptin, NDA 201280), Jentadueto tablets (linagliptin and metformin hydrochloride, NDA 201281) and Jentadueto XR tablets (linagliptin and metformin hydrochloride extended-release, NDA 208206)[1]. These products are indicated as an adjunct to diet and exercise to improve glycemic control in adults with T2D. 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 linagliptin for the glycemic control indication in pediatric patients aged 10 years and older with type 2 diabetes. Based on the results of the DINAMO study in which the effectiveness of linagliptin was not demonstrated, the Applicant is not requesting an expansion of the glycemic control indication for Tradjenta, Jentadueto or Jentadueto XR to pediatric patients aged 10 years and older. However, the Applicant has submitted proposed updates to the U.S. Prescribing Information (USPI) for Tradjenta, Jentadueto or Jentadueto XR to describe the pediatric study results and to fulfill the requirements under PREA.

1.2. Conclusions on the Substantial Evidence of Effectiveness

Effectiveness of linagliptin to improve glycemic control in pediatric patients with T2D was not established in an adequate and well-controlled study. After 26 weeks, treatment with linagliptin did not demonstrate significant improvement in hemoglobin A1c (HbA1c) compared to placebo [placebo-adjusted treatment difference -0.34% (95% CI -0.99 to 0.30; p=0.2935).

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 linagliptin and linagliptin and metformin hydrochloride, effective June 9, 2023, under section

[1] Linagliptin 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.

505A of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355a).

1.3. Benefit-Risk Assessment

APPEARS THIS WAY ON ORIGINAL

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[13]. 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 Tradjenta (linagliptin), Jentadueto (fixed dose combination product of linagliptin and metformin immediate release) and Jentadueto XR (fixed dose combination product of linagliptin and metformin extended release) proposing updates to the U.S. Prescribing Information (USPI) to describe the results of a single adequate and well-controlled pediatric phase 3 study, "DINAMO" (Study 1218.91). 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), 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)]. Treatment with 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)]. Subgroup analyses for age, sex, BMI, race, geographical region and background antidiabetic therapy were generally consistent with the overall study population. As agreed to under the pediatric Written Request, the Applicant also conducted supplementary Bayesian borrowing analyses using two models, a pharmacometrics-based

model derived from all the previously conducted adult studies for each treatment, and a model based on the available pediatric studies for products with the same mechanism of action (i.e., another dipeptidyl peptidase-4 (DPP-4) inhibitor). For the pharmacometrics-based model for linagliptin, there was a sizable difference between the model predicted effect and the observed effect in pediatrics (-0.64% predicted vs -0.34% observed) raising concerns about the use of this model. The model for linagliptin based pediatric studies of another DPP-4 inhibitor failed to reach the agreed decision threshold even with full pooling with the borrowed data.

No clinically meaningful changes were seen in exploratory analyses of key secondary endpoints (including fasting plasma glucose, proportion of subjects achieving HbA1c thresholds, body weight, or blood pressure). The mean HbA1c in subjects who received linagliptin rose by 0.8% above baseline by 52 weeks. Overall, these results suggest that although there may some pharmacologic effect in children, the response to linagliptin therapy is smaller in magnitude than the response in adults, and is not durable in pediatric patients with T2D.

The safety profile of linagliptin in pediatric subjects with T2D in the DINAMO study was similar to the known and labeled safety profile in adults with T2D. Serious adverse events (SAEs) occurred in 2 (3.8%) subjects treated with linagliptin during the placebo-controlled period and 6 (9.2%) subjects treated with linagliptin during the safety-extension period; none were assessed as treatment-related. All adverse events of special interest (AESIs) assessed as treatment-related reflect known and labeled safety issues in adults, and included hypersensitivity reactions and arthralgia. An increased risk of hypoglycemia was seen predominantly in subjects who received background insulin; consistent with the labeled safety profile of linagliptin in adults with T2D. No clinically significant changes in vital signs or laboratory studies were noted. The ability to draw conclusions regarding the impact of linagliptin 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.

In summary, the data submitted from the DINAMO study does not support the effectiveness of linagliptin in pediatric patients with T2D. These results are consistent with recently completed trials for other DPP-4 inhibitors (e.g., sitagliptin) in which pediatric efficacy was also not established. Differences in the demonstrated treatment response in adult and pediatric trials of linagliptin may reflect more rapid disease progression in the pediatric T2D study population.

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, 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). • 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 significant differences were seen in key secondary endpoints (fasting plasma glucose, proportion of subjects achieving HbA1c thresholds, body weight, or blood pressure) • Results of prespecified exploratory Bayesian analyses differed based	Linagliptin with or without baseline metformin and/or baseline insulin therapy was not superior to placebo for glycemic lowering at 26 weeks in pediatric patients with T2D. Differences between the pediatric and adult treatment response are likely due to more rapid disease progression in pediatric T2D subjects.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	on the models used. Results based on a pharmacometrics model that borrowed data from previously conducted studies of linagliptin in adults led to a sizable difference in the predicted effect (-0.64%) as compared to the observed effect (-0.34%), raising concerns regarding the use of this model. Results based on a model based on the pediatric study of another DPP-4 inhibitor failed to reach the agreed decision threshold even with full pooling with the borrowed data. • By 52 weeks, the mean HbA1c in subjects who received linagliptin rose by 0.8% above baseline.	
Risk and Risk Management	• No deaths occurred in the study • SAEs occurred in 3.8% of linagliptin-treated subjects; none were assessed as treatment-related. AESIs were consistent with the known safety profile in adults and included hypersensitivity reactions and arthralgia. • An increased risk of hypoglycemia was seen predominantly in linagliptin-treated subjects who received background insulin. No severe hypoglycemia events occurred. • No clinically significant changes in vital signs or laboratory studies were noted. • There were no detected differences in pubertal progression and growth between treatment arms; the study data were limited due to 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.	In the DINAMO study, the overall safety profile of linagliptin in pediatric T2D subjects was generally similar to the safety profile adults with T2D that is currently described in the USPI.

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[2]. 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)[3]. 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[4,5]. 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[6]. Data from the TODAY study also suggests that some youth with T2D may experience more rapid deterioration of β-cell function as compared to adults[7], while others may exhibit more durable glycemic control on metformin monotherapy[8]. The predictors of treatment response in pediatric T2D are not fully understood are 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[7,9,10].Diabetic ketoacidosis at the time of diagnosis of pediatric T2D also appears to predict greater β-cell decline over time[11].

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[12,13]. Compared to adults with T2D, diabetes-related complications appear early in youth with T2D and accumulate more rapidly. According to a longitudinal follow up study of youths with T2D[13], 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[13].

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[2]. 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, DPP-4 inhibitors, SGLT-2 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 in include any pediatric T2D efficacy trial data.

[2] 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. Warnings/Precautions: 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,	Common AEs: nausea, diarrhea, vomiting,

			Dosage: 2 mg once weekly	placebo-controlled trial in 82 pediatric T2D patients aged 10 to 17 years, estimated treatment difference in HbA1c reduction from baseline between bydureon and placebo was -0.71% (95% confidence interval of -1.42% to 0%, p<0.05)	constipation, headache, dyspepsia, injection-site nodule, injection site pruritis. Warnings/Precautions: thyroid C-cell tumors (contraindicated in patients with a personal or family history of MTC or MEN2), acute pancreatitis, acute kidney injury, gastrointestinal disease, hypersensitivity reactions, drug-induced immune mediated thrombocytopenia, serious injection site reactions, immunogenicity-associated decreased glycemic control, acute gallbladder disease, hypoglycemia with concomitant use of insulin secretagogues or insulin.
Trulicity (dulaglutide)	2022	Yes	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

Tradjenta tablets (linagliptin, NDA 201280) was approved on May 2, 2011 for the indication as an adjunct to diet and exercise and to improve glycemic control in adults with T2D. Fixed dose combination products with linagliptin and metformin hydrochloride (Jentadueto tablets, NDA 201281) and linagliptin and metformin hydrochloride extended release (Jentadueto XR tablets, NDA 208026) were subsequently approved on January 30, 2012 and May 27, 2016 respectively for the adult glycemic control indication in T2D. .

3.2. Summary of Presubmission/Submission Regulatory Activity

Regulatory History relating to PREA PMRs

- According to the approval letters for Tradjenta (NDA 201280), Jentadueto (NDA 201281) and Jentadueto XR (NDA 208026), the pediatric study requirement for ages 0 to 9 years (inclusive) was waived because necessary studies are impossible or highly impracticable due to too few children in this age range with T2D, and deferred pediatric clinical studies were required under the following Pediatric Research Equity Act (PREA) post-marketing requirements (PMRs):
    - PMR 1766-1: A randomized, placebo-controlled, dose-finding study under PREA evaluating at least two doses of linagliptin as monotherapy in pediatric patients ages 10 to 16 years (inclusive)
    - PMR 1766-2: Deferred randomized and controlled pediatric study under PREA to evaluate efficacy, safety and pharmacokinetics of linagliptin for the treatment of type 2 diabetes mellitus in pediatric patients ages 10 to 16 years (inclusive) as monotherapy and when added to metformin therapy.
- 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 August 31, 2016, the Applicant submitted the final report for study 1218.56, entitled "A randomized, double-blind, placebo-controlled parallel group dose-finding study of

linagliptin (1 mg or 5 mg administered orally once daily) over 12 weeks in children and adolescents from 10 to 17 years of age, with type 2 diabetes mellitus" to NDA 201280 (with cross referencing submissions to NDA 201281 and 208026). On July 18, 2017, the Agency considered PMR-1776-1 fulfilled.

- 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 (b) (4)
- 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.

<u>Regulatory History relating to labeling updates for Jentadueto XR:</u>

- On July 26, 2022, the Applicant proposed not to update the label for Jentadueto 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 Jentadueto 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 208026 (Jentadueto XR) to satisfy PREA PMR 3300-1.
- On April 4, 2023, the Agency updated prior advice regarding labeling updates for Jentadueto XR, noting that since Jentadueto 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. As such, the Agency requested that the Applicant submit an sNDA to NDA 208026 Jentadueto XR proposing updates to Section 8.4 of product labeling to describe the results of the pediatric study.

- On April 25, 2023, the Applicant submitted an sNDA for Jentadueto XR proposing updates to Section 8.4 of the product labeling to describe the results of the DINAMO study.

3.3. Foreign Regulatory Actions and Marketing History

As of May 2, 2022, Tradjenta is authorized for use in 103 countries, Jentadueto is authorized for use in 81 countries[3]. The three authorized doses for Jentadueto are 2.5 mg/500 mg, 2.5 mg/850 mg, and 2.5mg/1000mg (linagliptin/metformin HCl) twice daily with the exception of EU/EEA, Colombia, Dominican Republic, Jordan, Kazakhstan, Kuwait, Lebanon, Morocco, Myanmar, Nigeria, Oman, Pakistan, Qatar, Tunisia, Turkey and UAE, where only 2.5 mg/850 mg and 2.5 mg/1000 mg twice daily are approved. In Nepal, Taiwan and Uruguay only 2.5 mg/850 mg twice daily is approved. Jentadueto XR is only authorized for use in the United States.

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 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

[3] Periodic Benefit-Risk Evaluation Report, May 3, 2021 through May 2, 2022, submitted to NDAs for Tradjenta, Jentadueto and Jentadueto XR.

the clinical data submitted by the Applicant appear to be acceptable[4].

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 1218.56

Study 1218.56 was a phase 2b dose finding study comparing linagliptin 1 mg, linagliptin 5 mg and placebo in pediatric patients aged 10 to 17 years. Pediatric patients with inadequately controlled T2D (HbA1c >6.5% and ≤10.5%) on background treatment of diet and exercise, with or without metformin (≥1000 mg/day or maximally tolerated dose for 8 weeks prior to randomization), and with or without concomitant stable basal insulin therapy (total daily dose <0.5 U/kg) were enrolled. Eligible subjects were randomized 1:1:1 to 12-weeks treatment of linagliptin 1 mg, linagliptin 5 mg or placebo; randomization was stratified by gender, background therapy and pharmacokinetic (PK)/pharmacodynamic (PD) subgroup. The objective of the study was to identify the dose of linagliptin in pediatric T2D patients and to assess PK/PD. The primary endpoint was the change from baseline in HbA1c after 12 weeks of treatment; the key secondary endpoint was the PD endpoint DPP-4 inhibition at through at steady state. A pre-planned interim analysis of DPP-4 inhibition was performed by the data safety monitoring board (DSMB) to allow for early termination of a potentially ineffective dose of linagliptin 1 mg, and if superiority of the 5 mg dose was demonstrated on DPP-4 inhibition, to allow for early termination of the study.

A total of 83 subjects were screened, and 39 subjects were randomized to linagliptin 1 mg (N=10), linagliptin 5 mg (N=14) and placebo (N=15) once daily. 21 subjects (53.8%) were female, and the majority were White (59.0%). The mean age was 14.0 years, mean HbA1c was 7.86%. Almost all patients were obese or overweight. The majority (70.3%) were drug naïve at screening; all other subjects received metformin as background therapy and no subjects were

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

treated with insulin. 3 treated subjects prematurely discontinued the study medication; no discontinuations were due to an adverse event (AE).

At the time of the interim analysis, 38 subjects had been randomized and treated (linagliptin 1 mg: 10, linagliptin 5 mg: 12, placebo: 13) and 1 subject remained in the study. Based on the interim analysis, linagliptin 5 mg was superior to linagliptin 1 mg and the DSMB recommended early termination of the ineffective dose of linagliptin 1 mg. However, the Applicant subsequently decided to terminate the study.

As the study had originally been planned for a sample size of 117 subjects, there was inadequate statistical power to assess the primary endpoint. Based on the final analysis (including 39 subjects), after 12 weeks of randomized treatment, the adjusted mean change from baseline in HbA1c [%] was +0.45 (SE 0.31) in the placebo group, −0.03 (SE 0.38) in the linagliptin 1 mg group, and −0.19 (SE 0.30) in the linagliptin 5 mg group. The adjusted mean treatment difference for the change from baseline in HbA1c between linagliptin 5 mg and placebo was −0.63 (95% CI: −1.50, 0.23; p = 0.1447) and between linagliptin 1 mg and placebo was −0.48 (95% CI: −1.47, 0.51; p = 0.3295) (see Figure 1). The fasting plasma glucose change from baseline was 25.1 and -3.5 mg/dL following 1 mg and 5 mg.

In the linagliptin 5 mg group, median DPP-4 inhibition at trough at steady state was 78.9% (interquartile range [IQR] 67.7 to 84.0%), clearly higher than that for linagliptin 1 mg (median inhibition: 38.4% [IQR 26.9 to 48.8%]). With regard to PK, steady-state linagliptin trough levels in the linagliptin 5 mg group were higher than in the linagliptin 1 mg group (mean trough levels of 7.42 nmol/L and 3.80 nmol/L, respectively).

No serious AEs occurred in any subjects treated with linagliptin. Common AEs in subjects treated with linagliptin included nasopharyngitis, headache and hyperglycemia.

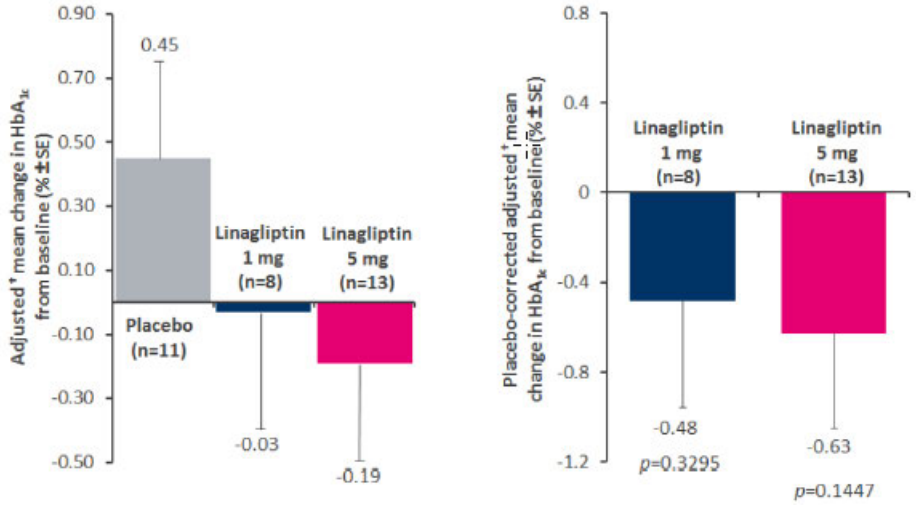
According to Dr. Chung's clinical pharmacology review,[5] although trough concentrations tended to be higher than those of adults, the overall range of linagliptin concentrations in pediatric subjects was comparable to those of adults, and DPP-4 inhibition was also comparable. Exploratory efficacy measures (HbA1c and fasting plasma glucose changes at week 12) also appeared comparable to adults following linagliptin 5 mg.

Reviewer Comment: The PK and PD of linagliptin 5 mg in pediatric subjects who participated in Study 1218.56 was generally comparable to that described in adults. In this phase 2 study, changes in HbA1c and fasting plasma glucose that were noted at week 12 were interpreted as suggesting "comparable" glycemic efficacy of linagliptin in adults and pediatric subjects; however, efficacy of linagliptin 5 mg in pediatric subjects was subsequently not established in the pivotal phase 3 study currently under review. The findings in study 1218.56 most likely represent the initial pharmacologic effect of linagliptin in pediatric subjects; a phenomenon that has occurred in other pediatric studies of DPP-4 inhibitors. In the sitagliptin pediatric

[5] See primary clinical pharmacology review by Dr. Chung, submitted on 1/5/2017 under NDA 201280.

study, a nominally significant treatment difference favoring sitagliptin over placebo was observed early after initiation of treatment; however, the magnitude of the treatment difference declined over time and was not statistically significant compared to placebo at the time of the primary outcome assessment 20 weeks.

Figure 1: Adjusted mean HbA1c (%) change from baseline to week 12, Study 1218.56



Source: Study 1218.56 CSR

PK data from Study 1218.91

Population PK Model: 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 linagliptin in children and adolescents with T2D observed in Study 1218.91 were generally comparable to those previously observed in adult T2D subjects. Results of the population PK analyses were also generally comparable to the results from the descriptive analysis.

Exposure-Response Analysis: The Applicant also conducted an exposure-response (E-R) analysis based on data from Study 1218.91 to assess the efficacy of linagliptin and patient/disease specific factors influencing efficacy in pediatric T2D subjects. The E-R analysis demonstrated that pediatric subjects requiring insulin had higher HbA1c at baseline as well as more pronounced disease progression, which resulted in a larger simulated magnitude of placebo-adjusted change in HbA1c in subjects requiring insulin. Compared to adults, pediatric T2D subjects had a smaller drug effect, but larger variability in response resulting in overlap with the response in adult subjects.

Reviewer Comment: Overall, the PK and exposure of linagliptin was comparable between pediatric and adult subjects. Based on the exposure-response analysis, pediatric T2D subjects

had a smaller drug effect as compared to adults, but a greater variability resulted in an overlap with adult response.

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 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 201280/S-027. The review of efficacy focused on the Applicant's analyses and confirmatory analyses conducted by the statistician, Dr. Wenda Tu.

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 also reviewed to evaluate for any differences in safety signals between subjects who received empagliflozin versus linagliptin. 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)

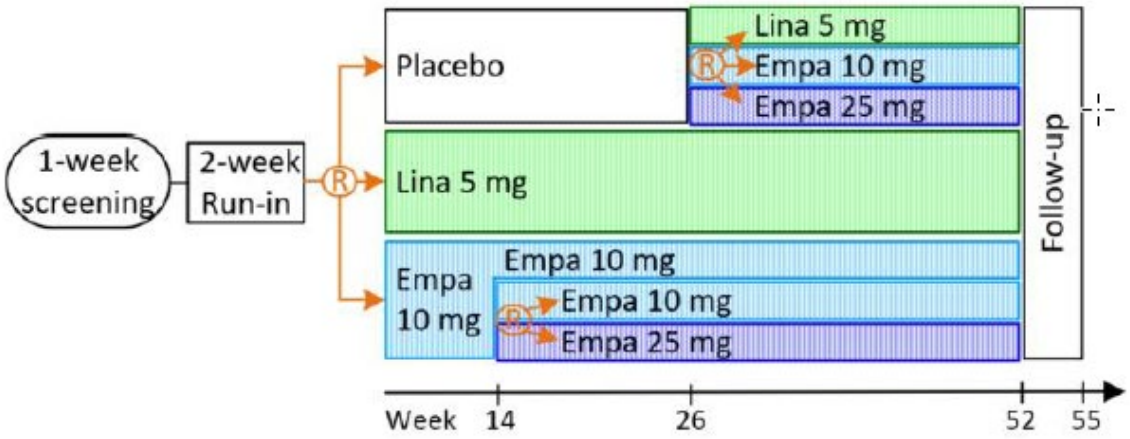
Primary Objective: The objective of DINAMO was to assess the efficacy and safety of 1 dose of linagliptin and an empagliflozin dosing regimen versus placebo after 26 weeks of treatment in children and adolescents with T2D treated with metformin and/or insulin or who were not tolerating metformin.

Study Design

The DINAMO study (Figure 2) was a randomized, placebo-controlled, double-blind, and parallel group study with 3 treatment arms (placebo, linagliptin 5 mg, empagliflozin) lasting 26 weeks in T2D subjects from 10 to ≤17 years of age who were treated with a background of metformin and/or insulin therapy. All subjects 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, subjects 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

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 subjects 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 2) appear adequate to maintain the double-blind condition.

Study 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, comprised of 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. Clinical research organizations (CROs) were used to provide study 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
- 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[6]) 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[7] 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) auto-antibodies
- 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)[8] < 60 ml/min/1.72 m^2

[6] 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.

[7] Non-fasting C-peptide was used for screening purposes, however fasting C-peptide was monitored as an exploratory efficacy endpoint.

[8] 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.

- 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)
- 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 trials of antihyperglycemic agents have employed a similar exclusion criterion. 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 subjects. Given that the occurrence of moderate to severe renal impairment in pediatric T2D subjects appears to be infrequent, 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 linagliptin and empagliflozin used in the DINAMO study were the same doses approved for use in adults with T2D.

The selection of the linagliptin 5 mg dose 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 Section 4.5)

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 subjects with T2D (see clinical review for NDA 204629/S-042).

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 below:

Table 2: Study Treatments in Study 1218.91

Treatment Groups	Study	Study Treatments (tablets)

	Weeks	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 week 26	X	X	X			
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: DINAMO 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[9]:

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)

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

Hypothesis Testing:

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

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.

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 subjects 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 subjects 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 $\geq$ 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 3.

Table 3: 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 subjects 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 subjects, possibility to replace subjects 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 subjects • 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 subjects 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 study 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 USA67 who received > $25,000 in payments from the Applicant for consulting services from June 6, 2017 through January 14, 2020. A total of 3 subjects were included in the safety population from study site USA67, including 1 subject who was randomized to placebo and 2 subjects who were randomized to empagliflozin. Among the measures taken to minimize the potential for bias, the Applicant has noted that randomization of subjects from this study site required approval from the clinical study manager, and that efficacy and safety data were reviewed by an independent data monitoring committee.

Reviewer Comment: Overall, the Applicant has adequately disclosed financial interests/arrangements with clinical investigators. With respect to the investigator at study site USA67 for whom FDA form 3455 was completed, given the relatively small proportion of subjects enrolled by this Investigator (3 out of 157 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 4**. 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 4: Subject Disposition in Study 1218.91

	Empagliflozin pooled n (%)[1]			Linagliptin 5 mg n (%)[1]	Placebo n (%)[1]	Total 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 generated 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:
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 linagliptin or empagliflozin.

Protocol Violations/Deviations

According to the TSAP, Protocol deviations (PDs) were defined as important if they affected the rights or safety or the study subjects, of if they could potentially influence the primary outcome measurement for the respective subjects 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 5. Overall, important protocol deviations occurred in 26.4% of subjects in the placebo arm and in 15.1% of subjects in the linagliptin 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). Relatively few important protocol deviations relating to the COVID-19 pandemic occurred.

Table 5: 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)
BMI out of range[10]	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 auto-antibodies*	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)

[10] 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, 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). See primary clinical review under NDA 204629/S-042 for further details regarding these subjects.

	Empagliflozin Pooled (N=52)	Linagliptin (N=53)	Placebo (N=53)	Total (N=158)
**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) auto-ant bodies 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.

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 6. 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 6: 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)
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				

	Empagliflozin (N=52)	Linagliptin (N=52)	Placebo (N=53)	Total (N=157)
>=-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 generated 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[11]. However, the racial/ethnic distributions of the study population may have also been influenced by enrollment of a third of subjects from non-US sites. In general, the vast majority (88.5%) of the study population had a BMI in the obese range.

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

Table 7 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 subjects (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 8). 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

[11] 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 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).

calculation)[12] 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.

Table 7: 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				

[12] 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.

	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)
>=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)
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 8: 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)

	Empagliflozin Pooled	Linagliptin	Placebo	Total

Source: Reviewer generated using 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 subjects with documented intolerance with 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 linagliptin in adults. This is consistent with published reports that 24 to 50% of pediatric subjects with T2D can experience hyperfiltration as a predictor of progressive diabetic kidney disease[13]. 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 2.1).

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 9) 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 subjects. Mean treatment compliance during the safety extension period (measured at weeks 30, 42 and 52) was 94.1% in subjects who received empagliflozin 10

[13] 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.

mg or 25 mg and 90.8% in subjects who received linagliptin.

Table 9: 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 generated using 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 Deviation.

· *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 7. Table 10 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[14].

Table 10: 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)

[14] 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).

	Empagliflozin Pooled (N=52)	Linagliptin (N=52)	Placebo (N=53)

Source: Reviewer generated using OCS Analysis Studio, Custom Table Tool. Columns - Dataset: Demographics; Filter: TRTFL = 'Y'. Subjects with New Antidiabetic 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[15] (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 subjects (11.3%) in the placebo group, 4 subjects (7.7%) in the linagliptin 5 mg group, and 5 subjects (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 10 above, or increase in insulin dose > 0.1 IU/kg for more than 21 days).

From week 26 to 52, 4 subjects (6.1%) in the linagliptin 5 mg group and 3 subjects (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 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 was 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 linagliptin versus placebo was not established, with a non-significant placebo-

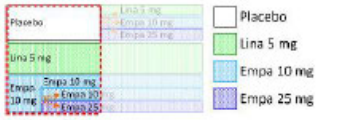
[15] Ergocalciferol, cholecalciferol and vitamin D not otherwise specified

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 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 Applicant's primary endpoint analysis for linagliptin was confirmed by the statistical review team (Dr. Tu), with no major statistical issues identified[16]. The overall missing data rate was 5.7% for linagliptin 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		Comparison vs placebo 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

Reviewer Comment: In linagliptin treated subjects, a non-significant numeric treatment difference of -0.34% change in HbA1c compared to placebo was observed. However, this treatment difference was primarily driven by worsening glycemic control in subjects in the placebo arm, who experienced an 0.68% increase in HbA1c from baseline by week 26. Subjects in the linagliptin arm also experienced an increase in HbA1c from baseline to week 26, but to a lesser degree (+0.33%).

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 11). This analysis confirmed the results of the primary efficacy analysis.

[16] See primary statistical review by Dr. Wenda Tu under NDA 201280/S-027

Table 11: HbA1c Change from Baseline at Week 26, Sensitivity Analysis to Primary Analysis

	Lina 5mg N=52	Placebo N=53
Baseline, mean (SD)	8.05 (1.11)	8.05 (1.23)
Change from baseline, LSMean[1] (SE)	0.28 (0.23)	0.66 (0.22)
Difference from Placebo, LSMean[1] (CI)	-0.36 (-0.99, 0.27)	
Two-sided p-value (unadjusted)	0.26	

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; adsl.xpt, adhba1c.xpt

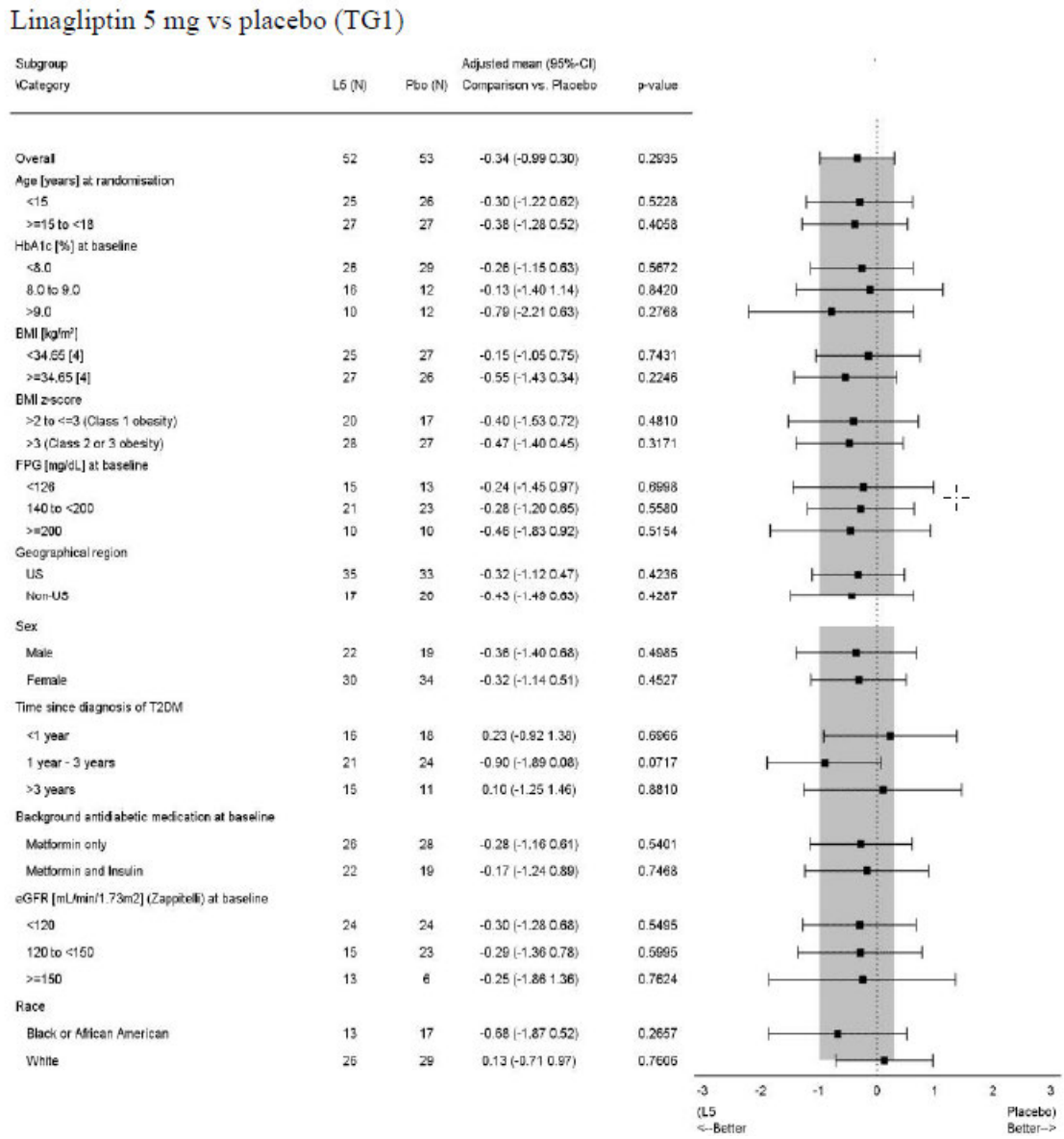
The Applicant's secondary hypothesis testing for the primary endpoint comparing empagliflozin subgroups versus placebo (TG2 and TG3) is not discussed here (see clinical review for NDA 204629/S-042 for details).

Subgroup Analyses for the Primary Efficacy Endpoint

The Applicant's primary analysis results were consistent across all subgroups (Figure 4), including age at randomization (<15 years, ≥15 years), baseline HbA1c (<8.0%, 8.0 to 9.0%, > 9%), BMI (≤34.65 kg/m^2, >34.65 kg/m^2), 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[17] (<120, 120 to < 150, >150 mL/min/1.73m^2) and race (Black or African American, White).

[17] For subgroup analyses, the Applicant used eGFR calculated by the Zappitelli equation as follows: eGFR (mL/min/1.73m²) = (507.76 x e0.003xheight) / (Cystatin C0.635xSerum Creatinine0.547 [µmol/L]), with height in cm, Cystatin C in mg/L and Serum Creatinine in µmol/L.

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



Dr. Tu also conducted subgroup analyses for the primary efficacy endpoint for the linagliptin 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 linagliptin and placebo arms[18].

Reviewer Comment: Results from sensitivity analyses and subgroup analyses of the primary endpoint were consistent with the results of the primary efficacy analysis.

Data Quality and Integrity

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

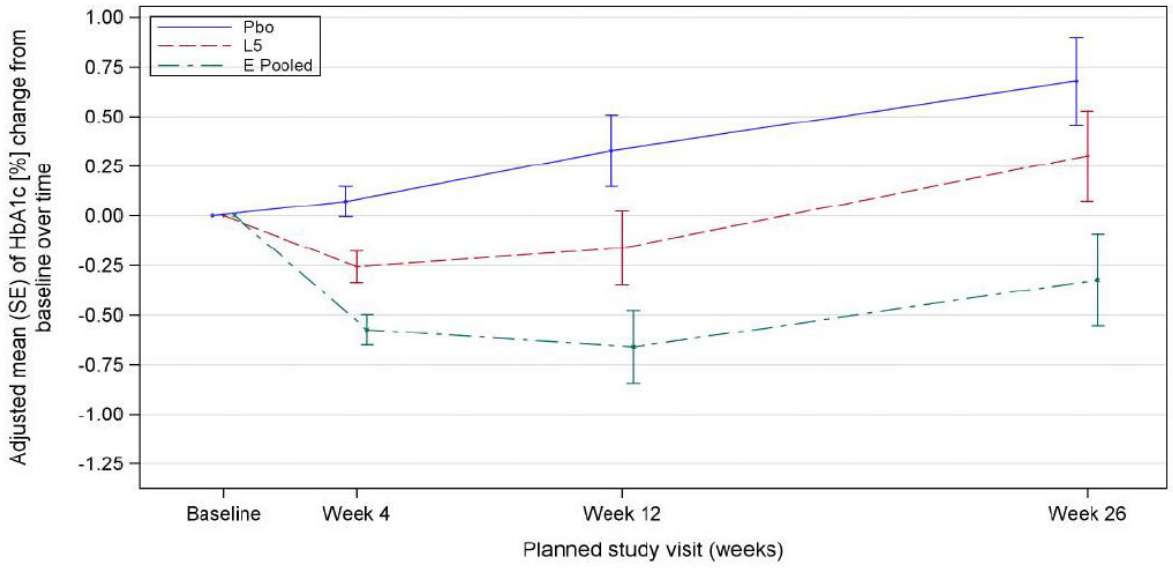
Efficacy Results – Secondary and other relevant endpoints

Based on the Applicant's MMRM analysis (

Table **12**, Figure 5), mean HbA1c in the linagliptin group dropped 0.26% below baseline at week 4, remained 0.16% below baseline at week 4, and then rose above baseline by 0.30% by week 26. In contrast, subjects in the placebo arm experienced a gradual rise in HbA1c above baseline throughout the study, reaching 0.68% above baseline by week 26.

[18] See Section 4.1 and Figure 8 of Dr. Tu's Primary Statistical Review

Figure 5: HbA1c (%) change from baseline, MMRM, through Week 26- mITT, Study 1218.91



Number of patients				
Pbo	52	50	52	50
L5	50	48	49	49
E Pooled	51	50	48	47

Pbo = Placebo, L5 = Linagliptin 5 mg, E Pooled = Empagliflozin pooled.
LS Mean +/- SE, adjusted for categorical age, treatment, visit, treatment-by-visit interaction, baseline HbA1c and baseline HbA1c-by-visit interaction.

Source: DINAMO CSR, Figure 15.2.1.2.1:1

Table 12: HbA1c (%) change from baseline, MMRM, through Week 26- mITT, Study 1218.91

Timepoint/ Treatment	Number analysed	Unadjusted [1] Mean	SD	Change from baseline adjusted [2] Mean	SE	95% confidence interval Lower	Upper	Comparison vs Placebo [2] Adjusted mean	SE	95% confidence interval Lower	Upper	p-value
Baseline												
Pbo	52	8.07	1.23									
L5	50	8.06	1.13									
E Pooled	51	7.95	1.25									
Week 4												
Pbo	50	8.17	1.56	0.07	0.08	-0.08	0.22					
L5	48	7.83	1.37	-0.26	0.08	-0.41	-0.10	-0.33	0.11	-0.55	-0.11	0.0030
E Pooled	50	7.39	1.05	-0.57	0.08	-0.73	-0.42	-0.65	0.11	-0.86	-0.43	<.0001
Week 12												
Pbo	52	8.40	1.96	0.33	0.18	-0.03	0.69					
L5	49	7.92	1.68	-0.16	0.18	-0.53	0.20	-0.49	0.26	-1.00	0.02	0.0576
E Pooled	48	7.24	1.50	-0.66	0.18	-1.03	-0.30	-0.99	0.26	-1.50	-0.48	0.0002
Week 26												
Pbo	50	8.77	2.41	0.68	0.22	0.23	1.12					
L5	49	8.33	1.79	0.30	0.23	-0.15	0.75	-0.38	0.32	-1.00	0.25	0.2409
E Pooled	47	7.58	1.69	-0.32	0.23	-0.78	0.13	-1.00	0.32	-1.63	-0.37	0.0022

Source: DINAMO CSR, Table 15.2.1.2.1: 1

Reviewer Comment: In Study 1218.91, there appears to have been an initial weak pharmacologic effect of linagliptin leading to a decline in HbA1c compared to baseline that was evident by week 4. However, HbA1c subsequently increased above baseline by week 26

in linagliptin-treated subjects. In contrast, subjects in the placebo arm experienced progressive rise in HbA1c from baseline throughout all study weeks. For linagliptin-treated subjects, the magnitude of the placebo-adjusted treatment was greatest at week 12 (-0.49%) but eventually declined by week 26 as the HbA1c rose above baseline in these subjects.

Similar findings were observed in the pediatric trial of sitagliptin, in which small reductions in HbA1c as compared to placebo were observed early on (by week 6 to 8) but diminished over time. These results support the conclusion that the two members of the DPP-4 inhibitor class for which pediatric trial data are available have demonstrated a weak treatment effect in pediatric T2D patients that is not durable, likely due rapid progression of underlying disease.

Given these findings, the failure to demonstrate superiority of linagliptin to placebo is most likely the result of inadequate efficacy; rather than insufficient sample size.

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 13. Overall, a small and non-significant reduction in fasting plasma glucose (-5.4 mg/dL) was observed with linagliptin as compared to placebo. No clinically meaningful changes in body weight or blood pressure occurred.

Table 13: Secondary endpoints based on FPG, body weight, SBP and DBP: change from baseline at Week 26- mITT, Study 1218.91

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				
Lina 5	51	162.81	56.01	10.29	−6.12	26.69	−5.41	−28.49	17.67	0.6438
Body weight [kg], MMRM (OC-AD)										
Placebo	52	98.87	29.62	−0.04	−1.40	1.32				
Lina 5	50	102.73	26.81	1.42	0.04	2.81	1.46	−0.48	3.41	0.1394
Systolic blood pressure (SBP) [mmHg], MMRM (OC-AD)										
Placebo	52	118.34	11.87	1.30	−1.01	3.61				
Lina 5	50	122.39	11.13	2.21	−0.14	4.56	0.91	−2.40	4.22	0.5870
Diastolic blood pressure (DBP) [mmHg], MMRM (OC-AD)										
Placebo	52	72.60	8.94	0.76	−1.01	2.53				
Lina 5	50	74.01	8.13	2.26	0.46	4.05	1.50	−1.03	4.02	0.2433

Although not shown in this table, the empagliflozin pooled group was included in the models.

Source: DINAMO CSR, Table 15.2.2:1 to 4

Other endpoints relating to HbA1c response:

Numerically greater number of subjects in the linagliptin arm achieved HbA1c <6.5% as

compared to placebo; however, the responder rate was similar for HbA1c < 7.0%.

Table 14: Secondary endpoints based on HbA1c responders at the end of 26 weeks- mITT, Study 1218.91

Treatment (TG1)	N analysed	Responder		Comparison vs placebo			
		n	%	Rate difference	95% CI		Nominal p-value
HbA_{1c} <6.5%							
Placebo	53	5	9.4				
Lina 5	52	8	15.4	6.0	−7.7	19.9	0.3536
HbA_{1c} <7.0%							
Placebo	53	13	24.5				
Lina 5	52	14	26.9	2.4	−15.2	19.5	0.7789

Source: DINAMO CSR, Tables 15.2.2:5 and 6

Reviewer Comment:

The overall trends based on the secondary endpoints (i.e., FPG, HbA1c responders) are generally consistent with the primary efficacy analysis and suggestive of a weak glycemic effect that was not sustained.

Dose/Dose Response

Only a single dose of linagliptin (5 mg) was evaluated in the DINAMO study. Results of the dose-finding phase 2 study 1218.56 were previously discussed (see Section 4.5).

Durability of Response

Interpretation of data beyond week 26 is limited by the absence of a placebo-control arm. Within the linagliptin arm, mean HbA1c progressively increased during the study period, reaching above-baseline values by week 26 and continuing to increase to 0.81% above baseline by week 52 (Table 15). In contrast, within the empagliflozin pooled arm, mean HbA1c change from baseline gradually reduced during the safety extension period reaching to just above baseline levels (0.1%) by week 52.

Table 15: HbA1c (%) through Week 52, Study 1218.91

	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

	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

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: Subjects treated with linagliptin experienced a rise in HbA1c by 0.81% above baseline at week 52. This further supports the conclusion that any initial glycemic lowering observed during the placebo-controlled period was not durable.

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 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 analysis using two different priors were provided. In the first approach (a pharmacometrics-based model), the informative component of the Bayesian prior distributions was derived from previously fitted pharmacokinetic and exposure-response models for linagliptin 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 102 to be less than total number (105) of enrolled pediatric subjects in the linagliptin and placebo arm. The exposure response-based Bayesian borrowing analysis

confirmed evidence for superior efficacy with posterior mean (SD) of -0.51% (0.22%) and a 95% credible interval of (−0.92%, −0.05%). Sensitivity analysis with full range of alternative weights showed that 0.54 (which corresponds to prior ESS of 78) was the tipping weight i.e., prespecified criterion for superiority of linagliptin compared to placebo would not have been met with any choice of prior weight smaller than 0.54.

In the second approach, the informative component of the Bayesian prior distributions was derived from the pediatric efficacy of other DPP-4 inhibitors (i.e., sitagliptin). The pre-specified weight for the informative component of the prior was 0.58 and the prior ESS was 102. The posterior mean (S.D) placebo-corrected treatment effect was −0.28% (0.20%) with a 95% credible interval (-0.69%, 0.09%) and it did not meet the pre-specified criterion for superiority of linagliptin compared to placebo. A tipping point sensitivity analysis using a full range of alternative weights showed that superior efficacy of linagliptin could not have been established for any choice of prior weight.

Reviewer Comment:
For the pharmacometrics-based model for linagliptin, there was a sizable difference between the model predicted effect and the observed effect in pediatrics (-0.64% predicted vs -0.34% observed). The model for linagliptin based on pediatric data from sitagliptin failed to reach the agreed decision threshold even with full pooling with the borrowed data. The most likely explanation for the discrepancy between the results of the two models is that there are differences in treatment response to DPP-4 inhibitors among adult and pediatric T2D subjects. Substantial borrowing of adult data (i.e., data from 78 adult subjects + 105 pediatric subjects, reflecting 42.6% of borrowed data) was required to establish superiority of linagliptin the pharmacometrics-based model; whereas no amount of borrowed pediatric data would have established efficacy.

Given that the efficacy of linagliptin was not established based on primary endpoint analysis for Study 1218.91, the Applicant did not seek a pediatric indication for linagliptin based on the results of the Bayesian analyses. Overall, we agree with the Applicant that the results of the supplementary Bayesian analyses do not change the overall conclusions regarding the absence of pediatric efficacy of linagliptin.

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 ins not applicable to the review.

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Postmarket Setting

Study 1218.91 investigated the effect of linagliptin added to standard of care. The majority of subjects enrolled in Study 1218.91 received metformin background therapy; subjects not on metformin background therapy were those with a documented intolerance to metformin. Current understanding of pediatric T2D suggests that there may be two subgroups of patients, those who are able to achieve durable glycemic control on metformin monotherapy and those who fail to respond to metformin and rapidly develop glycemic failure. Given that subjects enrolled in Study 1218.91 had inadequate glycemic control, the study was likely "enriched" with the pediatric T2D population who are likely to have rapid disease progression. An unanswered question is whether the efficacy outcome may have been different if linagliptin was studied in the subgroup of pediatric T2D patients who do not develop rapid disease progression. However, given that this subgroup typically achieves an HbA1c well below glycemic treatment goals on metformin monotherapy, there would not be an indication to seek additional treatment unless the patient was unable to tolerate metformin.

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. While having another oral therapeutic option may be more convenient, given the risk for rapid disease progression in the pediatric T2D population, other factors including magnitude of glycemic effect as well as durability of response are more important in

the benefit-risk consideration.

7.3. Integrated Assessment of Effectiveness

DINAMO was a 26-week, double-blind, randomized, placebo-controlled, parallel group study, with a double-blind active treatment safety extension period 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, to be tested simultaneously for the pooled empagliflozin dosing group vs placebo and for linagliptin vs. placebo. Key secondary efficacy endpoints included changes in fasting plasma glucose, systolic 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 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); however, treatment with empagliflozin was superior in reducing HbA1c from baseline versus placebo [placebo-adjusted treatment difference – 0.84% (95% confidence interval -1.50 to -0.19, p=0.0116)]. For linagliptin, the treatment difference was primarily driven by worsening glycemic control in subjects treated with placebo who experienced a 0.68% increase in HbA1c from baseline at week 26; subjects treated with linagliptin also experienced an increase in HbA1c from baseline to week 26 but to a lesser degree (increase of 0.33% from baseline). During the safety-extension period, subjects treated with linagliptin experienced a further rise in HbA1c to 0.81% above baseline by week 52.

Overall, there appears to have been a weak glycemic effect of linagliptin observed early on in treatment that was not sustained. Sensitivity analyses, subgroup analyses of the primary endpoint, and exploratory analyses of secondary endpoints were consistent with overall primary efficacy result for linagliptin.

Prespecified Bayesian borrowing analyses were conducted to compensate for an expected reduced statistical power in Study 1218.91, due to a greater than expected variability in the primary endpoint that was observed in a blinded interim assessment. However, these analyses provided conflicting results. For the pharmacometrics-based model for linagliptin that borrowed adult data, there was a sizable difference between the model predicted effect and the observed effect in pediatrics (-0.64% predicted vs -0.34% observed). The model for linagliptin based on pediatric data from sitagliptin failed to reach the agreed decision threshold even with full pooling with the borrowed data. The most likely explanation for the discrepancy between the results of the two models is that there are differences in treatment response to DPP-4 inhibitors among adult and pediatric patients. Given these findings, the failure to demonstrate superiority of linagliptin to placebo is most likely the result of inadequate efficacy; rather than of insufficient sample size.

Overall, the evidence from the DINAMO study does not support the effectiveness of linagliptin in pediatric patients with T2D. A small, non-significant treatment effect was observed (placebo-adjusted HbA1c change of-0.34%); lower than that described in adult studies of linagliptin (placebo-adjusted HbA1c changes ranging from -0.5% to -0.7% in monotherapy and add-on therapy trials). These results are consistent with recently completed trials for other DPP-4 inhibitors (e.g., sitagliptin) in which pediatric efficacy was also not established. Differences in demonstrated treatment response in adult and pediatric trials of linagliptin and other DPP-4 inhibitors may reflect more rapid disease progression in the pediatric trial population.

8. Review of Safety

8.1. Safety Review Approach

The safety of linagliptin has been well characterized in adult subjects with T2D. In adult studies of linagliptin, the most common adverse events (AEs with > 5% incidence) were nasopharyngitis, followed by diarrhea and cough. The USPI for linagliptin-containing products also describes Warnings and Precautions regarding the risks of pancreatitis, hypoglycemia with concomitant use of insulin or insulin secretagogues, hypersensitivity reactions, arthralgia, bullous pemphigoid and heart failure.

The safety review focused primarily on previously identified risks of linagliptin observed in adult studies, but also evaluated for 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 linagliptin, 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 empagliflozin; these data are presented for completeness but the results are discussed in more detail in the clinical review for NDA 204629/S-042.

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 linagliptin and empagliflozin 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. 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[19].

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.

[19] 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).

8.2. Review of the Safety Database

8.2.1. Overall Exposure

The duration of exposure through Week 26 is described in Table 16. The mean duration of exposure to linagliptin during the placebo-controlled treatment period was 24.8 weeks.

Table 16: 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 17. 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 linagliptin was 42.5 weeks.

Table 17: 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 6 and Table 7).

As discussed above, safety was also evaluated from weeks 26 to 52 to obtain to evaluate for

rare safety events in subjects treated with linagliptin. 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 18) below. Baseline and demographic characteristics during the safety extension period were generally comparable between the treatment arms. Some differences 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.

Table 18: 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)

	Empagliflozin 10 mg (N=47)	Empagliflozin 25 mg (N=28)	Linagliptin 5 mg (N=65)
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.

8.2.3. Adequacy of the safety database:

Because the safety profile of linagliptin 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 19 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 19: 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[20] 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[21] • Investigator assessment, based on ADA diagnostic criteria	Empagliflozin
Events involving lower limb amputation	• Investigator determined, including amputation, disarticulation, and auto-amputations[22].	Empagliflozin
Specific AEs		

[20] Complete listing of preferred terms provided in Listing 10 within document "1218-0091-17027-adverse-event-listings"
[21] PTs included diabetic hyperglycemic coma, diabetic ketoacidosis, diabetic ketoacidotic hyperglycemic coma, ketoacidosis, euglycemic diabetic ketoacidosis
[22] 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[20] • Investigator assessment	Empagliflozin
Urinary tract infections (UTI)	• Narrow sub BIcMQ for UTI predisposed by glucosuria • Investigator assessment[20]	Empagliflozin
Acute pyelonephritis or urosepsis	• Narrow BIcMQ for renal infections predisposed by glucosuria[20] AND PT of urosepsis	Empagliflozin
Bone fractures	• Narrow BIcMQ for bone fractures[20]	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[20]	Empagliflozin
Ketone measurement reported as an AE	• Narrow BIcMQ for increased ketones excluding acidosis and ketoacidosis[23]	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)

[23] 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 6

Figure 6: 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[24] if combined with a reported symptom[25] 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[25] suggestive of ketoacidosis, hospitalization or if reported as a serious adverse event.

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

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

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

Figure 7: 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[26]

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 Tests

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[27] Quantitative analysis for albumin, creatinine, human chorionic

[26] 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

[27] 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: Reviewer created based on 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 20 and Table 21, 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.

Table 20: 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 21: 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., linagliptin or empagliflozin) were reviewed and key findings and conclusions regarding relatedness of study treatment are summarized below:

SAEs associated with linagliptin treatment	Clinical reviewer Assessment of Relatedness to Study Treatment /Comments

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 discharged that same day. Study medication was not interrupted. This subject had a medical history of "other genital infections".	Not related
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).	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	Not related

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.	
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 days after treatment with insulin and other therapies. Study medication was not interrupted.	Not related
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.
SAEs associated with empagliflozin treatment	**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	The risk of genital mycotic infections is known to be increased with empagliflozin therapy. It is unclear whether this event involved

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.	a genital infection however the rash is described as appearing on the "groin" (in addition to other areas); therefore, this SAE was likely related 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 temporarily discontinued for 2 months but then resumed and the subject completed the study.	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 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 study treatment of empagliflozin.

Source: Reviewer generated

As displayed in Table 20, 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%) subjects treated with linagliptin during the placebo-controlled period, and in 6 (9.2%) subjects treated with linagliptin during the safety-extension period. Based on review of the subject narratives, no SAEs appeared to be related to treatment with linagliptin.

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 linagliptin or empagliflozin (see Table 22).

During the safety extension period (Table 23), 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 led to study drug discontinuation in a single subject (# (b) (4), (b) (6)) treated with linagliptin. This subject was a 16-year-old female treated with baseline metformin 2000 mg per day who was initially randomized to placebo and re-randomized to linagliptin during the safety extension period. 15 days after initiating linagliptin the subject developed moderate AEs of abdominal discomfort, abdominal pain, decreased appetite and diarrhea. Linagliptin was discontinued 16 days later; the AEs subsequently resolved 10 days after discontinuation of linagliptin (total duration of the AEs were 27 days).

Table 22: 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 23: 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).

Reviewer Comment: One subject (1.5%) treated with linagliptin during the safety extension period discontinued study treatment due to several gastrointestinal AEs. Due to the resolution of these AEs after discontinuation of linagliptin, it is possible that they were treatment-related; however, the subject was also treated with background metformin which is known to be associated with gastrointestinal AEs. During the placebo-controlled period, the overall incidence of gastrointestinal AEs in linagliptin-treated subjects was slightly higher than for placebo-treated subjects (23.1% vs. 18,9%), but during the safety extension period, the incidence of gastrointestinal AEs in linagliptin-treated subjects was lower than that for empagliflozin-treated subjects (29.2% vs. 33.3%, see Table 40 and Table 41). No imbalance in gastrointestinal AEs were observed in adult studies of linagliptin[28]. Based on these data, there is insufficient information to determine whether linagliptin treatment increases the risk for gastrointestinal AEs in pediatric T2D subjects.

8.4.4. Significant Adverse Events

Hypoglycemia events, AESIs and specific AEs (as defined in Table 19), and events adjudicated by the CEC are discussed in this section.

[28] See primary clinical review by Dr. Dunn submitted on March 11, 2011 under NDA 201280

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 Level 2 hypoglycemia[14] definition, and is pertinent for labeling.**

Reviewer Comment: The Applicant did not classify hypoglycemia events according to the ADA Level 1 hypoglycemia definition (i.e., hypoglycemia events associated with a glucose ≥54 but <70 mg/dL)[14].

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 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 24 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 8 (15.4%) of subjects treated with linagliptin versus 7.5% of subjects treated with placebo. Among subjects treated with insulin at baseline, Level 2 hypoglycemia occurred in 5 out of 22 subjects (22.7%) with treated linagliptin versus 3 out of 21 subjects (14.3%) treated with placebo. Among subjects not treated with insulin at baseline, Level 2 hypoglycemia occurred in 3 out of 30 subjects (10.0 %) treated with linagliptin versus 1 out of 32 subjects (3.1%) treated 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 higher with linagliptin versus placebo treatment in all subjects and in subjects with insulin use at baseline; the incidence was only marginally higher in subjects without insulin use at baseline. The frequency of hypoglycemia events was also greater with linagliptin treatment as compared to placebo among all categories of hypoglycemia, though the differences were marginal in subjects who were not treated with insulin at baseline.

Table 24: 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		5 (18.5)	16		6 (20.0)	40*		2 (6.3)	14

with BG ≤ 70									
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, there was an increased incidence and frequency of hypoglycemia events in subjects treated with linagliptin as compared to placebo. These differences appear to have been largely driven by an increased risk of hypoglycemia in subjects treated with linagliptin with concomitant insulin use at baseline. While the incidence of hypoglycemia events was marginally higher in linagliptin-treated subjects who were not on insulin at baseline; interpretation is limited due to the small number of subjects involved (e.g., 3 subjects in the linagliptin arm vs. 2 subjects in the placebo arm experienced hypoglycemia AE with BG ≤ 70 mg/dL).

As discussed above, the analysis presented in Table 24 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 24 represented as not receiving insulin at baseline had received rescue therapy with insulin through week 26[29]. 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; this subject had been treated with empagliflozin (see clinical review under NDA 204629/S-04 for additional details).

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 25. The Applicant's analysis of hypoglycemia AEs with BG < 54 mg/dL is displayed in Table 26. Overall, subjects treated with linagliptin had an increased risk for all types of hypoglycemic events compared to those treated with placebo, however, these differences did not reach statistical significance.

[29] 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.

Table 25: Analysis of Any Hypoglycemia Events* with BG <=70 mg/dL up to Week 26, Study 1218.91

	Lina 5mg (N = 52)	Placebo (N = 53)
Incidence (%)	8 (15.4)	4 (7.5)
Number of events	30	8
Total time at risk, patient year	24.76	25.08
Unadjusted event rate, events per patient year	1.21	0.32
Adjusted event rate[1], events per patient year (95% CI)	1.15 (0.47, 2.82)	0.31 (0.11, 0.91)
Comparison vs. placebo Adjusted event rate ratio[1] (95% CI)		3.65 (0.91, 14.69)
p-value (two-sided)		0.07

** including hypoglycemia adverse events with BG < 70 mg/dL and asymptomatic hypoglycemia events with BG > 54 and <70 mg/dL*
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 10 of Dr. Tu's statistical review, based on Applicant's analysis; submitted 4/27/2023 (SDN 3655).

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

	Lina 5mg (N = 52)	Placebo (N = 53)
Incidence (%)	15 (28.8)	7 (13.2)
Number of events	89	42
Total time at risk (patient year)	24.76	25.08
Unadjusted event rate	3.59	1.67
Adjusted event rate[1], events per patient year (95% CI)	3.32 (1.46, 7.56)	1.51 (0.64, 3.53)
Comparison vs. placebo Adjusted event rate ratio[1] (95% CI)		2.20 (0.68, 7.17)
p-value (two-sided)		0.19

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 11 of Dr. Tu's statistical review, based on Applicant's analysis; submitted 4/27/2023 (SDN 3655).

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 27, Table 28, Table 29, Table 30). With respect to hypoglycemia AEs

with BG < 54 mg/dL, the adjusted event rate ratio versus placebo was 6.2 (with a significant p value of 0.04) in subjects on background insulin. In subjects not on background insulin, the adjusted event rate ratio versus placebo was 2.9 (results not statistically significant). For hypoglycemia AEs with BG ≤ 70 mg/dL, the adjusted event rate ratio versus placebo was 2.9 in subjects on background insulin and 2.0 in subjects not on background insulin (neither result was statistically significant).

Table 27: Analysis of Hypoglycemia AEs with BG < 54 mg/dL through Week 26 in Subjects on Background Insulin at Baseline, Study 1218.91

	Lina 5mg (N = 22)	Placebo (N = 21)
Incidence (%)	5 (22.7)	3 (14.3)
Number of events	23	4
Total time at risk (patient year)	10.27	9.74
Unadjusted event rate	2.24	0.41
Adjusted event rate[1], events per patient year (95% CI)	1.71 (0.63, 4.67)	0.27 (0.06, 1.18)
Comparison vs. placebo Adjusted event rate ratio[1] (95% CI)		6.23 (1.12, 34.73)
p-value (two-sided)		0.04

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: Dr. Wenda Tu's analysis based on adsl.xpt, adae.xpt, and adhypo.xpt

Table 28: Analysis of Hypoglycemia AEs with BG < 54 mg/dL through Week 26 in Subjects Not on Background Insulin at Baseline, Study 1218.91

	Lina 5mg (N = 30)	Placebo (N = 32)
Incidence (%)	3 (10.0)	1 (3.1)
Number of events	7	4
Total time at risk (patient year)	14.49	15.35
Unadjusted event rate	0.48	0.26
Adjusted event rate[1], events per patient year (95% CI)	0.44 (0.09, 2.06)	0.15 (0.03, 0.89)
Comparison vs. placebo Adjusted event rate ratio[1] (95% CI)		2.88 (0.27, 30.24)
p-value (two-sided)		0.40

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: Dr. Wenda Tu's analysis based on adsl.xpt, adae.xpt, and adhypo.xpt

Table 29: Analysis of Hypoglycemia AEs with BG < 70 mg/dL through Week 26 in Subjects on Background Insulin at Baseline, Study 1218.91

	Lina 5mg (N = 22)	Placebo (N = 21)
Incidence (%)	7 (31.8)	3 (14.3)
Number of events	26	11
Total time at risk (patient year)	10.27	9.74
Unadjusted event rate	2.53	1.13
Adjusted event rate[1], events per patient year (95% CI)	2.15 (0.75, 6.20)	0.74 (0.20, 2.71)
Comparison vs. placebo Adjusted event rate ratio[1] (95% CI)		2.92 (0.55, 15.40)
p-value (two-sided)		0.21

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: Dr. Wenda Tu's analysis based on adsl.xpt, adae.xpt, and adhypo.xpt

Table 30: Analysis of Hypoglycemia AEs with BG < 70 mg/dL through Week 26 in Subjects Not on Background Insulin at Baseline, Study 1218.91

	Lina 5mg (N = 30)	Placebo (N = 32)
Incidence (%)	3 (10.0)	2 (6.3)
Number of events	8	5
Total time at risk (patient year)	14.49	15.35
Unadjusted event rate	0.55	0.33
Adjusted event rate[1], events per patient year (95% CI)	0.54 (0.12, 2.39)	0.27 (0.05, 1.31)
Comparison vs. placebo Adjusted event rate ratio[1] (95% CI)		2.02 (0.23, 17.97)
p-value (two-sided)		0.53

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: Dr. Wenda Tu's analysis based on adsl.xpt, adae.xpt, and adhypo.xpt

Reviewer Comment: In this reviewer's, the statistical 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 linagliptin therapy versus placebo. Overall, in pediatric T2D subjects, linagliptin appears to increase the risk of hypoglycemia predominantly in the setting of concomitant insulin use. This risk is similar to that described in adults, and is currently described in the warnings and

precautions section of the USPI.

An analysis of hypoglycemia events was also conducted during the safety extension period[30]. Table 31 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 31: 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
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 (1840084001). 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), (b) (4) *and 22 events of BG ≤ 70 mg/dL and 21 events of BG <54 mg/dL occurred in another subject* (b) (6)

[30] 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.

Source: Reviewer created based on adae.xpt and adhypo.xpt datasets

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 a large frequency of events.

Timeframe of hypoglycemia events

An analysis was conducted determine the proportion of subjects experiencing one or more hypoglycemia events within the first 30 days of treatment (Table 32). Among subjects treated with linagliptin, 9.4% experienced hypoglycemia events associated with blood glucose ≤ 70 mg/dL and 5.7% experienced hypoglycemia events associated with blood glucose < 54 mg/dL within the first 30 days. All subjects experiencing hypoglycemia events within the first 30 days of the study were treated with background insulin.

Table 32: 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: Within the linagliptin arm, hypoglycemia events within the first 30 days of the study occurred only in subjects who were treated with insulin at baseline. This finding may reflect the absence of any pre-specified adjustment in background insulin dose at randomization.

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 33 below. Overall, there appeared to be an imbalance in hypersensitivity reactions in pediatric subjects treated with linagliptin versus placebo.

No AESIs of pancreatitis or decreased renal function occurred in any subjects treated with linagliptin. 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 33: 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 linagliptin and empagliflozin through Week 26 were reviewed with key findings summarized below:

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.

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.

Reviewer Comment: Compared to placebo, a higher proportion of AEs relating to hypersensitivity reactions and hepatic injury occurred with linagliptin treatment. Based on review of subject narratives, none of the hepatic event AESIs occurring during the placebo-controlled period appeared related to linagliptin treatment. An increased risk of hypersensitivity reactions occurred in adult studies if linagliptin and is described in the USPI.

A summary of AESIs occurring during the safety extension period is described in Table 34. 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 34: 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'.

Reviewer Comment: Although a numerically higher number of AESIs involving hepatic injury occurred in subjects treated with linagliptin during the safety extension period, these events all occurred in subjects with baseline abnormalities of AST and/or ALT and resolved without any interruption of study medication. Hepatic safety is further discussed below for cases adjudicated by the CEC and in Section 8.4.6.

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 35. Arthralgia occurred with a higher incidence in the linagliptin arm 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 35: 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)**
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 generated using 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 36. 3 subjects (4.6%) in the linagliptin arm experienced arthralgia. 4 subjects (6.2%) in the linagliptin arm experienced genital infections; 2 events (cervicitis and anogenital warts) occurred in 1 subject on the same day. AEs relating to ketone measurements occurred in all three treatment arms.

Table 36: 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)

	Empagliflozin 10 mg (N=47)	Empagliflozin 25 mg (N=28)	Linagliptin (N=65)
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: There were no relevant imbalances in specific AEs in subjects treated with linagliptin versus placebo during the placebo-controlled period. Based on these limited data, no differences in the safety profile of linagliptin 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 37. 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; both in subject treated with linagliptin. These include an SAE of DKA that occurred in subject (b) (6), and a lab-related event (isolated elevated beta-hydroxybutyrate not accompanied by any additional details) in subject (b) (6) The DKA episode in subject (b) (6) appears to have been precipitated by non-compliance with background antidiabetic medication. Based on my review of the narrative for the lab-related event in subject (b) (6), there appears to be inadequate information to draw any certain conclusions regarding ketoacidosis (see reviewer comments below) or relatedness to study drug.

Table 37: 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: The CEC confirmed 2 episodes of DKA in linagliptin treated subjects; one episode appears to have been precipitated by non-compliance with background antidiabetic medication (insulin and metformin); the other episode was an isolated event of elevated beta-hydroxybutyrate noted on lab testing not accompanied by any related adverse events or any reported action taken with the study medication. DKA has not been identified as a safety signal associated with linagliptin treatment in adult studies; based on review of the narratives these DKA episodes are unlikely related to treatment.

Subjects with events that met the criteria for adjudication for myocardial infarction (MI) and hospitalization for heart failure (HHF) are displayed in Table 38. None of these events were confirmed as MI or HHF by the CEC.

Table 38: 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)

Abbreviations: CK= creatine kinase, AKI= acute kidney injury, MI= myocardial infarction, HHF= hospitalization for

heart failure. Source: Reviewer created.

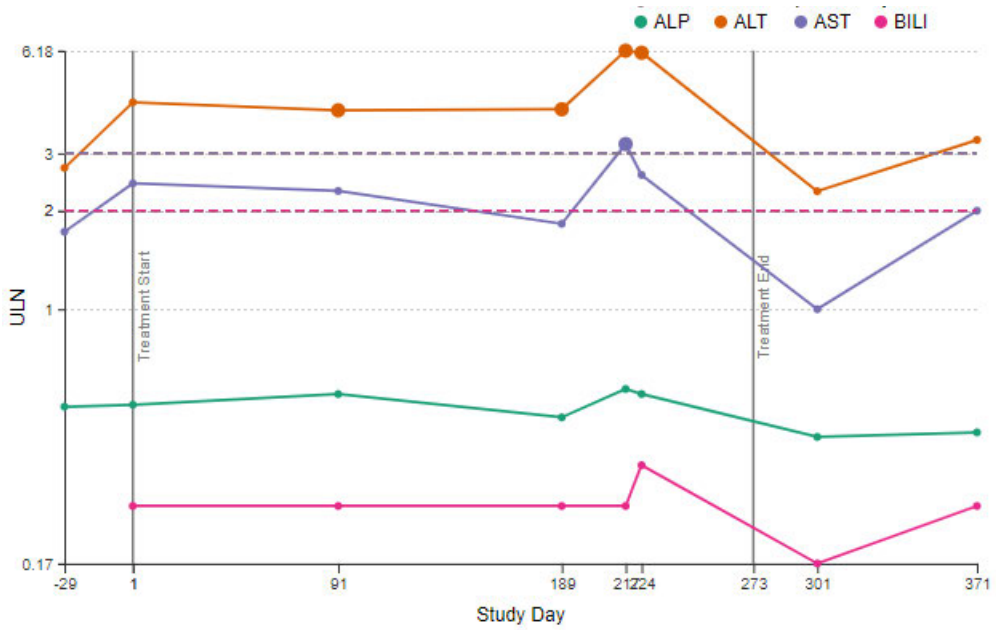
1 event met CEC criteria for adjudication for hepatic injury. This event was an AESI of liver injury that occurred in a 12-year-old female subject (b) (6) who received linagliptin from week 26 to 52. The event occurred 217 days after the first intake of linagliptin, and was also reported as an AESI of 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 39 below and also displayed in Figure 8 . All measured bilirubin and alkaline phosphatase levels were normal. The study medication was temporarily discontinued (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) (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 39: 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, (b) (6))	78*	40*
Visit 09 (follow up)	112*	80*

**measured off treatment*
Source: Reviewer created based on review of narrative

Figure 8: Hepatic Function Tests in Subject (b) (6) over time



Source: Reviewer generated using OCS Analysis Studio, Hepatic Explorer

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

Reviewer Comment: An AESI of mild to moderate hepatic injury occurred in a linagliptin-treated subject with baseline non-alcoholic fatty liver disease but does not appear to have been related to treatment with linagliptin after adjudication by the CEC.

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 linagliptin and with risk difference > 1% as compared to placebo through Week 26 is displayed in Table 40. A greater percentage of TEAEs occurred in the SOCs of infections and infestations in subjects treated with linagliptin versus placebo. Hypoglycemia was the most common PT in subjects treated with linagliptin, followed by headache.

Table 40: Summary of TEAEs by SOC and PT occurring in > 2% of subjects treated with Linagliptin and with Risk Difference > 1% through Week 26, Study 1218.91

System Organ Class - Preferred Term	Linagliptin (N=52) n (%)	Pbo (N=53) n (%)	Risk Difference RD (95% CI)	Forest Plot
Gastrointestinal disorders	**12 (23.1)**	**10 (18.9)**	4.21 (-11.35, 19.77)	
Abdominal pain upper	2 (3.8)	1 (1.9)	1.96 (-4.42, 8.34)	
Vomiting	5 (9.6)	2 (3.8)	5.84 (-3.67, 15.36)	
Infections and infestations	**23 (44.2)**	**13 (24.5)**	19.70 (1.91, 37.49)	
Influenza	3 (5.8)	0 (0.0)	5.77 (-0.57, 12.11)	
Sinusitis	2 (3.8)	1 (1.9)	1.96 (-4.42, 8.34)	
Upper respiratory tract infection	2 (3.8)	0 (0.0)	3.85 (-1.38, 9.07)	
Vulvovaginal mycotic infection	2 (3.8)	0 (0.0)	3.85 (-1.38, 9.07)	
Investigations	**11 (21.2)**	**7 (13.2)**	7.95 (-6.42, 22.31)	
Blood ketone body increased	4 (7.7)	2 (3.8)	3.92 (-4.96, 12.79)	
Metabolism and nutrition disorders	**16 (30.8)**	**12 (22.6)**	8.13 (-8.73, 24.99)	
Hypoglycemia	10 (19.2)	5 (9.4)	9.80 (-3.50, 23.09)	
Musculoskeletal and connective tissue disorders	**5 (9.6)**	**4 (7.5)**	2.07 (-8.65, 12.78)	
Nervous system disorders	**10 (19.2)**	**11 (20.8)**	-1.52 (-16.82, 13.77)	
Headache	9 (17.3)	7 (13.2)	4.10 (-9.64, 17.84)	
Psychiatric disorders	**3 (5.8)**	**1 (1.9)**	3.88 (-3.44, 11.20)	
Renal and urinary disorders	**6 (11.5)**	**3 (5.7)**	5.88 (-4.80, 16.56)	
Microalbuminuria	3 (5.8)	1 (1.9)	3.88 (-3.44, 11.20)	
Reproductive system and breast disorders	**3 (5.8)**	**1 (1.9)**	3.88 (-3.44, 11.20)	
Respiratory, thoracic and mediastinal disorders	**11 (21.2)**	**8 (15.1)**	6.06 (-8.64, 20.76)	
Epistaxis	3 (5.8)	0 (0.0)	5.77 (-0.57, 12.11)	

System Organ Class - Preferred Term	Linagliptin (N=52) n (%)	Pbo (N=53) n (%)	Risk Difference RD (95% CI)	Forest Plot
Skin and subcutaneous tissue disorders	**4 (7.7)**	**1 (1.9)**	5.81 (-2.31, 13.92)	

Source: Reviewer generated using OCS Analysis Studio, Safety Explorer.
Filters: TRT01A = "L5" and TRTFL = "Y" (Linagliptin); TRT01A = "Pbo" and TRTFL = "Y" (Pbo); TRTEMFL = "Y" and APERIODC = "Up to Week 14 (on-trt" or "Week 14 to Week 26 (on-trt" (Adverse Events).
Percent Threshold: Linagliptin ≥ 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 during the safety extension period is displayed in Table 41. The most common PT in the linagliptin arm was hypoglycemia, followed by headache, and blood ketone body increased. The most common SOCs for TEAEs included infections and infestations and metabolism and nutrition disorders.

Table 41: Summary of TEAEs by SOC and PT occurring in >5% of subjects treated with Linagliptin from Week 26 to Week 52, Study 1218.91.

System Organ Class - Preferred Term	Linagliptin (N=65) n (%)	Empagliflozin 10 mg and Empagliflozin 25 mg (N=75) n (%)
Gastrointestinal disorders	**19 (29.2)**	**25 (33.3)**
Abdominal pain	6 (9.2)	6 (8.0)
Diarrhea	8 (12.3)	8 (10.7)
Nausea	4 (6.2)	6 (8.0)
Vomiting	8 (12.3)	6 (8.0)
General disorders and administration site conditions	**7 (10.8)**	**8 (10.7)**
Fatigue	4 (6.2)	3 (4.0)
Infections and infestations	**37 (56.9)**	**33 (44.0)**
Influenza	4 (6.2)	3 (4.0)
Nasopharyngitis	8 (12.3)	4 (5.3)
Injury, poisoning and procedural complications	**9 (13.8)**	**6 (8.0)**
Investigations	**22 (33.8)**	**21 (28.0)**
Blood ketone body increased	9 (13.8)	8 (10.7)
Urine albumin/creatinine ratio increased	6 (9.2)	3 (4.0)
Metabolism and nutrition disorders	**29 (44.6)**	**31 (41.3)**
Hyperglycemia	7 (10.8)	5 (6.7)
Hypoglycemia	17 (26.2)	16 (21.3)
Vitamin d deficiency	7 (10.8)	9 (12.0)
Musculoskeletal and connective tissue disorders	**9 (13.8)**	**10 (13.3)**
Arthralgia	4 (6.2)	3 (4.0)
Nervous system disorders	**16 (24.6)**	**22 (29.3)**
Headache	12 (18.5)	16 (21.3)
Psychiatric disorders	**4 (6.2)**	**4 (5.3)**
Renal and urinary disorders	**9 (13.8)**	**4 (5.3)**

System Organ Class - Preferred Term	Linagliptin (N=65) n (%)	Empagliflozin 10 mg and Empagliflozin 25 mg (N=75) n (%)
Microalbuminuria	4 (6.2)	1 (1.3)
Reproductive system and breast disorders	**4 (6.2)**	**7 (9.3)**
Respiratory, thoracic and mediastinal disorders	**18 (27.7)**	**10 (13.3)**
Asthma	4 (6.2)	0 (0.0)
Cough	8 (12.3)	6 (8.0)
Skin and subcutaneous tissue disorders	**7 (10.8)**	**8 (10.7)**

Source: Reviewer generated using OCS Analysis Studio, Safety Explorer.
Filters: TRT03A = "L5" and TRTFL = "Y" (Linagliptin); TRT03A = "E10" or "E25" and TRTFL = "Y" (Empagliflozin 10 mg and Empagliflozin 25 mg); TRTEMFL = "Y" (Adverse Events).
Percent Threshold: Linagliptin ≥ 5%.

Reviewer Comment: The most common TEAE in linagliptin-treated subjects was hypoglycemia, followed by headache. Overall, the safety profile of linagliptin in pediatric subjects appears generally similar to that described in adult studies.

8.4.6. Laboratory Findings

The safety review focused on laboratory-related safety issues that have been reported in adult studies of linagliptin and specific laboratory studies relevant to pediatric subjects. In adult studies of linagliptin, increases in uric acid, lipase and amylase have been reported; however, amylase was not measured as a safety laboratory in the DINAMO study. The laboratory review was focused on the placebo-controlled period (through week 26).

Renal Function Parameters:

No clinically meaningful changes in serum creatinine, urine albumin/creatinine ratio or estimated GFR occurred in subjects treated with linagliptin. A shift table for renal impairment based on eGFR is displayed in Table 42. A small percentage of subjects with normal renal function at baseline developed mild renal impairment by week 26 in all three treatment arms, though the frequency was lowest in the linagliptin arm. 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 43) 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[31].

[31] 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

Table 42: 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 generated 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 43: 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%)
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%)

		Final Albuminuria		
Treatment Arm	**Baseline Albuminuria**	**Normoalbuminuria**	**Microalbuminuria**	**Macroalbuminuria**
	Macroalbuminuria	0	3 (6.1%)	0

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

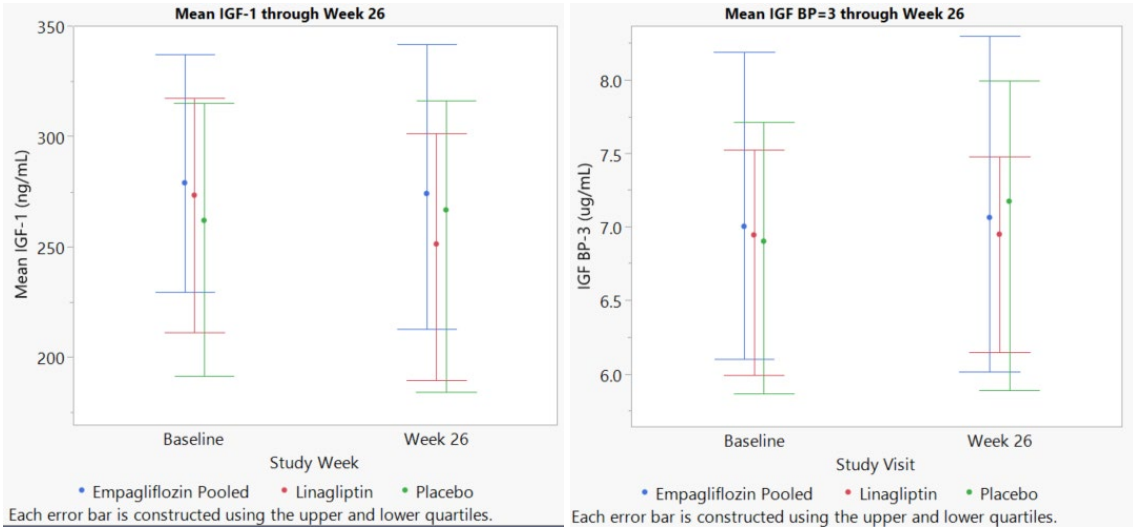
Growth-hormone dependent factors, markers of mineral and bone metabolism.

There were no clinically relevant treatment-related differences in change from baseline to week 26 mean IGFBP-3 or IGF-1 (Figure 9), alkaline phosphatase (Figure 10), calcium, phosphorus, intact PTH, N-telopeptide, procollagen 1 N-Terminal Propeptide[32], vitamin D[33] (data not shown).

An additional analysis of change from baseline to week 26 in mean 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 completed linear growth (Table 44). 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., $\geq$ 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 some 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); these increases also occurred in some subjects in the linagliptin arm though to a lesser extent (maximum change from baseline of 78 ng/dL).

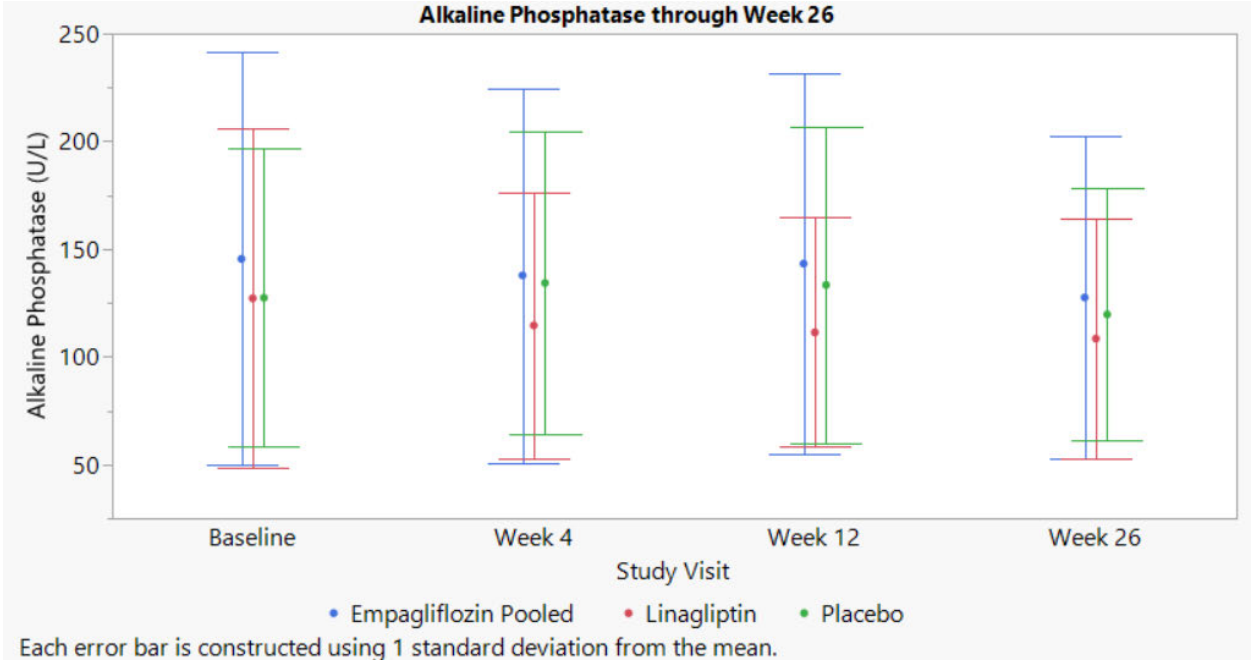
[32] Baseline differences in procollagen 1 N-terminal propeptide between the treatment arms (mean value 1.5 x greater at baseline in the empagliflozin pooled arm versus the placebo arm) limited the interpretation of treatment-related effects.
[33] The mean vitamin D levels measured at baseline, week 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.

Figure 9: Mean IGF-1 and IGFBP-3 through Week 26



Source: Reviewer generated using JMP

Figure 10: Mean Alkaline Phosphatase through Week 26



Source: Reviewer generated using JMP

Table 44: 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.

Reviewer Comment: Given the overall variability in IGF-1 measurements during the study, it is difficult to draw any conclusions. The finding that mean change in IGFBP-3 was not decreased from baseline in pubertal subjects treated with linagliptin is reassuring against any treatment-related impact on the growth-hormone axis. See Section 8.8.3 regarding safety analyses for growth and puberty.

Hepatic Function Parameters

A hepatocellular DILI plot analysis was conducted for the placebo-controlled treatment period (Figure 11) 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 45). 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.

Figure 11: Hepatocellular DILI Screening Plot through Week 26, Study 1218.91

Source: Reviewer generated using 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.

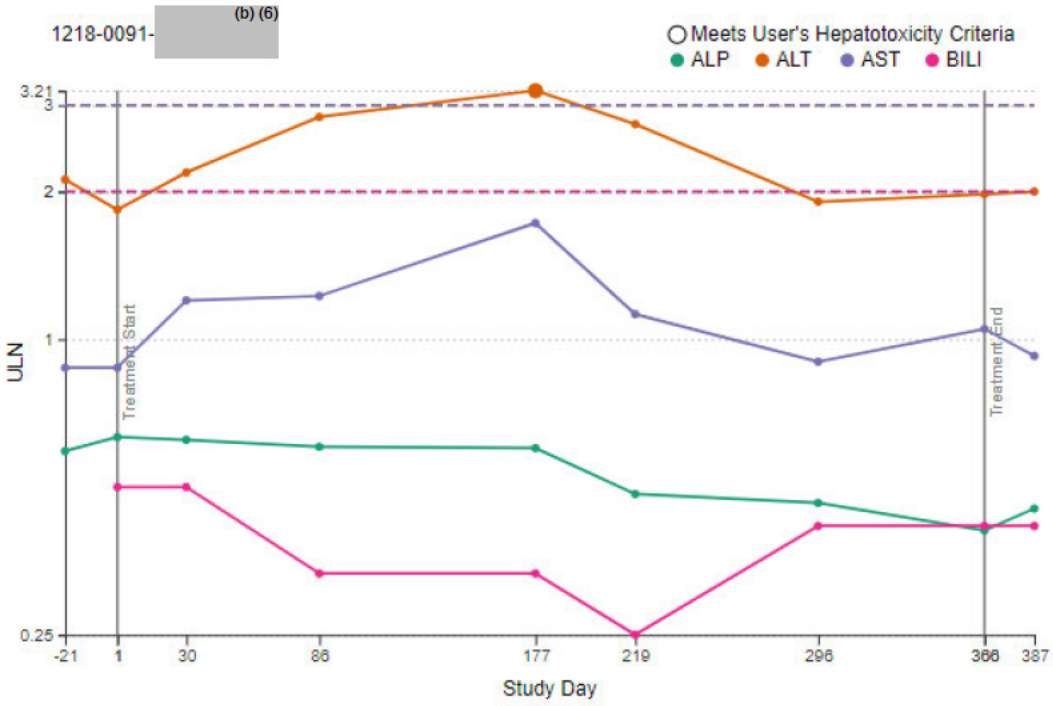
Table 45: Listing of Subjects in Temple's Corollary through Week 26

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
(b) (6)	E10	3.8837	0.75	Y	Y
(b) (6)	Pbo	3.6176	0.3333	Y	n/a
(b) (6)	L5	3.2093	0.5	Y	Y
(b) (6)	L5	4.0588	0.25	Y	Y
(b) (6)	L5	3.6512	0.4167	Y	Y

Source: Reviewer generated using OCS Analysis Studio, Hepatic Explorer.

As previously discussed, subject (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 8 in Section 8.4.4). Hepatic function tests for the two additional subjects treated with linagliptin who were in Temple's corollary are shown in Figure 12 (subject (b) (6)) and Figure 13 (subject (b) (6)).

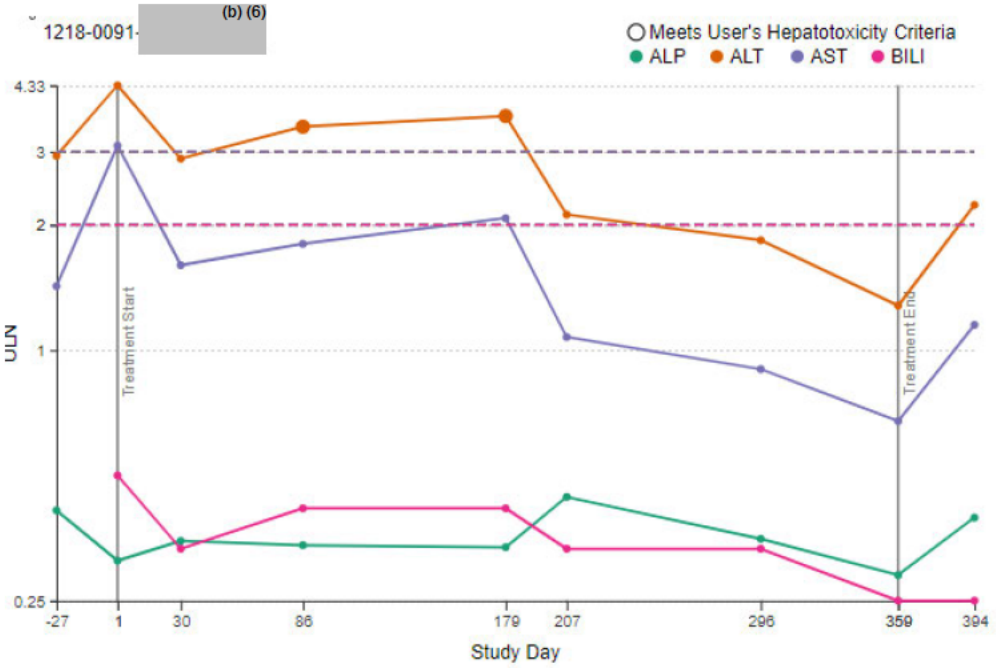
Figure 12: Hepatic Function Tests in Subject (b) (6) over time



Source: Reviewer generated using OCS Analysis Studio, Hepatic Explorer

Subject (b) (6) had no liver-related AEs during the study; however, a mild AE of viral infection occurred on study day 123 through study day 137 characterized by rash, diarrhea, fever and headache for which the subject was evaluated in the emergency room and found to have a negative COVID-19 test. Study medication was briefly interrupted during this time but resumed on study day 140. According to Figure 12, elevations in AST and ALT were apparent prior to this AE however appear to have worsened on follow up on study day 177 and subsequently improved over the course of the study without further interruption in study medication.

Figure 13: Hepatic Function Tests in Subject (b) (6) over time



Source: Reviewer generated using OCS Analysis Studio, Hepatic Explorer

Subject (b) (6) had a total of 14 TEAEs over the course of the study. On study day 11, the subject had AEs of fatigue, headache and yellow skin, which resolved by study day 15. Stat labs including AST, ALT and bilirubin were performed which were considered "normal" and not enough to trigger further evaluation for drug-induced liver injury. None of the other AEs were liver-related. Based on the trajectory of lab tests, the subject appears to have had elevated AST and ALT on day 1 of treatment that eventually normalized by the end of the study.

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

Lipids

There were no clinically relevant 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:

There were no clinically relevant changes in mean hematocrit, hemoglobin, creatine kinase, lipase or uric acid from baseline to week 26 in subjects treated with linagliptin or placebo (data not shown).

The Applicant's analysis of safety laboratory data was limited to the frequency of possibly

clinically significant abnormalities based on pre-defined criteria[34]. During the placebo-controlled period (Table 46), no subjects treated with linagliptin had possibly clinically significant low values in any safety laboratory parameter. More than 1 linagliptin-treated subjects had possibly clinically significant elevations in phosphate, triglycerides and urine albumin-to-creatinine ratio; however, the incidence was overall similar to that described in the placebo arm. Shifts in urine albumin to creatine ratio within linagliptin-treated subjects have been previously discussed (Table 43) and likely represent progression of underlying disease.

Table 46: Subjects with possibly clinically significant abnormal values through Week 26, Study 1218.91

Parameter [unit]	Possibly clinically significant low						Possibly clinically significant high					
	Placebo			Lina 5 mg			Placebo			Lina 5 mg		
	n	N	%	n	N	%	n	N	%	n	N	%
Haematocrit [%]	3	67	4.5	0			0			1	66	1.5
Haemoglobin [g/dL]	1	66	1.5	0			0			0		
Eosinophils [10^9/L]	0			0			0			1	62	1.6
Eosinophils/leukocytes [%]	0			0			1	64	1.6	1	61	1.6
Neutrophils [10^9/L]	0			0			1	63	1.6	0		
Phosphate [mmol/L]	0			0			5	62	8.1	5	60	8.3
Alanine aminotransferase [U/L]	0			0			1	67	1.5	1	64	1.6
Alkaline phosphatase [U/L]	0			0			1	68	1.5	0		
Creatine kinase [U/L]	0			0			0			1	65	1.5
Cholesterol [mmol/L]	0			0			2	67	3.0	1	60	1.7
Triglycerides [mmol/L]	0			0			16	55	29.1	12	48	25.0
UACR [g/kg]	0			0			4	64	6.3	2	61	3.3

n, number of patients with possibly clinically significant abnormal value on treatment; N, number of patients with at least 1 value on-treatment and no possibly clinically significant abnormality at baseline; UACR = urine albumin to creatinine ratio

Source: Applicant's summary of clinical safety, DINAMO CSR Table 6.2.1

Based on review of TEAEs within the SOC of investigations, 1 subject (b) (6) in the linagliptin arm was reported to have an AE of lipase increased. Upon review of the laboratory data, this subject experienced a mild elevation in lipase to 99 U/L on study day 295, however, follow up values subsequently normalized, and there were no other AEs suggestive of pancreatitis around the time of the mild lipase elevation. Another subject (b) (6) in the linagliptin arm was reported to have an AE of blood uric acid increased; upon review of the laboratory data a mild and transient increase in uric acid was noted that on study day 177 that subsequently declined; all uric acid levels measured were within the normal reference range.

Reviewer Comment: Overall, no clinically relevant findings were observed based on the safety analysis of laboratory parameters in pediatric T2D subjects aged 10 years and older.

[34] Full listing of possibly clinically significant laboratory abnormalities is available in listing 6.3.1, attached to the summary of clinical safety submitted under NDA 201280/S-027.

8.4.7. Vital Signs

There was no clinically meaningful change in mean systolic blood pressure (SBP), diastolic blood pressure (DBP) or heart rate from baseline to Week 26 in subjects treated with linagliptin. 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. Mean change from baseline in heart rate from baseline through Week 26 is shown in

8.4.8. Electrocardiograms (ECGs)

As discussed in Table 38 a mild AE of electrocardiogram ST segment elevation occurred in 1 subject (b) (6) treated with linagliptin. This event was reviewed by the CEC and determined not to meet criteria for myocardial infarction.

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. 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) (see Table 52, Table 53, Table 54, and Table 55 in Appendix 13.3). Based on the Applicant's analyses, a relatively higher incidence of AEs relating to gastrointestinal disorders, headache and blood ketone body increased occurred among subjects aged > 15 years as compared to subjects < 15 years, among female as compared to male subjects, among non-white subjects as compared to white subjects, and among non-Hispanic or Latino subjects as compared to Hispanic or Latino subjects. These

imbalances are most likely due to chance, considering the small number of subjects within these subgroups.

The risk of hypoglycemia was increased with linagliptin treatment versus placebo among all subgroups evaluated, however, the risk difference appeared more pronounced in subjects aged ≥15 years, in female subjects and among non-white subjects. Notably, the rate of background insulin use among baseline was also higher among female subjects as compared to male subjects, and among subjects ≥ 15 years as compared to subjects aged < 15 years, while background insulin use was comparable among subjects of white race and those of non-white race (Table 56).

Overall, no clear differences in safety signals were observed among demographic subgroups.

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.

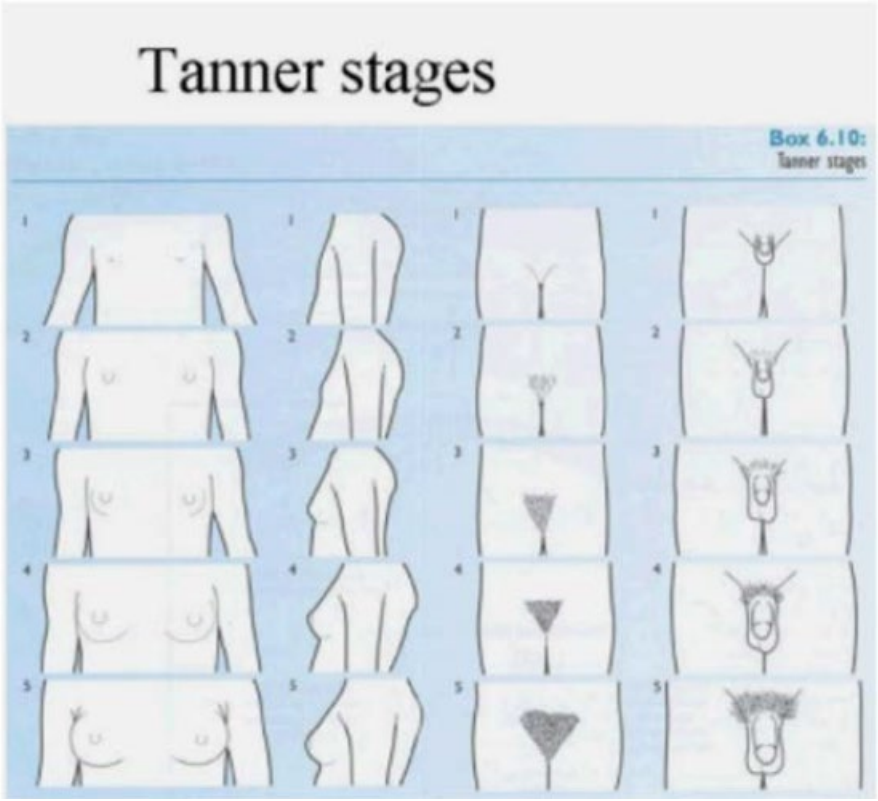
8.8.2. Human Reproduction and Pregnancy

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 14: "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 47. 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 47: 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)
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 and no subjects in the linagliptin arm were in Tanner stage 2 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 48). The Applicant concluded that there were no relevant differences between linagliptin versus placebo or between empagliflozin versus placebo with regard to shifts in Tanner staging score.

Table 48: Frequency of subjects 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. One subject in the linagliptin arm appears to have shifted multiple stages over the 26-week period (i.e., from Tanner stage 3 at baseline to Tanner stage 5); this pattern also appears to have occurred in the placebo arm and empagliflozin arm. Additionally, some subjects in both the empagliflozin and placebo arm 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 linagliptin 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 49. 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 50). 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 51). 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 49: 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)

	Empagliflozin Pooled (N=52)	Linagliptin (N=52)	Placebo (N=53)

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 50: 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 51: 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.

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-study 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 Tradjenta from May 2011 through April 2022 is estimated to be 25,874,424 patient years. The cumulative global post-marketing adult patient exposure to Jentadueto (IR and XR formulations) from February 2012 through April 2022 is estimated to be 5,468,957 patient years.

Following the initial approval of Tradjenta, important safety issues identified either in the postmarket setting or in clinical trials of linagliptin and/or other DPP-4 inhibitors include acute pancreatitis (including fatal pancreatitis), serious hypersensitivity reactions (including anaphylaxis, angioedema and exfoliative skin conditions), severe and disabling arthralgia, bullous pemphigoid, and heart failure. These safety issues are currently described in the PI for linagliptin-containing products.

No new safety issues were identified in a review of the most recent periodic Benefit-Risk

Evaluation Report for Tradjenta, Jentadueto or Jentadueto XR (reporting period reporting period from May 3, 2021 to May 2, 2022) or in the 4-month safety update submitted by the Applicant on April 5, 2023 (covering the period from May 3, 2022 through December 31, 2022). According to the Applicant, off-label use of linagliptin has been documented in 44 pediatric patients and off-label use of linagliptin/metformin (fixed-dose combination product) has been documented in 8 pediatric patients, but no relevant difference in the safety profile was observed between adults and off-label use in pediatric patients below 18 years of age.

8.9.2. Expectations on Safety in the Postmarket Setting

This section is not relevant since a pediatric indication is not being granted.

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 linagliptin in adults with T2D are well-characterized, and include pancreatitis, hypoglycemia with concomitant use of insulin or insulin secretagogues, hypersensitivity reactions, arthralgia, bullous pemphigoid and heart failure.

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

No deaths occurred in the study. SAEs occurred in 2 (3.8%) subjects treated with linagliptin during the placebo-controlled period and in 6 (9.2%) subjects treated with linagliptin during the safety-extension period; none were assessed as related to treatment. With regard to AESIs, no events of skin lesions, bullous pemphigoid or pancreatic cancer occurred in the study. No events of pancreatitis occurred in subjects treated with linagliptin. An AESI of mild to moderate hepatic injury occurred in a linagliptin-treated subject who had pre-study non-alcoholic liver disease however this event was considered unrelated to treatment after adjudication by the CEC. Other AESIs, including hypersensitivity reactions and arthralgia, reflected the safety profile of linagliptin described in adults. Common TEAEs appeared generally consistent with the reported safety profile of linagliptin in adults. No clinically meaningful changes in heart rate, blood pressure, or safety laboratory parameters were noted. Conclusions regarding the impact of linagliptin 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.

During the placebo-controlled period, there was an increased incidence and frequency of

hypoglycemia events in subjects treated with linagliptin as compared to placebo. Level 2 hypoglycemia, defined as blood glucose < 54 mg/dL, occurred in 15.4% of subjects treated with linagliptin versus 7.5% of subjects treated with placebo. These differences appear to have been largely driven by an increased risk of hypoglycemia in subjects treated with linagliptin with concomitant insulin use at baseline. Among subjects treated with insulin at baseline, Level 2 hypoglycemia occurred in 5 out of 22 subjects (22.7%) with treated linagliptin versus 3 out of 21 subjects (14.3%) treated with placebo. Overall, in pediatric T2D subjects, linagliptin appears to increase the risk of hypoglycemia predominantly in the setting of concomitant insulin use. This risk is similar to that described in adults, and is currently described in the Warnings and Precautions section of the USPI.

In summary, based on the submitted data from the DINAMO study, no new safety signals were identified in pediatric T2D subjects as compared to those described in adult studies.

9. Advisory Committee Meeting and Other External Consultations

An advisory committee meeting was not convened for this supplement.

10. Labeling Recommendations

10.1. Prescription Drug Labeling

Prescribing information is being addressed in internal labeling meetings and labeling negotiations with the Applicant (at the time of this review filing, labeling negotiations were ongoing). We recommend that Section 8.4 for the USPIs of Tradjenta, Jentadueto and Jentadueto XR be updated with an appropriate pediatric use statement clarifying that the safety and effectiveness have not been established in pediatric patients and summarizing the available evidence from the DINAMO study.

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.

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 52: Frequency of subjects with AEs with incidence > 5% in any treatment group prior to week 26 by system organ class, preferred term and Age

Age [years] at randomisation in categories: <15

System Organ Class/ Preferred Term	Pbo N	Pbo %	Pbo Time at risk [pt-yrs]	Pbo Rate/ [100 pt-yrs]	L5 N	L5 %	L5 Time at risk [pt-yrs]	L5 Rate/ [100 pt-yrs]
Number of patients in analysis set	26	100.0	12.1		25	100.0	12.1	
Number of patients with at least one adverse event	16	61.5	6.6	243.5	17	68.0	5.2	329.8
Infections and infestations	7	26.9	10.1	69.6	10	40.0	8.8	113.8
Nasopharyngitis	1	3.8	12.0	8.3	1	4.0	11.7	8.6
Urinary tract infection	0	0.0	12.1	0.0	1	4.0	11.7	8.5
Influenza	0	0.0	12.1	0.0	1	4.0	11.7	8.5
Metabolism and nutrition disorders	5	19.2	10.4	47.9	7	28.0	9.5	73.5
Hypoglycaemia	4	15.4	10.5	37.9	4	16.0	11.0	36.3
Vitamin D deficiency	1	3.8	11.6	8.6	2	8.0	11.1	18.0
Hyperglycaemia	1	3.8	11.9	8.4	0	0.0	12.1	0.0
Gastrointestinal disorders	4	15.4	10.8	37.2	3	12.0	10.9	27.5
Abdominal pain	3	11.5	11.1	27.0	1	4.0	11.7	8.5
Diarrhoea	2	7.7	11.6	17.3	1	4.0	11.8	8.5
Vomiting	1	3.8	11.8	8.4	0	0.0	12.1	0.0
Nausea	0	0.0	12.1	0.0	1	4.0	11.7	8.6
Nervous system disorders	3	11.5	10.9	27.6	4	16.0	10.8	36.9
Headache	2	7.7	11.3	17.7	3	12.0	11.2	26.8
Dizziness	1	3.8	11.7	8.6	0	0.0	12.1	0.0
Investigations	2	7.7	11.1	18.0	4	16.0	10.5	38.3
Blood ketone body increased	0	0.0	12.1	0.0	1	4.0	11.7	8.6
Respiratory, thoracic and mediastinal disorders	4	15.4	11.3	35.4	4	16.0	11.2	35.9
Cough	2	7.7	11.4	17.5	0	0.0	12.1	0.0
Epistaxis	0	0.0	12.1	0.0	2	8.0	11.7	17.1
Renal and urinary disorders	1	3.8	12.1	8.3	3	12.0	10.8	27.8
Microalbuminuria	0	0.0	12.1	0.0	2	8.0	11.2	17.8
Skin and subcutaneous tissue disorders	0	0.0	12.1	0.0	2	8.0	11.3	17.7
Rash	0	0.0	12.1	0.0	1	4.0	11.7	8.5
Immune system disorders	0	0.0	12.1	0.0	0	0.0	12.1	0.0
Seasonal allergy	0	0.0	12.1	0.0	0	0.0	12.1	0.0

Age [years] at randomisation in categories: >=15 to <18

System Organ Class/ Preferred Term	Pbo N	Pbo %	Pbo Time at risk [pt-yrs]	Pbo Rate/ [100 pt-yrs]	L5 N	L5 %	L5 Time at risk [pt-yrs]	L5 Rate/ [100 pt-yrs]
Number of patients in analysis set	27	100.0	13.0		27	100.0	12.6	
Number of patients with at least one adverse event	18	66.7	5.8	308.1	20	74.1	4.9	406.3
Infections and infestations	6	22.2	10.9	55.2	13	48.1	9.0	144.5
Nasopharyngitis	2	7.4	12.3	16.3	2	7.4	12.3	16.3
Urinary tract infection	1	3.7	12.6	8.0	0	0.0	12.6	0.0
Influenza	0	0.0	13.0	0.0	2	7.4	12.2	16.4
Metabolism and nutrition disorders	7	25.9	10.3	68.2	9	33.3	9.0	99.9
Hypoglycaemia	1	3.7	12.5	8.0	6	22.2	10.2	58.8
Vitamin D deficiency	4	14.8	11.4	35.1	1	3.7	12.2	8.2
Hyperglycaemia	2	7.4	12.3	16.2	0	0.0	12.6	0.0
Gastrointestinal disorders	6	22.2	11.3	53.2	9	33.3	10.4	86.3
Abdominal pain	1	3.7	12.9	7.7	3	11.1	11.9	25.3
Diarrhoea	3	11.1	11.9	25.1	2	7.4	12.2	16.5
Vomiting	1	3.7	13.0	7.7	5	18.5	11.8	42.5
Nausea	3	11.1	11.9	25.2	2	7.4	11.9	16.8
Nervous system disorders	8	29.6	10.7	74.6	6	22.2	10.5	57.0
Headache	5	18.5	11.3	44.3	6	22.2	10.5	57.0
Dizziness	2	7.4	12.5	16.0	1	3.7	12.3	8.1
Investigations	5	18.5	11.4	43.8	7	25.9	9.5	73.4
Blood ketone body increased	2	7.4	12.4	16.1	3	11.1	11.2	26.9
Respiratory, thoracic and mediastinal disorders	4	14.8	11.8	33.9	7	25.9	11.4	61.2
Cough	2	7.4	12.4	16.2	3	11.1	12.6	23.9
Epistaxis	0	0.0	13.0	0.0	1	3.7	12.6	7.9
Renal and urinary disorders	2	7.4	12.3	16.3	3	11.1	11.4	26.3
Microalbuminuria	1	3.7	12.5	8.0	1	3.7	12.1	8.2
Skin and subcutaneous tissue disorders	1	3.7	12.7	7.9	2	7.4	12.0	16.7
Rash	0	0.0	13.0	0.0	0	0.0	12.6	0.0
Immune system disorders	0	0.0	13.0	0.0	0	0.0	12.6	0.0
Seasonal allergy	0	0.0	13.0	0.0	0	0.0	12.6	0.0

Source: Applicants 5/23/2023 submission (SDN 527)
Pbo = Placebo, L5 = Linagliptin 5 mg.
Percentages are calculated using total number of patients per treatment as denominator.
MedDRA version used for reporting: 25.0

Table 53: Frequency of subjects with AEs with incidence > 5% in any treatment group prior to week 26 by system organ class, preferred term and sex

Sex: Male

System Organ Class/ Preferred Term	Pbo N	Pbo %	Pbo Time at risk [pt-yrs]	Pbo Rate/ [100 pt-yrs]	L5 N	L5 %	L5 Time at risk [pt-yrs]	L5 Rate/ [100 pt-yrs]
Number of patients in analysis set	19	100.0	9.3		22	100.0	10.1	
Number of patients with at least one adverse event	15	78.9	3.5	424.4	16	72.7	4.0	403.3
Infections and infestations	5	26.3	7.6	65.4	9	40.9	7.3	123.8
Nasopharyngitis	2	10.5	8.6	23.2	2	9.1	9.7	20.6
Urinary tract infection	0	0.0	9.3	0.0	1	4.5	9.6	10.4
Influenza	0	0.0	9.3	0.0	0	0.0	10.1	0.0
Metabolism and nutrition disorders	6	31.6	7.0	86.1	5	22.7	7.9	62.9
Hypoglycaemia	1	5.3	8.8	11.3	3	13.6	8.9	33.8
Vitamin D deficiency	3	15.8	8.2	36.8	1	4.5	9.6	10.4
Hyperglycaemia	2	10.5	8.7	23.1	0	0.0	10.1	0.0
Gastrointestinal disorders	3	15.8	8.5	35.3	3	13.6	9.6	31.2
Abdominal pain	2	10.5	8.8	22.7	0	0.0	10.1	0.0
Diarrhoea	1	5.3	9.3	10.8	1	4.5	10.0	10.0
Vomiting	0	0.0	9.3	0.0	1	4.5	9.8	10.2
Nausea	0	0.0	9.3	0.0	0	0.0	10.1	0.0
Nervous system disorders	5	26.3	8.1	61.5	3	13.6	9.0	33.3
Headache	4	21.1	8.2	48.6	3	13.6	9.0	33.3
Dizziness	0	0.0	9.3	0.0	0	0.0	10.1	0.0
Investigations	4	21.1	7.8	51.2	4	18.2	8.3	47.9
Blood ketone body increased	1	5.3	9.2	10.8	1	4.5	9.6	10.5
Respiratory, thoracic and mediastinal disorders	5	26.3	7.8	64.0	4	18.2	9.0	44.2
Cough	2	10.5	8.5	23.6	2	9.1	10.0	20.0
Epistaxis	0	0.0	9.3	0.0	1	4.5	10.1	9.9
Renal and urinary disorders	1	5.3	8.9	11.3	2	9.1	9.2	21.9
Microalbuminuria	1	5.3	8.9	11.3	2	9.1	9.2	21.9
Skin and subcutaneous tissue disorders	1	5.3	9.1	11.0	2	9.1	9.4	21.2
Rash	0	0.0	9.3	0.0	0	0.0	10.1	0.0
Immune system disorders	0	0.0	9.3	0.0	0	0.0	10.1	0.0
Seasonal allergy	0	0.0	9.3	0.0	0	0.0	10.1	0.0

Sex: Female

System Organ Class/ Preferred Term	Pbo N	Pbo %	Pbo Time at risk [pt-yrs]	Pbo Rate/ [100 pt-yrs]	L5 N	L5 %	L5 Time at risk [pt-yrs]	L5 Rate/ [100 pt-yrs]
Number of patients in analysis set	34	100.0	15.7		30	100.0	14.7	
Number of patients with at least one adverse event	19	55.9	8.9	214.0	21	70.0	6.1	343.6
Infections and infestations	8	23.5	13.3	60.2	14	46.7	10.5	133.1
Nasopharyngitis	1	2.9	15.7	6.4	1	3.3	14.2	7.0
Urinary tract infection	1	2.9	15.3	6.5	0	0.0	14.7	0.0
Influenza	0	0.0	15.7	0.0	3	10.0	13.9	21.6
Metabolism and nutrition disorders	6	17.6	13.7	43.7	11	36.7	10.6	104.0
Hypoglycaemia	4	11.8	14.2	28.1	7	23.3	12.4	56.6
Vitamin D deficiency	2	5.9	14.8	13.5	2	6.7	13.7	14.6
Hyperglycaemia	1	2.9	15.6	6.4	0	0.0	14.7	0.0
Gastrointestinal disorders	7	20.6	13.6	51.7	9	30.0	11.7	76.8
Abdominal pain	2	5.9	15.2	13.1	4	13.3	13.5	29.5
Diarrhoea	4	11.8	14.2	28.2	2	6.7	13.9	14.4
Vomiting	2	5.9	15.5	12.9	4	13.3	14.2	28.2
Nausea	3	8.8	14.7	20.5	3	10.0	13.5	22.2
Nervous system disorders	6	17.6	13.5	44.6	7	23.3	12.3	56.7
Headache	3	8.8	14.3	20.9	6	20.0	12.7	47.2
Dizziness	3	8.8	14.9	20.2	1	3.3	14.4	6.9
Investigations	3	8.8	14.7	20.4	7	23.3	11.6	60.1
Blood ketone body increased	1	2.9	15.3	6.5	3	10.0	13.3	22.6
Respiratory, thoracic and mediastinal disorders	3	8.8	15.3	19.6	7	23.3	13.5	51.7
Cough	2	5.9	15.3	13.1	1	3.3	14.7	6.8
Epistaxis	0	0.0	15.7	0.0	2	6.7	14.3	14.0
Renal and urinary disorders	2	5.9	15.5	12.9	4	13.3	13.0	30.7
Microalbuminuria	0	0.0	15.7	0.0	1	3.3	14.2	7.0
Skin and subcutaneous tissue disorders	0	0.0	15.7	0.0	2	6.7	13.8	14.5
Rash	0	0.0	15.7	0.0	1	3.3	14.3	7.0
Immune system disorders	0	0.0	15.7	0.0	0	0.0	14.7	0.0
Seasonal allergy	0	0.0	15.7	0.0	0	0.0	14.7	0.0

Source: Applicants 5/23/2023 submission (SDN 527)
Pbo = Placebo, L5 = Linagliptin 5 mg.
Percentages are calculated using total number of patients per treatment as denominator.
MedDRA version used for reporting: 25.0

Table 54: Frequency of subjects with AEs with incidence > 5% in any treatment group prior to week 26 by system organ class, preferred term and race

Race: White

System Organ Class/ Preferred Term	Pbo N	Pbo %	Pbo Time at risk [pt-yrs]	Pbo Rate/ [100 pt-yrs]	L5 N	L5 %	L5 Time at risk [pt-yrs]	L5 Rate/ [100 pt-yrs]
Number of patients in analysis set	29	100.0	14.6		26	100.0	12.6	
Number of patients with at least one adverse event	16	55.2	8.0	200.4	16	61.5	6.8	235.2
Infections and infestations	8	27.6	12.1	66.2	9	34.6	9.9	90.5
Nasopharyngitis	1	3.4	14.3	7.0	1	3.8	12.2	8.2
Urinary tract infection	0	0.0	14.6	0.0	1	3.8	12.2	8.2
Influenza	0	0.0	14.6	0.0	1	3.8	12.2	8.2
Metabolism and nutrition disorders	6	20.7	12.3	48.9	4	15.4	10.7	37.2
Hypoglycaemia	2	6.9	14.0	14.3	1	3.8	12.2	8.2
Vitamin D deficiency	3	10.3	13.1	22.9	1	3.8	12.2	8.2
Hyperglycaemia	2	6.9	13.9	14.4	0	0.0	12.6	0.0
Gastrointestinal disorders	5	17.2	12.6	39.8	5	19.2	10.9	46.0
Abdominal pain	1	3.4	14.1	7.1	2	7.7	11.9	16.8
Diarrhoea	4	13.8	13.1	30.6	1	3.8	12.2	8.2
Vomiting	1	3.4	14.4	7.0	3	11.5	12.1	24.8
Nausea	3	10.3	13.5	22.2	1	3.8	12.2	8.2
Nervous system disorders	5	17.2	13.2	37.8	2	7.7	11.7	17.1
Headache	3	10.3	13.5	22.2	2	7.7	11.7	17.1
Dizziness	1	3.4	14.4	6.9	0	0.0	12.6	0.0
Investigations	3	10.3	13.6	22.0	3	11.5	11.6	25.8
Blood ketone body increased	0	0.0	14.6	0.0	0	0.0	12.6	0.0
Respiratory, thoracic and mediastinal disorders	1	3.4	14.1	7.1	4	15.4	11.6	34.6
Cough	1	3.4	14.1	7.1	1	3.8	12.6	7.9
Epistaxis	0	0.0	14.6	0.0	2	7.7	12.2	16.4
Renal and urinary disorders	1	3.4	14.1	7.1	4	15.4	10.9	36.6
Microalbuminuria	1	3.4	14.1	7.1	3	11.5	11.2	26.7
Skin and subcutaneous tissue disorders	0	0.0	14.6	0.0	2	7.7	11.7	17.0
Rash	0	0.0	14.6	0.0	1	3.8	12.2	8.2
Immune system disorders	0	0.0	14.6	0.0	0	0.0	12.6	0.0
Seasonal allergy	0	0.0	14.6	0.0	0	0.0	12.6	0.0

Race: All other respondents (Including Multiple/missing race respondent)

System Organ Class/ Preferred Term	Pbo N	Pbo %	Pbo Time at risk [pt-yrs]	Pbo Rate/ [100 pt-yrs]	L5 N	L5 %	L5 Time at risk [pt-yrs]	L5 Rate/ [100 pt-yrs]
Number of patients in analysis set	24	100.0	10.5		26	100.0	12.1	
Number of patients with at least one adverse event	18	75.0	4.4	406.3	21	80.8	3.3	641.3
Infections and infestations	5	20.8	8.8	56.5	14	53.8	7.8	178.4
Nasopharyngitis	2	8.3	10.0	20.0	2	7.7	11.8	16.9
Urinary tract infection	1	4.2	10.1	9.9	0	0.0	12.1	0.0
Influenza	0	0.0	10.5	0.0	2	7.7	11.8	17.0
Metabolism and nutrition disorders	6	25.0	8.4	71.1	12	46.2	7.8	154.2
Hypoglycaemia	3	12.5	9.1	33.1	9	34.6	9.1	99.3
Vitamin D deficiency	2	8.3	9.9	20.2	2	7.7	11.1	17.9
Hyperglycaemia	1	4.2	10.3	9.7	0	0.0	12.1	0.0
Gastrointestinal disorders	5	20.8	9.5	52.8	7	26.9	10.4	67.0
Abdominal pain	3	12.5	9.9	30.2	2	7.7	11.7	17.1
Diarrhoea	1	4.2	10.4	9.6	2	7.7	11.7	17.1
Vomiting	1	4.2	10.5	9.5	2	7.7	11.8	16.9
Nausea	0	0.0	10.5	0.0	2	7.7	11.4	17.5
Nervous system disorders	6	25.0	8.4	71.8	8	30.8	9.6	83.1
Headache	4	16.7	9.1	44.1	7	26.9	10.0	70.1
Dizziness	2	8.3	9.8	20.5	1	3.8	11.9	8.4
Investigations	4	16.7	8.9	45.0	8	30.8	8.4	95.4
Blood ketone body increased	2	8.3	9.9	20.2	4	15.4	10.2	39.0
Respiratory, thoracic and mediastinal disorders	7	29.2	9.0	78.2	7	26.9	11.0	63.4
Cough	3	12.5	9.6	31.1	2	7.7	12.1	16.5
Epistaxis	0	0.0	10.5	0.0	1	3.8	12.1	8.3
Renal and urinary disorders	2	8.3	10.3	19.5	2	7.7	11.3	17.8
Microalbuminuria	0	0.0	10.5	0.0	0	0.0	12.1	0.0
Skin and subcutaneous tissue disorders	1	4.2	10.2	9.8	2	7.7	11.5	17.3
Rash	0	0.0	10.5	0.0	0	0.0	12.1	0.0
Immune system disorders	0	0.0	10.5	0.0	0	0.0	12.1	0.0
Seasonal allergy	0	0.0	10.5	0.0	0	0.0	12.1	0.0

Source: Applicants 5/23/2023 submission (SDN 527)
Pbo = Placebo, L5 = Linagliptin 5 mg.
Percentages are calculated using total number of patients per treatment as denominator.
MedDRA version used for reporting: 25.0

Table 55: Frequency of subjects with AEs with incidence > 5% in any treatment group prior to week 26 by system organ class, preferred term and ethnicity

Ethnicity: Not Hispanic or Latino

System Organ Class/ Preferred Term	Pbo N	Pbo %	Pbo Time at risk [pt-yrs]	Pbo Rate/ [100 pt-yrs]	L5 N	L5 %	L5 Time at risk [pt-yrs]	L5 Rate/ [100 pt-yrs]
Number of patients in analysis set	32	100.0	14.9		30	100.0	14.7	
Number of patients with at least one adverse event	23	71.9	6.3	363.2	23	76.7	5.1	447.3
Infections and infestations	7	21.9	13.0	53.9	15	50.0	9.9	151.1
Nasopharyngitis	1	3.1	14.9	6.7	2	6.7	13.9	14.4
Urinary tract infection	1	3.1	14.5	6.9	0	0.0	14.7	0.0
Influenza	0	0.0	14.9	0.0	2	6.7	13.9	14.4
Metabolism and nutrition disorders	11	34.4	11.1	99.4	10	33.3	10.8	92.4
Hypoglycaemia	5	15.6	12.9	38.7	8	26.7	11.6	69.0
Vitamin D deficiency	4	12.5	13.3	30.0	1	3.3	14.2	7.1
Hyperglycaemia	3	9.4	14.1	21.2	0	0.0	14.7	0.0
Gastrointestinal disorders	8	25.0	12.5	64.2	8	26.7	12.4	64.6
Abdominal pain	4	12.5	13.9	28.8	2	6.7	13.8	14.5
Diarrhoea	3	9.4	13.9	21.6	2	6.7	14.2	14.1
Vomiting	2	6.3	14.7	13.6	3	10.0	14.1	21.3
Nausea	2	6.3	14.4	13.9	2	6.7	13.9	14.4
Nervous system disorders	7	21.9	12.5	56.1	7	23.3	12.2	57.3
Headache	6	18.8	12.6	47.7	7	23.3	12.3	57.0
Dizziness	0	0.0	14.9	0.0	1	3.3	14.4	7.0
Investigations	7	21.9	12.4	56.6	9	30.0	10.6	84.8
Blood ketone body increased	2	6.3	14.4	13.9	4	13.3	12.8	31.4
Respiratory, thoracic and mediastinal disorders	7	21.9	13.5	51.9	7	23.3	13.4	52.2
Cough	4	12.5	13.6	29.3	1	3.3	14.6	6.8
Epistaxis	0	0.0	14.9	0.0	2	6.7	14.2	14.1
Renal and urinary disorders	3	9.4	14.2	21.1	3	10.0	13.3	22.6
Microalbuminuria	1	3.1	14.5	6.9	1	3.3	14.2	7.1
Skin and subcutaneous tissue disorders	1	3.1	14.7	6.8	2	6.7	14.1	14.2
Rash	0	0.0	14.9	0.0	1	3.3	14.2	7.0
Immune system disorders	0	0.0	14.9	0.0	0	0.0	14.7	0.0
Seasonal allergy	0	0.0	14.9	0.0	0	0.0	14.7	0.0

Ethnicity: Hispanic or Latino

System Organ Class/ Preferred Term	Pbo N	Pbo %	Pbo Time at risk [pt-yrs]	Pbo Rate/ [100 pt-yrs]	L5 N	L5 %	L5 Time at risk [pt-yrs]	L5 Rate/ [100 pt-yrs]
Number of patients in analysis set	21	100.0	10.1		22	100.0	10.1	
Number of patients with at least one adverse event	11	52.4	6.1	180.9	14	63.6	4.9	283.6
Infections and infestations	6	28.6	7.9	75.5	8	36.4	7.9	101.8
Nasopharyngitis	2	9.5	9.4	21.2	1	4.5	10.1	9.9
Urinary tract infection	0	0.0	10.1	0.0	1	4.5	9.7	10.3
Influenza	0	0.0	10.1	0.0	1	4.5	10.1	9.9
Metabolism and nutrition disorders	1	4.8	9.6	10.4	6	27.3	7.7	77.9
Hypoglycaemia	0	0.0	10.1	0.0	2	9.1	9.6	20.8
Vitamin D deficiency	1	4.8	9.6	10.4	2	9.1	9.1	21.9
Hyperglycaemia	0	0.0	10.1	0.0	0	0.0	10.1	0.0
Gastrointestinal disorders	2	9.5	9.6	20.9	4	18.2	8.9	44.7
Abdominal pain	0	0.0	10.1	0.0	2	9.1	9.8	20.5
Diarrhoea	2	9.5	9.6	20.9	1	4.5	9.7	10.3
Vomiting	0	0.0	10.1	0.0	2	9.1	9.8	20.4
Nausea	1	4.8	9.6	10.4	1	4.5	9.6	10.4
Nervous system disorders	4	19.0	9.1	44.0	3	13.6	9.1	32.8
Headache	1	4.8	10.0	10.0	2	9.1	9.4	21.2
Dizziness	3	14.3	9.3	32.4	0	0.0	10.1	0.0
Investigations	0	0.0	10.1	0.0	2	9.1	9.4	21.3
Blood ketone body increased	0	0.0	10.1	0.0	0	0.0	10.1	0.0
Respiratory, thoracic and mediastinal disorders	1	4.8	9.6	10.4	4	18.2	9.2	43.5
Cough	0	0.0	10.1	0.0	2	9.1	10.1	19.8
Epistaxis	0	0.0	10.1	0.0	1	4.5	10.1	9.9
Renal and urinary disorders	0	0.0	10.1	0.0	3	13.6	8.9	33.6
Microalbuminuria	0	0.0	10.1	0.0	2	9.1	9.2	21.7
Skin and subcutaneous tissue disorders	0	0.0	10.1	0.0	2	9.1	9.2	21.7
Rash	0	0.0	10.1	0.0	0	0.0	10.1	0.0
Immune system disorders	0	0.0	10.1	0.0	0	0.0	10.1	0.0
Seasonal allergy	0	0.0	10.1	0.0	0	0.0	10.1	0.0

Source: Applicants 5/23/2023 submission (SDN 527)
Pbo = Placebo, L5 = Linagliptin 5 mg.
Percentages are calculated using total number of patients per treatment as denominator.
MedDRA version used for reporting: 25.0

Table 56: Background Insulin Use at Baseline Among Selected Demographic Subgroups

	Empagliflozin pooled (N=52)	Linagliptin (N=52)	Placebo (N=53)
Female Subjects	15 (28.8)	13 (25.0)	14 (26.4)
Male Subjects	10 (19.2)	9 (17.3)	7 (13.2)
Subjects aged >/= 15 years	15 (28.8)	12 (23.1)	7 (13.2)

	Empagliflozin pooled (N=52)	Linagliptin (N=52)	Placebo (N=53)
Subjects aged <15 years	10 (19.2)	10 (19.2)	14 (26.4)
Subjects of Non-White Race	17 (32.7)	11 (21.2)	12 (22.6)
Subjects of White Race	8 (15.4)	11 (21.2)	9 (17.0)

Source: OCS Analysis Studio Custom Table Tool.
Columns - Dataset: Demographics Filter: TRTFL = 'Y'.
Female Subjects - Dataset: Demographics Filter: SEX = 'F' BGMEDBL = 'Insulin only' or 'Metformin and Insulin'.
Male Subjects - Dataset: Demographics; Filter: SEX = 'M', BGMEDBL = 'Insulin only' or 'Metformin and Insulin'.
Subjects aged >/= 15 years - Dataset: Demographics; Filter: AGEGR1 = '>=15 to <18', BGMEDBL = 'Insulin only' or 'Metformin and Insulin'.
Subjects aged <15 years - Dataset: Demographics; Filter: AGEGR1 = '<15', BGMEDBL = 'Metformin and Insulin' or 'Insulin only'.
Subjects of Non-White Race - Dataset: Demographics; Filter: BGMEDBL = 'Insulin only' or 'Metformin and Insulin', 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'.
Subjects of White Race - Dataset: Demographics; Filter: RACE = 'WHITE', BGMEDBL = 'Insulin only' or 'Metformin and Insulin'.

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