NDA Multi-Disciplinary Review and Evaluation

Application Type	505(b)(1) Supplemental New Drug Application (sNDA)
Application Number(s)	NDA 215866/S-039
Priority or Standard	Priority
Submit Date(s)	June 19, 2025
Received Date(s)	June 19, 2025
PDUFA Goal Date	December 19, 2025
Division/Office	Division of Diabetes, Lipid Disorders, and Obesity (DDLO) / Office of Cardiology, Hematology, Endocrinology and Nephrology (OCHEN)
Review Completion Date	November 26, 2025
Established/Proper Name	Tirzepatide
(Proposed) Trade Name	Mounjaro
Pharmacologic Class	Glucose-dependent insulinotropic polypeptide (GIP) receptor and glucagon-like peptide 1 (GLP 1) receptor agonist
Code name	LY3298176
Applicant	Eli Lilly and Company (Lilly)
Dosage form	Solution for Injection: 2.5 mg, 5 mg, 7.5 mg, 10 mg, 12.5 mg, or 15 mg per 0.5 mL in single-dose pen or single-dose vial
Applicant proposed Dosing Regimen	**Starting Dose:** 2.5 mg injected subcutaneously (SC) once weekly (QW) **Titration:** After 4 weeks, increase to 5 mg SC QW. If additional glycemic control is needed, the dosage may be increased in 2.5 mg increments after at least 4 weeks on the current dose. **Maximum Dosage:** 10 mg SC QW for pediatric patients.
Applicant Proposed Indication(s)/Population(s)	As an adjunct to diet and exercise to improve glycemic control in pediatric patients 10 years of age and older with type 2 diabetes mellitus.
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	As an adjunct to diet and exercise to improve glycemic control in pediatric patients 10 years of age and older with type 2 diabetes mellitus.
Recommended Dosing Regimen	The recommended dosing regimen is the same as that proposed by the Applicant.

Reference ID: 5715650

Table of Contents

Table of Tables 4
Table of Figures 6
Reviewers of Multi-Disciplinary Review and Evaluation 7
1 Applicant's Proposed Indication, Dose, and Schedule 7
2 Executive Summary 7
2.1. Introduction 7
2.2. Conclusions on the Substantial Evidence of Effectiveness 8
2.3. Benefit-Risk Assessment 9
3 Background 12
3.1. Patient Experience Data 12
3.2. Regulatory Background 13
4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety 13
4.1. Office of Scientific Investigations (OSI) 13
4.2. Division of Medication Error Prevention and Analysis (DMEPA) 1 14
4.3. Clinical Pharmacology 14
4.3.1. Executive Summary 14
4.3.2. Clinical Pharmacology Questions 15
5 Statistical/Clinical Efficacy 16
5.1. Study Design 16
5.2. Eligibility criteria 18
5.3. Study Endpoints 18
5.4. Statistical Analysis Plan/Statistical Methodology 19
5.5. Study Results 22
5.5.1. Subject Disposition 23
5.5.2. Protocol Violations/Deviations 23
5.5.3. Demographic and Baseline Characteristics 24
5.5.4. Treatment Compliance, Concurrent Medications, Rescue 25
5.5.5. Primary Endpoint 26
5.5.6. Subgroup Analyses 27
5.5.7. Key Secondary Endpoints 29
5.5.8. Dose-Response 31
5.5.9. Durability of Response 32
5.5.10. Statistical Issues 32

Reference ID: 5715650

6 Clinical Safety 33
6.1. Safety Results 33
6.1.1. Deaths 33
6.1.2. Serious Adverse Events 34
6.1.3. Dropouts and/or Discontinuations Due to Adverse Effects 34
6.1.4. Adverse Events of Special Interest 35
6.1.5. Treatment Emergent Adverse Events 40
6.1.6. Laboratory Findings 41
6.1.7. Vital Signs 42
6.1.8. Electrocardiograms (ECGs) 42
6.1.9. Immunogenicity 43
6.2. Safety Analyses by Demographic Subgroups 44
6.3. Additional Safety Explorations 44
6.4. Safety in the Postmarket Setting 45
7 Labeling Recommendations 46
8 Appendices 48
8.1. Financial Disclosure 48
8.2. Safety Table for Treatment-Emergent Adverse Events – Trial GPGV 49
8.3. Abnormal Liver Laboratory 52
8.4. Additional Statistical Analyses 56
8.5. Summary of Clinical Pharmacology Assessment 62
8.5.1. Pharmacology and Clinical Pharmacokinetics 62
8.5.2. Therapeutic Individualization 62
8.5.3. General Pharmacology and Pharmacokinetic Characteristics 62
8.6. OCP Appendices (Technical documents supporting OCP recommendations) 65
8.6.1. Pharmacometric Analysis 65
8.7. Approved Antihyperglycemics for Pediatric Type 2 Diabetes 91
8.8. Summary of Presubmission/Submission Regulatory History 99
8.9. Glossary 101
8.10. References 106

Reference ID: 5715650

Table of Tables

Table 1: Subject Disposition for Trial GPGV (Double-blind, Open-label, Follow-up)..... 23
Table 2: Important Protocol Deviations (Randomized Subjects, Double-Blind)..... 24
Table 3: Demographic Characteristics 24
Table 4: Other Baseline Characteristics 25
Table 5: Data Capture for the Primary Endpoint 27
Table 6: Primary Analysis Results for Change in A1C from Baseline to Week 30..... 27
Table 7: Results for the Incidence of ≤6.5% A1C at Week 30..... 30
Table 8: Results for Change in BMI from Baseline to Week 30 30
Table 9: Results for Change in BMI-SDS from Baseline to Week 30..... 31
Table 10: Results for Change in FSG from Baseline to Week 30 31
Table 11: Summary of Level 2 and 3 Hypoglycemic Episodes During 30-Week Treatment Period 39
Table 12: Rate Ratios of Level 2 Hypoglycemic Episodes During the 30-Week Treatment Period 39
Table 13: Level 2 Hypoglycemic Episodes During 30-Week Treatment Period by Insulin Use 40
Table 14: Key Labeling Changes and Considerations for Selected Sections of the Prescribing Information 46
Table 15: Summary of Clinical Investigator Financial Disclosure Information 48
Table 16: Summary of Treatment-Emergent Adverse Events During 30-Week Treatment Period 49
Table 17: Abnormal Liver Laboratory Test Results by Study Visit 52
Table 18: Applicant's Results for the Primary and Key Secondary Endpoints..... 56
Table 19: Tabulation of A1C Measurements Relative to Day 211..... 56
Table 20: Disposition of 10 Subjects with Week 30 Measurement Outside the 7-Day Window. 57
Table 21: Disposition of Missing Data for Window Analysis 57
Table 22: Sensitivity Window Analysis Results for Change in A1C from Baseline to Week 30 57
Table 23: Sensitivity Analysis Considering all Subjects on Tirzepatide, Irrespective of EOT Status, with Placebo Wash-Out 58
Table 24: Treatment Differences as A1C Increases 60
Table 25: Specific Comments on Applicant's Final Population PK model 65
Table 26: Summary of Study with PK Sampling Included in Population PK Analysis. 67
Table 27: Summary of Baseline Demographic for Continuous Covariates by Treatment Arm for Analysis 67
Table 28: Summary of Baseline Demographic for Categorical Covariates by Treatment Arm for Analysis 68
Table 29: Parameter Estimates (RSE) and Median (95% CI) for the Applicant's Final Model..... 70
Table 30: Summary of simulated steady-state tirzepatide exposures in pediatrics and adults. . 74
Table 31. Data summary of subjects (number) and observations (number and percent) by treatment arm for the ER analysis dataset. 77

Reference ID: 5715650

Table 32: Parameter estimates for the final ER model for fasting glucose and A1C..... 79
Table 33: ER of fasting glucose and A1C final model: model-predicted change from baseline and percentage change from baseline of fasting glucose and hemoglobin A1c at 30 and 52 weeks for different doses. 82
Table 34: ER of body weight: data summary of subjects (number) and observations (number and percent)..... 83
Table 35: Parameter estimates for the final ER model for body weight. 84
Table 36: ER of body weight final model: model-predicted dose-response after 30 and 52 weeks of treatment..... 87
Table 37: Summary of Method Validation and Performance..... 89
Table 38: FDA Approved Therapies for the Proposed Pediatric Indication..... 91

Reference ID: 5715650

Table of Figures

Figure 1: Trial design -SURPASS-PEDS 17
Figure 2: Graphical testing scheme to strongly control the type 1 error at a 2-sided alpha of 0.05 for the primary and key secondary endpoints 22
Figure 3: Forest Plot of Subgroup Analyses: Sex, Age, and Region 28
Figure 4: Forest Plot of Subgroup Analyses: Race and Ethnicity 29
Figure 5: DILI Plot of Peak On-Treatment Liver Laboratory Test 38
Figure 6: A1C – Two-Way Tipping Point Analysis (Heatmap) for the Primary Endpoint 59
Figure 7: Scatter Plot and Regression Lines Based on Completers for Individual Doses and Placebo 60
Figure 8: Scatter Plot and Regression Lines Based on Completers for Pooled Tirzepatide and Placebo 61
Figure 9: Standard goodness of fit plots for the Applicant's final covariate model 71
Figure 10: pcVPC of the Applicant's final tirzepatide population PK Model 72
Figure 11: Simulated steady-state tirzepatide concentration versus time in pediatrics and adults. 73
Figure 12: Simulated tirzepatide area under the concentration-time curve over the dosing interval at steady state AUC_{ss} and steady state $C_{max,ss}$ in pediatrics and adults 74
Figure 13: Simulated tirzepatide area under the concentration-time curve over the dosing interval at steady state (AUC_{ss}) and maximum concentration in the dosing interval at steady state ($C_{max,ss}$) over a range of baseline body weights. 75
Figure 14: Simulated tirzepatide area under the concentration-time curve over the dosing interval. 76
Figure 15: Basic structure of the ER model for fasting glucose and A1C 78
Figure 16: ER of fasting glucose and A1C final model: prediction corrected visual predictive check of fasting glucose and hemoglobin A1c versus time stratified by treatment arm 80
Figure 17: ER of fasting glucose and A1C final model: Dose response plots of percentage change from baseline of fasting glucose and hemoglobin A1c at 30 and 52 weeks stratified by treatment arm. 81
Figure 18: Basic structure of the ER model for body weight. 83
Figure 19: ER of body weight final model: prediction-corrected visual predictive check of the change from baseline of fat-free mass, fat mass, and total body weight versus time by treatment. 85
Figure 20: ER of bodyweight final model: dose response plots of percent change from baseline of fat-free mass, fat mass, and total body weight 30 and 52 weeks stratified by treatment arm and dose 86

Reference ID: 5715650

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1 Applicant's Proposed Indication, Dose, and Schedule

Proposed indication: As an adjunct to diet and exercise to improve glycemic control in pediatric patients 10 years of age and older with type 2 diabetes mellitus.

The recommended starting dosage is 2.5 mg injected subcutaneously once weekly. After 4 weeks, increase to 5 mg injected subcutaneously once weekly. If additional glycemic control is needed, increase the dosage in 2.5 mg increments after at least 4 weeks on the current dose.

The adult maximum dosage is 15 mg subcutaneously once weekly. The pediatric maximum dosage is 10 mg subcutaneously once weekly. The label states "Administer once weekly at any time of day, with or without meals. Inject subcutaneously in the abdomen, thigh, or another person should inject in the back of the upper arm. Rotate injection sites with each dose".

2 Executive Summary

2.1. Introduction

The approval of Mounjaro for the treatment of type 2 diabetes (T2D) in adults included a Postmarketing Requirement (PMR 4271-1) to conduct a study in pediatric patients with T2D. This requirement was fulfilled by trial I8F-MC-GPGV (hereafter referred to as GPGV).

Tirzepatide is a long-acting glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptor agonist that selectively binds to and activates both GIP and GLP-1 receptors, enhancing glucose-dependent insulin secretion and reducing glucagon

Reference ID: 5715650

levels. The product received initial marketing authorization on May 13, 2022, in the United States (US) and September 15, 2022, in the European Union (EU) as an adjunct to diet and exercise to improve glycemic control in adults with T2D. Subsequent approvals in the US include chronic weight management (CWM) in adults with obesity or overweight with weight-related comorbidities (November 8, 2023) and the treatment of moderate-to-severe obstructive sleep apnea (OSA) in adults with obesity (December 20, 2024).

2.2. Conclusions on the Substantial Evidence of Effectiveness

This submission demonstrated substantial evidence of effectiveness for the proposed indication based on trial GPGV, a phase 3, 52-week, randomized, double-blind, placebo-controlled study of 99 pediatric subjects with T2D. The study showed highly persuasive results demonstrating improvement in glycemic control compared to placebo. Although T2D in pediatrics and adults has similar pathophysiology based on insulin resistance and hyperglycemia, pediatric T2D appears to have a more aggressive disease course and earlier onset of complications. This has been supported by the unsuccessful clinical trials for the dipeptidyl peptidase 4 product class in pediatric trials; these products are weak antihyperglycemic agents and have only modest efficacy in adults. Based on this, the FDA has generally required one adequate and well-controlled trial in pediatric patients to demonstrate efficacy while leveraging the extensive experience in adults to fully establish substantial evidence of effectiveness as required under 21 CFR 314.126(a)(b). Study GPGV showed statistically significant and clinically meaningful improvement in glycemic control (A1C reduction) compared to placebo (least-squares mean difference of -1.82%; 95% confidence interval: -2.42, -1.21). The key secondary glycemic endpoints were supportive of the primary efficacy finding, and clinically meaningful reductions from baseline in body mass index were also observed.

2.3. Benefit-Risk Assessment

Type 2 diabetes mellitus (T2D) in pediatric patients is an aggressive metabolic disorder characterized by severe insulin resistance and a rapid decline in β-cell function, leading to a high burden of early-onset microvascular and macrovascular complications.[1-3] The therapeutic landscape for pediatric patients is limited, and existing treatments often fail to provide durable glycemic control, representing a significant unmet medical need.

The 52-week phase 3 trial GPGV successfully demonstrated tirzepatide's (pooled 5 mg and 10 mg) superiority over placebo, achieving a -1.82% reduction in A1C ($p<0.0001$) with 74.5% of subjects reaching A1C ≤6.5% (key secondary endpoint) compared to 28.1% on placebo, along with significant body mass index (BMI) reduction (-8.31% versus placebo). Both the 5 mg and 10 mg doses were individually superior to placebo. These glycemic and weight-related benefits were sustained through the 52-week study duration, an important finding given the progressive nature of youth-onset T2D. Reduction in A1C is a validated surrogate endpoint in patients with diabetes based on large landmark outcomes trials demonstrating that improvement in glycemic control leads to reduction in the incidence of microvascular events, namely progression of diabetic retinopathy, nephropathy, and neuropathy. Improvement in glycemic control based on A1C reduction has served as the basis of approval for numerous drugs intended for use in T2D. A1C reduction of the magnitude observed in this trial is clinically meaningful.

The safety profile was consistent with the known adult safety data and the GLP-1 receptor agonist class and was characterized primarily by mild-to-moderate gastrointestinal events during dose escalation that diminished over time, manageable hypoglycemia risk (particularly with concomitant insulin use), and few aminotransferase elevations that were generally confounded by hepatic steatosis in subjects with baseline liver enzyme elevations. Serious adverse events (SAEs) were infrequent and no severe hypoglycemia was reported. Two subjects (6.3%) in the tirzepatide 5 mg group discontinued treatment due to adverse events (nausea and suicidal ideation). While no adverse effects on linear growth or pubertal development were observed, the one-year treatment duration in a pediatric population in which the majority had already reached puberty limits the interpretation of these data. The most serious risks, including but not limited to hypoglycemia, hypersensitivity reactions, gallbladder disease, and severe gastrointestinal reactions, have previously been characterized in trials of adults, and may be sufficiently mitigated with information in labeling.

The overall benefit-risk assessment is favorable, as tirzepatide provides substantial and durable improvements in both glycemic control and weight management that address key pathophysiological aspects of this progressive disease, with identified risks being manageable and consistent with known safety profiles, making the significant clinical benefits outweigh the risks in a condition with limited therapeutic options and high complication burden. All review disciplines support approval.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• The incidence of T2D is increasing in pediatric populations, with a 5.3% annual increase in the United States from 2002-2018, disproportionately affecting racial and ethnic minority populations and typically manifesting around puberty.[4] • Pediatric T2D is characterized by high treatment failure rates with standard-of-care therapies and rapid onset of complications, with the TODAY[1] study showing 15-year cumulative incidence of 80.1% for any microvascular complication.[5]	• While similar to adult T2D, pediatric T2D progresses more rapidly, and drugs effective in adults (e.g., sitagliptin) have failed in pediatric patients, thus requiring dedicated pediatric trials rather than full extrapolation from adult data. However, pediatric and adult T2D are sufficiently similar to leverage adequate and well-controlled trials in adults to provide confirmatory evidence of effectiveness as well as safety data.
Current Treatment Options	• Currently approved pharmacologic options include biguanides (metformin), insulins, some GLP-1 receptor agonists, sodium-glucose co-transportor-2 inhibitors (SGLT2i),[6] with metformin plus lifestyle interventions recommended as first-line therapy (Table 38).[7,8] • GLP-1 receptor agonists or SGLT2is are recommended as add-on therapy for inadequate glycemic control, while insulin is indicated for marked hyperglycemia (A1C ≥8.5%) or ketoacidosis but carries risks of weight gain and hypoglycemia.[7]	• Despite multiple available medications, many pediatric patients fail to achieve or maintain adequate glycemic control, thus highlighting the need for additional safe and effective treatment options.

[1] Treatment Options for Type 2 Diabetes in Adolescents and Youth

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• In trial GPGV, tirzepatide demonstrated superiority to placebo with a -1.82% reduction in A1C from baseline to Week 30, with 74.5% of patients achieving A1C ≤6.5% versus 28.1% on placebo. • Tirzepatide showed clinically meaningful reductions in BMI (-8.31% versus placebo) and BMI-standard deviation score (SDS; -0.51 vs. placebo), addressing the important comorbidity of obesity in this population.	• The glycemic and weight-related benefits of tirzepatide were maintained through 52 weeks of treatment, with additional improvements in cardiometabolic risk factors including fasting glucose, lipids, and blood pressure. • Tirzepatide was evaluated only as an add-on to background antihyperglycemic therapy, however, there is no reason to expect efficacy of tirzepatide would be different when used as monotherapy.
Risk and Risk Management	• Serious adverse events were infrequent. The most common treatment-emergent adverse events (TEAEs) were mild-to-moderate, transient gastrointestinal (GI) events (nausea, diarrhea, vomiting) consistent with the GLP-1 receptor agonist class, and one case of cholecystitis (open-label period). • Increased level 2 hypoglycemia (<54 mg/dL) occurred primarily with concomitant basal insulin use. • Aminotransferase elevations (>5× upper limit of normal [ULN]) were observed in three subjects with pre-existing hepatic steatosis but were transient and did not meet criteria for severe drug-induced liver injury (DILI).	• The safety profile is consistent with adult data and manageable through labeling, with dose-escalation regimens improving GI tolerability and appropriate warnings for hypoglycemia risk with concomitant insulin or insulin secretagogue use. • The full impact of significant weight loss on growth and development in a younger, pre-pubertal population has not been fully characterized, as the trial population was predominantly post-pubertal.

3 Background

3.1. Patient Experience Data

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

			Section of review where discussed, if applicable
☒	**The patient experience data that were submitted as part of the application include:**		
	☒	Clinical outcome assessment (COA) data, such as	
		☒ 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	
	☐	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	
	☐	Observational survey studies designed to capture patient experience data	
	☐	Other: (Please specify):	
☐	**Patient experience data was not submitted as part of this application.**		

The study assessed quality of life (QOL) using pediatric patient-reported outcome instruments including the Pediatric Quality of Life Inventory (PedsQL) Generic Core Scales and Diabetes Module (Version 3.2),[9,10] and EuroQol 5-Dimension Youth questionnaire (EQ-5D-Y-3L)

Reference ID: 5715650

questionnaires, which measured health-related quality of life across physical, emotional, social, and diabetes-specific domains. At Week 30, there were no statistically significant or clinically meaningful differences between tirzepatide and placebo groups on any QOL measures, and while both groups showed numerical improvements from baseline, these could not be attributed to tirzepatide treatment effects. Therefore, the QOL data do not provide supportive evidence of treatment benefit for tirzepatide in the pediatric population evaluated. As these PRO endpoints were not part of the statistical hierarchy and therefore not controlled for Type I error, no further discussion is provided in this review.

3.2. Regulatory Background

The pediatric development program for T2D began under Investigation New Drug (IND) 128801 with an initial Pediatric Study Plan (iPSP) submitted in November 2018 proposing to enroll subjects aged 10 to <18 years, though regulatory agreement was not reached until April 2020 following disagreements over timelines and statistical methodology. After the FDA deemed a Proposed Pediatric Study Request inadequate in May 2021, a Written Request was issued in April 2022 outlining four required studies, leading to initiation of the phase 3 pediatric study GPGV. Most recently, the FDA denied a Breakthrough Therapy Designation request in June 2025, concluding that while the clinical evidence demonstrated clinically meaningful effects, it did not establish substantial improvement over existing therapies. Section 8.8 contains the comprehensive regulatory history.

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

No new nonclinical studies were submitted with this sNDA.

4.1. Office of Scientific Investigations (OSI)

The Office of Scientific Investigations (OSI) inspected two clinical sites from trial GPGV based on risk assessment factors, including a high-risk domestic site in Los Angeles and a site in Mexico with no prior FDA inspection history. Both sites enrolled 10 subjects each, and OSI identified minor compliance issues including underreporting of non-serious adverse events at both sites, use of outdated informed consent forms, and failure to report concomitant medications at the domestic site. Despite these findings, OSI concluded that the clinical data were reliable and acceptable, determining that the minor issues did not compromise data integrity or study conduct. The Division agreed that the inspection findings do not prevent approval of the supplemental application. Refer to the OSI review for details, available in the Document Archiving, Reporting, and Regulatory Tracking System (DARRTS) under the following link: https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af807eaae6

Reference ID: 5715650

4.2. Division of Medication Error Prevention and Analysis (DMEPA) 1

In support of this sNDA, the Applicant submitted a comparative analysis (CA) of the Mounjaro (tirzepatide) and Trulicity (dulaglutide) autoinjectors. The purpose of the analysis was to justify leveraging existing human factors (HF) data from the dulaglutide sNDA to support the tirzepatide pediatric submission without conducting a new HF validation study. Trulicity utilizes the same autoinjector platform and is approved for the treatment of T2D in pediatric patients. DMEPA 1 reviewed the CA and concluded that there were no significant differences between the two devices that would warrant additional HF data. Therefore, they determined that a new HF study was not necessary and made no recommendations for this supplement. For more information refer to the DMEPA 1 review, available in DARRTS under the following link: https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af807efa4c

4.3. Clinical Pharmacology

4.3.1. Executive Summary

The Office of Clinical Pharmacology (OCP) has reviewed the clinical pharmacology data submitted in sNDA 215866-039, finds the data acceptable, and recommends approval. No outstanding issues were identified.

This submission contains results from trial GPGV and a population pharmacokinetic (PK) report to support proposed revisions to Section 12 (Clinical Pharmacology) of the Mounjaro labeling. The clinical pharmacology of tirzepatide was well characterized in the original NDA 215866 submission, which included PK, pharmacodynamics (PD), tolerability, and efficacy and safety evaluation in adults. The OCP reviews for that submission are available in DARRTS (Reference IDs 4954959[2] and 5258712[3]).

The route of administration and starting dose are the same for the adult and pediatric populations. In trial GPGV, tirzepatide was administered using a stepwise dose-escalation scheme (2.5 mg for 4 weeks, 5 mg for 4 weeks, 7.5 mg for 4 weeks, and 10 mg for the remainder of the study) to improve GI tolerability. As specified in the Agreed iPSP (Reference ID: 4584772[4]), the tirzepatide 15 mg dose was not evaluated in this study. This decision was based on phase 2 data (study GPGB) showing significant weight loss (-11.3 kg) at the 15 mg dose, which was considered potentially undesirable for a pediatric population, and concerns that puberty could increase unintended effects on growth at this higher dose. The 5 mg and 10 mg doses provided adequate efficacy with an acceptable safety profile (see clinical and

[2] Reference ID: 4954959 (dated 18 Mar 2022), available in DARRTS under the following link: https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af806501ed

[3] Reference ID: 5258712 (dated 11 Oct 2023), available in DARRTS under the following link: https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af806fd67c

[4] Reference ID: 4584772 (dated 1 Apr 2020), available in DARRTS under the following link: https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af805522fd

biometrics sections of this review) and were supportive of the proposed dosing regimen for the pediatric T2D population.

Both 5 mg and 10 mg doses showed clear dose-related efficacy improvements in blood glucose, A1C, and weight at 30 and 52 weeks. The dose-response analysis showed that most benefits occurred up to 5 mg, with diminishing returns from 5 mg to 10 mg, supporting 10 mg as an appropriate maximum dose for the pediatric population. Refer to the Summary of Clinical Pharmacology assessment for additional details in Appendix 8.5.

4.3.2. Clinical Pharmacology Questions

4.3.2.1. Does the clinical pharmacology program provide supportive evidence of effectiveness?

Yes, the clinical pharmacology program supports tirzepatide effectiveness in the pediatric T2D population. PK modeling of tirzepatide 5 mg and 10 mg doses in 93 pediatric subjects (≥10 years old) with T2D demonstrated that drug exposure levels were similar to those observed in adults, with generally overlapping steady-state exposures between the two populations (Figure 12). Pediatric subjects had slightly higher exposure (9% higher area under the curve [AUC] and 14% higher maximum plasma concentration [C_{max}] at steady state). Although pediatric subjects exhibited greater exposure variability, the highest estimated steady-state C_{max} and AUC values following 10 mg QW dosing in the pediatric population remained within the observed exposure range for adult patients receiving 15 mg once-weekly (QW) dosing.

4.3.2.2. Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes, the proposed dosing regimen is appropriate for the general pediatric patient population (children and adolescents aged 10 to less than 18 years with T2D) for which the indication is being sought. The proposed dosing regimen consists of a starting dose of 2.5 mg QW, with a a dose escalation of 2.5 mg every 4 weeks to achieve maintenance doses of 5 mg or 10 mg QW.

The clinical pharmacology program provides quantitative evidence that tirzepatide 5 mg and 10 mg QW are effective in pediatric patients with T2D. The PK/PD modeling demonstrated a clear dose-dependent improvement in glycemic targets across all key efficacy endpoints: (1) fasting serum glucose (FSG) dose-dependent reductions at Weeks 30 and 52, (2) A1C improvements with increasing doses up to 10 mg, and (3) dose-related reductions in both fat mass and total body weight. At 52 weeks, the exposure-response analysis for the 10 mg tirzepatide dose showed a -2.35% reduction from baseline in A1C (-26.9% relative change), a -3.36 mmol/L change from baseline in FSG (-28.6% relative change), a -13.5 kg reduction in body weight (-14.8% relative change), and a -9.07 kg reduction in fat mass (-24% relative change) (Table 33 and Table 36).

Population PK and exposure-response models for pediatric subjects provide supportive evidence for the dose selection rationale for this population. Population PK modeling

Reference ID: 5715650

demonstrated comparable exposure between adults and pediatrics following 5 mg and 10 mg QW dosing (Figure 12). Exposure-response modeling for fasting glucose and A1C revealed dose-dependent improvements in glycemic control, with substantial efficacy observed at 5 mg and smaller incremental benefit from 5 mg to 10 mg (Figure 17), indicating limited additional benefit from further increasing the dose to 15 mg. Exposure-response modeling for body weight showed a linear or sublinear relationship between dose and loss of fat-free mass, fat mass, and total body weight **(**Figure 20**)**. Considering the physiological changes associated with adolescent development, restricting the maximum maintenance dose to 10 mg ensures therapeutic efficacy while maintaining an acceptable safety profile and preventing excessive weight reduction.

The collective evidence supports a two-dose maintenance regimen (5 mg and 10 mg QW) to enable individualized therapy optimization based on efficacy response and tolerability profiles. The 10 mg dose provides meaningful additional therapeutic benefit for patients who demonstrate adequate tolerance to the 5 mg dose.

4.3.2.3. Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

No, alternative dosing regimens or management strategies are not required for subpopulations based on intrinsic patient factors, including age or body weight.

Population PK analysis indicated that there was minimal impact of age, sex, race/ethnicity, or renal function on PK across the 10 to 17-year age range. Body weight effects on the dosing regimen were evaluated in the target population using the enrolled weight range of 57 to 191 kg (median 96.7 kg). Exposure in lower body weight (e.g., 50 kg) pediatric patients remained within the range of exposure observed in adult patients at the same dose. Compared to a 90 kg reference subject, tirzepatide steady-state AUC and C_{max} are estimated to decrease by approximately 21% and 45% at body weights of 120 kg and 190 kg, respectively. Dose adjustment is not necessary for patients weighing 120 kg. Given the adolescent population, body weights of 190 kg are uncommon and represent an unlikely clinical scenario.

Overall, a fixed dosing regimen is appropriate for pediatric patients aged 10 to 17 years. Refer to the pharmacometrics review Figure 13 under Section 8.6.1.1.4 for the assessment of body weight and age effects on the steady-state exposure in pediatric patients.

5 Statistical/Clinical Efficacy

This supplement reviewed only one clinical trial: I8F-MC-GPGV (SURPASS-PEDS). No amendments were made to the finally agreed upon protocol for trial GPGV.

5.1. Study Design

Trial GPGV was a 30-week, randomized (1:1:1), double-blind, placebo-controlled, 3-arm

Reference ID: 5715650

(tirzepatide 10 mg, tirzepatide 5 mg, or placebo), parallel-group study conducted in 99 pediatric subjects aged 10 to <18 years with T2D inadequately controlled with metformin, and/or basal insulin. The study assessed the efficacy, safety, and PK/PD of tirzepatide. Following the double-blind period, subjects entered a 22-week open-label extension period, during which subjects initially randomized to placebo were switched to tirzepatide 2.5 mg and escalated to a 5 mg maintenance dose according to the prespecified schedule, while subjects in the tirzepatide 5 mg and 10 mg groups continued their assigned treatment. The study was adequately powered with a planned enrollment of at least 90 subjects.[5]

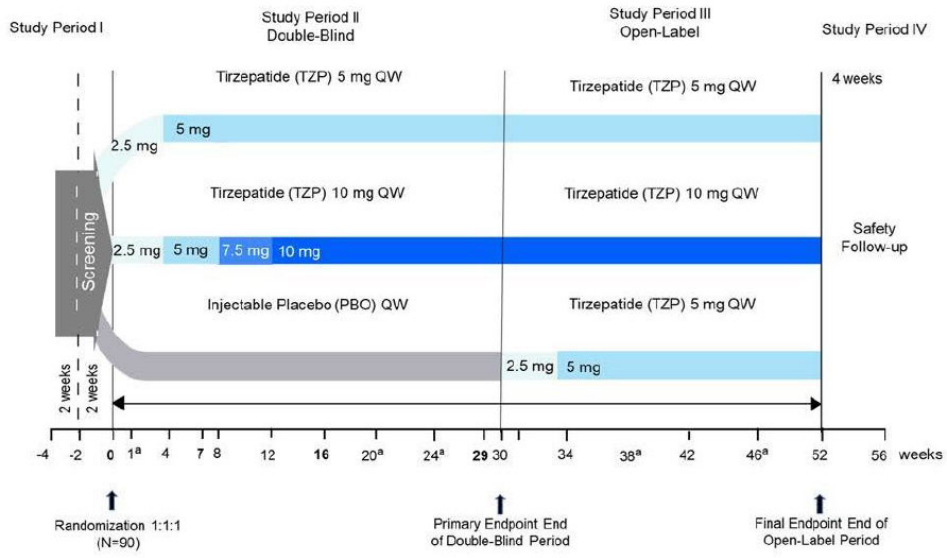
The trial consisted of 4 periods:

1. Period I: 4-Week screening period
2. Period II: 30-Week double-blind treatment period
3. Period III: 22-Week open-label extension period
4. Period IV: 4-Week safety follow-up period

Stratification factors were:

1. Age (10 to ≤14 years; 15 to <18 years)
2. Baseline antihyperglycemic medication (Metformin only; Basal Insulin only; Metformin and Basal Insulin)

Figure 1: **Trial Design -SURPASS-PEDS**



Abbreviations: N = number of participants in the analysis population; PBO = placebo; QW = once weekly; TZP = tirzepatide.

a Phone visit.

Note: visits indicated in bold fonts = pharmacokinetic assessments.

[5] The assumed subject-level SD was 1.5 for all groups, and a treatment effect of -1.1, under a 2-sided α=0.05, for the power 90% using 90 subjects. Under the FDA preferred analysis, the observed subject-level variance is 1.92 (standard deviation (SD)=1.39). Under the actual 99 subjects, the retrospective power is 92.6%, corresponding to a width of 1.25 for the 95% confidence interval (CI). The observed width of the 95% CI for the FDA preferred analysis is 1.21.

Source: Clinical Study Report, page 73, available from: \\CDSESUB1\EVSPROD\nda215866\1374\m5\53-clin-stud-rep\535-rep-effic-safety-stud\diabetes\5351-stud-rep-contr\i8f-mc-gpgv\gpgv-csr-04-body.pdf

5.2. Eligibility criteria

Key Inclusion Criteria:

- Age 10 to <18 years
- T2D treated with metformin and/or basal insulin
- A1C >6.5% to ≤11%
- Body weight ≥50 kg
- BMI >85th percentile (age and sex matched for country/region)

Key Exclusion Criteria:

- Type 1 diabetes or positive diabetes-associated autoantibodies (GAD65 and/or IA2)
- ≥1 episode of severe hypoglycemia or hypoglycemic unawareness within last 6 months
- History of diabetic ketoacidosis (DKA) or hyperosmolar syndrome after T2D diagnosis
- Proliferative diabetic retinopathy, diabetic macular edema, OR nonproliferative diabetic retinopathy requiring acute treatment
- Chronic or acute pancreatitis
- Family or personal history of medullary thyroid carcinoma (MTC) or multiple endocrine neoplasia syndrome type 2 (MEN2) or elevation of serum calcitonin ≥35 ng/L at screening
- Renal impairment (estimated glomerular filtration rate [eGFR] <45 mL/min/1.73 m^2)
- Hepatic impairment (alanine aminotransferase [ALT] or aspartate aminotransferase [AST] >5x age-adjusted ULN; total bilirubin ≥1.5x ULN except Gilbert's syndrome), acute or chronic hepatitis or signs/symptoms of liver disease (other than metabolic dysfunction-associated steatotic liver disease)
- Pregnancy or breastfeeding
- Gastric emptying abnormality, bariatric surgery (prior or planned), or use of weight loss medications within 90 days
- Use of chronic systemic glucocorticoids, or antihyperglycemic medications besides metformin or insulin

5.3. Study Endpoints

Primary Endpoint: Change in A1C (%) from baseline to Week 30 (pooled tirzepatide vs placebo)

Key Secondary Endpoints:

- Change in A1C from baseline to Week 30 (tirzepatide 10 mg and 5 mg vs placebo)
- Incidence of A1C ≤6.5% at Week 30 (tirzepatide pooled, 10 mg, and 5 mg vs placebo)
- Percent change in BMI from baseline to Week 30 (tirzepatide pooled, 10 mg, and 5 mg vs placebo)
- Change in BMI-SDS from baseline to Week 30 (tirzepatide pooled, 10 mg, and 5 mg vs

placebo)
- Change in FSG from baseline to Week 30 (tirzepatide pooled, 10 mg, and 5 mg vs placebo)

5.4. Statistical Analysis Plan/Statistical Methodology[6]

Primary Endpoint

- Definitions of analysis sets:
  - Modified Intent-to-Treat (mITT): All randomly assigned subjects who are exposed to at least 1 dose of study intervention
  - Full Analysis Set (FAS): Data obtained during the double-blind period from the mITT population, regardless of adherence to study intervention or initiation of rescue antihyperglycemic medication.

- Primary estimand: Treatment policy estimand
  - Population: Pediatric and adolescent subjects (aged 10 to <18 years) with T2D inadequately controlled with metformin, or basal insulin, or both
  - Endpoint: See above
  - Treatment condition: The randomly assigned treatment regardless of treatment discontinuation or influence of rescue antihyperglycemic medication
  - Population level summary measure: Difference in mean changes in A1C from baseline to Week 30
  - Intercurrent events (ICE):
    - Treatment discontinuation
    - Influence of rescue antihyperglycemic medication
  - Handling of data after intercurrent events: Per the treatment condition, all available data, regardless of ICEs will be used in the analysis

- Primary analysis model for the treatment regimen estimand: The pre-specified method of imputing missing data is described as follows:

Step 1: Impute missing Week 30 A1C measurements as follows:
  - Jump-to-reference[7] for subjects with tirzepatide and off treatment. Here, intermediate measurements are used in the imputation.

  - Missing at random (MAR) using intermediate measurements, based on completers from the same treatment arm for 1) subjects with tirzepatide and on treatment or 2) subjects with placebo or 3) subjects with tirzepatide who inadvertently enrolled.

[6] There were 3 versions of the SAP. Statistical reviews were entered into DARRTS on 11/18/24 and 3/11/25. There was only 1 version of the protocol. Statistical reviews for protocols were entered into DARRTS on 10/22/21 and 1/26/22.

[7] Carpenter JR, Roger JH, Kenward MG. Analysis of longitudinal trials with protocol deviation: a framework for relevant, accessible assumptions, and inference via multiple imputation. J Biopharm Stat. 2013;23(6):1352–1371. https://doi.org/10.1080/10543406.2013.834911

Step 2: For each subject with missing Week 30 data, 100 measurements will be imputed, thus generating 100 complete datasets. Each dataset will be analyzed using Analysis of Covariance (ANCOVA) with treatment, stratification factors of age group, baseline antihyperglycemic medication, and baseline A1C as factors and covariates.

Step 3: Rubin's rule will be applied for inference.

Statistical reviewer's comments:

- *For the jump-to-reference approach, the statistical analysis plan (SAP) stated that only baseline and endpoint values would be used, and that no intermediate values would be used in the imputation. However, in the programming, intermediate values were used. In a response to an information request sent on 9/2/25, with response date on 9/16/25, the Applicant stated that the SAP was in error.*

- *The Applicant's programming included replacing extreme imputed values (i.e., (b) (4)% and (b) (4)% percentiles of observed measurements) with the 2.5% and 97.5% percentiles, respectively. This was not described in the SAP.*

- FDA preferred method for the primary analysis:
  - Impute missing Week 30 A1C measurements as follows:
    - Placebo wash-out approach, whereby intermediate measurements are removed, and measurements are then imputed based on all placebo completers for subjects with tirzepatide and off treatment, regardless of whether they inadvertently enrolled.

    - MAR using intermediate measurements, based on completers from the same treatment arm for 1) subjects with tirzepatide and on treatment or 2) subjects with placebo.

  - Use all imputed measurements and not replace extreme values with 2.5% and 97.5% percentiles of observed measurements.

- Reviewer's sensitivity analysis for the primary endpoint:

  1. A 2-way tipping point analysis to assess the robustness of the primary analysis with respect to missing data assumptions. The analysis is performed by beginning with the primary analysis described above (FDA preferred analysis), followed by adding positive (detrimental) penalties to tirzepatide and negative (beneficial) penalties to placebo, and considering when results tip from superiority of pooled tirzepatide to not superior, and then considering the clinical plausibility of such scenarios.

  2. Placebo wash-out for all subjects on tirzepatide, irrespective of whether they were on or off treatment.

Reference ID: 5715650

Key Secondary Endpoints

- Continuous: Same as the primary endpoint, except replace baseline A1C with the baseline variable under evaluation.

- Binary: Step 1: For each of the 100 completed datasets for continuous A1C, derive the corresponding achievement of A1C ≤6.5% at Week 30 status (yes; no) for each subject.

  Step 2: For each of the 100 completed datasets, run a logistic regression with the same factors and covariates as the ANCOVA model, to obtain the predicted and counterfactual predictions for each subject and then obtain the unconditional treatment difference in proportions (i.e., g-computation). Subsequently, obtain robust standard errors proposed by Ye et al., 2023.[8]

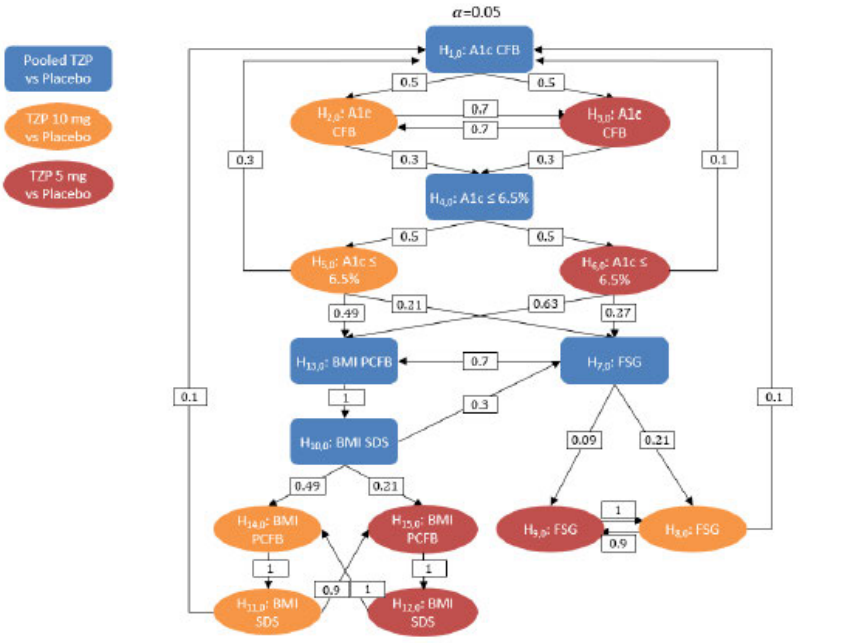
  Step 3: Synthesize with Rubin's rule.

Multiplicity Adjustment

Figure 2 shows the graphical testing scheme to strongly control the Type I error at a 2-sided alpha of 0.05 for the primary and key secondary endpoints. Since the treatment-regimen and efficacy estimands were intended for different purposes and objectives, no adjustment between the estimands was made.

[8] Ye T, Bannick M, Yi Y, Shao J. Robust variance estimation for covariate-adjusted unconditional treatment effect in randomized clinical trials with binary outcomes. Stat Theory Relat Fields 2023;7:159-63. https://doi.org/10.1080/24754269.2023.2205802

Figure 2: Graphical testing scheme to strongly control the type 1 error at a 2-sided alpha of 0.05 for the primary and key secondary endpoints



Abbreviation: A1c = glycated hemoglobin; BMI = body mass index; CFB = change from baseline; FSG = fasting serum glucose; PCFB = percent change from baseline; SDS = standard deviation score; TZP = tirzepatide.

Figure GPGV.2.1. Graphical testing scheme.

Source: Statistical Analysis Plan (version 3.0), page 23, available from: \\CDSESUB1\EVSPROD\nda215866\1374\m5\53-clin-stud-rep\535-rep-effic-safety-stud\diabetes\5351-stud-rep-contr\i8f-mc-gpgv\gpgv-sap.pdf

5.5. Study Results

The Applicant states that trial GPGV was conducted in accordance with the protocol, and consensus ethical principles derived from international guidelines (including the Declaration of Helsinki[11] and Council for International Organizations of Medical Sciences [CIOMS] International Ethical Guidelines), applicable International Conference on Harmonisation Good Clinical Practice (ICH GCP) guidelines,[12] and applicable laws and regulations.

The submitted data were of high quality and there were no concerns with integrity. Findings from OSI inspections of two clinical study sites and the data quality assessment by Dr. Roberto Crackel did not reveal any issues that would compromise the study's integrity.
The Applicant submitted financial disclosure information for 93 unique clinical investigators from eight countries participating in the study (Table 15). After reviewing the financial disclosure information and the Applicant's certification that no disclosable financial interests exist, the clinical reviewer concluded that the study data reliability is not compromised by investigator financial bias.

5.5.1. Subject Disposition

A total of 146 subjects were screened, of whom 99 were randomized: 34 to the placebo group, 32 to the tirzepatide 5 mg group, and 33 to the tirzepatide 10 mg group (Table 1). The study retention rate was relatively high, with 90 of the 99 randomized subjects (90.9%) completing the 52-week study.

A total of nine subjects (9.1%) prematurely discontinued from the study. The number of discontinuations was low and comparable across the treatment groups. The most common reason for discontinuation was withdrawal by the subject. Two subjects discontinued due to an adverse event (nausea and suicidal ideation), both in the tirzepatide 5 mg group. The remaining discontinuations were due to loss to follow-up (n=1), withdrawal due to caregiver circumstances (n=1), and other (n=1). All discontinuations occurred during the 30-week double-blind treatment period; no subjects discontinued study during the subsequent 22-week open-label extension.

Table 1: Subject Disposition for Trial GPGV (Double-blind, Open-label, Follow-up)

Disposition Category	Placebo (N=34)	TZP 5 mg (N=32)	TZP 10 mg (N=33)	Pooled TZP (N=65)
Randomized	34	32	33	65
Completed Study (Week 30)	32 (94.1%)	29 (90.6%)	29 (87.9%)	58 (89.2%)
Completed Study (Week 52)	32 (94.1%)	29 (90.6%)	29 (87.9%)	58 (89.2%)
Discontinued from Study	2 (5.9%)	3 (9.4%)	4 (12.1%)	7 (10.8%)
Reasons for Discontinuation:				
Adverse Event	0	2 (6.3%)	0	2 (3.1%)
Withdrawal by Subject	1 (2.9%)	1 (3.1%)	2 (6.1%)	3 (4.6%)
Lost to Follow-up	1 (2.9%)	0	0	0
Withdrawal due to Caregiver Circumstances	0	0	1 (3.0%)	1 (1.5%)
Other	0	0	1 (3.0%)	1 (1.5%)

Source: Derived from the adsl.xpt and ds.xpt datasets and adapted from the Clinical Study Report, Tables GPGV.8.2, page 441, available from: \\CDSESUB1\EVSPROD\nda215866\1374\m5\53-clin-stud-rep\535-rep-effic-safety-stud\diabetes\5351-stud-rep-contr\i8f-mc-gpgv\gpgv-csr-04-body.pdf; Abbreviations: N = number; TZP = tirzepatide.

5.5.2. Protocol Violations/Deviations

Important protocol deviations were reported for 17 of the 99 randomized subjects (17.2%) during double-blind treatment period. The incidence of deviations was higher in the tirzepatide groups (5 mg: 25%; 10 mg: 18.2%) compared to the placebo group (8.8%). The most frequent deviations were related to informed consent procedures and non-compliance with laboratory procedures. The Applicant concluded that these deviations were unlikely to impact the study conclusions. Given the limited number and nature of the deviations, the Applicant's assessment is reasonable.

Table 2: Important Protocol Deviations (Randomized Subjects, Double-Blind)

Protocol Deviation Category	Placebo (N=34)	TZP 5 mg (N=32)	TZP 10 mg (N=33)	TZP ALL (N=65)
≥1 Important Protocol Deviation	3 (8.8)	8 (25.0)	6 (18.2)	14 (21.5)
Informed Consent	1 (2.9)	7 (21.9)	3 (9.1)	10 (15.4)
Laboratory Procedure Compliance	2 (5.9)	4 (12.5)	1 (3.0)	5 (7.7)
Study Procedure Compliance	2 (5.9)	0	1 (3.0)	1 (1.5)
Eligibility Criteria	0	0	1 (3.0)	1 (1.5)
Study Procedure Compliance	0	0	1 (3.0)	1 (1.5)
Treatment Assignment/Randomization	0	0	1 (3.0)	1 (1.5)

Source: Adapted from the Clinical Study Report, Table GPGV.8.3, page 443, available from: \\CDSESUB1\EVSPROD\nda215866\1374\m5\53-clin-stud-rep\535-rep-effic-safety-stud\diabetes\5351-stud-rep-contr\i8f-mc-gpgv\gpgv-csr-04-body.pdf; Abbreviations: N = number; TZP = tirzepatide.

5.5.3. Demographic and Baseline Characteristics

In the trial, 44.4% were 14 years and younger, 60.6% were female, 67.7% were outside the US, and 57.6% were white (Table 3). In general, demographics were similar between treatment groups except for the lower proportions of Hispanic/Latino and female subjects in the tirzepatide 10 mg group compared to the placebo and tirzepatide 5 mg groups.

Table 3: Demographic Characteristics

	TZP 10 mg (N=33)	TZP 5 mg (N=32)	Placebo (N=34)	Total (N=99)
Age Group [n(%)]				
≤14 years	15 (45.5)	13 (40.6)	16 (47.1)	44 (44.4)
>14 years	18 (54.5)	19 (59.4)	18 (52.9)	55 (55.6)
Sex [n(%)]				
Female	18 (54.5)	21 (65.6)	21 (61.8)	60 (60.6)
Male	15 (45.5)	11 (34.4)	13 (38.2)	39 (39.4)
Region [n(%)]				
US	11 (33.3)	11 (34.4)	10 (29.4)	32 (32.3)
Non-US	22 (66.7)	21 (65.6)	24 (70.6)	67 (67.7)
Race [n(%)]				
White	19 (57.6)	17 (53.1)	21 (61.8)	57 (57.6)
Black or African American	4 (12.1)	5 (15.6)	2 (5.9)	11 (11.1)
Asian	2 (6.1)	1 (3.1)	3 (8.8)	6 (6.1)
American Indian or Alaska Native	5 (15.2)	7 (21.9)	8 (23.5)	20 (20.2)
Native Hawaiian or Other Pacific Islander	2 (6.1)	1 (3.1)	0	3 (3.0)
Multiple	1 (3.0)	1 (3.1)	0	2 (2.0)
Ethnicity [n(%)]				
Hispanic or Latino	17 (51.5)	24 (75.0)	24 (70.6)	65 (65.7)
Not Hispanic or Latino	16 (48.5)	8 (25.0)	9 (26.5)	33 (33.3)
Not Reported	0	0	1 (2.9)	1 (1.0)

N = # randomized = mITT; Source: Statistical Reviewer's Analysis

The mean A1C at baseline was 8.04%, and more than two-thirds of the trial population was on background metformin only. The average age was 14.75 years, and the mean duration of T2D

was 2.37 years. In general, baseline characteristics were similar between treatment groups, albeit a lower mean A1C, and a higher mean BMI and body weight, and a shorter mean duration of T2D were observed in subjects in the tirzepatide 10 mg group.

Table 4: Other Baseline Characteristics

	TZP 10 mg (N=33)	TZP 5 mg (N=32)	Placebo (N=34)	Total (N=99)
Antihyperglycemic use [n(%)]				
Basal Insulin Only	3 (9.1)	3 (9.4)	2 (5.9)	8 (8.1)
Metformin + Basal Insulin	8 (24.2)	7 (21.9)	8 (23.5)	23 (23.2)
Metformin Only	22 (66.7)	22 (68.8)	24 (70.6)	68 (68.7)
A1C group [n(%)]				
≤8.0%	21 (63.6)	17 (53.1)	20 (58.8)	58 (58.6)
>8.0%	12 (36.4)	15 (46.9)	14 (41.2)	41 (41.4)
A1C (%)				
Mean (SD)	7.89 (1.22)	8.22 (1.17)	8.02 (1.30)	8.04 (1.23)
Min, Max	5.9, 11.1	6.0, 10.5	6.1, 11.3	5.9, 11.3
Duration of T2D (years)				
Mean (SD)	1.93 (1.33)	2.54 (1.63)	2.65 (2.27)	2.37 (1.80)
Min, Max	0.14, 5.06	0.31, 6.70	0.23, 10.80	0.14, 10.80
Fasting glucose (mg/dL)				
Mean (SD)	151.62 (68.31)	147.80 (52.34)	156.08 (77.83)	152.01 (66.91)
Min, Max	73.00, 389.12	80.00, 269.00	75.66, 434.00	73.00, 434.00
Age (years)				
Mean (SD)	14.64 (1.83)	14.97 (1.93)	14.65 (1.79)	14.75 (1.84)
Min, Max	11, 17	11, 17	10, 17	10, 17
Body weight (kg)				
Mean (SD)	103.18 (29.55)	93.18 (27.05)	93.54 (25.69)	96.64 (27.58)
Min, Max	60.6, 191.3	57.8, 166.0	53.2, 144.5	53.2, 191.3
BMI (kg/m^2)				
Mean (SD)	37.66 (8.43)	33.90 (7.17)	34.74 (7.69)	35.44 (7.87)
Min, Max	25.06, 61.13	24.02, 50.16	23.05, 50.03	23.05, 61.13
BMI SDS				
Mean (SD)	3.48 (1.23)	2.86 (1.01)	2.99 (1.18)	3.11 (1.17)
Min, Max	1.63, 7.17	1.07, 5.04	1.25, 5.27	1.07, 7.17

N = # randomized = mITT; Source: Statistical Reviewer's Analysis; Abbreviations: A1C = hemoglobin A1C; BMI = body mass index; Max = maximum; Min = minimum; N= number; SD = standard deviation; SDS = standard deviation score; TZP = tirzepatide.

5.5.4. Treatment Compliance, Concurrent Medications, Rescue

Compliance[9]*:* Overall, treatment compliance was high. A total of 90.9% of subjects completed the 52-week study on the investigational product (placebo: 94.1%; tirzepatide 5 mg: 90.6%; tirzepatide 10 mg: 87.9%). Compliance, defined as receiving at least 75% of scheduled doses during the double-blind period, was achieved in 94.1%, 100%, and 100% of subjects receiving

[9] Investigator assessment of adherence to the investigational product occurred at each visit and included: (1) reviewing the subject's recorded administration data in the study e-diary, (2) evaluating adherence to the visit schedule, (3) examining completion of study diaries, and (4) assessing any other parameters the investigator considered necessary. For drug accountability, subjects and/or their parents/guardians were required to return unused study medication and empty cartons at each visit. Subjects identified as poorly compliant received additional training and instruction on the importance of protocol adherence.

Reference ID: 5715650

placebo, tirzepatide 5 mg, and tirzepatide 10 mg, respectively.

Concomitant Medications[10]*:* The majority of subjects (91.9%) were taking metformin at baseline (Table 4):

- 68.7% on metformin only
- 23.2% on metformin plus basal insulin
- 8.1% on basal insulin only

The proportion of participants in each antihyperglycemic medication category was generally balanced across treatment groups.

Rescue[11]*:* During the double-blind period, rescue therapy was initiated in six subjects (17.6%) in the placebo group. No subjects in either tirzepatide group required rescue therapy.

5.5.5. Primary Endpoint

Notes: This section reports the results under the FDA preferred analysis. Results of the Applicant's analyses are shown in Appendix 8.4.

Tirzepatide demonstrated superiority in lowering A1C compared to placebo, both under the Applicant's analysis and the FDA preferred analysis. The difference in results between the two is minor. Sensitivity analyses demonstrated that the amount and handling of missing data were robust and supported the conclusion that tirzepatide lowers A1C in pediatric subjects aged 10 to <18 years. Further, tirzepatide demonstrated superiority in all key secondary endpoints, including the incidence of A1C ≤6.5%, BMI, BMI-SDS, and FSG, compared to placebo. Further, tirzepatide was favored and consistent in all subgroups. The study appears to have fulfilled the requirements for PMC/PMR 4271-1 from a statistical perspective.

Table 5 summarizes the disposition of observed Week 30 measurements for the primary endpoint. In total, there were 11 (11.1%) missing Week 30 A1C measurements. One subject on tirzepatide 10 mg was inadvertently enrolled.

[10] The study documented all concomitant medications and required subjects to be on stable background diabetes medications (metformin ≥1000 mg/day and/or basal insulin) for at least 90 days before enrollment, with doses maintained throughout the study except for safety adjustments. At baseline, most subjects (68.7%) were on metformin alone, 23.2% were on metformin plus basal insulin, and 8.1% were on basal insulin only.

[11] The protocol established criteria for rescue therapy when subjects had severe persistent hyperglycemia, with FSG thresholds that decreased over time (>270 mg/dL baseline-Week 6; >240 mg/dL Week 7-16; >200 mg/dL Week 17+). Before initiating rescue therapy, investigators confirmed treatment compliance and ruled out acute conditions. Rescue therapy included increasing metformin by ≥500 mg, using insulin for >2 weeks, or for those already on insulin, increasing the dose by >15% or adding another insulin type. All rescue interventions were documented in the electronic case report form (eCRF).

Reference ID: 5715650

Table 5: Data Capture for the Primary Endpoint

	TZP 10 mg (N=33)	TZP 5 mg (N=32)	Placebo (N=34)	Total (N=99)
# with observed Week 30 data [n(%)]	27 (81.8%)	29 (90.6%)	32 (94.1%)	88 (88.9%)
On treatment [n]	27	29	30	86
Off treatment (Retrieved Drop-outs) [n]	0	0	2	2
# with missing Week 30 data [n(%)]	6 (18.2%)	3 (9.4%)	2 (5.9%)	11 (11.1%)
Study discontinuation [n]	4[a]	3	0	7
On treatment [n]	2	0	2	4

[a] 1 subject was inadvertently enrolled; Source: Statistical Reviewer's Analysis; Abbreviations: N = number, TZP = tirzepatide.

Table 6 summarizes the results for the primary and key secondary endpoints of change in A1C from baseline to Week 30. For the primary hypothesis of pooled tirzepatide compared to placebo, the estimated treatment effect is -1.82 with 95% CI: (-2.42, -1.21), and a p-value <0.0001. Therefore, tirzepatide demonstrated superiority over placebo in reducing A1C at Week 30.

The individual doses of tirzepatide 10 mg and 5 mg also demonstrated superiority over placebo in reducing A1C at Week 30. The estimated treatment effect for tirzepatide 10 mg is -1.95 with 95% CI: (-2.65, -1.26), and the estimated treatment effect for tirzepatide 5 mg is -1.69 with 95% CI: (-2.40, -0.97).

Table 6: Primary Analysis Results for Change in A1C from Baseline to Week 30

	Pooled TZP (N=65)	TZP 10 mg (N=33)	TZP 5 mg (N=32)	Placebo (N=34)
# with Baseline measurement	65	33	32	34
Baseline, mean (SD)	8.05 (1.20)	7.89 (1.22)	8.22 (1.17)	8.02 (1.30)
# without Week 30 data (%)	9 (13.8%)	6 (18.2%)	3 (9.4%)	2 (5.9%)
LS mean (SE) Change from baseline	-2.04 (0.19)	-2.18 (0.26)	-1.91 (0.27)	-0.23 (0.24)
Difference at Week 30 (SE) (95% CI)	-1.82 (0.31) (-2.42, -1.21)	-1.95 (0.36) (-2.65, -1.26)	-1.69 (0.37) (-2.40, -0.97)	
P-value	<0.0001	<0.0001	<0.0001	

Missing measurements for subjects with tirzepatide and off treatment were handled with placebo wash-out. Missing measurements for subjects on tirzepatide and on treatment, or subjects on placebo were handled as missing at random.
100 datasets were generated. ANCOVA was used with treatment, stratification factors of age group, and basal antihyperglycemic medication, and baseline A1C as factors and covariates.
Source: Statistical Reviewer's Analysis; Abbreviations: A1C = hemoglobin A1c; CI = confidence interval; LS = least squares; N = number; SD = standard deviation; SE = standard error; TZP = tirzepatide.

5.5.6. Subgroup Analyses

The subgroups and levels explored for the primary endpoint are:

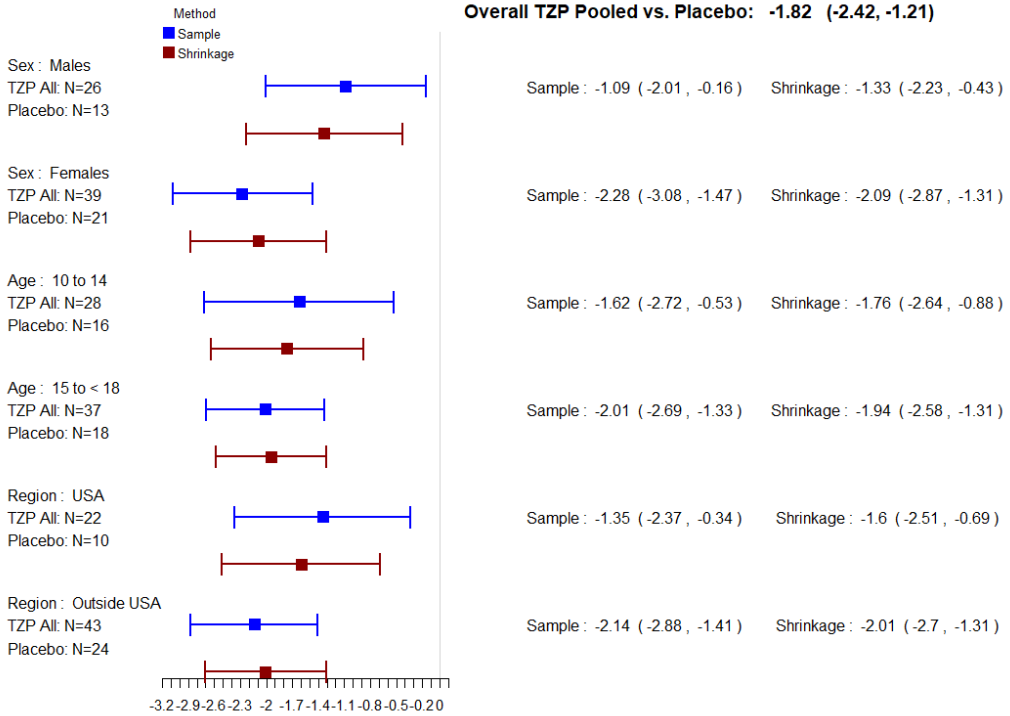
- Sex (Male; Female)
- Age (10 to 14; 15 to <18)
- Region (USA; Not US)

- Race (White; Asian; Black or African American; American Indian or Alaska Native)
- Ethnicity (Hispanic or Latino; Not Hispanic or Latino)

Forest plots are shown below, where sample estimates are derived from analyzing each subgroup level in isolation and shrinkage estimates are derived from Bayesian hierarchical modeling (see Appendix 8.4 for details) under the FDA preferred analysis for handling missing data.

Figure 3 shows the subgroup results for sex, age, and region. There is a significant interaction p-value of less than 0.10 for sex, meaning that there is a significant difference in the magnitude of the treatment effect between males and females. However, this is not of concern since the treatment effect favors tirzepatide in both males and females and the confidence intervals overlap. For all levels in sex, age, and region, the confidence interval (sample estimate) and credible interval (shrinkage estimate) exclude 0, and are in favor of pooled tirzepatide.

Figure 3: Forest Plot of Subgroup Analyses: Sex, Age, and Region

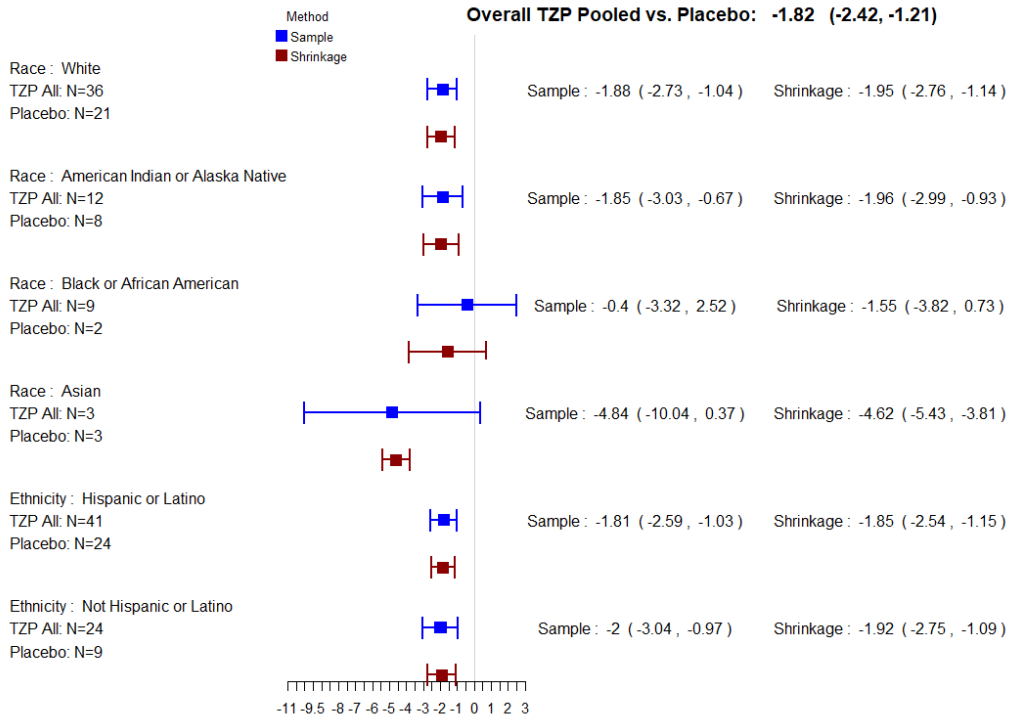


Note: Values less than 0 favor Pooled Tirzepatide; Parentheses indicate 95%; Confidence/Credible Intervals for sample/shrinkage estimates, respectively; Source: Statistical Reviewer's Analysis

Figure 4 shows the subgroup results for race and ethnicity. Native Hawaiian or Other Pacific Islander was not explored, since there were no subjects randomized to placebo. There are no significant interactions. In Black or African American, the estimate of the treatment effect (sample and shrinkage) favors tirzepatide; however, the confidence interval includes 0, as does the credible interval. However, this is not surprising since the sample size is small, and only 2 subjects were on placebo. Similarly, in Asian, the estimate of the treatment effect

(sample and shrinkage) favors tirzepatide, however, the confidence interval includes 0, but the credible interval does not. This is not surprising since the sample size is small. For all other levels of race and both levels of ethnicity, the confidence interval (sample estimate) and credible interval (shrinkage estimate) exclude 0, and are in favor of tirzepatide.

Figure 4: Forest Plot of Subgroup Analyses: Race and Ethnicity



Note: Values less than 0 favor Pooled Tirzepatide; Parentheses indicate 95% Confidence/Credible Intervales for sample and shrinkage estimates, respectively; Source: Statistical Reviewer's Analysis

The Applicant's analyses, additional sensitivity analyses, and an evaluation of baseline A1C as an effect modifier are provided in Appendix 8.4.

5.5.7. Key Secondary Endpoints

Table 7 displays the results for the incidence of achieving ≤6.5% A1C at Week 30. Pooled tirzepatide and the individual doses demonstrated superiority over placebo.

Table 7: Results for the Incidence of ≤6.5% A1C at Week 30

	Pooled TZP (N=65)	TZP 10 mg (N=33)	TZP 5 mg (N=32)	Placebo (N=34)
# known responders / N (%)	45 / 65 (69.23%)	24 / 33 (72.73%)	21 / 32 (65.63%)	9 / 34 (26.47%)
Average # responders across imputed datasets / N (%)	48.45 / 65 (74.54%)	26.79 / 33 (81.18%)	21.66 / 32 (67.69%)	9.56 / 34 (28.12%)
Model based proportion (SE)	74.67% (5.65)[a]	80.20% (7.53)[b]	69.40% (8.09)[b]	27.74% (7.84)[b]
Difference in proportions (SE) 95% CI	46.96% (9.50) (28.34%, 65.57%)[a]	52.46% (10.75) (31.38%, 73.54%)[b]	41.66% (11.14) (19.82%, 63.49%)[b]	
P-value	<0.0001	<0.0001	0.0002	

G-computation used with underlying logistic regression with treatment, stratification factors of age group, and baseline antihyperglycemic medication, and baseline A1C as factors and covariates; a Model fitted with pooled TZP and placebo
b Model fitted with TZP 10 mg, 5 mg, and placebo; Source: Statistical Reviewer's Analysis; Abbreviations: CI = confidence interval; N = number; SE = standard error; TZP = tirzepatide.

The numbers of subjects achieving an A1C <7.0%[12] at Week 30 with pooled TZP, TZP 10 mg, TZP 5 mg, and placebo are 50, 25, 25, and 12, respectively. The proportions of subjects achieving an A1C <7.0% (average number achieving A1C <7.0% across imputed datasets / N) for pooled TZP, TZP 10 mg, TZP 5 mg, and placebo are 83.38%, 86.09%, 80.59%, and 37.12%, respectively.

Table 8-10 show the analysis results for BMI, BMI-SDS, and FSG, respectively. Pooled tirzepatide and the individual doses demonstrated superiority over placebo for each of these endpoints.

Table 8: Results for Change in BMI from Baseline to Week 30

	Pooled TZP (N=65)	TZP 10 mg (N=33)	TZP 5 mg (N=32)	Placebo (N=34)
# with Baseline measurement	65	33	32	34
Baseline, mean (SD)	35.81 (8.00)	37.66 (8.43)	33.90 (7.17)	34.74 (7.69)
# without Week 30 data (%)	7 (10.8%)	4 (12.1%)	3 (9.4%)	0
Change from baseline				
LS mean (SE) Change from baseline	-3.02 (0.28)	-3.81 (0.39)	-2.23 (0.40)	-0.33 (0.37)
Difference at Week 30 (SE) (95% CI)	-2.69 (0.47) (-3.60, -1.77)	-3.48 (0.54) (-4.55, -2.41)	-1.90 (0.55) (-2.97, -0.83)	
% Change from baseline				
LS mean (SE) % Change from baseline	-8.83 (0.83)	-10.79 (1.17)	-6.88 (1.19)	-0.52 (1.12)
Difference at Week 30 (SE) (95% CI)	-8.31 (1.39) (-11.04, -5.58)	-10.26 (1.63) (-13.46, -7.07)	-6.35 (1.63) (-9.55, -3.16)	
P-value	<0.0001	<0.0001	<0.0001	

Missing measurements for subjects with tirzepatide and off treatment, were handled with placebo wash-out. Missing measurements for subjects on tirzepatide and on treatment, or subjects on placebo were handles as missing at random.
100 datasets were generated. ANCOVA was used with treatment, stratification factors of age group, and basal antihyperglycemic medication, and baseline BMI as factors and covariates. Source: Statistical Reviewer's Analysis

[12] At baseline, 9 subjects on TZP 10 mg, 4 subjects on TZP 5 mg, and 7 subjects on placebo had A1C <7.0%.

Abbreviations: BMI = body mass index; CI = confidence interval; LS = least squares; N = number; SE = standard error; TZP = tirzepatide.

Table 9: Results for Change in BMI-SDS from Baseline to Week 30

	Pooled TZP (N=65)	TZP 10 mg (N=33)	TZP 5 mg (N=32)	Placebo (N=34)
# with Baseline measurement	65	33	32	34
Baseline, mean (SD)	3.17 (1.16)	3.48 (1.23)	2.86 (1.01)	2.99 (1.18)
# without Week 30 data (%)	7 (10.8%)	4 (12.1%)	3 (9.4%)	0
LS mean (SE) Change from baseline	-0.60 (0.05)	-0.74 (0.07)	-0.47 (0.07)	-0.09 (0.07)
Difference at Week 30 (SE) (95% CI)	-0.51 (0.09) (-0.68, -0.35)	-0.65 (0.10) (-0.84, -0.45)	-0.38 (0.10) (-0.58, -0.18)	
P-value	<0.0001	<0.0001	0.0001	

Missing measurements for subjects with tirzepatide and off treatment, were handled with placebo wash-out. Missing measurements for subjects on tirzepatide and on treatment, or subjects on placebo were handled as missing at random.
100 datasets were generated. ANCOVA was used with treatment, stratification factors of age group, and basal antihyperglycemic medication, and baseline BMI-SDS as factors and covariates.
Source: Statistical Reviewer's Analysis; Abbreviations: CI = confidence interval; LS = least squares; N = number; SD = standard deviation; SE = standard error; TZP = tirzepatide.

For FSG, there are 7 subjects with missing baseline measurements (1 with TZP 10 mg, 4 with TZP 5 mg, and 2 with placebo). Since these subjects are in the mITT, baseline measurements are multiply imputed, where the imputation was performed as missing at random, using the baseline measurements from the 92 subjects with observed baseline measurements, with no distinction between treatment arms.

Table 10: Results for Change in FSG from Baseline to Week 30

	Pooled TZP (N=65)	TZP 10 mg (N=33)	TZP 5 mg (N=32)	Placebo (N=34)
# with Baseline measurement	60	32	28	32
Baseline, mean (SD)	149.84 (60.90)	151.62 (68.31)	147.80 (52.34)	156.08 (77.83)
# without Week 30 data (%)	9 (13.8%)	5 (15.2%)	4 (12.5%)	1 (3.1%)
LS mean (SE) Change from baseline	-42.67 (6.18)	-50.59 (8.47)	-34.75 (8.55)	-4.57 (7.80)
Difference at Week 30 (SE) (95% CI)	-38.10 (9.85) (-57.41, -18.79)	-46.02 (11.43) (-68.43, -23.61)	-30.18 (11.48) (-52.69, -7.66)	
P-value	0.0001	<0.0001	0.0086	

Missing baseline measurements were handled as missing at random utilizing all observed baseline measurements with no distinction between treatment arms
Missing endpoint measurements for subjects with tirzepatide and off treatment, were handled with placebo wash-out. Missing endpoint measurements for subjects on tirzepatide and on treatment, or subjects on placebo were handled as missing at random. 100 datasets were generated. ANCOVA was used with treatment, stratification factors of age group, and basal antihyperglycemic medication, and baseline FSG as factors and covariates. Source: Statistical Reviewer's Analysis; Abbreviations: CI = confidence interval; FSG = fasting serum glucose; N = number; SD = standard deviation; SE = standard error; TZP = tirzepatide.

5.5.8. Dose-Response

Both the 5 mg and 10 mg tirzepatide doses demonstrated statistically significant superiority to placebo for the primary and key secondary endpoints. Although a greater numerical

improvement was observed with the 10 mg dose, this phase 3 trial was not designed or powered to formally compare the two active treatment groups.

5.5.9. Durability of Response

The study design limited placebo-controlled evaluation to 30 weeks since placebo subjects switched to tirzepatide afterward, preventing formal assessment of treatment durability through Week 52. However, descriptive analyses showed that tirzepatide's effects were sustained through Week 52, with continued reductions in A1C (-2.01%) and BMI (-11.44%) from baseline.

5.5.10. Statistical Issues

A summary of statistical issues and resolutions is as follows:

i. Missing data were 11.1% in total for the primary endpoint (18.2% in TZP 10 mg, 9.4% in TZP 5 mg, and 5.9% in placebo)
ii. The Applicant mis specified that the jump-to-reference in the SAP would only include baseline and endpoint measurements and not intermediate measurements. The jump-to-reference did include intermediate measurements.
iii. Extreme imputed values (b) (4)% percentile or (b) (4)% of the observed measurements were replaced with the 2.5% and 97.5% percentiles, respectively. This was not specified in the SAP.
iv. The subject on tirzepatide 10 mg who was inadvertently enrolled and discontinued from the study was treated as missing at random. This was specified in the SAP, but the FDA does not agree.

Resolution for i-iv: The FDA preferred analysis was performed using a placebo washout for subjects on tirzepatide who discontinued treatment. Further, all imputed values were used, and the subject on tirzepatide 10 mg who was inadvertently enrolled and discontinued from the study was handled with placebo washout. Additional sensitivity analyses addressing missing data were performed, with no overturn in conclusions (see Appendix 19.6 for results).

v. 10 measurements were outside the protocol-specified 7-day window.

Resolution: Sensitivity analyses forcing these measurements as missing were performed. The results are similar to the FDA preferred analysis and did not overturn the conclusion. Further, these 10 measurements were within a 14-day window. Hence, there is no concern with these measurements being used in the primary analysis. See Appendix 19.6 for results.

vi. 7 subjects had missing baseline values for the key secondary endpoint of FSG.

Resolution: Missing baseline values were multiply imputed under missing at random.

Reference ID: 5715650

6 Clinical Safety

The safety review analyzed data from the 30-week double-blind period of trial GPGV using all randomized subjects who received at least one dose (safety analysis set). The Applicant's safety findings were independently verified by FDA reviewers.[13]

Mean exposure duration was 30.2 weeks for placebo, 49.5 weeks for tirzepatide 5 mg, and 48.1 weeks for tirzepatide 10 mg groups. Total tirzepatide exposure was 74.1 patient-years with a mean duration of 39.9 weeks, which is acceptable and consistent with other pediatric T2D development programs.

6.1. Safety Results

The safety profile of tirzepatide in pediatric subjects aged 10 to <18 years with T2D is consistent with the established safety profile in adults with T2D. In trial GPGV, the most frequently reported treatment-emergent adverse events (TEAEs) were mild-to-moderate GI events (e.g., nausea, diarrhea, and vomiting), which occurred primarily during the dose-escalation period and were generally transient. Serious adverse events (SAE) were infrequent (2 SAEs of appendicitis and mastoiditis in the tirzepatide group during the double-blind treatment period) with no apparent causal relationship to tirzepatide.

While no severe (level 3) hypoglycemia was reported, an increased incidence of clinically significant (level 2) hypoglycemia was observed, particularly in subjects receiving concomitant basal insulin; this is a known risk for this drug class, and the label will be updated to describe the hypoglycemia data in pediatrics. No cases of pancreatitis or MTC were reported, and a single SAE of cholecystitis, a known class effect, was observed during the open-label period. The data did not suggest any adverse effects on linear growth or pubertal development including height, height velocity, and Tanner staging, over the study duration despite significant weight loss. However, interpretation of these data is limited by the post-pubertal status of the study population (i.e., 62.6% reached Tanner stage 5) and the relatively short treatment duration of 52 weeks.

6.1.1. Deaths

No deaths were reported throughout trial GPGV. This finding was verified across all submitted safety data and was consistently reported in key study documents, including the complete study report (CSR), Table of Significant and Notable Patients, Summary of Clinical Safety (SCS), and the associated peer-reviewed publication.[13]

[13] Dr. Nhi Beasley from the Division of Biomedical Informatics, Research, and Biomarker Development (DBIRBD) and Sara Ripp from the Office of Computational Science (OCS) assisted in the safety analyses.

Reference ID: 5715650

6.1.2. Serious Adverse Events

During the 30-week double-blind treatment period, 3 SAEs (2 in tirzepatide and 1 in placebo) were reported: SAEs of appendicitis and mastoiditis (the latter secondary to recurrent otitis media) were reported in tirzepatide 5 and 10 mg, respectively, with no apparent causal relationship to tirzepatide, and SAE of suicidal attempt in placebo.

During the open-label extension and safety follow-up periods, two additional SAEs were reported:

1. SAE (severe) cholecystitis (with a concurrent non-SAE event of severe cholelithiasis) in the 5 mg tirzepatide group in a 17-year-old subject with past medical history of obesity, hepatic steatosis, and hyperlipidemia who experienced about 15% weight loss during the study. The subject required laparoscopic cholecystectomy. The study drug was not modified. The subject was discharged from the hospital on Study Day 291 and completed the study.

2. SAE of severe depression and suicide attempt during the safety follow-up period approximately 31 days after completion of the study (tirzepatide 10 mg) in the same subject who previously experienced SAE mastoiditis. The subject was referred to psychiatric inpatient hospitalization. According to the psychiatric report, she had experienced prior thoughts of suicide since the age of 13 following a family stressor.

6.1.3. Dropouts and/or Discontinuations Due to Adverse Effects

During the 30-week double-blind treatment period of trial GPGV, 6.3% (2/32) subjects discontinued the study drug due to AEs (nausea; suicidal ideation). Both discontinuations occurred in the tirzepatide 5 mg treatment group. No subjects in the tirzepatide 10 mg or placebo groups discontinued treatment due to AEs during the double-blind period, and no additional discontinuations due to AEs were reported during the subsequent 22-week open-label extension period.

The first case involved a 13-year-old male subject ((b) (6)) who experienced mild nausea on Study Day 25, which resolved the following day. The subject permanently discontinued the study drug on Study Day 53 due to this event.

The second case involved a 14-year-old female subject ((b) (6)) with no reported past medical history who experienced a non-serious, severe TEAE of suicidal ideation on Study Day 194. She discontinued the study drug on the following day, and the event resolved approximately one week later. The investigator noted that the subject made “suicidal threats” to her mother in the context of a family event. The subject also experienced a related moderate AE of “mood altered” from Study Day 72 to 202. Several factors confound the causality assessment to drug as described below; therefore, it is unlikely this was related to tirzepatide:

- The subject's underlying comorbidities (T2D and obesity) are associated with an

increased risk of psychiatric events.[14-17]
- The occurrence of the event in the context of a reported psychosocial stressor.
- The resolution of the event approximately eight days after the last dose, a time when substantial drug concentrations would still be present given the drug's half-life of approximately 5 days.[18]

6.1.4. Adverse Events of Special Interest (AESI)

In trial GPGV, the AESIs included the following:

- Hypoglycemia (documented in accordance with American Diabetes Association [ADA] levels 1-3 criteria)[19]
- Severe persistent hyperglycemia
- Pancreatitis (with independent adjudication)
- Thyroid malignancies
- Arrhythmias and cardiac conduction disorders
- Diabetic retinopathy complications
- Hypersensitivity reactions
- Injection site reactions
- Anti-drug antibodies
- Severe GI AEs
- Acute renal events
- Major depressive disorder/suicidal ideation
- Metabolic acidosis (including DKA)
- Hepatobiliary disorders

No new safety signal related to AESI was identified beyond the known safety profile labeled for tirzepatide in adults. Below is a summary of AESI findings adequately described in the approved label.

1. Severe hyperglycemia requiring rescue therapy occurred in 17.6% of placebo subjects but in none of the tirzepatide-treated subjects, with no cases of DKA reported in any group.

2. No adverse events of pancreatitis were reported or confirmed by adjudication during the study.

3. Asymptomatic increases in mean pancreatic amylase and lipase occurred in the tirzepatide groups but were not considered clinically significant. For pancreatic (p)-amylase, mean (SE) increases from baseline of 21.0% (5.9) and 20.1% (5.9) were observed in the 5 mg and 10 mg tirzepatide groups, respectively, compared with a 2.2% (4.7) increase in the placebo group. For lipase, mean (SE) levels increased from baseline by 17.2% (7.5) in the 5 mg group and 15.5% (7.5) in the 10 mg group, whereas a mean decrease of 1.2% (6.0) was observed in the placebo group. The magnitude of these

Reference ID: 5715650

increases was lower than that reported in the adult development program (p-amylase: 33-38%; lipase: 31-42%),[18] which may be attributable to the lower maximum dose studied in the pediatric trial (10 mg versus 15 mg).

3. No instances of MTC were reported. Mean serum calcitonin levels increased from baseline in the tirzepatide groups by 22.9% (10.2) in the tirzepatide 5 mg group and 15.9% (9.4) in the tirzepatide 10 mg group, compared to a mean decrease of 15.9% (6.4) in the placebo group, but these changes were not considered clinically significant, and no subject had a calcitonin value exceeding 35 ng/L with a ≥50% increase from baseline.

4. No diabetic retinopathy adverse events were observed.

5. TEAEs of tachycardia or increased heart rate were reported in four subjects (4.1%) treated with tirzepatide (two in the 10 mg group during the double-blind period and one each in the 5 mg and 10 mg groups during the open-label extension). All events were assessed as mild in severity. A mean increase in pulse rate of 2.8 to 3.8 beats per minute was observed in the tirzepatide 5 and 10 mg arms (sustained through Week 52), respectively, compared to a mean decrease of 2.1 (1.5) bpm in the placebo group. No clinically significant changes in electrocardiogram (ECG) intervals, including QTcF, were observed.

6. No severe GI adverse events were reported.

7. The incidence of renal adverse events was low. One subject (3%) in the tirzepatide 10 mg group reported an event of nephrolithiasis during the double-blind treatment period, and one event of moderate dehydration was reported during the open-label extension period.

8. Four adolescent female subjects (aged 13-15) experienced TEAEs related to major depressive disorder or suicidal ideation/behavior; 3 in tirzepatide-treated subjects and 1 in placebo. All subjects had pre-existing risk factors (e.g., psychiatric history, obesity, psychosocial issues). Based on the small number of events and baseline risk factors, a causal relationship to drug appears unlikely. Routine pharmacovigilance is adequate post-approval.

Liver safety

During the open-label extension period, severe hepatobiliary TEAEs occurred in three subjects randomized to the tirzepatide 5 mg arm; all three subjects had pre-existing hepatic conditions and elevated baseline serum ALT levels (>3x ULN). The events included one case each of hepatic steatosis, acute cholecystitis with cholelithiasis, and hepatic enzyme elevations (transient with one episode temporally associated with dengue fever).

Reference ID: 5715650

Additionally, 12 subjects met Temple's Corollary criteria for aminotransferase elevations >3× ULN during the trial (Figure 5), with 11 having pre-existing elevations at baseline. The proportion of subjects with aminotransferase over 3 times ULN was higher in tirzepatide-treated subjects (5 mg: 18.8% and 10 mg: 12.1%) compared to placebo (5.9%). Three of these subjects had post-baseline aminotransferases over 5 times the ULN compared to none receiving placebo. No patient developed jaundice, bilirubin >2 ULN, or other signs of liver failure.

The Applicant's rationale for not labeling the imbalance in aminotransferase elevations described above was reasonable:

1. Pre-existing liver enzyme elevations were common at baseline, with the study protocol permitting enrollment of subjects with ALT or AST elevations up to 5× ULN, and 12.3% of tirzepatide subjects and 9.4% of placebo subjects already having baseline ALT levels between 3-5× ULN.

2. Most tirzepatide-treated subjects with baseline elevations showed improvement, with 6 of 8 subjects reducing their ALT levels below 3× ULN during the study, while only 2 tirzepatide subjects (compared to none in placebo) entered with baseline ALT >5× ULN.

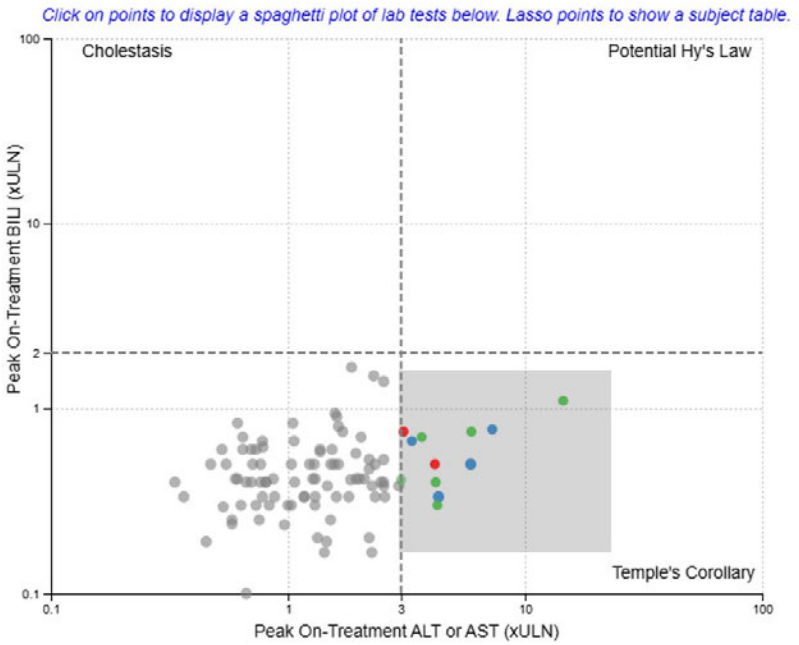
3. Tirzepatide-treated subjects had a mean ALT reduction of 35.6% compared to 10.6% in the placebo group.

4. Post-baseline elevations were confounded with hepatic steatosis. Additionally, liver enzyme levels in some subjects were elevated during the off-drug follow-up period.

Additionally, the Division of Hepatology and Nutrition (DHN) consultant concluded that most cases were "unlikely DILI" and attributed to alternative causes such as metabolic dysfunction-associated steatotic liver disease or gallstone disease.

Reference ID: 5715650

Figure 5: DILI Plot of Peak On-Treatment Liver Laboratory Test



Source: Analysis was conducted by Sara Ripp using the Office of Computational Science Analysis Studio, Hepatic Explorer. Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; BILI = total bilirubin; and ULN = upper limit of normal.

Below the AESIs considered for labeling are discussed:

Hypoglycemia[14]

The trial classified hypoglycemic events into three levels according to the ADA definitions:[19]

- *Level 1 Hypoglycemia (Glucose Alert):* blood glucose (BG) level ≥54 mg/dL and <70 mg/dL.
- *Level 2 Hypoglycemia (Clinically Significant):* BG level of <54 mg/dL, regardless of whether symptoms were present.
- *Level 3 Hypoglycemia (Severe):* Characterized by severe cognitive impairment that required assistance from another person to administer carbohydrates, glucagon, or other resuscitative actions; a BG measurement was not required.

There were no severe hypoglycemic episodes in the study (Table 11). The 95% CIs for pooled tirzepatide and the individual doses relative to placebo excluded 1, showing an increase in level 2 events on tirzepatide (Table 12). However, note that 1 subject experienced 12 level 2 episodes on tirzepatide 5 mg. Additionally, the percentage of subjects on insulin with at least 1 level 2 event is higher than the percentage of subjects on metformin alone (Table 13), which is

[14] Subjects and their guardians were trained to recognize hypoglycemia symptoms and perform blood glucose monitoring three times weekly while fasting and whenever experiencing hypoglycemic symptoms. All episodes were documented in an electronic diary including blood glucose levels, symptoms, and treatments, with investigators reviewing and classifying events at each visit using protocol-defined criteria.

consistent with the established safety profile for tirzepatide and the GLP-1 receptor agonist class.[18,20-23] The currently approved product labeling already includes a warning and precaution regarding the increased risk of hypoglycemia, including severe hypoglycemia, when tirzepatide is used concomitantly with an insulin secretagogue or insulin.[18] The product labeling will be updated to reflect the higher incidence of hypoglycemia compared to placebo observed in pediatric subjects, particularly in those on concomitant insulin therapy.

Table 11: Summary of Level 2 and 3 Hypoglycemic Episodes During 30-Week Treatment Period

	TZP Pooled (N=65)		TZP 10 mg (N=33)		TZP 5 mg (N=32)		Placebo (N=34)	
Hypoglycemic category	**# Subjects ≥1 episode (%)**	**# episodes**	**# Subjects ≥1 episode (%)**	**# episodes**	**# Subjects ≥1 episode (%)**	**# episodes**	**# Subjects ≥1 episode (%)**	**# episodes**
Severe	0	0	0	0	0	0	0	0
Documented hypoglycemia with blood glucose <54 mg/dL[a]	10 (15.4%)	29	5 (15.2%)	9	5 (15.6%)	20	2 (5.9%)	3

Source: Statistical Reviewer's Analysis; Abbreviations: N = number; TZP = tirzepatide. [a] No events occurred after the introduction of new glucose-lowering treatment.

Table 12: Rate Ratios of Level 2 Hypoglycemic Episodes During the 30-Week Treatment Period

	Rate Ratio 95% CI TZP Pooled / Placebo	Rate Ratio 95% CI TZP 10 mg / Placebo	Rate Ratio 95% CI TZP 5 mg / Placebo
All documented hypoglycemia with blood glucose <54 mg/dL	11.60 (2.19, 61.55)	7.24 (1.34, 38.98)	16.04 (2.51, 102.48)

Rate ratios obtained from negative binomial model with treatment and incidence of baseline hypoglycemia, with log (exposure in days/365.25) as an offset variable. Source: Applicant's response to an information request dated 7/24/25 (page 23) and CSR page 1176. The results from the statistical reviewer were similar.[15] Abbreviations: CI = confidence interval; N = number; TZP = tirzepatide.

[15] Using negative binomial model with treatment and incidence of baseline hypoglycemia, with log (exposure in days/365.25) as an offset variable. A classical empirical estimation of the covariance matrix was used. Results were 12.07 (2.11, 68.88), 8.11 (1.29, 50.92), and 17.94 (2.51, 128.34) for TZP pooled, TZP 10 mg and TZP 5 mg vs placebo respectively.

Table 13: Level 2 Hypoglycemic Episodes During 30-Week Treatment Period by Insulin Use

	TZP 10 mg (N=33)		TZP 5 mg (N=32)		Placebo (N=34)	
	Add on to basal insulin with or without metformin (N=11)	Add on to metformin alone (N=22)	Add on to basal insulin with or without metformin (N=10)	Add on to metformin alone (N=22)	Add on to basal insulin with or without metformin (N=10)	Add on to metformin alone (N=24)
# Subjects ≥ 1 episode (%)	3 (27.3%)	2 (9.1%)	3 (30%)	2 (9.1%)	1 (10%)	1 (4.2%)
# episodes	6	3	16	4	2	1

Source: Statistical Reviewer's Analysis; Abbreviations: N = number; TZP = tirzepatide. No events after the introduction of new glucose-lowering treatment.

Hypersensitivity and Injection Site Reactions

The incidence of hypersensitivity and injection site reactions was low. Non-serious hypersensitivity reactions (urticaria and bronchospasm) were reported in two subjects (6.3%) in the tirzepatide 5 mg group, compared to none in the tirzepatide 10 mg or placebo groups. Injection site reactions were also infrequent, occurring in 4.6% of subjects in the pooled tirzepatide groups compared to 2.9% in the placebo group, and were predominantly mild in severity. A higher incidence of both hypersensitivity and injection site reactions was observed in subjects who were anti-drug antibody (ADA) positive (Section 6.1.9). These findings are consistent with the established safety profile of tirzepatide[18,23]. The label will be updated to include the pediatric data related to hypersensitivity and injection site reactions.

6.1.5. Treatment Emergent Adverse Events[16]

Refer to Section 8.2 of this review for a tabular display of TEAEs. During the 30-week double-blind period of trial GPGV, the overall incidence of TEAEs was higher in the tirzepatide groups (65.6% in the 5 mg group and 69.7% in the 10 mg group) compared to the placebo group (44.1%). The majority of TEAEs were mild to moderate in severity; severe events were infrequent and occurred at comparable rates across treatment groups.

The most frequently reported TEAEs in tirzepatide-treated subjects were GI; during the 30-week placebo-controlled period, vomiting occurred in 3%, 16%, and 12% of subjects and abdominal pain occurred in 9%, 22%, and 15% of subjects treated with placebo, tirzepatide 5 mg, and 10 mg, respectively. This will be reflected in labeling.

The TEAEs occurring in ≥5% of tirzepatide-treated subjects included diarrhea, nausea, abdominal pain, vomiting, dyspepsia, decreased appetite, cough, oropharyngeal pain, headache, tonsillitis, anxiety, nasopharyngitis, and injection site reactions. Tirzepatide-treated

[16] Adverse events in trial GPGV were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 27.1. The severity of AEs was graded as mild, moderate, or severe based on ICH E2A standards.

subjects experienced more recurrent GI adverse events compared to placebo, as evidenced by a greater disparity between the total number of GI events and the number of affected subjects in the tirzepatide groups. Hyperglycemia was reported as a TEAE in five placebo-treated subjects but was not reported in the tirzepatide treatment groups.

6.1.6. Laboratory Findings

Clinical laboratory assessments, performed primarily by a central laboratory, included hematology, clinical chemistry (e.g., hepatic and renal function, electrolytes), endocrine parameters (e.g., A1C, insulin, C-peptide, calcitonin, and thyroid function), fasting lipids, pancreatic enzymes, and urinalysis with assessment of urine albumin-to-creatinine ratio (UACR).

The safety laboratory profile for tirzepatide in the pediatric cohort for this trial is consistent with the established profile in adults and with the GLP-1 receptor agonist class. No new safety signals were identified in this study.

Estimated Glomerular Filtration Rate (eGFR):
The eGFR was calculated using two methods: the Bedside Schwartz equation[24] and the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.[25] A similar pattern was observed, with both methods showing a dose-dependent decrease in eGFR from baseline in the tirzepatide groups relative to placebo. However, given the high baseline eGFR values, with subjects remaining within the normal ranges, these observed changes do not appear to represent clinically meaningful reductions in renal function.

Using the Bedside Schwartz equation:

- Mean baseline eGFRs were approximately 119.1, 115.5, 119.9, and 117.8 mL/min/1.73 m² for the placebo, tirzepatide 5 mg, 10 mg, and pooled treatment groups.
- At Week 30, the LSM change from baseline was -4.3 mL/min/1.73 m² for the placebo group, compared to -15.0 mL/min/1.73 m² and -17.3 mL/min/1.73 m² for the tirzepatide 5 mg and 10 mg groups, respectively.

Using the CKD-EPI equation:

- Mean baseline eGFRs were 143.7, 143.4, and 145.9 mL/min/1.73 m² for the placebo, tirzepatide 5 mg, and 10 mg groups, respectively.
  At Week 30, the LSM change from baseline was -4.6 mL/min/1.73 m² for the placebo group, compared to -9.2 mL/min/1.73 m² and -10.5 mL/min/1.73 m² for the tirzepatide 5 mg and 10 mg groups, respectively.

Reference ID: 5715650

6.1.7. Vital Signs[17]

During the 30-week double-blind period, tirzepatide was associated with dose-dependent reductions in blood pressure. At baseline, vital signs were comparable across all treatment groups. At Week 30, the following mean (SE) changes from baseline were observed:

- Systolic Blood Pressure (SBP): A decrease of 1.0 (1.5) mmHg in the 5 mg group and 7.3 (1.5) mmHg in the 10 mg group, compared to an increase of 1.3 (1.4) mmHg in the placebo group.
- Diastolic Blood Pressure (DBP): A decrease of 2.0 (1.3) mmHg in the 5 mg group and 5.3 (1.3) mmHg in the 10 mg group, compared to an increase of 0.3 (1.2) mmHg in the placebo group.

The reductions in blood pressure were sustained through the 52-week study period. Consistent with these findings, the incidence of new or worsening hypertension was numerically lower in the tirzepatide arms (five subjects in the 5 mg group and two subjects in the 10 mg group) compared to the placebo arm (10 subjects).

6.1.8. Electrocardiograms (ECGs)[18]

Overall, the ECG data from trial GPGV did not reveal any clinically significant effects on cardiac repolarization. The cardiac safety profile of tirzepatide in this pediatric population is consistent with that observed in adult T2D clinical trials.

At Week 30, mean changes from baseline in QTcF were small and not clinically significant across all treatment groups. The mean change was -1.6 msec in the placebo group, -5.6 msec in the tirzepatide 5 mg group, and -1.7 msec in the tirzepatide 10 mg group. No subject met the prespecified criteria[19] for an abnormal ECG finding at Week 30. Through Week 52, one subject in the tirzepatide 10 mg group had a QTcF value of 452 msec, representing an increase of 33 msec from baseline; no other clinically significant ECG abnormalities were reported.

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[17] Vital signs, including blood pressure and pulse, were measured in triplicate using automated equipment and evaluated against age-appropriate thresholds. Anthropometric assessments, including height, weight, waist circumference, and Tanner staging, followed World Health Organization protocols.

[18] Twelve-lead ECGs were obtained at baseline, Week 30, and Week 52 using centralized equipment and underwent dual interpretation: immediate local review for clinical management and independent central interpretation for analysis.

[19] The study defined abnormal ECG findings using prespecified, age- and sex-stratified criteria. For heart rate, bradycardia was defined as <60 bpm for subjects aged 10-11 years or <50 bpm for those ≥12 years, while tachycardia thresholds were >140 bpm (10-11 years), >120 bpm (12-14 years), or >100 bpm (≥15 years); post-baseline assessments also required a significant change from baseline. PR interval prolongation was identified as >190 msec for ages 10-12 or >210 msec for ages 13-18. Abnormal QTcF prolongation was defined by absolute thresholds stratified by age and sex (>460 msec for ≤15 years; >450 msec for males ≥16 years; >470 msec for females ≥16 years), an overall value >500 msec, or a change from baseline exceeding 30, 60, or 75 msec.

6.1.9. Immunogenicity

The immunogenicity assessment for trial GPGV utilized the same multi-tiered assay strategy as previously validated for the adult T2D indication, which consisted of ligand-binding methods for ADA assessment, cross-reactivity testing against native GLP-1 and GIP, and cell-based neutralizing antibody (NAb) assays. The same disease-state cut points (DSCP) used previously in the adult T2D program were used for the ADA assays in trial GPGV. Immunogenicity samples were collected at Weeks 0, 4, 12, 30, 42, 52, and 56 to characterize ADA kinetics in this pediatric population. The immunogenicity review team from the Office of Pharmaceutical Quality Research (OPQR) reviewed the suitability of the DSCP for assessing the incidence of ADAs in GPGV and deemed that the cutpoints were suitable for the intended purpose.

During the 30-week double-blind period, 49.2% (30/61) of tirzepatide-treated subjects developed treatment-emergent (TE) ADAs, with 47.5% (29 subjects) classified as treatment-induced and 1.6% (1 subject) as treatment-boosted. Through the entire 52-week treatment period, 53.8% (50/93) of all subjects developed ADAs, with maximum titers ranging from 1:40 to 1:20,480 (median 1:320). Cross-reactivity to native GIP or GLP-1 was observed in 26% and 8% of tirzepatide-treated subjects, respectively. No NAbs against tirzepatide activity on GIP or GLP-1 receptors were detected. The Applicant's proposed labeling includes these pediatric immunogenicity findings in Section 12.6, stating that the immunogenicity profile in pediatric subjects was consistent with adult data and had no clinically significant effect on PK or effectiveness. Notably, a higher incidence of hypersensitivity and injection site reactions was observed in TE ADA-positive subjects compared to TE ADA-negative subjects. Specifically, hypersensitivity reactions were reported in 4% (2/50) of TE ADA-positive subjects versus none in the ADA-negative group, while injection site reactions were reported in 6% (3/50) of TE ADA-positive subjects versus none in the ADA-negative group. These findings warrant inclusion in the final product labeling.

The OPQR immunogenicity review team found the assay strategy acceptable and noted that the ADA incidence in pediatric subjects (49-54%) was consistent with that reported in adult clinical trials, where 51% (2,570/5,025) of tirzepatide-treated subjects developed measurable ADAs. However, the small pediatric study size (99 subjects total) was insufficient to adequately characterize the incidence of NAbs, which were reported at a low frequency (2%) in the larger adult program.

The approved labeling for tirzepatide in adults includes specific NAb incidence rates. In contrast, due to the smaller study population of trial GPGV, the proposed pediatric labeling does not contain definitive conclusions regarding NAb. OPQR recommends approval of this sNDA.

Reference ID: 5715650

6.2. Safety Analyses by Demographic Subgroups

The Applicant identified no specific populations at a clinically meaningful increased risk for AEs based on age, sex, or race. Formal subgroup analyses for notable safety events (deaths, SAEs, discontinuations due to AEs, and AESIs) were not performed, as the low incidence of these events precluded a meaningful assessment of risk across these demographic subgroups.

6.3. Additional Safety Explorations

No cases of overdose, drug abuse, withdrawal symptoms, or rebound phenomena were reported in trial GPGV.

No pregnancies were reported during the trial.

Pediatrics and Assessment of Effects on Growth

Physical growth was assessed via measurements of height, height SDS, height velocity, and height velocity SDS collected from baseline through the safety follow-up period. Pubertal development was evaluated using Tanner staging for breast development (females), genital development (males), and pubic hair (both sexes) at baseline and at Weeks 16, 30, and 52. Per the protocol, Tanner stage assessments were discontinued for any subject who reached Stage 5.

Physical Growth

Linear growth parameters were analyzed at Week 30 and Week 52.

- **Change in Height and Height SDS (Week 30):** At Week 30, no clinically meaningful or statistically significant differences in the mean change from baseline in height or height SDS were observed between the tirzepatide and placebo groups.
    - Height: The LSM change from baseline was +0.50 cm and +0.57 cm for the 5 mg and 10 mg groups, respectively, compared to +0.49 cm for placebo.
    - Height SDS: The LSM change from baseline was -0.09 in the 5 mg group and -0.11 in the 10 mg group, compared to -0.11 for placebo.
- **Change in Height and Height SDS (Week 52):** Through 52 weeks of treatment, subjects in all groups demonstrated continued increases in height and slight decreases in height SDS, consistent with expected growth trajectories. At Week 52, the LSM change from baseline in height ranged from +0.75 cm to +1.01 cm across treatment groups, and the LSM change from baseline in height SDS ranged from -0.15 to -0.17. No clinically meaningful differences were observed between groups.
- **Height Velocity and Height Velocity SDS**: No clinically relevant differences were observed between tirzepatide and placebo groups in height velocity or height velocity

Reference ID: 5715650

SDS at Week 30. At Week 52, the LSM for height velocity was 0.78 cm/year for the placebo/tirzepatide 5 mg group, 0.89 cm/year for the tirzepatide 5 mg group, and 1.12 cm/year for the tirzepatide 10 mg group. The corresponding LSM values for height velocity SDS were -0.18, -0.33, and -0.21, respectively.

Pubertal Progression

Assessment of pubertal progression via Tanner staging revealed no clinically relevant imbalances between the tirzepatide and placebo groups. The study population was predominantly post-pubertal, with 66.7% of female subjects and 56.4% of male subjects at Tanner Stage 5 at baseline. Analyses of shifts in Tanner stage from baseline to Week 52 showed no clinically meaningful differences in the progression of genital or breast development scores between the tirzepatide and placebo groups, and the observed progression was consistent with normal pubertal development.

Conclusion on Growth and Development

Overall, the data from trial GPGV do not suggest that treatment with tirzepatide at doses of 5 mg or 10 mg for up to 52 weeks has a clinically meaningful adverse effect on linear growth or pubertal progression in adolescents with T2D, despite causing significant reductions in weight and BMI. However, interpretation of these findings is limited by the duration of exposure and high enrollment of subjects who were already sexually mature, which precludes a definitive assessment of tirzepatide's effects on the timing and progression of puberty in younger, pre-pubertal subjects. Although the available data are reassuring, they are insufficient to definitively rule out potential effects on pubertal development.

6.4. Safety in the Postmarket Setting

Based on pharmacologic effects on GI motility and postmarketing reports, there is concern that GLP-1 receptor agonists, including tirzepatide, may be associated with intestinal obstruction and severe constipation. This safety signal has been identified in NISS 5517, and the product labeling will be updated to include warnings about severe GI adverse reactions in Section 5 (Warnings and Precautions) and information about intestinal obstruction and severe constipation in Section 6.2 (Postmarketing Experience).

The Applicant has not proposed a Risk Evaluation and Mitigation Strategy (REMS) or pediatric-specific pharmacovigilance activities beyond routine monitoring, expecting the pediatric safety profile to be consistent with adults. The FDA will continue routine post-marketing surveillance of tirzepatide and other GLP-1 receptor agonists, focusing on growth and development issues, emerging safety signals, and known adverse reactions already identified in product labeling.

Reference ID: 5715650

7 Labeling Recommendations

Table 14: Key Labeling Changes and Considerations for Selected Sections of the Prescribing Information

Full PI Section	Summary of Labeling Revisions
1 INDICATIONS AND USAGE	Expanded the glycemic control indication to include pediatric patients aged 10 years and older.
2 DOSAGE AND ADMINISTRATION	• The recommended starting dosage and titration in pediatric patients is the same as for adults (2.5 mg injected subcutaneously once weekly upon initiation and after 4 weeks, increase to 5 mg once weekly. The dosage may be increased by 2.5 mg after at least 4 weeks on the current dose.) • However, the maximum recommended dosage is 10 mg in pediatric patients. • Included minor revision to clarify that caregivers may inject into the back of the upper arm. Clarified that a patient may self-inject if a healthcare provider determines this is appropriate.
5 WARNINGS AND PRECAUTIONS	• Clarified safety information reported in adults versus pediatric patients for applicable Warnings and Precautions. • Revised language in the Warnings and Precautions for Acute Pancreatitis (5.2), Acute Kidney Injury Due to Volume Depletion (5.5), and Severe Gastrointestinal Adverse Reactions (5.6) to align with recent changes to other GLP-1 receptor agonists and changes made with the Newly Identified Safety Signal (NISS) 5517 (Intestinal Obstruction).
6 ADVERSE REACTIONS	• Identified safety data reported in adult vs pediatric patients. • Added the incidence of hypersensitivity and injection site reactions in pediatric patients who developed anti-tirzepatide antibodies vs those who did not. • Reported that the incidences of adverse reactions in the clinical trial of pediatric patients were consistent with those reported for adult patients, with the exception of a higher incidence of vomiting, abdominal pain, and hypoglycemia in pediatric patients. Included rates for these events in pediatric patients. • Included postmarketing events of intestinal obstruction, severe constipation including fecal impaction as described in the NISS 5517.
8.4 USE IN SPECIFIC POPULATIONS, Pediatric Use	Described the basis of approval for the pediatric indication and differences in the safety profile in pediatric patients versus adults.
12 CLINICAL PHARMACOLOGY	• Pharmacokinetics (12.3): ○ Described the population pharmacokinetic analysis of pediatric

Full PI Section	Summary of Labeling Revisions
	patients and concluded that exposure was comparable to adults. • Immunogenicity (12.6): ○ Reported the incidence of anti-tirzepatide antibodies observed in the pediatric clinical trial and the higher incidence of hypersensitivity reactions and injection site reactions in pediatric patients who developed anti-tirzepatide antibodies compared to those who did not develop these antibodies.
14 CLINICAL STUDIES	• Clarified data from clinical trials reported in adults versus pediatric patients, as needed. • Summarized the pertinent results from SURPASS-PEDS, described elsewhere in this review.

Source: FDA edits to the PI as of December 10, 2025.

The Highlights Section, Patient Counseling Section, and Medication Guide were revised to incorporate the changes described above, as applicable.

DMEPA, the Patient Labeling Team in the Division of Medical Policy Programs (DMPP), and the Office of Prescription Drug Promotion (OPDP) also reviewed sNDA 215866/S-039. Their collaborative review, which provides additional details regarding their input on labeling, is available under DARRTS Reference ID 5708124 at:
https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af807f245f

8 Appendices

8.1. Financial Disclosure

Covered Clinical Study (Name and/or Number): Study I8F-MC-GPGV, titled "*A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study with an Open-Label Extension Assessing the Efficacy, Safety, and Pharmacokinetics/Pharmacodynamics of Tirzepatide in Pediatric and Adolescent Participants With Type 2 Diabetes Mellitus Inadequately Controlled With Metformin, or Basal Insulin, or Both*"

Table 15: Summary of Clinical Investigator Financial Disclosure Information

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 93		
Number of investigators who are Applicant employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: Not Applicable (N/A) Significant payments of other sorts: N/A Proprietary interest in the product tested held by investigator: N/A Significant equity interest held by investigator in Study: N/A Applicant of covered study: N/A		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐ N/A	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐ N/A	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____		
Is an attachment provided with the reason:	Yes ☐ N/A	No ☐ (Request explanation from Applicant)

8.2. Safety Table for Treatment-Emergent Adverse Events – Trial GPGV

Table 16: Summary of Treatment-Emergent Adverse Events During 30-Week Treatment Period

	TZP Pooled (N=65)		*TZP 10 mg (N = 33)*		*TZP 5 mg (N = 32)*		*PLACEBO (N = 34)*	
Preferred Term	***Events***	***No. (%) of Subjects***	***Events***	***No. (%) of Subjects***	***Events***	***No. (%) of Subjects***	***Events***	***No. (%) of Subjects***
Subject with ≥1 Event	**—**	**59 (59.6)**	**—**	**23 (69.7)**	**—**	**21 (65.6)**	**—**	**15 (44.1)**
Diarrhoea	34	16 (24.6)	11	8 (24.2)	23	8 (25)	7	2 (5.9)
Nausea	34	13 (20)	7	6 (18.2)	27	7 (21.9)	3	3 (8.8)
Vomiting	31	9 (13.8)	24	4 (12.1)	7	5 (15.6)	1	1 (2.9)
Dyspepsia	7	6 (9.2)	5	4 (12.1)	2	2 (6.3)	0	0
Abdominal pain upper	22	6 (9.2)	4	4 (12.1)	18	2 (6.3)	4	3 (8.8)
Decreased appetite	5	4 (6.2)	5	4 (12.1)	0	0	0	0
Headache	12	5 (7.7)	5	3 (9.1)	7	2 (6.3)	1	1 (2.9)
Anxiety	4	3 (4.6)	2	2 (6.1)	2	1 (3.1)	0	0
Nasopharyngitis	3	3 (4.6)	2	2 (6.1)	1	1 (3.1)	3	2 (5.9)
Injection site reaction	6	2 (3.1)	6	2 (6.1)	0	0	0	0
Abdominal pain	6	6 (9.2)	1	1 (3)	5	5 (15.6)	1	1 (2.9)
Cough	5	4 (6.2)	1	1 (3)	4	3 (9.4)	2	1 (2.9)
Oropharyngeal pain	5	4 (6.2)	1	1 (3)	4	3 (9.4)	3	2 (5.9)
Abdominal discomfort	2	2 (3.1)	1	1 (3)	1	1 (3.1)	0	0
Dizziness	3	2 (3.1)	1	1 (3)	2	1 (3.1)	0	0
Ear infection	3	2 (3.1)	2	1 (3)	1	1 (3.1)	0	0
Rhinitis	2	2 (3.1)	1	1 (3)	1	1 (3.1)	0	0
Influenza	2	2 (3.1)	1	1 (3)	1	1 (3.1)	2	1 (2.9)
Suicidal ideation	2	2 (3.1)	1	1 (3)	1	1 (3.1)	1	1 (2.9)
Pharyngitis	1	1 (1.5)	1	1 (3)	0	0	1	1 (2.9)
COVID-19	1	1 (1.5)	1	1 (3)	0	0	0	0
Constipation	1	1 (1.5)	1	1 (3)	0	0	0	0
Depression	1	1 (1.5)	1	1 (3)	0	0	0	0
Gastrooesophageal reflux disease	1	1 (1.5)	1	1 (3)	0	0	0	0
Hand fracture	1	1 (1.5)	1	1 (3)	0	0	0	0
Heart rate increased	1	1 (1.5)	1	1 (3)	0	0	0	0
Malabsorption	1	1 (1.5)	1	1 (3)	0	0	0	0
Mastoiditis	1	1 (1.5)	1	1 (3)	0	0	0	0
Nasal congestion	1	1 (1.5)	1	1 (3)	0	0	0	0
Nephrolithiasis	1	1 (1.5)	1	1 (3)	0	0	0	0
Non-cardiac chest pain	2	1 (1.5)	2	1 (3)	0	0	0	0
Otitis externa	1	1 (1.5)	1	1 (3)	0	0	0	0
Petechiae	1	1 (1.5)	1	1 (3)	0	0	0	0

	TZP Pooled (N=65)		*TZP 10 mg (N = 33)*		*TZP 5 mg (N = 32)*		*PLACEBO (N = 34)*	
Preferred Term	***Events***	***No. (%) of Subjects***	***Events***	***No. (%) of Subjects***	***Events***	***No. (%) of Subjects***	***Events***	***No. (%) of Subjects***
Pyrexia	1	1 (1.5)	1	1 (3)	0	0	0	0
Skin lesion	1	1 (1.5)	1	1 (3)	0	0	0	0
Tachycardia	1	1 (1.5)	1	1 (3)	0	0	0	0
Tonsillitis	2	2 (3.1)	0	0	2	2 (6.3)	0	0
Abscess jaw	1	1 (1.5)	0	0	1	1 (3.1)	0	0
Alopecia	1	1 (1.5)	0	0	1	1 (3.1)	0	0
Amenorrhoea	1	1 (1.5)	0	0	1	1 (3.1)	0	0
Anxiety disorder	1	1 (1.5)	0	0	1	1 (3.1)	0	0
Appendicitis	1	1 (1.5)	0	0	1	1 (3.1)	0	0
Asthenia	1	1 (1.5)	0	0	1	1 (3.1)	0	0
Asthma	1	1 (1.5)	0	0	1	1 (3.1)	0	0
Blood triglycerides increased	1	1 (1.5)	0	0	1	1 (3.1)	0	0
Bronchospasm	1	1 (1.5)	0	0	1	1 (3.1)	0	0
Candida infection	1	1 (1.5)	0	0	1	1 (3.1)	0	0
Cellulitis	1	1 (1.5)	0	0	1	1 (3.1)	0	0
Conjunctival hyperaemia	1	1 (1.5)	0	0	1	1 (3.1)	0	0
Dysmenorrhoea	5	1 (1.5)	0	0	5	1 (3.1)	0	0
Eructation	1	1 (1.5)	0	0	1	1 (3.1)	0	0
Flatulence	2	1 (1.5)	0	0	2	1 (3.1)	0	0
Gastritis	1	1 (1.5)	0	0	1	1 (3.1)	0	0
Gastrointestinal viral infection	1	1 (1.5)	0	0	1	1 (3.1)	0	0
Helicobacter test positive	1	1 (1.5)	0	0	1	1 (3.1)	0	0
Hyperphagia	2	1 (1.5)	0	0	2	1 (3.1)	0	0
Joint dislocation	1	1 (1.5)	0	0	1	1 (3.1)	0	0
Ligament rupture	1	1 (1.5)	0	0	1	1 (3.1)	0	0
Ligament sprain	3	1 (1.5)	0	0	3	1 (3.1)	0	0
Malaise	1	1 (1.5)	0	0	1	1 (3.1)	0	0
Mood altered	1	1 (1.5)	0	0	1	1 (3.1)	0	0
Oesophagitis	1	1 (1.5)	0	0	1	1 (3.1)	0	0
Oligomenorrhoea	1	1 (1.5)	0	0	1	1 (3.1)	0	0
Ovarian cyst	1	1 (1.5)	0	0	1	1 (3.1)	0	0
Rectal haemorrhage	1	1 (1.5)	0	0	1	1 (3.1)	0	0
Respiratory tract congestion	1	1 (1.5)	0	0	1	1 (3.1)	0	0
Rhinorrhoea	1	1 (1.5)	0	0	1	1 (3.1)	0	0
Suspected COVID-19	1	1 (1.5)	0	0	1	1 (3.1)	0	0
Trismus	1	1 (1.5)	0	0	1	1 (3.1)	0	0

	TZP Pooled (N=65)		*TZP 10 mg (N = 33)*		*TZP 5 mg (N = 32)*		*PLACEBO (N = 34)*	
Preferred Term	***Events***	***No. (%) of Subjects***	***Events***	***No. (%) of Subjects***	***Events***	***No. (%) of Subjects***	***Events***	***No. (%) of Subjects***
Upper respiratory tract infection	1	1 (1.5)	0	0	1	1 (3.1)	0	0
Urticaria	1	1 (1.5)	0	0	1	1 (3.1)	0	0
Viral infection	1	1 (1.5)	0	0	1	1 (3.1)	0	0
Back pain	1	1 (1.5)	0	0	1	1 (3.1)	1	1 (2.9)
Dry skin	1	1 (1.5)	0	0	1	1 (3.1)	1	1 (2.9)
Injection site pain	1	1 (1.5)	0	0	1	1 (3.1)	1	1 (2.9)
Anaemia	0	0	0	0	0	0	1	1 (2.9)
Borderline personality disorder	0	0	0	0	0	0	2	1 (2.9)
Contusion	0	0	0	0	0	0	1	1 (2.9)
Hyperlipidaemia	0	0	0	0	0	0	1	1 (2.9)
Hypertriglyceridaemia	0	0	0	0	0	0	1	1 (2.9)
Ingrowing nail	0	0	0	0	0	0	1	1 (2.9)
Insomnia	0	0	0	0	0	0	1	1 (2.9)
Myalgia	0	0	0	0	0	0	1	1 (2.9)
Peripheral swelling	0	0	0	0	0	0	1	1 (2.9)
Seizure	0	0	0	0	0	0	2	1 (2.9)
Snoring	0	0	0	0	0	0	1	1 (2.9)
Suicide attempt	0	0	0	0	0	0	1	1 (2.9)
Tooth extraction	0	0	0	0	0	0	1	1 (2.9)
Urine albumin/creatinine ratio abnormal	0	0	0	0	0	0	1	1 (2.9)
Wound	0	0	0	0	0	0	1	1 (2.9)
Gastroenteritis	0	0	0	0	0	0	2	2 (5.9)
Hyperglycaemia	0	0	0	0	0	0	5	5 (14.7)

Source: Analysis conducted by Dr. Nhi Beasley, DBIRBD. Derived from the adsl.xpt and adae.xpt datasets.
Abbreviations: N= number; TZP = tirzepatide.
* Sorted by the proportions of subjects with events for the tirzepatide 10 mg arm.

Reference ID: 5715650

8.3. Abnormal Liver Laboratories-Trial GPGV

Table 17: Abnormal Liver Laboratory Test Results by Study Visit

Unique Subject Identifier / *TREATMENT*	ALT		AST		BILI		ALP		GGT	
Study Week (Day)	Result (IU/L)	x ULN	Result (IU/L)	x ULN	Result (mg/dL)	x ULN	Result (IU/L)	x ULN	Result (IU/L)	x ULN
I8F-MC-GPGV (b) (4)										
PLACEBO										
Week -4 (Day -24)	62	2.07	30	0.97	0.3	0.3	149	0.8	31	1.29
Baseline (Day 1)	79	2.63	48	1.55	0.2	0.2	171	0.92	49	2.04
Week 8 (Day 61)	40	1.33	25	0.81	0.2	0.2	129	0.69	25	1.04
Week 16 (Day 119)	45	1.5	26	0.84	0.4	0.4	126	0.68	26	1.08
Week 30 (Day 218)	24	0.8	19	0.61	0.4	0.4	107	0.58	25	1.04
TIRZEPATIDE 5 mg										
Week 42 (Day 295)	25	0.83	27	0.87	0.5	0.5	99	0.53	22	0.92
Week 52 (Day 365)	30	1	18	0.58	0.2	0.2	79	0.42	96	4
Safety Follow-up (Day 393)	125	4.17	37	1.19	0.3	0.3	97	0.52	215	8.96
Unscheduled Visit (Day 399)	14	0.47	19	0.61	0.5	0.5	275	1.48	17	0.71
I8F-MC-GPGV (b) (4)										
PLACEBO										
Week -4 (Day -32)	134	3.27	85	2.3	0.4	0.33	95	0.24	130	2.13
Baseline (Day 1)	126	3.07	72	1.95	0.5	0.42	104	0.27	152	2.49
Week 8 (Day 61)	91	2.22	50	1.35	0.6	0.5	103	0.26	103	1.69
Week 16 (Day 113)	126	3.07	71	1.92	0.6	0.5	99	0.77	134	2.2
Week 30 (Day 219)	91	2.22	38	1.03	0.9	0.75	115	0.89	103	1.69
TIRZEPATIDE 5 mg										
Week 42 (Day 296)	82	2	32	0.86	0.3	0.25	107	0.83	89	1.46
Week 52 (Day 365)	87	2.12	40	1.08	0.4	0.33	105	0.81	90	1.48
Safety Follow-up (Day 393)	83	2.02	38	1.03	0.3	0.25	128	0.99	97	1.59
I8F-MC-GPGV (b) (4)										
TIRZEPATIDE 5 mg										
Week -4 (Day -38)	156	5.2	41	1.32	0.7	0.58	180	0.97	340	9.44
Unscheduled Visit (Day -24)	128	4.27	40	1.29	0.5	0.42	171	0.92	215	5.97
Baseline (Day 1)	97	2.94	58	1.87	0.7	0.58	145	0.78	167	4.64
Week 8 (Day 57)	84	2.55	36	1.16	0.9	0.75	148	0.8	129	3.58
Week 16 (Day 114)	196	5.94	87	2.81	0.6	0.5	223	1.2	177	4.92
Week 20 (Day 141)	100	3.03								

Unique Subject Identifier	ALT		AST		BILI		ALP		GGT	
TREATMENT										
Study Week (Day)	**Result (IU/L)**	**x ULN**	**Result (IU/L)**	**x ULN**	**Result (mg/dL)**	**x ULN**	**Result (IU/L)**	**x ULN**	**Result (IU/L)**	**x ULN**
Week 30 (Day 218)	123	3.73	56	1.81	0.7	0.58	161	0.87	167	4.64
Week 42 (Day 297)	160	4.85	67	2.16	0.5	0.42	193	1.04	180	5
Safety Follow-up (Day 387)	180	5.45	75	2.42	0.6	0.5	202	1.94	184	5.11
I8F-MC-GPGV- (b) (6)										
TIRZEPATIDE 5 mg										
Week -4 (Day -27)	63	2.1	42	1.17	0.3	0.3	180	0.6	27	1.23
Baseline (Day 1)	126	4.2	107	2.97	0.2	0.2	166	0.56	33	1.5
Week 8 (Day 50)	82	2.73	51	1.65	0.2	0.2	187	1.01	31	1.29
Week 16 (Day 100)	67	2.23	50	1.61	0.4	0.4	148	0.8	21	0.88
Week 30 (Day 205)	44	1.47	33	1.06	0.2	0.2	165	0.89	18	0.75
Week 42 (Day 294)	44	1.47	25	0.81	0.3	0.3	145	0.78	18	0.75
Week 52 (Day 364)	29	0.97	24	0.77	0.4	0.4	123	0.66	19	0.79
Safety Follow-up (Day 394)	32	1.07	20	0.65			118	0.63	14	0.58
I8F-MC-GPGV- (b) (6)										
TIRZEPATIDE 5 mg										
Week -4 (Day -25)	126	4.2	91	2.94	0.4	0.4	126	0.68	53	2.21
Baseline (Day 1)	110	3.67	62	2	0.5	0.5	118	0.63	40	1.67
Week 8 (Day 51)	29	0.97	24	0.77	0.7	0.7	92	0.49	23	0.96
Week 16 (Day 116)	18	0.6	20	0.65	0.4	0.4	101	0.54	27	1.13
Week 30 (Day 211)	21	0.7	18	0.58	0.4	0.4	93	0.5	31	1.29
Week 42 (Day 288)	11	0.37	12	0.39	0.3	0.3	92	0.49	23	0.96
Week 52 (Day 361)	12	0.4	17	0.55	0.6	0.6	102	0.55	23	0.96
Safety Follow-up (Day 389)	11	0.37	10	0.32	0.5	0.5	103	0.55	23	0.96
I8F-MC-GPGV (b) (6)										
TIRZEPATIDE 5 mg										
Week -4 (Day -21)	100	3.33	67	1.76	0.3	0.3	169	0.43	53	1.26
Baseline (Day 1)	128	4.27	76	2	0.3	0.3	163	0.42	60	1.43
Week 7 (Day 53)	58	1.93	35	0.92	0.3	0.3	145	0.37	34	0.81
Safety Follow-up (Day 88)	78	2.6	27	0.71			205	0.53	50	1.19
I8F-MC-GPGV (b) (6)										
TIRZEPATIDE 5 mg										
Week -4 (Day -47)	96	3.2	35	1.13	0.6	0.6	101	0.54	153	6.38
Baseline (Day 1)	107	3.57	52	1.68	0.8	0.67	98	0.53	195	5.42
Week 8 (Day 57)	147	4.9	48	1.55	0.3	0.25	112	0.6	216	6

Unique Subject Identifier	ALT		AST		BILI		ALP		GGT	
TREATMENT										
Study Week (Day)	**Result (IU/L)**	**x ULN**	**Result (IU/L)**	**x ULN**	**Result (mg/dL)**	**x ULN**	**Result (IU/L)**	**x ULN**	**Result (IU/L)**	**x ULN**
Week 16 (Day 114)	197	6.57	95	3.06	0.3	0.25	119	0.64	256	7.11
Unscheduled Visit (Day 122)	273	9.1	86	2.77	0.3	0.25	135	0.73	266	7.39
Week 20 (Day 143)	160.2	4.58	71.9	2.05			107	0.91	248	10.33
Unscheduled Visit (Day 177)	124	4.13	56	1.81	0.6	0.5	102	0.55	218	6.06
Week 30 (Day 213)	119	3.97	46	1.48	0.3	0.25	99	0.53	203	5.64
Week 34 (Day Visit 15) (Day 242)	223	7.43	104	3.35	0.3	0.25	149	0.8	336	9.33
Week 38 (Day Visit 16) (Day 270)	255	8.5	141	4.55	0.2	0.17	151	0.81	437	12.14
Week 42 (Day 298)	200	6.67	143	4.61	0.3	0.25	120	0.65	339	9.42
Week 46 (Day 316)	257.7	7.36	160.7	4.59	1.1	1.1	119	1.02	632	26.33
Unscheduled Visit (Day 330)	46.7	1.33	107.3	3.07	0.1	0.1	111	1.04	296	12.33
Unscheduled Visit (Day 347)	118	3.93	65	2.1	0.5	0.42	101	0.54	322	8.94
Week 52 (Day 361)	255	7.73	79	2.55	0.3	0.25	129	0.69	338	9.39
Unscheduled Visit (Day 373)	478	14.48	216	6.97	0.4	0.33	163	0.88	542	15.06
Safety Follow-up (Day 389)	209	6.33	73	2.35	0.5	0.42	124	0.67	414	11.5
I8F-MC-GPGV (b) (6)										
TIRZEPATIDE 5 mg										
Week -4 (Day -28)	55	1.83	47	1.52	0.46784	0.47	125	0.67	39	1.63
Week 8 (Day 51)	45	1.5	39	1.26	0.2924	0.29	115	0.62	41	1.71
Week 16 (Day 118)	56	1.87	50	1.61	0.40936	0.41	108	0.58	39	1.63
Week 29 (Day 195)	90	3	79	2.55	0.35088	0.35	117	0.63	50	2.08
Safety Follow-up (Day 218)	66	2.2	51	1.65	0.17544	0.18	94	0.51	40	1.67
I8F-MC-GPGV- (b) (6)										
TIRZEPATIDE 10 mg										
Week -4 (Day -25)	83	2.77	52	1.37	0.23392	0.24	148	0.38	32	0.76
Baseline (Day 1)	130	4.33	71	1.87	0.40936	0.41	171	0.44	55	1.31
Week 4 (Day 32)	223	4.46	195	3.9	0.77	0.77	178	0.4	101	1.68
Unscheduled Visit (Day 39)	176	5.87	125	3.29	0.52632	0.53	176	0.45	99	2.36
Week 7 (Day Visit 6) (Day 50)	207	6.9	166	4.37	0.52632	0.53	187	0.48	102	2.43
Unscheduled Visit (Day 63)	215.5	7.185	190.5	5.015	0.26316	0.265	205.5	0.53	135	3.215

Unique Subject Identifier	ALT		AST		BILI		ALP		GGT	
TREATMENT										
Study Week (Day)	**Result (IU/L)**	**x ULN**	**Result (IU/L)**	**x ULN**	**Result (mg/dL)**	**x ULN**	**Result (IU/L)**	**x ULN**	**Result (IU/L)**	**x ULN**
Week 12 (Day Visit 8) (Day 87)	218	7.27	197	5.18	0.40936	0.41	196	0.5	148	3.52
Safety Follow-up (Day 121)	174	5.8	225	5.92	0.70176	0.71	228	0.59	238	5.67
I8F-MC-GPGV (b) (6)										
TIRZEPATIDE 10 mg										
Week -4 (Day -35)	172	4.2	85	2.3	0.5	0.42	105	0.81	101	1.66
Baseline (Day 1)	177	4.32	93	2.51	0.4	0.33	105	0.81	86	1.41
Week 8 (Day 63)	120	2.93	47	1.27	0.2	0.17	97	0.75	91	1.49
Week 16 (Day 120)	106	2.59	48	1.3	0.3	0.25	93	0.72	69	1.13
Week 30 (Day 208)	110	2.68	45	1.22	0.3	0.25	79	0.61	70	1.15
Week 42 (Day 294)	55	1.34	29	0.78	0.2	0.17	77	0.6	68	1.11
Week 52 (Day 365)	52	1.27	33	0.89			73	0.57	62	1.02
Safety Follow-up (Day 393)	73	1.78	44	1.19			65	0.5	77	1.26
I8F-MC-GPGV (b) (6)										
TIRZEPATIDE 10 mg										
Week -4 (Day -28)	143	4.77	50	1.61	0.4	0.33	94	0.51	33	0.92
Baseline (Day 1)	177	5.9					105	0.56	36	1
Unscheduled Visit (Day 22)	71	2.37	38	1.23	0.3	0.25	110	0.59	28	0.78
Week 8 (Day 57)	32	1.07	20	0.65			96	0.52	16	0.44
Week 16 (Day 120)	20	0.61	21	0.68	0.4	0.33	86	0.46	14	0.39
Week 30 (Day 211)	15	0.45	26	0.84	0.4	0.33	73	0.39	10	0.28
Week 42 (Day 295)	14	0.42	17	0.55	0.3	0.25	83	0.45	9	0.25
Week 52 (Day 372)	11	0.33	13	0.42	0.6	0.5	74	0.4	9	0.25
Safety Follow-up (Day 393)	37	1.12	25	0.81	0.2	0.17	73	0.39	21	0.58
I8F-MC-GPGV- (b) (6)										
TIRZEPATIDE 10 mg										
Week -4 (Day -38)	18	0.6	13	0.42	0.4	0.33	83	0.45	11	0.31
Baseline (Day 1)	15	0.5	9	0.29	0.8	0.67	90	0.48	11	0.31
Week 8 (Day 52)	100	3.33	50	1.61	0.5	0.42	120	0.65	61	1.69
Unscheduled Visit (Day 63)	48	1.6	22	0.71	0.8	0.67	83	0.45	26	0.72
Week 16 (Day 117)	23	0.7	19	0.61	0.7	0.58	69	0.37	12	0.33
Safety Follow-up (Day 269)	28	0.85	15	0.48	0.5	0.42	98	0.53	14	0.39

Source: Analysis conducted by Sara Ripp, OCS. Derived from the adsl.xpt and adlb.xpt datasets.
Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BILI = bilirubin; GGT = gamma-glutamyl transferase; ULN = upper limit of normal.

8.4. Additional Statistical Analyses

Table 18 displays the results of the Applicant's analyses for the primary and key secondary endpoints (see Statistical Methodology Section 8.1.1). The results are similar to the FDA's preferred analyses.

Table 18: Applicant's Results for the Primary and Key Secondary Endpoints

	Pooled TZP - Placebo	TZP 10 mg - Placebo	TZP 5 mg - Placebo
Endpoint	**LS Mean Change from baseline to Week 30 in:**		
Change in A1C	-1.80 (-2.35, -1.25)	-1.93 (-2.57, -1.29)	-1.67 (-2.31, -1.02)
Change in FSG	-36.43 (-54.21, -18.65)	-43.98 (-64.32, -23.63)	-28.88 (-49.72, -8.05)
Change in BMI	-2.71 (-3.60, -1.81)	-3.59 (-4.64, -2.54)	-1.82 (-2.86, -0.78)
Change in BMI-SDS	-0.51 (-0.68, -0.34)	-0.66 (-0.86, -0.47)	-0.36 (-0.55, -0.16)
	LS Mean % Change from baseline to Week 30 in:		
% Change in BMI	-8.35 (-11.05, -5.66)	-10.52 (-13.67, -7.38)	-6.18 (-9.31, -3.05)
	Difference in proportions		
A1C ≤6.5%	45.79% (27.48%, 64.11%)	51.62% (31.06%, 72.18%)	40.15% (18.56%, 61.74%)

Source: Statistical Reviewer's Analysis and CSR page 112 (A1C), page 123 (FSG), page 539 (BMI), page 133 (BMI-SDS), page 138 (% change in BMI), page 520 (A1C ≤6.5%)

Table 19 displays the disposition of Week 30 A1C measurements relative to the target analysis day of 211=30*7+1. The protocol-specified window was 7 days. Of the observed 88 measurements used in the primary analysis, 78 were within the 7-day window, 5 measurements were between 1 and 2 weeks before Day 211, and 5 measurements were between 1 and 2 weeks after Day 211. Hence, all 88 measurements were within 2-weeks of Day 211.

Table 19: Tabulation of A1C Measurements Relative to Day 211

ADY	TZP 10 mg	TZP 5 mg	Placebo	Total
197 ≤ADY ≤203 - (1-2 Weeks)	1	1	3	5
204 ≤ADY ≤218 +/- 1 Week	25	28	25	78
219 ≤ADY ≤225 + (1-2 Weeks)	1	0	4	5
Total	27	29	32	88

Source: Statistical Reviewer's Analysis

Table 20 displays the disposition of the 10 measurements outside the 7-day window, and whether the measurements were collected while the subject was on or off treatment.

Reference ID: 5715650

Table 20: Disposition of 10 Subjects with Week 30 Measurement Outside the 7-Day Window

	TZP 10 mg	TZP 5 mg	Placebo
On treatment	2	1	6
Off treatment	0	0	1
Total	**2**	**1**	**7**

Source: Statistical Reviewer's Analysis

As a sensitivity analysis, the 10 measurements were forced as missing. Hence, there are now 21 missing measurements. Table 21 summarizes the disposition of missing data.

Table 21: Disposition of Missing Data for Window Analysis

	TZP 10 mg (N=33)	TZP 5 mg (N=32)	Placebo (N=34)	Total (N=99)
# with observed Week 30 data [n(%)]	25 (75.8%)	28 (87.5%)	25 (73.5%)	78 (78.8%)
On treatment [n]	25	28	24	77
Off treatment (Retrieved Drop-outs) [n]	0	0	1	1
# with missing Week 30 data [n(%)]	8 (24.2%)	4 (12.5%)	9 (26.5%)	21 (21.2%)
Study discontinuation [n]	4	3	1	8
On treatment [n]	4	1	8	13

Source: Statistical Reviewer's Analysis

Table 22 displays the results for the window analyses. The results are similar to the FDA preferred analysis, and there is no overturn in the conclusion of superiority of tirzepatide over placebo in reducing A1C.

Table 22: Sensitivity Window Analysis Results for Change in A1C from Baseline to Week 30

	Pooled TZP (N=65)	TZP 10 mg (N=33)	TZP 5 mg (N=32)	Placebo (N=34)
# without Week 30 data (%)	12 (18.5%)	8 (24.2%)	4 (12.5%)	9 (26.5%)
LS mean (SE) Change from baseline	-2.09 (0.21)	-2.27 (0.29)	-1.91 (0.28)	-0.24 (0.26)
Difference at Week 30 (SE) (95% CI)	-1.84 (0.34) (-2.51, -1.18)	-2.03 (0.40) (-2.81, -1.24)	-1.66 (0.39) (-2.43, -0.89)	

Source: Statistical Reviewer's Analysis

Table 23 displays the results of the sensitivity analysis that handles all subjects on tirzepatide with missing data with a placebo wash-out, irrespective of their end-of-treatment status (i.e., on or off treatment) at Week 30. The results are similar to the FDA preferred analysis in Table 6. There is no overturn in the conclusion of superiority of tirzepatide over placebo in reducing A1C.

Table 23: Sensitivity Analysis Considering all Subjects on Tirzepatide, Irrespective of EOT Status, with Placebo Wash-Out

	Pooled TZP (N=65)	TZP 10 mg (N=33)	TZP 5 mg (N=32)	Placebo (N=34)
# without Week 30 data (%)	9 (13.8%)	6 (18.2%)	3 (9.4%)	2 (5.9%)
LS mean (SE) Change from baseline	-2.00 (0.21)	-2.10 (0.30)	-1.91 (0.29)	-0.23 (0.26)
Difference at Week 30 (SE) (95% CI)	-1.78 (0.33) (-2.42, -1.13)	-1.87 (0.39) (-2.64, -1.10)	-1.68 (0.38) (-2.43, -0.93)	

Source: Statistical Reviewer's Analysis

2-Way Tipping Point

A 2-way tipping point analysis was performed to assess the robustness of the primary analysis with respect to missing data assumptions. The 2-way tipping point analysis is with respect to the FDA preferred analysis.

The results are shown in Figure 6 below. The point (0, 0) represents the results of the primary analysis (upper right hand in the figure). Since the unit for the primary analysis is change in A1C, the benefit added to placebo (penalty added to pooled tirzepatide) are changes in A1C. The x-axis represents the benefit added to the imputed values for placebo, and the y-axis represents the penalty added to the imputed values for pooled tirzepatide.

Each unit in the figure is worth a penalty of 1.4%. For example, the point (-1, 0) means a benefit of -1.4% is added to each imputed value on placebo and no penalty added to each imputed value on pooled tirzepatide. The point (0, 1) means no benefit is added to each imputed value on placebo and a penalty of 1.4% is added to each imputed value of pooled tirzepatide. Likewise, the point (-6, 7) means a benefit of -8.4% is added to each imputed value on placebo and a penalty of 9.8% is added to each imputed value on pooled tirzepatide.

From the primary analysis (FDA preferred), the average imputed change in A1C for the 9 subjects with missing data on tirzepatide is -0.42%, and the average imputed change in A1C for the 2 subjects with missing data on placebo is -0.78%. Let us consider the following scenarios where the results would tip the conclusion of superiority to not superior, and the clinical plausibility:

i. When the penalty on tirzepatide is 0, so that the average imputed change remains -0.42%, the benefit on placebo needed is -10*1.4= -14.0%, so that the average imputed change is -0.78% - 14.0% = -14.78% [(-10, 0) on the map]. This is clearly not possible.

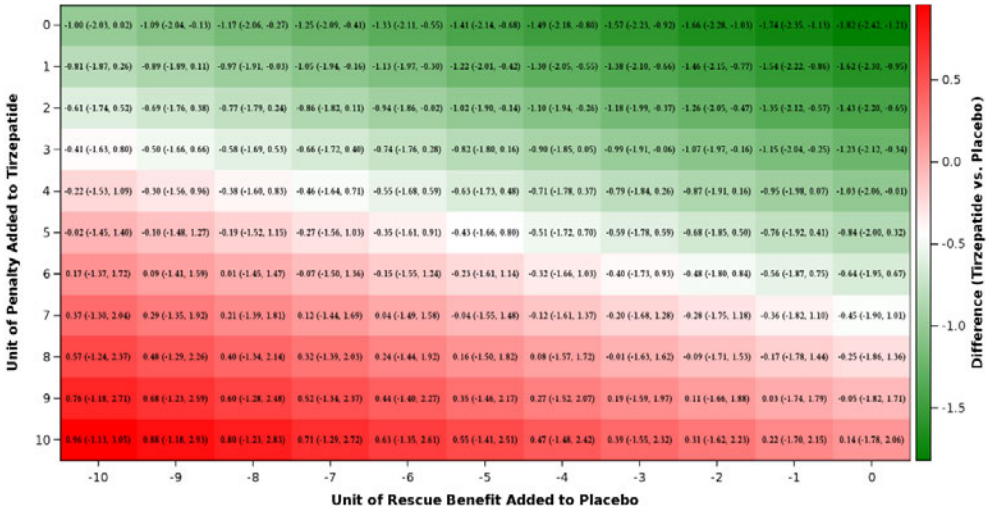
ii. When the benefit on placebo is 0, so that the average imputed change remains -0.78%, the penalty on tirzepatide needed is 5*1.4=7.0%, so that the average imputed change is -0.42% + 7.0%=6.58% [(0, 5) on the map], which is extremely unlikely.

Reference ID: 5715650

iii. The 9 subjects on tirzepatide experience a penalty of 3*1.4%=4.2%, so that the average imputed change is -0.42% +4.2%=3.78%. To tip results, the average imputed change for the 2 subjects on placebo is -4*1.4% = -5.6%, so that the average imputed change is -0.78%-5.6%=-6.38% [(-4, 3) on the map]. This scenario is extremely unlikely.

Thus, the robustness of the primary analysis with respect to how missing data were handled, under the treatment regimen estimand is confirmed.

Figure 6: A1C – Two-Way Tipping Point Analysis (Heatmap) for the Primary Endpoint



Each unit = 1.4
Each cell contains the mean difference and 95% CI between pooled tirzepatide and placebo.
The x-axis represents the benefits added to the imputed values for placebo.
The y-axis represents the penalties added to the imputed values for pooled tirzepatide.
Source: Statistical Reviewer's Analysis

Baseline A1C as an Effect Modifier

It is well known that baseline A1C is an effect modifier (i.e., the treatment effect on A1C change will depend on a subject's baseline A1C measurement). Table 24 below is a scatter plot and regression lines based on the completers from tirzepatide 10 mg, tirzepatide 5 mg, and placebo. Regression lines were computed and superimposed over the scatter points.

Here, the difference in slopes between tirzepatide 10 mg and placebo is -0.51%, which means that for every 1% increase in baseline A1C, then $\Delta_{TZP10} - \Delta_{Placebo}$ decreases by 0.51% (i.e., the effect of tirzepatide 10 mg decreases by 0.51). Figure 7 illustrates this below. When baseline A1C is 6%, the mean change from baseline between tirzepatide 10 mg and placebo is $\Delta_{TZP10} - \Delta_{Placebo}$ = -1.26, and when baseline A1C is 7%, the mean change from baseline between tirzepatide 10 mg and placebo is $\Delta_{TZP10} - \Delta_{Placebo}$ = -1.77, and so forth.

Table 24: Treatment Differences as A1C Increases

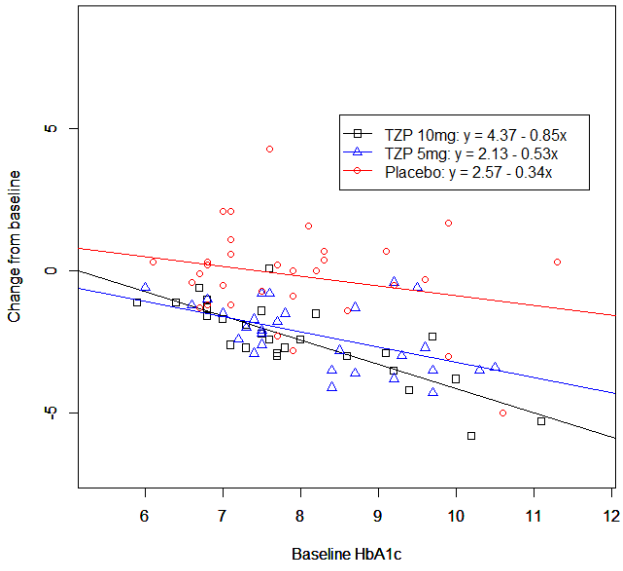
	Baseline A1C			
	6%	**7%**	**8%**	**9%**
	Mean change from baseline			
Tirzepatide 10 mg	-0.73	-1.58	-2.43	-3.28
Placebo	0.53	0.19	-0.15	-0.49
Difference	**-1.26**	**-1.77**	**-2.28**	**-2.79**

Source: Statistical Reviewer's Analysis

Similarly, the difference in slopes between tirzepatide 5 mg and placebo is -0.19%, so for every 1% increase in baseline A1C, then Δ_{TZP5} - $\Delta_{Placebo}$ decreases by 0.19% (i.e., the effect of tirzepatide 5 mg decreases by 0.19).

Hence, the higher the baseline A1C, the larger the treatment effect. In the primary analysis, baseline A1C was included in the ANCOVA model to adjust for this modification effect. The p-value for a test for no difference in slopes between tirzepatide 10 mg and placebo is 0.08, while the p-value for a test for no difference in slopes between tirzepatide 5 mg and placebo is 0.53.

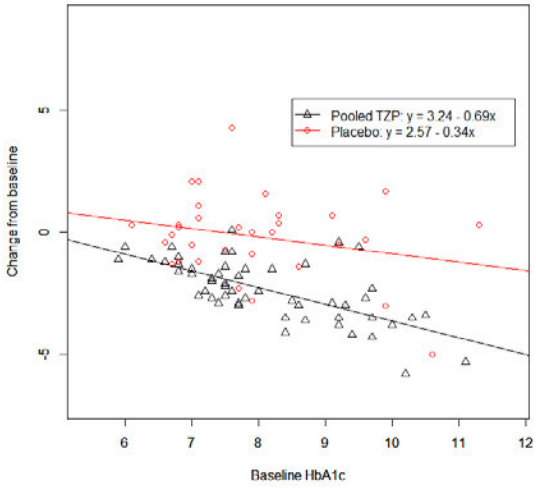
Figure 7: Scatter Plot and Regression Lines Based on Completers for Individual Doses and Placebo



Source: Statistical Reviewer's Analysis

Figure 8 below is a scatter plot and regression lines based on the completers from pooled tirzepatide and placebo. The difference in slopes between pooled tirzepatide and placebo is -0.35%, so for every 1% increase in baseline A1C, then Δ_{TZP_Pooled} - $\Delta_{Placebo}$ decreases by 0.35% (i.e., the effect of pooled tirzepatide decreases by 0.35). The p-value for a test for no difference in slopes between pooled tirzepatide and placebo is 0.13. So, baseline A1C does not significantly modify the treatment effect in pooled tirzepatide.

Figure 8: Scatter Plot and Regression Lines Based on Completers for Pooled Tirzepatide and Placebo



Source: Statistical Reviewer's Analysis

Bayesian Hierarchical Modeling for Subgroup Analyses

Bayesian hierarchical modeling produces shrinkage estimates of the individual study treatment effects by removing the within study variability. Further, treatment effects are regarded as exchangeable, which allows them to be different but related. Therefore, shrinkage estimates tend to be more precise and provide narrower credible intervals. Below is the model used in the analysis for sex, age, region, race, and ethnicity:

$$Y_i \sim N(\mu_i, \sigma_i^2), i = 1, \ldots, k$$

$$\mu_i \sim N(\mu, \tau^2), i = 1, \ldots, k$$

$$\mu \sim \mathrm{N}(0, \sigma_0^2), \quad \tau \sim Half - N(0,1)$$

We assume that before seeing data, the treatment effect is 0 based on one-eighth of a subject on each treatment group. The observed subject-level standard deviation can be used to compute the variance of the prior distribution of the treatment effect. The observed subject level standard deviation was estimated to be 1.384 (under the FDA preferred analysis), thus the variance of the prior distribution of the treatment effect is $\sigma_0^2 = 16 * 1.384^2 \approx 31$.

8.5. Summary of Clinical Pharmacology Assessment

8.5.1. Pharmacology and Clinical Pharmacokinetics

The population PK analysis of 93 pediatric subjects with T2D demonstrated that tirzepatide PK was well characterized by a two-compartment model with first-order absorption and linear clearance, with body weight incorporated as a covariate using fixed allometric exponents and age showing minimal clinically relevant effects on drug exposure. Simulations confirmed that the mean steady-state (SS) exposures (AUC_{ss} and $C_{max,ss}$) for tirzepatide were similar between pediatric and adult subjects at the same dose levels (5 mg and 10 mg), with pediatric exposures being 9% and 14% higher, respectively, with higher variability observed in the pediatric population (Table 30). Given that the highest approved maintenance dose in adults is 15 mg QW, the exposures observed in pediatric subjects following 5 mg and 10 mg QW doses remained within the established safety and efficacy exposure range observed in adults.

Exposure-response modeling for FSG and A1C revealed dose-dependent improvements in glycemic control, with a steep increase up to the 5 mg tirzepatide dose and smaller increments from 5 mg to 10 mg (Figure 17), indicating limited additional benefit from further increasing the dose to 15 mg. Exposure-response modeling for body weight showed a linear relationship between dose and loss of fat-free mass, and a sublinear relationship for loss of fat mass and total body weight (Figure 20), with a predicted 8.4% loss in total body weight at 5 mg and a 14.8% loss at 10 mg at Week 52. Limiting the maximum maintenance dose to 10 mg provided adequate efficacy with an acceptable safety profile without the risk of excessive body weight loss.

Overall, the new clinical pharmacology information from the detailed PK/PD modeling report provides the scientific foundation supporting the rationale for using lower maximum maintenance doses (5-10 mg) in pediatric patients compared to the 15 mg maximum maintenance dose approved for adults. The pediatric data demonstrated exposure matching when compared at the same dose levels (5 mg and 10 mg) and provided favorable efficacy and safety profiles.

8.5.2. Therapeutic Individualization

The intrinsic factors of age, gender, race, ethnicity, body weight, or renal or hepatic impairment do not have a clinically relevant effect on the PK of tirzepatide.

8.5.3. General Pharmacology and Pharmacokinetic Characteristics

Mechanism of Action

Tirzepatide is a GIP receptor and GLP-1 receptor agonist. It is an amino-acid sequence including a C20 fatty diacid that enables albumin binding and prolongs the half-life. Tirzepatide selectively binds to and activates both the GIP and GLP-1 receptors, the targets for native GIP

Reference ID: 5715650

and GLP-1. Tirzepatide enhances first- and second-phase insulin secretion, and reduces glucagon levels, both in a glucose-dependent manner.

Pharmacodynamics

Tirzepatide lowers fasting and postprandial glucose concentration, decreases food intake, and reduces body weight in patients with T2D.

First and Second-Phase Insulin Secretion

Tirzepatide enhances the first- and second-phase insulin secretion.

Insulin Sensitivity

Tirzepatide increases insulin sensitivity, as demonstrated in a hyperinsulinemic euglycemic clamp study after 28 weeks of treatment.

Glucagon Secretion

Tirzepatide reduces fasting and postprandial glucagon concentrations. Tirzepatide 15 mg reduced fasting glucagon concentration by 28% and glucagon AUC after a mixed meal by 43%, compared with no change for placebo after 28 weeks of treatment.

Gastric Emptying

Tirzepatide delays gastric emptying. The delay is largest after the first dose and this effect diminishes over time. Tirzepatide slows post-meal glucose absorption, reducing postprandial glucose.

Pharmacokinetics

The PK of tirzepatide is similar between healthy subjects and patients with T2D. Steady-state plasma tirzepatide concentrations were achieved following 4 weeks of QW administration. Tirzepatide exposure increases in a dose-proportional manner.

Absorption

Following SC administration, the time to maximum plasma concentration of tirzepatide ranges from 8 to 72 hours. The mean absolute bioavailability of tirzepatide following SC administration is 80%. Similar exposure was achieved with SC administration of tirzepatide in the abdomen, thigh, or upper arm.

Distribution

The mean apparent steady-state volume of distribution of tirzepatide following SC administration in patients with T2D is approximately 10.3 L. Tirzepatide is highly bound to plasma albumin (99%).

Elimination

The apparent population mean clearance of tirzepatide is 0.061 L/h with an elimination half-life of approximately 5 days, enabling once-weekly dosing.

Metabolism

Tirzepatide is metabolized by proteolytic cleavage of the peptide backbone, beta-oxidation of the C20 fatty diacid and amide hydrolysis.

Excretion

The primary excretion routes of tirzepatide metabolites are via urine and feces. Intact tirzepatide is not observed in urine or feces.

Specific Populations

The intrinsic factors of age, gender, race, ethnicity, or body weight do not have a clinically relevant effect on the PK of tirzepatide.

Pediatric Patients (newly proposed text)

A population pharmacokinetic analysis was conducted for tirzepatide 5 mg and 10 mg using data from 93 pediatric patients 10 years of age and older with T2D. The tirzepatide exposure in pediatric patients was within the range observed in adult patients.

Patients with Renal Impairment

Renal impairment does not impact the PK of tirzepatide. The PK of tirzepatide after a single 5 mg dose was evaluated in patients with different degrees of renal impairment (mild, moderate, severe, end stage renal disease [ESRD]) compared with subjects with normal renal function. This was also shown for patients with both T2D and renal impairment based on data from clinical studies

Patients with Hepatic Impairment

Hepatic impairment does not impact the PK of tirzepatide. The PK of tirzepatide after a single 5 mg dose was evaluated in patients with different degrees of hepatic impairment (mild, moderate, severe) compared with subjects with normal hepatic function

Drug Interactions Studies

Potential for Tirzepatide to Influence the Pharmacokinetics of Other Drugs

In vitro studies have shown low potential for tirzepatide to inhibit or induce cytochrome P450 (CYP) enzymes, and to inhibit drug transporters.

MOUNJARO delays gastric emptying and thereby has the potential to impact the absorption of concomitantly administered oral medications

The impact of tirzepatide on gastric emptying was greatest after a single dose of 5 mg and diminished after subsequent doses.

Following a first dose of tirzepatide 5 mg, acetaminophen C_{max} was reduced by 50%, and the median peak plasma concentration (t_{max}) occurred 1 hour later. After coadministration at week 4, there was no meaningful impact on acetaminophen C_{max} and t_{max}. Overall acetaminophen exposure (AUC_{0-24hr}) was not influenced.

Following administration of a combined oral contraceptive (0.035 mg ethinyl estradiol and 0.25 mg norgestimate) in the presence of a single dose of tirzepatide 5 mg, mean C_{max} of ethinyl estradiol, norgestimate, and norelgestromin was reduced by 59%, 66%, and 55%, while mean AUC was reduced by 20%, 21%, and 23%, respectively. A delay in t_{max} of 2.5 to 4.5 hours was observed.

8.6. OCP Appendices (Technical documents supporting OCP recommendations)

8.6.1. Pharmacometric Analysis

8.6.1.1. Population PK analysis

8.6.1.1.1. Review Summary

On 20 June 2025, Eli Lilly and Company (Lilly) submitted a supplemental NDA for tirzepatide (NDA 215866/S-039) seeking approval of tirzepatide in children and adolescents with T2D aged between 10 and less than 18 years who had inadequate glycemic control, despite diet and exercise, with metformin and/or basal insulin. The proposed maintenance doses of tirzepatide are 5 and 10 mg SC QW. A pediatric phase 3 trial GPGV was conducted to investigate the efficacy, safety, and PK/PD of tirzepatide in the pediatric and adolescent population. The clinical trial lasted for 30 weeks with 3 arms (i.e., tirzepatide 5 mg, 10 mg, and placebo), followed by a 22-week, open-label period. This study met the primary efficacy endpoint of superiority of tirzepatide (pooled dose group) versus placebo for change from baseline A1C at Week 30. In addition, population PK model confirmed that tirzepatide PK exposures from the pediatric subjects were similar to adult subjects at the same dose level for both 5 mg and 10 mg doses, with higher variabilities observed in pediatric subjects. Exposures were higher in pediatric subjects with lower body weights; however, these exposures remained within the expected range for adults of similar body weight and tirzepatide dosage capped at 15 mg.

In general, the Applicant's population PK analysis is considered acceptable for characterizing tirzepatide exposure in plasma in children and adolescents aged 10 and less than 18 years. The reviewer verified the Applicant's analyses and identified no discrepancies.

More specifically, the developed model was used to support the current submission as outlined in Table 25.

Table 25: Specific Comments on Applicant's Final Population PK model

Utility of the final model			**Reviewer's Comments**
Support applicant's proposed labeling statements about intrinsic and extrinsic factors	**Intrinsic factor**	*Pediatric subjects* A population pharmacokinetic analysis was conducted for tirzepatide 5 mg and 10 mg using data from 93 pediatric subjects 10 years of age and older with T2D. Tirzepatide exposure in pediatric subjects was within the range observed in adult subjects.	The statement is acceptable. Both weight and age were identified as significant covariates in the pediatric population PK model for tirzepatide. Simulations from the population PK model demonstrate that median steady-state AUCss and Cmax,ss values for tirzepatide in pediatric subjects (>10 to 17 years) and adult populations are similar, with greater variability observed in the pediatric

Utility of the final model			Reviewer's Comments
			population compared to adults. Tirzepatide exposure in pediatric subjects following 5 mg and 10 mg doses fell within the range of that observed in adult subjects during clinical trials.
Derive exposure metrics for Exposure-response analyses	Cmin,ss, Cmax,ss, AUCss		The applicant's final pediatric model is generally acceptable for generating exposure metrics for exposure-response analyses.

Source: Pharmacometrics reviewer's summary.
Abbreviations: AUCss = area under the concentration-time curve at steady state; Cmax,ss = maximum concentration at steady state; Cmin,ss = minimum concentration at steady state; PK = pharmacokinetic; T2D = type 2 diabetes.

8.6.1.1.2. Objectives

The primary objectives of applicant's analysis were to:

1) To evaluate the population PK of tirzepatide in children and adolescents aged between 10 and less than 18 years.
2) Generate individual plasma exposure estimates of tirzepatide in children and adolescents.

8.6.1.1.3. Model development

Data

The analyses were based on PK data from trial GPGV. The study design, study population, and timing of blood samples are presented in Table 26.

The NONMEM data file from the Applicant's proposed final model for analysis contained 664 PK observations from 93 subjects. Of these, 599 (90.2%) were non-below limit of quantification (BLQ) observations, and 65 (9.8%) were BLQ samples. Table 27 and Table 28 provide summary statistics of the baseline demographic covariates in the analysis dataset.

Reference ID: 5715650

Table 26: Summary of Study with PK Sampling Included in Population PK Analysis.

Protocol # & Study Design	Dosage Regimen & Study Description	Number of Subjects in PopPK Analysis,	Dose(s) [mg]
GPGV (Phase 3 pediatric Study)	A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study with an Open-Label Extension Assessing the Efficacy, Safety, and PK/PD of Tirzepatide in Pediatric and Adolescent Participants with T2D Inadequately Controlled with Metformin, or Basal Insulin, or Both	N = 93	5 mg, 10 mg and placebo

Source: Applicant's Study Report GPGV

Table 27: Summary of Baseline Demographic for Continuous Covariates by Treatment Arm for Analysis

Variable	n	Mean	Median	SD	Min / Max
Age (years)	93	14.8	15.0	1.80	11.0 / 17.0
Weight (kg)	93	96.8	96.7	26.8	57.0 / 191
Body mass index (kg/m^2)	93	35.5	34.9	7.85	23.1 / 61.1
Lean body mass (kg)	93	55.4	55.3	11.8	36.1 / 93.3
Fat-free mass (kg)	93	55.1	52.9	13.2	35.9 / 93.8
Fat mass (kg)	93	41.7	39.7	17.1	12.7 / 102
Waist circumference (cm)	93	107	108	19.0	75.0 / 156
Body surface area (m^2)	93	2.01	2.03	0.294	1.53 / 2.86
Aspartate aminotransferase (U/L)	93	29.6	23.0	19.4	8.00 / 107
Alanine aminotransferase (U/L)	93	43.1	28.0	38.4	7.00 / 177
Estimated GFR (mL/min/1.73m^2)	93	129	132	20.7	74.3 / 225
Estimated GFR BSA (mL/min)	93	150	147	34.2	89.0 / 271
Diabetes duration (years)	93	2.41	2.15	1.80	0.140 / 10.8
Fasting glucose (mmol/L)	93	8.41	7.83	3.48	4.20 / 24.1
Hemoglobin A1c (%)	93	8.06	7.70	1.25	5.90 / 11.3

Source: Applicant's pediatric population PK report, Table S6, Page 83, available from: \\CDSESUB1\EVSPROD\nda215866\1374\m5\53-clin-stud-rep\533-rep-human-pk-stud\5335-popul-pk-stud-rep\pop-pk-00-stf\peds-poppk-report.pdf
Abbreviations: BSA = body surface area; GFR = glomerular filtration rate; Max = maximum; Min = minimum; n = number of subjects summarized; and SD = standard deviation.
Estimated GFR is calculated using CKD-Epi 2021 equation if subject is greater than or equal to 16 years old and using Bedside Schwartz equation if subject is less than 16 years old.
Estimated GFR BSA is calculated using estimated GFR multiplied by BSA and divided by 1.73.

Table 28: Summary of Baseline Demographic for Categorical Covariates by Treatment Arm for Analysis

	Treatment arm			
	Placebo / Tirzepatide 5 mg n = 30	Tirzepatide 5 mg n = 32	Tirzepatide 10 mg n = 31	Summary n = 93
Ethnicity				
Hispanic or Latino	23 (76.7)	24 (75.0)	17 (54.8)	64 (68.8)
Not Hispanic or Latino	7 (23.3)	8 (25.0)	14 (45.2)	29 (31.2)
Sex				
Female	19 (63.3)	21 (65.6)	18 (58.1)	58 (62.4)
Male	11 (36.7)	11 (34.4)	13 (41.9)	35 (37.6)
Race				
White	19 (63.3)	17 (53.1)	19 (61.3)	55 (59.1)
Black or African American	2 (6.7)	5 (15.6)	3 (9.7)	10 (10.8)
Asian	1 (3.3)	1 (3.1)	1 (3.2)	3 (3.2)
Native Hawaiian or Other Pacific Islander	0 (0.0)	1 (3.1)	2 (6.5)	3 (3.2)
American Indian or Alaska Native	8 (26.7)	7 (21.9)	5 (16.1)	20 (21.5)
Mixed Race or Multiple	0 (0.0)	1 (3.1)	1 (3.2)	2 (2.2)
Country				
Australia	0 (0.0)	1 (3.1)	1 (3.2)	2 (2.2)
Brazil	2 (6.7)	8 (25.0)	5 (16.1)	15 (16.1)
U.K.	1 (3.3)	0 (0.0)	0 (0.0)	1 (1.1)
India	1 (3.3)	1 (3.1)	1 (3.2)	3 (3.2)
Israel	3 (10.0)	1 (3.1)	4 (12.9)	8 (8.6)
Italy	1 (3.3)	0 (0.0)	2 (6.5)	3 (3.2)
Mexico	13 (43.3)	10 (31.2)	8 (25.8)	31 (33.3)
U.S.	9 (30.0)	11 (34.4)	10 (32.3)	30 (32.3)
Age group 1				
10 to <14 years	6 (20.0)	8 (25.0)	8 (25.8)	22 (23.7)
14 to <18 years	24 (80.0)	24 (75.0)	23 (74.2)	71 (76.3)
Age group 2				
10 to <16 years	19 (63.3)	16 (50.0)	18 (58.1)	53 (57.0)
16 to <18 years	11 (36.7)	16 (50.0)	13 (41.9)	40 (43.0)
Estimated GFR (mL/min/1.73m^2)				
60 to <90	1 (3.3)	0 (0.0)	0 (0.0)	1 (1.1)
>90	29 (96.7)	32 (100.0)	31 (100.0)	92 (98.9)
Metformin use				
No	3 (10.0)	4 (12.5)	2 (6.5)	9 (9.7)
Yes	18 (60.0)	19 (59.4)	20 (64.5)	57 (61.3)
Not reported	9 (30.0)	9 (28.1)	9 (29.0)	27 (29.0)
Insulin use				
No	13 (43.3)	15 (46.9)	15 (48.4)	43 (46.2)
Yes	8 (26.7)	8 (25.0)	7 (22.6)	23 (24.7)
Not reported	9 (30.0)	9 (28.1)	9 (29.0)	27 (29.0)

Source: Applicant's pediatric population PK report, Table S7, Pages 85-86, available from: \\CDSESUB1\EVSPROD\nda215866\1374\m5\53-clin-stud-rep\533-rep-human-pk-stud\5335-popul-pk-stud-rep\pop-pk-00-stf\peds-poppk-report.pdf
Abbreviations: GFR = glomerular filtration rate; n = number of subjects summarized; Summary = count (percent).
Estimated GFR is calculated using CKD-Epi 2021 equation if subject is greater than or equal to 16 years old and using Bedside Schwartz equation if subject is less than 16 years old.

Applicant's Base Model

A population PK model for tirzepatide was verified in the previous review cycle with pooled data from phase 1, 2, and 3 studies supporting the initial T2D application in adults (refer to the

Reference ID: 5715650

pharmacometrics review by Drs. Kronfol, Dahmane and Earp on 03/18/2022). The model structure and parameter estimates from the previous adult model were used to inform the development for pediatric tirzepatide population PK model which uses sparse PK data from trial GPGV alone.

The pediatric tirzepatide population PK model was described by a two-compartment model with first-order absorption and linear clearance with interindividual variability on clearance (CL) and central volume of distribution (Vc). Interindividual variability (IIV) was described using an exponential error model. Residual variability was modeled with a proportional error model.

The population PK analysis was conducted using NONMEM® software implementing the first-order conditional estimation (FOCE) method with interaction.

Covariate analysis

The previous adult population PK analysis in adults did not find significant effects of sex, race, ethnicity, hepatic impairment, or renal impairment on tirzepatide PK.

In the current pediatric base model, trends were observed in the plots of conditional weighted residual (CWRES) versus time-varying body size metrics (e.g., body weight, fat-free mass (FFM), and fat mass), where CWRES tended to be lower with greater body sizes. The bodyweight, BMI, FFM, and fat mass were highly correlated. Body weight was included as a covariate on CL/F, apparent intercompartmental clearance (Q/F), apparent volume of the central compartment (V2/F), and apparent volume of the peripheral compartment (V3/F), and age effect on CL/F was included in the final covariate model.

Applicant's Final Model

The parameter estimates for the final covariate model are listed in Table 29. The goodness-of-fit plots for the final covariate model are shown in Figure 9. The Visual Predictive Check (VPC) plot for the final covariate model is shown in Figure 10.

Reference ID: 5715650

Table 29: Parameter Estimates (RSE) and Median (95% CI) for the Applicant's Final Model

			Estimate	Shrinkage (%)	95% CI
Structural model parameters					
CL/F (L/h)	θ_1	Apparent clearance	0.0450	-	0.0422, 0.0479
V2/F (L)	θ_2	Apparent central volume of distribution	2.45	-	1.58, 3.31
Q/F (L/h)	θ_3	Apparent intercompartmental clearance	0.126	-	0.107, 0.145
V3/F (L)	θ_4	Apparent peripheral volume of distribution	3.95	-	3.64, 4.26
k_a (h^{-1})	θ_5	First-order absorption rate constant	0.0367	-	0.0254, 0.0481
Covariate effect parameters					
CL/F ~ Weight	θ_6	Effects of time-varying weight on CL/F and Q/F	0.800	-	FIXED
V/F ~ Weight	θ_7	Effects of time-varying weight on V2/F and V3/F	1.00	-	FIXED
CL/F ~ Age	θ_8	Effect of baseline age on CL/F	-0.439	-	-0.969, 0.0911
Interindividual variance parameters					
IIV-CL/F	$\Omega_{(1,1)}$	Variance of apparent clearance	0.0649 [CV%=25.9]	7.85	0.0109, 0.119
IIV-V2/F	$\Omega_{(2,2)}$	Variance of apparent central volume of distribution	0.622 [CV%=92.9]	20.3	0.124, 1.12
IIV-ResErr	$\Omega_{(6,6)}$	Variance of residual error	0.169 [CV%=43.0]	9.21	0.0353, 0.303
Residual variance					
Proportional	$\Sigma_{(1,1)}$	Variance	0.134 [CV%=36.6]	4.41	0.0946, 0.173

Source: Applicant's pediatric population PK report, Table S9, Page 88, available from: \\CDSESUB1\EVSPROD\nda215866\1374\m5\53-clin-stud-rep\533-rep-human-pk-stud\5335-popul-pk-stud-rep\pop-pk-00-stf\peds-poppk-report.pdf

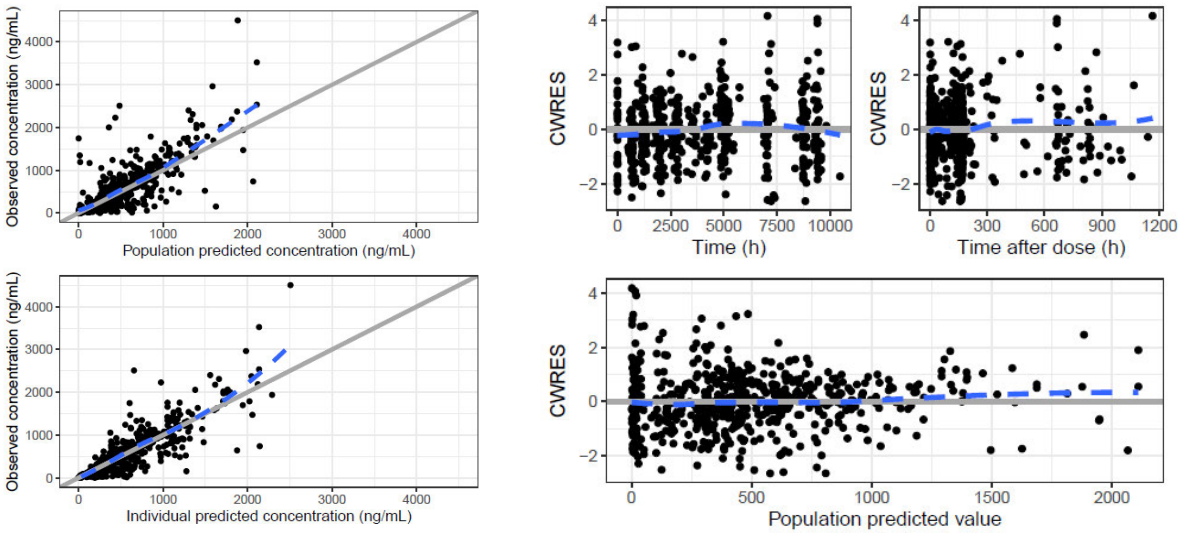
Abbreviations: CI = confidence interval; CV = coefficient of variation; IIV = interindividual variability; SE = standard error.

Confidence intervals = estimate ± 1.96 · SE.

CV% of log-normal omegas = sqrt(exp(estimate) - 1) · 100.

CV% of sigma = sqrt(estimate) · 100.

Figure 9: Standard goodness of fit plots for the Applicant's final covariate model



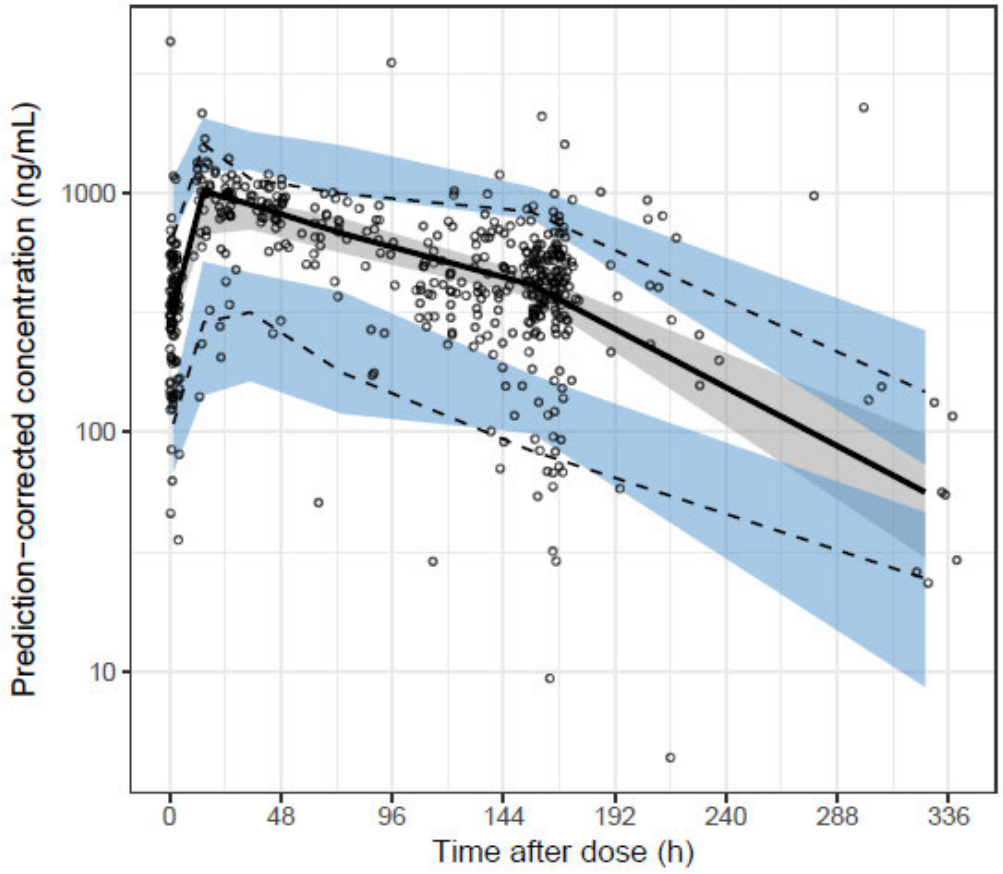
Source: Applicant's pediatric population PK report, Figures S43 and S44, Pages 157 – 158, available from: \\CDSESUB1\EVSPROD\nda215866\1374\m5\53-clin-stud-rep\533-rep-human-pk-stud\5335-popul-pk-stud-rep\pop-pk-00-stf\peds-poppk-report.pdf

Abbreviations: CWRES = Conditional weighted residual

Left Two Figures: Black circles indicate the observed values on the y-axis and predicted values on the x-axis. The line of identity (solid gray) is included for reference (x = y). The dashed blue line represents a LOESS smooth through the data.

Right Three Figures: solid black circles represent the individual CWRES values associated with each observation record. The solid horizontal gray lines (residuals = 0) are included for reference. The dashed blue lines represent a LOESS smooth through the data.

Figure 10: pcVPC of the Applicant's final tirzepatide population PK Model



Source: Applicant's pediatric population PK report, Figures S62, Page 176, available from: \\CDSESUB1\EVSPROD\nda215866\1374\m5\53-clin-stud-rep\533-rep-human-pk-stud\5335-popul-pk-stud-rep\pop-pk-00-stf\peds-poppk-report.pdf
Observed values are indicated by black circles. Black lines represent the median (solid) or 5th and 95th (dashed) percentiles of the observed data. Shaded areas represent the 95% prediction intervals for the median (gray) or 5th and 95th percentiles (blue) of the simulated data.

Reviewer's Comments:

The applicant's population PK model for pediatrics is considered acceptable. The visual predictive checks (Figure 10) show agreement between the observed and predicted medians and 90% CI percentiles for tirzepatide. As a result, the reviewer concluded that the model is considered acceptable for describing tirzepatide exposure in plasma and covariates effects on tirzepatide exposure.

8.6.1.1.4. Model Simulations

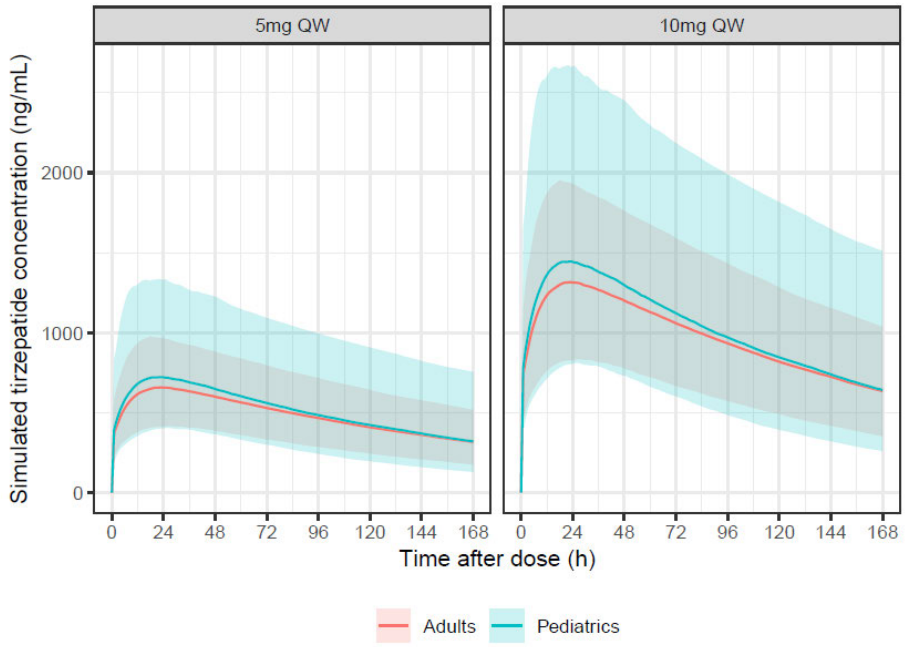
Comparing tirzepatide exposure between pediatrics and adults

Tirzepatide exposures (AUCss and Cmax,ss) were compared between pediatrics and adults. One thousand (1000) pediatric subjects and 1000 adult subjects with their associated covariates were randomly sampled from the pediatric dataset and the previous adult T2D dataset, respectively. Tirzepatide exposures at steady state were simulated following tirzepatide 5 mg

Reference ID: 5715650

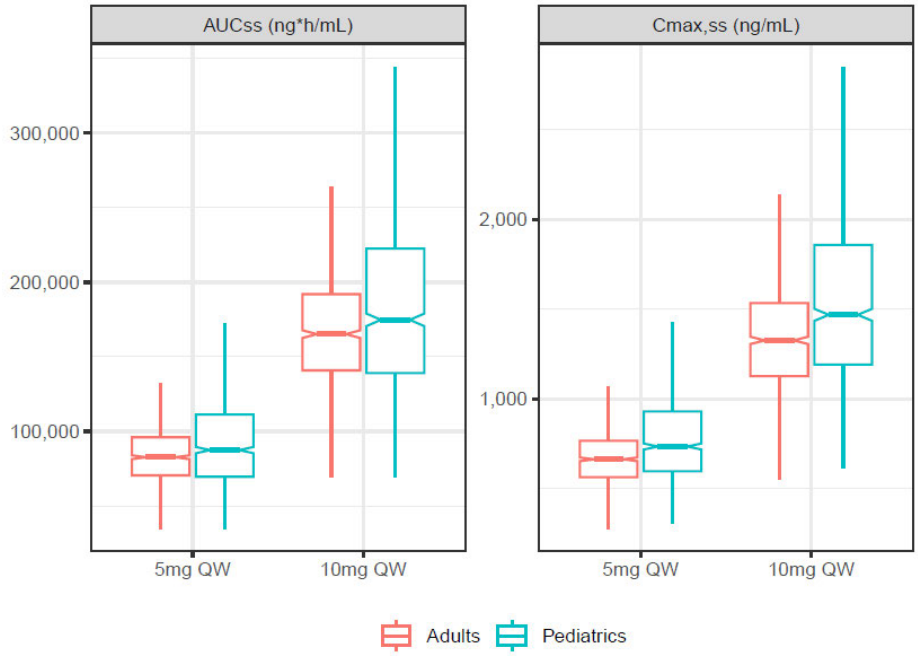
QW and 10 mg QW dosing using the final pediatric PK model and the previous adult PK model. The results show that simulated steady-state tirzepatide exposures were overlapping and similar between pediatric and adult subjects for both 5 mg QW and 10 mg QW dosing (Figure 11 and Figure 12). Across 200 simulated trials with 150 pediatric and 150 adult subjects, the mean of the simulated AUCss and Cmax,ss were 9% and 14% higher in pediatrics than adults, respectively (Table 30).

Figure 11: Simulated steady-state tirzepatide concentration versus time in pediatrics and adults.



Source: Applicant's pediatric population PK report, Figures S65, Page 179, available from: \\CDSESUB1\EVSPROD\nda215866\1374\m5\53-clin-stud-rep\533-rep-human-pk-stud\5335-popul-pk-stud-rep\pop-pk-00-stf\peds-poppk-report.pdf
Abbreviations: QW = once weekly.
The solid-colored lines represent the medians, and the shaded colored areas represent the 95% intervals (2.5th and 97.5th percentiles of the simulated data). Mean baseline body weight in simulated data was 95.9 kg for pediatrics and 89.8 kg for adults. Mean baseline age in simulated data was 14.8 years for pediatrics and 58.2 years for adults.

Figure 12: Simulated tirzepatide area under the concentration-time curve over the dosing interval at steady state AUC_{ss} and steady state $C_{max,ss}$ in pediatrics and adults.



Source: Applicant's pediatric population PK report, Figures S66, Page 180, available from: \\CDSESUB1\EVSPROD\nda215866\1374\m5\53-clin-stud-rep\533-rep-human-pk-stud\5335-popul-pk-stud-rep\pop-pk-00-stf\peds-poppk-report.pdf
Abbreviations: AUCss = area under the concentration-time curve over the dosing interval at steady state; CI = confidence interval; Cmax,ss = maximum concentration in the dosing interval at steady state; QW = once weekly.
The median is designated by a solid line in the center of the box. The box indicates the interquartile range (IQR) with whiskers extending to 1.5 · IQR. Mean baseline body weight in simulated data was 95.9 kg for pediatrics and 89.8 kg for adults. Mean baseline age in simulated data was 14.8 years for pediatrics and 58.2 years for adults.

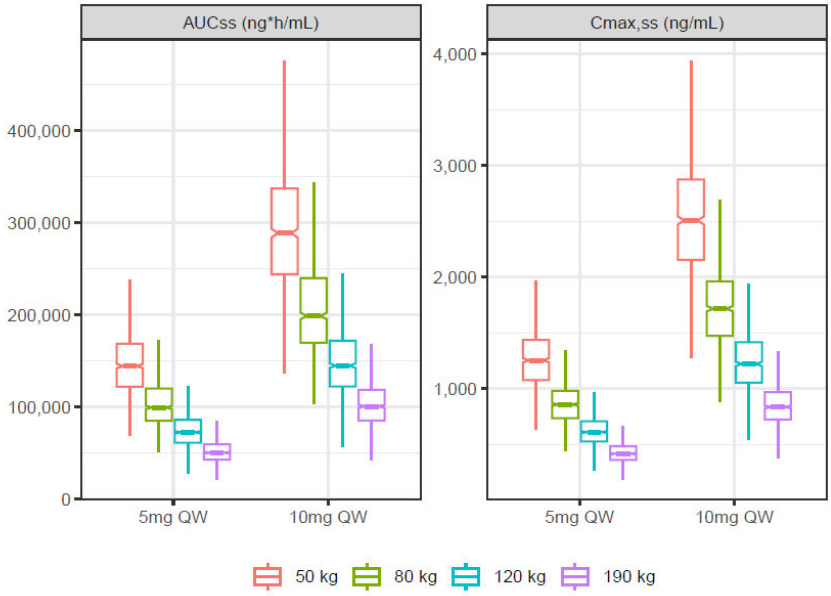
Table 30: Summary of simulated steady-state tirzepatide exposures in pediatrics and adults.

Exposure	Population	Mean (95% CI)	Ratio (95% CI)
5mg QW			
AUCss (ng*h/mL)	Pediatrics	92100 (85700, 98600)	1.09 (1.01, 1.17)
AUCss (ng*h/mL)	Adults	84500 (81400, 87900)	1.00 (1.00, 1.00)
Cmax,ss (ng/mL)	Pediatrics	772 (712, 825)	1.14 (1.06, 1.24)
Cmax,ss (ng/mL)	Adults	675 (651, 706)	1.00 (1.00, 1.00)
10mg QW			
AUCss (ng*h/mL)	Pediatrics	184000 (171000, 197000)	1.09 (1.01, 1.17)
AUCss (ng*h/mL)	Adults	169000 (163000, 176000)	1.00 (1.00, 1.00)
Cmax,ss (ng/mL)	Pediatrics	1540 (1420, 1650)	1.14 (1.06, 1.24)
Cmax,ss (ng/mL)	Adults	1350 (1300, 1410)	1.00 (1.00, 1.00)

Source: Applicant's pediatric population PK report, Table S10, Page 89.
Abbreviations: AUCss = area under the concentration-time curve over the dosing interval at steady state; CI = confidence interval; Cmax,ss = maximum concentration in the dosing interval at steady state; QW = once weekly; Ratio = ratio of value in pediatrics to adults.
Mean baseline body weight in simulated data was 96.9 kg for pediatrics and 90.5 kg for adults.
Mean baseline age in simulated data was 14.8 years for pediatrics and 58.0 years for adults.

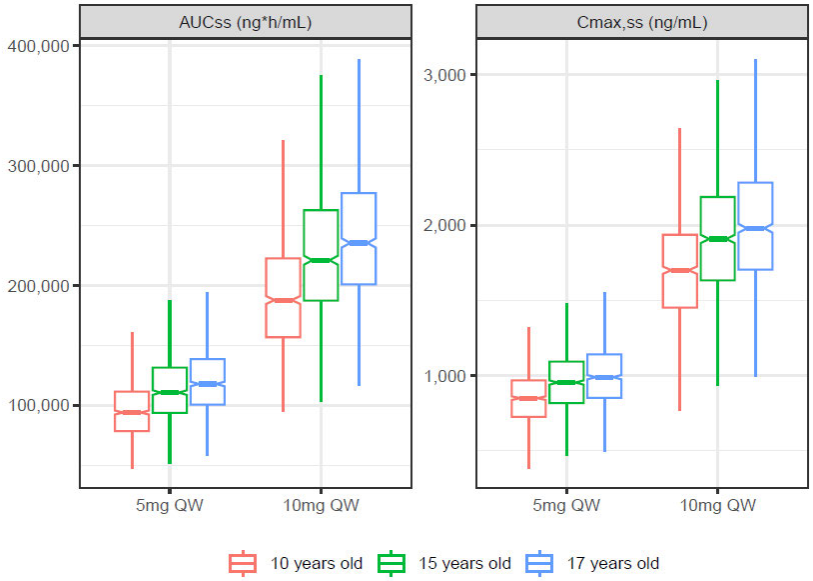
Simulations were also conducted to investigate the covariate effects of weight and age on tirzepatide exposures at steady state. The steady-state exposures were higher in subjects with lower body weights (Figure 13), while the steady-state exposures were generally overlapping and comparable across different ages (Figure 14).

Figure 13: Simulated tirzepatide area under the concentration-time curve over the dosing interval at steady state (AUC_{ss}) and maximum concentration in the dosing interval at steady state ($C_{max,ss}$) over a range of baseline body weights.



Source: Applicant's pediatric population PK report, Figures S68, Page 182, available from: \\CDSESUB1\EVSPROD\nda215866\1374\m5\53-clin-stud-rep\533-rep-human-pk-stud\5335-popul-pk-stud-rep\pop-pk-00-stf\peds-poppk-report.pdf
Abbreviations: AUCss = area under the concentration-time curve over the dosing interval at steady state; Cmax,ss = maximum concentration in the dosing interval at steady state; QW = once weekly.
The median is designated by a solid line in the center of the box. The box indicates the interquartile range (IQR) with whiskers extending to 1.5 · IQR.

Figure 14: Simulated tirzepatide area under the concentration-time curve over the dosing interval.



Source: Applicant's pediatric population PK report, Figures S70, Page 184, available from: \\CDSESUB1\EVSPROD\nda215866\1374\m5\53-clin-stud-rep\533-rep-human-pk-stud\5335-popul-pk-stud-rep\pop-pk-00-stf\peds-poppk-report.pdf
Abbreviations: AUCss = area under the concentration-time curve over the dosing interval at steady state; Cmax,ss = maximum concentration in the dosing interval at steady state; QW = once weekly.
The median is designated by a solid line in the center of the box. The box indicates the interquartile range (IQR) with whiskers extending to 1.5 · IQR.

Reviewer's Comments:

The pediatric tirzepatide population PK model was used to simulate tirzepatide exposures in both pediatric and adult subjects with T2D following 5 mg and 10 mg QW dosing. The results show that median AUCss and Cmax,ss values in pediatric and adult populations are similar, with greater variability observed in pediatrics than adults. However, considering that the highest approved maintenance dose in adults is 15 mg QW, the exposure of tirzepatide following 10 mg QW remained within the observed range in adults.

Body weight and age were identified as significant covariates in the pediatric population PK model. Simulations demonstrated that AUCss and Cmax,ss decreased with increasing body weight. Compared to a 90 kg reference subject, tirzepatide AUCss and Cmax,ss decreased by approximately 21% and 45% at weights of 120 kg and 190 kg (approximately 85th percentile and maximum weight in the current dataset), respectively. Conversely, tirzepatide AUCss and Cmax,ss increased by approximately 60% at a weight of 50 kg (approximately the minimum weight in the current dataset) compared to the 90 kg reference subject. Age effects on tirzepatide steady-state exposures were minimal, with slightly increasing exposure observed with increasing age between 10 and 17 years. Dose adjustment is not necessary for patients weighing 120 kg. Given the adolescent population, body weights of 190 kg are uncommon and represent an unlikely clinical scenario, and dose adjustment is not recommended in the USPI.

8.6.1.2. Exposure- Response (ER) Analysis

8.6.1.2.1. ER Analysis for Fasting Glucose and Hemoglobin A1c

Datasets

The current analysis pediatric population included 93 subjects contributing 898 fasting glucose (FG) and 896 A1C observations. The summary of subjects and observations by treatment arms are summarized in Table 31.

Table 31. Data summary of subjects (number) and observations (number and percent) by treatment arm for the ER analysis dataset.

	Number		Group percent	Overall percent
Treatment arm	SUBJ	OBS	OBS	OBS
Fasting glucose (mmol/L)				
Placebo / Tirzepatide 5 mg	30	292	32.5	16.3
Tirzepatide 10 mg	31	302	33.6	16.8
Tirzepatide 5 mg	32	304	33.9	16.9
Hemoglobin A1c (%)				
Placebo / Tirzepatide 5 mg	30	290	32.4	16.2
Tirzepatide 10 mg	31	297	33.1	16.6
Tirzepatide 5 mg	32	309	34.5	17.2
All data	93	1794	—	100.0

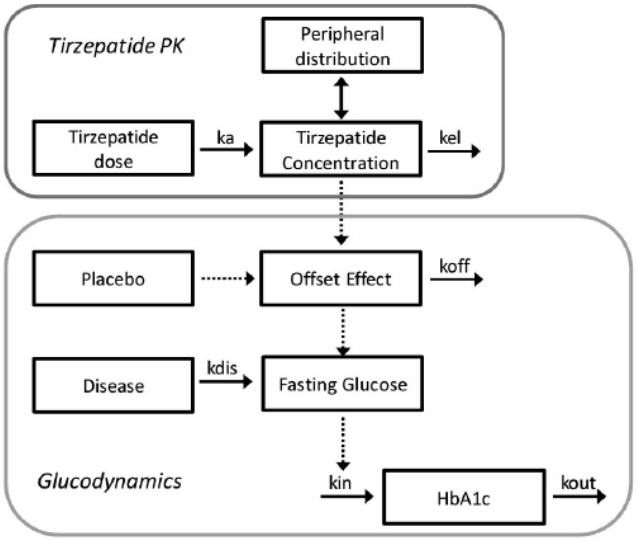
Source: Applicant's pediatric population PK report, Table S11, Page 90, available from: \\CDSESUB1\EVSPROD\nda215866\1374\m5\53-clin-stud-rep\533-rep-human-pk-stud\5335-popul-pk-stud-rep\pop-pk-00-stf\peds-poppk-report.pdf
Abbreviations: SUBJ = subjects; OBS = observations

Final ER model for fasting serum glucose and A1C in pediatrics

An existing ER FG and A1C model was updated using pediatric subjects with T2D. A joint linked model was used to characterize the time course of FG and A1C, where FG was described using a disease progression model that integrated an offset compartment with tirzepatide and placebo effects, and A1C was described using an indirect response model dependent on FG. The structure of the ER model for tirzepatide is described in Figure 15.

Reference ID: 5715650

Figure 15: Basic structure of the ER model for fasting glucose and A1C.



The solid arrows denote rates or rate constants. The dashed arrows denote an effect.
Source: Applicant's pediatric population PK report, Figure 8.1, Page 364, available from: \\CDSESUB1\EVSPROD\nda215866\1374\m5\53-clin-stud-rep\533-rep-human-pk-stud\5335-popul-pk-stud-rep\pop-pk-00-stf\peds-poppk-report.pdf
Abbreviations: ka = absorption rate constant; kdis = disease progression rate; kel = elimination rate constant; kin = input rate; koff =; kout = offset rate constant; PK = pharmacokinetics.

After exploring various covariate effects (sex, age, body weight, ethnicity), the final ER FG and A1C model included an ethnicity effect on baseline FG. The final model parameter estimates and 95% CIs are provided in Table 32. VPC plots were generated for FG and A1C over time. Overall, the VPCs demonstrated that model-predicted FG and A1C were in reasonable agreement with observed values at the 5th, 50th, and 95th percentiles stratified by treatment arms (Figure 16).

Table 32: Parameter estimates for the final ER model for fasting glucose and A1C.

			Estimate	95% CI
Structural model parameters				
$E0_G$ (mmol/L)	θ_1	Baseline fasting glucose	9.76	8.90, 10.6
$E0_H$ (%)	θ_2	Baseline HbA1c	8.03	7.73, 8.32
PLAC	θ_3	Placebo fractional reduction of FG	0.127	0.0243, 0.230
k_{OFF} (1/hour)	$\exp(\theta_4)$	Offset rate constant	0.00150	0.000971, 0.00232
k_{OUT} (1/hour)	$\exp(\theta_5)$	Turnover rate constant for HbA1c	0.00150	0.00104, 0.00215
k_{DIS} (mmol/hour)	$\exp(\theta_6)$	FG disease progression rate	0.000186	8.44e-05, 0.000410
HLIM	θ_7	Limit for HbA1c-Emax	4.43	3.78, 5.07
EC50 (ng/mL)	$\exp(\theta_8)$	Tirzepatide concentration with 50% of maximum effect	148	74.5, 293
γ	θ_9	Exponent for effect of FG on HbA1c	0.761	0.658, 0.865
Covariate effect parameters				
$E0_G \sim$ Ethnicity	θ_{11}	Effect of ethnicity on $E0_G$	-0.0939	-0.177, -0.0105

			Estimate	Shrinkage (%)	95% CI
Interindividual variance parameters					
IIV-$E0_G$	$\Omega_{(1,1)}$	Variance of baseline fasting glucose	0.0884 [CV%=30.4]	5.34	-0.0307, 0.208
IIV-$E0_H$	$\Omega_{(2,2)}$	Variance of baseline HbA1c	0.0203 [CV%=14.3]	4.94	-0.00471, 0.0453
IIV-PLAC	$\Omega_{(3,3)}$	Variance of placebo effect	0.0538 [SD=0.232]	14.3	0.0151, 0.0924
IIV-k_{OFF}	$\Omega_{(4,4)}$	Variance of offset rate constant	0.833 [CV%=114]	17.8	-1.56, 3.22
IIV-HLIM	$\Omega_{(7,7)}$	Variance of limit for HbA1c-Emax	0.0691 [CV%=26.7]	6.86	-0.122, 0.260
Residual variance					
Proportional error for FG	$\Sigma_{(1,1)}$	Variance	0.0491 [CV%=22.1]	6.30	0.0377, 0.0604
Proportional error for HbA1c	$\Sigma_{(2,2)}$	Variance	0.00352 [CV%=5.93]	15.4	0.00254, 0.00450

Source: Applicant's pediatric population PK report, Tables S17 and S18, Pages 96-97, available from: \\CDSESUB1\EVSPROD\nda215866\1374\m5\53-clin-stud-rep\533-rep-human-pk-stud\5335-popul-pk-stud-rep\pop-pk-00-stf\peds-poppk-report.pdf

Abbreviations: CI = confidence interval; CV = coefficient of variation; Emax = maximum effect; FG = fasting glucose; A1C = hemoglobin A1c; SE = standard error; IIV = interindividual variability.

Parameters estimated in the log-domain were back-transformed for clarity.

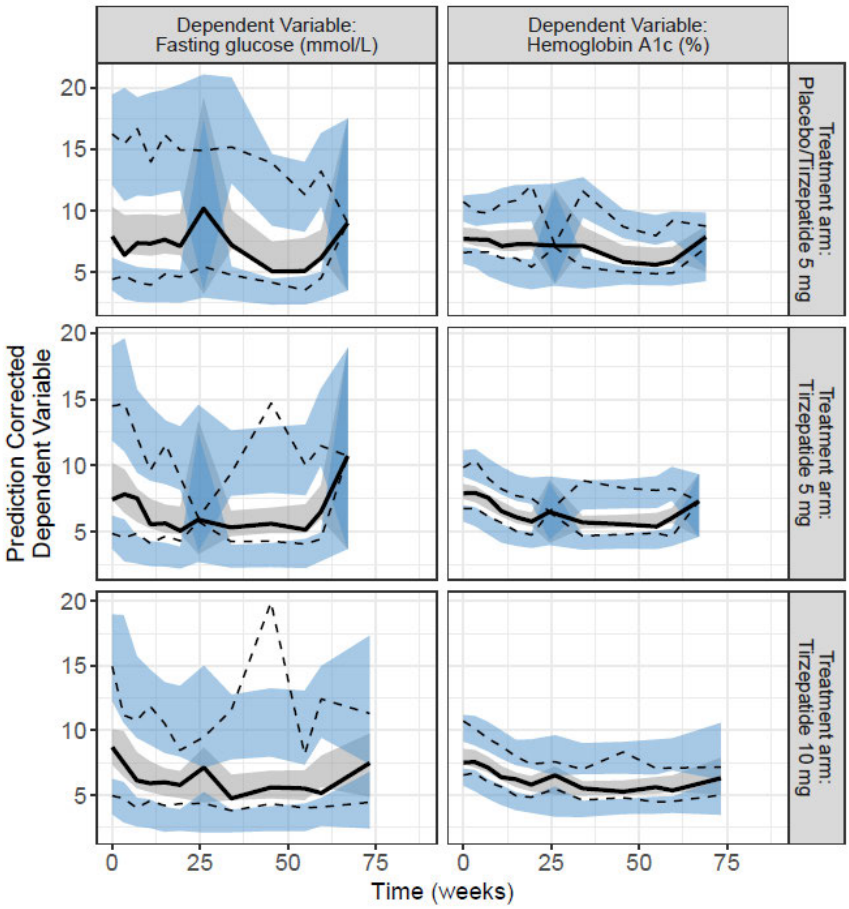
Confidence intervals = estimate ± 1.96 · SE.

CV% of log-normal omegas = sqrt(exp(estimate) - 1) · 100.

CV% of sigma = sqrt(estimate) · 100.

Reference ID: 5715650

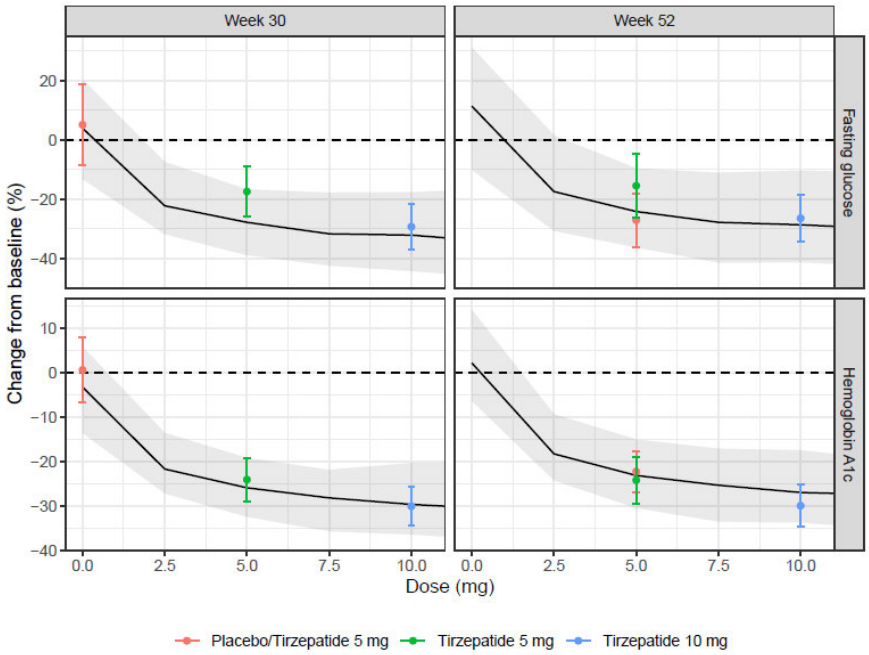
Figure 16: ER of fasting glucose and A1C final model: prediction corrected visual predictive check of fasting glucose and hemoglobin A1c versus time stratified by treatment arm.



Source: Applicant's pediatric population PK report, Figure S124, Page 238, available from: \\CDSESUB1\EVSPROD\nda215866\1374\m5\53-clin-stud-rep\533-rep-human-pk-stud\5335-popul-pk-stud-rep\pop-pk-00-stf\peds-poppk-report.pdf
Black lines represent the median (solid) or 5th and 95th (dashed) percentiles of the observed data. Shaded areas represent the 95% prediction intervals for the median (gray) or 5th and 95th percentiles (blue) of the simulated data. All data and summaries have been prediction-corrected.

The model predicted dose-response were generated for FG and A1C at Week 30 and 52 (Figure 17 and Table 33). The dose response plots indicated a steep decreasing response up to 5 mg and a smaller increase from 5 mg to 10 mg. The plots show under-prediction of the 5 mg dose response group at Week 30 and 52 for FG, but percentage change from baseline showed good alignment between observed response and model-predictions for both FG and A1C.

Figure 17: ER of fasting glucose and A1C final model: Dose response plots of percentage change from baseline of fasting glucose and hemoglobin A1c at 30 and 52 weeks stratified by treatment arm.



Source: Applicant's pediatric population PK report, Figure S134, Page 248, available from: \\CDSESUB1\EVSPROD\nda215866\1374\m5\53-clin-stud-rep\533-rep-human-pk-stud\5335-popul-pk-stud-rep\pop-pk-00-stf\peds-poppk-report.pdf
Solid black lines denote the mean of 200 trials and the shaded areas denote the 95% confidence interval of the mean. Colored symbols and error bars denote mean observed data and confidence interval.

Table 33: ER of fasting glucose and A1C final model: model-predicted change from baseline and percentage change from baseline of fasting glucose and hemoglobin A1c at 30 and 52 weeks for different doses.

Metric	Dose (mg)	Week 30	Week 52
Fasting glucose			
Change from baseline (mmol/L)	2.5 mg	-2.72 (-4.14, -1.3)	-2.28 (-3.91, -0.487)
	5 mg	-3.27 (-4.66, -2.21)	-2.92 (-4.18, -1.75)
	7.5 mg	-3.66 (-4.96, -2.13)	-3.35 (-4.78, -1.82)
	10 mg	-3.64 (-5.04, -2.26)	-3.36 (-4.75, -1.9)
Percent change from baseline	2.5 mg	-22.2 (-31.8, -7.47)	-17.4 (-30.7, 1.53)
	5 mg	-27.8 (-38.8, -16.7)	-24.2 (-36.2, -9.61)
	7.5 mg	-31.7 (-42.4, -17.8)	-27.8 (-41.4, -11.1)
	10 mg	-32.1 (-44.2, -17.6)	-28.6 (-41.2, -10.3)
Hemoglobin A1c			
Change from baseline (%)	2.5 mg	-1.85 (-2.4, -1.2)	-1.59 (-2.1, -0.908)
	5 mg	-2.2 (-2.82, -1.58)	-1.97 (-2.62, -1.32)
	7.5 mg	-2.43 (-3.12, -1.78)	-2.19 (-2.86, -1.56)
	10 mg	-2.5 (-3.23, -1.63)	-2.35 (-3, -1.5)
Percent change from baseline	2.5 mg	-21.7 (-27.1, -13.5)	-18.3 (-24.2, -9.37)
	5 mg	-25.9 (-32.4, -19.2)	-23.1 (-30.4, -15)
	7.5 mg	-28.1 (-35.6, -21.8)	-25.3 (-33.5, -17.1)
	10 mg	-29.6 (-36.4, -20.3)	-26.9 (-33.7, -17.4)

Source: Applicant's pediatric population PK report, Table S19, Page 98, available from: \\CDSESUB1\EVSPROD\nda215866\1374\m5\53-clin-stud-rep\533-rep-human-pk-stud\5335-popul-pk-stud-rep\pop-pk-00-stf\peds-poppk-report.pdf
Values are medians and 95% confidence intervals of the mean.

Reviewer's Comments:

Overall, the ER model for FG and A1C in pediatrics is acceptable, as demonstrated by the VPC plots that capture the longitudinal FG and A1C trends by treatment groups. Sex, age, body weight, and insulin use were explored as potential covariates in the model but were not found to have clinically relevant impacts on the effect of tirzepatide on FG or A1C. Dose-response analysis demonstrates a steep increase in response for change from baseline in fasting glucose and A1C up to 5 mg, with smaller incremental benefits from 5 mg to 10 mg at both 30 and 52 weeks, indicating that capping the maintenance dose at 10 mg is appropriate for pediatric patients.

8.6.1.2.2. ER model for body weight

Datasets

The current analysis population included 93 subjects contributing 910 body weight observations, each of which was divided into a fat-free mass (FFM) and a fat mass (FM) component. The data summary for the ER dataset for body weight were presented in Table 34.

Reference ID: 5715650

Table 34: ER of body weight: data summary of subjects (number) and observations (number and percent).

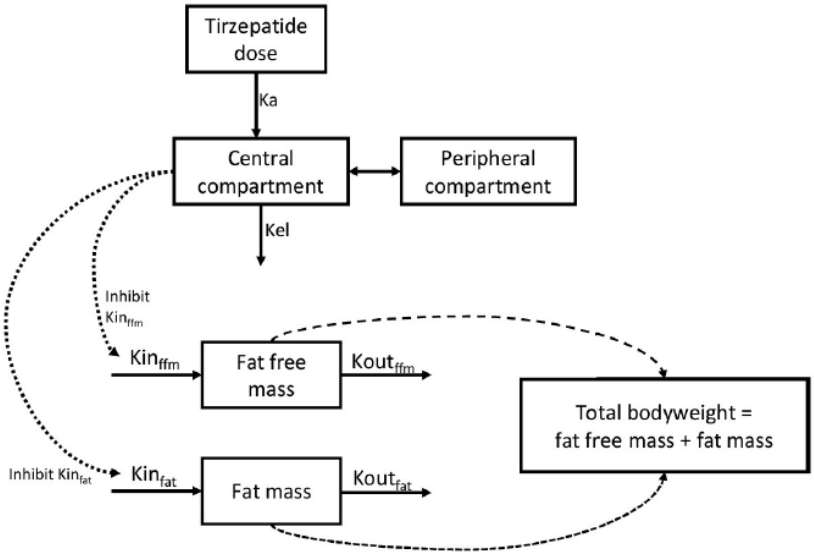
	Number		Group percent	Overall percent
Treatment arm	SUBJ	OBS	OBS	OBS
Weight (kg)				
Placebo / Tirzepatide 5 mg	30	298	32.7	10.9
Tirzepatide 5 mg	32	311	34.2	11.4
Tirzepatide 10 mg	31	301	33.1	11.0
Fat-free mass (kg)				
Placebo / Tirzepatide 5 mg	30	298	32.7	10.9
Tirzepatide 5 mg	32	311	34.2	11.4
Tirzepatide 10 mg	31	301	33.1	11.0
Fat mass (kg)				
Placebo / Tirzepatide 5 mg	30	298	32.7	10.9
Tirzepatide 5 mg	32	311	34.2	11.4
Tirzepatide 10 mg	31	301	33.1	11.0
All data	93	2730	—	100.0

Source: Applicant's pediatric population PK report, Table S20, page 99, available from: \\CDSESUB1\EVSPROD\nda215866\1374\m5\53-clin-stud-rep\533-rep-human-pk-stud\5335-popul-pk-stud-rep\pop-pk-00-stf\peds-poppk-report.pdf
Abbreviations: SUBJ = subjects; OBS = observations.

Final ER model for body weight

The previously developed model for the loss of FFM and fat mass in adults treated with tirzepatide was updated with pediatric data. The base model consisted of two indirect response models, one for FFM and one for fat mass, coupled by a shared turnover rate constant. All parameters included an exponential variance model for IIV. The structure of the base model is described in Figure 18.

Figure 18: Basic structure of the ER model for body weight.



Source: Applicant's pediatric population PK report, Figure 8.3, Page 367, available from: \\CDSESUB1\EVSPROD\nda215866\1374\m5\53-clin-stud-rep\533-rep-human-pk-stud\5335-popul-pk-stud-rep\pop-pk-00-stf\peds-poppk-report.pdf

The final model parameter estimates are summarized in Table 35. Model parameters were estimated with relatively small SEs of the estimates and associated CIs, except for the effect of sex on baseline fat mass; the maximal shrinkage for interindividual and residual variances was 24.8%.

VPC plots showed that the final model adequately described FFM, fat mass, and total body weight change from baseline over time. Overall, the VPCs demonstrated that model-predicted FFM and fat mass change from baseline were in reasonable agreement with observed values at the 5th, 50th, and 95th percentiles stratified by treatment group (Figure 19).

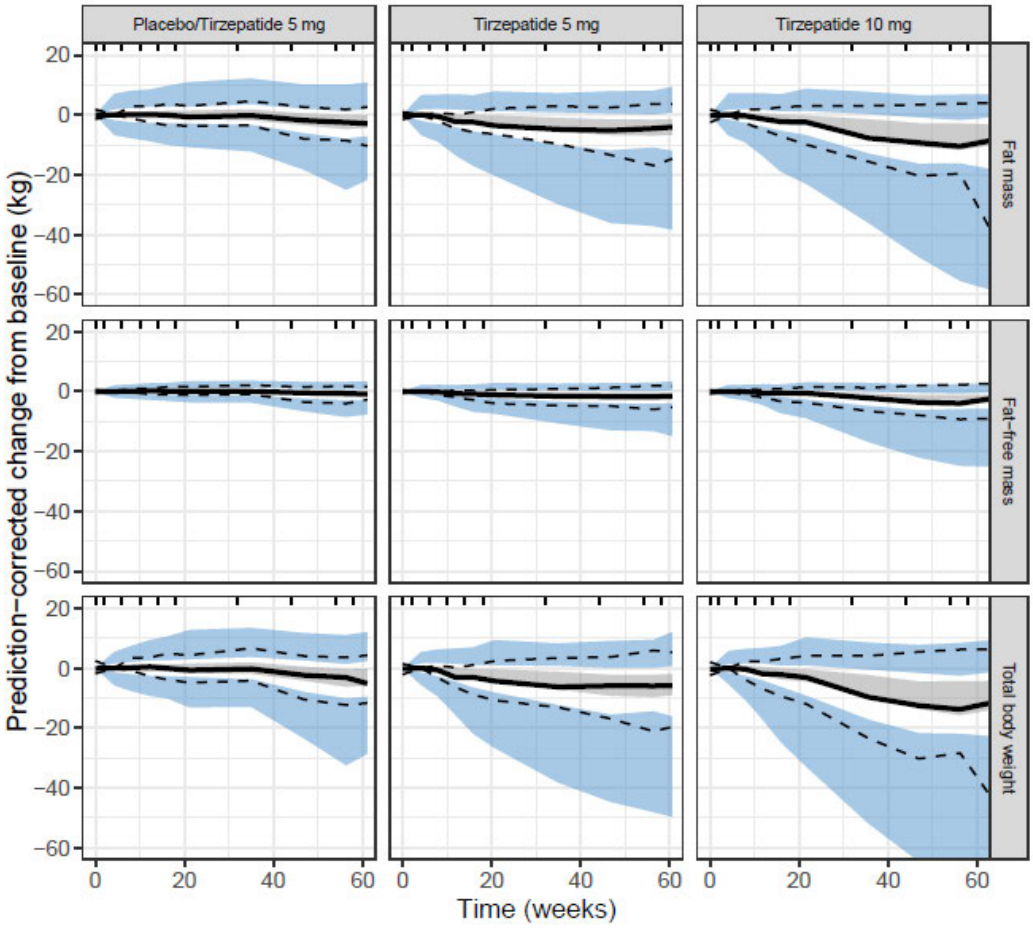
Table 35: Parameter estimates for the final ER model for body weight.

			Estimate	95% CI
Structural model parameters				
BSL-FFM (kg)	θ_1	Fat-free mass at baseline	65.7	61.8, 69.6
BSL-FM (kg)	θ_2	Fat mass at baseline	34.9	28.9, 40.9
KOUT (1/week)	$\exp(\theta_3)$	First-order weight loss rate constant	0.0280	0.0201, 0.0390
SLP-FFM (1/(ng/mL))	θ_4	Slope drug effect on fat-free mass	8.20e-05	6.29e-05, 0.000101
SLP-FM (1/(ng/mL))	θ_5	Slope drug effect on fat mass	0.000278	0.000215, 0.000341
Covariate effect parameters				
FFM ~ Sex	θ_8	Fractional decrease in fat-free mass in females	0.281	0.232, 0.330
FM ~ Sex	θ_9	Fractional increase in fat mass in females	0.144	-0.0763, 0.364
SLP-FFM/FM ~ INSB	$\exp(\theta_{10})$	Insulin use effect on slopes	0.409	0.367, 0.455
SLP-FFM/FM ~ INSB	$\exp(\theta_{11})$	Unreported insulin use effect on slopes	1.62	0.940, 2.79

			Estimate	Shrinkage (%)	95% CI
Interindividual variance parameters					
IIV-FFM	$\Omega_{(1,1)}$	Variance of fat-free mass at baseline	0.0260 [CV%=16.2]	0.117	-0.0282, 0.0803
IIV-FM	$\Omega_{(2,2)}$	Variance of fat mass at baseline	0.184 [CV%=44.9]	0.157	-0.0253, 0.392
IIV-KOUT	$\Omega_{(3,3)}$	Variance of weight loss rate constant	1.36 [CV%=170]	12.4	0.774, 1.95
IIV-SLP-FFM	$\Omega_{(4,4)}$	Variance of slope of fat-free mass loss	0.597 [CV%=90.4]	24.4	0.284, 0.910
IIV-SLP-FM	$\Omega_{(5,5)}$	Variance of slope of fat mass loss	0.619 [CV%=92.5]	24.8	0.334, 0.904
IIV-PLC-FFM	$\Omega_{(6,6)}$	Variance of placebo loss of fat-free mass	0.00212 [CV%=4.51]	17.3	-0.00773, 0.0120
IIV-PLC-FM	$\Omega_{(7,7)}$	Variance of placebo loss of fat mass	0.0228 [CV%=15.2]	15.7	-0.166, 0.211
Interindividual covariance parameters					
BSL-FFM-FM	$\Omega_{(2,1)}$	Covariance of BSL-FFM and BSL-FM	0.0648 [Corr=0.937]	-	-0.0102, 0.140
BSL-FFM-KOUT	$\Omega_{(3,1)}$	Covariance of BSL-FFM and KOUT	-0.0867 [Corr=-0.461]	-	-0.199, 0.0257
BSL-FM-KOUT	$\Omega_{(3,2)}$	Covariance of BSL-FM and KOUT	-0.202 [Corr=-0.404]	-	-0.336, -0.0679
SLP-FFM-FM	$\Omega_{(5,4)}$	Covariance of SLP-FFM and SLP-FM	0.559 [Corr=0.920]	-	0.305, 0.812
PLC-FFM-FM	$\Omega_{(7,6)}$	Covariance of PLC-FFM and PLC FM	0.00642 [Corr=0.924]	-	-0.0356, 0.0485
Residual variance					
Proportional error for FFM	$\Sigma_{(1,1)}$	Variance	0.000126 [CV%=1.12]	10.8	7.82e-05, 0.000174
Proportional error for FM	$\Sigma_{(2,2)}$	Variance	0.00131 [CV%=3.62]	10.8	0.000885, 0.00173
RUV-FFM-FM	$\Sigma_{(2,1)}$	Covariance of RUV-FFM and RUV-FM	0.000390 [Corr=0.959]	-	0.000249, 0.000530

Source: Applicant's pediatric population PK report, Table S24, Page 103, available from: \\CDSESUB1\EVSPROD\nda215866\1374\m5\53-clin-stud-rep\533-rep-human-pk-stud\5335-popul-pk-stud-rep\pop-pk-00-stf\peds-poppk-report.pdf
Abbreviations: CI = confidence interval; IIV = interindividual variability; SE = standard error
Parameters estimated in the log-domain were back-transformed for clarity.
Confidence intervals = estimate ± 1.96 · SE.
CV% of log-normal omegas = sqrt(exp(estimate) - 1) · 100.
CV% of sigma = sqrt(estimate) · 100.

Figure 19: ER of body weight final model: prediction-corrected visual predictive check of the change from baseline of fat-free mass, fat mass, and total body weight versus time by treatment.



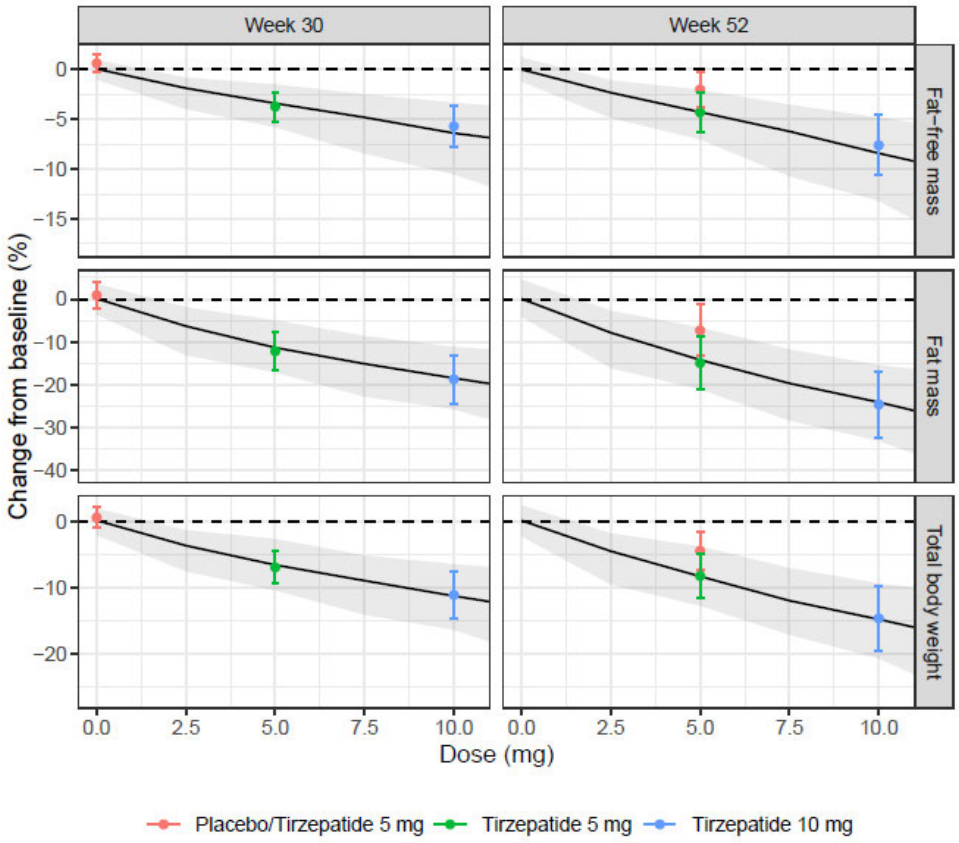
Source: Applicant's pediatric population PK report, Figure S207, Page 321, available from: \\CDSESUB1\EVSPROD\nda215866\1374\m5\53-clin-stud-rep\533-rep-human-pk-stud\5335-popul-pk-stud-rep\pop-pk-00-stf\peds-poppk-report.pdf
Black lines represent the median (solid) or 5th and 95th (dashed) percentiles of the observed data. Shaded areas represent the 95% prediction intervals for the median (gray) or 5th and 95th percentiles (blue) of the simulated data. All data and summaries have been prediction-corrected.

Model-predicted Dose-Response

Model predicted dose-response for the change in FFM, fat mass and total body weight were generated for the treatment of 5 mg and 10 mg QW tirzepatide for up to 30 and 52 Weeks (Figure 20 and Table 36). Simulated responses matched observed responses for all dose levels, time points, and end points (FFM, fat mass, and total body weight). The loss in FFM increased linearly with doses up to 10 mg, reaching 4.26% and 8.41% after 52 Weeks of dosing with 5 and 10 mg of tirzepatide, respectively. The loss in fat mass increased sub-linearly with doses up to 10 mg; after 52 Weeks of treatment, loss of fat mass was approximately 14.2% with 5 mg and

24% with 10 mg of tirzepatide. The loss of total body weight was similarly sublinear, reaching 8.4% with 5 mg and 14.8% with 10 mg of tirzepatide.

Figure 20: ER of bodyweight final model: dose response plots of percent change from baseline of fat-free mass, fat mass, and total body weight 30 and 52 weeks stratified by treatment arm and dose.



Source: Applicant's pediatric population PK report, Figure S212, Page 326; available from: \\CDSESUB1\EVSPROD\nda215866\1374\m5\53-clin-stud-rep\533-rep-human-pk-stud\5335-popul-pk-stud-rep\pop-pk-00-stf\peds-poppk-report.pdf
Solid black lines denote the mean of 200 trials and the shaded areas denote the 95% confidence interval of the mean. Colored symbols and error bars denote mean observed data and confidence interval.

Table 36: ER of body weight final model: model-predicted dose-response after 30 and 52 weeks of treatment.

Dose (mg)	Week 30	Week 52
CFB fat-free mass (kg)		
2.5	-0.96 (-2.01, -0.39)	-1.22 (-2.41, -0.55)
5	-1.77 (-3, -0.776)	-2.29 (-3.82, -1.07)
7.5	-2.49 (-4.47, -1.31)	-3.3 (-5.79, -1.89)
10	-3.25 (-5.46, -1.81)	-4.34 (-6.99, -2.54)
CFB fat mass (kg)		
2.5	-2.41 (-5.02, -0.74)	-3.07 (-5.96, -1.02)
5	-4.24 (-7.12, -1.68)	-5.54 (-9.02, -2.37)
7.5	-5.91 (-8.84, -3.37)	-7.68 (-11.5, -4.54)
10	-6.85 (-10.1, -4.17)	-9.07 (-13.6, -5.8)
CFB total body weight (kg)		
2.5	-3.36 (-6.9, -1.07)	-4.34 (-8.4, -1.58)
5	-6.02 (-10, -2.5)	-7.76 (-12.4, -3.56)
7.5	-8.34 (-13.1, -4.86)	-10.9 (-16.9, -6.84)
10	-10.1 (-15.3, -6.23)	-13.5 (-19.8, -8.71)
CFB fat-free mass (%)		
2.5	-1.86 (-3.96, -0.794)	-2.31 (-4.85, -1.07)
5	-3.38 (-5.78, -1.48)	-4.26 (-7, -2.03)
7.5	-4.8 (-8.44, -2.48)	-6.21 (-10.7, -3.53)
10	-6.38 (-10.5, -3.32)	-8.41 (-13.2, -4.81)
CFB fat mass (%)		
2.5	-6.31 (-13.1, -1.9)	-7.84 (-16.1, -2.74)
5	-11.3 (-17.1, -4.99)	-14.2 (-21, -6.63)
7.5	-15.1 (-22.7, -8.59)	-19.6 (-28.3, -11.7)
10	-18.4 (-25.6, -11.2)	-24 (-33, -15.4)
CFB total body weight (%)		
2.5	-3.7 (-7.59, -1.37)	-4.55 (-9.56, -1.85)
5	-6.63 (-10.5, -2.7)	-8.36 (-12.8, -3.83)
7.5	-9 (-14.1, -5.21)	-12 (-17.2, -7.1)
10	-11.3 (-16.4, -6.51)	-14.8 (-20.7, -9.45)

Source: Applicant's pediatric population PK report, Table S25, Page 104, available from: \\CDSESUB1\EVSPROD\nda215866\1374\m5\53-clin-stud-rep\533-rep-human-pk-stud\5335-popul-pk-stud-rep\pop-pk-00-stf\peds-poppk-report.pdf
CFB: change from baseline. Values are medians and 95% confidence intervals of the mean.

Reviewer's Comments:

Overall, the ER model for body weight in pediatrics is acceptable, as demonstrated by the VPC plots that capture the longitudinal fat-free mass and fat mass trends in pediatrics by treatment groups. Dose-response plots demonstrate a linear relationship between dose and the loss in FFM. The loss in fat mass increased sub-linearly with doses up to 10 mg. The loss of total body weight was similarly sublinear, reaching 8.4% with 5 mg and 14.8% with 10 mg of tirzepatide at week 52. Given that adolescents are still developing, limiting the maximum dose to 10 mg provides effective treatment with acceptable safety and avoids excessive weight loss.

8.6.1.3. Summary of Bioanalytical Method Validation and Performance

The PK samples collected in trial GPGV were analyzed utilizing the same method that was used over the course of the clinical development with slight modification. The method was a validated liquid chromatography with mass spectrometry (LC/MS) assay, which detected tirzepatide intact mass, comprising the full-length peptide plus the linker and acyl side chain. The LC/MS method was developed and validated by (b) (4). The summary of the bioanalytical method validation is presented in Table 37 below. Partial method validation report 191444PVDJSEIIR5 verified accuracy and precision of the method using a shortened LC gradient to reduce cycle time with a calibration range of 2 to 500 ng/mL in human plasma with K3EDTA anticoagulant. Briefly, tirzepatide was extracted from human plasma using immunoaffinity in a 96-well format and LSN3316897 (stable isotope-labeled tirzepatide) as the internal standard. Next, tirzepatide and internal standard were identified and quantified using a Q Exactive or Q Exactive Plus quadrupole-orbitrap mass spectrometer equipped with Heated Electrospray Ionization and high mass resolution accurate mass monitoring detection over a standard curve range of 2.00 to 500 ng/mL. The concentrations were calculated using peak area ratios, and the linearity of the calibration curve was determined using linear regression analysis employing a $1/x^2$ weighting. The interassay accuracy (% relative error) during validation ranged from -2.1% to 2.8%. The interassay precision (% coefficient of variation) during validation was 8.1% to 12.9%. The interassay precision and interassay accuracy values passed all predefined acceptance criteria. Quality control samples across the standard curve range were included in each sample analysis batch. Plasma samples with concentrations of tirzepatide above the upper limit of quantitation of 500 ng/mL were diluted up to a 100-fold dilution. Incurred sample reanalysis (ISR) was conducted for trial GPGV, and the results indicated that the assay method performed according to established ISR acceptance criteria, with ≥2/3 of ISR results within 30% difference. Samples from trial GPGV were kept at -70°C for up to 508 days which is adequate since the extended long-term stability is up to 842 days at -70°C (See Table 37).

Reference ID: 5715650

Table 37: Summary of Method Validation and Performance

Bioanalytical method validation report name, amendments, and hyperlinks	Report 191444PVDJS_EII_R5		
Method description	Partial Method Validation for the Quantitation of LY3298176 (GIP707) in Human Plasma by HRAM LC/MS		
Materials used for standard calibration curve and concentration	Tirzepatide lot RS1058, 0.89 mg/mL Internal standard (IS): LSN3316897 lot BCA-BE03935-132, 1 mg/mL		
Validated assay range	2.00 to 500 ng/mL		
Material used for quality controls (QCs) and concentration	Tirzepatide lot RS1058, 0.89 mg/mL Internal standard (IS): LSN3316897 lot BCA-BE03935-132, 1 mg/mL		
Minimum required dilutions (MRDs)	Not applicable		
Source and lot of reagents	Not applicable		
Regression model and weighting	Weighted $1/x^2$ least squares linear regression		
Validation parameters	**Method validation summary**		**Source location**
Standard calibration curve performance during accuracy and precision runs	Number of standard calibrators from LLOQ to ULOQ	8	191444PVDJS_EII_R5
	Cumulative accuracy (%bias) from LLOQ to ULOQ	-2.8% to 4.8%	
	Cumulative precision (%CV) from LLOQ to ULOQ	≤4.8%	
Performance of QCs during accuracy and precision runs	Cumulative accuracy (%bias) in 3 QCs:	-2.1% to 2.8%	
	Inter-batch %CV QCs:	≤12.9%	
	Total error (TE) QCs:	Not applicable	
Selectivity and matrix effect	Six lots of blank plasma were tested. Response was ≤12.3% of LLOQ.		
Interference and specificity	Not applicable		
Hemolysis effect	One lot of 2% hemolytic plasma was tested. Response was 6.9% of LLOQ.		
Lipemic effect	One lot of lipemic plasma was tested. Response was 7.3% of LLOQ.		
Dilution linearity and hook effect	A 100-fold dilution was validated. Hook effect was not applicable.		
Bench-top/process stability	Plasma: 24 hours at room temperature Extracted plasma: 177 hours at room temperature		
Freeze-thaw stability	5 freeze-thaw cycles at -20°C and -70°C		
Long-term storage	378 days at -20°C and 842 days at -70°C		

Parallelism	Not applicable	
Carryover	There was no significant carryover.	
Method performance in study		
Assay passing rate	GPGV: 19 out of 20 runs passed (95%)	GPGV
Standard curve performance	• Cumulative bias range: GPGV: -1.7% to 3.0% • Cumulative precision: GPGV: ≤8.1% CV	
QC performance	• Cumulative bias range: GPGV: -3.3% to -2.1% • Cumulative precision: GPGV: ≤8.7% CV	
Method reproducibility	GPGV: 12% of samples were run in ISR and 94% passed the criteria.	
Study sample analysis/ stability	Samples were kept at -70°C for up to 508 days. Stability was established for 680 days at -70°C.	

Abbreviations: CV = coefficient of variation; GPGV = Study I8F-MC-GPGV; HRAM = high mass resolution, accurate mass monitoring; ISR = incurred sample reanalysis; LC/MS = liquid chromatography with mass spectrometry; LLOQ = lower limit of quantitation; ULOQ = upper limit of quantitation.

Source Table APP.2.7.1.4.2 page 7 Summary of bioanalytical methods Document ID VV-CLIN-185809, available from: \\CDSESUB1\EVSPROD\nda215866\1374\m2\27-clin-sum\clinical-summary-appendix.pdf
Abbreviations: CV = coefficient of variation; HRAM = high mass resolution, accurate mass monitoring; ISR = incurred sample reanalysis; LC/MS = liquid chromatography with mass spectrometry; LLOQ = lower limit of quantitation; ULOQ = upper limit of quantitation.

8.7. Approved Antihyperglycemics for Pediatric Type 2 Diabetes

Table 38: FDA Approved Therapies for the Proposed Pediatric Indication

Class Product Name (Approval Date)	Indication*	Pediatric Dosing/ Administration*	Efficacy Information	Safety and Tolerability Issues
Biguanides				
Metformin[6] (Dec 2000)	As an adjunct to diet and exercise to improve glycemic control in pediatric patients aged 10 years and older with T2D.	***Immediate release:*** • Starting dose: 500 mg PO BID, with meals. • Increase dosage in increments of 500 mg weekly up to a maximum of 2,000 mg, given in divided doses twice daily. ***Extended release:*** • Starting dose: 500 mg PO QD. • Increase dosage in increments of 500 mg weekly up to a maximum of 2,000 mg QD, with the evening meal.	***Study Design*** • Duration: 16-week randomized, double-blind, placebo-controlled trial • Population: 73 pediatric subjects aged 10-16 years with T2D • Treatment: Metformin HCl immediate-release tablet (up to 2,000 mg/day) vs placebo for up to 16 weeks (mean duration of treatment 11 weeks) ***Baseline Demographics*** • Age: Mean 13.8 years (range 10-16 years) • Disease characteristics: Mean baseline FPG 182.2 mg/dL, mean baseline body weight (BW) 93 kg (metformin group) vs 86 kg (placebo group) ***Efficacy Results at Week 26*** Fasting Plasma Glucose (FPG): • Placebo: +21.4 mg/dL increase from baseline (n=36, baseline 192.3 mg/dL) • Metformin HCl: -42.9 mg/dL reduction from baseline (n=37, baseline 162.4 mg/dL) • Difference from placebo: -64.3 mg/dL (p<0.001) Body Weight (BW): • Placebo: mean change at Week 16 in BW was -0.9 kg • Metformin: mean change at Week 16 in BW was -1.5 kg	**Boxed Warning:** Lactic Acidosis. **Contraindications:** Severe renal impairment (eGFR below 30 mL/min/1.73 m2), hypersensitivity to metformin, and acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma. **Warnings and Precautions:** Vitamin B12 deficiency, hypoglycemia with concomitant use of insulin/insulin secretagogues. **Common Adverse Reactions (>5%):** Diarrhea, nausea/vomiting, flatulence, asthenia, indigestion, abdominal discomfort, and headache.
GLP-1 RA				
Dulaglutide[22] (17 Nov 2022)	As an adjunct to diet and exercise to improve glycemic control in pediatric patients 10 years of age and older with T2D.	• Recommended starting dosage is 0.75 mg injected SC QW. • If additional glycemic control is needed, increase dosage to the maximum	***Study Design*** • Duration: 26-week randomized, double-blind, placebo-controlled trial with 26-week open-label extension • Population: 154 pediatric subjects aged 10-17 years with type 2 diabetes and inadequate glycemic control despite diet and exercise • Treatment: Dulaglutide 0.75 mg, 1.5 mg, or placebo SC QW, with or without metformin and/or basal insulin	**Boxed Warning:** Risk of Thyroid C-Cell Tumors. **Contraindications:** Patients with a personal or family history of medullary thyroid carcinoma (MTC) or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN2), and patients

Class Product Name (Approval Date)	Indication*	Pediatric Dosing/ Administration*	Efficacy Information	Safety and Tolerability Issues
		recommended dosage of 1.5 mg QW after at least 4 weeks on the 0.75 mg dosage.	***Baseline Demographics*** • Age: Mean 14.5 years (range 10-17 years), 71% female • Race/Ethnicity: 55% White, 15% Black/African American, 12% Asian, 10% American Indian/Alaska Native, 55% Hispanic/Latino • Disease characteristics: Mean diabetes duration 2 years, mean A1C 8.1%, mean weight 90.5 kg, mean BMI 34.1 kg/m² ***Efficacy Results at Week 26*** A1C reduction: • Placebo: +0.6% increase from baseline • Dulaglutide 0.75 mg: -0.6% reduction (difference from placebo: -1.2%, 95% CI: -1.8, -0.6) • Dulaglutide 1.5 mg: -0.9% reduction (difference from placebo: -1.5%, 95% CI: -2.1, -0.9) • Dulaglutide pooled: -0.8% reduction (difference from placebo: -1.4%, 95% CI: -1.9, -0.8) A1C incidence <7.0%: • Placebo: 14% of subjects • Dulaglutide 0.75 mg: 55% of subjects • Dulaglutide 1.5 mg: 48% of subjects • Dulaglutide pooled: 52% of subjects Fasting Blood Glucose (FBG) reduction: • Placebo: +17.1 mg/dL increase • Dulaglutide 0.75 mg: -12.8 mg/dL reduction (difference from placebo: -29.9 mg/dL, 95% CI: -50.7, -9.1) • Dulaglutide 1.5 mg: -24.9 mg/dL reduction (difference from placebo: -42 mg/dL, 95% CI: -63, -20.9) • Dulaglutide pooled: -18.9 mg/dL reduction (difference from placebo: -35.9 mg/dL, 95% CI: -54.2, -17.6) ***Safety profile*** • The safety profile in pediatric subjects was consistent with that observed in adult studies, with the exception of a higher incidence of injection site reactions in the pediatric population. The incidence of injection site reactions was 3.9% in the 0.75 mg group and 3.8% in the 1.5 mg group, compared to 2.0% in the placebo group.	with a serious hypersensitivity reaction to dulaglutide or any of the product components. **Warnings and Precautions:** Acute pancreatitis, hypoglycemia, hypersensitivity reactions, acute kidney injury, severe GI adverse reactions, diabetic retinopathy complications, and acute gallbladder disease. **Common Adverse Reactions (≥5%):** Nausea, diarrhea, vomiting, abdominal pain, and decreased appetite.
Exenatide[6] (23 Jul 2021)	As an adjunct to diet and exercise to improve glycemic	2 mg SC QW, at any time of day and with or without meals.	***Study Design*** • Duration: 24-week randomized, double-blind, placebo-controlled, parallel-group trial, which included a 28-week open-	**Contraindications:**

Class Product Name (Approval Date)	Indication*	Pediatric Dosing/ Administration*	Efficacy Information	Safety and Tolerability Issues
	control in pediatric patients 10 years of age and older with T2D.		label extension where all subjects received exenatide (Bydureon) • Population: 82 pediatric subjects aged 10 to 17 years with type 2 diabetes, whose condition was managed with diet and exercise alone or in combination with a stable dose of oral antidiabetic agents and/or insulin • Treatment: Exenatide 2 mg administered SQ QW or a placebo, in addition to their existing therapy ***Baseline Demographics*** • Age: Mean 15.1 years, with a range of 10 to 17 years • Gender: 42% of the subjects were male • Race/Ethnicity: 43% White, 31% Black or African American, 6% American Indian or Alaska Native, and 4% Asian; 44% of subjects were of Hispanic or Latino ethnicity • Disease characteristics: Mean duration of diabetes was 2.3 years, with a mean A1C of 8.17%. The mean body weight was 100.6 kg, and the mean BMI was 36.4 kg/m² ***Efficacy Results at Week 26*** A1C reduction: • Placebo: Subjects experienced a +0.45% increase from baseline. • Exenatide 2 mg: subjects experienced a -0.25% reduction from baseline, resulting in a treatment difference from placebo of -0.71% (95% CI: -1.42, 0). A1C incidence <7.0%: • Placebo: 8.3% of subjects • Exenatide 2 mg: 31% of subjects FPG reduction: • Placebo: +16.2 mg/dL increase from baseline of 170.5 mg/dL • Exenatide: -1.3 mg/dL reduction from baseline of 165.2 mg/dL ***Safety profile*** • The safety profile was similar to that seen in adult populations • In the 24-week pediatric trial, 3.4% of exenatide-treated subjects experienced level 2 hypoglycemia (blood glucose <54 mg/dL), and 1.7% experienced severe hypoglycemia. • A higher proportion of pediatric subjects (64%) developed high-titer anti-exenatide antibodies compared to adults, and these subjects appeared to have a lower glycemic response	• Patients with a personal or family history of medullary thyroid carcinoma or in patients with MEN2. • Serious hypersensitivity reaction to liraglutide or any of the excipients. **Warnings and Precautions:** Acute pancreatitis, hypoglycemia, acute kidney injury, severe GI adverse reactions, immunogenicity, hypersensitivity, drug-induced thrombocytopenia, acute gallbladder disease. **Common Adverse Reactions (≥5%):** Nausea, hypoglycemia, vomiting, diarrhea, feeling jittery, dizziness, headache, dyspepsia.

Class Product Name (Approval Date)	Indication*	Pediatric Dosing/ Administration*	Efficacy Information	Safety and Tolerability Issues
Liraglutide[26] (17 Jun 2019)	As an adjunct to diet and exercise to improve glycemic control in pediatric patients aged 10 years and older with T2D.	• The recommended starting dosage of liraglutide is 0.6 mg SC QD. • If additional glycemic control is required, increase the dosage in 0.6 mg increments after at least one week on the current dosage, to reduce the risk of GI adverse reactions. • The maximum recommended dosage is 1.8 mg SC QD.	***Study Design*** • Duration: 26-week, double-blind, randomized, parallel group, placebo-controlled multi-center trial, with a 26-week open-label extension • Population: 134 pediatric subjects aged 10 to 17 years with T2D • Treatment: Liraglutide SC QD (dose was titrated weekly by 0.6 mg for 2 to 3 weeks to a maximum of 1.8 mg) or placebo QD, in combination with metformin with or without basal insulin treatment ***Baseline Demographics*** • Age: Mean 14.6 years; 29.9% were ages 10-14 years, and 70.1% were greater than 14 years of age • Gender: 38.1% male • Race/Ethnicity: 64.9% White, 13.4% Asian, 11.9% Black or African American; 29.1% Hispanic or Latino • Disease characteristics: Mean diabetes duration 1.9 years, mean A1C 7.8%, mean BMI 33.9 kg/m², mean BMI SDS 2.9, 18.7% of subjects were using basal insulin at baseline ***Efficacy Results at Week 26*** A1C reduction: • Placebo: +0.42% increase from baseline. • Liraglutide: -0.64% reduction from baseline (difference from placebo: -1.06%, 95% CI: -1.65, -0.46) A1C incidence <7.0%: • Placebo: 36.5% of subjects • Liraglutide: 63.7% of subjects FBG reduction: • Placebo: +14.4 mg/dL increase from baseline. • Liraglutide: -19.4 mg/dL reduction from baseline (difference from placebo: -33.83 mg/dL, 95% CI: -55.74, -11.92) ***Safety profile*** • The type and severity of AEs in pediatric subjects were generally comparable to those observed in the adult population. • A higher risk of hypoglycemia in pediatric subjects treated with liraglutide compared to placebo was observed, regardless of concomitant insulin and/or metformin use. In the clinical trial, 21.2% of liraglutide-treated subjects experienced level 2	**Boxed Warning:** Risk of Thyroid C-Cell Tumors. **Contraindications:** • Patients with a personal or family history of medullary thyroid carcinoma or in patients with MEN2. • Serious hypersensitivity reaction to liraglutide or any of the excipients. **Warnings and Precautions:** Acute pancreatitis, hypoglycemia, acute kidney injury, severe GI adverse reactions, immunogenicity, hypersensitivity, drug-induced thrombocytopenia, acute gallbladder disease. **Common Adverse Reactions (≥5%):** Nausea, hypoglycemia, vomiting, diarrhea, feeling jittery, dizziness, headache, dyspepsia.

Class Product Name (Approval Date)	Indication*	Pediatric Dosing/ Administration*	Efficacy Information	Safety and Tolerability Issues
			hypoglycemia (blood glucose <54 mg/dL), with or without symptoms.	
Insulin Products				
Multiple[6]	To improve glycemic control in pediatric patients with diabetes mellitus.	Multiple	Labeled use primarily supported by trials conducted in pediatric subjects with T1D.	**Contraindications:** During episodes of hypoglycemia, hypersensitivity to insulin product or excipients. **Warnings and Precautions:** Hyperglycemia or hypoglycemia with changes in insulin regimen, hypoglycemia, medication errors, hypersensitivity reactions, hypokalemia, fluid retention and heart failure with concomitant use of TZDs. **Common Adverse Reactions (≥5%):** Hypoglycemia, allergic reactions, injection/infusion site reactions, lipodystrophy, pruritus, rash, edema, and weight gain.
SGLT2i				
Canagliflozin[27] (18 Dec 2025)	As an adjunct to diet and exercise to improve glycemic control in pediatric patients aged 10 years and older with T2D.	• Recommended starting dosage is 100 mg PO QD. • Can be increased to 300 mg PO QD for additional glycemic control in patients tolerating 100 mg QD with eGFR ≥60 mL/min/1.73 m^2.	***Study Design*** • Duration: 52-week double-blind, placebo-controlled, parallel-group trial. • Population: 171 pediatric subjects aged 10 to 17 years with inadequately controlled T2D (A1C ≥6.5% and ≤11.0%). • Treatment: Canagliflozin 100 mg (with optional up-titration to 300 mg at Week 13) or placebo, as an add-on to diet and exercise and background antihyperglycemic therapy (metformin and/or insulin). ***Baseline Demographics*** • Age: Mean 14.3 years. • Gender: 68% female. • Race/Ethnicity: 42% Asian, 42% White, 11% Black or African American, 5% American Indian/Alaska Native; 36% Hispanic or Latino. • Disease characteristics: Mean diabetes duration 2 years, mean baseline A1C 8.0%, mean BMI 30.8 kg/m^2, mean eGFR 157.3 mL/min/1.73 m^2. Background therapy included metformin only (46%), metformin and insulin (29%), diet and exercise only (14%), and insulin only (11%). ***Efficacy Results at Week 26*** A1C reduction:	**Contraindications:** History of serious hypersensitivity reaction to dapagliflozin or any of the excipients in dapagliflozin. **Warnings and Precautions:** Ketoacidosis, volume depletion, urosepsis and pyelonephritis, hypoglycemia, necrotizing fasciitis of the perineum (Fournier's Gangrene), genital mycotic infections. **Common Adverse Reactions (≥5%):** Female genital mycotic infections, nasopharyngitis, and urinary tract infections.

Class Product Name (Approval Date)	Indication*	Pediatric Dosing/ Administration*	Efficacy Information	Safety and Tolerability Issues
			• Placebo: +0.34% increase from a baseline of 8.3%. • Canagliflozin: -0.38% reduction from a baseline of 7.8% (difference from placebo: -0.73%, 95% CI: -1.26, -0.19). FPG reduction: • Placebo: +17.29 mg/dL increase from a baseline of 156.5 mg/dL. • Canagliflozin: -8.22 mg/dL reduction from a baseline of 154.8 mg/dL (difference from placebo: -25.51 mg/dL, 95% CI: -49.55, -1.47). ***Safety profile*** The safety profile of canagliflozin in pediatric subjects was similar to that observed in adults with T2D.	
Dapagliflozin[28] (12 Jun 2024)	As an adjunct to diet and exercise to improve glycemic control in pediatric patients aged 10 years and older with T2D.	• Recommended starting dosage is 5 mg PO QD. • Can be increased to 10 mg PO QD for additional glycemic control.	***Study Design*** • Duration: 26-week randomized, double-blind, placebo-controlled trial with 26-week safety extension • Population: 157 pediatric subjects aged 10-17 years with T2D and inadequate glycemic control (A1C ≥6.5% and ≤10.5%) • Treatment: Dapagliflozin 5 mg or placebo PO QD as add-on to metformin, insulin, or combination of metformin and insulin. At Week 14, subjects with A1C ≥7% were randomized to continue 5 mg or up-titrate to 10 mg ***Baseline Demographics*** • Age: Mean 14.4 years (dapagliflozin group) and 14.7 years (placebo group) • Gender: 61% female (dapagliflozin) and 58% female (placebo) • Race/Ethnicity: Dapagliflozin group: 52% White, 22% Asian, 9% Black/African American, 56% Hispanic/Latino; Placebo group: 42% White, 32% Asian, 4% Black/African American, 45% Hispanic/Latino • Disease characteristics: Mean diabetes duration 2.3 years (dapagliflozin) and 2.5 years (placebo), mean A1C 8.2% (dapagliflozin) and 8.0% (placebo), mean BMI 29.7 kg/m² (dapagliflozin) and 28.5 kg/m² (placebo), mean eGFR 115 mL/min/1.73 m² (dapagliflozin) and 113 mL/min/1.73 m² (placebo) ***Efficacy Results at Week 26*** A1C reduction: • Placebo: +0.4% increase from baseline • Dapagliflozin 5 mg and 10 mg: -0.6% reduction (difference from placebo: -1.0%, 95% CI: -1.6, -0.5)	**Contraindications:** History of serious hypersensitivity reaction to dapagliflozin or any of the excipients in dapagliflozin. **Warnings and Precautions:** Ketoacidosis, volume depletion, urosepsis and pyelonephritis, hypoglycemia, necrotizing fasciitis of the perineum (Fournier's Gangrene), genital mycotic infections. **Common Adverse Reactions (≥5%):** Female genital mycotic infections, nasopharyngitis, and urinary tract infections.

Class Product Name (Approval Date)	Indication*	Pediatric Dosing/ Administration*	Efficacy Information	Safety and Tolerability Issues
			A1C incidence <7.0%: • Placebo: 25% of subjects • Dapagliflozin: 34.6% of subjects FPG reduction: • Placebo: +9.2 mg/dL increase • Dapagliflozin: -10.3 mg/dL reduction (difference from placebo: -19.5 mg/dL, 95% CI: -36.4, -2.6) ***Safety profile*** • The safety profile observed in the placebo-controlled trial in pediatric subjects with T2D was similar to that observed in adults. No new adverse reactions were identified in the pediatric population.	
Empagliflozin[29] (20 Jun 2023)	As an adjunct to diet and exercise to improve glycemic control in pediatric patients aged 10 years and older with T2D.	• Recommended dosage is 10 mg PO QD in the morning, taken with or without food. • For additional glycemic control, may increase to 25 mg PO QD in patients tolerating 10 mg QD.	***Study Design*** • Duration: 26-week, double-blind, randomized, placebo-controlled, parallel-group trial with a safety extension period of up to 52 weeks • Population: 157 pediatric subjects aged 10 to 17 years with inadequately controlled T2D (A1C 6.5% to 10.5%) • Treatment: Empagliflozin 10 mg, a dipeptidyl peptidase-4 (DPP-4) inhibitor, or a placebo—background therapies included metformin (51%), a combination of metformin and insulin (40.1%), insulin alone (3.2%), or no background therapy (5.7%) ***Baseline Demographics*** • Age: Mean 14.5 years, with a range of 10 to 17 years • Race/Ethnicity: 50% White, 31% Black or African American, 6% Asian, and 38% of Hispanic or Latino ethnicity • Disease characteristics: Mean duration of T2D was 2.1 years, with a mean baseline A1C of 8.0% and a mean BMI of 36.0 kg/m^2 ***Efficacy Results at Week 26*** A1C reduction: • Placebo: +0.7% increase from a baseline of 8.1%. • Jardiance (10 mg and 25 mg): -0.2% reduction from a baseline of 8.0% (difference from placebo: -0.8%, 95% CI: -1.5, -0.2) FPG reduction: • Placebo: +17 mg/dL increase from a baseline of 159 mg/dL.	**Contraindications:** History of serious hypersensitivity reaction to empagliflozin or any of the excipients in empagliflozin. **Warnings and Precautions:** Ketoacidosis, volume depletion, genitourinary infections (including urosepsis, pyelonephritis, Fournier's Gangrene), hypoglycemia, lower limb amputation, hypersensitivity reactions. **Common Adverse Reactions (≥5%):** Urinary tract infections and female genital mycotic infections.

Class Product Name (Approval Date)	Indication*	Pediatric Dosing/ Administration*	Efficacy Information	Safety and Tolerability Issues
			• Empagliflozin (10 mg and 25 mg): -19 mg/dL reduction from a baseline of 154 mg/dL (difference from placebo: -36 mg/dL, 95% CI: -60.7, -10.7) ***Safety profile*** • The safety profile in pediatric subjects was similar to that observed in adults with T2D, with the exception of a higher risk of hypoglycemia, regardless of whether they were also using insulin • In the clinical trial, level 2 hypoglycemia (blood glucose <54 mg/dL) occurred in 19.2% of subjects treated with empagliflozin compared to 7.5% of subjects treated with placebo	

Source: Drugs@FDA,[6] available from: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm
Abbreviations: A1C = hemoglobin A1c; AE = adverse events; BID = twice daily (bis in die); BMI = body mass index; BW = body weight; CI = confidence interval; eGFR = estimated glomerular filtration rate; FBG = fasting blood glucose; FPG = fasting plasma glucose; GI = gastrointestinal; GLP-1 RA = glucagon-like peptide-1 receptor agonist; HCl, hydrochloride; MEN2 = multiple endocrine neoplasia syndrome type 2; MTC medullary thyroid carcinoma; PO = oral (per os); QD = once daily (quaque die); QW = once weekly; SC = subcutaneous; SDS = standard deviation score; SGLT2i = sodium-glucose cotransporter-2 inhibitor; T2D = type 2 diabetes; TID = thrice daily (ter in die).
*Children ≥10 years and adolescents unless otherwise specified.

8.8. Summary of Presubmission/Submission Regulatory History

Date	Regulatory Interactions Between FDA and Applicant
05 Nov 2018	The Applicant submitted an Initial Pediatric Study Plan (iPSP) to IND 128801. EDR Location: \\Cdsesub1\evsprod\IND128801\0048\
01 Feb 2019	FDA's issued an initial Pediatric Study Plan – Written Response to the Applicant's 05 Nov 2018 iPSP submission which included proposed FDA revisions. Available from: https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af804d8a74
24 Apr 2019	The Applicant submitted responses to the FDA's 01 Feb 2019 Written Response. The submission included a revised iPSP and regulatory response document that addressed development timelines, long-term open-label safety study, and study design changes. EDR Location: \\Cdsesub1\evsprod\IND128801\0064\
06 May 2019	At the FDA's request, the Applicant submitted an Agreed iPSP to adhere to statutory timelines. The submission noted that this resubmission did not constitute a final agreement. EDR Location: \\Cdsesub1\evsprod\IND128801\0066\
05 Jun 2019	FDA issued an Agreed iPSP – No Agreement Letter. Topics of non-agreement included the following: • Pediatric nonclinical and clinical development timelines • Request for additional details on the proposed placebo borrowing approach • Proposed Human Factors plan Available from: https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af804fa7b0
08 Aug 2019	The Applicant submitted an updated iPSP with revisions to the 06 May 2019 submission, along with a Regulatory Response addressing the FDA's 05 June 2019 non-agreement comments. EDR Location: \\Cdsesub1\evsprod\IND128801\0072\
15 Nov 2019	FDA issued an iPSP – Other letter in response to the Applicant's 08 Aug 2019 submission. Topics of non-agreement included the development program's timelines and the proposed placebo-borrowing approach. Available from: https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af805282a0
16 Dec 2019	In an email, the FDA canceled a planned teleconference and advised the following: • FDA agreed with the proposed pediatric timelines included in the Applicant 08 August 2019 Regulatory Response. • FDA disagreed with the proposal to borrow historical placebo data from AWARD-PEDS. FDA requested that a revised iPSP be submitted with the agreed-upon timelines and a traditional statistical approach for sample size determination. Available from: https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af80530b6f
05 Feb 2020	The Applicant submitted a revised iPSP based on the FDA's 16 Dec 2019 feedback. EDR Location: \\Cdsesub1\evsprod\IND128801\0087\
03 Mar 2020	In an email communication, the FDA noted no further comments on the iPSP and requested that the 05 Feb 2020 iPSP be submitted as an Agreed iPSP. Available from: https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af805458cf
05 Mar 2020	The Applicant submitted the Agreed iPSP. EDR Location: \\Cdsesub1\evsprod\IND128801\0093\
01 Apr 2020	FDA issued an agreement letter for the Agreed iPSP. Available from: https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af805522fd

Date	Regulatory Interactions Between FDA and Applicant
21 Jan 2021	The Applicant submitted a Proposed Pediatric Study Request (PPSR). EDR Location: \\Cdsesub1\evsprod\IND128801\0139\
13 May 2021	FDA issued an Inadequate Study Request Letter in response to the Applicant's 21 Jan 2021 PPSR submission. The FDA agreed not to include studies for cardiovascular (CV) risk reduction and heart failure with preserved ejection fraction (HFpEF) but noted issues related to the T2D, chronic weight management (CWM), and nonalcoholic steatohepatitis (NASH) studies. Available from: https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af805f00f6
25 Aug 2021	During a Type C Meeting, the FDA agreed with the Applicant's plan to submit a draft protocol in accordance with the Agreed iPSP. The Applicant also committed to providing additional information regarding the challenges of implementing standard retinal fundus photographs in trial GPGV. Available from: https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af8060d476 https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af80617807
22 Sep 2021	The Applicant submitted the draft protocol for Study I8F-MC-GPGV, as agreed to during the Type C Meeting on 25 Aug 2021. EDR Location: \\Cdsesub1\evsprod\IND128801\0179\
20 Apr 2022	FDA issued a Written Request (WR). Available from: https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af80659d16
13 May 2022	Mounjaro is approved as an adjunct to diet and exercise to improve glycemic control in adults with T2D. The approval included a Postmarketing Requirement (PMR 4271-1) to conduct a 30-week, randomized, double-blind, placebo-controlled, multicenter, parallel-arm study, followed by a 22-week open-label extension, to assess the safety and efficacy of tirzepatide for the treatment of T2D in pediatric patients aged 10 to 17 years. The approval letter is available from: https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2022/215866Orig1s000ltr.pdf
14 Jul 2022	The Applicant formally agreed to the WR in a submission to NDA 215866. EDR Location: \\Cdsesub1\evsprod\NDA215866\0088\
23 May 2024	The Applicant submitted proposed revisions to the WR in a submission to NDA 215866. Available from: \\Cdsesub1\evsprod\NDA215866\0611\
18 Sep 2024	FDA issued WR Amendment 1. Available from: https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af8076bb64
09 Dec 2024	The Applicant submitted a proposed revision to WR Amendment 1 in a submission to NDA 215866. EDR Location: \\Cdsesub1\evsprod\NDA215866\1199\
09 Apr 2025	FDA issued an Inadequate Proposed Amendment to Written Request Letter regarding the Applicant's 09 Dec 2024 submission. Available from: https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af807ae6ff
23 Apr 2025	The Applicant submitted a Breakthrough Therapy Designation (BTD) Request. EDR Location: \\Cdsesub1\evsprod\IND128801\0458\
20 Jun 2025	FDA issued a letter denying the Applicant's request for BTD. Available from: https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af807c3c45

Source: Adapted from the Applicant's Note to Reviewer submission, available from: \\CDSESUB1\EVSPROD\nda215866\1374\m1\us\note.pdf

Abbreviations: BTD = Breakthrough Therapy Designation; CV = cardiovascular; CWM = chronic weight management; FDA = Food and Drug Administration; HFpEF = heart failure with preserved ejection fraction; IND = Investigational New Drug; iPSP = initial Pediatric Study Plan; NASH = nonalcoholic steatohepatitis; NDA = New Drug Application; PMR = postmarketing requirement; PPSR = Proposed Pediatric Study Request; T2D = type 2 diabetes mellitus; WR = Written Request.

8.9. Glossary

A1C	Hemoglobin A1c
ADA	American Diabetes Association AND Anti-drug antibody
AE	Adverse event
AESI	Adverse events of special interest
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
AUCss	Area under the concentration-time curve at steady state
BG	Blood glucose
BID	Twice daily (bis in die)
BILI	Bilirubin
BLA	Biologics license application
BLQ	Below limit of quantification
BMI	Body mass index
BMI-SDS	BMI standard deviation score
BPM	Beats per minute
BSA	Body surface area
BTD	Breakthrough Therapy Designation
BW	Body weight
CA	Comparative analysis
CFR	Code of Federal Regulations
CI	Confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CL	Clearance
CL/F	Apparent clearance
ClinRO	Clinician reported outcome
Cmax	Maximum plasma concentration
Cmax,ss	Maximum concentration at steady state
COA	Clinical outcome assessment
CRF	Case report form
CrL	Credible interval
CRO	Contract research organization
CSR	Clinical study report
CT	Computed tomography
CV	Cardiovascular AND Coefficient of variation
CV%	Percent coefficient of variation
CWM	Chronic weight management
CWRES	Conditional weighted residual
CYP	Cytochrome P450
DARRTS	Document Archiving, Reporting, and Regulatory Tracking System
DBP	Diastolic blood pressure
DBIRBD	Division of Biomedical Informatics, Research, and Biomarker Development

Reference ID: 5715650

DDLO	Division of Diabetes, Lipid Disorders, and Obesity
DHN	Division of Hepatology and Nutrition
DILI	Drug-induced liver injury
DKD	Diabetic kidney disease
DKA	Diabetic ketoacidosis
DMEPA	Division of Medication Error Prevention and Analysis
DMPP	Division of Medical Policy Programs
DPM	Division of Pharmacometrics
DPP-4i	Dipeptidyl peptidase-4 inhibitors
DSCP	Disease-state cut point
DSURs	Development Safety Update Reports
E0G	Baseline fasting glucose
E0H	Baseline hemoglobin A1c
EBE	Empirical Bayes estimate
EC50	Concentration with half-maximal effect
ECG	Electrocardiogram
eCRF	Electronic case report form
EE	Efficacy estimand
eGFR	Estimated glomerular filtration rate
EOT	End of treatment
EQ-5D-Y-3L	EuroQol 5-Dimension Youth questionnaire 3-level
ER	Exposure-response
ESRD	End stage renal disease
EU	European Union
F	Bioavailability
FAS	Full Analysis Set
FDA	Food and Drug Administration
FFM	Fat-free mass
FG	Fasting glucose
FOCE	First-order conditional estimation
FPG	Fasting plasma glucose
FSG	Fasting serum glucose
GCP	Good clinical practice
GGT	Gamma-glutamyl transferase
GI	Gastrointestinal
GIP	Glucose-dependent insulinotropic polypeptide
GIPR	Glucose-dependent insulinotropic polypeptide receptor
GLP-1	Glucagon-like peptide-1
GLP-1 RA	Glucagon-like peptide-1 receptor agonist
GPGV	Study I8F-MC-GPGV
H	Hour
HF	Human factors
HFpEF	Heart failure with preserved ejection fraction
ICE	Intercurrent events

Reference ID: 5715650

ICF	Informed consent forms
ICH	International Conference on Harmonisation
IIV	Interindividual variability
IND	Investigational New Drug
iPSP	Initial Pediatric Study Plan
ISR	Incurred sample reanalysis
ISS	Integrated summary of safety
ITT	Intention-to-treat
ka	Absorption rate constant
kDIS	FG disease progression rate
kOFF	Offset rate constant
kout	Turnover rate constant for body weight
kOUT	Turnover rate constant for hemoglobin A1c
ktol	Tolerance rate constant
L	Liter
LC/MS	Liquid chromatography with mass spectrometry
Level 1	Glucose Alert (BG level <70 mg/dL and ≥54 mg/dL)
Level 2	Clinically Significant Hypoglycemia (BG level <54 mg/dL)
Level 3	Severe Hypoglycemia (severe cognitive impairment requiring assistance)
LLOQ	Lower limit of quantitation
LS	Least squares
LSM	Least-squares mean
MAP	Maximum a posteriori
MAR	Missing at random
MASLD	Metabolic dysfunction-associated steatotic liver disease
MedDRA	Medical Dictionary for Regulatory Activities
MEN2	Multiple endocrine neoplasia syndrome type 2
mITT	Modified intent-to-treat
MMRM	Mixed model for repeated measures
msec	Milliseconds
MTC	Medullary thyroid carcinoma
Nab	Neutralizing antibody
NAI	No action indicated
NASH	Nonalcoholic steatohepatitis
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	New Drug Application
NISS	Newly Identified Safety Signal
NME	New molecular entity
NONMEM	Nonlinear mixed-effects modeling
NPDE	Normalized prediction distribution error
ObsRO	Observer reported outcome
OCHEN	Office of Cardiology, Hematology, Endocrinology and Nephrology
OCP	Office of Clinical Pharmacology
OCS	Office of Computational Science

Reference ID: 5715650

OPDP	Office of Prescription Drug Promotion
OPQ	Office of Pharmaceutical Quality
OPQR	Office of Pharmaceutical Quality Research
OSA	Obstructive sleep apnea
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
OTS	Office of Translational Sciences
PD	Pharmacodynamics
PDUFA	Prescription Drug User Fee Act
PedsQL	Pediatric Quality of Life Inventory
PerfO	Performance outcome
PI	Prescribing information
PIP	Pediatric investigational plan
PK	Pharmacokinetics
PLCFM	Placebo fractional reduction of fat mass
PLCFFM	Placebo fractional reduction of fat-free mass
PMC	Postmarketing commitment
PMR	Postmarketing requirement
PP	Per protocol
PPSR	Proposed Pediatric Study Request
PREA	Pediatric Research Equity Act
PRO	Patient reported outcome
PSP	Pediatric study plan
PSUR	Periodic Safety Update report
PT	Preferred term
PY	Patient-years
QD	Once daily (quaque die)
QF	Apparent intercompartmental clearance
QOL	Quality-of-life
OPQR	Office of Pharmaceutical Quality Research
QTcF	QT interval corrected using Fridericia's correction
QW	Once weekly
REMS	Risk evaluation and mitigation strategy
RUV	Residual unexplained variability
SAE	Serious adverse event
SAEM	Stochastic approximation expectation maximization
SAFPOP	Safety population
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SC	Subcutaneous
SCF	Summary of Clinical Safety
SD	Standard deviation
SDP	Single-dose pen
SDS	Standard deviation score

Reference ID: 5715650

SE	Standard error
SE5	Supplement – Efficacy to add new clinical study data to labeling
SEARCH	SEARCH for Diabetes in Youth study
SGLT2i	Sodium-glucose cotransporter-2 inhibitors
sNDA	Supplemental New Drug Application
SOC	Standard of care AND system organ class
SS	Steady state
t1/2	Terminal elimination half-life
T1D	Type 1 diabetes
T2D	Type 2 diabetes
TE	Treatment-emergent
TEAE	Treatment-emergent adverse event
TID	Thrice daily (ter in die)
Tmax	Time to maximum plasma concentration
TODAY	Treatment Options for Type 2 Diabetes in Adolescents and Youth study
TRE	Treatment-regimen estimand
TZD	Thiazolidinediones
TZP	Tirzepatide
UACR	Urine albumin-to-creatinine ratio
ULN	Upper limit of normal
US	United States
V2/F	Apparent volume of the central compartment
V3/F	Apparent volume of the peripheral compartment
VAI	Voluntary Action Indicated
Vc	Central volume of distribution
Vd/F	Mean apparent volume of distribution
Vp	Peripheral volume of distribution
VPC	Visual predictive check
vs	Versus
WHO	World Health Organization
WR	Written Request

Reference ID: 5715650

8.10. References

1. Bacha F, Hannon TS, Tosur M, et al. Pathophysiology and Treatment of Prediabetes and Type 2 Diabetes in Youth. Diabetes Care 2024;47:2038-49.
2. Nadeau KJ, Mayer-Davis EJ, Gubitosi-Klug R, et al. Youth-Onset Type 2 Diabetes: What We've Learned From Key Youth-Onset Type 2 Diabetes Studies, What We Still Don't Know, and Why It Is Important. Diabetes Care 2025;48:1136-49.
3. Mottl AK, Tryggestad JB, Isom S, et al. Major adverse events in youth-onset type 1 and type 2 diabetes: The SEARCH and TODAY studies. Diabetes Res Clin Pract 2024;210:111606.
4. Wagenknecht LE, Lawrence JM, Isom S, et al. Trends in incidence of youth-onset type 1 and type 2 diabetes in the USA, 2002-18: results from the population-based SEARCH for Diabetes in Youth study. Lancet Diabetes Endocrinol 2023;11:242-50.
5. TODAY Study Group, Bjornstad P, Drews KL, et al. Long-Term Complications in Youth-Onset Type 2 Diabetes. N Engl J Med 2021;385:416-26.
6. Drugs@FDA: FDA approved drug products. Silver Spring, MD: U.S. Food and Drug Administration [cited 2025 Nov 23]. Avalable from: https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2022/215866Orig1s000ltr.pdf.
7. American Diabetes Association Professional Practice Committee. 14. Children and Adolescents: Standards of Care in Diabetes-2025. Diabetes Care 2025;48:S283-S305.
8. Shah AS, Barrientos-Perez M, Chang N, et al. ISPAD Clinical Practice Consensus Guidelines 2024: Type 2 Diabetes in Children and Adolescents. Horm Res Paediatr 2024;97:555-83.
9. Varni JW. SCALING AND SCORING for the acute and standard versions of the Pediatric Quality of Life Inventory™ PedsQL™. Lyon, France: Mapi Research Trust; 2023 Mar [cited 2025 Nov 18]. Available from: https://www.pedsql.org/PedsQL-Scoring.pdf 2023.
10. Varni JW, Delamater AM, Hood KK, et al. Pediatric Quality of Life Inventory (PedsQL) 3.2 Diabetes Module for youth with Type 2 diabetes: reliability and validity. Diabet Med 2019;36:465-72.
11. WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects. Last amended by the 75th WMA General Assembly, Helsinki, Finland. 2024 Oct. Ferney-Voltaire, France: World Medical Association; 2024 Oct 19 [cited 2025 Nov 26]. Available from: https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/.
12. ICH Harmonised Guideline. Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice E6(R2). Geneva, Switzerland: International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH); 2018 Mar [cited 2025 Nov 26]. Available from: https://www.fda.gov/media/93884/download.
13. Hannon TS, Chao LC, Barrientos-Perez M, et al. Efficacy and safety of tirzepatide in children and adolescents with type 2 diabetes (SURPASS-PEDS): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 2025;406:1484-96.

14. Barnes AJ, Eisenberg ME, Resnick MD. Suicide and self-injury among children and youth with chronic health conditions. Pediatrics 2010;125:889-95.
15. Eaton DK, Lowry R, Brener ND, Galuska DA, Crosby AE. Associations of body mass index and perceived weight with suicide ideation and suicide attempts among US high school students. Arch Pediatr Adolesc Med 2005;159:513-9.
16. Gulley LD, Shomaker LB. Depression in Youth-Onset Type 2 Diabetes. Curr Diab Rep 2020;20:51.
17. McVoy M, Hardin H, Fulchiero E, et al. Mental health comorbidity and youth onset type 2 diabetes: A systematic review of the literature. Int J Psychiatry Med 2023;58:37-55.
18. Mounjaro [package insert]. Indianapolis, IN: Eli Lilly and Company; 2025 Sep 25 [cited 2025 Oct 27]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/215866s034lbl.pdf.
19. American Diabetes Association Professional Practice Committee. 6. Glycemic Goals and Hypoglycemia: Standards of Care in Diabetes-2025. Diabetes Care 2025;48:S128-S45.
20. Ozempic [package insert]. Plainsboro, NJ: Novo Nordisk Inc.; 2025 Oct 14 [cited 2025 Nov 13]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/209637s035,209637s037lbl.pdf.
21. Rybelsus [package insert]. Plainsboro, NJ: Novo Nordisk Inc.; 2025 Oct 17 [cited 2025 Nov 13]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/213051s024,s028s029lbl.pdf.
22. Trulicity [package insert]. Indianapolis, IN: Eli Lilly and Company; 2025 May 28 [cited 2025 Nov 24]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/125469s063lbl.pdf.
23. Zepbound [package insert]. Indianapolis, IN: Eli Lilly and Company; 2024 Sep 25 [cited 2025 Nov 29]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/217806s031lbl.pdf.
24. Schwartz GJ, Munoz A, Schneider MF, et al. New equations to estimate GFR in children with CKD. J Am Soc Nephrol 2009;20:629-37.
25. Inker LA, Eneanya ND, Coresh J, et al. New Creatinine- and Cystatin C-Based Equations to Estimate GFR without Race. N Engl J Med 2021;385:1737-49.
26. Victoza [package insert]. Plainsboro, NJ: Novo Nordisk Inc.; 2025 Oct 14 [cited 2025 Nov 24]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/022341s046lbl.pdf.
27. Invokana [package insert]. Titusville, NJ: Janssen Pharmaceuticals, Inc.; 2024 Dec 18 [cited 2025 Dec 5]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/204042s043lbl.pdf.

28. Farxiga [package insert]. Wilmington, DE: AstraZeneca AB; 2024 Jun 12 [cited 2025 Nov 24]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/202293s031lbl.pdf.

29. Jardiance [package insert]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc.; 2025 Oct 24 [cited 2025 Nov 24]. Available from https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/204629s063lbl.pdf.

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12/19/2025 01:46:39 PM
I am signing off on behalf of myself and Justin Earp, who served as the secondary pharmacometrics reviewer

ROBERTO C CRACKEL
12/19/2025 01:50:04 PM

YOONHEE KIM
12/19/2025 02:06:23 PM
I concur

MAHTAB NIYYATI
12/19/2025 02:08:36 PM

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