CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215866Orig1s000

CLINICAL REVIEW(S)

CLINICAL REVIEW

Application Type	505(b)(1) New Drug Application (NDA)
Application Number(s)	NDA 215866
Priority or Standard	Priority
Submit Date(s)	September 15, 2021
Received Date(s)	September 15, 2021
PDUFA Goal Date	May 15, 2022
Division/Office	Division of Diabetes, Lipid Disorders, and Obesity (DDLO)
Reviewer Name(s)	Frank Pucino, PharmD, MPH
Review Completion Date	May 6, 2022
Established/Proper Name	Tirzepatide
Trade Name	Mounjaro
Applicant	Eli Lilly and Company (Lilly)
Dosage Form(s)	Injection 2.5 mg/0.5 mL in a single-dose pen Injection 5 mg/0.5 mL in a single-dose pen Injection 7.5 mg/0.5 mL in a single-dose pen Injection 10 mg/0.5 mL in a single-dose pen Injection 12.5 mg/0.5 mL in a single-dose pen Injection 15 mg/0.5 mL in a single-dose pen
Applicant Proposed Dosing Regimen(s)	The recommended initiating dosage of tirzepatide is 2.5 mg injected subcutaneously once weekly. After 4 weeks, increase the dosage 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 maximum dosage of tirzepatide is 15 mg injected subcutaneously once weekly.
Applicant Proposed Indication(s)/Population(s)	As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
Recommendation on Regulatory Action	**Approval.** In accordance with 21CFR314.126, the Applicant has provided substantial evidence of effectiveness for the proposed indication as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.
Recommended Indication(s)/Population(s) (if applicable)	As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus

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Glossary

A	Asian
A1c	Hemoglobin A1c
AACE	American Association of Clinical Endocrinologists
ABI	Ankle-Brachial Index
AC	Advisory Committee
ACE	American College of Endocrinology
ACP	American College of Physicians
ADA	American Diabetes Association
ADaM	Analysis Dataset Model
ADBMI	Associate Director Biomedical Informatics
AE	Adverse Event
AESI	Adverse Event of Special Interest
AHA	Antihyperglycemic Agent
AI	Autoinjector
AIAN	American Indian or Alaska Native
AKI	Acute Kidney Injury
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
API	Active Pharmaceutical Ingredient
APPADL	Ability to Perform Physical Activities of Daily Living
ARIA	Active Risk Identification and Analysis
AS	Analysis Set
ASCVD	Atherosclerotic Cardiovascular Disease
AST	Aspartate Aminotransferase
AUC	Area Under the Curve
B-CELL	Beta-Cell
BA	Bioavailability
BE	Bioequivalence
BL	Baseline
BMI	Body Mass Index
BP	Blood Pressure
BPM	Beats Per Minute
BW	Body Weight
C5R	Cleveland Clinic Coordinating Center for Clinical Research
CAC	Carcinogenicity Committee
CAD	Coronary Artery Disease

CCIT	Container Closure Integrity Test
CD	Circular Dichroism
CDC	Center for Disease Control and Prevention
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CEC	Clinical Events Committee
CFB	Change from Baseline
CFR	Code of Federal Regulations
CHF	Congestive Heart Failure
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CIOMS	Council for International Organizations of Medical Sciences
CKD	Chronic Kidney Disease
CKD-EPI	Chronic Kidney Disease-Epidemiology Collaboration
CL/F	Clearance/Fraction
ClinRO	Clinician Reported Outcome
CM	Continuous Manufacturing
Cmax	Maximum Plasma Concentration
Cmaxss	Maximum Plasma Concentration at Steady State
CMQ	Custom MedDRA Query
COA	Clinical Outcome Assessment
COC	Combined Oral Contraceptive
CRF	Case Report Form
CLINRO	Clinician Reported Outcome
COC	Combined Oral Contraceptive
COVID-19	Corona Virus Disease 2019
CrCL	Creatinine Clearance
CRT	Clinical Review Template
CSR	Clinical Study Report
CT	Computerized Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CV	Cardiovascular
CVD	Cardiovascular Disease
CVMA	Cardiovascular Meta-Analysis
CVOT	Cardiovascular Outcomes Trial
CWM	Chronic Weight Management
CYP	Cytochrome P450
Da	Dalton
DAP	Data Access Plan
DBIL	Direct Bilirubin
DBIRBD	Division of Biomedical Informatics, Research, and Biomarker Development
DBP	Diastolic Blood Pressure

DCCT	Diabetes Control and Complication Trial
DCEP	Division of Cardiometabolic and Endocrine Pharmacology
DCRI	Duke Clinical Research Institute
DDI	Drug-Drug Interaction
DDLO	Division of Diabetes, Lipid Disorders, and Obesity (DDLO)
DEPI	Division of Epidemiology
DIO	Diet-Induced Obese
DKA	Diabetic Ketoacidosis
DMC	Data Monitoring Committee
DMEPA	Division of Medication Error Prevention and Analysis
DNDAPI	Division of New Drug Active Pharmaceutical Ingredient
DPM	Division of Pharmacometrics
DPMA	Division of Microbiology Assessment
DPP-4i	Dipeptidyl Peptidase-4 Inhibitor
DRBPMI	Division of Regulatory and Business Process Management
DTSQc	Diabetes Treatment Satisfaction Questionnaire Change
DTSQs	Diabetes Treatment Satisfaction Questionnaire Status
DULA	Dulaglutide
EASD	European Association for the Study of Diabetes
EC	Ethics Committee
eCRF	Electronic Case Report Form
ECG	Electrocardiogram
EF	Ejection Fraction
eGFR	Estimated Glomerular Filtration Rate
EMA	European Medicines Agency
Emax	Maximum Drug Effect
EOP2	End of Phase 2
EPC	Established Pharmacologic Class
EQ-5D-5L	European Quality of Life Five Dimension Five Level
ESRD	End Stage Renal Disease
ETT	Emerging Technology Team
EU	European Union
F	Female
F1	First Generation
FAERS	FDA Adverse Event Reporting System
FAS	Full Analysis Set
FBG	Fasting Blood Glucose
FCDP	Fixed Combination Drug Product
FDA	Food and Drug Administration
FDCA	Food Drug and Cosmetic Act
FBG	Fasting Blood Glucose
FPG	Fasting Plasma Glucose

FSG	Fasting Serum Glucose
GCP	Good Clinical Practice
GGT	Gamma-Glutamyl Transpeptidase
GI	Gastrointestinal
GIP	Glucose-Dependent Insulinotropic Polypeptide
GIP RA	Glucose-Dependent Insulinotropic Polypeptide Receptor Agonist
GLP-1	Glucagon-Like Peptide-1
GLP-1 RA	Glucagon-Like Peptide-1 Receptor Agonist
GM	Geometric Mean
HbA1c	Hemoglobin A1c (Glycosylated Hemoglobin)
HDL-C	High-Density Lipoprotein Cholesterol
hERG	Human Ether-A-Go-Go
HEV	Hepatitis E Virus
HF	Human Factors
Hgb	Hemoglobin
HFpEF	Heart Failure with Preserved Ejection Fraction
HHF	Hospitalization for Heart Failure
HIV	Human Immunodeficiency Virus
HLGT	High Level Group Term
HLT	High Level Term
HR	Hazard Ratio
Hx	History
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IFU	Instructions for Use
IND	Investigational New Drug
INS DEG	Insulin Degludec
INS GLAR	Insulin Glargine
IP	Investigational Product
iPSP	Initial Pediatric Study Plan
IR	Incidence Rate
IRB	Institutional Review Board
IRT	Interdisciplinary Review Team
ISE	Integrated Summary of Effectiveness
ISO	International Organization for Standardization
ISS	Integrated Summary of Safety
ITT	Intention-To-Treat
IWRS	Integrated Web Response System
IWQOL-Lite-CT	Impact of Weight on Quality of Life-Lite Clinical Trials Version
IW-SP	Impact of Weight on Self-Perception
Kg	Kilogram

LC-MS	Liquid Chromatography with Mass Spectrometry
LDL-C	Low-Density Lipoprotein Cholesterol
[redacted]	(b) (4)
LLN	Lower Limit of Normal
LS	Least Squares
LSS	Lilly Safety System
LVEF	Left Ventricular Ejection Fraction
LVH	Left Ventricular Hypertrophy
LY	LY3298176
M	Male
MACE	Major Adverse Cardiovascular Events
MACE+	Major Adverse Cardiovascular Events Plus
MAX	Maximum
MCC	Merkel Cell Carcinoma
MedDRA	Medical Dictionary for Regulatory Activities
MEN 2	Multiple Endocrine Neoplasia Syndrome Type 2
MET	Metformin
MI	Myocardial Infarction
Min	Minimum
mITT	Modified Intention-To-Treat
MOS	Months
MRHD	Maximum Recommended Human Dose
MRI	Magnetic Resonance Imaging
4MSU	Four Month Safety Update
MTC	Medullary Thyroid Carcinoma
N/A	Not Applicable
NAb	Neutralizing Antibody
NAFLD	Nonalcoholic Fatty Liver Disease
NAI	No Action Indicated
NASH	Nonalcoholic Steatohepatitis
NCT	National Clinical Trial
NDA	New Drug Application
nGIP	Native Glucose-Dependent Insulinotropic Polypeptide
nGLP-1	Native Glucagon-Like Peptide-1
NGSP	National Glycohemoglobin Standardization Program
NHE_1	Sodium-hydrogen exchanger-1
NHE_3	Sodium-hydrogen exchanger-3
NI	Noninferiority
NIM	Noninferiority Margin
NIS	Needle-Based Injection System
NISS	Newly Identified Safety Signal
NOAEL	No-Observed-Adverse-Effect-Level

NR	Not Reported
NYHA	New York Heart Association
OAM	Oral Antihyperglycemic Medication
OBP	Office of Biotechnology Products
ObsRO	Observer Reported Outcome
OCP	Office of Clinical Pharmacology
OCS	Office of Computational Science
ONDP	Office of New Drug Policy
OPMA	Office of Pharmaceutical Manufacturing
OPRO	Office of Regulatory Operations
ORA	Office of Regulatory Affairs
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PAT	Process Analytical Technology
PBL	Postbaseline
PBPK	Physiologically Based Pharmacokinetic
PD	Pharmacodynamics
PeRC	Pediatric Review Committee
PerfO	Performance Outcome
PK	Pharmacokinetic
PLLR	Pregnancy and Lactation Labeling Rule
PMC	Postmarketing Commitment
PMR	Postmarketing Requirement
PO	Oral (‘Per Os’)
PPB	Part Per Billion
PPI	Proton Pump Inhibitor
PQS	Pharmaceutical Quality System
PREA	Pediatric Research Equity Act
Pre-NDA	Pre-New Drug Application
PRO	Patient Reported Outcome
PT	Preferred Term
PV	Process Validation
PY	Patient-Year
PYE	Patient Years at Risk
Q&A	Question and Answer
QD	Once Daily (‘Quaque Die’)
QRG	Quick Reference Guide
QTcF	Fridericia Corrected QT
QW	Once Weekly
RA	Receptor Agonist
REMS	Risk Evaluation and Mitigation Strategy
RTB	Return to Baseline

RTD	Residence Time Distributions
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SC	Subcutaneous
SD	Standard Deviation
SE	Standard Error
SGLT2i	Sodium-Glucose Cotransporter 2 Inhibitor
SMBG	Self-Monitored Blood Glucose
SMQ	Standardized MedDRA Query
SOC	System Organ Class
SOP	Standard Operating Procedures
SPA	Special Protocol Assessment
	(b) (4)
SrCr	Serum Creatinine
SS	Steady State
SU	Sulfonylurea
SUP	Superior
T1/2	Half-Life
T1D	Type 1 Diabetes Mellitus
T2D	Type 2 Diabetes Mellitus
TBL	Total Bilirubin
TEAE	Treatment-Emergent Adverse Event
TIA	Transient Ischemic Attack
ToSNP	Table of Significant and Notable Patients
TQT	Thorough QT
TTT	Treat-To-Target
TZD	Thiazolidinedione
TZP	Tirzepatide
UACR	Urine Albumin-To-Creatinine Ratio
UKPDS	United Kingdom Prospective Diabetes Study
ULN	Upper Limit of Normal
US	United States
USP	United States Pharmacopoeia
USPI	United States Package Insert
USUBJID	Unique Subject Identifier
UTI	Urinary Tract Infection
UV	Ultraviolet
VD	Volume of Distribution
VLDL-C	Very Low-Density Lipoprotein Cholesterol
VS	Versus
W	White

WK	Week
WT	Weight
YR	Year

1. Executive Summary

1.1. Product Introduction

The Applicant, Eli Lilly and Company (Lilly), has submitted a New Drug Application (NDA 215866) requesting approval of tirzepatide (proposed trade name Mounjaro, also known as LY3298176), an injectable antihyperglycemic product, for the indication "as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus." Tirzepatide is a selective, glucose-dependent insulinotropic polypeptide (GIP) receptor and glucagon-like peptide-1 (GLP-1) receptor agonist (RA) intended for once weekly (QW) subcutaneous (SC) administration. This product is the first-in-class to activate both incretin receptor types. By binding to these receptors, tirzepatide enhances first- and second-phase insulin secretion, and reduces glucagon serum concentrations, both in a glucose-dependent manner. In subjects with type 2 diabetes (T2D), tirzepatide lowers fasting and postprandial glucose concentrations, decreases food intake, and reduces body weight.

Tirzepatide is a drug-device combination product that will be marketed as pre-filled single-dose pens for SC administration in the following dose strengths: 2.5 mg, 5 mg, 7.5 mg, 10 mg, 12.5 mg, and 15 mg (each containing 0.5 mL of solution). Following SC administration, the maximum plasma concentrations occur within 8 to 72 hours. The observed mean half-life of approximately five days (116.7 hours) supports the use of a QW dose regimen.[1] Renal and hepatic impairment do not appear to meaningfully affect the pharmacokinetics (PKs) of tirzepatide. As with other approved products with GLP-1 RA activity,[2-11] the use of tirzepatide will be contraindicated in patients with a personal or family history of medullary thyroid carcinoma (MTC) or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2) due to concerns of the risk of thyroid C-cell tumors observed in rodents. Similarly, labeling also will include Warnings and Precautions for the risk of pancreatitis, hypoglycemia with concomitant use of insulin or an insulin secretagogue, hypersensitivity, acute kidney injury, severe gastrointestinal disease, diabetic retinopathy complications, and acute gallbladder disease.

1.2. Conclusions on the Substantial Evidence of Effectiveness

I believe that the Applicant has provided substantial evidence of effectiveness to support approval of tirzepatide for the proposed indication as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

To support the efficacy and safety of tirzepatide for the proposed indication, the Applicant has provided clinical data from nine phase 2/3 clinical trials, of which five global phase 3 trials (GPGH,

GPGI, GPGK, GPGL, and GPGM) were used to demonstrate efficacy. These five multicenter, randomized, double-blind and open-label, placebo- or active comparator-controlled, clinical trials randomized 6,278 subjects with T2D to tirzepatide or comparator, of whom 4,199 received at least one dose of tirzepatide. The efficacy of tirzepatide (5, 10, and 15 mg) was evaluated as monotherapy and in combination with metformin, sulfonylureas (SU), and SGLT2 inhibitors (SGLT2i) alone or combined, and in combination with basal insulin (insulin glargine) with or without metformin. The efficacy of tirzepatide was compared to placebo (trial GPGK as monotherapy and trial GPGI as add-on to insulin glargine), insulin glargine as add-on to metformin and/or a SU and/or a SGLT2i (trial GPGM), insulin degludec as add-on to metformin with or without a SGLT2i (trial GPGH), and semaglutide 1 mg (trial GPGL) as add-on to metformin. The Applicant intends to include all five efficacy trials in Section 14 of product labeling.

Based on the Agency analysis of the primary efficacy endpoint (i.e., mean change in HbA1c from baseline to endpoint [Weeks 40 or 52]), tirzepatide 5, 10, and 15 mg SC QW resulted in statistically significant (all p-values <0.05) and clinically meaningful reductions in HbA1c concentrations compared to the placebo (-1.2 to -1.6% placebo-subtracted) or active comparator (-0.2 to -1.0% comparator-subtracted) in all five trials for all three tirzepatide doses. Key secondary endpoints (adjusted for multiplicity) included the incidence of subjects achieving HbA1c <7% and <5.7%, reductions in fasting serum glucose (FSG; in trials GPGK and GPGI), and reductions in body weight (BW). The average comparator-subtracted reductions in BW ranged from -1.9 to -8.9 kg in the tirzepatide 5 mg arms, -3.6 to -11.5 kg in the tirzepatide 10 mg arms, and -5.5 to -13.2 kg in the tirzepatide 15 mg arms. Except for the incidence of subjects achieving an HbA1c <7% for tirzepatide 5 mg SC QW compared to semaglutide 1 mg SC QW (trial GPGL), all comparisons for key secondary endpoints were supportive (i.e., comparator-subtracted p-values <0.05) across the three tirzepatide doses and five trials.

In summary, the efficacy findings in this NDA were robust, and showed that tirzepatide was statistically superior to placebo, semaglutide, insulin glargine and insulin degludec with respect to the mean change in HbA1c from baseline to endpoint.

1.3. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

Type 2 diabetes (T2D), a metabolic disorder associated with impaired glucose homeostasis, affects approximately 30 million people in the United States (US), and accounts for 90-95% of all diabetes mellitus cases.[12-14] Individuals with T2D typically have insulin resistance, a defect in glucose-stimulated insulin secretion (i.e., a relative insulin deficiency) and/or increased hepatic glucose output due to glucagon dysregulation, resulting in chronic hyperglycemia and an increased risk of microvascular (i.e., retinopathy, nephropathy, neuropathy) and macrovascular (i.e., myocardial infarction, stroke) complications.[13,15,16] Adequate glycemic control (i.e., reduction in HbA1c concentrations) reduces the risk of microvascular complications and may improve macrovascular outcomes.[17] While there are multiple antihyperglycemic drug products approved both as individual drugs and as fixed combination drug products (FCDPs),[17] many patients are often unable to achieve the desired glycemic targets.[18-22]

To support marketing approval of tirzepatide (NDA 215866), a GIP receptor and GLP-1 receptor agonist, the Applicant conducted five global phase 3 clinical trials that evaluated the efficacy and safety of tirzepatide 5, 10, and 15 mg doses administered SC QW as monotherapy and in combination with metformin, SU, and SGLT-2i alone or combined, and in combination with basal insulin with or without metformin. The efficacy of tirzepatide was compared to placebo (trials GPGI and GPGK), insulin glargine (trial GPGM), insulin degludec (trial GPGH), and semaglutide 1 mg (trial GPGL). Based on the Agency analysis of the primary efficacy endpoint (i.e., mean change in HbA1c from baseline to endpoint), the tirzepatide 5, 10, and 15 mg SC QW doses resulted in robust, statistically significant (all p-values <0.05 for superiority) reductions in HbA1c concentrations compared to the comparator arms for all five trials and all three doses. Except for a modest reduction in HbA1c reported in trial GPGL for subjects randomized to the tirzepatide 5 mg arm compared to the semaglutide 1 mg arm (comparator-subtracted reduction of -0.2%, 95% CI: -0.3, -0.0), the improvements in glycemic control for each tirzepatide dose arm were considered clinically meaningful (i.e., all other comparator-subtracted reductions in HbA1c -0.4 to -1.6%).[23]

The safety of this product was primarily based on clinical data from nine completed phase 2/3 clinical trials (AS3) that randomized 5415 subjects to tirzepatide for a total treatment exposure of 4833.1 patient years (PYs). Generally, the safety findings reported in these trials were consistent with the known safety profiles of other products with GLP-1 RA properties.[2-11,24-26] Compared to placebo, higher proportions of subjects experienced the following common AEs (≥5% of subjects): nausea, diarrhea, decreased appetite, vomiting, constipation, dyspepsia, and abdominal pain.

Of concern, there was an increased risk of acute pancreatitis associated with tirzepatide (i.e., 0.11 vs. 0.23 events/100 PY in the placebo and

tirzepatide treatment arms, respectively). This risk is appropriately described in Section 5 (Warnings and Precautions) of proposed labeling. Additionally, the Agency has recently determined that products with GLP-1 RA activity represent a class of products that may have a risk of acute gallbladder disease, and therefore this new safety information will be included in labeling of these products. As tirzepatide was associated with relatively rapid and substantial weight loss across the five global phase 3 trials, and higher numbers of tirzepatide-treated subjects experienced these events (e.g., cholelithiasis, biliary colic, and cholecystectomy), the risk of acute gallbladder disease will be included in Section 5 of labeling.

Except for AEs common to injectable GLP-1 RAs (e.g., gastrointestinal disorders, hypersensitivity reactions, and injection site reactions), numeric imbalances that were both interpretable and clinically meaningful were not observed for other adverse events of special interest (AESI) across the Applicant's phase 2/3 clinical program.

I believe that the overall benefit-risk of tirzepatide for T2D patients is favorable, and that the identified safety concerns can be addressed through labeling and routine pharmacovigilance.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Type 2 diabetes, which affects approximately 30 million people in the United States (US), is a chronic medical condition characterized by insulin resistance and inadequate insulin secretion, resulting in hyperglycemia.[12,13] • Patients with T2D are at increased risk for serious microvascular (i.e., retinopathy, nephropathy, and neuropathy)[27-29] and macrovascular (i.e., myocardial infarction, stroke)[15,30] complications. • Despite known benefits of glycemic control, approximately one-third to one-half of T2D patients in the US fail to achieve recommended treatment goals.[18-22]	Type 2 diabetes mellitus is a serious and life-threatening condition that if left untreated leads to an increased risk of morbidity and mortality.
Current Treatment Options	• There are currently 12 pharmacologic classes of antihyperglycemic medications (generally with multiple members within each class), approved to improve glycemic control in patients with T2D.[17] Many of these medications are also approved as fixed combination drug products (FCDPs).	Despite the many available treatment options, many patients continue to have difficulty achieving adequate glycemic control.[18-22] Further, T2D is a progressive disorder and

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• There are different safety concerns for each class. • National/international medical organizations have generally recommended initiating treatment with lifestyle interventions and metformin, with the choice of additional therapies and/or alternatives based on factors such as baseline cardiovascular (CV) and renal comorbidities, efficacy, hypoglycemia risk, impact on weight, and patient preference, and cost.[17,31-33] • While all approved antihyperglycemic medications for T2D have been shown to improve glycemic control, data on the ability of these agents to improve clinical outcomes in patients with T2D (i.e., adverse CV or renal outcomes) is generally limited to SGLT2i[34-39] or GLP-1 RA products.[2,5,11,40-42]	patients typically need additional agents added as the course of the disease progresses. Several GLP-1 RA products have shown CV benefit,[40-42] and have an indication to reduce the risk of major adverse cardiovascular events (MACE) in adults T2D patients with or at risk of CV disease (CVD).[2,5,11] As the Applicant's CV outcomes trial (CVOT, trial GPGN) is ongoing, tirzepatide is not indicated to reduce the risk of MACE in this population. However, data from the Applicant's CV meta-analysis (CVMA) did not show an increased CV risk.
Benefit	• Five global phase 3 trials, that met the criteria for adequate and well-controlled studies (21 CFR 314.126),[43] were submitted to support marketing approval of tirzepatide. For the primary endpoint (change from baseline in HbA1c at endpoint), the results showed that all tirzepatide doses (5, 10, and 15 mg SC QW) were statistically superior to placebo as monotherapy (-1.6%) or as add-on to insulin glargine (-1.3 to -1.5%), and to semaglutide (-0.2 to -0.5%), insulin degludec (-0.5 to -0.9%), and insulin glargine (-0.8 to -1%). Secondary efficacy endpoints (adjusted for type I error) for these trials (e.g., incidence of subjects with HbA1c concentrations <7% and <5.7%, and reductions in fasting serum glucose, and body weight) demonstrated statistical superiority of the tirzepatide 10 mg and 15 mg doses for all comparisons across all trials, and for the tirzepatide 5 mg dose for all comparisons except when compared to semaglutide 1 mg for the incidence of subjects achieving an HbA1c <7% in trial GPGL.	The submitted clinical trial data provides compelling evidence to support the efficacy of tirzepatide for the proposed indication, as adjunct to diet and exercise to improve glycemic control in adults with T2D. The data from the five global phase 3 trials, which evaluated the use tirzepatide as monotherapy and in combination with other antihyperglycemic products (i.e., metformin, SU, SGLT2i, and/or basal insulin), showed statistical superiority of the tirzepatide 5, 10, and 15 mg treatment arms compared to placebo, semaglutide, and basal insulin (insulin glargine and insulin degludec). Therefore, the benefit of this product would be relevant to many patients with T2D.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	Uncertainties of Benefit: • The trial populations were predominantly White (88%), with underrepresentation of some racial subgroups (e.g., <4% of subjects were Black). • There is limited efficacy and safety data on persons 75 years of age or older (<5% of trial subjects).	Under-representation of some racial subgroups and individuals ≥75 years of age in the adult clinical trials, make it difficult to generalize study results to other patient populations who may benefit from tirzepatide use.
Risk	• The safety findings, based primarily on data from nine phase 2/3 clinical trials, were consistent with those of GLP-1 RA products. • Tirzepatide was associated with higher incidences of nausea, diarrhea, decreased appetite, vomiting, constipation, dyspepsia, and abdominal pain compared to placebo. • Acute pancreatitis was more frequent in the tirzepatide treatment arms. ***Uncertainties for Risks:*** • Tirzepatide has not been studied in patients with severe gastrointestinal (GI) disease. • Limited information is available on the use of tirzepatide in patients with an estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2 or end stage renal disease (ESRD). • No safety data was provided on the risk of diabetic retinopathy complications in patients with a history of nonproliferative diabetic retinopathy requiring acute therapy, proliferative diabetic retinopathy, or diabetic macular edema. • Durations of treatment exposures and follow-up in the clinical trials were not adequate to evaluate long-term safety concerns (e.g., thyroid cancers). • The clinical relevance of abnormal increases in heart rate (HR) observed in Japanese subjects is uncertain.	No new safety findings were observed in the tirzepatide clinical development program. The reported AEs also were consistent with the known safety profiles of GLP-1 RA products and the benefits for the proposed indication notably outweigh these potential risks in the intended patient population. As with GLP-1 RA class labeling, the Warnings and Precautions in proposed tirzepatide labeling will include the risk of pancreatitis, hypoglycemia with concomitant use of insulin or an insulin secretagogue, hypersensitivity, acute kidney injury, severe gastrointestinal disease, diabetic retinopathy complications, and acute gallbladder disease. Tirzepatide has not been studied in patients with severe GI disease (e.g., gastroparesis), and therefore is not recommended in these patients. Additionally, GI AEs (e.g., nausea, vomiting, and diarrhea), if severe, could potentially lead to dehydration, worsening of chronic renal failure, or acute kidney injury (AKI). There is limited

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• The effects of discontinuation of tirzepatide on glycemic control in subjects who develop neutralizing antibodies against native GIP or GLP-1 is unknown. • Risks associated with tirzepatide exposure during pregnancy or breastfeeding is uncertain.	information on the use of tirzepatide in patients with severe renal impairment or ESRD. Subjects at high risk for diabetic retinopathy complications were excluded from study participation in the tirzepatide clinical development program. Since rapid improvement in glycemic control has been associated with a temporary worsening of diabetic retinopathy, patients with a history of diabetic retinopathy should be monitored for further disease progression. The risk of diabetic retinopathy progression is being evaluated in the Applicant's ongoing CVOT. The durations of treatment exposure and follow-up in the completed clinical trials were not sufficient to assess carcinogenic potential of tirzepatide (e.g., thyroid cancers). The Applicant will participate in a MTC registry-based case series study as a postmarketing requirement (PMR). For patients enrolled in studies conducted in Japan, episodes of sinus tachycardia, associated with a concomitant increase from baseline in HR of ≥15 beats per minute were reported in 7% (3/43), 7.1% (3/42), 9.3% (4/43), and 23% (10/43) of patients treated with placebo, tirzepatide 5,

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		10, and 15 mg, respectively. The clinical relevance of heart rate increases is uncertain. In seven phase 3 trials, 2,570 (51.1%) of 5,025 tirzepatide-treated subjects developed antidrug antibodies (ADAs). Although no clinically significant effects of ADAs on the PKs or effectiveness of tirzepatide were observed, more tirzepatide-treated subjects who developed ADAs experienced hypersensitivity reactions or injection site reactions than those who did not develop these antibodies. Additionally, 2% and 2% of the 2,570 ADA positive subjects developed neutralizing antibodies (NAbs) against tirzepatide activity on the GIP or GLP-1 receptors, respectively, and 0.9% and 0.4% developed NAbs against native GIP or GLP-1, respectively. Effects on glycemic control following discontinuation of tirzepatide treatment in subjects who develop NAbs against native GIP or GLP-1 are unknown, as the follow-up period in the clinical trials may not have been adequate assess this risk. There is limited information on the risks of tirzepatide exposure during pregnancy and no information during breastfeeding. The Applicant will conduct a milk-only lactation study to assess tirzepatide concentrations in breast milk as a PMR.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk Management	• No risk evaluation and mitigation strategy (REMS) is recommended for this product.	The identified safety concerns described above can be communicated through labeling and further addressed through routine pharmacovigilance.

1.4. Patient Experience Data

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

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

Patient-reported outcome (PRO) measures were reported for the five global phase 3 trials (GPGK, GPGL, GPGH, GPGM, and GPGI), and included the Ability to Perform Physical Activities of Daily

Living (APPADL), Diabetes Treatment Satisfaction Questionnaire change (DTSQc), Diabetes Treatment Satisfaction Questionnaire status (DTSQs), European Quality of Life Five Dimension Five Level (EQ-5D-5L), Impact of Weight on Self-Perception (IW-SP) and/or Impact of Weight on Quality of Life-Lite Clinical Trials Version (IWQOL-Life-LCT) scores. As these data were considered "other secondary endpoints" or "tertiary/exploratory" endpoints, and not included in the hierarchical testing strategy to control for type I error or intended for proposed product labeling, they were not formally reviewed. For additional information on these data and results, please refer to the respective clinical study reports (CSRs), available at: \\CDSESUB1\evsprod\NDA215866\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\type-2-diabetes-mellitus\5351-stud-rep-contr

2. Therapeutic Context

2.1. Analysis of Condition

Diabetes mellitus is a disease of impaired glucose homeostasis that results in chronic hyperglycemia. There are two main types of diabetes mellitus: type 1 diabetes mellitus (T1D; characterized by autoimmune destruction of pancreatic β-cells and loss of insulin secretion) and type 2 diabetes mellitus (T2D; characterized by β-cell dysfunction, resistance to insulin activity with inadequate insulin production to maintain euglycemia, and increased hepatic glucose output due to glucagon dysregulation).[14,16,44] According to the 2020 National Diabetes Statistics Report, diabetes affects an estimated 34.2 million people within the US, of which T2D accounts for 90-95% of all diagnosed cases (i.e., more than 30 million people).[12] Globally, 537 million adults are living with diabetes, accounting for approximately 10% of the world's adult population.[45] As of 2013, diabetes also is the most expensive medical condition to diagnose and treat in the U.S., accounting for $101.4 billion in healthcare spending.[46]

Patients with T1D may present with classic symptoms of hyperglycemia (e.g., polyuria, polydipsia, nocturia, blurred vision, and diabetic ketoacidosis), while patients with T2D may present similarly but may also be asymptomatic. As a result of chronic hyperglycemia, patients with diabetes mellitus are at an increased risk for microvascular (e.g., retinopathy, nephropathy and neuropathy)[27-29] and macrovascular (e.g., myocardial infarction, stroke) complications.[15,30] For patients with T2D, the presence of microvascular and macrovascular disease are independently associated with a 10-year risk of death, MACE (i.e., nonfatal myocardial infarction, nonfatal stroke, or CV death), and major clinical microvascular events (end-stage renal disease, death due to renal disease, retinal photocoagulation, or diabetes-related blindness), while coexistence of both micro- and macrovascular disease is associated with a 2.0-, 2.9- and 6.3-fold greater risk of these complications, respectively.[47] Diabetes remains a leading cause of kidney failure,[48] adult-onset blindness,[49,50] and non-traumatic lower limb amputations.[51,52] Additionally, people with

diabetes are more than twice as likely to have cardiovascular disease (CVD) or stroke as nondiabetic individuals—and at an earlier age.[53,54] Several reports suggest that CVD may affect approximately 40% of T1D patients over 65 years of age and 32% of persons with T2D.[55] Diabetes was the seventh leading cause of death in 2017,[12] and CVD remains a major cause of death among patients with T2D.[56-58] Additionally, between 2009 and 2015, an increase in diabetes-related lower extremity amputations was observed nationally, annual emergency department visits for hyperglycemic crisis almost doubled (i.e., from 16.2 to 29.4 per 1000), hospitalizations increased by 73% (from 15.3 to 24.2 per 1000), and deaths increased by 55% (from 15.7 to 24.2 per 1000).[59,60] Based on the results of the Diabetes Control and Complication Trial (DCCT),[61-67] the United Kingdom Prospective Diabetes Study (UKPDS),[15,68-71] and the Kumamoto Study,[72] improved glycemic control (as measured using hemoglobin A1c [HbA1c]) is believed to result in improved clinical outcomes.

Heart failure also is a common comorbidity in patients with T2D,[73-77] and is associated with significant morbidity and mortality, even when ejection fraction (EF) is preserved.[78] Compared to non-diabetics, patients with diabetics may have a 2- to 4-fold increase in the risk of HF.[77,79-81] The relatively high risk of heart failure in patients with T2D and the associated morbidity and mortality for individuals with these comorbidities remain important public health concerns, underscoring the need for additional antihyperglycemic therapies to effectively manage diabetes in high-risk patient populations.[82]

2.2. Analysis of Current Treatment Options

Type 2 diabetes mellitus can be treated with a combination of proper diet, exercise, and one or more of the drug products presented in Table 1. The 2015 American Diabetes Association (ADA)/European Association for the Study of Diabetes (EASD) position statement[83] and their 2018[84] and 2019[85] updates advocate the use of a patient-centered approach for the management of T2D, which includes the assessment of glycemic efficacy, hypoglycemia risk, impact on weight, risks for adverse effects, adherence, costs, and patient preference. The 2020 American Association of Clinical Endocrinologist (AACE)/American College of Endocrinology (ACE) consensus statement[32] and the 2017 clinical practice guidelines issued by the U.S. Department of Veterans Affairs/US Department of Defense[33] also support individualized treatment plans based on many of these same factors. Age (e.g., individuals over the age of 65 years[86,87]) and comorbidities (e.g., atherosclerotic CVD, heart failure [HF], and chronic kidney disease [CKD])[17,31] also should be considered and used to guide selection of an antihyperglycemic regimen. The ADA and EASD recommend the use of an sodium-glucose transportor-2 inhibitor (SGLT2i) or a GLP-1 RA with demonstrated CV benefit as part of the antihyperglycemic regimen for T2D patients with established atherosclerotic CVD or indicators of high atherosclerotic CVD risk (e.g., age ≥55 years with coronary, carotid or lower extremity artery stenosis >50%, or left ventricular hypertrophy [LVH]).[17,31] Similarly, the AACE/ACE also recommend the use of an SGLT2i or GLP-1 RA, independent of glycemic control, in patients at high risk for or with established atherosclerotic CVD risk and/or chronic kidney disease.[32] For patients with established kidney disease (e.g., eGFR

≥30 mL/min/1.73 m^2 and urine albumin-to-creatinine ratio [UACR] >300 mg/g),[28] or HF (particularly in individuals with a left ventricular ejection fraction ([LVEF] <45%), the ADA recommends the use of an SGLT2i with proven benefit, independent of baseline HbA1c, individualized HbA1c target or metformin use, and in consideration of the patient-specific factors discussed above.[17]

The ADA and EASD generally recommend initiating antihyperglycemic therapy for the management of T2D with metformin as monotherapy in addition to comprehensive lifestyle modification unless it is contraindicated or not tolerated.[17,31] According to a 2008-2015 Medical Expenditure Panel Survey, approximately 56% of adult diabetics in the US used a single antihyperglycemic medication, of which 51% of these individuals used metformin.[88] Should a single agent alone fail to achieve/maintain the HbA1c target over three months, the next step would be to add a second agent, such as a GLP-1 RA, SGLT2i, dipeptidyl peptidase inhibitor-4 (DPP-4i), thiazolidinedione (TZD), basal insulin, or sulfonylurea (SU), with addition of a third agent should dual antihyperglycemic therapy fail to achieve the desired HbA1c target over the subsequent three-month period.[83] Similar recommendations also have been published in the ADA's Standards of Medical Care in Diabetes–2022,[17] and suggested by the American College of Physicians (ACP)[89,90] and the AACE/ACE.[32]

The AACE/ACE also recommends initiating metformin plus a second antihyperglycemic agent for patients presenting with an HbA1c >7.5%.[32] Additionally, when the HbA1c concentration is ≥1.5-2% above the glycemic target, many patients may benefit from dual combination therapy.[17,91] Early combination antihyperglycemic therapy in some patients may extend the time to treatment failure.[17] In a retrospective cohort study that included patients with an HbA1c ≥8% after at least three months of metformin therapy, earlier antihyperglycemic treatment intensification was associated with lower HbA1c concentrations.[92] A meta-analysis of 15 randomized controlled trials reported potential benefit of initial dual combination therapy with metformin on glycemic outcomes compared to metformin monotherapy across a wide range of baseline HbA1c concentrations in untreated T2D patients.[93] This approach has been reported to be superior to sequential addition of medications for extending primary and secondary failure.[94] Several studies also have reported advantages from adding a third noninsulin agent,[83,95-106] as well as triple therapy with both oral and injectable antihyperglycemic agents.[107-110] Intensive treatment with triple oral antihyperglycemic therapy in newly diagnosed T2D patients also has been shown to have a durable antihyperglycemic effect (i.e., maintenance of β-cell function and glycemic control for ≥6 years).[111]

Over time, due to progressive loss of β-cell function (i.e., decreased insulin secretion), many patients with T2D may require and benefit from the addition of insulin therapy.[17,112] Initiation of insulin therapy also may be considered earlier when hyperglycemia is severe (e.g., blood glucose is ≥300 mg/dL or hemoglobin A1c [HbA1c] >10%), hyperglycemic symptoms (e.g., polyuria or polydipsia) are present, or there is evidence of increased catabolism (e.g., weight loss, hypertriglyceridemia, or ketosis).[17] The ADA recommends that metformin be continued upon

initiation of insulin therapy for ongoing glycemic and metabolic benefits, unless it is contraindicated or not tolerated.[17] If the basal insulin dose has been titrated to an acceptable fasting blood glucose (FBG) concentration or is >0.5 units/kg/day and the HbA1c remains above the desired glycemic target, the ADA suggests that the use of combination therapy with a GLP-1 RA as add-on to insulin therapy could be considered to improve efficacy and durability of the treatment effect.[17] In patients with T2D, a GLP-1 RA is preferred to insulin when possible.

Table 1: Approved Therapeutic Options for the Management of Type 2 Diabetes Mellitus

Pharmacologic Class	Antihyperglycemic Drug Products
Alpha-Glucosidase Inhibitors	Acarbose; Miglitol
Amylin Mimetics	Pramlintide
Biguanides	Metformin
Bile Acid Sequestrants	Colesevelam
Dopamine-2 Agonists	Bromocriptine
DPP-4 Inhibitors	Alogliptin; Linagliptin; Saxagliptin; Sitagliptin
GLP-1 Receptor Agonists	Albiglutide; Dulaglutide; Exenatide; Exenatide extended-release; Liraglutide; Lixisenatide, Semaglutide
Insulins and Insulin Analogues	Inhaled insulin human; Insulin aspart: Insulin aspart protamine plus insulin aspart; Insulin degludec; Insulin degludec plus insulin aspart; Insulin detemir; Insulin glargine; Insulin glulisine; Insulin isophane (NPH); Insulin isophane plus regular; Insulin lispro; Insulin lispro protamine plus insulin lispro; Insulin regular (human); Premixed insulins (various)
Meglitinides	Nateglinide; Repaglinide
SGLT2 Inhibitors	Canagliflozin; Dapagliflozin; Empagliflozin, Ertugliflozin
Sulfonylureas	Chlorpropamide; Glimepiride; Glipizide; Glipizide extended-release; Glyburide; Tolazamide; Tolbutamide
Thiazolidinediones	Pioglitazone; Rosiglitazone

Source: Drugs@FDA: FDA Approved Drug Products, available at: http://www.accessdata.fda.gov/scripts/cder/daf/
Abbreviations: DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; and SGLT2, sodium-glucose cotransporter 2.

A summary table of approved GLP-1 RA products is also presented in Appendix 13.2.

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

MOUNJARO (tirzepatide)

Tirzepatide is a new molecular entity that is a selective, glucose-dependent insulinotropic polypeptide (GIP) receptor and glucagon-like peptide-1 (GLP-1) receptor agonist. This product is the first-in-class to activate both incretin receptor types. It is a 39-amino acid peptide with a C20 fatty diacid moiety that enables albumin binding and prolongs the half-life. Tirzepatide has been shown to selectively bind to and activate both the GIP and GLP-1 receptors in vitro. In humans, tirzepatide enhances the first- and second-phase insulin secretion rate, reduces fasting and postprandial glucagon concentrations, and delays gastric emptying. In subjects with T2D, tirzepatide administration is associated with dose-dependent decreases in fasting and postprandial glucose concentrations and reductions in body weight.

In addition to the proposed indication for this NDA (i.e., as an adjunct to diet and exercise to improve glycemic control in adults with T2D), (b) (4)

Tirzepatide is currently not marketed in any country. Approved GLP-1 RA products include:

- Albiglutide (BLA 125431, TANZEUM, approved April 15, 2014; discontinued)[113]
- Dulaglutide (BLA 125469, TRULICITY, approved September 18, 2014)[114]
- Exenatide extended-release (NDA 022200, BYDUREON, approved January 27, 2012; discontinued)[115]
- Exenatide extended-release (NDA 209210, BYDUREON BCISE, approved October 20, 2017)[116]
- Exenatide (NDA 021773, BYETTA, approved April 28, 2005)[117]
- Liraglutide (NDA 022341, VICTOZA, approved January 25, 2010)[118]
- Liraglutide (NDA 206321, SAXENDA, approved December 23, 2014)[119]
- Liraglutide plus insulin degludec (BLA 208583, XULTOPHY, approved November 21, 2016)[120]
- Lixisenatide (BLA 208471, ADLYXIN, approved July 27, 2016)[121]
- Lixisenatide plus insulin glargine (BLA 208673, SOLIQUA 100/33, approved November 21, 2016)[122]
- Semaglutide (NDA 209637, OZEMPIC, approved December 5, 2017)[123]
- Semaglutide (NDA 213051, RYBELSUS, approved September 20, 2019)[124]
- Semaglutide (NDA 215256, WEGOVY, approved June 4, 2021)[125]

Please refer to Appendix 13.2 (Table 57) for more detailed product-specific information.

3.2. Summary of Presubmission/Submission Regulatory Activity

The relevant regulatory history for tirzepatide included in this NDA is presented in Table 2. The IND for this product (IND 128801) was opened on March 29, 2016. At the End-of-Phase 2 (EOP2) meeting (September 6, 2018), the Agency recommended that the Applicant include adequate numbers of subjects with renal impairment in the tirzepatide clinical development program and provided a list of adverse events of special interest (AESI) which the Applicant agreed to assess. The Agency felt that the key design features of the five global phase 3 trials were reasonable but recommended extending the trial durations to provide at least 18 weeks of exposure at the planned tirzepatide dose. At the pre-NDA meeting (June 24, 2021), the Agency also felt that the clinical data package would be sufficient to review the Application, and the NDA was submitted on September 15, 2021.

Table 2: Summary of Relevant Presubmission/Submission Regulatory History

Date of Interaction	Description of Regulatory Interaction
March 29, 2016	**Applicant Submission:** Tirzepatide initial Investigational New Drug (IND 128801) application was filed on April 28, 2016.
August 1, 2018	**Type C Meeting:** FDA Written Responses Only to a meeting request Applicant submitted on May 24, 2018, and subsequently granted by FDA on June 11, 2018, regarding tirzepatide's Tier 1-3 method validation and the NAb assay development and validation. • FDA agreed that the multitiered antidrug antibody (ADA) testing strategy described in the Briefing Document is consistent with Agency recommendations • FDA indicated that the approach to validating Tier 1-3 immunogenicity assays was reasonable FDA agreed that the format and testing strategy of Tier 4 cell-based NAb assays were reasonable and that it is appropriate for the Tier 4 validation work to be completed
July 13, 2018	**FDA Advice/Information Request:** Request for submission of the characterization of the genotoxicity potential of tirzepatide, including an assessment in an in vivo assay in a mammalian species for the Active Pharmaceutical Ingredient (API), unless evidence that all nonpeptide moieties in tirzepatide have already been appropriately qualified per the International Council for Harmonization (ICH). An additional request for an assessment of the genotoxicity potential of nonpeptide impurities related to synthesis of the API should also be included.
July 23, 2018	**FDA Information Request:** FDA request to have a *Highlights of Clinical Pharmacology and Cardiac Safety* table filled out for tirzepatide.
July 26, 2018	**Applicant Regulatory Response:** Submission of Highlights of Clinical Pharmacology and Cardiac Safety Table as requested by FDA on July 23, 2018.
13 August 2018	**Applicant Regulatory Response:** Submission of regulatory response document containing a proposed study design to conduct an in vivo rat bone marrow micronucleus study to characterize genotoxicity potential.

Date of Interaction	Description of Regulatory Interaction
September 6, 2018	**End of Phase 2 (EOP2) Meeting:** Applicant submitted a Type B meeting request on June 15, 2018, to discuss development plans for phase 3. The meeting was subsequently granted as a face-to-face meeting by FDA on July 3, 2018. Official Meeting Minutes were dated October 5, 2018. Briefing Material for the meeting was submitted on July 17, 2018. Key Topics: • Nonclinical Safety o FDA found the nonclinical safety program generally acceptable, requesting characterization of the genotoxicity potential of tirzepatide, an evaluation of the metabolic fate of the organic linker with a hazard assessment, and an assessment of conduction abnormalities in monkeys. The Applicant agreed. • Clinical Pharmacology o FDA found the proposed clinical pharmacology studies reasonable. o FDA requested a separate interaction to discuss physiologically based pharmacokinetic (PBPK) model for evaluation of potential drug-drug interaction (DDI) and rationale for DDI studies. o FDA recommended combining all PK data from phase 1 to 3 studies for the final population PK analysis. The Applicant agreed. o FDA recommended that the Applicant conduct in vitro evaluation (human ether-a-go-go related gene [hERG] assay) which Applicant agreed to. FDA agreed that safety electrocardiogram (ECG) collection at Week 26 is acceptable. Clinical Development o FDA requested that the development program ensures adequate numbers of subjects with various stages of renal impairment are enrolled. The Applicant agreed. o FDA provided a recommended list of prespecified adverse events of special interests (AESIs), which the Applicant agreed to. o FDA commented that the key design aspects of the 5 individual phase 3 glycemic control studies appear to be reasonable, recommending extending trial durations to provide at least 18 to 24 weeks of exposure to tirzepatide. The Applicant agreed. o FDA agreed that the proposed immunogenicity sampling and assessment appears reasonable. o FDA recommended increasing the targeted number of major adverse cardiovascular events-4 (MACE-4) in the primary database to 133 events to rule out the 1.8 risk margin. The Applicant agreed. • Statistics o FDA recommended against an interim analysis of trial GPGN (SURPASS-CVOT) to help rule out the 1.8 risk margin. o FDA found the proposed primary efficacy analysis and the method of dealing with missing data acceptable, noting alternative analyses may be needed should not enough retrieved dropouts be available for a reliable imputation model. • Device o FDA agreed to the use of 5 mg dosage strength in the planned

Date of Interaction	Description of Regulatory Interaction
	device PK comparability study, noting the use of the single-dose PK comparison and population PK analysis from the phase 3 studies to support PK comparability between prefilled syringe and the autoinjector is reasonable. • Efficacy Measurement, Incidence of Hemoglobin A1c (HbA1c) Target o FDA commented sufficient evidence would need to be provided to justify why observed differences between treatment arms for the proposed exposure durations are clinical meaningful with respect to incidence of subjects achieving an HbA1c <5.7%. • Additional Comments o FDA commented on the importance that the phase 3 program adequately evaluate subjects for diabetic retinopathy. o FDA recommended including HbA1c rescue criteria for persistent hyperglycemia. The Applicant agreed. o FDA recommended serum bicarbonate concentration be measured as part of the clinical chemistry panel. The Applicant agreed. o FDA agreed with the Applicant's proposal not to use pancreatic enzyme elevations as an exclusion criterion in Phase 3 studies. o FDA recommended adequate documentation on the use of antiemetic or antidiarrheal medications to manage gastrointestinal symptoms. The Applicant agreed to document use as concomitant medications with documentation of study drug interruptions and dose reductions due to intolerable/persistent GI adverse events.
November 5, 2018	**Applicant Submission:** Initial Pediatric Study Plan (iPSP) was submitted to the IND.
December 20, 2018	**Applicant Submission:** Request for Special Protocol Assessment (SPA) for a carcinogenicity study protocol entitled "Selection of Doses for a 2-Year Rat Carcinogenicity Study with Tirzepatide (LY3298176)."
January 8, 2019	**FDA Advice/Information Request:** FDA sent the Applicant 2 Advice/Information Request letters. One letter was regarding the CV meta-analysis (CVMA) and the other regarding clinical Study I8F-MC-GPGM. CVMA: • Request submission of an updated meta-analysis statistical analysis plan to address the CV safety and test the prespecified hazard ratio margin of 1.8 for MACE-4. Study I8F-MC-GPGM: • Request submission of the statistical analysis plan of the CVMA Request clarification whether the tirzepatide titration scheme used in trial GPGM will be the same across the phase 3 clinical development program.
January 16, 2019	**Applicant Regulatory Response:** In their response to FDA Information Requests (dated January 8, 2019), the Applicant committed to submitting the statistical analysis plan (SAP) for the CVMA once complete. The Applicant also confirmed that the dose escalation used in Study GPGM is used across all phase 3 clinical trials.
January 31, 2019	**FDA Communication:** FDA provided the Applicant the Executive Carcinogenicity Assessment Committee (CAC) Protocol Minutes for the Applicant's December 20, 2018, carcinogenicity SPA. The committee had the following

Date of Interaction	Description of Regulatory Interaction
	recommendations: • Doses of 0, 0.15, 0.5, and 1.5 mg/kg (twice weekly) for both males and females with the high dose based on the maximum tolerated dose (MTD) in the 6-month toxicology study. • Mid and low doses for both males and females were based on one-third area under the concentration-time curve (AUC) exposure margin increments. If there are survival issues during the study, the Applicant should contact the Division before any changes are made.
February 1, 2019	**FDA Communication:** FDA's *initial Pediatric Study Plan (iPSP) – Written Response* to Applicant's iPSP submission (dated November 5, 2018).
February 13, 2019	**FDA Advice/Information Request:** FDA requested clarification why the Applicant did not intend to recycle all unused alpha to the side with nonsignificant testing results as outlined in the SAP for trial I8F-MC-GPGM.
February 26, 2019	**Applicant Regulatory Response: The** Applicant's response to FDA's Information Request (dated February 13, 2019) in which the Applicant indicated the trial GPGM SAP will be updated to reflect the changes necessary to address FDA's comments.
March 20, 2019	**FDA Advice/Information Request:** FDA requested clarification on the purpose of 2 substudies for Study I8F-MC-GPGH (Addendum #1 and Addendum #2).
April 2, 2019	**Applicant Regulatory Response:** In their response to FDA's Information Request (dated March 20, 2019), the Applicant indicated the addenda are for publication, and scientific interest and will not be used for regulatory purposes. The Applicant noted that Addendum #2 could provide additional information to further understand the metabolic profile of tirzepatide and its pharmacodynamic effects.
April 11, 2019	**Applicant Submission:** The Applicant submitted a Request for Comments to continue discussions held at the EOP2 Meeting regarding their planned approach to (1) utilize integrated model-based approaches to evaluate potential DDI (PPBK modeling for DDI evaluation of tirzepatide), and (2) the dose of tirzepatide to be used in a proposed oral contraceptive DDI study.
April 24, 2019	**Applicant Submission:** Responses to FDA's *iPSP – Written Response* (dated February 1, 2019). The revised iPSP and accompanying regulatory response document addressed development timelines, consideration for a long-term open-label safety study, and certain study design changes.
May 6, 2019	**Applicant Submission:** Agreed iPSP submitted at FDA's request. It is noted that the request was made to keep with statutory timelines and process for iPSPs and that the resubmission of the iPSP documents contained herewith does not constitute agreement at this time.
June 5, 2019	**FDA Communication:** FDA Agreed iPSP – No Agreement Letter. Topics of nonagreement include the following: • Pediatric nonclinical and clinical development timelines • Request for additional details on the proposed placebo borrowing approach • Proposed Human Factors (HF) plan
June 28, 2019	**Type C Meeting:** FDA Written Responses Only to a meeting request the Applicant submitted on April 19, 2019, and subsequently granted by FDA on May 2, 2019, regarding tirzepatide's NAb assay validation and the

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	implementation of an in silico method to classify cross-reactive NAb. Briefing Material for the meeting was submitted on May 19, 2019. • FDA agreed that the Tier 4 cell-based NAb assays appear suitable, noting that a comprehensive review will occur during review of the NDA • FDA agreed in general that the proposed in silico method is appropriate for classifying cross-reactive neutralizing ADA, noting a final determination will be a review issue FDA agreed in general with implementing the in silico method for classifying cross-reactive NAb and with the discontinuation of the Tier 4c and 4d assays, noting FDA may propose an alternative approach to classifying cross-reactive NAb based on the results
July 11, 2019	**FDA Advice/Information Request:** FDA responses to the Applicant's April 11, 2019, request for comments on plans to use integrated model-based approaches to evaluate the potential effect of tirzepatide on gastric emptying time and thus drug-drug interactions, and dose justification for a planned oral contraceptive study. • FDA commented the proposed modeling approach is reasonable from a PBPK methodology perspective, noting a definitive determination can only be provided during review. • FDA provided comments on the submitted PBPK-related files, which should be addressed in the NDA submission • FDA agreed that the dose of tirzepatide in the proposed oral contraceptive DDI study was reasonable, noting the adequacy of the data and the results will be a review issue.
August 8, 2019	**Applicant Submission:** Updated iPSP with revisions to the Agreed iPSP submitted on May 6, 2019, and a Regulatory Response addressing FDA's nonagreement comments (dated June 5, 2019).
November 15, 2019	**FDA Communication:** iPSP responses to the Applicant's August 2019 updated iPSP. Topics of nonagreement included the development program's timelines and the proposed placebo-borrowing approach.
November 25, 2019	**Applicant Submission:** In an email communication to the Center for Drug Evaluation and Research's (CDER's) Emerging Technology Team (ETT), the Applicant requested a Type C meeting to discuss the tirzepatide program's participation in the FDA Emerging Technology Program.
December 6, 2019	**FDA Communication: T**he FDA ETT confirmed (via email correspondence) the tirzepatide program's acceptance into the Emerging Technology Program.
December 18, 2019	**Applicant Submission:** Request for SPA for a carcinogenicity study protocol entitled "A Carcinogenicity and Toxicokinetic Study in 001178 RasH2 Mice Administered LY3298176 Twice Weekly by Subcutaneous Injection for 26 Weeks."
January 24, 2020	**FDA Communication:** FDA provided the Applicant the Executive CAC Protocol Minutes for their carcinogenicity SPA (dated December 18, 2019). The committee had the following recommendations: • Addition of a saline or water control group. • Doses of 0 (water/saline), 0, 1, 3, and 10 mg/kg twice weekly for both males and females with the high dose based on mortality at 30 mg/kg twice weekly in the 1-month toxicity study.

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	• Mid and low doses for both were selected to provide adequate AUC spacing between dose levels. • Dose volume administered should be equal for all dosing groups. • Diet supplementations should not be administered to control animals. • If the dietary supplementation is switched from DietGel to some other form, the doses may not be considered appropriate if the body weight effects differ from those observed in the dose-range finding study conducted with DietGel. If there are survival issues during the study, the Applicant should contact the Division before any changes are made.
February 5, 2020	**Applicant Submission:** Revised iPSP based on FDA agreeing with the proposed pediatric timelines proposed in the Applicant's August 8, 2019, iPSP – Other submission and disagreeing with the proposal to borrow historical placebo data from trial H9X-MC-GBGC (AWARD-PEDS) as indicated in an email communication (dated December 16, 2019).
February 14, 2020	**Applicant Communication:** In an email communication, the Applicant requested advice from FDA regarding trial I8F-MC-GPGN (SURPASS-CVOT) and the handling of inadvertently enrolled patients and their data relative to preservation of the intent-to-treat principle. Specifically, the Applicant proposed to discontinue such patients not only from study treatment but also from the study to harmonize between global regulatory authorities. The new primary efficacy analysis would be based on a modified intention-to-treat (mITT) population excluding inadvertently enrolled subject data (even if the subject is treated and/or experienced an event). The Applicant proposed conducting a sensitivity analysis, which would include these subjects' endpoint data, should there be any before discontinuation.
February 21, 2020	**FDA Communication:** In response to the Applicant's February 14, 2020, inquiry, FDA noted the following: as the SURPASS-CVOT is a blinded study, if the discontinuation decision is not based on any outcome-related observations, then discontinuation of these patients is acceptable. We agree with your proposal to conduct a sensitivity analysis as described and with your plan to take every possible measure to minimize inadvertent enrollment.
March 5, 2020	**Applicant Submission:** A final Agreed iPSP was submitted after FDA agreement was received in an email communication on March 3, 2020.
March 26, 2020	**Type C Meeting:** Teleconference with FDA under the Emerging Technology Program based on a meeting request Lilly submitted on January 8,2020, and subsequently granted by FDA on January 31, 2020, to discuss drug substance manufacturing approach being used with tirzepatide. • FDA found the outlined start up, shutdown, start of collection, and state of control approaches planned for tirzepatide to be reasonable, noting a conclusive comment could not be provided as the final commercial process control strategy was pending further development work. • FDA commented that Applicant should clearly define "state of control" and specifically list all operations and controls that will be used for product release decisions. • FDA commented that a better picture of the control strategy was

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	needed detailing the relationship between the parametric controls and the Process Analytical Technology (PAT) explaining their interrelationship to enable FDA evaluation of each control point. • FDA agreed with a medium-impact classification of the material tracking model and with the Applicant's proposed risk-based model verification approach. Furthermore, reporting categories for model changes could be risk-based to determine potential impact on product quality. • FDA expressed interest and instructed the Applicant to make a formal request for an "ETT Site Visit" for a Preoperational Visit at its drug substance manufacturing facility.
March 31, 2020	**FDA Communication:** In an email communication, FDA responded to Applicant's March 26 consultation request, indicating that the team has reviewed the information provided and found the proposed amendments acceptable without any further comments.
April 1, 2020	**FDA Communication:** Agreement letter containing the Agreed iPSP.
April 22, 2020	**FDA Advice/Information request:** FDA had the following comments and requests for trial I8F-MC-GPGR: • Clarify whether the study intends to enroll and expose subjects with Common Terminology Criteria for Adverse Events (CTCAE) Grade 2 hypertriglyceridemia to 3-months of ethinyl estradiol/norgestimate. • Consider PK sampling for norelgestromin and norgestrel to 72 hours after the last oral contraceptive dose, noting the proposed PK sampling for 48 hours postdose may not be adequate and results in the extrapolated AUC from last measurable oral contraceptive concentration to infinity to be more than 20% of the AUC(0-∞).
April 24, 2020	**Type C Meeting:** FDA Written Responses Only to a meeting request the Applicant submitted on March 26, 2020, and subsequently granted by FDA on April 13, 2020, regarding a proposed interim analysis to the CVMA and the applicability of FDA's new draft T2D guidance for industry to the tirzepatide development program. Briefing Material for the meeting was submitted on April 13, 2020. • FDA found the proposed interim analysis of trial GPGM and the proposed CVMA to rule out a risk margin of MACE-4 greater than 1.8 generally acceptable. • FDA commented that the proposed stratified analysis with 2 strata (GPGM, and all other trials) was acceptable. • FDA recommended that Applicant submit a data access plan (DAP) for trial GPGM. • FDA noted that the current tirzepatide development program pertaining to the size of the proposed safety database and patient characteristics are reasonable for submitting an NDA, provided there are no new safety issues.
April 30, 2020	**Applicant Submission:** Regulatory Response to FDA's trial GPGR information request (dated 22 April 2020). The Applicant noted that it will amend the protocol to exclude healthy participants with a serum triglyceride level >300 mg/dL at screening and proposes to change the current primary endpoints from AUC(0-∞), AUC(0-tlast), and maximum plasma concentration (C_{max}) to

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	AUC(0-tau), AUC(0-tlast), and C_{max}.
May 5, 2020	**Type C Meeting Minutes:** FDA issued the official meeting minutes of the Emerging Technology Program teleconference held on March 26, 2020.
August 21, 2020	**FDA Advice/Information Request:** FDA letter containing comments and requests related to protocol amendments submitted on July 31, 2020, for trials GPGH, GPGI, GPGL, GPGM in response to the COVID-19 pandemic.
August 27, 2020	**Type C NDA Logistics Meeting:** FDA Written Responses Only to a meeting request the Applicant submitted on June 15, 2020, and subsequently granted by FDA on June 17, 2020, to obtain feedback on the analysis plans and administrative topics supporting the NDA, including the table of contents for the NDA, criteria for notable events, and formatting of the TOSNP/patient narratives. FDA agreed that an integrated efficacy database and ISE will not be required for the NDA based on the rationale that pooling of the data across studies would not be informative due to difference between the studies (e.g., background therapies, treatment durations, patient characteristics, and comparators).
September 9, 2020	**FDA Advice/Information Request:** FDA advice letter issued in response to a 03 September 2020 Applicant submission (Sequence #0116) in which Applicant requested feedback on a proposal to terminate Study 8392734, "A Carcinogenicity and Toxicokinetic Study in Rats Administered Ly3298176 Twice Weekly by Subcutaneous Injection for 104 Weeks." In the letter, FDA recommended stopping should occur when the number of rats of a sex within the control group declined to 20 animals.
September 28, 2020	**Applicant Submission:** Regulatory Response to FDA August 21, 2020, COVID-19 protocol amendment advice/information request letter. The submission also included the requested GPGM and GPGH Data Monitoring Committee (DMC) charters, and the CVMA SAP.
September 30, 2020	**Applicant Submission:** Regulatory Responses to FDA's August 27, 2020, Type C NDA Logistics Meeting Minutes regarding feedback on the analysis plans and administrative topics supporting an NDA submission. The Applicant provided and sought clarifications and updated submission plans in response to specific FDA comments. Topics included updated plans and responses to FDA comments on: • Listings noted in the Biopharmaceutics and Clinical Pharmacology Integrated Summary of Safety • Applicant agreement to provide tables with summaries of participants' historical and preexisting conditions specific to diabetes complications, CV disease, and gallbladder disease • Applicant agreement to use multiple imputations guided by "retrieved dropouts" • Applicant's updated plans for providing a TOSNPs, notable events, and patient narratives • Applicant's agreement to submit programs for efficacy estimand analyses and sensitivity analyses of primary endpoints if conducted. The Applicant also agreed to submit the Pinnacle 21 validation report prior to the NDA if time permitted • Applicant's updated plans for the 4-month safety update

Date of Interaction	Description of Regulatory Interaction
	(4MSU).
October 20, 2020	**FDA Advice/Information Request:** FDA letter made in response to the Applicant's September 28, 2020, COVID-19 Regulatory Response in which FDA noted concerns about the use of an internal Data Monitoring Committee (DMC) for trials GPGH and GPGM and requested the Applicant to provide justification for why an independent DMC was not necessary or possible.
October 26, 2020	**FDA Advice/Information Request:** FDA responses to the Applicant's September 30, 2020, Regulatory Response, which provided clarifications and updated submission plans based on FDA's August 27, 2020, NDA Logistics Written Responses. FDA provided further comment on their request for Analysis Dataset Model (ADaM) datasets for phase 1 studies. In an email communication, FDA noted no additional comments on the other topics the Applicant provided in the Regulatory Response and could therefore consider there to be alignment on those items.
November 10, 2020	**Applicant Submission:** Regulatory Response to FDA's October 20, 2020, GPGH and GPGM DMC charter advice/information request letter. The response provided Applicant's justification for continued use of an internal DMC for the referenced studies.
November 9, 2020 & November 12, 2020	**Virtual ETT Site Visit under Emerging Technology Program:** Teleconference with FDA under the Emerging Technology Program that consisted of two 3-hour teleconferences on November 9th and 12th. A premeeting briefing document was submitted to ETT via an email on October 2, 2020. The meetings consisted of a series of virtual presentations and videos of the tirzepatide continuous manufacturing (CM) operations focused on openly sharing process information and allowing FDA ETT question and answer (Q&A) dialogue. Topics covered included (1) overview of critical quality attributes (CQAs) and major impurity classifications; (2) integrated process control strategy; (3) site Pharmaceutical Quality System (PQS) topics of batch definition, investigations, and process validation (PV) strategy; and (4) residence time distributions (RTD) and material tracking model development and verification. The Applicant did not formally seek answers to specific questions but was instead focused on ensuring ETT understood the tirzepatide CM process in preparation for planned NDA submission in the third/fourth quarter (Q3/Q4) of 2021.
November 19, 2020	**FDA Advice/Information Request:** FDA comments and request for additional information related to the Applicant's September 29, 2020, amendment containing the statistical analysis plans for trial I8F-MC-GPHD and I8F-MC-GPGI. FDA disagreed with the proposed subgroup analyses using the efficacy estimand for trials GPGI and GPHD, requesting subgroup analyses by age, gender, race, and region based on the treatment-regimen estimand.
December 1, 2020	**FDA Advice/Information Request:** FDA recommendation to use an external DMC in future studies. The letter was issued in response to the Applicant's November 10, 2020, DMC response.
December 2, 2020	**Applicant Submission:** Regulatory Response to FDA's November 19, 2020, letter. The Applicant agreed to the additional subgroup analysis, and also noted plans to update the SAP for trial GPGI prior to database lock.
December 15, 2020	**FDA Advice/Information Request:** FDA request for a comparison of 3 degradation products used in toxicology study No. 8394210 and in the clinical

Date of Interaction	Description of Regulatory Interaction
	batches.
December 18, 2020	**Applicant Submission: The** Applicant request for FDA review of tirzepatide's HF Validation Study protocol.
December 21, 2020	**Applicant Submission:** Request for a Type C meeting to obtain feedback on the Applicant's planned approach to use interface differentiation of the tirzepatide combination product with the proposed container label and secondary packaging carton. This Type C meeting was denied by FDA in a letter dated January 7, 2021; however, FDA committed to provide responses to Applicant's questions as part of the HF protocol advice letter.
January 28, 2021	**FDA Letter:** FDA letter issuing the preassigned NDA number as 215866.
January 29, 2021	**Applicant Submission:** Regulatory Response to FDA's December 15, 2020, degradation products information request.
February 1, 2021	**FDA Advice/Information Request:** FDA letter agreeing with the Applicant's plans to move the remaining DMC reviews for trials GPGH and GPGM to an external DMC as indicated in an email communication by Applicant on January 11, 2020. FDA requested confirmation that internal DMC members will no longer be involved. The Applicant confirmed that the former internal DMC members will not be involved in DMC activities in a submission dated February 3, 2021.
April 1, 2021	**FDA Advice Letter:** FDA letter noting identified issues and recommendations based on their review of the HF validation study protocol. Applicant accepted FDA's recommendations.

June 24, 2021	**Pre-NDA Meeting: The** Applicant submitted a Type B meeting request on April 26, 2021, to gain agreement that the proposed NDA submission provides a complete application in support of filing and approval of tirzepatide. The meeting was subsequently granted as a teleconference by FDA on May 4, 2021. Official Meeting Minutes were dated July 23, 2021. Briefing Material for the meeting was submitted on May 24, 2021. Key topics and agreements are captured below with more detailed information provided in the Annotated Meeting Minutes found in Module 1.6.3.
	• Chemistry, Manufacturing, and Control
	  ○ FDA agreed the proposed organization of Module 3 is suitable for review.
	• Nonclinical
	  ○ FDA agreed that the scope of the nonclinical information described should be sufficient to support review of the NDA.
	  ○ FDA requested rationale be included in the NDA for conducting chronic studies in non-rodents of 6-months in duration.
	• Clinical Pharmacology
	  ○ FDA found the biopharmaceutics and clinical pharmacology packages sufficient to support filing of the tirzepatide NDA.
	  ○ FDA recommended several topics to be addressed in the Clinical Pharmacology section of the NDA.
	• Clinical
	  ○ FDA found the clinical data package to be sufficient to review the NDA submission. FDA also provided Additional Comments to help facilitate their review.
	• Administrative
	  ○ FDA noted that while the final determination of whether a Risk

Date of Interaction	Description of Regulatory Interaction
	Evaluation and Mitigation Strategy (REMS) will be required is a review issue, it appeared, based on data provided to-date, that additional risk management strategies beyond the recommended labeling may not be necessary. ○ Based on review of the draft Table of Contents, FDA found the planned contents of the NDA to be sufficient for filing of the application. ○ FDA and Applicant agreed to submission of the 120-Day Safety Update approximately 90 days of the NDA submission, and if subsequently requested would provide datasets where available. ○ FDA noted that an Advisory Committee is not anticipated at this time. ○ FDA provided feedback on the updated Study Data Standardization Plan which the Applicant clarified prior to the meeting. • Additional Comments ○ FDA had several additional requests pertaining to clinical and statistical trial materials which would be included in the NDA submission. The Applicant and FDA reached agreement on these materials as noted in the Annotated Meeting Minutes. ○ FDA and Applicant agreed that a complete application will be provided in the original submission, and that no major components are subject for late submission.
July 15, 2021	**FDA Advice Letter:** As agreed to in the Pre-NDA meeting, on July 2, 2021, the Applicant submitted a Request for Comments pertaining to FDA Additional Comments #7 and #13. FDA found the proposed list of programs and detailed flow chart adequate to meet their request from the Pre-NDA meeting.
July 28, 2021	**FDA Communication:** In an email dated July 28, 2021, as a follow-up to the Pre-NDA Meeting Minutes, FDA agreed that integration of Phase 2 and Phase 3 notable events into a single ToSNP would be acceptable.

Source: Adapted from the Applicant's Regulatory History document, available at: \\CDSESUB1\evsprod\nda215866\0001\m1\us\note.pdf

Abbreviations: 4MSU, four-month safety update report; A1c, HbA1c; ADA, anti-drug antibody; ADaM, Analysis Dataset Model; AESI, adverse event of special interest; API, Active Pharmaceutical Ingredient; AUC, area under the concentration-time curve; AUC(0-∞), area under the plasma concentration-time curve from time 0 to infinity; AUC(0-tau), area under the concentration-time curve within a dosing interval where tau is the dosing interval; AUC(0-tlast), area under the concentration-time curve from time 0 to time of last measurable concentration; CAC, Carcinogenicity Assessment Committee; CDER, Center for Drug Evaluation and Research; CM, continuous manufacturing; Cmax, maximum plasma concentration; CQA, critical quality attributes; COVID-19, coronavirus disease 2019; CTCAE, Common Terminology Criteria for Adverse Events; CV, cardiovascular; CVMA, cardiovascular meta-analysis; CVOT, cardiovascular outcomes trial; DAP, data access plan; DDI, drug-drug interaction; DMC, data monitoring committee; ECG, electrocardiogram; EOP2, end of phase 2; ETT, Emerging Technology Team; FDA, Food and Drug Administration; GI, gastrointestinal; HbA1c, glycosylated hemoglobin A1c; hERG, human ether-a-go-go related gene; HF, Human Factors; ICH, International Council for Harmonization; IND, Investigational New Drug; iPSP, initial pediatric study plan; ITT, intent-to-treat; MACE-4, major adverse cardiovascular events (death due to CV causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for unstable angina); MTD, maximum tolerated dose; Nab, neutralizing antibody; NDA, new drug application; PAT, Process Analytical Technology; PBPK, physiologically based pharmacokinetic(s); PK, pharmacokinetic(s); PQS, Pharmaceutical Quality System; PV, process validation; Q&A, questions and answers; REMS, Risk Evaluation and Mitigation Strategy; RTD, residence time distribution; SAP, statistical analysis plan; SPA, special protocol assessment; T2D, type 2 diabetes mellitus; and ToSNP, Table of Significant and Notable Patients.

3.3. Foreign Regulatory Actions and Marketing History

Not applicable – Tirzepatide is not marketed in any country at the time of this review.

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

4.1. Office of Scientific Investigations (OSI)

Drs. Cynthia Kleppinger and Ling Yang, from the Office of Scientific Investigations (OSI), were asked to inspect three domestic clinical sites and two foreign sites (Table 3), accounting for 175 of 6,278 (2.8%) subjects randomized in the five global phase 3 trials (i.e., GPGK, GPGL, GPGH, GPGM, and GPGI). The two foreign sites (both in Germany) were selected due to limited domestic data for trial GPGI. Because of the ongoing COVID-19 global pandemic, the ability of the Office of Regulatory Affairs (ORA) to conduct onsite inspections at international sites was restricted. The clinical site inspections primarily focused on review of informed consent forms (ICFs), institutional review board (IRB)/ethics committee (EC) correspondences, 1572s/investigator agreements, financial disclosures, training records, curricula vitae and licenses, delegation of duties, monitoring logs and reports, inclusion/exclusion criteria, enrollment logs, and subject source documents (e.g., medical history records, drug accountability, concomitant medication records, and AE reports). The source records also were compared to the Applicant's data line listings. The rationale for the five selected clinical sites for inspection was primarily based on the site risk ranking (identified through the site selection tool) for the following: higher than average subject enrollment or enrollment of subjects screened, safety numbers, treatment response, protocol deviations, number of discontinuations, and rates of SAEs, lower than average discontinuations, site participation in more than one phase 3 trial, and lack of previous compliance inspection.

Following review of the full Establishment Inspection Reports and the documents submitted with those reports, the data from the three domestic sites (i.e., Drs. Frias, Hsia, and Mohseni) and two foreign sites (Drs. Dahl and Zeller-Stefan) were considered reliable. The Agency did not identify any objectionable conditions or practices for these study sites, and the classification for all three sites was No Action Indicated (NAI).

A for-cause inspection was recently completed for Dr. Harold Miller (US Site 117), an investigator who enrolled seven subjects into trial GPGH. This site was closed by the Applicant due to noncompliance with Good Clinical Practice (GCP). A subject was enrolled on a prohibited medication, and the source data had conflicting information regarding subject eligibility,

specifically with the required concomitant medication amounts and prohibited medications. No Form FDA-483 (Inspectional Observations) was issued for these findings, and the classification was NAI. Following review of the full Establishment Inspection Report and the documents submitted with that report, Drs. Kleppinger concluded that the violations did not significantly impact the primary efficacy and safety analyses.

Table 3: Protocol/Site Identification

Investigator Location	Site #	Protocol ID	Subjects Enrolled	Rationale for Site Selection	Classification (Inspection Dates)
Domestic					
Juan Frias Los Angeles, CA	113	GPGL	11	• Ranked #50 for site risk • Higher protocol deviations • Inspection of >1 trial (GPGH) • Participated in trials GPGK, GPGL, and GPGM	**NAI** (May 2, 2022)
	118	GPGH	23	• Ranked #30 for site risk • 3rd highest enrolling US site • Higher SAEs • Higher protocol deviations • Higher discontinuations • Site has never been inspected • Inspection of >1 study (GPGL) • Participated in trials GPGK, GPGL, and GPGM	
Stanley Hsia Huntington Park, CA	116	GPGH	40	• Ranked #8 for site risk (2nd highest ranked site for US) • Highest enrolling US site • Higher discontinuations • Higher protocol deviations • Site has never been inspected • Inspection of >1 trial (GPGL) • Participated in trials GPGK, GPGL, and GPGM	**NAI** (March 15, 2022)
	114	GPGL	27	• Ranked #27 for site risk • Highest enrolling US site • Higher discontinuations • Site has never been inspected • Inspection of >1 trial (GPGH) • Participated in trials GPGH, GPGK, and GPGM	
Rizwana Mohseni Montclair, CA	118	GPGL	24	• Ranked #28 for site risk • 2nd highest enrolling US site • Higher discontinuations • Site has never been inspected • Inspection of >1 trial (GPGH) • Participated in trials GPGH and GPGK	**NAI** (March 15, 2022)
	115	GPGH	18	• Ranked #39 for site risk • Higher discontinuations • Site has never been inspected	

Investigator Location	Site #	Protocol ID	Subjects Enrolled	Rationale for Site Selection	Classification (Inspection Dates)
				• Inspection of >1 trial (GPGL) • Participated in trials GPGK and GPGL	
Foreign					
Dominik Dahl Hamburg, Germany	300	GPGI	18	• Ranked #2 for site risk • Higher treatment effect • Higher SAEs • Lower discontinuations • Higher protocol deviations • Site has never been inspected	**NAI** (March 15, 2022)
Helga Zeller-Stefan Nordrhein-Westfalen, Germany	309	GPGI	14	• Ranked #6 for site risk • Higher site-specific treatment effect • Higher safety numbers • Higher discontinuations • Site has never been inspected	**NAI** (March 15, 2022)

Abbreviations: AEs, adverse events; NAI, No Action Indicated; and SAEs, serious adverse events.

During the site inspections, the OSI inspector noted that there were dosing errors caused by the interactive web response system (IWRS) validation failure in trials GPGH and GPGI. The IWRS uses a computer-generated random sequence to assign subjects to treatment groups. For trial GPGI, 17 subjects were dispensed 15 mg of tirzepatide instead of 10 mg on Visit 13 (Week 12) due to errors in the IWRS. According to the CSR, none of these subjects reported SAEs or hypoglycemic events during the remainder of the trial. At the subsequent dispensation visit (Week 16), one subject was impacted by the incorrect configuration, but the IWRS team reconfigured the system prior to dosing for the remaining 16 subjects. One of the 17 subjects was lost to follow-up, and 16 subjects completed the treatment period as planned. No additional subjects were affected by this issue. The unique subject identifiers (USUBJIDs) for the 16 affected subjects were not provided and it was unclear whether the unintentional increased dosage may have affected the efficacy analysis of primary endpoint.

In a second IWRS deviation, Subject (b) (6) was dispensed the wrong dose (i.e., tirzepatide 15 mg instead of 7.5 mg) at Visits 12 (Week 10), but subsequently received the correct dose of 10 mg at Visit 13 (Week 12) without experiencing AEs or additional dose escalation issues.

An information request (IR) was sent to the Applicant on March 8, 2022, asking the Applicant to provide the following additional information for the IWRS deviations:

1. USUBJIDs, assigned doses, dispensed doses, and any AEs related to the Visit 13 dosing errors for the 17 subjects in trial GPGI.
2. An evaluation of the impact of the IWRS errors on patient safety and the primary efficacy outcome assessment for both study trials GPGH and GPGI.

In their response (dated March 15, 2022), the Applicant stated that the incorrect configuration input to IWRS led to dispensation of a higher dose of investigational product (IP) in the tirzepatide 15 mg during the titration period, with the 15 mg dose being dispensed instead of the expected 10 mg dose at Week 12 (Visit 13). All 17 subjects subsequently received the 12.5 mg dose at the next scheduled dispensing visit (Week 16). The dosing errors for all subjects were reported as a protocol deviation in the Application (Table 14). Fourteen of the 17 subjects had no related AEs within four weeks of the incorrect dispensation, while two subjects had adverse events of diarrhea (Subjects (b) (6) and (b) (6) and a third experienced vomiting and decreased appetite (Subject (b) (6)). Additionally, Subject (b) (6) had AEs of 'Lipase increased' and 'Amylase increased'. The Applicant claimed that subject safety was not significantly impacted and noted that 16 of the 17 subjects completed the study on study drug. As all subjects received the correct dose at the next dispensing visit and the treatment periods were 40 (trial GPGI) and 52 weeks, no formal assessment on efficacy was performed by the Applicant. They also confirmed that there were no other unreported dosing issues due to IWRS errors during the conduct of all five trials.

In her review, Dr. Yang noted that there were no significant regulatory violations identified. She felt that based on the inspectional findings and regulatory assessments, trials GPGH, GPGI, and GPGL were adequately conducted, and that the data generated by the clinical inspection sites and submitted by the Applicant were acceptable in support of the proposed indication. I concur with this assessment. Please refer to Dr. Yang's review (March 24, 2022) for further details.

On April 25, 2022, the Agency issued a Voluntary Action Indicated (VAI) letter to the Applicant related to the inspectional findings of inadequate IWRS dispensing process of IP, which resulted in improper dosing of subjects enrolled in trials GPGH and GPGI. The Applicant was informed to make appropriate corrections to their procedures to ensure that the findings noted during the inspection (i.e., conducted at Eli Lilly and Company between January 4, 2022, and January 13, 2022) were not repeated in any ongoing or future studies.

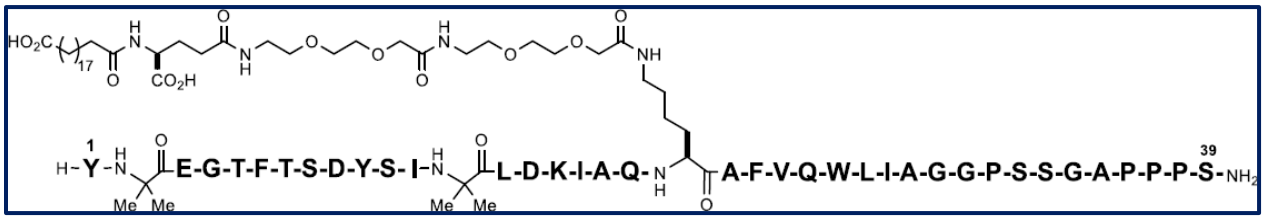
4.2. **Product Quality**

The Product Quality review for this Application was conducted by Drs. Theodore Carver (Application Technical Lead, from the Division of New Drug Products III [DNDPIII]/Office of New Drug Products [ONDP]), Joseph Leginus (Drug Substance reviewer, Division of New Drug Active Pharmaceutical Ingredient [DNDAPI]/ONDP), Rao Kambhampati (Drug Product, Labeling, and Environmental Assessment reviewer, DNDPIII/ONDP), Carl Lee (Process and Facility reviewer, Division of Pharmaceutical Manufacturing IV [DPMAIV]/Office of Pharmaceutical Manufacturing Assessment [OPMA]), Adita Das (Microbiology reviewer, Division of Microbiology Assessment I [DMAI]/Office of Pharmaceutical Manufacturing Assessment [OPMA]), and Nowrin Kakon (Regulatory Business Process Manager, Division of Regulatory and Business Process Management I [DRBPMI]/Office of Program and Regulatory Operations [OPRO]). Brief summaries of their

reviews will be discussed below. Please refer to the Integrated Quality Assessment Review (dated February 15, 2022) for more detailed information.

Drug Substance: Tirzepatide is a synthetic 39-amino acid modified peptide engineered from the GIP sequence containing 2 non-coded amino acids (aminoisobutyric acid, Aib) in positions 2 and 13, a C-terminal amide, and a Lys residue at position 20 that is attached to a 1,20-eicosanedioic acid via a linker (Figure 1). The molecular weight is 4813.53 Da and the empirical formula is $C_{225}H_{348}N_{48}O_{68}$.

Figure 1: Chemical Structure of Tirzepatide



Source: Excerpt from the Applicant's 32.S.1.2 Structure – v001 document, available at: \\CDSESUB1\evsprod\nda215866\0001\m3\32-body-data\32s-drug-sub\tirzepatide-all\32s1-gen-info\32s12-structure-v001.pdf

Dr. Leginus reviewed the tirzepatide manufacturing process, (b) (4)

Tirzepatide was structurally characterized using a variety of methods (e.g., liquid chromatography with mass spectrometry [LC-MS], tandem mass spectrometry [LC-MS/MS], LC-MS peptide mapping analysis, and circular dichroism [CD] spectroscopy). Dr. Leginus felt that the (b) (4) adequate. Additionally, the release and stability specification were felt to include appropriate analytical procedures to confirm the quality of drug substance. Four related substance impurities (b) (4) were felt to be adequately qualified at their respective proposed limits by the Pharmacology/Toxicology review team, and levels of potential elemental impurities at the maximum proposed dose were lower than the International Conference on Harmonisation (ICH) Q3D limits. Additionally, genotoxic impurities were extremely low, and there was negligible risk of (b) (4) for the drug substance in the manufacturing process. A retest date of (b) (4) months was granted for the tirzepatide drug substance (b) (4)

Drug Product: This drug-device combination product consists of a single-dose pen containing a semifinished syringe and autoinjector. Each single-dose pen contains a 0.5 mL solution of 2.5 mg, 5 mg, 7.5 mg, 10 mg, 12.5 mg, or 15 mg of tirzepatide and the following compendial grade excipients (same amounts in each dosage strength): dibasic sodium phosphate heptahydrate (b) (4)

(b) (4) sodium chloride (b) (4) and hydrochloric acid and sodium hydroxide (for pH adjustment; product pH range 6.5 to 7.5). There are no novel or animal or human derived excipients. The injection solution is packaged in a (b) (4) (b) (4) (Figure 2). Dr. Kambhampati concluded that adequate information was provided for the container closure components and adequate formulation development and product design studies were conducted. (b) (4) and overfill of the solution in the semi-finished syringe complied with US Pharmacopoeia (USP) <1151>. Results of extractable and leachable studies confirmed the safety and compatibility of the syringe container closure systems for use in the tirzepatide injection products. Further, the drug product specification included appropriate tests to ensure the quality of the drug product (e.g., tests for identity, impurities, color, clarity, pH, osmolality, particulate matter, syringe/device functionality, sterility, and endotoxins). The limits for impurities in the proposed release and shelf-life specifications were felt to be appropriately justified and found acceptable. Dr. Kambhampati concluded that the drug product information submitted to this Application was acceptable.

Figure 2: Tirzepatide Injection Primary Container Closure System

Source: Excerpt from the Applicant's 32p7-container-closure-v001 document, labeled as Figure 3.2.P.7.1-1, available at: \\CDSESUB1\evsprod\nda215866\0001\m3\32-body-data\32p-drug-prod\tirzepatide-injection-all-01\32p7-cont-closure-sys\32p7-container-closure-v001.pdf

Manufacturing: (b) (4)

(b) (4)

Overall, the process and controls were found to be adequate for the commercial manufacturing process. Dr. Lee concluded that the manufacturing process and controls were adequate to support the Application.

Microbiological Aspects: The manufacturing process and in-process controls, description of the environmental monitoring program, validation studies (b) (4) were reviewed by Dr. Das and felt to be adequate. Similarly, the description of the container closure integrity test (CCIT) and data following CCIT validation studies, as well as the analytical procedures and acceptance criteria for endotoxins and sterility in the drug product specification were considered acceptable. Dr. Das concluded that the information to support microbiological quality was adequate.

Stability, Storage Conditions and Expiration Date: The Applicant provided 18 months of real-time long-term stability data (5°C) and six months accelerated stability data at (30°C/65% relative humidity [RH]) for three registration batches of the lowest (2.5 mg/0.5 mL) and highest (15 mg/0.5 mL) tirzepatide dosage strengths, as well as 30 months supportive data for two clinical batches and statistical analyses of the stability data. Additionally, they provided 30 day in-use

stability data at 30°C to support the period of unrefrigerated storage of drug product prior to product use. Following review of these data by Dr. Kambhampati, an expiration of 24 months was granted for all dosage strengths of tirzepatide drug product when stored in refrigerator at 2°C to 8°C (36°F - 46°F) and protected from light. (b) (4) storage period of 21 days (b) (4) was granted for the drug product stored at temperatures less than 30°C (86°F) and protected from light.

Quality Labeling: Product quality aspects of the product labeling were reviewed by Dr. Kambhampati, and the prescribing information was considered adequate. However, he recommended the addition of storage conditions to the medication guide, and the addition of active and inactive ingredient information and storage conditions to the container label on the pen injector. Labeling will be considered adequate pending inclusion of the proposed labeling revisions by the Applicant.

Assessment of Manufacturing Facilities: (b) (4) In his facility assessment review, Dr. Lee recommended approval based on the previous history for each manufacturing facility, with no deficiencies noted for any facility.

Environmental Assessment: In accordance with the exclusion allowed by 21 CFR 25.31(b)[126] and (c),[127] the Applicant claimed a categorical exclusion from the requirement for an environmental assessment (21 CFR 25.15(d)).[128] Based on their projections, annual sales of tirzepatide would result in <1 ppb of tirzepatide at the point of entry into the aquatic environment (i.e., the maximum expected introduction concentration of tirzepatide would be < (b) (4) µg/L), and thus would not be considered an environmental risk.[126] (b) (4) Additionally, the Applicant stated that they know of no extraordinary circumstances that would require an environmental assessment.[128] OPQ concurred with the Applicant's claim for categorical exclusion from an environmental assessment.

In the Integrated Quality Assessment Review, Dr. Carver stated that there were no outstanding deficiencies related to product quality for this Application. With respect to the Chemistry, Manufacturing, and Controls (CMC), OPQ determined that this Application met all applicable standards to support the identity, strength, quality, and purity that it purports to have, and therefore recommended approval from a quality perspective.

4.3. Clinical Microbiology

Dr. Aditi Das was the OPQ Microbiology reviewer for this Application. Please refer to the previous section and to the Integrated Quality Assessment Review (dated February 15, 2022) for information on the microbiology assessment for this Application.

4.4. Nonclinical Pharmacology/Toxicology

Dr. Elena Braithwaite was the Pharmacology/Toxicology reviewer for this Application. Generally, she felt that many of the nonclinical findings associated with tirzepatide were consistent with those observed with GLP-1 RA products. Below is summary of select nonclinical data from the Application and her review. Please refer to Dr. Braithwaite's review (dated March 16, 2022) for a detailed discussion of the nonclinical findings.

Nonclinical Pharmacokinetics/Pharmacology: Tirzepatide's long chain C20 fatty diacid moiety enables albumin binding (98% in rats and >99% in monkeys) and prolongs its half-life. In rats and monkeys, tirzepatide is metabolized by proteolytic cleavage of the peptide backbone, β-oxidation of the C20-fatty diacid moiety, and amide hydrolysis, and parent drug is not present in the urine or feces across species. This product is a GIP analogue that shares 100% homology with the E3-I12 portion of the GIP molecule and is a GLP-1 analogue that shares 100% homology with the A29-S39 portion of GLP-1. In vitro, tirzepatide has been shown to selectively bind to and activate both the GIP and GLP-1 receptors. Therefore, two pharmacological class designations are used to describe the pharmacological activities of tirzepatide (i.e., GIP receptor agonist and GLP-1 receptor agonist).

To characterize the GIP and GLP-1 agonist activity of tirzepatide, the Applicant conducted studies in GIP receptor (GIPR) and GLP-1 receptor (GIP-1R) null mice, which showed that tirzepatide improves glucose tolerance (i.e., reduces the blood glucose area-under-the-curve [AUC]). In male Long Evans rats and diet-induced obese (DIO) mice, subcutaneously administered tirzepatide (10 nmol/kg) decreased food intake, reduced body weight, increased the glucose infusion rate, and increased 2-deoxyglucose uptake in muscle and adipose tissue compared to control animals. Tirzepatide doses of 10, 30 or 100 nmol/kg in DIO mice also resulted in reductions in fat mass, fat-free mass, plasma cholesterol and liver triglycerides.

Repeat-Dose Rat and Monkey Toxicology Studies: The pivotal toxicology studies for this Application included 1- and 6-month repeat-dose studies in Sprague Dawley rats and cynomolgus monkeys. Cardiovascular, respiratory, and central nervous system functions were evaluated in the 1-month monkey study. In this study, no significant drug-related findings in neurological and respiratory parameters were noted at tirzepatide doses up to twice the maximum recommended human dose (MRHD) of 15 mg once weekly (based on AUC). Increases in heart rate were observed

in male telemetry-instrumented conscious cynomolgus monkeys following single 0.15 or 0.5 mg/kg SC doses of tirzepatide. The 0.15 mg/kg dose also resulted in increased diastolic and mean arterial pressure and reduced pulse pressure.

In the 6-month repeat-dose toxicology studies conducted in rats and monkeys, SC administration of tirzepatide resulted in dose-dependent reductions in food consumption, body weight and body weight gains when compared to control animals. At clinically relevant tirzepatide exposures, pancreatic effects also were observed, and included lobular atrophy associated with zymogen depletion in rats and decreased pancreatic zymogen granules in female monkeys. In rats, decreases in splenic extramedullary hematopoiesis were associated with changes in red cell parameters at tirzepatide doses ≥1.5 mg/kg (1x MRHD). The no-observed-adverse-effect-level (NOAEL) in rats was 1.5 mg/kg (1x MRHD) due to findings of minimal to slight thyroid C-cell hyperplasia and pancreatic lobular atrophy. The NOAEL in monkeys was 0.15 mg/kg/week (0.5x MRHD) due to test article-related weight loss observed in five monkeys at tirzepatide doses of 0.5 mg/kg/week (1x MRHD). Nonsignificant increases in heart rate also were reported in male monkeys following tirzepatide exposures of ≥0.5x MRHD. Dr. Braithwaite felt that the findings in rats and monkeys in the 6-month toxicology studies were typical of the GLP-1 RA pharmacologic class. Similarly, the heart rate changes observed at clinically relevant doses in both the 1- and 6-month monkey toxicology studies were consistent with other GLP-1 RA products.

Cardiovascular function also was evaluated in a single-dose safety pharmacology study in monkeys, and a human ether-a-go-go related gene (hERG) in vitro assay was performed to assess the QT prolongation potential of tirzepatide. Single as well as repeat tirzepatide dosing in monkeys did not show a QTc prolongation. This is consistent with the ECG data in humans from the Applicant's phase 1 (i.e., GPGA) and phase 3 trials. Additionally, the hERG assay showed that tirzepatide did not inhibit hERG at the highest concentration tested (i.e., 300 μM).

Mutagenesis and Carcinogenesis: An in vivo micronucleus genotoxicity study was conducted in rats to evaluate the genotoxic potential of tirzepatide, and carcinogenicity potential was evaluated in a 26-week study in RasH2 transgenic mice, and a 2-year carcinogenicity study in rats.

The Applicant reported that tirzepatide was not genotoxic primarily based on the results of their in vivo rat bone marrow micronucleus assay.

In a 26-week carcinogenicity study in RasH2 transgenic mice, SC doses of tirzepatide up to 10 mg/kg administered twice weekly were not associated with increases in thyroid C cell hyperplasia or neoplasia.

In their 2-year carcinogenicity study, tirzepatide was administered twice weekly at SC doses of 0.15, 0.50, and 1.5 mg/kg (0.12x, 0.36x, and 1.02x MRHD) to male and female rats. Statistically significant increases in the incidences of thyroid C-cell adenomas were reported at tirzepatide doses of ≥0.5 mg/kg in male rats, and at doses of ≥0.15 mg/kg in female rats, while significant

increases in C-cell combined adenomas and carcinomas were observed in both sexes at all doses evaluated. Dr. Braithwaite stated that due to species specific differences in GLP-1 receptor expression and activation, the relevance of these findings to humans is unclear. In rodents, GLP-1 receptors are localized to C-cells, and GLP-1 RAs stimulate calcitonin release, up-regulation of calcitonin gene expression, with subsequent C-cell hyperplasia, while in humans and monkeys, GLP-1 receptor expression in thyroid C-cells is low and GLP-1 RAs do not appear to activate adenylate cyclase or generate calcitonin release.[129] Overall, the clinical relevance of the observed increase of C-cell neoplasms in tirzepatide-treated rats (i.e., whether tirzepatide may cause thyroid C-cell tumors, including medullary thyroid carcinoma [MTC] in humans) has not been determined. Similar to the labeling of GLP-1 RA products, proposed tirzepatide labeling will include a boxed warning stating that in rats, tirzepatide causes thyroid C-cell tumors.

Tirzepatide also was associated with non-neoplastic findings in rats in the thyroid (C-cell hyperplasia, common with advancing age in many strains of laboratory rats), adrenal gland (diffuse hypertrophy/hyperplasia of the zona glomerulosa), pancreas (acinar atrophy), skin/subcutis (adipose tissue atrophy), and kidney (mixed cell inflammation of the pelvis). Some of these findings could be compensatory responses to reductions in food and water consumption associated with tirzepatide exposure.

Reproduction and Fertility: The Applicant conducted fertility, embryo-fetal development, and prenatal and postnatal development studies in Sprague Dawley rats. They also conducted an embryo-fetal development study in a second species, New Zealand White rabbits, as well as a juvenile toxicology study in rats to evaluate tirzepatide effects on growth and development in support of clinical pediatric development.

In the rat embryo-fetal development study, pregnant rats were exposed to twice weekly SC tirzepatide doses of 0.02 0.1, and 0.5 mg/kg (0.03x, 0.07x, and 0.45x MRHD) during organogenesis, starting from implantation through lactation (i.e., gestation day 6 through 17). Increases in the incidences of external (i.e., fetal anasarca, proboscis-like nose, microstomia), visceral (double aorta), and skeletal malformations (rib anomaly), and visceral and skeletal developmental variations, and decreases in fetal weights were associated with reductions in maternal body weights and food consumption at the tirzepatide 0.5 mg/kg dose level. The NOAEL for maternal toxicity was 0.02 mg/kg based on adverse reductions in mean body weight with the higher tirzepatide doses. The NOAEL for embryo-fetal development was 0.1 mg/kg based on lower mean fetal body weights and increased incidences of malformations and developmental variations observed at the 0.5 mg/kg dose.

In pregnant rabbits, once weekly SC tirzepatide doses of 0.01, 0.03, or 0.1 mg/kg (0.01x, 0.06x, and 0.23x MRHD) resulted in pharmacodynamically-mediated effects on food consumption, body weight, and gastrointestinal lesions, with maternal mortality or spontaneous abortions observed at all dose levels. The tirzepatide 0.1 mg/kg dose level resulted in reduced fetal weights which were associated with decreased maternal food consumption and body weights. The NOAEL for

this study was 0.03 mg/kg due to lower mean fetal body weights likely due to tirzepatide-mediated pharmacodynamic effects.

In a pre- and postnatal development toxicity study in pregnant rats exposed to twice weekly SC tirzepatide doses of 0.02 0.1, and 0.25 mg/kg, starting from implantation through lactation (i.e., gestation day 6 through lactation day 18). Compared to control animals, tirzepatide doses ≥0.1 mg/kg resulted in statistically significant decreases in food consumption, resulting in decreases in maternal body weights, which persisted throughout lactation. Maternal exposures ≥0.1 mg/kg also resulted in lower mean body weights in first generation (F1) pups, with the observed weight reductions at the highest dose tested (0.25 mg/kg) considered adverse.

In the Applicant's fertility and early embryonic development studies, male and female rats were administered tirzepatide doses of 0.5, 1.5, or 3 mg/kg (0.30x, 1.03x, and 1.72x and 0.29x, 0.90x, and 1.88x MRHD, respectively) twice weekly. No effects were observed on male fertility (sperm morphology, mating, fertility, or conception). However, prolonged estrous cycles or persistent/prolonged diestrus was observed at all doses examined, and a decrease in the mean number of corpora lutea, resulting in a decrease in the mean number of implantation sites and viable embryos were reported at doses ≥1.5 mg/kg or ≥1 times the MRHD in female rats. Dr. Braithwaite felt that these effects were probably due to the pharmacodynamic effects of tirzepatide on food consumption and body weight.

In the Applicant's juvenile toxicology study in rats, tirzepatide exposure resulted in reductions in body weight and body weight gain that were considered adverse and associated with decreased food consumption, adipocyte atrophy in the skin/subcutis, and changes in red blood cell parameters. The NOAEL for this study was 1.5 mg/kg (1x MRHD), the highest tirzepatide dose tested.

The Pharmacology/Toxicology review team felt that many of the nonclinical findings described above were consistent with GLP-1 RAs and recommended approval of this Application. I concur that there did not appear to be additional safety concerns associated with tirzepatide based on the nonclinical findings identified in Dr. Braithwaite's review.

4.5. Clinical Pharmacology

The clinical pharmacology data for this Application were reviewed by Dr. Mohamad Kronfol, from the Division of Cardiometabolic and Endocrine Pharmacology (DCEP); Dr. Elyes Dahmane from the Division of Pharmacometrics (DPM), Office of Clinical Pharmacology (OCP); and Dr. Yuching Yang from DPM/OCP. The OCP/DCEP determined that the clinical pharmacology data submitted to this NDA were acceptable, and recommended approval from a clinical pharmacology perspective. Please refer to their review (dated March 18, 2022) for more detailed information.

Below is a summary of their review, as well as clinical pharmacology data/information provided in the Application.

The clinical pharmacology of tirzepatide was evaluated using data from 19 studies—10 phase 1 studies (GPGE, GPGS, GPHI, GPHX, GPGA, GPGC, GPGG, GPGQ, GPGR, and GPGT), two phase 2 trials (i.e., GPGB, and GPGF), five phase 3 trials (GPGK, GPGL, GPGH, GPGM, and GPGI), and two regional phase 3 trials conducted in Japan (GPGO and GPGP). Subjects in these trials were exposed to tizepatide doses of 0.25 to 15 mg SC QW for up to 104 weeks. Population pharmacokinetics and exposure-response analyses were performed using pooled data from these studies.

4.5.1. Mechanism of Action/Pharmacodynamics

Tirzepatide is a long-acting, GIP receptor and GLP-1 receptor agonist, intended for SC QW administration. The chemical structure of tirzepatide includes a 39-amino acid modified peptide with a C_{20} fatty diacid moiety that enables albumin binding and prolongs the elimination half-life ($T_{1/2}$).[130] Its molecular weight is 4810.53 Daltons.[1] Tirzepatide selectively binds to and activates both the GIP and GLP-1 receptors, the targets for native GIP and GLP-1.[130] In subjects with T2D, tirzepatide lowered fasting and postprandial glucose concentrations and reduced body weight. Additionally, based on a hyperglycemic clamp study (GPGT), tirzepatide enhanced the first- and second-phase insulin secretion rate, and improved insulin sensitivity (increase in the M-value, a measure of insulin sensitivity).[131] In study GPGA, tirzepatide delayed gastric emptying, which became less evident with continued weekly dosing. However, the Clinical Pharmacology review team had concerns that the observed delay in gastric emptying could potentially affect the absorption of concomitant orally administered drugs.

4.5.2. Pharmacokinetics

Absorption: Tirzepatide is administered as a SC QW injection into the abdomen, thigh, or upper arm. Following SC administration, approximately 80% of an administered dose is absorbed, with maximum plasma concentrations (Cmax) occurring between 8 to 72 hours (Tmax). Due to a prolonged half-life ($T_{1/2}$), steady-state (SS) plasma concentrations are typically achieved following four weeks of QW dosing. The accumulation ratio (based on $AUC_{0\text{-}tau}$) is 1.6 by four weeks, and exposure increases in a dose-proportional manner. The starting dose of tirzepatide is 2.5 mg SC QW, with 2.5 mg up-titrations in dose every four weeks up to response, tolerability, or a maximum dose of 15 mg. The Clinical Pharmacology team felt that the proposed dosing regimen was appropriate for the intended patient population for whom tirzepatide would be prescribed based on the supporting data submitted from studies GPGB and GPGF.

Additionally, study GPGS, a dedicated bioavailability (BA) study, evaluated the relative bioavailability of tirzepatide administered with a prefilled syringe (used in phase 3 trial GPGM) compared to the single-dose pen (i.e., the intended to-be-marketed presentation used in all other phase 3 trials). The results of this study showed comparable BA between these two

presentations, providing support for the use of the single-dose pen as the commercial device.

Distribution: The mean volume of distribution (VD) of tirzepatide following SC administration is approximately 10.3 L, and it is extensively bound (99%) to plasma albumin.

Metabolism and Elimination: Tirzepatide is primarily eliminated by metabolism (i.e., proteolytic cleavage of the peptide backbone, beta-oxidation of the C_{20} fatty diacid moiety, and amide hydrolysis), with a mean clearance of 0.061 L/h and an elimination $T_{1/2}$ of approximately 5 days. This relatively long $T_{1/2}$ enables once-weekly dosing. The four minor tirzepatide metabolites produced by proteolytic cleavage of tirzepatide, each accounting for <5.7% of circulating radioactivity from a 4.1 mg radiolabeled dose of tirzepatide in study GPHX, were primarily eliminated in the urine (50%) and feces (20%).

Intrinsic Factors: The pharmacokinetics of tirzepatide do not appear to be significantly altered by intrinsic factors (e.g., age, gender, race, ethnicity, body weight, or renal or hepatic impairment), and therefore, no specific dosing recommendations are necessary for these patient subgroups. Following a single tirzepatide 5 mg dose in subjects with renal (mild, moderate, severe, and end stage renal disease [ESRD]; study GPGG) and hepatic (Child-Pugh classification of mild, moderate, and severe; study GPGQ) impairment, no meaningful changes in tirzepatide pharmacokinetics (AUC, Cmax, and $T_{1/2}$) were observed compared to subjects with normal renal and normal hepatic function, respectively. Additionally, following review of the data from study GPHI, Dr. Kronfol felt that dose adjustments would not be necessary based on differences in BMI or selected injection site (abdomen, thigh, or upper arm).

Drug-Drug Interactions: In vitro data showed that tirzepatide does not appear to inhibit or induce cytochrome P450 (CYP) enzymes or inhibit renal and hepatic drug transporters. Therefore, the potential for tirzepatide to interact with drugs dependent on these enzymes or transporters for metabolism or elimination is low. However, in study GPGA, tirzepatide delayed gastric emptying, and thus could potentially affect the absorption of concomitant orally administered medications. The Applicant claimed that their physiologically based pharmacokinetic (PBPK) modeling predictions did not show clinically meaningful changes in absorption of concomitant medications (e.g., atorvastatin, digoxin, lisinopril, metformin, metoprolol, sitagliptin, and S-warfarin), and therefore no dosage adjustments would be required. Dr. Yang reviewed the Applicant's PBPK analysis and felt that it was adequate to provide qualitative assessment of the effect of tirzepatide-mediated delayed gastric emptying on the pharmacokinetics of these medications. However, in study GPGR, coadministration of a single 5mg dose of tirzepatide with a combination oral contraceptive (COC; ethinyl estradiol 0.35 mg and norgestimate 0.25 mg) lowered the AUC_{tau} of ethinyl estradiol by approximately 21% (geometric mean 0.788, 90% CI: 0.73, 0.85), norelgestromin by 23% (0.775, 90% CI: 0.71, 0.84), and norgestimate by 21% (0.792, 90% CI: 0.614, 1.02), compared to administration of the COC alone. In addition, the C_{max} of ethinyl estradiol, norelgestromin, and norgestimate were lowered by approximately 59% (i.e., geometric mean 0.41, 90% CI: 0.355, 0.473), 55% (0.451, 95% CI: 0.402, 0.505), and 66% (0.345, 90% CI:

0.274, 0.436), respectively. In accordance with the draft guidance for industry: Clinical Drug Interactions Studies with Combined Oral Contraceptives (November 2020),[132] [(1)] if the 90 percent confidence intervals (CIs) for the geometric mean systemic exposure ratios fall outside the no-effect boundaries of 80 to 125 percent for the COC, the totality of evidence (e.g., safety and efficacy of the COC) should be considered when determining the clinical impact of the DDI on the COC. Due to the findings reported in study GPGR, the Clinical Pharmacology review team recommended that proposed labeling be revised to inform prescribers that concomitant use of tirzepatide with oral hormonal contraceptives may reduce the efficacy of the oral hormonal contraceptive. They acknowledged that tachyphylaxis may develop after multiple dosing as evident by the acetaminophen marker data from study GPGA in the tirzepatide 5 mg dose cohort. However, they expressed concern of the risk for a loss of efficacy of the COC during the time when tachyphylaxis is taking place (i.e., after initiation and following each dose escalation of tirzepatide). Considering that animal reproduction studies report that there may be risks to the fetus from exposure to tirzepatide during pregnancy, patients using oral hormonal contraceptives should be advised to switch to a non-oral contraceptive method or add a barrier method of contraception for four weeks after initiation and for four weeks after each dose escalation of tirzepatide.

4.6. **Devices and Companion Diagnostic Issues**

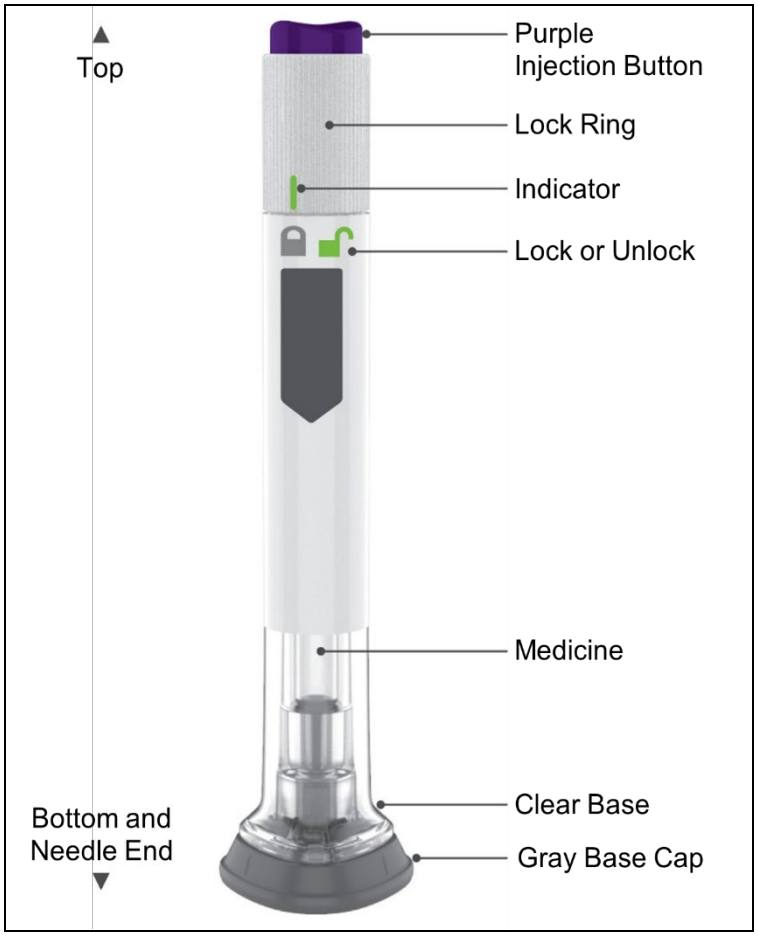
Dr. Sreya Tarafdar, from the Division of Health Technology 3 C (Division of Drug Delivery, General Hospital & Human Factors), Center for Devices and Radiological Health (CDRH), was consulted to review the device constituent parts (i.e., auto-injector) of this combination product (in accordance with 21 CFR 880.6920, product code KZH).[133] The tirzepatide auto-injector is a single-use needle-based injection system (NIS) that automatically inserts the needle into the SC tissue and delivers 0.5 mL of tirzepatide drug product when activated (i.e., a single injection delivers the entire volume stored in [(b) (4)] glass syringe). Device components of the autoinjector do not come in contact with tirzepatide drug product (Figure 3).

Safety features of this autoinjector include the following: a device locking mechanism to prevent inadvertent actuation; an audible indication of activation (audible click) when the button is pressed to activate the autoinjector; needle insertion to the SC injection depth; automatic delivery of a 0.5 mL dose of drug product; a retraction delay to ensure complete dose delivery (device should be held against the skin for up to 10 seconds); automatic retraction of the needle from injection site to a sub-flush position with an audible indication of injection completion (i.e., a second audible click); and a retraction lock to prevent the device from being returned to an activatable state. The autoinjector for this Application was first developed for dulaglutide (Trulicity), the Applicant's approved GLP-1 RA product, and designed according to the International Organization for Standardization (ISO) standard for NISs with automated features,

[(1)] The Agency updates guidances periodically. For the most recent version of this guidance, check the FDA Guidance Documents Database: https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

in addition to requirements derived from patient and user needs. The device constituent hazards for the tirzepatide autoinjector were considered equivalent to those of the approved Trulicity autoinjector.

Figure 3: Components of the Tirzepatide Autoinjector



Source: Excerpt from the Applicant's Instructions for Use, available at: \\CDSESUB1\evsprod\nda215866\0001\m1\us\proposed-usermanual-clean.docx

Based on her review, Dr. Tarafdar considered the following to be acceptable: device description, labeling (contains all required elements), design controls, risk analysis, design verification, clinical validation (no AEs reported that would indicate a device issue), and facilities and quality systems. There also were no outstanding deficiencies for this Application from the device perspective, and CDRH did not recommend any Postmarketing Commitments (PMCs) or Requirements (PMRs). Dr. Tarafdar felt that the device constituent parts of the combination product were approvable, and

recommended approval for the proposed indication. Please refer to her review (dated January 31, 2022) for further details.

4.7. Consumer Study Reviews

Dr. Neha Kumar from the Division of Medication Error Prevention and Analysis 1 (DMEPA1) reviewed the human factors (HF) validation study reports submitted to this Application. Based on the review of these data, several use errors with critical tasks were identified which could result in harm. DMEPA1 provided recommendations for the Applicant of additional mitigations that could be implemented to address use errors that occurred with critical tasks. Although these changes would not require additional HF validation testing data for Agency review, revised labeling would need to be submitted. The autoinjector labeling, rationale for concern, and recommendations are provided in Table 4. Please refer to Dr. Kumar's review (dated February 15, 2022) for additional information.

Table 4: Identified Issues and Recommendations

Identified Issue	Rationale for Concern	Recommendation
Autoinjector (AI) label		
1. The added color-coded arrow graphic (see below) on the AI label is not labeled to indicate that it is pointing to the needle end. 	We are concerned that if the user places/actuates the autoinjector upside down on the injection site this may lead to: • injection of an incorrect site, such as the thumb, and there is risk of pain, injury • injection of someone other than the patient and there is risk of hypoglycemia, nausea, diarrhea, vomiting • drug expelled in the wrong direction and there is risk of mild, symptomatic, or asymptomatic hyperglycemia • drug product coming in contact with patient or caregiver eye and there is risk of eye irritation or injury	We recommend that you consider adding text to the autoinjector label to indicate to the user which end is the needle-end.
Instructions for Use (IFU) and Quick Reference Guide (QRG)		
1. The step "Preparing to inject Mounjaro" is not numbered as a step that is to be completed when using each autoinjector and thus may be overlooked.	We are concerned that if a user omits or does not perform the tasks associated with "Preparing to inject Mounjaro" there is risk of pain, injury, capillary embolism, granuloma, toxicity, immune response, mild, symptomatic or asymptomatic	We recommend you number the step "Preparing to inject Mounjaro" in the IFU.

Identified Issue	Rationale for Concern	Recommendation
	hyperglycemia, and infection from needle stick. The human factors (HF) validation study results identified subjective feedback that indicated that participants did not notice the "Preparing to inject Mounjaro" step in the IFU. Several participants thought that relevant information would be stated in the preceding "Important information you need to know before injecting Mounjaro".	
2. The step "Choose your injection site" is not numbered as a step that is to be completed when using each autoinjector and thus may be overlooked.	We are concerned that if a user injects at the wrong injection site there is risk of pain, injury, wheals at injection site. The HF validation study results identified subjective feedback that indicated that participants did not notice the "Choose your injection site" step. Instead, participants proceeded to "Step 1 Pull off the gray base cap", which is the task listed immediately after "Choose your injection site".	We recommend you number the step "Choose your injection site" in the IFU and QRG.
3. The IFU and QRG text under (b) (4) Press and Hold up to 10 seconds" states "Press and Hold the purple injection button" but does not state the appropriate hold time of 10 seconds.	We are concerned that if this task is omitted or not performed correctly this may lead to mild, symptomatic or asymptomatic hyperglycemia. The HF validation study results identified a participant who overlooked the bolded header for (b) (4) and only read the text underneath which states, "Press and Hold the purple injection button".	We recommend that you make the following change to (b) (4) Press and Hold up to 10 seconds" of the QRG and IFU: Change the statement, "Press and Hold the purple injection button" to "Press and Hold the purple injection button for up to 10 seconds".
4. The instructions "After your injection, place the used Pen in a sharps container" in the IFU and "Put used Pen in a sharps container" in the QRG lack prominence and clarity.	We are concerned that if a user omits or does not perform the disposal task then there is risk of injury. The HF validation study results identified several participants who did not see the disposal instruction. In the IFU the full disposal instructions, "Disposing of your used Pen" is the only task that is on the back of the IFU. Additionally, some participants who referred to the QRG did not know to dispose of the autoinjector after each injection.	• We recommend you revise the QRG statement, "Put used Pen in a sharps container" to align with the IFU and state the following: "After your injection, place the used Pen in a sharps container". • We recommend that you make the aforementioned disposal instructions in the IFU and QRG more prominent. • We recommend that in IFU Step 3, after the statement, "After your injection, place the used Pen in a sharps container", include instructions for the user to flip the IFU to the back to see

Identified Issue	Rationale for Concern	Recommendation
		the "Disposing of your used Pen" step. • We recommend you number the step "Disposing of your used Pen" in the IFU.
5. The QRG text and illustrations may not be large enough for users to read or see.	We are concerned that patients with diabetes mellitus who are visually impaired may have difficulty reading the QRG due to small text size and illustrations.	We recommend that you increase the QRG text and illustration size.

Source: Dr. Neha Kumar's Human Factors Study Report Review, Table A, pages 21-23 of 39.
Abbreviations: AI, autoinjector; HF, human factors; IFU, Instructions for Use; and QRG, quick reference guide.

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

The tirzepatide clinical development program consisted of 19 completed clinical studies with a data cutoff date of June 2, 2021, which included three biopharmaceutic studies (GPHI, GPGS, and GPGE), seven clinical pharmacology studies (GPGR, GPGA, GPGG, GPGQ, GPHX, GPGT, and GPGC), two phase 2 clinical trials (GPGB, and GPGF), five global phase 3 trials (GPGK, GPGL, GPGH, GPGM, and GPGI), and two regional Japanese phase 3 trials (GPGO, and GPGP).

This review will primarily focus on the nine phase 2/3 clinical trials used to support the efficacy and safety of tirzepatide for the proposed indication (Table 5). In the phase 2 trials (treatment durations of 12-26 weeks), varying doses of tirzepatide were compared to placebo or dulaglutide. In the phase 3 trials (treatment durations of 40-104 weeks), tirzepatide (5 mg, 10 mg, and 15 mg) were compared to placebo, insulin glargine 100 U/mL, insulin degludec 100 U/mL, dulaglutide 0.75 mg, and semaglutide 1 mg. The phase 3 trials all used the dose titration schedule as proposed for tirzepatide product labeling.

Table 5: Listing of Phase 2/3 Clinical Trials Relevant to the Proposed Indication

Trial Identifier/ Title	Trial Design and Primary Objective	Regimen/ Route/ Schedule	Study Endpoints	Treatment Duration	No. of Subjects Randomized/ Completed	Study Population	No. of Centers and Countries
Phase 2 Clinical Trials							
18F-MC-GPGB **NCT03131687** **First Patient Enrolled:** 12 Jun 2017 **Last Patient Completed or Data Cutoff Date:** 28 Mar 2018 **Title:** A Phase 2 Study of Once-Weekly LY3298176 Compared with Placebo and Dulaglutide in Patients with Type 2 Diabetes Mellitus	***Design:*** Multicenter, double-blind, parallel-group, placebo- and active comparator-controlled, randomized phase 2 trial ***Objective:*** To demonstrate a dose-response relationship of QW SC TZP on HbA1c change from baseline compared to placebo in T2D subjects inadequately controlled with diet and exercise alone or treated with a stable dose of Met	**1:1:1:1:1:1 allocation** • TZP 1 mg SC QW • TZP 5 mg SC QW • TZP 10 mg SC QW ***Dose Escalation:*** 5 mg for 2 weeks followed by up-titration to 10 mg • TZP 15 mg SC QW ***Dose Escalation:*** 5 mg for 2 weeks followed by up-titration to 10 mg for 4 weeks; followed by up-titration to 15 mg • Dula 1.5 mg SC QW • Placebo SC QW ***Glycemic Rescue:*** Adjust/add AHA (dose held constant for initial 18 wks)	*Primary* • Change from Baseline in HbA1c at Week 26	• 26 weeks	• TZP 1 mg: 53/44 • TZP 5 mg: 55/52 • TZP 10 mg: 52/48 • TZP 15 mg: 53/45 • Dula 1.5 mg: 54/49 • Placebo: 51/45	• T2D (≥6 mos) • 18-75 years old • HbA1c 7-10.5% • Stable dose x3 mos if on Met • BMI ≥23 to <50 kg/m^2 ***Background Therapy:*** • Diet/exercise alone or on a stable dose of Met	**47 Sites,** **4 Countries:** Poland, Puerto Rico, Slovakia, United States
18F-MC-GPGF **NCT03311724** **First Patient Enrolled:** 2 Nov 2017 **Last Patient Completed or Data Cutoff Date:** 24 Apr 2018 **Title:** A Phase 2, Double-Blind, Placebo-Controlled, 3-Month	***Design:*** Multicenter, double-blind, placebo-controlled, randomized, parallel-arm, dose-escalation phase 2 titration trial ***Objective:*** To demonstrate that at least 1 TZP escalation titration scheme is superior	**1:1:1:1 allocation** Group 1: • TZP 15 mg SC QW ***Dose Escalation:*** 2.5, 5 mg; each dose for 2 weeks; followed by 10 mg for 4 weeks; followed by 15 mg for 4 weeks Group 2 • TZP 15 mg SC QW	*Primary* • Mean change from baseline in HbA1c at Week 12	• 12 weeks	Group 1: • TZP 15 mg: 28/26 Group 2: • TZP 15 mg: 28/27 Group 3 • TZP 12 mg: 29/28 • Placebo: 26/23	• T2D (≥6 mos) • 18-75 years old • HbA1c 7-10.5% • Stable dose x3 mos if on Met • BMI ≥23 to 45 kg/m^2 ***Background Therapy:*** • Diet/exercise alone or on a stable dose of Met	**13 Sites,** **1 Country:** United States

Trial Identifier/ Title	Trial Design and Primary Objective	Regimen/ Route/ Schedule	Study Endpoints	Treatment Duration	No. of Subjects Randomized/ Completed	Study Population	No. of Centers and Countries
Trial of LY3298176 Versus Placebo in Patients with Type 2 Diabetes Mellitus	to placebo in HbA1c reduction at 3 months in T2D subjects inadequately controlled with diet and exercise alone or treated with a stable dose of Met	***Dose Escalation:*** 2.5, 7.5, 15 mg; each dose for 4 weeks **Group 3** • TZP 12 mg SC QW ***Dose Escalation:*** 4, 8, 12 mg; each dose for 4 weeks • Placebo SC QW ***Glycemic Rescue:*** Adjust/add AHA (dose held constant for initial 18 wks)					
Global Phase 3 Efficacy and Safety Trials*							
18F-MC-GPGK **NCT03954834** **First Patient Enrolled:** 3 Jun 2019 **Last Patient Completed or Data Cutoff Date:** 28 Oct 2020 **Title:** A Randomized, Double-blind, Placebo-Controlled Trial Comparing the Efficacy and Safety of Three Tirzepatide Doses Versus Placebo in Patients with Type 2 Diabetes, Inadequately Controlled with Diet and Exercise Alone **(SURPASS-1)**	***Design:*** Multicenter, double-blind, placebo-controlled, randomized, parallel-group phase 3 trial ***Objective:*** To demonstrate that QW TZP 5, 10, and/or 15 mg is superior to placebo in mean change in HbA1c from baseline to 40 weeks	**1:1:1:1 allocation** • TZP 5 mg SC QW • TZP 10 mg SC QW • TZP 15 mg SC QW • Placebo SC QW ***Dose Escalation:*** Initiate with 2.5 mg SC QW, and up-titrate by 2.5 mg every 4 weeks to the randomized TZP dose ***Glycemic Rescue:*** Adjust/add AHA (dose held constant for initial 18 wks)	*Primary* • Mean change from baseline in HbA1c at Week 40 *Key Secondary* • Incidence of subjects with an HbA1c <7.0% at Week 40 • Incidence of subjects with an HbA1c <5.7% at Week 40 • Mean change from baseline in FSG at Week 40 • Mean change from baseline in BW at Week 40	• 40 weeks	• TZP 5 mg: 121/114 • TZP 10 mg: 121/112 • TZP 15 mg: 121/103 • Placebo: 115/99	• T2D • ≥18 years old • HbA1c 7-9.5% • Naïve to injectable AHAs and have not used OAMs ≥3 mos • Stable BW ≥3 mos • BMI ≥23 kg/m^2 ***Background Therapy:*** • Diet/exercise alone	**52 Sites,** **4 Countries:** India, Japan, Mexico, United States

Trial Identifier/ Title	Trial Design and Primary Objective	Regimen/ Route/ Schedule	Study Endpoints	Treatment Duration	No. of Subjects Randomized/ Completed	Study Population	No. of Centers and Countries
18F-MC-GPGL **NCT03987919** **First Patient Enrolled:** 30 Jul 2019 **Last Patient Completed or Data Cutoff Date:** 15 Feb 2021 **Title:** A Phase 3, Randomized, Open-Label Trial Comparing Efficacy and Safety of Tirzepatide Versus Semaglutide Once Weekly as Add-on Therapy to Metformin in Patients with Type 2 Diabetes **(SURPASS-2)**	***Design:*** Multicenter, open-label, active-controlled, randomized, parallel-group, phase 3 trial ***Objective:*** To demonstrate that QW TZP 10 and/or 15 mg is noninferior to QW Sema 1 mg for mean change in HbA1c from baseline at 40 weeks	**1:1:1:1 allocation** • TZP 5 mg SC QW • TZP 10 mg SC QW • TZP 15 mg SC QW • Sema 1 mg SC QW ***Dose Escalation:*** Initiate with 2.5 mg SC QW, and up-titrate by 2.5 mg every 4 weeks to the randomized TZP dose The Sema starting dose was 0.25 mg SC QW, and the dose was doubled every 4 weeks until the 1 mg dose was reached. ***Glycemic Rescue:*** Adjust/add AHA (dose held constant for initial 18 wks)	*Primary* • Mean change from baseline in HbA1c at Week 40 for the TZP 10, and 15 mg dose only (noninferiority) *Key Secondary* • Mean change from baseline in HbA1c at Week 40 for the TZP 5 mg dose (noninferiority) • Mean change from baseline in HbA1c at Week 40 (superiority) • Incidence of subjects with an HbA1c <7.0% at Week 40 • Mean change from baseline in BW at Week 40 • Incidence of subjects with an HbA1c <5.7% at Week 40	• 40 weeks	• TZP 5 mg: 471/452 • TZP 10 mg: 469/442 • TZP 15 mg: 470/446 • Sema 1 mg: 469/443	• T2D • ≥18 years old • HbA1c ≥7 to ≤10.5% • Stable dose of Met (>1500 mg/d) ≥3 mos • Stable BW (±5%) ≥3 mos • BMI ≥25 kg/m^2 ***Background Therapy:*** • Stable dose of Met	**128 Sites,** **8 Countries:** Argentina, Australia, Brazil, Canada, Israel, Mexico, United Kingdom, United States

Trial Identifier/ Title	Trial Design and Primary Objective	Regimen/ Route/ Schedule	Study Endpoints	Treatment Duration	No. of Subjects Randomized/ Completed	Study Population	No. of Centers and Countries
18F-MC-GPGH **NCT03882970** **First Patient Enrolled:** 1 Apr 2019 **Last Patient Completed or Data Cutoff Date:** 4 Jan 2021 **Title:** A Randomized, Phase 3, Open-Label Trial Comparing the Effect of LY3298176 Versus Titrated Insulin Degludec on Glycemic Control in Patients with Type 2 Diabetes **(SURPASS-3)**	***Design:*** International, multicenter, randomized, open-label, parallel-group, phase 3 trial ***Objective:*** To demonstrate that QW TZP 10 and/or 15 mg is noninferior to Ins Deg for mean change in HbA1c from baseline at 52 weeks	**1:1:1:1 allocation** • TZP 5 mg SC QW • TZP 10 mg SC QW • TZP 15 mg SC QW • Ins Deg SC QD ***Dose Escalation:*** Initiate with 2.5 mg SC QW, and up-titrate by 2.5 mg every 4 weeks to the randomized TZP dose Dosing of Ins Deg started at 10 units/day, and subjects adjusted the dose QW to a TTT FBG <90 mg/dL ***Glycemic Rescue:*** AHA (except DPP-4i, GLP-1 RA, or pramlintide)	*Primary* • Mean change from baseline in HbA1c at Week 52 for the TZP 10, and 15 mg dose only (noninferiority) *Key Secondary* • Mean change from baseline in HbA1c at Week 52 for the TZP 5 mg dose (noninferiority) • Mean change from baseline in HbA1c at Week 52 (superiority) • Mean change from baseline in BW at Week 52 • Incidence of subjects with an HbA1c <7.0% at Week 52	• 52 weeks	• TZP 5 mg: 359/333 • TZP 10 mg: 361/321 • TZP 15 mg: 359/340 • Ins Deg: 365/331	• T2D • ≥18 years old • HbA1c ≥7 to ≤10.5% • Stable dose of Met ± SGLT2i ≥3 mos • Stable BW (±5%) ≥3 mos • BMI ≥25 kg/m^2 ***Background Therapy:*** • Stable dose of Met± SGLT2i	**121 Sites,** **12 Countries:** Argentina, Austria, Greece, Hungary, Italy, Poland, Romania, South Korea, Spain, Taiwan, Ukraine, United States
18F-MC-GPGM **NCT03730662** ***First Patient Enrolled:*** 20 Nov 2018 *Last Patient Completed or Data Cutoff Date:* 22 Apr 2021 **Title:** Efficacy and Safety of LY3298176 Once Weekly Versus Insulin Glargine in Patients with Type 2 Diabetes and Increased Cardiovascular Risk **(SURPASS-4)**	***Design:*** International, multicenter, randomized, open-label, parallel-group, phase 3 trial ***Objective:*** To demonstrate that QW TZP 10 and/or 15 mg is noninferior to Ins Glar for mean change in HbA1c from baseline at 52 weeks	**1:1:1:3 allocation** • TZP 5 mg SC QW • TZP 10 mg SC QW • TZP 15 mg SC QW • Ins Glar SC QD ***Dose Escalation:*** Initiate with 2.5 mg SC QW, and up-titrate by 2.5 mg every 4 weeks to the randomized TZP dose Dosing of Ins Glar started at 10 units/day, and subjects adjusted the dose QW to a TTT	*Primary* • Mean change from baseline in HbA1c at Week 52 for the TZP 10, and 15 mg dose only (noninferiority) *Key Secondary* • Mean change from baseline in HbA1c at Week 52 for the TZP 5 mg dose (noninferiority) • Mean change from baseline in HbA1c at Week 52 (superiority) • Mean change from	Up to 104 weeks • 52 weeks (primary endpoint) plus • 52 weeks variable treatment period up to 104 weeks	• TZP 5 mg: 329/294 • TZP 10 mg: 330/312 • TZP 15 mg: 338/313 • Ins Glar: 1005/882	• T2D • ≥18 years old • HbA1c ≥7.5 to ≤10.5% • Stable dose of 1-3 AHAs (Met, SGLT2i, and/or SU) ≥3 mos • Increased CV risk • Stable BW (±5%) • BMI ≥25 kg/m^2 ***Background Therapy:*** • Stable dose of Met, SGLT2i, and/or SU	**187 Sites,** **14 Countries:** Argentina, Australia, Brazil, Canada, Greece, Israel, Mexico, Poland, Romania, Russian Federation, Slovakia, Spain,

Trial Identifier/ Title	Trial Design and Primary Objective	Regimen/ Route/ Schedule	Study Endpoints	Treatment Duration	No. of Subjects Randomized/ Completed	Study Population	No. of Centers and Countries
		FBG <100 mg/dL ***Glycemic Rescue:*** AHA (except DPP-4i, GLP-1 RA, or pramlintide)	baseline in BW at Week 52 • Incidence of subjects with an HbA1c <7.0% at Week 52				Taiwan, United States
18F-MC-GPGI **NCT04039503** **First Patient Enrolled:** 30 Aug 2019 **Last Patient Completed or Data Cutoff Date:** 13 Jan 2021 **Title:** Randomized, Phase 3, Double-blind Trial Comparing the Effect of the Addition of Tirzepatide Versus Placebo in Patients with Type 2 Diabetes Inadequately Controlled on Insulin Glargine with or Without Metformin **(SURPASS-5)**	***Design:*** Multicenter, double-blind, placebo-controlled, randomized, parallel-group phase 3 trial ***Objective:*** To demonstrate that QW TZP 10 and/or 15 mg is superior to placebo when added to titrated Ins Glar ± Met for mean change in HbA1c from baseline at 40 weeks	**1:1:1:1 allocation** • TZP 5 mg SC QW • TZP 10 mg SC QW • TZP 15 mg SC QW • Placebo SC QW ***Dose Escalation:*** Initiate with 2.5 mg SC QW, and up-titrate by 2.5 mg every 4 weeks to the randomized TZP dose ***Glycemic Rescue:*** AHA, including prandial insulin (except DPP-4i, GLP-1 RA, pramlintide, or other basal insulins)	*Primary* • Mean change from baseline in HbA1c at Week 40 for the TZP 10, and 15 mg dose *Key Secondary* • Mean change from baseline in HbA1c at Week 40 for the TZP 5 mg dose • Incidence of subjects with an HbA1c <7.0% at Week 40 • Incidence of subjects with an HbA1c <5.7% at Week 40 • Mean change from baseline in FSG at Week 40 • Mean change from baseline in BW at Week 40	• 40 weeks	• TZP 5 mg: 116/109 • TZP 10 mg: 119/115 • TZP 15 mg: 120/110 • Placebo: 120/117	• T2D • ≥18 years old • HbA1c ≥7 to ≤10.5% • Stable dose of Ins Glar (U100) ± Met ≥3 mos • Stable BW (±5%) ≥3 mos • BMI ≥23 kg/m^2 ***Background Therapy:*** • Stable dose of Ins Glar (TTT FBG <100 mg/dL) ± Met	**45 Sites,** **7 Countries:** Czech Republic, Germany, Japan, Poland, Slovakia, Spain, United States (including Puerto Rico)
Regional Phase 3 Clinical Trials (Japan)							
18F-JE-GPGO **NCT03861052** **First Patient Enrolled:** 07 May 2019	***Design:*** Multicenter, randomized, double-blind, parallel, active-controlled, 52-week, phase 3 trial	**1:1:1:1 allocation** • TZP 5 mg SC QW • TZP 10 mg SC QW • TZP 15 mg SC QW • Dula 0.75 mg SC QW ***Dose Escalation:*** Initiate	*Primary* • Mean change from baseline in HbA1c at Week 52 *Key Secondary* • Mean change from	• 52 weeks	• TZP 5 mg: 159/155 • TZP 10 mg: 158/151 • TZP 15 mg: 160/155 • Dula 0.75 mg: 159/154	• T2D • ≥20 years old • HbA1c ≥7 to ≤10.0% for OAM-naïve subjects; HbA1c ≥6.5 to ≤9.0% for	**46 Sites** **1 Country:** Japan

Trial Identifier/ Title	Trial Design and Primary Objective	Regimen/ Route/ Schedule	Study Endpoints	Treatment Duration	No. of Subjects Randomized/ Completed	Study Population	No. of Centers and Countries
Last Patient Completed or Data Cutoff Date: 31 Mar 2021 **Title:** A Phase 3 Study of Tirzepatide Monotherapy Compared to Dulaglutide 0.75 mg in Patients with Type 2 Diabetes Mellitus **(SURPASS J-mono)**	***Objective:*** To demonstrate that QW TZP 5, 10, and/or 15 mg is superior to Dula 0.75 mg in HbA1c change from baseline at 52 weeks	with 2.5 mg SC QW, and up-titrate by 2.5 mg every 4 weeks to the randomized TZP dose ***Glycemic Rescue:*** AHAs, including insulins (except DDP-4i or GLP-1 RA)	baseline in BW at Week 52			OAM monotherapy subjects (washout x8 weeks) • Stable BW (±5%) ≥3 mos • BMI ≥23 kg/m^2 ***Background Therapy:*** • Diet/exercise alone	
18F-JE-GPGP **NCT03861039 (SURPASS J-combo)** **First Patient Enrolled:** 30 Mar 2019 **Last Patient Completed or Data Cutoff Date:** 16 Feb 2021 **Title:** A Phase 3, Long-Term Safety Study of Tirzepatide in Combination with Monotherapy of Oral Antihyperglycemic Medications in Patients with Type 2 Diabetes Mellitus **(SURPASS J-combo)**	***Design:*** Multicenter, randomized, 52 week, add-on treatment phase 3 trial ***Objective:*** To assess safety and tolerability of QW TZP in terms of incidence of TEAEs during 52 weeks of treatment as an add-on to OAM monotherapy	**1:1:1 allocation** • TZP 5 mg SC QW • TZP 10 mg SC QW • TZP 15 mg SC QW ***Dose Escalation:*** Initiate with 2.5 mg SC QW, and up-titrate by 2.5 mg every 4 weeks to the randomized TZP dose ***Glycemic Rescue:*** Basal or rapid-acting insulins (or other AHA except DDP-4i or GLP-1 RA)	*Primary* • Incidence of TEAEs	• 52 weeks	• TZP 5 mg: 148/145 • TZP 10 mg: 147/139 • TZP 15 mg: 148/133	• T2D • ≥20 years old • HbA1c ≥7 to ≤11.0% • Stable dose of a single OAM (SU, biguanides, TZD, alpha-glucosidase inhibitor, glinides, SGLT2i, or SU) ≥3 mos • Stable BW (±5%) ≥3 mos • BMI ≥23 kg/m^2 ***Background Therapy:*** • Stable dose of a SU, biguanides, TZD, alpha-glucosidase inhibitor, glinides, SGLT2i, or SU	**34 Sites** **1 Country:** Japan

Source: Adapted from the Applicants Tabular Listing of Clinical Studies, available at: \\CDSESUB1\evsprod\nda215866\0001\m5\52-tab-list\tabular-listing-of-clinical-studies--t2dm-.pdf
Abbreviations: +/-, with or without; AHA, antihyperglycemic agent; BL, baseline; BMI, body mass index; BW, body weight; DPP-4i, dipeptidyl peptidase-4 inhibitor; Dula, dulaglutide; FBG, fasting blood glucose; FPG, fasting plasma glucose; FSG, fasting serum glucose; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA1c, hemoglobin A1c (glycosylated hemoglobin); DPP-4i, dipeptidyl peptidase-4 inhibitor; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA1c, hemoglobin A1c; Ins Deg, insulin degludec; Ins Glar, insulin glargine; Met, metformin; mos, months; NCT, National Clinical Trial; OAM, oral antihyperglycemic medication; PO, orally; QD, daily; QW, every week; SBP, sitting systolic blood pressure; SC, subcutaneous; Sema, semaglutide; SGLT2i, sodium-glucose cotransporter 2 inhibitor; SU,

sulfonylureas; T2D, type 2 diabetes mellitus; wks, weeks; TEAE, treatment-emergent adverse event; TTT, treat-to-target; TZD, thiazolidinedione; TZP, tirzepatide; vs., versus; and yr, year.

* Intended to support the claimed indication (T2D) and inclusion in Section 14 of product labeling. Hypothesis testing performed with a 2-sided alpha of 0.05, and the Type I error rate was controlled by following a fixed testing sequence.

5.2. Review Strategy

This review will focus primarily on the efficacy findings (i.e., the prespecified primary and key secondary endpoints) from the five global phase 3 trials, and the safety findings from the nine phase 2/3 clinical trials used to support the efficacy and safety of tirzepatide for the proposed indication (Table 5). For a detailed discussion of the statistical analyses of these trials, please refer to the Statistical Review (dated February 15, 2022) of Dr. Wenda Tu, the primary statistical reviewer for this Application. The review strategy for the safety findings is presented in Section 8.1.

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. Phase 3 Trials

6.1.1. Study Design

Overview and Objective:

Five global phase 3 trials (GPGK, GPGL, GPGH, GPGM, and GPGI) and two phase 2 trials (GPGB and GPGF) were used to support efficacy of tirzepatide for the proposed T2D indication. The Applicant intends to include the five phase 3 trials in Section 14 of product labeling. The primary and key secondary objectives of each trial are presented in Table 12. These trials were conducted in 24 countries (six regions), and were all multicenter, randomized, controlled trials, and met the regulatory standards for adequate and well-controlled studies (21 CFR 314.126).[43] Two trials were placebo-controlled (GPGK and GPGI) and thee were active-controlled (GPGH, GPGL, and GPGM). Tirzepatide was evaluated as monotherapy and in combination with metformin, SU, and SGLT2i alone or combined, and in combination with basal insulin (insulin glargine) with or without metformin. The efficacy of tirzepatide (5, 10, and 15 mg SC QW doses) was compared with placebo, insulin glargine, insulin degludec, and semaglutide 1 mg.

Trial Designs:

The respective illustrations of the study designs of the five global phase 3 trials are presented in Appendix 13.3. A brief description of the study design of each trial is as follow:

- **Trial 18F-MC-GPGK (SURPASS-1):** A multicenter, randomized, double-blind, parallel-group, placebo-controlled, phase 3 trial in subjects with T2D, naive to antihyperglycemic injectable therapy, inadequately controlled with diet and exercise alone, and had not been treated with any oral antihyperglycemic medication during the three months preceding to the start of the trial. This trial consisted of 3 periods: a 3-week screening/lead-in period, followed by a 40-

week treatment period, and a 4-week safety follow-up period. Subjects were randomized in a 1:1:1:1 ratio (tirzepatide 5, 10, or 15 mg, or injectable placebo SC QW).

- **Trial 18F-MC-GPGL (SURPASS-2):** A multicenter, randomized, open-label, parallel-group, active-controlled, phase 3 trial with subjects with T2D, inadequately controlled on ≥1500 mg/day of metformin alone during the three months preceding to the start of the trial. This trial consisted of 3 periods: a 3-week screening/lead-in period, followed by a 40-week treatment period, and a 4-week safety follow-up period. Subjects were randomized in a 1:1:1:1 ratio (tirzepatide 5, 10, or 15 mg [doses double-blinded], or semaglutide 1 mg [not blinded] SC QW).
- **Trial 18F-MC-GPGH (SURPASS-3):** A multicenter, randomized, open-label, parallel-group phase 3 trial in subjects with T2D, inadequately controlled on stable doses of metformin (≥1500 mg/day) with or without a SGLT2i during the three months preceding to the start of the trial. This trial consisted of 3 periods: a 3-week screening/lead-in period, followed by a 52-week treatment period, and a 4-week safety follow-up period. Subjects were randomized in a 1:1:1:1 ratio (tirzepatide 5, 10, or 15 mg SC QW, or insulin degludec SC QD).
- **Trial 18F-MC-GPGM (SURPASS-4):** A multicenter, randomized, open-label, parallel-group, active-controlled, phase 3 trial in subjects with T2D with increased CV risk, inadequately controlled on stable doses of at least one and no more than three oral antihyperglycemic medications during the three months preceding to the start of the trial. This trial consisted of 3 periods: a 3-week screening/lead-in period, followed by a ≥52 to 104-week treatment period (i.e., treatment continued for ≥52 weeks from the time the last subject was randomized), and a 4-week safety follow-up period. Subjects were randomized in a 1:1:1:3 ratio (tirzepatide 5, 10, or 15 mg SC QW, or insulin glargine SC QD). The starting dose of insulin glargine was 10 units/day at bedtime, titrated to a fasting blood glucose (FBG) <100 mg/dL, following a treat-to-target (TTT) algorithm.
- **Trial 18F-MC-GPGI (SURPASS-5):** A multicenter, randomized, double-blind, parallel-group, placebo-controlled, phase 3 study with 3 study periods in subjects with T2D, inadequately controlled on stable doses of titrated basal insulin glargine (>0.25 units/kg/day or >20 units/day) with or without metformin during the three months preceding to the start of the trial. This trial consisted of 3 periods: a 3-week screening/lead-in period, followed by a 40-week treatment period, and a 4-week safety follow-up period. Subjects were randomized in a 1:1:1:1 ratio (tirzepatide 5, 10, or 15 mg, or injectable placebo SC QW).

Please refer to Table 5 for a brief description of the trial designs for the supporting phase 2 (GPGB and GPGF) and regional phase 3 (GPGO, and GPGP) trials .

Key Inclusion and Exclusion Criteria:

The key inclusion and exclusion criteria for the five global phase 3 trials are presented in Table 6. Except for trial GPGM, which was enriched with subjects at increased CV risk, these trials generally enrolled relatively healthy adult subjects with T2D. Additionally, the Applicant is

currently conducting a dedicated cardiovascular outcomes trial (CVOT, trial GPGN) which is enrolling higher CV risk subjects. However, to maintain the blinding of treatment allocations and data integrity, the data from this trial were not evaluated.

Table 6: Summary of Key Inclusion and Exclusion Criteria by Phase 3 Trial

Trials	GPGK	GPGL	GPGH	GPGM	GPGI
INCLUSION CRITERIA					
Age ≥18 yrs	X	X	X	X	X
T2D men/women (WHO criteria or other locally applicable standards)	X	X	X	X	X
HbA1c 7-9.5%	X				
HbA1c 7-10.5%		X	X		X
HbA1c 7.5-10.5%				X	
Insulin-naïve (except use of insulin for gestational diabetes or <14 days for acute conditions)	X				
Stable doses of background metformin ≥1500 mg/day for ≥3 mos		X			
Stable doses of background metformin ≥1500 mg/day ± SGLT2i ≥3 mos			X		
Stable doses of 1 to 3 oral antihyperglycemic meds of either metformin, SGLT2i, and/or SU ≥3 mos				X	
Stable doses (±20%) of insulin glargine ≥0.25 units/kg/day or >20 units/day ± metformin (≥1500 mg/d) for ≥3 mos, and requires further insulin glargine dose increase per TTT algorithm based on SMBG data during the prior week					X
Willing to use an adequate method of contraception	X	X	X	X	X
Stable weight (±5%) ≥3 months, without intent to initiate an intensive diet and/or exercise program	X	X	X	X	X
BMI ≥23 kg/m^2	X				X
BMI ≥25 kg/m^2		X	X	X	
Increased risk of CV events*				X	
EXCLUSION CRITERIA					
T1D	X	X	X	X	X
Hx of DKA/hyperosmolar state/coma	X	X	X	X	X
Hx of chronic or acute pancreatitis	X	X	X	X	X
Proliferative retinopathy or maculopathy or nonproliferative retinopathy requiring acute treatment (confirmed by dilated fundoscopic examination)	X	X	X	X	X
Severe hypoglycemia/hypoglycemia unawareness within 6 mos	X	X	X	X	X
Gastric emptying abnormality, or undergone/plan to undergo gastric bypass surgery or restrictive bariatric surgery, or receiving meds affecting GI motility	X	X	X	X	X
Acute MI, stroke, or HHF within 2 mos	X	X	X	X	X
NYHA Class IV heart failure	X	X		X	
NYHA Class III and IV heart failure			X		X
Acute or chronic hepatitis, or signs/symptoms of other liver disease other than NAFLD	X	X	X	X	X
Significant/uncontrolled endocrine abnormality (e.g., thyrotoxicosis, adrenal crisis)	X	X	X	X	X
Family or personal history of MTC or MEN2	X	X	X	X	X
Significant, active autoimmune abnormality (e.g., lupus or rheumatoid arthritis) likely to require systemic glucocorticoids within 12 mos	X	X	X	X	X

Trials	GPGK	GPGL	GPGH	GPGM	GPGI
Hx of hypersensitivity to study meds or related products	X	X	X	X	X
Hx of hypersensitivity to insulin glargine				X	
Transplanted organ or awaiting organ transplantation	X	X	X	X	X
Active or untreated malignancy or in remission from a clinically significant malignancy for <5 years	X	X	X	X	X
Conditions (e.g., known drug, alcohol abuse, or psychiatric disorder) that may preclude subjects from following/completing the study	X	X	X	X	X
Hematological condition that may interfere with HbA1c measurement (e.g., hemolytic anemias, sickle cell disease)	X	X	X	X	X
Received any oral antihyperglycemic meds other than stated in the inclusion criteria within 3 mos	X				
Hx of receiving any injectable antihyperglycemic medication (except use of insulin for gestational diabetes or <14 days for acute conditions)	X				
Hx of receiving insulin therapy (except use of insulin for gestational diabetes or <14 days for acute conditions)				X	
Received any oral antihyperglycemic meds other than stated in the inclusion criteria within 3 mos (except use of insulin for gestational diabetes or for <14 days for acute conditions)		X			
Received any antihyperglycemic meds other than stated in the inclusion criteria within 3 mos			X	X	X
Receiving chronic (>2 wks) systemic glucocorticoids or received such therapy within 1 month	X	X	X	X	X
Received meds that promote weight loss within 3 mos	X	X	X	X	X
Pregnant or breastfeeding	X	X	X	X	X
Abnormal clinical labs					
ALT level >3x ULN	X	X	X	X	X
eGFR <30 mL/min/1.73 m^2	X				X†
eGFR <45 mL/min/1.73 m^2		X	X		X†
Serum calcitonin level ≥35 ng/L	X	X	X		X
Serum calcitonin level ≥20 ng/L if eGFR ≥60 mL/min/1.73m^2 or ≥35 ng/L if eGFR <60 mL/min/1.73 m^2				X	

Source: Adapted from the Clinical Study Protocols for trials GPGK, GPGL, GPGH, GPGM, and GPGI, available at:
GPGK: \\CDSESUB1\evsprod\nda215866\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\type-2-diabetes-mellitus\5351-stud-rep-contr\i8f-mc-gpgk\gpgk-05-protocol--b-.pdf
GPGL: \\CDSESUB1\evsprod\nda215866\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\type-2-diabetes-mellitus\5351-stud-rep-contr\i8f-mc-gpgl\gpgl-05-protocol--b-.pdf
GPGH: \\CDSESUB1\evsprod\nda215866\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\type-2-diabetes-mellitus\5351-stud-rep-contr\i8f-mc-gpgh\gpgh-05-protocol--c-.pdf
GPGM: \\CDSESUB1\evsprod\nda215866\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\type-2-diabetes-mellitus\5351-stud-rep-contr\i8f-mc-gpgm\gpgm-05-protocol--b-.pdf
GPGI: \\CDSESUB1\evsprod\nda215866\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\type-2-diabetes-mellitus\5351-stud-rep-contr\i8f-mc-gpgi\gpgi-05-protocol--b-.pdf

Abbreviations: ADA, American Diabetes Association; ALT, alanine aminotransferase; BMI, body mass index; BW, body weight; d, day; CV, cardiovascular; CVD, cardiovascular disease; DKA, diabetic ketoacidosis; eGFR, estimated glomerular filtration rate (Chronic Kidney Disease-Epidemiology [CKD-EPI]); HbA1c, hemoglobin A1c; HHF, hospitalization due to chronic heart failure; Hx, history; meds, medications; MEN2, multiple endocrine neoplasia syndrome type 2; MI, myocardial infarction; MOS, month; MTC, medullary thyroid carcinoma; mos, months; NAFLD, nonalcoholic fatty liver disease; NYHA, New York Heart Association classification; SGLT2i, sodium-glucose cotransporter 2 inhibitor; SMBG, SU, sulfonylurea; T1D, type 1 diabetes mellitus; T2D, type 2 diabetes mellitus; ULN, upper limit of normal; wk, week; and yr, years.

***Increased risk of CV events:** 1) Coronary heart disease (history of acute MI, stenosis of ≥50% in a least 1 major coronary artery by cardiac imaging, coronary calcium score ≥300, stable angina pectoris treated with antianginal meds, asymptomatic cardiac ischemia documented by cardiac imaging on exercise or pharmacological stress test, history of coronary revascularization); OR 2) peripheral arterial disease of atherosclerotic origin (current or intermittent claudication, resting limb ischemia, stenosis of >50%

in an iliac, femoral, popliteal, or subclavian artery, ankle-brachial index ≤0.9, peripheral arterial revascularization or amputation due to atherosclerotic vascular disease, asymptomatic carotid artery stenosis ≥70%, carotid artery revascularization, abdominal aortic aneurysm); OR 3) cerebrovascular disease of atherosclerotic origin (transient ischemic attack [TIA] in subjects ≥50 years of age or ischemic stroke); OR 4) age ≥50 years, history of CKD, and an estimated eGFR <60 mL/min/1.73 m2 (CKD-EPI, based on two consecutive measurements); OR 5) Age ≥50 years and CHF (NYHA III).
† eGFR <30 mL/min/1.73 m^2 or <45 mL/min/1.73 m^2 if on metformin.

Overall, I thought that the trial designs, including the inclusion/exclusion criteria, patient populations, exposures, and treatment durations, were adequate and consistent with other antihyperglycemic phase 3 clinical development programs, including GLP-RA products, submitted to the Division. Additionally, enrichment of subjects with high CV risk (e.g., GPGM), inclusion of subjects with renal impairment, allowed concomitant antihyperglycemic mediations (e.g., basal insulin or up to three antihyperglycemic medications) and relevant active comparators (e.g., semaglutide, basal insulins) is reflective of the intended patient populations and clinical use of this product (e.g., antihyperglycemic treatment progression), and consistent with the draft guidance for industry: Type 2 Diabetes Mellitus: Evaluating the Safety of New Drugs for Improving Glycemic Control (March 2020).[(2)]

Study Administrative Structure and Committees:

The study governance and oversight for each of the five phase 3 clinical trials included a coordinating principal investigator, and a responsible medical officer. The Applicant or a designee was responsible for the central recruitment strategy of subjects, review of the informed consent form (ICF), site monitoring/audits, and statistical analysis. An Independent Ethics Committee (IEC) and/or Institutional Review Board (IRB) reviewed the protocol, protocol amendments, informed consent form (ICF), Investigator's Brochure, and other relevant documents (e.g., advertisements) prior to initiation/approval. The protocol and ICF also were approved by the Applicant prior to initiating the trial. A Data Monitoring Committee (DMC) supplemented the routine study monitoring conducted under the protocol and monitored the interim unblinded safety data from the Cardiovascular Meta-Analysis (CVMA). The Statistical Analysis Center (SAC), an unblinded group of statisticians and statistical analysts external to the Applicant's study team, provided statistical support to the DMC. Additionally, all suspected cases of acute or chronic pancreatitis, deaths, and nonfatal CV AEs were adjudicated by an independent Clinical Endpoint Committee (CEC) with internal medicine and cardiology expertise. The Duke Clinical Research Institute (DCRI) CEC was responsible for adjudicating clinical events in the phase 2 trials, and the Cleveland Clinic Coordinating Center for Clinical Research (C5R) CEC was responsible for adjudicating clinical events in the phase 3 trials. Clinical laboratory tests were performed by the Applicant's designated central laboratory unless otherwise noted. Clinical trial data were managed by a central vendor (e.g., laboratory test data), and stored electronically in the central vendor's database system. Electronic transfers were provided to the investigator(s) for review and retention, and subsequently transferred from the central vendor to the Applicant's data

[(2)] The Agency updates guidances periodically. For the most recent version of the guidance, check the FDA Guidance Documents Database: https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

warehouse. The trials were conducted in accordance with the protocol and with the consensus ethics principles derived from internal ethics guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines, applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines, and applicable laws and regulations. The Applicant's responsible medical officer and statistician approved the final Clinical Study Report (CSR) for each trial.

I felt that the study governance and oversight for the phase 3 trials were adequate.

Investigational Drug Dosing:

For all phase 3 trials, tirzepatide was dosed using the following titration schedule: Initiate with 2.5 mg SQ QW and increase the dose in 2.5 mg increments every four weeks up to the planned tirzepatide dose (i.e., 5, 10, or 15 mg). Unless administration of IP was interrupted, subjects should have achieved the planned 5 , 10, and 15 mg tirzepatide doses at Weeks 4, 12, and 20, respectively. For blinded trials (GPGK, and GPGI), subjects randomized to the placebo arm injected matched placebo (identical in appearance to the tirzepatide single-dose pen) SC QW for the entire treatment period. Subjects in these trials were randomly assigned (1:1:1:1 allocation) to tirzepatide 5, 10, or 15 mg, or placebo.

For the open-label trials (GPGL, GPGH, and GPGM), the dose and schedule of the active comparators were as follows:

- **GPGL:** Subjects in this trial were randomly assigned (1:1:1:1) to tirzepatide 5, 10, 15 mg SC QW, or semaglutide. Semaglutide was initiated at 0.25 mg SC QW for four weeks; increased to 0.5 mg SC QW for 4 weeks; and increased to and maintained at 1 mg SC QW for the duration of the trial.
- **GPGH:** Subjects in this trial were randomly assigned (1:1:1:1) to tirzepatide 5, 10, or 15 mg SC QW, or insulin degludec SC QD. The starting dose of insulin degludec (provided as a prefilled devise containing 3 mL [100 units/mL]) was 10 units/day at bedtime and titrated to a FBG <90 mg/dL (based on the median value of the last three self-monitored blood glucose [SMBG] values) using a TTT algorithm (Table 7).[134-136] Subjects titrated the insulin degludec dose weekly (with assistance from the investigator for the first 8 weeks). For dose titrations from Weeks 8-15, the subjects had a phone or clinic visit every other week. The insulin degludec dose was decreased by 2 to 4 units in the following situations: 1) if multiple episodes of nonsevere hypoglycemia were recorded during the assessment period at any time during the day; and/or 2) if at least 1 episode met the criteria for severe hypoglycemia (events requiring assistance to administer therapy) or was associated with SMBG value <54 mg/dL. During the treatment period, office visits occurred weekly or every other week during the first 16 weeks, and thereafter, every 4 to 8 weeks to monitor subjects' usage of the TTT algorithm.

Table 7: Titration of Insulin Degludec (Trial GPGH)

Median of 3 Prebreakfast SMBG Values[a]	Adjustment: Units
≤70 mg/dL	Decrease by 2 to 4 units
71 to 90 mg/dL	No adjustment
91 to 126 mg/dL	Increase by 2 units
127 to 144 mg/dL	Increase by 4 units
145 to 162 mg/dL	Increase by 6 units
>162 mg/dL	Increase by 8 units

Source: Adapted from the Applicant's Clinical Study Protocol, page 41 of 94, available at: \\CDSESUB1\evsprod\nda215866\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\type-2-diabetes-mellitus\5351-stud-rep-contr\i8f-mc-gpgh\gpgh-05-protocol--c-.pdf
Abbreviation: SMBG, self-monitored blood glucose.
[a] If only 2 prebreakfast SMBG values are available, the average of these 2 values will be used.

- **GPGM:** Subjects in this trial were randomly assigned (1:1:1:3) to tirzepatide 5, 10, or 15 mg SC QW, or insulin glargine SC QD. The starting dose of insulin glargine (provided as a prefilled devise containing 3 mL [100 units/mL]) was 10 units/day (typically at bedtime) and titrated to a FBG <100 mg/dL (based on the median value of the last three SMBG values) using a TTT algorithm (Table 8).[137] Subjects titrated the insulin glargine dose weekly for the first 8 weeks (with insulin doses reviewed/revised at subsequent office visits). The insulin glargine dose was decreased by 2 to 4 units in the following situations: 1) if multiple episodes of nonsevere hypoglycemia were recorded during the assessment period at any time during the day; and/or 2) if at least 1 episode met the criteria for severe hypoglycemia (events requiring assistance to administer therapy) or was associated with SMBG value <54 mg/dL. There was no central oversight of insulin glargine titration.

Table 8: Titration of Insulin Glargine (Trial GPGM)

Median of 3 Prebreakfast SMBG Values[a]	Adjustment: Units
≤70 mg/dL	Decrease by 2 to 4 units
71 to 99 mg/dL	No adjustment
100 to 119 mg/dL	Increase by 2 units
120 to 139 mg/dL	Increase by 4 units
140 to 179 mg/dL	Increase by 6 units
>180 mg/dL	Increase by 8 units

Source: Adapted from the Applicant's Clinical Study Protocol, page 41 of 94, available at: \\CDSESUB1\evsprod\nda215866\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\type-2-diabetes-mellitus\5351-stud-rep-contr\i8f-mc-gpgm\gpgm-05-protocol--b-.pdf
Abbreviation: SMBG, self-monitored blood glucose.
[a] Based on the last 3 SMBG values.
If only 2 prebreakfast SMBG values are available, the average of these 2 values will be used.

The doses and titration schedules of active comparators were acceptable (i.e., semaglutide was dosed and titrated according to product labeling,[2] and insulin products were initiated at typical clinical doses and titrated throughout the treatment period using TTT algorithms to achieve FBG

values <90 or 100 mg/dL). The current glycemic goal recommended by the ADA for nonpregnant adults with diabetes is a preprandial capillary plasma glucose of 80-130 mg/dL, with more or less stringent glycemic goals for individual patients as appropriate.[138]

Concomitant Medications:

Antihyperglycemic Medications. The Applicant claimed that the concomitant antihyperglycemic medications were chosen to reflect treatment progression in a broad T2D population and clinical practice. Except for trial GPGK, for which tirzepatide monotherapy was evaluated in subjects naïve to injectable antihyperglycemic products, trials GPGL, GPGH, GPGM, and GPGI allowed one to three concomitant antihyperglycemic medications. Allowed medications for these trials included the following:

- **GPGL:** Metformin (≥1500 mg/day, required therapy)
- **GPGH:** Metformin (≥1500 mg/day, required therapy) ± SGLT2i (optional therapy)
- **GPGM:** Metformin (≥1500 mg/day, optional therapy) ± SGLT2i (optional therapy) ± SU (optional therapy)
- **GPGI:** Insulin glargine (SC QD, required therapy) ± metformin (≥1500 mg/day, optional therapy)

To enable assessment of glycemic efficacy for the phase 3 trials, subjects were to have been receiving stable doses of these background antihyperglycemic medications for at least three months (please refer to Table 6). Doses and formulations were to remain stable throughout the treatment period except in situations where dose adjustment or complete discontinuation was required (e.g., per local labeling, protocol-specific hypoglycemic episodes, permitted per study protocol, and/or subjects developed contraindications to respective antihyperglycemic medication use). For trial GPGI, subjects used a TTT algorithm for adjusting background insulin glargine use (Table 9).[137] Subjects were required to perform a 4-point SMBG (i.e., fasting, pre-midday meal, pre-evening meal, and bedtime) at least QW.

Table 9: Titration of Insulin Glargine (Trial GPGI)

Median Fasting Blood Glucose Values[a]	Adjustment: Units (If Insulin Glargine Dose <20 Units)	Adjustment: Units (If Insulin Glargine Dose ≥20 Units)
≤70 mg/dL	Decrease by 1 to 2 units[b,c]	Decrease by 2 to 4 units[b,c]
71 to 100 mg/dL	No adjustment	No adjustment
101 to 119 mg/dL	Increase by 1 unit	Increase by 2 units
120 to 139 mg/dL	Increase by 2 units	Increase by 4 units
140 to 179 mg/dL	Increase by 3 units	Increase by 6 units
≥180 mg/dL	Increase by 4 units	Increase by 8 units

Source: Adapted from the Applicant's Clinical Study Protocol, page 42 of 99, available at: \\CDSESUB1\evsprod\NDA215866\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\type-2-diabetes-mellitus\5351-stud-rep-contr\i8f-mc-gpgi\gpgi-05-protocol--b-.pdf

Abbreviation: SMBG, self-monitored blood glucose.

[a] Based on the last 3 SMBG values.

[b] The insulin dose was decreased by 1 to 2 units or 2 to 4 units in the following situations: multiple episodes of nonsevere hypoglycemia were recorded during the assessment period at any time during the day; and/or if at least 1 episode that met the criteria for severe hypoglycemia (events requiring assistance of a third person to administer therapy) or was associated with SMBG value <54 mg/dL was recorded during the assessment period.

[c] Based on the last 3 SMBG values. If only 1 hypoglycemic episode with SMBG value ≥54 mg/dL and ≤70 mg/dL was recorded, the insulin dose was not be changed.

Antihyperglycemic Rescue Medications. Rescue therapy (as add-on to randomized treatment) was permitted for severe, persistent hyperglycemia. Hyperglycemia criteria and allowed glycemic rescue therapy for the five global phase 3 trials are presented in Table 10.

Table 10: Hyperglycemia Criteria and Allowed Rescue Therapy (Global Phase 3 Trials)

Trial	Severe/Persistent Hyperglycemia Criteria	Allowed Glycemic Rescue
GPGK	FBG (within 1 wk for ≥2 consecutive wks): • >270 mg (BL to Wk 6); or • >240 mg/dL (Wks 6-12); or • >200 mg/dL (Wk 12 to EOT); or HbA1c ≥8.5% (at/after Wk 24)	New antihyperglycemic medication, except for a GLP-1 RA, DPP-4i, or pramlintide. Preference: • Metformin • Basal insulin (if average FBG ≥300 mg/dL or rapid glycemic control warranted)
GPGL	Average QD BG (QW 4-point SMBG profile for ≥2 consecutive wks) • >270 mg/dL (BL to Wk 8); or • >240 mg/dL (Wks 9-16); or • >200 mg/dL (>Wk 16); or HbA1c ≥8.5% at Wk 24 with <0.3% improvement over 3 mos (Wks 12-24)	New antihyperglycemic medication, except for a GLP-1 RA, DPP-4i, or pramlintide. Preference: • SGLT2i • SU or TZD (if contraindication to SGLT2i) • Basal insulin (if average FBG ≥300 mg/dL or above rescue med is inadequate after 3 mos)
GPGH	Average QD BG (QW 4-point SMBG profile for ≥2 consecutive wks) • >270 mg/dL (BL to Wk 8); or • >240 mg/dL (Wks 9-16); or • >200 mg/dL or HbA1c ≥8.5% (> Wk 16); or HbA1c ≥8.5% at Wk 24 with <0.3% improvement over 3 mos (Wks 12-24)	New antihyperglycemic medication (including prandial insulin), except for a GLP-1 RA, DPP-4i, pramlintide , or basal insulin. Allowed: • SGLT2i • Insulin • Meglitinide • Alpha-glucosidase inhibitor • SU • TZD • Metformin

Trial	Severe/Persistent Hyperglycemia Criteria	Allowed Glycemic Rescue
GPGM	Average QD BG (QW 4-point SMBG profile for ≥2 consecutive wks) • >270 mg/dL (BL to Wk 8); or • >240 mg/dL (Wks 8-16); or • >200 mg/dL (≥Wk 16); or HbA1c ≥8.5% on 2 consecutive measurements (≥8 wks apart) after Wk 24	New antihyperglycemic medication, except for a GLP-1 RA, DPP-4i, or pramlintide. Preference: • Further insulin titration in insulin glargine arm
GPGI	Average QD BG (QW 4-point SMBG profile for ≥2 consecutive wks) • >270 mg/dL (Wks 16-24); or • >240 mg/dL (Wks 25-32); or • >200 mg/dL (>Wk 32); or HbA1c ≥8.5% at Wk 24 with <0.3% improvement over 3 mos (Wks 12-24)	New antihyperglycemic medication (including prandial insulin), except for a GLP-1 RA, DPP-4i, pramlintide, or other basal insulin. Preference: • Insulin glargine (BL-Wk 16, TTT)

Source: Adapted from the Clinical Study Protocols for trials GPGK, GPGL, GPGH, GPGM, and GPGI, available at:
GPGK: \\CDSESUB1\evsprod\nda215866\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\type-2-diabetes-mellitus\5351-stud-rep-contr\i8f-mc-gpgk\gpgk-05-protocol--b-.pdf
GPGL: \\CDSESUB1\evsprod\nda215866\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\type-2-diabetes-mellitus\5351-stud-rep-contr\i8f-mc-gpgl\gpgl-05-protocol--b-.pdf
GPGH: \\CDSESUB1\evsprod\nda215866\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\type-2-diabetes-mellitus\5351-stud-rep-contr\i8f-mc-gpgh\gpgh-05-protocol--c-.pdf
GPGM: \\CDSESUB1\evsprod\nda215866\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\type-2-diabetes-mellitus\5351-stud-rep-contr\i8f-mc-gpgm\gpgm-05-protocol--b-.pdf
GPGI: \\CDSESUB1\evsprod\nda215866\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\type-2-diabetes-mellitus\5351-stud-rep-contr\i8f-mc-gpgi\gpgi-05-protocol--b-.pdf
Abbreviations: BL, baseline; DPP-4i, dipeptidyl peptidase inhibitor; FBG, fasting blood glucose; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA1c, hemoglobin A1c; med, medication; QD, daily; QW, once weekly; SGLT2i, sodium-glucose cotransporter-2 inhibitor; SMBG, self-monitored blood glucose; SU, sulfonylurea; TZD, thiazolidinedione; and WK, week.

Other Concomitant Medications. Subjects were allowed to take other concomitant medications that they required during the trial provided they would not interfere with the assessment of efficacy or safety. To mitigate gastrointestinal (GI) symptoms, investigators also could prescribe antiemetic or antidiarrheal medications per local country availability as needed.

Generally, the use of concomitant medications (antihyperglycemics, rescue medications, antiemetics, antidiarrheals, and other medications) was acceptable.

Discontinuation of Investigational Product/Study:

Dose de-escalation of tirzepatide to a lower maintenance dose was only permitted in trial GPGH, GPGM, and GPGP. Subjects in these trials could have their dose de-escalated only once and were not allowed to re-escalate. In the event of intolerable AEs (e.g., GI), the investigators were to do the following: discontinue IP if the subjects were receiving tirzepatide 5 mg, decrease the dose to 5 mg if they were receiving 7.5 mg or 10 mg, and decrease the dose to 10 mg if they were receiving 12.5 mg or 15 mg. The criteria for permanent discontinuation of IP and study in the global phase 3 trials are presented in Table 11. Subjects who permanently discontinued IP were asked to continue to participate in the trial according to the protocol to collect all planned

efficacy and safety measurements. Generally, the discontinuation criteria were consistent across trials, and adequate.

Table 11: Discontinuation Criteria for Global Phase 3 Trials

Discontinuation Criteria	GPGK	GPGL	GPGH	GPGM	GPGI
PERMANENT DISCONTINUATION FROM STUDY TREATMENT					
Subject decision	X	X	X	X	X
Increased risk of hypoglycemia*	X	X			
Hepatic event or liver test abnormality (in consultation with Applicant-designated medial monitor):					
ALT or AST >8x ULN	X	X	X	X	X
ALT or AST >5x ULN for >2 wks	X	X	X	X	X
ALT or AST >3x ULN and TBL >2x ULN or INR >1.5	X	X	X	X	X
ALT or AST >3x ULN and fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)	X	X	X	X	X
ALP >3x ULN	X	X	X	X	X
ALP >2.5x ULN and TBL >2x ULN	X	X	X	X	X
ALP >2.5x ULN and fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)	X	X	X	X	X
Inadvertently enrolled and it is determined that continued treatment with IP would not be medically appropriate	X	X	X	X	X
Acute or chronic pancreatitis	X	X	X	X	X
Diagnosed with MTC after randomization or has a post-randomization calcitonin value ≥35 ng/L that has increased at least 50% over baseline	X	X	X		X
Diagnosed with MTC after randomization				X	
Diagnosed with an active or untreated malignancy (other than basal or squamous cell skin cancer, in situ carcinomas of the cervix, or in situ prostate cancer)	X	X	X	X	X
Significant IP-related hypersensitivity reaction	X	X	X	X	X
TEAE, SAE, or clinically significant laboratory value for which the investigator believes that permanent study discontinuation is the appropriate measure to be taken	X	X	X	X	X
Pregnancy	X	X	X	X	X
Diagnosed with T1D	X	X	X	X	X
PERMANENT DISCONTINUATION FROM STUDY					
Enrollment in any other clinical study involving an IP or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study	X	X	X	X	X
Participation in the study needs to be stopped for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP	X	X	X	X	X
Pregnancy	X	X	X	X	X
Diagnosed with T1D	X	X	X	X	X
Subject requests to be withdrawn from the study	X	X	X	X	X

Source: Adapted from the Clinical Study Protocols for trials GPGK, GPGL, GPGH, GPGM, and GPGI, available at:
GPGK: \\CDSESUB1\evsprod\nda215866\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\type-2-diabetes-mellitus\5351-stud-rep-contr\i8f-mc-gpgk\gpgk-05-protocol--b-.pdf

GPGL: \\CDSESUB1\evsprod\nda215866\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\type-2-diabetes-mellitus\5351-stud-rep-contr\i8f-mc-gpgl\gpgl-05-protocol--b-.pdf
GPGH: \\CDSESUB1\evsprod\nda215866\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\type-2-diabetes-mellitus\5351-stud-rep-contr\i8f-mc-gpgh\gpgh-05-protocol--c-.pdf
GPGM: \\CDSESUB1\evsprod\nda215866\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\type-2-diabetes-mellitus\5351-stud-rep-contr\i8f-mc-gpgm\gpgm-05-protocol--b-.pdf
GPGI: \\CDSESUB1\evsprod\nda215866\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\type-2-diabetes-mellitus\5351-stud-rep-contr\i8f-mc-gpgi\gpgi-05-protocol--b-.pdf

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; GCP, Good Clinical Practice; INR, international normalized ratio; IP, investigational product; MTC, medullary thyroid carcinoma; SAE, serious adverse event; T1D, type 1 diabetes; TBL, total bilirubin; TEAE, treatment-emergent adverse event; ULN, upper limit of normal; and wks, weeks.

*Increased risk of hypoglycemia: Single episode of severe hypoglycemia or having more than 1 episode of documented symptomatic hypoglycemia within a 1-week period at any time during the treatment period (GPGL).

Study Endpoints:

The primary and key secondary objectives (controlled for type I error) and endpoints for each of five global phase 3 trials are presented in Table 12.

Table 12: Objectives and Endpoints for Five Global Phase 3 Trials

Objectives	Endpoints
Trial GPGK (SURPASS-1)	
Primary • To demonstrate that tirzepatide QW 5 mg, and/or 10 mg, and/or 15 mg are superior to placebo at 40 weeks for:	• Mean change in HbA1c from baseline
Key Secondary (controlled for type 1 error) • To demonstrate superiority of tirzepatide QW 5 mg, and/or 10 mg, and/or 15 mg to placebo at 40 weeks for:	• Mean change in body weight from baseline • Incidence of subjects with HbA1c target values of <7.0% • Mean change in fasting serum glucose (FSG) (central laboratory) from baseline • Incidence of subjects with HbA1c target values of <5.7%
Trial GPGL (SURPASS-2)	
Primary To demonstrate that tirzepatide 10 mg and/or 15 mg QW are noninferior to semaglutide 1 mg QW at 40 weeks for:	• Mean change in HbA1c from baseline

Objectives	Endpoints
Key Secondary (controlled for type 1 error) Efficacy	
• To demonstrate that tirzepatide 5 mg QW is noninferior to semaglutide 1 mg QW at 40 weeks for:	• Mean change in HbA1c from baseline
• To demonstrate that tirzepatide 5 mg, 10 mg, and/or 15 mg QW is superior to semaglutide 1 mg QW at 40 weeks for:	• Mean change in body weight from baseline • Mean change in HbA1c from baseline • Incidence of subjects with HbA1c target values of <7.0%
• To demonstrate that tirzepatide 10 mg and/or 15 mg QW is superior to semaglutide 1 mg QW at 40 weeks for:	• Incidence of subjects with HbA1c target values of <5.7%
Trial GPGH (SURPASS-3)	
Primary To demonstrate that QW tirzepatide 10 mg and/or 15 mg are noninferior to insulin degludec at 52 weeks for:	• Mean change in HbA1c from baseline
Key Secondary (controlled for type 1 error) **Efficacy**	
• To demonstrate that QW tirzepatide 5 mg is noninferior to insulin degludec at 52 weeks for:	• Mean change in HbA1c from baseline
• To demonstrate that QW tirzepatide 5 mg, 10 mg, and/or 15 mg is superior to insulin degludec at 52 weeks for:	• Mean change in body weight from baseline
• To demonstrate that QW tirzepatide 5 mg, 10 mg, and/or 15 mg is superior to insulin degludec at 52 weeks for:	• Mean change in HbA1c from baseline
• To demonstrate QW tirzepatide 5 mg, 10 mg, and/or 15 mg is superior to insulin degludec at 52 weeks for:	• Incidence of subjects with HbA1c target values of <7.0%
Trial GPGM (SURPASS-4)	
Primary To demonstrate that QW tirzepatide 10 mg and/or 15 mg is noninferior to insulin glargine at 52 weeks for:	• Mean change in HbA1c from baseline

Objectives	Endpoints
Key Secondary (controlled for type 1 error) Efficacy • To demonstrate that QW tirzepatide 5 mg is noninferior to insulin glargine at 52 weeks for:	• Mean change in HbA1c from baseline
• To demonstrate that QW tirzepatide 5 mg, 10 mg, and/or 15 mg is superior to insulin glargine at 52 weeks for:	• Mean change in body weight from baseline
• To demonstrate that QW tirzepatide 5 mg, 10 mg, and/or 15 mg is superior to insulin glargine at 52 weeks for:	• Mean change in HbA1c from baseline
• To demonstrate that QW tirzepatide 5 mg, 10 mg, and/or 15 mg is superior to insulin glargine at 52 weeks for:	• Incidence of subjects with HbA1c target values of <7.0%
Trial GPGI (SURPASS-5)	
Primary To demonstrate superiority of QW tirzepatide 10 mg and/or 15 mg versus placebo when added to titrated basal insulin glargine, with or without metformin, at 40 weeks for:	• Mean change in HbA1c from baseline

Objectives	Endpoints
Key Secondary (controlled for type 1 error) Efficacy	
• To demonstrate superiority of QW tirzepatide 5 mg versus placebo when added to titrated basal insulin glargine, with or without metformin, at 40 weeks for:	• Mean change in HbA1c from baseline
• To demonstrate superiority of QW tirzepatide 5 mg, 10 mg, and/or 15 mg versus placebo when added to titrated basal insulin glargine, with or without metformin, at 40 weeks for:	• Mean change in body weight from baseline • Incidence of subjects with HbA1c target values of <7.0% • Mean change in FSG (central laboratory) from baseline
• To demonstrate superiority of QW tirzepatide 10 mg, and/or 15 mg versus placebo when added to titrated basal insulin glargine, with or without metformin, at 40 weeks for:	• Incidence of subjects with HbA1c target values of <7.0%
• To demonstrate superiority of QW tirzepatide 10 mg and/or 15 mg versus placebo when added to titrated basal insulin glargine, with or without metformin, at 40 weeks for:	• Incidence of subjects with HbA1c target values of <5.7%

Source: Adapted from the Clinical Study Protocols for trials GPGK (page 23 of 90), GPGL (page 24 of 98), GPGH (page 25 of 94), GPGM (page 25 of 93), and GPGI (page 25 of 99), available at:
GPGK: \\CDSESUB1\evsprod\nda215866\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\type-2-diabetes-mellitus\5351-stud-rep-contr\i8f-mc-gpgk\gpgk-05-protocol--b-.pdf
GPGL: \\CDSESUB1\evsprod\nda215866\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\type-2-diabetes-mellitus\5351-stud-rep-contr\i8f-mc-gpgl\gpgl-05-protocol--b-.pdf
GPGH: \\CDSESUB1\evsprod\nda215866\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\type-2-diabetes-mellitus\5351-stud-rep-contr\i8f-mc-gpgh\gpgh-05-protocol--c-.pdf
GPGM: \\CDSESUB1\evsprod\nda215866\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\type-2-diabetes-mellitus\5351-stud-rep-contr\i8f-mc-gpgm\gpgm-05-protocol--b-.pdf
GPGI: \\CDSESUB1\evsprod\nda215866\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\type-2-diabetes-mellitus\5351-stud-rep-contr\i8f-mc-gpgi\gpgi-05-protocol--b-.pdf
Abbreviations: FSG, fasting serum glucose; HbA1c, hemoglobin A1c; and QW, once weekly.

Primary Efficacy Endpoint:

- Mean change from baseline in HbA1c (%) at Endpoint (Weeks 40 or 52)

The primary efficacy endpoint for all five Phase 3 trials was the change from baseline (randomization) in HbA1c (%) to Week 40 (GPGK, GPGL, and GPGI) or Week 52 (GPGH, and GPGM). Scheduled measurements of HbA1c used for eligibility criteria, efficacy analyses, and need for glycemic rescue, were performed at a Central Laboratory.

HbA1c is considered an appropriate efficacy endpoint, and a positive result would indicate a clinically meaningful benefit for the following reasons:

- HbA1c has been considered a widely-accepted, objective, surrogate measure of glycemic control that correlates well with mean blood glucose over the preceding 1-3 months.[139]
- The National Glycohemoglobin Standardization Program (NGSP) has established and promulgated standardized assays for HbA1c based on data from the Diabetes Control and Complications Trial (DCCT). Use of standardized methodology has reduced inter-laboratory coefficients of variation to <5%.[140,141]
- HbA1c has excellent reliability, predicts some of the diabetes-specific complications, and continues to provide a basis for treatment decisions in patients with T2D.[138,142]
- Lowering HbA1c reduces microvascular complications[61,67,68,138,143-148] and may lower the risk of macrovascular complications[15,63,71] in patients with diabetes (T1D and T2D).

For purposes of drug approval and labeling, the Agency still considers that the final demonstration of efficacy should be based on a reduction in HbA1c (i.e., HbA1c is the primary endpoint of choice, albeit a surrogate) to support a T2D indication of glycemic control.

Key Secondary Endpoints:

In addition to the primary efficacy endpoint, the Applicant also evaluated other glycemic endpoints (i.e., FSG in trials GPGK and GPGI, the incidence of subjects with an HbA1c <7% in all five trials, and the incidence of subjects with an HbA1c <5.7% in trials GPGK, GPGL, GPGI), and changes in BW (all five trials). The key secondary endpoints were assessed at Week 40 for trials GPGK, GPGL, and GPGI, and at Week 52 for trials GPGH, and GPGM. The following secondary endpoints were included in the Applicant's hierarchical testing procedure:

- Mean change from baseline at Endpoint (Weeks 40 or 52)in:
  - FSG (mg/dL)
  - BW (kg)
- Incidence of subjects at Endpoint (Weeks 40 or 52) with an:
  - HbA1c <7%
  - HbA1c <5.7% (trials GPGK, GPGL, and GPGI)

The analyses of key secondary endpoints were based on measurements performed by a Central Laboratory. To control for a two-sided family wise type I error of 5%, the Applicant used sequentially rejective graphical procedures to adjust for multiple comparisons (Appendix 13.4).[149] Please refer to Dr. Tu's Statistical Review for further details on the hierarchy testing strategy for these endpoints.

The glycemic endpoints, FSG, and incidence of subjects achieving an HbA1c <7%, and mean changes in body weight are considered supportive measures of efficacy and have been included in product labeling of other approved antihyperglycemic products, including GLP-1 RAs.[2,3,5,7-11,24-26] The Applicant did not propose to include the analyses of the incidence of subjects with HbA1c

target values of <5.7% in product labeling. This secondary endpoint is not included in labeling of GLP-1 RA products, and the clinical meaningfulness of this endpoint (i.e., compared to achieving an HbA1c <7%) is unclear at this time.

Other Secondary Endpoints:

Other supportive secondary endpoints for the phase 3 trials included:

- Incidence of subjects with HbA1c target of ≤6.5%, <5.7%
- Mean change in daily average 7-point self-monitored blood glucose profiles from baseline
- Incidence of subjects who achieved weight loss of ≥5%, ≥10%, and ≥15%
- Patient-reported outcomes: Ability to Perform Physical Activities of Daily Living (APPADL), Diabetes Treatment Satisfaction Questionnaire change (DTSQc), Diabetes Treatment Satisfaction Questionnaire status (DTSQs), European Quality of Life Five Dimension Five Level (EQ-5D-5L), and Impact of Weight on Self-Perception (IW-SP).
- Safety: Treatment-emergent adverse event (TEAEs), clinical laboratory tests (including assessment of anti-drug antibodies), electrocardiogram findings (ECGs), vital signs, physical examination findings, and initiation of glycemic rescue therapy.
- Pharmacokinetics: population PK and PD parameters

Statistical Analysis Plan:

Drs. Wenda Tu and Shanti Gomatam were efficacy and safety statisticians for this Application, respectively. Please refer to their reviews (dated February 15, 2022, and April 21, 2022) for detailed discussion of statistical analysis plans (SAPs) for the efficacy and safety analyses, respectively.

Sample Size Requirements

The assumptions used for the sample size calculations for the five global phase 3 trials are presented in Table 13. All five trials had ≥90% power to demonstrate superiority or noninferiority of tirzepatide to the respective comparator. Based on these assumptions/estimates, the actual numbers of subjects randomized in these trials were adequate.

Table 13: Sample Size Determinations for the Five Global Phase 3 Trials

Assumptions	GPGK	GPGL	GPGH	GPGM	GPGI
Hypothesis tested	Superiority	Noninferiority	Superiority*	Superiority*	Superiority
Comparison	TZP 5 or 10 or 15 mg vs. PBO	TZP 10 or 15 mg vs. Sema 1 mg	TZP 10 or 15 mg vs. Ins Deg	TZP 10 or 15 mg vs. Ins Glar	TZP 10 or 15 mg vs. PBO
Treatment difference —TZP vs. comparator (%)	-0.65	NIM 0.3†	-0.35	-0.3	-0.6

Assumptions	GPGK	GPGL	GPGH	GPGM	GPGI
Two-sided alpha level (%)	0.0167	0.025	0.025	0.025	0.025
Common SD (%)					
Efficacy estimand[a]	1.1	1.1	1.1	1.1	1.1
Treatment-effect estimand[b]	1.3	1.3	1.3	1.3	1.3
Discontinuation/rescue rate (%)‡	25 (TZP) 35 (PBO)	28	28	28	28
Estimated sample size (n)	472	1872	1420	1878	472
Subjects randomized (n)	478	1879	1444	2002	475
Treatment allocation	TZP 5 or 10 or 15 mg or PBO (1:1:1:1)	TZP 5 or 10 or 15 mg or Sema 1 mg (1:1:1:1)	TZP 5 or 10 or 15 mg or Ins Deg (1:1:1:1)	TZP 5 or 10 or 15 mg or Ins Glar (1:1:1:3)	TZP 5 or 10 or 15 mg or PBO (1:1:1:1)
Power (%)	90	90	90	90	90

Source: Adapted from the Clinical Study Protocols for trials GPGK (page 60 of 90), GPGL (page 67 of 98), GPGH (page 66 of 94), GPGM (page 64 of 93), and GPGI (page 68 of 99), available at:
GPGK: \\CDSESUB1\evsprod\nda215866\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\type-2-diabetes-mellitus\5351-stud-rep-contr\i8f-mc-gpgk\gpgk-05-protocol--b-.pdf
GPGL: \\CDSESUB1\evsprod\nda215866\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\type-2-diabetes-mellitus\5351-stud-rep-contr\i8f-mc-gpgl\gpgl-05-protocol--b-.pdf
GPGH: \\CDSESUB1\evsprod\nda215866\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\type-2-diabetes-mellitus\5351-stud-rep-contr\i8f-mc-gpgh\gpgh-05-protocol--c-.pdf
GPGM: \\CDSESUB1\evsprod\nda215866\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\type-2-diabetes-mellitus\5351-stud-rep-contr\i8f-mc-gpgm\gpgm-05-protocol--b-.pdf
GPGI: \\CDSESUB1\evsprod\nda215866\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\type-2-diabetes-mellitus\5351-stud-rep-contr\i8f-mc-gpgi\gpgi-05-protocol--b-.pdf
Abbreviations: Ins Deg, insulin degludec; Ins Glar, insulin glargine; NIM, noninferiority margin; PBO, placebo; QW, once weekly; SC, subcutaneous; SD, standard deviation; Sema, semaglutide; TZP, tirzepatide; and vs., versus.

* The primary objective of the trial was to demonstrate that the tirzepatide 10 mg and 15 mg doses (tested in parallel vs. comparator) were noninferior to comparator (0.3% noninferiority boundary), the trial was powered to assess superiority.
† Noninferiority margin of 0.3% to demonstrate noninferiority of the tirzepatide 10 mg and/or 15 mg SC QW doses to semaglutide 1 mg SC QW.
‡ Anticipated proportion of subjects who would discontinue IP prematurely or require antihyperglycemic rescue therapy.
[a] Efficacy estimand: takes into account data collected prior to intercurrent events (e.g., discontinuation of IP or initiation of glycemic rescue therapy), and thus the SD is relatively small (i.e., 1.1%).
[b] Treatment-effect estimand: includes all data regardless of intercurrent events, and thus the SD is relatively large (i.e., 1.3%) and there is no need to consider discontinuation of IP or initiation of glycemic rescue therapy.

Primary and Key Secondary Endpoints

Two estimands (i.e., estimated measures of treatment effect), the "treatment-effect" estimand (the Agency's preferred approach) and the "efficacy" estimand (the Applicant's preferred approach), were used by the Applicant to evaluate the treatment effect from different perspectives, which accounted for intercurrent events differently. The treatment-effect estimand was the treatment effect among all randomized subjects, irrespective of premature discontinuation of IP or introduction of glycemic rescue therapy. The efficacy estimand was the treatment effect between tirzepatide and comparator among all randomized participants who continued to receive IP (i.e., on-treatment efficacy) without the use of glycemic rescue therapy. The target population for the primary and key secondary analyses of both estimands was the modified intention-to-treat (mITT) population, defined as all randomized subjects who took at least one dose of IP. Participants who were inadvertently enrolled (e.g., randomized but failed inclusion criteria or met exclusion criteria) were excluded from these analyses. The full analysis

set (i.e., all available data obtained during the treatment period, regardless of adherence to IP or initiation of glycemic rescue therapy) was the analysis set. The Applicant used an analysis of covariance (ANCOVA) model (adjusted for treatment, baseline HbA1c, country/pooled country, and past/baseline use of antihyperglycemic medications) for the primary efficacy analysis, and ANCOVA (adjusted for treatment, baseline measures of the variable, country/pooled country, and baseline HbA1c category) for continuous key secondary endpoint data. The analysis of dichotomous data for key secondary endpoints (e.g., incidence of subjects achieving an HbA1c <7% or <5.7%) was performed using logistic regression (adjusted using the same covariates as were included in the primary efficacy analysis). Missing primary endpoint data was imputed using a retrieved dropout approach (which assumes subjects with missing primary endpoint data had a similar treatment effect as subjects from the same treatment arm who discontinued IP but still had their primary efficacy endpoint measured) for trials GPGL, GPGH, and GPGM. For the placebo-controlled trials (GPGK and GPGI), a placebo-based multiple imputation approach (which assumes subjects with missing primary endpoint data had a similar treatment effect as the placebo-treated subjects who have completed the study) was used due to insufficient retrieved dropout data. The Applicant also performed sensitivity analyses of the primary efficacy endpoint using a return-to-baseline approach (which assumes subjects with missing primary endpoint data had zero treatment effect [or "returned to baseline"]) for missing endpoint data.

Protocol Amendments:

Many of the protocol amendments involved technical corrections and clarifications. However, the COVID-19 pandemic occurred during the conduct of the five global phase 3 trials, and therefore, operational guidances were created and respective protocols were amended to allow some flexibility in the conduct of these trials (e.g., adjusting the timing of visit windows, allow use of mobile [in-home] healthcare visits) to maintain study feasibility, data integrity, and subject safety. Generally, COVID-19-related disruptions, which resulted in missing primary endpoint data in 0.2-0.9% of subjects and missing key secondary endpoint data in 0.2-2.3% of subjects across the five trials, would not be expected to meaningfully alter the efficacy conclusions. Please refer to Table 2 above for additional information.

6.1.2. Study Results

Compliance with Good Clinical Practices:

The Applicant states that the five global phase 3 trials were conducted in accordance with the protocol, and consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines, applicable ICH GCP guidelines, and applicable laws and regulations.

Financial Disclosure:

Across seven phase 2/3 covered trials (GPGB, GPGF, GPGH, GPGI, GPGK, GPGL, GPGM) in the

tirzepatide development program, 24 Form FDA 3455 reports were submitted that involved 18 individual investigators with financial interests/arrangements ($27,241.49 to $204,371.78) to disclose. In total, these investigators enrolled 177 (2.6%) of the 6690 subjects randomized across these trials. A single investigator was not certified (no longer at study site). The three investigators with the highest disclosable incomes (≥$177,055.73 to $204,371.78) randomized ≤5 subjects each. The Applicant stated that the trial design elements, including but not limited to the number of clinical investigators, the number of global study sites, and prespecified and standardized objective endpoints, were implemented to minimize site personnel bias due to disclosable financial interest. The Applicant's rationale for the steps taken to minimize site personnel bias is reasonable.

I believe there was no undue bias or influence that could affect the outcome of the studies or the review of this NDA.

Subject Disposition:

The overall subject disposition of all seven phase 3 trials, including the five global phase 3 trials, is presented as a side-by-side comparison in Table 23. Across the five global phase 3 trials, which randomized 6278 subjects, 89.5% to 95.4% of subjects completed the respective trials, and 85.2% to 91.2% completed the treatment. Similar percentages of subjects completed the trials across study arms. However, in each of the five trials, higher proportions of subjects discontinued IP due to AEs in the tirzepatide treatment arms. Please refer to Section 8.4 for additional information on subject disposition.

Protocol Violations/Deviations:

Important protocol deviations, including but not limited to, the informed consent, eligibility, study drug, and study procedures, were assessed and captured in the Trial Issues Management Plan. In the five global phase 3 trials, there were one or more important protocol deviations for 68 (14.2%) subjects in trial GPGK, 186 (9.9%) subjects in trial GPGL, 229 (15.9%) subjects in trial GPGH, 265 (13.2%) subjects in trial GPGM, and 157 (33.1%) subjects in trial GPGI. Deviations appeared to be randomly distributed across treatment arms (Table 14). The most common deviations in the tirzepatide arms were related to IP (e.g., compliance <75%) and study procedures (e.g., missing HbA1c or weight data).

A review of the above important protocol deviations did not reveal any obvious/relevant trends or treatment differences across trial arms. The Applicant felt that due to the limited number and similar distribution across the treatment groups, these protocol deviations were not likely to impact the analyses or conclusions presented in the clinical study reports (CSRs) for the respective trials.

I concur that the reported important protocol deviations are unlikely to have affected the overall conclusions of the five phase 3 trials.

In addition to important protocol deviations, an IWRS deviation, due to an incorrect configuration, led to dispensation of a higher dose of IP to 17 subjects randomized to the tirzepatide 15 mg arm in trial GPGI. Please refer to Section 4.1 for additional information.

Table 14: Important Protocol Deviations Across the Five Global Phase 3 Trials*

	GPGK		GPGL		GPGH		GPGM		GPGI	
System Organ Class MedDRA PT	PBO (N=115)	TZP ALL (N=363)	Sema 1 mg (N=469)	TZP ALL (N=1410)	Ins Deg (N=365)	TZP ALL (N=1079)	Ins Glar (N=1005)	TZP ALL (N=997)	PBO (N=120)	TZP ALL (N=355)
Subjects with ≥1 deviation — no. (%)	**20 (17.4)**	**48 (13.2)**	**44 (9.4)**	**142 (10.1)**	**46 (12.6)**	**183 (17.0)**	**107 (10.6)**	**158 (15.8)**	**44 (36.7)**	**113 (31.8)**
Eligibility	**3 (2.6)**	**5 (1.4)**	**2 (0.4)**	**13 (0.9)**	**11 (3.0)**	**28 (2.6)**	**19 (1.9)**	**28 (2.8)**	**9 (7.5)**	**23 (6.5)**
All inclusion and exclusion criteria deviations	3 (2.6)	5 (1.4)	2 (0.4)	13 (0.9)	11 (3.0)	28 (2.6)	19 (1.9)	28 (2.8)	9 (7.5)	23 (6.5)
Informed consent	**—**	**—**	**—**	**—**	**3 (0.8)**	**9 (0.8)**	7 (0.7)	3 (0.3)	**—**	**—**
Procedure conducted prior to or without consent	—	—	—	—	3 (0.8)	9 (0.8)	4 (0.4)	3 (0.3)	—	—
Informed consent not assigned	—	—	—	—	—	—	3 (0.3)	0	—	—
Safety	**0**	**2 (0.6)**	**2 (0.4)**	**9 (0.6)**	**1 (0.3)**	**2 (0.2)**	**7 (0.7)**	**5 (0.5)**	**0**	**1 (0.3)**
SAEs not reported within 24 hours	0	1 (0.3)	1 (0.2)	6 (0.4)	1 (0.3)	2 (0.2)	7 (0.7)	5 (0.5)	0	1 (0.3)
Pregnant and/or breastfeeding	0	1 (0.3)	1 (0.2)	3 (0.2)	—	—	—	—	—	—
Investigational product	**14 (12.2)**	**30 (8.3)**	**31 (6.6)**	**99 (7.0)**	**10 (2.7)**	**78 (7.2)**	**32 (3.2)**	**103 (10.3)**	**1 (0.8)**	**19 (5.4)**
Subject took medication not fit for use	0	1 (0.3)	—	—	—	—	2 (0.2)	1 (0.1)	—	—
Overdose	0	5 (1.4)	8 (1.7)	16 (1.1)	0	7 (0.6)	0	25 (2.5)	1 (0.8)	2 (0.6)
Overall investigational product compliance <75%	9 (7.8)	15 (4.1)	23 (4.9)	80 (5.7)	8 (2.2)	65 (6.0)	10 (1.0)	54 (5.4)	0	13 (3.7)
Incorrect stratification category	5 (4.3)	10 (2.8)	0	3 (0.2)	2 (0.5)	6 (0.6)	20 (2.0)	25 (2.5)	0	4 (1.1)
Other	—	—	—	—	—	—	1 (0.1)	0	—	—
Study procedures	**3 (2.6)**	**15 (4.1)**	**12 (2.6)**	**28 (2.0)**	**26 (7.1)**	**85 (7.9)**	**51 (5.1)**	**36 (3.6)**	**37 (30.8)**	**83 (23.4)**
Subjects met study drug discontinuation criteria but continued to receive study drug	—	—	—	—	—	—	1 (0.1)	1 (0.1)	—	—
Subjects met study discontinuation criteria but continued in the study	—	—	—	—	—	—	—	—	—	—
Subjects received excluded antihyperglycemic concomitant medications	—	—	5 (1.1)	9 (0.6)	5 (1.4)	23 (2.1)	3 (0.3)	2 (0.2)	0	5 (1.4)
Subjects received weight loss medications	—	—	—	—	—	—	—	—	—	—
Missing HbA1c at baseline, primary endpoint, or the early termination visit	1 (0.9)	5 (1.4)	4 (0.9)	11 (0.8)	4 (1.1)	12 (1.1)	39 (3.9)	30 (3.0)	0	2 (0.6)
Missing FSG at baseline, primary endpoint, or the early termination visit	3 (2.6)	13 (3.6)	—	—	—	—	—	—	2 (1.7)	1 (0.3)
Missing weight at baseline, primary endpoint, or the early termination visit	1 (0.9)	4 (1.1)	2 (0.4)	12 (0.9)	4 (1.1)	13 (1.2)	27 (2.7)	23 (2.3)	0	1 (0.3)
Follow-up dilated fundoscopic exam was not performed when clinically indicated	—	—	—	—	—	—	—	—	—	—

	GPGK		GPGL		GPGH		GPGM		GPGI	
System Organ Class MedDRA PT	PBO (N=115)	TZP ALL (N=363)	Sema 1 mg (N=469)	TZP ALL (N=1410)	Ins Deg (N=365)	TZP ALL (N=1079)	Ins Glar (N=1005)	TZP ALL (N=997)	PBO (N=120)	TZP ALL (N=355)
Subject met IP discontinuation criteria but continued to receive IP	—	—	1 (0.2)	2 (0.1)	—	—	—	—	—	—
CGM compliance 3 days or less per CGM session	—	—	—	—	15 (4.1)	42 (3.9)	—	—	—	—
Missing MRI at baseline or primary endpoint	—	—	—	—	2 (0.5)	3 (0.3)	—	—	—	—
Equipment not available	—	—	—	—	—	—	—	—	2 (1.7)	0
Insulin dose not reduced 20% when applicable	—	—	—	—	—	—	—	—	17 (14.2)	30 (8.5)
Noncompliance with TTT algorithm per protocol weeks -2 to 0	—	—	—	—	—	—	—	—	9 (7.5)	27 (7.6)
Noncompliance with TTT algorithm per protocol weeks 0 to 4	—	—	—	—	—	—	—	—	14 (11.7)	31 (8.7)

Source: Adapted from the Clinical Study Reports for trials GPGK (pages 68-69 of 2367), GPGL (pages 86-87 of 3625, GPGH (pages 76-77 of 3104), GPGM (pages 86-87 of 5827), and GPGI (pages 73-74 of 2898), available at: \\CDSESUB1\evsprod\NDA215866\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\type-2-diabetes-mellitus\5351-stud-rep-contr

Abbreviations: —, not reported/not applicable; CGM, continuous glucose monitoring; FSG, fasting serum glucose; IP, investigational product; MRI, magnetic resonance imaging; no., number; SAE, serious adverse effect; and TTT, treat-to-target.

* All randomized population (N=6,278 subjects).

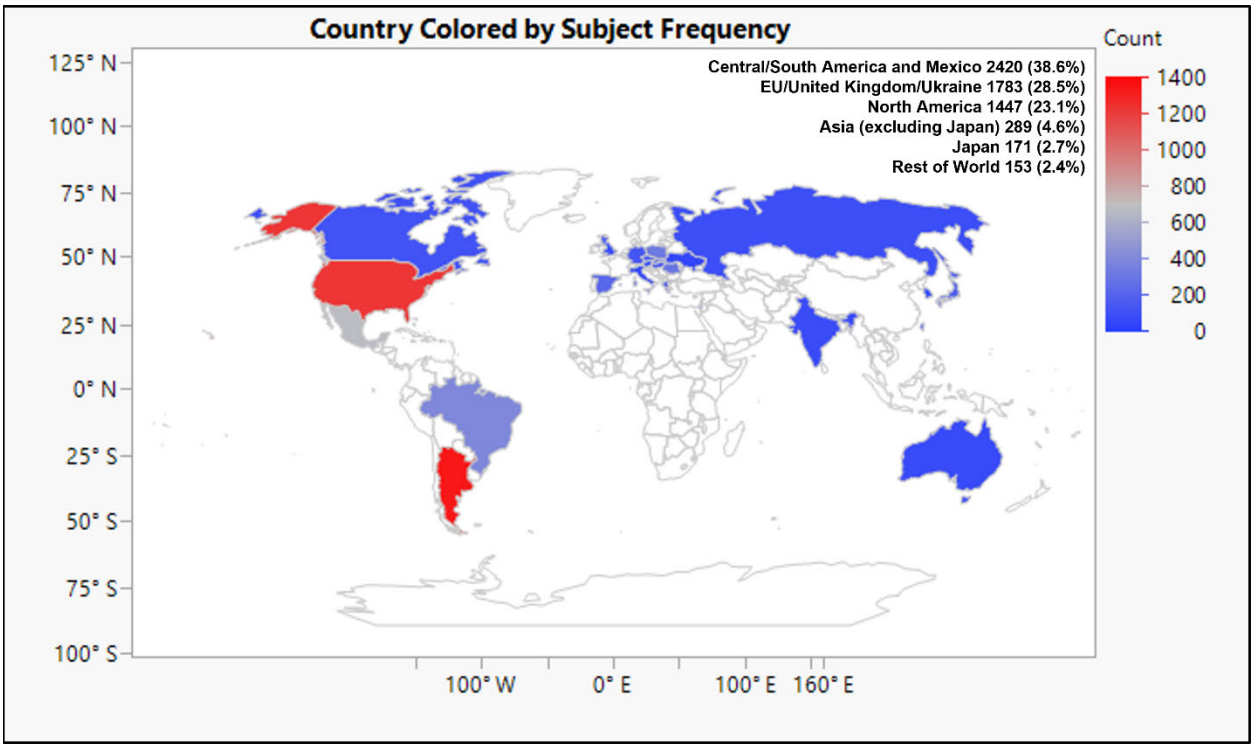
Demographics and Clinical Characteristics:

Applicability of Foreign Data

The five global phase 3 trials were conducted worldwide; with the approximately 23.1% of the 6,263 randomized and treated subjects (mITT population) in these trials residing in North America, 38.6% in Central/South America and Mexico, 28.5% in the EU/United Kingdom/Ukraine, 4.6% Asia (excluding Japan), 2.7% Japan, and 2.4% from the rest of the world (Figure 4).

In their rationale for why the foreign data for this NDA is applicable to the US population/practice of medicine, the Applicant noted that all trials were conducted in accordance with GCP, and they claim that the five global phase 3 trials met the conditions of 21 CFR 312.120 (Foreign Clinical Studies Not Conducted Under an Investigational New Drug Application).[150] Except for differences in trial design intended to reflect different stages of T2D progression, these trials included similar inclusion (e.g., diagnosis of T2D based on the WHO classification was consistent with ADA criteria[14]) and exclusion criteria (e.g., similar demographics and disease characteristics). The US and non-US regions also were similar with the selection of background and glycemic rescue therapies in accordance with ADA, EASD, and International Diabetes Federation guidelines.[17,31,151]

Figure 4: Subject Accrual by Geographic Region for the Five Global Phase 3 Trials



Source: Derived from the integrated-database adsl.xpt datasets, available at: \\CDSESUB1\evsprod\NDA215866\0001\m5\datasets
Abbreviation: EU, European Union.

I agree with the Applicant's rationale for the applicability of foreign data and acknowledge that the proportion of subjects from North America included in this Application is consistent with other antihyperglycemic clinical development programs.

Baseline Demographics and Clinical Characteristics

The baseline demographics and clinical characteristics of the randomized/treated subjects (mITT population) in the five global phase 3 trials are summarized below (Table 15). Within and across trials, treatment groups were reasonably balanced for demographics/clinical characteristics at baseline, except for differences in eligibility criteria and study designs intended to reflect different stages of T2D progression. Overall, the trial populations were predominantly White (80%) and male (55%). The mean age was approximately 58 years, of which 33% of the population was over age 65 years and 5% were 75 years and older. The populations also were overweight (mean BMI was approximately 33 kg/m^2).

Relatively low proportions of several non-White racial subgroups make it somewhat difficult to generalize efficacy and safety findings to all patient populations. However, Dr. Tu performed subgroup analyses of the primary endpoint (i.e., HbA1c change from baseline) using shrinkage estimates to account for limited sample sizes, which did not reveal obvious treatment differences

by race (i.e., racial subgroups favored the tirzepatide arms). Of interest, approximately 25% and 11% of subjects randomized in trials GPGK and GPGL, respectively, were of American Indian or Alaska Native ancestry, a population often underrepresented in antihyperglycemic development programs. Additionally, the patient demographics and clinical characteristics of subjects randomized in trial GPGM (enriched with high CV risk subjects) and GPGI (receiving basal insulin), were reflective of patient populations with more advanced T2D (e.g., older age, long-standing T2D, more concomitant background antihyperglycemic medications, and higher proportions of subjects with renal impairment).

Table 15: Baseline Demographics and Clinical Characteristics of the Five Global Phase 3 Trials*

Region	n (%)				
	GPGK	GPGL	GPGH	GPGM	GPGI
Region, n (%)	**478**	**1878**	**1437**	**1995**	**475**
North America	152 (31.8)	534 (28.4)	330 (23.0)	385 (19.3)	46 (9.7)
Central/South America and Mexico	164 (34.3)	1139 (60.6)	224 (15.6)	893 (44.8)	-
Asia (excluding Japan)	73 (15.3)	87 (4.6)	70 (4.9)	59 (3.0)	-
Japan	89 (18.6)	-	-	-	82 (17.3)
EU/United Kingdom/Ukraine	-	72 (3.8)	813 (56.6)	551 (27.6)	347 (73.1)
Rest of World	-	46 (2.4)	-	107 (5.4)	-
Sex, n (%)					
Male	247 (51.7)	882 (47.0)	802 (55.8)	1246 (62.5)	264 (55.6)
Female	231 (48.3)	996 (53.0)	635 (44.2)	749 (37.5)	211 (44.4)
Age (years)					
Mean ± SD	54.1 ± 11.9	56.6 ± 10.4	57.4 ± 10.0	63.6 ± 8.6	60.6 ± 9.9
Median	54.5	57.0	58.0	64.0	61.0
Min; Max	18; 88	21; 91	22; 84	32; 91	27; 83
Age Group 1, n (%)					
<65 years	373 (78.0)	1420 (75.6)	1058 (73.6)	1047 (52.5)	283 (59.6)
≥65 years	105 (22.0)	458 (24.4)	379 (26.4)	948 (47.5)	192 (40.4)
Age Group 2, n (%)					
<75 years	468 (97.9)	1835 (97.7)	1395 (97.1)	1797 (90.1)	451 (94.9)
≥75 years	10 (2.1)	43 (2.3)	42 (2.9)	198 (9.9)	24 (5.1)
Age Group 3, n (%)					
<85 years	477 (99.8)	1876 (99.9)	1437 (100.0)	1985 (99.5)	475 (100.0)
≥85 years	1 (0.2)	2 (0.1)	0	10 (0.5)	0
Ethnicity, n (%)					
Hispanic/Latino	207 (43.3)	1317 (70.1)	421 (29.3)	950 (47.6)	22 (4.6)
Not Hispanic/Latino	184 (38.5)	561 (29.9)	1009 (70.2)	1030 (51.6)	380 (80.0)
Not Reported	87 (18.2)	0	7 (0.5)	15 (0.8)	73 (15.4)
Race, n (%)					
White	170 (35.6)	1551 (82.6)	1307 (91.0)	1629 (81.8)	380 (80.0)
Asian	168 (35.1)	25 (1.3)	76 (5.3)	70 (3.5)	85 (17.9)

Region	n (%)				
	GPGK	GPGL	GPGH	GPGM	GPGI
American Indian or Alaska Native	118 (24.7)	208 (11.1)	4 (0.3)	173 (8.7)	2 (0.4)
Black or African American	22 (4.6)	79 (4.2)	44 (3.1)	73 (3.7)	6 (1.3)
Multiple	0	12 (0.6)	2 (0.1)	43 (2.2)	2 (0.4)
Native Hawaiian or other Pacific Islander	0	3 (0.2)	4 (0.3)	3 (0.2)	0
Weight (kg)					
Mean ± SD	85.9 ± 19.77	93.7 ± 21.86	94.3 ± 20.06	90.3 ± 18.66	95.2 ± 21.64
Median	82.9	90.1	91.6	88.3	93.5
Min; Max	44.6; 175.0	50.1; 222.1	53.2; 229.0	51.5; 227.0	43.1; 198.0
BMI (kg/m^2)					
Mean ± SD	31.9 ± 6.59	34.2 ± 6.93	33.5 ± 6.06	32.6 ± 5.54	33.4 ± 6.06
Median	30.4	32.8	32.6	31.7	32.8
Min; Max	21.6; 68.3	22.7; 89.3	21.5; 67.4	21.7; 67.9	22.7; 55.2
BMI Group, n (%)					
<30 kg/m^2	224 (46.9)	552 (29.4)	446 (31.0)	718 (36.0)	152 (32.0)
≥30 to <35 kg/m^2	123 (25.7)	636 (33.9)	496 (34.5)	721 (36.1)	143 (30.1)
≥35 kg/m^2	131 (27.4)	690 (36.7)	495 (34.4)	556 (27.9)	180 (37.9)
Duration of Diabetes (years)					
Mean ± SD	4.7 ± 5.4	8.62 ± 6.46	8.38 ± 6.24	11.78 ± 7.51	13.3 ± 7.3
Median	2.8	7.06	7.27	10.53	11.93
Min; Max	0.0; 32.8	0.3; 42.0	0.0; 59.7	0.3; 48.7	0.6; 39.7
Duration of Diabetes Group, n (%)					
≤5 years	323 (67.6)	643 (34.2)	502 (35.0)	368 (18.4)	58 (12.2)
>5 to ≤10 years	89 (18.6)	599 (31.9)	465 (32.4)	1058 (53.0)	111 (23.4)
>10 years	66 (13.8)	636 (33.9)	469 (32.7)	569 (28.5)	306 (64.4)
Antihyperglycemic Treatment, n (%)					
No oral antihyperglycemic medication	478 (100.0)	0	0	0	0
1 oral antihyperglycemic medication	0	1878 (100.0)	979 (68.1)	725 (36.3)	0
2 oral antihyperglycemic medications	0	0	458 (31.9)	1052 (52.7)	0
3 oral antihyperglycemic medications	0	0	0	217 (10.9)	0
Insulin	0	0	0	0	81 (17.1)
Insulin + metformin	0	0	0	0	394 (82.9)
HbA1c (%)					
Mean ± SD	7.94 ± 0.87	8.28 ± 1.03	8.17 ± 0.91	8.52 ± 0.88	8.31 ± 0.85
Median	7.80	8.10	8.00	8.40	8.20
Min; Max	5.2; 11.5	5.6; 12.2	4.9; 11.5	5.5; 15.8	6.3; 11.0
HbA1c (%) Group, n (%)					
≤8.5%	378 (79.1)	1192 (63.5)	1005 (69.9)	1131 (56.7)	N/A
≥8.5%	100 (20.9)	686 (36.5)	432 (30.1)	864 (43.3)	N/A
FSG (mg/dL)					
Mean ± SD	153.6 ± 39.83	172.9 ± 51.46	169.3 ± 45.89	171.2 ± 50.75	162.4 ± 51.27
Median	147.9	163.0	162.1	164.0	151.3

Region	n (%)				
	GPGK	GPGL	GPGH	GPGM	GPGI
Min; Max	52.2; 329.7	20.0; 394.0	47.0; 485.0	41.0; 549.0	46.0; 505.0
eGFR CKD-EPI (mL/min/1.73 m^2)					
Mean ± SD	94.1 ± 19.70	96.0 ± 17.07	94.1 ± 17.04	81.3 ± 21.11	85.5 ± 17.78
Median	96.0	98.0	97.0	86.0	87.0
Min; Max	43.0; 144.0	45.0; 151.0	44.0; 141.0	16.0; 133.0	35.0; 140.0
<60 mL/min/1.73 m^2	28 (5.9)	64 (3.4)	56 (3.9)	342 (17.1)	47 (9.9)
≥60 mL/min/1.73 m^2	450 (94.1)	1814 (96.6)	1381 (96.1)	1653 (82.9)	428 (90.1)

Source: Adapted from the Applicant's Summary of Clinical Efficacy, pages 141-145 of 190, available at: \\CDSESUB1\evsprod\nda215866\0001\m2\27-clin-sum\2-7-3-clin-efficacy-sum.pdf
Abbreviations: BMI, body mass index; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; EU, European Union; HbA1c, hemoglobin A1c; IP, investigational product; max, maximum; min, minimum; mITT, modified intention-to-treat population (i.e., all subjects randomized and treated with at least 1 dose of IP); n, number; N/A, not applicable; and SD, standard deviation.
*mITT population.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use:

Compliance with Investigational Product

For purposes of identifying subjects that were not adherent to study treatment in the five global phase 3 trials, the applicant chose to use a threshold of 75% (i.e., subjects who reported use of 75% or more of IP were considered adherent). Compliance was typically determined by the number of injections entered in the exposure case report form (CRF) divided by the total number of injections planned (expected to be administered) multiplied by 100. The study drug administration data was recorded in diaries by the subject and reviewed by the investigator. Accountability of IP was evaluated at the respective study sites based on unused IP and/or empty cartons provided by subjects at scheduled visits. Subjects also were considered noncompliant if the investigator felt that they intentionally or repeatedly took more than the prescribed amount of medication. Subjects considered poorly compliant with the study medication and/or study procedures received additional training or instruction.

In the five phase 3 trials, the reported compliance with administration of IP during the respective treatment periods were: 95% (454/478 subjects) for trial GPGK; 94.9% (1783/1878 subjects) for trial GPGL; 95.5% (1372/1437) for trial GPGH; 96.8% (1932/1995) for trial GPGM, and 97.3% (462/475) for trial GPGI. The proportions of subjects who adhered to IP were relatively similar across treatment arms for each of the trials (data not shown).

Adherence to oral antihyperglycemic therapy has been reported to range from 36-93% in patients remaining on treatment for six to 24 months.[152] Additionally, prospective electronic monitoring studies have documented that patients took 67-85% of their oral antihyperglycemic doses as prescribed.[152] Publications of injectable GLP-1 RAs report that approximately 38-84% of patients using these products are adherent (>80% compliance) at six months.[153-160]

Although there is no universally accepted definition for what constitutes adequate adherence, the compliance threshold of approximately 75% (used in the five phase 3 trials) was reasonable.[161-163] Additionally, the observed treatment adherence rates for these trials (all ≥94%) were adequate.

Compliance with the Insulin Treat-To-Target Algorithms

For trials GPGH (TTT FSG <90 mg/dL),[134-136] GPGM (TTT FSG <100 mg/dL),[137] and GPGI (TTT FSG <100 mg/L),[137] subjects were expected to adhere to protocol-specific insulin TTT algorithms (please refer to Section 6.1.1). Insulin degludec and insulin glargine were the active comparators for trials GPGH, and GPGM, respectively, while insulin glargine (with or without metformin) was required antihyperglycemic background therapy for trial GPGI. The proportions of subjects achieving FSG targets, rates of Level 2 and/or 3 hypoglycemia (Dr. Tu's Statistical Review, pages 33-34), and increases in insulin dose from baseline for these trials are briefly summarized as follows:

- **GPGH:** At the end of the treatment period (Week 52), the insulin degludec dose was increased from 10 to 49 units/day. In this trial, the mean FSG concentrations at baseline were 166.6, 171.7, 170.4, 168.4 mg/dL for the insulin degludec, and tirzepatide 5, 10, and 15 mg treatment arms, respectively (Table 17). The mean FSG concentrations at Week 52 were 118.8, 122.3, 119.1, and 115 mg/dL, respectively. For subjects randomized to the insulin icodec arm, the mean reduction in FSG at Week 52 was -50.5 mg/dL. Based on the Applicant's analysis, approximately 25.7% of insulin degludec-treated subjects, and 6.9%, 14.6%, and 16.3% of subjects in the tirzepatide 5, 10, and 15 mg arms achieved the FSG target of <90 mg/dL at Week 52, and 50% of insulin degludec-treated subjects achieved this target value during the treatment period. Level 2 or Level 3 hypoglycemia occurred in 7.3%, 1.4%, 1.1%, and 2.2% of subjects, respectively. The change from baseline in HbA1c at Week 52 for subjects in the insulin degludec arm was -1.23%, and the effect sizes (comparator-subtracted differences) for the tirzepatide treatment arms were -0.6 to -0.91% (please refer to the Applicant's analysis in Table 16).
- **GPGM:** At the end of the treatment period (Week 52), the insulin glargine dose was increased from 10 to 44 units/day. At baseline, mean FSG concentrations were 168.4, 172.3, 175.7, and 174.1 for the insulin glargine, and tirzepatide 5, 10, and 15 mg treatment arms, respectively (Table 17). The mean FSG concentrations at Week 52 were 120, 121, 116.4, and 112 mg/dL, respectively. For subjects randomized to the insulin glargine arm, the mean reduction in FSG at Week 52 was -48.8 mg/dL. Based on the Applicant's analysis, approximately 30.3% of insulin glargine-treated subjects, and 28%, 30.9%, and 39.4% of subjects in the tirzepatide 5, 10, and 15 mg arms achieved the FSG target of <100 mg/dL. Level 2 or Level 3 hypoglycemia occurred in 20%, 9.4%, 6.1%, and 8.6% of subjects, respectively. The change from baseline in HbA1c at Week 52 for subjects in the insulin glargine arm was -1.38%, and the effect sizes (comparator-subtracted

differences) for the tirzepatide treatment arms were -0.71 to -1.03% (please refer to the Applicant's analysis in Table 16).

- **GPGI:** At the end of the treatment period (Week 40), background insulin glargine doses were increased from 10 units/day to 59, 38, 36, and 29 units/day for subjects randomized to placebo, and tirzepatide 5, 10, and 15 mg, respectively. At baseline, mean FSG concentrations were 164.4, 162.9, 162.6, and 160.4 mg/dL for the placebo, and tirzepatide 5, 10, and 15 mg arms, respectively. The mean FSG concentrations at Week 40 were 123.4, 104.4, 98.6, and 100 mg/dL, respectively, and were associated with mean reductions from baseline of -39.2, -58.2, -64, and -62.6 mg/dL, respectively. Based on the Applicant's analysis, approximately 29.1% of placebo-treated subjects, and 54.8%, 61.1%, and 64.1% of subjects in the tirzepatide 5, 10, and 15 mg arms achieved the FSG target of <100 mg/dL. Level 2 or Level 3 hypoglycemia occurred in 13.3%, 15.5%, 20.2%, and 15% of subjects, respectively. Change from baseline in HbA1c at Week 52 were -0.88%, -2.21, -2.44, and -2.44, respectively, and the effect sizes (placebo-subtracted differences) for the tirzepatide treatment arms were -1.33 to -1.56% (please refer to the Applicant's analysis in Table 16).

For trials GPGH and GPGM, only 30-34% of subjects randomized to the insulin treatment arms achieved the desired FSG targets. However, based on the observed increases in insulin doses, reductions in FSG and HbA1c concentrations, and rates of clinically meaningful hypoglycemia, I felt that adherence to the protocol-specified TTT algorithms were adequate. Additionally, the relatively large effect sizes of tirzepatide for HbA1c reduction at endpoint support the superiority of tirzepatide versus the insulin comparator. Similarly, for trial GPGI, insulin titrations for the placebo and tirzepatide treatment arms appeared to be acceptable. It also is acknowledged that the ADA currently recommends a less stringent glycemic target (e.g., preprandial capillary plasma glucose of 80-130 mg/dL) for many nonpregnant adults with diabetes.[138]

Concomitant Antihyperglycemic Medications and Glycemic Rescue Therapy:

Please refer to Section 6.1.1 for a description of concomitant antihyperglycemic medications and allowed glycemic therapies for the respective trials.

For trial GPGK subjects were not receiving background antihyperglycemic medication, and for trial GPGL, metformin background therapy was required. Therefore, the Applicant did not perform subgroup analyses of the primary endpoint by background antihyperglycemic medication use for these trials. For trial GPGH, metformin background therapy was required, and SGLT2i use was optional. The Applicant reported that there was no statistically significant interaction effect due to background SGLT2i use (p=0.552). Trial GPGM allowed up to three antihyperglycemic medications (i.e., metformin and/or SU and/or SGLT2i) as background therapy. In this trial, the Applicant reported a statistically significant interaction (p<0.0584; treatment-by-subgroup interaction p<0.1 was considered significant) and subgroup (p=0.0004) effect using different background therapies. The Applicant acknowledged the limitations of these

findings, stating that there were fewer subjects receiving background metformin plus a SU plus a SGLT2i (n=204) or metformin plus a SGLT2i (n=234), and a lack of a dose response in the "Other" group (n=93). For this analysis, LSMean differences versus insulin glargine for the primary endpoint were statistically significant for each tirzepatide arm regardless of background medication therapy. For trial GPGI all subjects received background insulin glargine therapy with/without metformin. In this trial, 82.9% of subjects were taking metformin in addition to insulin glargine. A significant interaction (p=0.083) and subgroup (p=0.008) effect was observed, but the Applicant again recommended caution in interpreting these results due to the small number of subjects not receiving metformin (n=75). The LSMean differences versus placebo for the primary endpoint were significant in favor of all tirzepatide dose groups regardless of metformin use.

In the five global phase 3 trials, glycemic rescue therapy was initiated in 7.7% (37/478) of subjects in trial GPGK, 1.6% (31/1879) in trial GPGL, 1% (14/1444) in trial GPGH, 0.4% (9/2002) in trial GPGM, and 1.3% (6/475) in trial GPGI. Although rescue medication use was relatively low for four of the trials, in trial GPGK, rescue medication was required for 24.3% (28/115) of subjects in the placebo arm, and 1.7% (2/121), 3.3% (4/121), and 2.5% (3/121) of subjects in the tirzepatide 5 , 10, and 15 mg arms, respectively. Since the treatment effect estimand (i.e., the treatment effect among all randomized subjects, irrespective of premature discontinuation of IP or initiation of glycemic rescue therapy) was used by the Agency to evaluate the treatment effect of the primary endpoint for all five trials, the observed differences in rescue medication use among treatment arms in trial GPGK do not alter the interpretation of the primary efficacy analysis (which reflects the treatment effect of what would be observed in a real world setting where subjects would be offered a chance to receive rescue therapy).

Overall, I do not believe that the observed differences in the use of concomitant background medications or glycemic rescue therapy reported in the five global phase 3 trials influenced the interpretation of the Agency's efficacy findings.

Efficacy Results – Primary Endpoint:

The results of Applicant's and Agency's primary endpoint analyses (i.e., change in HbA1c at endpoint) for the five global phase 3 trials are presented in Table 16. For these analyses, the mITT population (i.e., all randomized subjects who took at least one dose of IP, excluding inadvertently enrolled participants) and FAS (i.e., all available data obtained during the treatment period regardless of adherence to study drug or initiation of rescue medication) were used. For detailed discussion of these analyses, please refer to the Dr. Tu's Statistical Review (dated February 15, 2022). Additionally, for information of efficacy results using the Applicant's preferred approach (i.e., efficacy estimand; all randomized participants who continued to receive IP without the use of glycemic rescue therapy), please refer to the published reports of the five global phase 3 trials.[164-168]

The comparator-subtracted differences across all five trials for each tirzepatide dose (5, 10, and 15 mg) were statistically significant, and favored the respective tirzepatide treatment arm. Additionally, except for a -0.16% difference in HbA1c between the tirzepatide 5 mg and semaglutide 1 mg treatment arms in trial GPGL, the differences in HbA1c reductions for all comparisons across the five phase 3 trials were considered clinically meaningful. Sensitivity analyses performed using a return-to-baseline analytical approach were similar (i.e., all p=values for superiority <0.05; data not shown, please refer to Dr. Tu's Statistical Review).

Table 16. Primary Analysis Results: HbA1c Change from Baseline at Endpoint (mITT)

Trial	Comparator	Tirzepatide 5 mg	Tirzepatide 10 mg	Tirzepatide 15 mg
GPGK (SURPASS-1)	**Placebo**			
mITT Population (N)[a]	113	121	121	120
HbA1c (%)				
Baseline – LSmean (SE)	8.07 (0.08)	7.97 (0.08)	7.90 (0.08)	7.85 (0.08)
Change at Week 40[b] – LSmean (SE)	-0.09 (0.11)	-1.75 (0.10)	-1.71 (0.11)	-1.69 (0.11)
Applicant's Analysis				
Difference from comparator[b] (95% CI)	--	-1.66 (-1.96, -1.36)	-1.62 (-1.92, -1.32)	-1.60 (-1.91, -1.29)
p-value[c]	–	p<0.001	p<0.001	p<0.001
FDA Analysis				
Difference from comparator[b] (95% CI)	--	-1.64 (-1.94, -1.34)	1.60 (-1.90, -1.30)	-1.59 (-1.90, -1.28)
p-value[c]	–	p<0.001	p<0.001	p<0.001
Missing HbA1c data (%)[d]	12	6	7	14
Rescue therapy (%)[e]	25	2	3	2
GPGL (SURPASS-2)	**Semaglutide 1 mg**			
mITT Population (N)[a]	468	470	469	469
HbA1c (%)				
Baseline – LSmean (SE)	8.25 (0.05)	8.32 (0.05)	8.30 (0.05)	8.26 (0.05)
Change at Week 40[b] – LSmean (SE)	-1.84 (0.05)	-2.01 (0.05)	-2.24 (0.05)	-2.30 (0.05)
Applicant's Analysis				
Difference from comparator[b] (95% CI)	–	-0.16 (-0.29, -0.04)	-0.40 (-0.52, -0.27)	-0.46 (-0.59, -0.33)
p-value[c]	–	p<0.05	p<0.001	p<0.001
FDA Analysis				
Difference from comparator[b] (95% CI)	–	-0.16 (-0.29, -0.04)	-0.41 (-0.53, -0.28)	-0.48 (-0.60, -0.36)

Trial	Comparator	Tirzepatide 5 mg	Tirzepatide 10 mg	Tirzepatide 15 mg
p-value[c]	–	p<0.05	p<0.001	p<0.001
Missing HbA1c data (%)[f]	5	4	5	5
Rescue therapy (%)[e]	3	2	1	1
GPGH (SURPASS-3)	**Insulin degludec**			
mITT Population (N)[a]	359	358	360	358
HbA1c (%)				
Baseline (mean) – LSmean (SE)	8.11 (0.05)	8.17 (0.05)	8.18 (0.05)	8.21 (0.05)
Change at Week 52[b] – LSmean (SE)	-1.23 (0.06)	-1.83 (0.06)	-2.02 (0.05)	-2.13 (0.05)
Applicant's Analysis				
Difference from comparator[b] (95% CI)	–	-0.60 (-0.77, -0.44)	-0.79 (-0.96, -0.62)	-0.91 (-1.07, -0.74)
p-value[c]	–	p<0.001	p<0.001	p<0.001
FDA Analysis				
Difference from comparator[b] (95% CI)	–	-0.54 (-0.78, -0.30)	-0.73 (-0.98, -0.48)	-0.85 (-1.10, -0.60)
p-value[c]	–	p<0.001	p<0.001	p<0.001
Missing HbA1c data (%)[f]	9	6	10	5
Rescue therapy (%)[e]	1	1	1	2
GPGM (SURPASS-4)	**Insulin glargine**			
mITT Population (N)[a]	998	328	326	337
HbA1c (%)				
Baseline (mean) – LSmean (SE)	8.50 (0.03)	8.52 (0.05)	8.60 (0.05)	8.52 (0.05)
Change at Week 52[b] – LSmean (SE)	-1.38 (0.04)	-2.09 (0.06)	-2.31 (0.06)	-2.42 (0.05)
Applicant's Analysis				
Difference from comparator[b] (95% CI)	–	-0.71 (-0.85, -0.57)	-0.92 (-1.06, -0.78)	-1.03 (-1.16, -0.90)
p-value[c]	–	<0.001	<0.001	<0.001
FDA Analysis				
Difference from comparator[b] (95% CI)		-0.76 (-0.89, -0.64)	-0.92 (-1.04, -0.79)	-1.02 (-1.14, -0.89)
p-value[c]		<0.001	<0.001	<0.001
Missing HbA1c data (%)[f]	9	9	6	4
Rescue therapy (%)[e]	1	0	0	1
GPGI (SURPASS-5)	**Placebo**			
mITT Population (N)[a]	119	116	118	118

Trial	Comparator	Tirzepatide 5 mg	Tirzepatide 10 mg	Tirzepatide 15 mg
HbA1c (%)				
Baseline (mean) – LSmean (SE)	8.38 (0.08)	8.30 (0.08)	8.36 (0.08)	8.22 (0.08)
Change at Week 40[b] – LSmean (SE)	-0.88 (0.08)	-2.21 (0.08)	-2.44 (0.08)	-2.44 (0.08)
Applicant's Analysis				
Difference from comparator[b] (95% CI)	–	-1.33 (-1.56, -1.10)	-1.56 (-1.78, -1.33)	-1.56 (-1.77, -1.33)
p-value[c]	–	<0.001	<0.001	<0.001
FDA Analysis				
Difference from comparator[b] (95% CI)	–	-1.25 (-1.49, -1.01)	-1.53 (-1.77, -1.30)	-1.48 (-1.72, -1.24)
p-value[c]	–	<0.001	<0.001	<0.001
Missing HbA1c data (%)[d]	2	6	3	7
Rescue therapy (%)[e]	4	1	0	1

Source: Adapted from Dr. Wenda Tu's Statistical Review (dated February 15, 2022), page 29.

Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; FDA, Food and Drug Administration; HbA1c, hemoglobin A1c; LSMean, least squares mean; mITT, modified intention-to-treat; and N, number.

[a] The modified intent-to-treat population consists of all randomly assigned participants who were exposed to at least 1 dose of study drug. Subjects who discontinued study treatment due to inadvertent enrollment were excluded.

[b] Least-squares mean from ANCOVA adjusted for baseline value and other stratification factors.

[c] p-value (two-sided) for superiority vs. comparator, based on ANCOVA, adjusted for multiplicity.

[d] Missing HbA1c data at endpoint (data were imputed using placebo-based multiple imputation).

[e] Initiation of glycemic rescue medication (additional antihyperglycemic medication) during the trial.

[f] Missing HbA1c data at endpoint (data were imputed using multiple imputation with retrieved dropout).

Data Quality and Integrity

The Applicant states that the global phase 3 trials of the tirzepatide clinical development program were conducted as randomized, parallel-group trials that were rigorously designed to maintain data integrity and patient safety. Additionally, prior to Filing (i.e., November 14, 2021), the FDA Core Data Fit Service and the Office of Computational Science (OCS) JumpStart Team reviewed the data submitted to this Application to identify any data quality issues. Based on their assessments no filing issues were identified. Dr. Ling Yang, the OSI reviewer, also felt that the data generated by the CI sites and submitted by the Applicant were acceptable to support the proposed indication, and Dr. Wenda Tu, the statistical reviewer for this Application, concluded that the quality of the datasets was acceptable.

I concur that there were no data quality or data integrity issues, and that the data submitted to this Application were adequate.

Efficacy Results – Secondary and other relevant endpoints:

The results of the key secondary endpoints for the five global phase 3 trials are presented in Table 17. Similar to the primary efficacy analyses, the results of these secondary analyses favored each tirzepatide treatment arm for all comparisons, with statistically significant differences reported for all trials, except for the difference in the incidence of subjects achieving an HbA1c <0.7% between the tirzepatide 5 mg and semaglutide 1 mg treatment arms in trial GPGL. These efficacy results, which were adjusted for multiplicity, are supportive of the primary efficacy analyses, and relevant to the intended patient population for this product. Therefore, I feel these findings should be included in product labeling.

For trials GPGK and GPGI, FSG was a key secondary endpoint (i.e., included in the testing hierarchy). However, the Applicant also requested to report the FSG changes from baseline for trials GPGL, GPGH, and GPGM in tirzepatide product labeling, stating that FSG is an important component of overall glycemia that supplements the HbA1c data and provides useful information for prescribers and patients to assess the pattern of glycemic control. As inclusion of similar fasting glucose data is consistent with the labeling for several GLP-1 RA products[2,3,7-9,11,25,26] and help to inform prescribers of the adequacy of the TTT insulin titration algorithms for trials GPGH and GPGM, the Division concurred with reporting these data in product labeling.

The results for the incidence of subjects achieving an HbA1c <5.7% in trials GPGK, GPGL, and GPGI showed that tirzepatide was superior to placebo. Currently, the Agency has not accepted this endpoint for labeling, and the Applicant's proposed labeling also did not include these data.

Table 17: Key and Other Relevant Secondary Endpoints for Five Global Phase 3 Trials (mITT)

Trial	Comparator	Tirzepatide 5 mg	Tirzepatide 10 mg	Tirzepatide 15 mg
GPGK (SURPASS-1)	**Placebo**			
mITT Population (N)[a]	113	121	121	120
Patients (%) achieving HbA1c <7%	23.0 (4.2)	81.8 (3.7)	84.5 (3.5)	78.3 (4.1)
p-value[b]	—	<0.001	<0.001	<0.001
Patients (%) achieving HbA1c <5.7%	1.4 (1.3)	30.9 (4.2)	26.8 (4.1)	38.4 (4.5)
p-value[b]	—	<0.001	<0.001	<0.001
Fasting Serum Glucose (mg/dL)				
Baseline – LSmean (SE)	155.2 (3.8)	153.7 (3.6)	152.6 (3.6)	155.2 (3.8)
Change at Week 40[c] – LSmean (SE)	3.7 (4.4)	-39.6 (4.0)	-39.8 (4.1)	-38.6 (4.4)
Difference from comparator[c] (95% CI)	—	-43.2 (-54.8, -31.6)	-43.4 (-55.1, -31.7)	-42.3 (-54.4, -30.3)
p-value	—	<0.001	<0.001	<0.001
Body Weight (kg)				
Baseline – LSmean (SE)	84.5 (1.9)	87.0 (1.8)	87.0 (1.8)	85.5 (1.8)

Trial	Comparator	Tirzepatide 5 mg	Tirzepatide 10 mg	Tirzepatide 15 mg
Change from baseline at Week 40[c] – LSmean (SE)	-1.0 (0.5)	-6.3 (0.5)	-7.0 (0.5)	-7.8 (0.5)
Difference from comparator[c] (95% CI)	—	-5.3 (-6.8, -3.9)	-6.0 (-7.4, -4.6)	-6.9 (-8.3, -5.4)
p-value[d]	—	<0.001	<0.001	<0.001
GPGL (SURPASS-2)	**Semaglutide 1 mg**			
mITT Population (N)[a]	468	470	469	469
Patients (%) achieving HbA1c <7%	79.0 (2.0)	82.0 (1.8)	85.6 (1.7)	86.2 (1.7)
p-value[b]	—	NS	<0.01	<0.01
Patients (%) achieving HbA1c <5.7%	18.9 (1.8)	27.1 (2.1)	39.8 (2.3)	45.7 (2.3)
p-value[b]	—	—	<0.001	<0.001
Body Weight (kg)				
Baseline – LSmean (SE)	93.7 (1.0)	92.5 (1.0)	94.8 (1.0)	93.8 (1.0)
Change from baseline at Week 40[c] – LSmean (SE)	-5.7 (0.3)	-7.6 (0.3)	-9.3 (0.3)	-11.2 (0.3)
Difference from comparator[c] (95% CI)	—	-1.9 (-2.8, -1.0)	-3.6 (-4.5, -2.7)	-5.5 (-6.4, -4.6)
p-value[d]	—	<0.05	<0.001	<0.001
Fasting Serum Glucose (mg/dL)[e]				
Baseline – LSmean (SE)	171.2 (2.4)	173.8 (2.4)	174.2 (2.4)	172.4 (2.4)
Change at Week 40[c] – LSmean (SE)	-49.4 (1.6)	-54.8 (1.5)	-59.1 (1.6)	-60.2 (1.5)
GPGH (SURPASS-3)	**Insulin degludec**			
mITT Population (N)[a]	359	358	360	358
Patients (%) achieving HbA1c <7%	58.0 (2.7)	79.2 (2.3)	81.5 (2.4)	83.5 (2.0)
p-value[b]	—	<0.001	<0.001	<0.001
Body Weight (kg)				
Baseline – LSmean (SE)	94.0 (1.1)	94.4 (1.1)	93.8 (1.1)	94.9 (1.1)
Change from baseline at Week 52[c] – LSmean (SE)	1.9 (0.4)	-7.0 (0.4)	-9.6 (0.4)	-11.3 (0.4)
Difference from comparator[c] (95% CI)	—	-8.9 (-10.0, -7.8)	-11.5 (-12.6, -10.4)	-13.2 (-14.3, -12.1)
p-value[d]	—	<0.001	<0.001	<0.001
Fasting Serum Glucose (mg/dL)[e]				
Baseline – LSmean (SE)	166.6 (2.4)	171.7 (2.4)	170.4 (2.4)	168.4 (2.4)
Change at Week 40[c] – LSmean (SE)	-50.5 (2.5)	-47.0 (2.0)	-50.1 (2.1)	-54.2 (1.9)
GPGM (SURPASS-4)	**Insulin glargine**			

Trial	Comparator	Tirzepatide 5 mg	Tirzepatide 10 mg	Tirzepatide 15 mg
mITT Population (N)[a]	998	328	326	337
Patients (%) achieving HbA1c <7%	48.8 (1.8)	75.1 (2.7)	82.9 (2.3)	84.9 (2.0)
p-value[b]	—	<0.001	<0.001	<0.001
Body Weight (kg)				
Baseline – LSmean (SE)	90.2 (0.6)	90.3 (1.0)	90.6 (1.0)	90.0 (0.6)
Change from baseline at Week 52[c]	1.7 (0.2)	-6.4 (0.4)	-8.9 (0.4)	-10.6 (0.3)
Difference from comparator[c] (95% CI)	—	-8.1 (-8.9, -7.3)	-10.6 (-11.4, -9.8)	-12.2 (-13.0, -11.5)
p-value[d]	—	<0.001	<0.001	<0.001
Fasting Serum Glucose (mg/dL)[e]				
Baseline – LSmean (SE)	168.4 (1.6)	172.3 (2.8)	175.7 (2.8)	174.1 (2.8)
Change at Week 40[c] – LSmean (SE)	-48.8 (1.7)	-44.3 (2.6)	-50.3 (2.4)	-54.5 (2.3)
GPGI (SURPASS-5)	**Placebo**			
mITT Population (N)[a]	119	116	118	118
Patients (%) achieving HbA1c <7%	34.5 (4.4)	87.3 (3.3)	89.6 (2.9)	84.7 (3.6)
p-value[b]	—	<0.001	<0.001	<0.001
Patients (%) achieving HbA1c <5.7%	2.7 (1.5)	24.4 (4.0)	41.6 (4.5)	49.6 (4.7)
p-value[b]	—	—	<0.001	<0.001
Fasting Serum Glucose (mg/dL)				
Baseline – LSmean (SE)	164.4 (4.8)	162.9 (4.8)	162.6 (4.8)	160.4 (4.8)
Change at Week 40[c] – LSmean (SE)	-39.2 (2.7)	-58.2 (2.8)	-64.0 (2.7)	-62.6 (2.8)
Difference from comparator[c] (95% CI)	—	-19.0 (-26.6, -11.4)	-24.9 (-32.3, -17.4)	-23.4 (-31.0, -15.8)
p-value[d]	—	<0.001	<0.001	<0.001
Body Weight (kg)				
Baseline – LSmean (SE)	94.2 (2.0)	95.8 (2.0)	94.6 (2.0)	96.0 (2.0)
Change from baseline[c] – LSmean (SE)	1.6 (0.6)	-5.4 (0.6)	-7.5 (0.6)	-8.8 (0.6)
Difference from comparator[c] (95% CI)	—	-7.1 (-8.7, -5.4)	-9.1 (-10.7, -7.5)	-10.5 (-12.1, -8.8)
p-value[d]	—	<0.001	<0.001	<0.001

Source: Adapted from Dr. Wenda Tu's Statistical Review (dated February 15, 2022), page 29.
Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; HbA1c, hemoglobin A1c; LSMean, least squares mean; and mITT, modified intention-to-treat; and NS, not significant.
[a] The modified intent-to-treat population consists of all randomly assigned participants who were exposed to at least 1 dose of study drug. Subjects who discontinued study treatment due to inadvertent enrollment were excluded.
[b] p-value (two-sided) for superiority vs. comparator, based on logistic regression, adjusted for multiplicity.
[c] Least-squares mean from ANCOVA adjusted for baseline value and other stratification factors.
[d] p-value (two-sided) for superiority vs. comparator, based on ANCOVA, adjusted for multiplicity.
[e] Not included in hierarchical testing strategy, and therefore the results are considered descriptive.

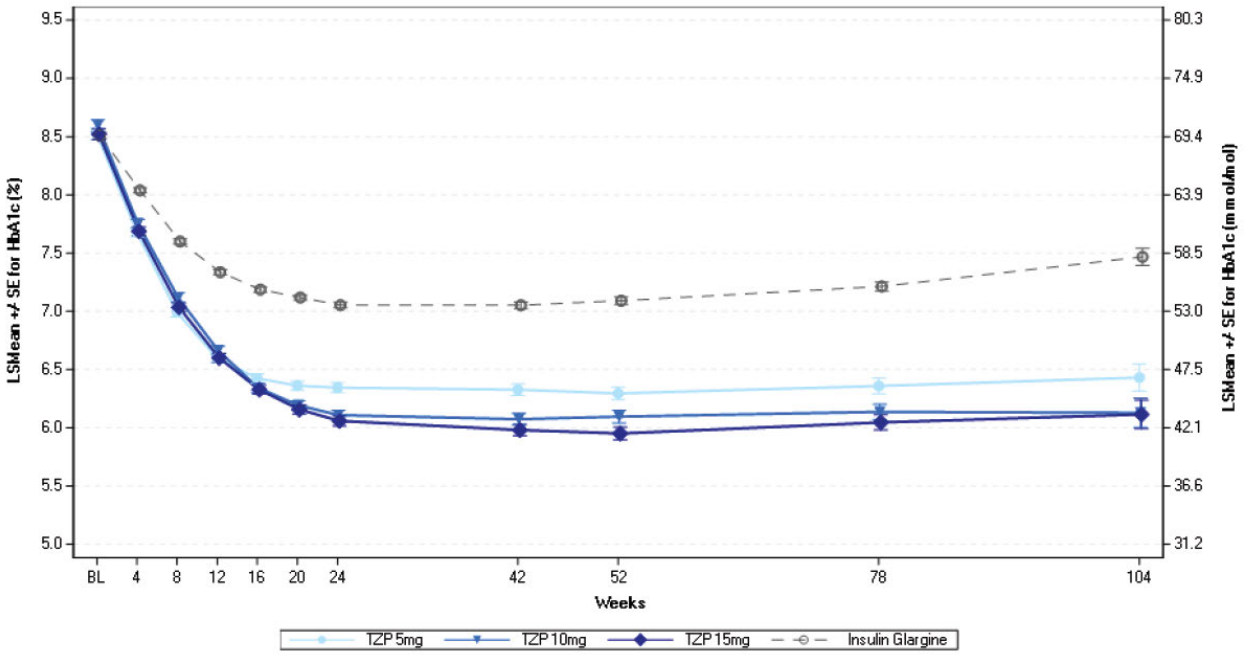
Dose/Dose Response

Although subjects were randomized to either the tirzepatide 5, 10, or 15 mg dose arm, the five phase 3 trials were not intended to compare differences between tirzepatide doses, but rather to compare each individual dose to the respective comparator. For each of the five trials, all doses were superior to comparator for the primary endpoint (HbA1c change from baseline at endpoint) and most of the secondary endpoints.

Durability of Response

The Applicant was able to demonstrate durability of effect throughout the intended 40 or 52 week planned treatment durations. For antihyperglycemic clinical development programs, 52-week treatment periods would be considered adequate to support durability of response. In trial GPGM, the Applicant also provided data to show changes from baseline in HbA1c concentrations over 104 weeks using the efficacy analysis set (Figure 5). They felt that the reductions in HbA1c were sustained up to 104 weeks for all three tirzepatide doses. I concur that the durability of tirzepatide response on HbA1c reductions observed in this trial, as well as that reported in the other four global phase 3 trials, was adequate.

Figure 5: Mean HbA1c Over Time - Baseline to Week 104 – Trial GPGM (mITT- Efficacy)*



Source: Excerpt from Trial GPGM CSR, page 143 of 5827, available at: file://cdsesub1/evsprod/NDA215866/0001/m5/53-clin-stud-rep/535-rep-effic-safety-stud/type-2-diabetes-mellitus/5351-stud-rep-contr/i8f-mc-gpgm/gpgm-04-body.pdf
Abbreviations: ANOVA, analysis of variance; HbA1c, hemoglobin A1c; LSMean, least squares mean; mITT, modified intention-to-treat (randomized subjects who received at least one dose of IP); MMRM, mixed model repeated measures; and SE, standard error.

* Plot of estimated mean HbA1c versus time, MMRM by treatment and visit from baseline to 104 weeks; mITT-Efficacy Analysis Set.
Note 1: MMRM model for post-baseline measures: Actual Value = Baseline + Pooled Country + Baseline SGLT2i use (Yes, No) + Treatment + Time + Treatment*Time (Type III sum of squares). Variance-Covariance structure (Actual Value) = Heterogenous Toeplits.
Note 2: ANOVA model for baseline measures: Actual Value = Treatment (Type III sum of squares).

Persistence of Effect

Not applicable for this Application. The follow-up for the phase 3 trials only included a four-week (off-treatment) safety follow-up period.

Additional Analyses Conducted on the Individual Trial

Please refer to the additional analyses presented above.

7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

In the written responses provided for the Type C NDA logistics meeting (dated August 27, 2020), the Agency agreed that an integrated efficacy database and ISE would not be required for the NDA based on the rationale that pooling of the data across five global phase 3 trials would not be informative due to difference between the studies (e.g., background therapies, treatment durations, patient characteristics, and comparators). Please refer to Table 2 above.

7.1.1. Primary Endpoints

Please refer to Section 6.1.2.

7.1.2. Secondary and Other Endpoints

Please refer to Section 6.1.2.

7.1.3. Subpopulations

Please refer to Section 6.1.2.

7.1.4. Dose and Dose-Response

Please refer to Section 6.1.2.

7.1.5. Onset, Duration, and Durability of Efficacy Effects

Please refer to Section 6.1.2.

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Postmarket Setting

Currently, the ADA recommends that among individuals with T2D who have established atherosclerotic CVD or indicators of high CV risk, established kidney disease, or heart failure, a SGLT2i and/or GLP-1 RA with demonstrated CVD benefit is recommended as part of the glucose-lowering regimen and comprehensive CV risk reduction, independent of HbA1c and in consideration of patient-specific factors.[17] Although tirzepatide was associated with clinically meaningful improvements in glycemic control and reductions in body weight, which are anticipated to have beneficial effects on CV risk reduction, the Applicant's CVOT (trial GPGN) is ongoing. Therefore, this product is not recommended to reduce the risk of major adverse cardiovascular events in adults with T2D and established cardiovascular disease or multiple CV risk factors, as labeled for several approved GLP-1 RA products.[2,5,11] The NDA also did not provide data to show evidence of benefit in patients with or at risk of heart failure, or to reduce CKD progression. Additionally, the trial populations were predominantly White (88%), with underrepresentation of some racial subgroups (i.e., <4% of subjects were Black and <5% were 75 years of age or older), and limited data was available for subjects with an eGFR <30 mL/min/1.73 m^2, making it somewhat difficult to generalize study results across all populations that may benefit from tirzepatide use. Further, there is currently no efficacy and safety data from a pediatric population (<18 years of age), and no or limited information on the benefits and risks associated with tirzepatide exposure for lactating or pregnant females (some pregnancies did occur during clinical trials).

7.2.2. Other Relevant Benefits

In the placebo-controlled phase 3 trials, tirzepatide resulted in a mean decrease in systolic and diastolic blood pressure of approximately 6-9 mmHg and 3-4 mmHg, respectively, while placebo-treated subjects had a mean decrease of approximately 2 mmHg and 2 mmHg, respectively (Section 8.4.6). Additionally, compared to placebo, all three tirzepatide doses in trial GPGK reduced triglycerides, total cholesterol, and very low-density lipoprotein cholesterol (VLDL-C), and increased high-density cholesterol (HDL-C) at Week 40. Similarly, in trial GPGI, all three tirzepatide doses reduced triglycerides, total cholesterol, low-density lipoprotein cholesterol

(LDL-C), and VLDL-C. As these data (i.e., blood pressure and lipid parameter endpoints) were not included in the hierarchical testing strategy, and the Applicant is not pursuing efficacy claims for the management of hypertension or dyslipidemia, they were not included in proposed tirzepatide product labeling. Please refer to Section to Section 6.1.2 for additional discussion of efficacy findings from the five global phase 3 trials.

7.3. Integrated Assessment of Effectiveness

To support marketing approval of tirzepatide (NDA 215866), the Applicant conducted five global phase 3 clinical trials that evaluated the efficacy and safety of tirzepatide 5, 10, and 15 mg doses administered SC QW as monotherapy and in combination with metformin, SU, and SGLT-2i alone or combined, and in combination with basal insulin with or without metformin. The efficacy of tirzepatide was compared to placebo (trials GPGI and GPGK), insulin glargine (trial GPGM), insulin degludec (trial GPGH), and semaglutide 1 mg (trial GPGL). Based on the Agency analysis of the primary efficacy endpoint (i.e., mean change in HbA1c from baseline to endpoint, treatment-effect estimand), all three tirzepatide doses resulted in robust, statistically significant (all $p<0.05$ for superiority) reductions in HbA1c concentrations compared to the comparator arms for all five trials. Except for the tirzepatide 5 mg SC QW dose compared to semaglutide 1 mg SQ QW dose (comparator-subtracted reduction of 0.2%, 95% CI: -0.3, -0.0), the improvement in glycemic control for each tirzepatide dose arm was considered clinically meaningful (i.e., all other comparator-subtracted reductions in HbA1c -0.4 to -1.6%).[23]

8. Review of Safety

8.1. Safety Review Approach

The safety evaluation for this NDA was primarily based on the safety data from the Applicant's nine completed phase 2/3 clinical trials (see Table 5), including the clinical study reports (CSRs), submitted datasets (analysis and tabulation), and information requests to the Applicant. This review included routine assessments, as well as Special Safety Topics (i.e., potential risks associated with GLP-1 RAs), which will be referred to as adverse events of special interest (AESI) throughout this review. The Applicant performed safety analyses using the mITT population (i.e., all subjects randomized who received at least one dose of IP) and all data (on or off IP) from the start of treatment to the end of the 4-week safety follow-up. They considered the following AESI as potential or established GLP-1 RA class-related safety concerns: immunogenicity, thyroid safety, exocrine pancreas safety, hypoglycemia, hypersensitivity reactions, injection site reactions, renal safety, gastrointestinal AEs, acute gallbladder disorders, dehydration-related AEs, diabetic retinopathy complications, cardiovascular safety, amputation or peripheral revascularization, hepatobiliary disorders, malignancy, major depressive disorders/suicidal ideation or behavior metabolic acidosis, severe, and persistent hyperglycemia. In the phase 2/3 clinical program, AESI were primarily identified by searching the AE datasets using standardized Medical Dictionary for Regulatory Activities (MedDRA) queries (SMQs) and customized MedDRA queries (CMQs). The Applicant's search strategy for select AESI is presented in Appendix 13.8. All deaths, AEs of acute or chronic pancreatitis, and major adverse cardiovascular events (MACE), were adjudicated by an independent CEC. Selected AEs and laboratory abnormalities were crosschecked with those provided with the NDA documents.

The Applicant presented safety summaries using five analysis datasets (AS1 to AS5; Table 18). All seven phase 3 trials submitted to this Application used the same dose escalation scheme as proposed for tirzepatide labeling. Analysis Set 1 (AS1) included a pool of two 40-week phase 3 placebo-controlled trials (GPGK, and GPGI). These data were used to detect a drug effect. The phase 3 dose effect analysis set (AS2) was the integrated dataset that was used for dose comparison (i.e., tirzepatide 5, 10, and 15 mg) and to assess potential dose-related AEs, and included all seven phase 3 trials (i.e., GPGK, GPGL, GPGH, GPGM, GPGI, GPGO, and GPGP). The phase 2/3 analysis set (AS3) included a pool of two phase 2 trials (GPGB, and GPGF) and the seven phase 3 trials included in AS2. This uncontrolled integrated analysis set was used to assess rarer events and AESI. The phase 2/3 placebo-controlled analysis set (AS4) included trials GPGB, GPGF, GPGK, and GPGI, and was used to assess any additional safety signals associated with a drug effect. Finally, the CVMA set (AS5) included phase 2/3 trials with treatment durations ≥26 weeks (GPGB, GPGK, GPGL, GPGH, GPGM, GPGI, and GPGO). These data were used to evaluate CV safety

Table 18: Applicant's Analysis Sets for Integrated Phase 2/3 Clinical Trial Data

Analysis Set	Studies	Time Period	Description	Treatment
AS1: Phase 3 Placebo-Controlled Analysis Set	GPGK GPGI	1st dose of IP to end of safety follow-up visit/study withdrawal	Integrated data of TZP doses (same dose-escalation schedule proposed for labeling) compared to placebo.	TZP 5 mg (N=237) TZP 10 mg (N=240) TZP 15 mg (241) TZP_ALL (N=718) Placebo (N=235)
AS2: Phase 3 Dose Effect Analysis Set	GPGK GPGL GPGH GPGM GPGI GPGO GPGP	1st dose of IP to end of safety follow-up visit/study withdrawal	Integrated data intended for dose comparisons (same dose-escalation schedule proposed for labeling).	TZP 5 mg (N=1701) TZP 10 mg (N=1702) TZP 15 mg (N=1716) TZP_ALL (N=5119)
AS3: Phase 2/3 Analysis Set	GPGB GPGF GPGK GPGL GPGH GPGM GPGI GPGO GPGP	1st dose of IP to end of safety follow-up visit/study withdrawal	Integrated data for pooled TZP doses. Includes all phase 2/3 trials and all TZP doses.	TZP_ALL (N=5415) Pooled comparators (N=2354)
AS4: Phase 2/3 Placebo-Controlled Analysis Set	GPGB GPGF GPGK GPGI	1st dose of IP to earliest date of: last dose + 14 days; withdrawal from study; initiation of new antihyperglycemic	Integrated data with all placebo-controlled phase 2/3 trials: TZP 1 mg doses excluded and TZP doses were pooled.	TZP_ALL (N=962) Placebo (N=312)
AS5: CV Meta-Analysis Set	GPGB GPGK GPGL GPGH GPGM GPGI GPGO	1st dose of IP to end of safety follow-up visit/study withdrawal	Integrated dataset for CVMA to assess CV safety.	TZP_ALL (N=4887) Pooled comparators (N=2328)

Source: Adapted from the Applicant's Summary of Clinical Safety, page 35 of 327, available at: \\CDSESUB1\evsprod\nda215866\0001\m2\27-clin-sum\clin-safety-sum--tzp-t2dm-.pdf
Abbreviations: AS, Analysis Set; CV, cardiovascular; CVMA, cardiovascular meta-analysis; IP, investigational product; and TZP, tirzepatide.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

The safety database for the nine completed phase 2/3 trials (AS3) included 7769 randomized and treated subjects (i.e., took at least one dose of IP), of which 5415 subjects received tirzepatide for a total treatment exposure of 4833.1 patient-years (PYs). Planned treatment exposures ranged from 12-26 weeks for the two phase 2 trials and from 40-104 week for the seven phase 3 trials. In the phase 3 trials (AS2), 5119 subjects were randomized to tirzepatide (5, 10, or 15 mg),

of which 2375 subjects were exposed for ≥52 weeks, and 535 were exposed for ≥78 weeks. The total exposure to tirzepatide in these trials was 4721 PYs (1587.7 PYs for the 5 mg arm, 1569.0 PYs for the 10 mg arm, and 1564.3 PYs for the 15 mg arm). The durations of exposure were similar across the tirzepatide treatment arms, as shown in Figure 6. A summary of durations of exposure to IP for the safety population included in the phase 2/3 trials (AS3) is presented in Table 19.

Due to possible dose interruptions for subjects randomized to the tirzepatide arms (e.g., due to intolerable GI AEs), an additional analysis to evaluate actual treatment exposures, excluding any temporary discontinuations of IP were derived from the datasets from the individual phase 2/3 clinical trials. The mean±SD duration of exposure for tirzepatide-treated subjects was approximately 43±21.3 weeks, and similar to that reported by the Applicant (i.e., 46.6±20.09 weeks). Due to the long half-life of tirzepatide (approximately 5 days), I do not feel that this difference will alter the interpretation of safety findings.

In the 4MSU, the Applicant also provided safety data from 15 ongoing tirzepatide clinical trials that included five phase 1 pharmacology trials in subjects with T2D (b) (4) one phase 2 trial in subjects (b) (4) and nine phase 3 trials that enrolled subjects with T2D (3 trials), (b) (4) (5 trials), and (b) (4) . In these trials, 17,879 subjects have been randomized and treated with either tirzepatide or comparator for a total exposure of 6665.7 PYs.

Generally, the sample sizes, durations of exposure, and follow-up were adequate to evaluate the safety data of this Application.

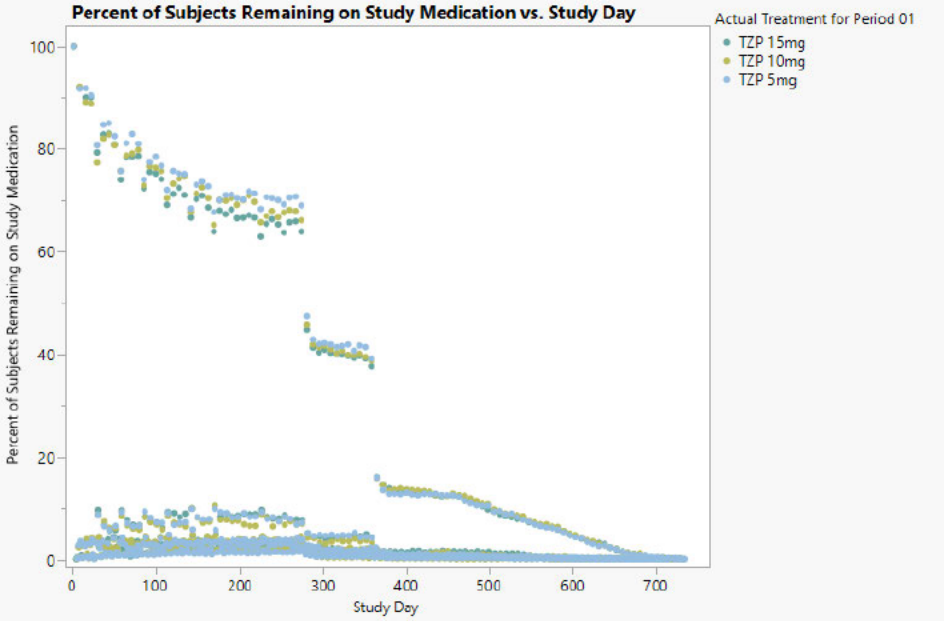
Table 19: Phase 2/3 Safety Populations, Size and Duration of Exposure (AS3)

	All Comparators (N=2354)	TZP 5 mg (N=1756)	TZP 10 mg (N=1753)	TZP 15 mg (N=1825)	TZP All* (N=5415)
Weeks of Exposure†					
Mean±SD (Range)	—	—	—	—	46.6±20.1 (1-106)
Median (IQ Range)	—	—	—	—	41.0 (40.0-52.0)
Exposure by Weeks — no. (%)					
>0	—	—	—	—	5415 (100)
≥4	—	—	—	—	5324 (98.3)
≥8	—	—	—	—	5211 (96.2)
≥12	—	—	—	—	5107 (94.3)
≥16	—	—	—	—	4948 (91.4)
≥20	—	—	—	—	4870 (89.9)
≥24	—	—	—	—	4821 (89)
≥38	—	—	—	—	4476 (82.7)
≥50	—	—	—	—	2579 (47.6)

	All Comparators (N=2354)	TZP 5 mg (N=1756)	TZP 10 mg (N=1753)	TZP 15 mg (N=1825)	TZP All* (N=5415)
≥52	—	—	—	—	2375 (43.9)
≥78	—	—	—	—	535 (9.9)
≥104	—	—	—	—	17 (0.3)
Patient-Years of Exposure by Trial					
All Phase 2/3 Trials – PY	**2475.9**	**1613.7**	**1593.1**	**1596.1**	**4833.1**
GPGB	48.8	25.9	24.1	19.6	93.6
GPGF	5.2	NA	NA	12.2	18.5
GPGH	330.1	329.1	315.3	321.9	966.3
GPGI	90	83.6	83.7	80.6	247.9
GPGK	79.6	87.7	86.7	81.3	255.6
GPGL	336.9	339.4	331.3	332.3	1003
GPGM	1434.8	461.8	469.8	471.9	1403.5
GPGO	150.6	146.8	142.2	145.5	434.4
GPGP	—	139.4	140	130.9	410.3

Source: Derived from the ISS adsl.xpt, adex.xpt datasets, and adapted from the Applicant's ISS, pages 59-63 of 7807, available at: \\CDSESUB1\evsprod\nda215866\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\type-2-diabetes-mellitus\5353-rep-analys-data-more-one-stud\iss\iss-46-integrated-sum-of-safety--t2dm-.pdf
Abbreviations: AS3, Analysis Set 3 (pool of 9 phase 2/3 trials); IQ, interquartile range; no., number; PY, patient-years; SD, standard deviation; and TZP, tirzepatide.
*Populations and exposures include additional tirzepatide doses (i.e., in addition to the 5 mg, 10 mg or 15 mg doses).
†Derived from the first exposure to the last day of exposure plus 7 days.

Figure 6: Exposure Summary by Tirzepatide Treatment Arm (AS2)



Source: Derived from the ISS adsl.xpt and adex.xpt datasets, available at:

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\\CDSESUB1\evsprod\NDA215866\0014\m5\datasets\integrated-database\analysis\adam\datasets
Abbreviations: AS2, Analysis Set 2 (pool of 7 phase 3 trials).

8.2.2. **Relevant characteristics of the safety population:**

The placebo-controlled phase 3 trial pool (AS1) included a tirzepatide monotherapy trial (GPGK) and an add-on to insulin glargine±metformin trial (GPGI). Approximately 953 adult T2D subjects were randomized (718 to tirzepatide and 235 to placebo) for a mean treatment duration of 36.6 weeks. The mean age of the population was 57.3 years, 46% were female, and 58% White. Approximately 24% of the population identified as Hispanic or Latino ethnicity. Subjects had T2D for an average duration of approximately 9 years, with a mean HbA1c of 8.1%. The baseline BMI was approximately 32.7 kg/m^2. The baseline eGFR was ≥60 mL/min/1.73 m^2 in 92% of subjects, and <60 mL/min/1.73 m^2 in 8% of subjects. Approximately 13% of the population had retinopathy based on fundoscopic examination (data not shown).

In the pool of seven phase 3 trial (AS2), that included two regional trials conducted in Japan, tirzepatide was evaluated as monotherapy and add-on therapy to oral antihyperglycemic medications or insulin. In this pool, 7,342 adult T2D subjects were randomized, of which 5,119 were treated with tirzepatide for a mean duration of approximately 48 weeks. Across the study pool, the mean age of subjects was 58 years, 32% were 65 years or older, and 42% were female. The population was predominantly White (69%), 20% Asian, 7% American Indian/Alaska Native, and 3% Black. Approximately 40% of the population identified as Hispanic or Latino ethnicity. At baseline, subjects had T2D for an average duration of 8.9 years, with a mean HbA1c of 8.3%. The baseline BMI was approximately 31.7 kg/m^2. The baseline eGFR was <60 mL/min/1.73 m^2 in 8% of subjects. Based on fundoscopic examination, 14.6% of tirzepatide-treated subjects had retinopathy at baseline (data not shown).

In the pool of nine phase 2/3 trials (AS3), 7,769 adult T2D subjects were randomized, of which 5,415 were treated with tirzepatide for a mean duration of approximately 47 weeks. Approximately 23% of the randomized population was from North America. As approximately 95% of subjects in this safety pool were from the phase 3 trials (i.e., AS2), the demographics and clinical characteristics (please refer to Table 20) were consistent with those reported for AS2.

Table 20: Baseline Demographics and Clinical Characteristics of the Phase 2/3 Trials (AS3)

	N (%)								
	GPGK	GPGI	GPGF	GPGM	GPGH	GPGO	GPGB	GPGL	GPGP
N	**478**	**475**	**111**	**1995**	**1437**	**636**	**316**	**1878**	**443**
Region									
North America	152 (31.8)	46 (9.7)	111 (100)	385 (19.3)	330 (23.0)	0	250 (79.1)	534 (28.4)	0
Central/South America/Mexico	164 (34.3)	0	0	893 (44.8)	224 (15.6)	0	0	1139 (60.6)	0
Asia (excluding Japan)	73 (15.3)	0	0	59 (3.0)	70 (4.9)	0	0	87 (4.6)	0
Japan	89 (18.6)	82 (17.3)	0	—	0	636 (100)	0	-	443 (100)
EU/United Kingdom/Ukraine	0	347 (73.1)	0	551 (27.6)	813 (56.6)	0	66 (20.9)	72 (3.8)	0
Rest of World	0	0	0	107 (5.4)	0	0	0	46 (2.4)	0
Age (years)									
Mean ± SD	54.1 ± 11.9	60.6 ± 9.9	57.4 ± 9.1	63.6 ± 8.6	57.4 ± 10.0	56.6 ± 10.3	57.2 ± 8.54	56.6 ± 10.4	57.0 ± 10.8
Age Group 1, n (%)									
<65 years	373 (78.0)	283 (59.6)	86 (77.5)	1047 (52.5)	1058 (73.6)	478 (75.2)	258 (81.6)	1420 (75.6)	328 (74.0)
≥65 years	105 (22.0)	192 (40.4)	25 (22.5)	948 (47.5)	379 (26.4)	158 (24.8)	58 (18.4	458 (24.4)	115 (26.0)
Sex, n (%)									
Male	247 (51.7)	264 (55.6)	66 (59.5)	1246 (62.5)	802 (55.8)	481 (75.6)	168 (53.2)	882 (47.0)	336 (75.8)
Female	231 (48.3)	211 (44.4)	45 (40.5)	749 (37.5)	635 (44.2)	155 (24.4)	148 (46.8)	996 (53.0)	107 (24.2)
Race, n (%)*									
White	170 (35.6)	380 (80.0)	87 (78.4)	1629 (81.8)	1307 (91.0)	0	253 (80.6)	1551 (82.6)	0
Asian	168 (35.1)	85 (17.9)	4 (3.6)	70 (3.5)	76 (5.3)	636 (100)	5 (1.6)	25 (1.3)	443 (100)
American Indian/Alaska Native	118 (24.7)	2 (0.4)	3 (2.7)	173 (8.7)	4 (0.3)	0	15 (4.8)	208 (11.1)	0
Black or African American	22 (4.6)	6 (1.3)	15 (13.5)	73 (3.7)	44 (3.1)	0	30 (9.6)	79 (4.2)	0
Multiple	0	2 (0.4)	2 (1.8)	43 (2.2)	2 (0.1)	0	9 (2.9)	12 (0.6)	0
Native Hawaiian or other Pacific Islander	0	0	0	3 (0.2)	4 (0.3)	0	2 (0.6)	3 (0.2)	0
Ethnicity, n (%)									
Hispanic/Latino	207 (43.3)	22 (4.6)	59 (53.2)	950 (47.6)	421 (29.3)	0	142 (50.5)	1317 (70.1)	0
Not Hispanic/Latino	184 (38.5)	380 (80.0)	52 (46.8)	1030 (51.6)	1009 (70.2)	636 (100)	139 (49.5)	561 (29.9)	443 (100)
Not Reported	87 (18.2)	73 (15.4)	0	15 (0.8)	7 (0.5)	0	35	0	0
Weight (kg)									
Mean ± SD	85.9 ± 19.77	95.2 ± 21.64	89±18.88	90.3 ± 18.66	94.3 ± 20.06	78.2 ± 14.5	91.5 ± 20.94	93.7 ± 21.86	77.51 ± 16.06
BMI (kg/m^2)									
Mean ± SD	31.9 ± 6.59	33.4 ± 6.06	31.9 ± 5.14	32.6 ± 5.54	33.5 ± 6.06	28.1 ± 4.4	32.6 ± 5.83	34.2 ± 6.93	27.90 ± 4.81
Duration of Diabetes (years)									
Mean ± SD	4.7 ± 5.4	13.3 ± 7.3	9.1 ± 6.47	11.8 ± 7.51	8.4 ± 6.24	5.9 ± 5.2	8.5 ± 6.2	8.6 ± 6.46	9.8 ± 6.29
Antihyperglycemic Use, n (%)									
No OAM	478 (100.0)	0	11 (9.9)	0	0	636	31 (9.8)	0	0
1 OAM	0	0	100 (90.1)	725 (36.3)	979 (68.1)	0	285 (90.2)	1878 (100.0)	443 (100)
2 OAMs	0	0	0	1052 (52.7)	458 (31.9)	0	0	0	0
3 OAMs	0	0	0	217 (10.9)	0	0	0	0	0
Insulin	0	81 (17.1)	0	0	0	0	0	0	0
Insulin + metformin	0	394 (82.9)	0	0	0	0	0	0	0

	N (%)								
	GPGK	GPGI	GPGF	GPGM	GPGH	GPGO	GPGB	GPGL	GPGP
N	**478**	**475**	**111**	**1995**	**1437**	**636**	**316**	**1878**	**443**
HbA1c (%)									
Mean ± SD	7.9 ± 0.87	8.3 ± 0.85	8.4 ± 1.09	8.5 ± 0.88	8.2 ± 0.91	8.2 ± 0.87	8.14 ± 0.97	8.3 ± 1.03	8.6 ± 1.09
eGFR CKD-EPI (mL/min/1.73 m^2)									
Mean ± SD	94.1 ± 19.70	85.5 ± 17.78	95.1 ± 15.89	81.3 ± 21.11	94.1 ± 17.04	78.1 ± 12.0	93.1 (17.25)†	96.0 ± 17.07	78.7 ± 12.58
<60 mL/min/1.73 m^2	28 (5.9)	47 (9.9)	4 (3.6)	342 (17.1)	56 (3.9)	44 (6.9)	15 (4.8)†	64 (3.4)	40 (9)
≥60 mL/min/1.73 m^2	450 (94.1)	428 (90.1)	107 (96.4)	1653 (82.9)	1381 (96.1)	592 (93.1)	299 (95.22)†	1814 (96.6)	403 (91)

Source: Adapted from the Applicant's Summary of Clinical Efficacy, pages 141-145 of 190, and from the individual CSRs, available at:
\\CDSESUB1\evsprod\nda215866\0001\m2\27-clin-sum\2-7-3-clin-efficacy-sum.pdf
\\CDSESUB1\evsprod\NDA215866\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\type-2-diabetes-mellitus\5351-stud-rep-contr
Abbreviations: AS3, Analysis Set 3 (pool of phase 2/3 trials); BMI, body mass index; CSR, Clinical Study Report; eGFR, estimated glomerular filtration rate; EU, European Union; FSG, fasting serum glucose; HbA1c, hemoglobin A1c; Min, minimum; Max, maximum; N, subjects randomized; n, number; OAM, oral antihyperglycemic medication; and SD, standard deviation.
*Data on race was not reported for 4 subjects in trial GPGM, and 2 subjects in trial GPGB.
† Note: N=314; two subjects missing baseline values; data derived from the adlb.xpt dataset.

8.2.3. **Adequacy of the safety database:**

At the End-of-Phase 2 meeting (September 6, 2018), the Applicant was informed that although the safety database was in accordance with the 2008 Diabetes Guidance (subsequently withdrawn) and International Council for Harmonisation (ICH) E1A Guidance,[169] the adequacy would depend on whether any new or emerging safety issues became apparent during phase 3 clinical development. Additionally, in Type C meeting responses, dated April 24, 2020 (one month after publication of the March 2020 Diabetes Guidance[170]),[(3)] the Division again confirmed that provided no new safety issues arise during phase 3 development, the size of the proposed safety database and patient characteristics were reasonable for submitting a NDA.

Following review of this Application, I feel that the safety database for the tirzepatide clinical development program is adequate to support the review of this Application. The sample sizes, demographics (1600 tirzepatide-treated subjects were >65 years of age), clinical characteristics (at least 1213 tirzepatide-treated subjects had CV disease and 405 had an eGFR <60 mL/min/1.73 m^2), and exposure durations (i.e., 5415 subjects receiving tirzepatide for 4833.1 PY, with 2375 subjects exposed to tirzepatide for at least 52 weeks, and 535 subjects exposed for at least 78 weeks) for the submitted phase 2/3 clinical trials are acceptable. The exposure durations also were sufficient to evaluate the prespecified AESI.

[3] The Agency updates guidances periodically. For the most recent version of this guidance, check the FDA Guidance Documents Database: https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

Prior to Filing (i.e., November 14, 2021), the FDA Core Data Fit Service and the OCS JumpStart Team reviewed the data submitted to this Application to identify any data quality issues. Based on their assessments no filing issues were identified. Additionally, Drs. Nhi Beasley, Associate Director Biomedical Informatics (ADBMI) and Douglas Warfield, ADBMI from the Division of Biomedical Informatics, Research, and Biomarker Development (DBIRBD) assisted with the evaluation of key safety findings (e.g., deaths, SAEs, discontinuations due to AEs, AESI, AEs, laboratory/vital sign changes) and confirmed that the data were reproducible using the submitted datasets. The findings from OSI inspections of five clinical sites from the five global phase 3 trials, and the assessment of data quality by Dr. Tu also were supportive. Overall, I feel that the quality of the safety data submitted to this NDA was adequate.

8.3.2. Categorization of Adverse Events

The safety analysis was conducted primarily using the data from the AS1, AS2, AS3, and AS5 study pools, which included all subjects who were randomized and treated (i.e., all subjects who received ≥1 dose of IP). The safety assessments performed by the Applicant were based on all available data through the treatment period and four-week safety follow-up visit, regardless of whether they were obtained after discontinuation of IP or whether subjects received glycemic rescue therapy (i.e., another antihyperglycemic medication). The treatment duration was considered the last dose of study medication plus seven days. Since tirzepatide has approximately a five day half-life, assessment of safety through the safety follow-up visit was reasonable.

Adverse events were classified by System Organ Class (SOC) and/or Preferred Term (PT) and coded based on Medical Dictionary for Regulatory Activities (MedDRA) version 23.1. For select safety endpoints, the Applicant also used the Cochran-Mantel-Haenszel (CMH) test, stratified by study, for categorical data to make treatment comparisons of percentages, and analysis of covariance (ANCOVA) and mixed-model repeated measure (MMRM) analytical approaches for assessing treatment differences in mean changes for continuous data. Additionally, exposure-adjusted incidence rates were performed for select AEs. For this Application, I also estimated study size adjusted incidence rates[171,172] for AESI across the comparator arms for eight of the nine phase 2/3 trials (i.e., excluding trial GPGP which did not include a comparator arm).

The Applicant used the following definitions in their protocols and/or safety analyses. An adverse event was defined as any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. Treatment-emergent adverse events were defined as AEs that first occurred or worsened in severity after baseline. The AE information obtained and documented in the electronic case report form (eCRF) included: the onset and duration, the

seriousness and severity, relatedness to IP, the actions taken with respect to study treatment, and outcome.

A SAE was defined as any untoward medical occurrence that:

- Resulted in death
- Was life-threatening
- Required inpatient hospitalization or caused prolongation of existing hospitalization
- Resulted in persistent or significant disability/incapacity
- Was a congenital anomaly/birth defect
- Was an important medical event

The definitions, coding, and cutoff dates for inclusion of TEAEs after discontinuing investigational product were acceptable. Also, the verbatim terms (i.e., AE CRF text, and analysis datasets) provided by the investigators and the MedDRA PTs for which these AEs were coded were screened for correctness, and the coding of these data appeared appropriate.

For completeness, I performed an evaluation of clinically meaningful AEs (e.g., serious and fatal events, or resulting in treatment discontinuations) using the FDA Medical Queries (FMQs), standardized groupings of MedDRA PTs for select medical concepts intended to identify potential safety issues. Based on this analysis (data not shown), no additional safety issues/concerns were identified besides those already reported in the Application.

8.3.3. **Routine Clinical Tests**

Blood and urine samples were obtained at baseline and typically at scheduled visits during and at the end of the treatment/early termination for evaluation of standard safety laboratory panels (chemistry, hematology, and urinalysis). Central tendency measures and categorical shifts (e.g., from normal or high to low, and from normal or low to high) were evaluated. Blood specimens for evaluation of lipid and glycemic parameters were typically evaluated as efficacy endpoints and collected under fasted conditions. Vital signs were measured in triplicate for the phase 2 trials, and in duplicate for the phase 3 trials. The blood pressure (sitting position) was evaluated using an automated machine for all phase 3 trials. A 12-lead electrocardiogram (ECG) was typically performed at baseline, at the time of the primary endpoint, and at the 4-week safety follow-up visit to assess mean changes from baseline (screening visit) in ECG parameters (PR, QRS, and QT intervals) over time. All digital ECGs were obtained using centrally provided ECG machines and electronically transmitted to a designated central ECG laboratory.

8.4. Safety Results

In the Applicant's phase 3 placebo-controlled pool (AS1) approximately 69.8% (501/718) of tirzepatide-treated subjects (i.e., 70.9%, 67.5%, and 71% of subjects in the 5, 10, and 15 mg arms, respectively), and 66.8% (157/235) of subjects in the placebo arms experienced at least one TEAE, with similar proportions of subjects in each arm. Across the Applicant's phase 2/3 clinical trials (AS3), TEAEs were reported in 71.2% (3853/5415) of tirzepatide-treated subjects. Please refer to Section 8.4.4 for detailed discussion of common TEAEs. Additionally, disposition summaries for the AS1 (Table 21) and AS2 (Table 22) study pools, which used the same tirzepatide dose and titration schedule, as well as a side-by-side comparison of the individual phase 3 trials (Table 23), are presented below.

In the placebo-controlled study pool (AS1), the proportions of subjects who completed the trials were similar in the tirzepatide and placebo arms (approximately 92%). However, a higher proportion of subjects in the placebo arm completed the treatment period (i.e., 91.1% of subjects randomized to placebo, and 86.6% of tirzepatide-treated subjects). This was primarily due to treatment discontinuations due to AEs, which appeared to be dose-related (Table 21).

Table 21: Disposition Summary (AS1)

Disposition	PBO (N=235)	TZP 5mg (N=237)	TZP 10mg (N=240)	TZP 15mg (N=241)	TZP ALL (N=718)
Completed Study	**216 (91.9)**	**223 (94.1)**	**227 (94.6)**	**213 (88.4)**	**663 (92.3)**
Discontinued Study	**19 (8.1)**	**14 (5.9)**	**13 (5.4)**	**28 (11.6)**	**55 (7.7)**
Adverse Event	1 (0.4)	4 (1.7)	3 (1.3)	3 (1.2)	10 (1.4)
Death	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Lost to Follow-Up	5 (2.1)	3 (1.3)	2 (0.8)	4 (1.7)	9 (1.3)
Other	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.1)
Physician Decision	2 (0.9)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.1)
Protocol Deviation	2 (0.9)	1 (0.4)	1 (0.4)	2 (0.8)	4 (0.6)
Withdrawal by Subject	8 (3.4)	6 (2.5)	6 (2.5)	18 (7.5)	30 (4.2)
Completed Treatment	**214 (91.1)**	**215 (90.7)**	**214 (89.2)**	**193 (80.1)**	**622 (86.6)**
Discontinued Treatment	**21 (8.9)**	**22 (9.3)**	**26 (10.8)**	**48 (19.9)**	**96 (13.4)**
Adverse Event	5 (2.1)	11 (4.6)	16 (6.7)	21 (8.7)	48 (6.7)
Death	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Failure to Meet Randomization Criteria	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.1)
Lost to Follow-Up	4 (1.7)	3 (1.3)	1 (0.4)	3 (1.2)	7 (1.0)
Other	0 (0.0)	1 (0.4)	0 (0.0)	2 (0.8)	3 (0.4)
Physician Decision	4 (1.7)	0 (0.0)	2 (0.8)	3 (1.2)	5 (0.7)
Protocol Deviation	2 (0.9)	1 (0.4)	1 (0.4)	2 (0.8)	4 (0.6)
Withdrawal by Subject	5 (2.1)	6 (2.5)	6 (2.5)	16 (6.6)	28 (3.9)

Source: Derived from the adsl.xpt and adae.xpt datasets, available at: \\CDSESUB1\evsprod\NDA215866\0001\m5\datasets

Abbreviation: AS1, Analysis Set 1 (pool of 2 placebo-controlled phase 3 trials); COVID-19, coronavirus disease 2019; Dula, dulaglutide; Ins Deg, insulin degludec; Ins Glar, insulin glargine; MedDRA, Medical Dictionary for Regulatory Activities; no., number; PBO, placebo; PT, preferred term; Sema, semaglutide; SOC, system organ class; TEAE, treatment-emergent adverse event; and TZP, tirzepatide

Similarly, across the phase 3 trials (AS2), discontinuations of IP due to AEs appeared to be dose-related (Table 22), with higher proportions of tirzepatide-treated subjects discontinuing treatment in each of the eight trials that included a comparator arm (Table 23). The highest numbers of deaths (60 across all treatment groups) were reported in trial GPGM, which was enriched with subjects at higher CV risks. Deaths resulting in discontinuation of treatment and study were similar, but higher in the insulin glargine arm. Please refer to Section 8.4.1 for additional information related to the deaths reported in this Application.

Table 22: Disposition Summary – Phase 3 Pool (AS2)

Disposition	PBO (N=235)	Ins Glar (N=1000)	Ins Deg (N=360)	Dula 0.75mg (N=159)	Sema 1 mg (N=469)	TZP 5mg (N=1701)	TZP 10mg (N=1702)	TZP 15mg (N=1716)
Completed Study — no. (%)	**216 (91.9)**	**882 (88.2)**	**331 (91.9)**	**154 (96.9)**	**443 (94.5)**	**1602 (94.2)**	**1592 (93.5)**	**1600 (93.2)**
Discontinued Study	**19 (8.1)**	**118 (11.8)**	**29 (8.1)**	**5 (3.1)**	**26 (5.5)**	**99 (5.8)**	**110 (6.5)**	**116 (6.8)**
Adverse Event	1 (0.4)	10 (1.0)	1 (0.3)	4 (2.5)	3 (0.6)	17 (1.0)	24 (1.4)	20 (1.2)
Death	1 (0.4)	35 (3.5)	1 (0.3)	0 (0.0)	1 (0.2)	20 (1.2)	8 (0.5)	13 (0.8)
Lost to Follow-Up	5 (2.1)	22 (2.2)	5 (1.4)	1 (0.6)	12 (2.6)	22 (1.3)	19 (1.1)	23 (1.3)
Other	0 (0.0)	8 (0.8)	3 (0.8)	0 (0.0)	0 (0.0)	6 (0.4)	10 (0.6)	5 (0.3)
Physician Decision	2 (0.9)	6 (0.6)	1 (0.3)	0 (0.0)	4 (0.9)	1 (<0.1)	6 (0.4)	2 (0.1)
Pregnancy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (<0.1)	0 (0.0)	1 (<0.1)
Protocol Deviation	2 (0.9)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.2)	4 (0.2)	3 (0.2)
Study Terminated by Sponsor	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Withdrawal by Subject	8 (3.4)	36 (3.6)	18 (5.0)	0 (0.0)	4 (0.9)	29 (1.7)	39 (2.3)	49 (2.9)
Completed Treatment — no. (%)	**214 (91.1)**	**861 (86.1)**	**320 (88.9)**	**145 (91.2)**	**428 (91.3)**	**1521 (89.4)**	**1474 (86.6)**	**1445 (84.2)**
Discontinued Treatment— no. (%)	**21 (8.9)**	**139 (13.9)**	**40 (11.1)**	**14 (8.8)**	**41 (8.7)**	**180 (10.6)**	**228 (13.4)**	**271 (15.8)**
Adverse Event	5 (2.1)	19 (1.9)	5 (1.4)	9 (5.7)	18 (3.8)	105 (6.2)	137 (8.0)	160 (9.3)
Death	1 (0.4)	35 (3.5)	0 (0.0)	0 (0.0)	1 (0.2)	17 (1.0)	8 (0.5)	9 (0.5)
Failure to Meet Randomization Criteria	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.2)	1 (<0.1)	1 (<0.1)	2 (0.1)
Lost to Follow-Up	4 (1.7)	16 (1.6)	4 (1.1)	1 (0.6)	9 (1.9)	18 (1.1)	13 (0.8)	19 (1.1)
Other	0 (0.0)	10 (1.0)	2 (0.6)	0 (0.0)	1 (0.2)	6 (0.4)	10 (0.6)	11 (0.6)
Physician Decision	4 (1.7)	9 (0.9)	2 (0.6)	0 (0.0)	2 (0.4)	3 (0.2)	13 (0.8)	10 (0.6)
Pregnancy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (<0.1)	0 (0.0)	1 (<0.1)
Protocol Deviation	2 (0.9)	3 (0.3)	0 (0.0)	2 (1.3)	1 (0.2)	3 (0.2)	3 (0.2)	7 (0.4)
Withdrawal by Subject	5 (2.1)	47 (4.7)	26 (7.2)	2 (1.3)	7 (1.5)	26 (1.5)	43 (2.5)	52 (3.0)

Source: Derived from the adsl.xpt and adae.xpt datasets, available at: \\CDSESUB1\evsprod\NDA215866\0001\m5\datasets
Abbreviation: AS2, Analysis Set 2 (pool of 7 phase 3 trials); Dula, dulaglutide; Ins Deg, insulin degludec; Ins Glar, insulin glargine; no., number; PBO, placebo; PT, preferred term; Sema, semaglutide; SOC, system organ class; TEAE, treatment-emergent adverse event; and TZP, tirzepatide.

Table 23: Disposition Summary – Side-by-Side Comparison of Phase 3 Trials (AS2)

	GPGK		GPGI		GPGM		GPGH		GPGO		GPGL		GPGP
System Organ Class MedDRA PT	**PBO (N=115)**	**TZP ALL (N=363)**	**PBO (N=120)**	**TZP ALL (N=355)**	**Ins Glar (N=1000)**	**TZP ALL (N=995)**	**Ins Deg (N=360)**	**TZP ALL (N=1077)**	**Dula 0.75 mg (N=159)**	**TZP ALL (N=477)**	**Sema 1 mg (N=469)**	**TZP ALL (N=1409)**	**TZP ALL (443)**
Completed Study — no. (%)	**99 (86.1)**	**329 (90.6)**	**117 (97.5)**	**334 (94.1)**	**882 (88.2)**	**919 (92.4)**	**331 (91.9)**	**994 (92.3)**	**154 (96.9)**	**461 (96.6)**	**443 (94.5)**	**1340 (95.1)**	**417 (94.1)**
Discontinued Study	**16 (13.9)**	**34 (9.4)**	**3 (2.5)**	**21 (5.9)**	**118 (11.8)**	**76 (7.6)**	**29 (8.1)**	**83 (7.7)**	**5 (3.1)**	**16 (3.4)**	**26 (5.5)**	**69 (4.9)**	**26 (5.9)**
Adverse Event	1 (0.9)	5 (1.4)	0 (0.0)	5 (1.4)	10 (1.0)	8 (0.8)	1 (0.3)	15 (1.4)	4 (2.5)	4 (0.8)	3 (0.6)	6 (0.4)	18 (4.1)
Death	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	35 (3.5)	25 (2.5)	1 (0.3)	4 (0.4)	0 (0.0)	0 (0.0)	1 (0.2)	12 (0.9)	0 (0.0)
Lost to Follow-Up	5 (4.3)	8 (2.2)	0 (0.0)	1 (0.3)	22 (2.2)	15 (1.5)	5 (1.4)	21 (1.9)	1 (0.6)	0 (0.0)	12 (2.6)	19 (1.3)	0 (0.0)
Other	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	8 (0.8)	7 (0.7)	3 (0.8)	6 (0.6)	0 (0.0)	1 (0.2)	0 (0.0)	6 (0.4)	0 (0.0)
Physician Decision	2 (1.7)	1 (0.3)	0 (0.0)	0 (0.0)	6 (0.6)	1 (0.1)	1 (0.3)	4 (0.4)	0 (0.0)	1 (0.2)	4 (0.9)	2 (0.1)	0 (0.0)
Pregnancy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	2 (0.1)	0 (0.0)
Protocol Deviation	1 (0.9)	1 (0.3)	1 (0.8)	3 (0.8)	1 (0.1)	3 (0.3)	0 (0.0)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Study Terminated by Sponsor	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
Withdrawal by Subject	6 (5.2)	18 (5.0)	2 (1.7)	12 (3.4)	36 (3.6)	17 (1.7)	18 (5.0)	31 (2.9)	0 (0.0)	10 (2.1)	4 (0.9)	21 (1.5)	8 (1.8)
Completed Treatment — no. (%)	**98 (85.2)**	**314 (86.5)**	**116 (96.7)**	**308 (86.8)**	**861 (86.1)**	**845 (84.9)**	**320 (88.9)**	**910 (84.5)**	**145 (91.2)**	**415 (87.0)**	**428 (91.3)**	**1250 (88.7)**	**398 (89.8)**
Discontinued Treatment— no. (%)	**17 (14.8)**	**49 (13.5)**	**4 (3.3)**	**47 (13.2)**	**139 (13.9)**	**150 (15.1)**	**40 (11.1)**	**167 (15.5)**	**14 (8.8)**	**62 (13.0)**	**41 (8.7)**	**159 (11.3)**	**45 (10.2)**
Adverse Event	**2 (1.7)**	**18 (5.0)**	**3 (2.5)**	**30 (8.5)**	**19 (1.9)**	**80 (8.0)**	**5 (1.4)**	**100 (9.3)**	**9 (5.7)**	**44 (9.2)**	**18 (3.8)**	**97 (6.9)**	**33 (7.4)**
Death	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	35 (3.5)	21 (2.1)	0 (0.0)	2 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	11 (0.8)	0 (0.0)
Failure to Meet Randomization Criteria	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (<0.1)	0 (0.0)
Lost to Follow-Up	4 (3.5)	6 (1.7)	0 (0.0)	1 (0.3)	16 (1.6)	12 (1.2)	4 (1.1)	15 (1.4)	1 (0.6)	0 (0.0)	9 (1.9)	16 (1.1)	0 (0.0)
Other	0 (0.0)	2 (0.6)	0 (0.0)	1 (0.3)	10 (1.0)	11 (1.1)	2 (0.6)	4 (0.4)	0 (0.0)	1 (0.2)	1 (0.2)	8 (0.6)	0 (0.0)
Physician Decision	4 (3.5)	5 (1.4)	0 (0.0)	0 (0.0)	9 (0.9)	4 (0.4)	2 (0.6)	7 (0.6)	0 (0.0)	5 (1.0)	2 (0.4)	3 (0.2)	2 (0.5)
Pregnancy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	2 (0.1)	0 (0.0)
Protocol Deviation	1 (0.9)	1 (0.3)	1 (0.8)	3 (0.8)	3 (0.3)	2 (0.2)	0 (0.0)	2 (0.2)	2 (1.3)	2 (0.4)	1 (0.2)	1 (<0.1)	2 (0.5)
Withdrawal by Subject	5 (4.3)	16 (4.4)	0 (0.0)	12 (3.4)	47 (4.7)	18 (1.8)	26 (7.2)	37 (3.4)	2 (1.3)	10 (2.1)	7 (1.5)	20 (1.4)	8 (1.8)

Source: Derived from the adsl.xpt and adae.xpt datasets, available at: \\CDSESUB1\evsprod\NDA215866\0001\m5\datasets
Abbreviation: AS2, Analysis Set 2 (pool of 7 phase 3 trials); Dula, dulaglutide; Ins Deg, insulin degludec; Ins Glar, insulin glargine; no., number; PBO, placebo; Sema, semaglutide; and TZP, tirzepatide.

8.4.1. **Deaths**

A summary of the AEs resulting in death is presented in Table 24. There were no deaths in the three biopharmaceutic studies (GPHI, GPGS, and GPGE) or seven clinical pharmacology (GPGR, GPGA, GPGG, GPGQ, GPHX, GPGT, and GPGC) studies. Across the nine phase 2/3 clinical trials (AS3) there were 80 deaths, of which 41 deaths (study size adjusted percentage [adj 0.92%]) occurred in the pooled tirzepatide arm and 39 deaths [adj 1.09%] in the pooled comparator arm. Across all treatment arms, the 'Infections and infestations' (27 subjects), and the 'Cardiac disorders' (23 subjects) were the SOCs associated with the most deaths. Most of the deaths (60 subjects) occurred in trial GPGM, which was enriched with high CV risk subjects and included a longer treatment duration. In this trial, more deaths were observed in the insulin glargine arm (i.e., 3.5% vs. 2.5%). However, in trial GPGL, more deaths were reported in the tirzepatide arms (i.e., 0.9% vs. 0.2% in the semaglutide arm). Six of the 13 deaths reported in this trial were reported as related to COVID-19 infection (1 subject in the semaglutide arm, 1 subject randomized to tirzepatide 5 mg, and two subjects each in the tirzepatide 10 mg and 15 mg arms), five deaths were confirmed as CV deaths, and two were "undetermined" by the external CEC.

Overall, these data do not show relevant imbalances between treatment arms by SOC or MedDRA PTs. However, it is acknowledged that the numbers of deaths by individual PT were limited. In the CVMA, it is notable that adjudicated deaths from all causes favored the pooled tirzepatide arm (HR 0.93, 95% CI: 0.80, 1.08). Please refer to Section 8.5.11 (Cardiovascular Safety) for additional information.

In the 4MSU, deaths were reported across all treatment arms in approximately 0.82% (111/13,603) of subjects, of which 106 deaths occurred in the Applicant's CVOT (GPGN). As the treatment allocation for this ongoing trial remained blinded, these additional deaths were not informative. The most frequently reported cause of death across all treatment arms were related to infections (i.e., 44 deaths coded to the 'Infections and Infestations' SOC), of which 34 subjects (0.25%) died of COVID-19.

Table 24: Fatal Adverse Events by System Organ Class and Trial (AS3)

	GPGK		GPGI		GPGF		GPGM		GPGH		GPGO		GPGB			GPGL		GPGP
System Organ Class MedDRA PT	PBO (N=115)	TZP ALL (N=363)	PBO (N=120)	TZP ALL (N=355)	PBO (N=26)	TZP ALL (N=85)	Ins Glar (N=1000)	TZP ALL (N=995)	Ins Deg (N=360)	TZP ALL (N=1077)	Dula 0.75 mg (N=159)	TZP ALL (N=477)	PBO (N=51)	Dula 1.5 mg (N=54)	TZP ALL (N=211)	Sema 1 mg (N=469)	TZP ALL (N=1409)	TZP ALL (443)
ALL DEATHS	**ALL Comparators: 39 deaths/2354 subjects (1.66%) [adj 1.09%] — TZP: 41 deaths/5415 subjects (0.76%) [adj 0.92%]**																	
Total Deaths — no. (%)	**1 (0.9)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**35 (3.5)**	**25 (2.5)**	**1 (0.3)**	**4 (0.4)**	**0 (0.0)**	**0 (0.0)**	**1 (2.0)**	**0 (0.0)**	**0 (0.0)**	**1 (0.2)**	**12 (0.9)**	**0 (0.0)**
Infections and infestations	***0 (0.0)***	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**10 (1.0)**	**10 (1.0)**	**0 (0.0)**	**1 (<0.1)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**1 (0.2)**	**5 (0.4)**	**0 (0.0)**
COVID-19	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (0.5)	3 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
COVID-19 pneumonia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.3)	3 (0.3)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	2 (0.1)	0 (0.0)
Cellulitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pneumonia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Septic shock	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Urosepsis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Nosocomial infection	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pyelonephritis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Sepsis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Suspected COVID-19	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Cardiac disorders	**1 (0.9)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**9 (0.9)**	**8 (0.8)**	**0 (0.0)**	**2 (0.2)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**3 (0.2)**	**0 (0.0)**
Acute myocardial infarction	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Cardiac failure	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cardiac arrest	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.1)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cardiorespiratory arrest	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)*	0 (0.0)
Coronary artery disease	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Ischaemic cardiomyopathy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cardiac disorder	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cardiac failure congestive	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cardiogenic shock	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

	GPGK		GPGI		GPGF		GPGM		GPGH		GPGO		GPGB			GPGL		GPGP
System Organ Class MedDRA PT	PBO (N=115)	TZP ALL (N=363)	PBO (N=120)	TZP ALL (N=355)	PBO (N=26)	TZP ALL (N=85)	Ins Glar (N=1000)	TZP ALL (N=995)	Ins Deg (N=360)	TZP ALL (N=1077)	Dula 0.75 mg (N=159)	TZP ALL (N=477)	PBO (N=51)	Dula 1.5 mg (N=54)	TZP ALL (N=211)	Sema 1 mg (N=469)	TZP ALL (N=1409)	TZP ALL (443)
Myocardial infarction	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
General disorders and administration site conditions	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**4 (0.4)**	**3 (0.3)**	**1 (0.3)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**2 (0.1)**	**0 (0.0)**
Death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Sudden cardiac death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Multiple organ dysfunction syndrome	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Sudden death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Neoplasms benign, malignant and unspecified	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**2 (0.2)**	**2 (0.2)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**1 (2.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**
Neoplasm malignant	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pancreatic carcinoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Lung adenocarcinoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Lung adenocarcinoma stage IV	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Lung neoplasm malignant	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Nervous system disorders	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**1 (0.1)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**1 (<0.1)**	**0 (0.0)**
Haemorrhagic stroke	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cerebrovascular accident	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**7 (0.7)**	**1 (0.1)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**
Pulmonary embolism	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Acute pulmonary oedema	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Acute respiratory failure	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Respiratory failure	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Injury, poisoning and procedural complications	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**1 (0.1)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**
Spinal column injury	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Musculoskeletal and connective tissue disorders	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**1 (0.1)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**
Arthropathy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

	GPGK		GPGI		GPGF		GPGM		GPGH		GPGO		GPGB			GPGL		GPGP
System Organ Class MedDRA PT	PBO (N=115)	TZP ALL (N=363)	PBO (N=120)	TZP ALL (N=355)	PBO (N=26)	TZP ALL (N=85)	Ins Glar (N=1000)	TZP ALL (N=995)	Ins Deg (N=360)	TZP ALL (N=1077)	Dula 0.75 mg (N=159)	TZP ALL (N=477)	PBO (N=51)	Dula 1.5 mg (N=54)	TZP ALL (N=211)	Sema 1 mg (N=469)	TZP ALL (N=1409)	TZP ALL (443)
Psychiatric disorders	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**1 (<0.1)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**
Depression suicidal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Renal and urinary disorders	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**1 (0.1)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**1 (<0.1)**	**0 (0.0)**
End stage renal disease	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Renal impairment	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Source: Derived from the adsl.xpt and adae.xpt datasets, available at: \\CDSESUB1\evsprod\NDA215866\0001\m5\datasets
Abbreviation: adj, study size adjusted percentage; AS3, Analysis Set 3 (pool of 9 phase 2/3 trials); COVID-19, coronavirus disease 2019; Dula, dulaglutide; Ins Deg, insulin degludec; Ins Glar, insulin glargine; MedDRA, Medical Dictionary for Regulatory Activities; no., number; PBO, placebo; PT, preferred term; Sema, semaglutide; SOC, system organ class; TEAE, treatment-emergent adverse event; and TZP, tirzepatide.
*An SAE of 'Cardiorespiratory arrest', was reported for a subject (GPGL-650-3049) who tested positive for COVID-19. The death was adjudicated as non-cardiovascular due to infection (COVID-19).

8.4.2. Serious Adverse Events

A listing of SAEs by treatment arm and SOC for the placebo-controlled study pool (AS1) is presented in Table 25. In these trials, SAEs were reported for 5.5% of subjects randomized to the placebo arm and 5.4% randomized to the pooled tirzepatide arm. Several SOCs had numerically higher SAEs in the tirzepatide arms, but events were generally limited. Review of these events by High Level Group Terms (HLGTs), High Level Terms (HLTs), and PTs did not reveal meaningful differences between arms.

Table 25: Serious Adverse Events – Phase 3 Placebo-Controlled Pool (AS1)

System Organ Class MedDRA PT	PBO (N=235)	TZP 5mg (N=237)	TZP 10mg (N=240)	TZP 15mg (N=241)	TZP ALL (N=718)
Subjects with ≥1 SAE— no. (%)	**13 (5.5)**	**14 (5.9)**	**15 (6.3)**	**10 (4.1)**	**39 (5.4)**
Cardiac disorders	**4 (1.7)**	**4 (1.7)**	**2 (0.8)**	**3 (1.2)**	**9 (1.3)**
Cardiac failure	1 (0.4)	3 (1.3)	1 (0.4)	0 (0.0)	4 (0.6)
Acute myocardial infarction	1 (0.4)	0 (0.0)	1 (0.4)	1 (0.4)	2 (0.3)
Coronary artery disease	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.8)	2 (0.3)
Angina pectoris	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.1)
Atrial fibrillation	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.1)
Supraventricular tachycardia	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.1)
Myocardial infarction	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Tachycardia	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Infections and infestations	**1 (0.4)**	**2 (0.8)**	**4 (1.7)**	**2 (0.8)**	**8 (1.1)**
Cellulitis	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.1)
Clostridium difficile infection	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.1)
Coronavirus infection	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.1)
Gastroenteritis	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.1)
Pneumonia	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.1)
Postoperative wound infection	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.1)
Pyelonephritis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.1)
Urinary tract infection	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.1)
COVID-19 pneumonia	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	**1 (0.4)**	**2 (0.8)**	**1 (0.4)**	**2 (0.8)**	**5 (0.7)**
Chronic obstructive pulmonary disease	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.8)	2 (0.3)
Respiratory failure	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.4)	2 (0.3)
Dyspnoea	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.1)
Sleep apnoea syndrome	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.1)
Pulmonary embolism	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Ear and labyrinth disorders	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**1 (0.4)**	**1 (0.1)**

System Organ Class MedDRA PT	PBO (N=235)	TZP 5mg (N=237)	TZP 10mg (N=240)	TZP 15mg (N=241)	TZP ALL (N=718)
Deafness unilateral	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.1)
General disorders and administration site conditions	**0 (0.0)**	**1 (0.4)**	**0 (0.0)**	**1 (0.4)**	**2 (0.3)**
Asthenia	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.1)
Impaired healing	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.1)
Injury, poisoning and procedural complications	**1 (0.4)**	**0 (0.0)**	**2 (0.8)**	**1 (0.4)**	**3 (0.4)**
Hip fracture	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.1)
Humerus fracture	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.1)
Spinal compression fracture	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.1)
Intestinal anastomosis complication	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Metabolism and nutrition disorders	**0 (0.0)**	**0 (0.0)**	**1 (0.4)**	**1 (0.4)**	**2 (0.3)**
Hypoglycaemia	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.4)	2 (0.3)
Musculoskeletal and connective tissue disorders	**0 (0.0)**	**0 (0.0)**	**2 (0.8)**	**1 (0.4)**	**3 (0.4)**
Musculoskeletal chest pain	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.1)
Spinal stenosis	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.1)
Synovial cyst	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.1)
Nervous system disorders	**1 (0.4)**	**1 (0.4)**	**2 (0.8)**	**1 (0.4)**	**4 (0.6)**
Hypoglycaemic unconsciousness	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.1)
Orthostatic intolerance	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.1)
Syncope	1 (0.4)	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.1)
Transient ischaemic attack	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.1)
Renal and urinary disorders	**1 (0.4)**	**1 (0.4)**	**0 (0.0)**	**1 (0.4)**	**2 (0.3)**
Calculus urinary	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.1)
Nephrolithiasis	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.1)
Bladder disorder	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Vascular disorders	**1 (0.4)**	**1 (0.4)**	**1 (0.4)**	**1 (0.4)**	**3 (0.4)**
Peripheral arterial occlusive disease	0 (0.0)	1 (0.4)	1 (0.4)	1 (0.4)	3 (0.4)
Aortic stenosis	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Gastrointestinal disorders	**2 (0.9)**	**2 (0.8)**	**0 (0.0)**	**0 (0.0)**	**2 (0.3)**
Colitis ischaemic	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.1)
Faecaloma	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.1)
Abdominal hernia	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pancreatic disorder	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**2 (0.9)**	**3 (1.3)**	**1 (0.4)**	**0 (0.0)**	**4 (0.6)**
Adenocarcinoma	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.1)
Papillary renal cell carcinoma	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.1)
Renal neoplasm	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.1)
Uterine cancer	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.1)

System Organ Class MedDRA PT	PBO (N=235)	TZP 5mg (N=237)	TZP 10mg (N=240)	TZP 15mg (N=241)	TZP ALL (N=718)
Cholangiocarcinoma	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Transitional cell carcinoma	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Psychiatric disorders	**0 (0.0)**	**0 (0.0)**	**1 (0.4)**	**0 (0.0)**	**1 (0.1)**
Anxiety	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.1)
Surgical and medical procedures	**1 (0.4)**	**0 (0.0)**	**1 (0.4)**	**0 (0.0)**	**1 (0.1)**
Cardiac ablation	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.1)
Pancreatic lesion excision	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Source: Derived from the adsl.xpt and adae.xpt datasets, available at: \\CDSESUB1\evsprod\NDA215866\0001\m5\datasets
Abbreviation: AS1, Analysis Set 1 (pool of 2 placebo-controlled phase 3 trials); MedDRA, Medical Dictionary for Regulatory Activities; no., number; PBO, placebo; PT, preferred term; SOC, system organ class; TEAE, treatment-emergent adverse event; and TZP, tirzepatide.

The seven phase 3 trials (AS2) also were reviewed by SOCs and PTs in the individual tirzepatide dose arms (i.e., 5, 10, and 15 mg) to evaluate any trends related to possible dose effects, as well to perform a side-by-side comparison to evaluate differences between the combined tirzepatide arms and the individual comparators.

The occurrence of SAEs in the tirzepatide arms did not appear to be dose related, with SAEs reported in 7.9% (134/1701), 7.9% (135/1702), and 7.1% (122/1716) of subjects randomized to the tirzepatide 5, 10, and 15 mg arms, respectively, and without apparent meaningful imbalances between these arms by individual SOCs (please refer to Appendix 13.7, Table 60).

By individual trial, SAEs were generally similar between comparator and the pooled tirzepatide arms except for trial GPGL. In this trial, SAEs were reported more often in the pooled tirzepatide arm compared to the semaglutide arm (6% of vs. 2.8%), with higher proportions of subjects reported for most SOCs. Event counts by individual PTs were limited to draw meaningful conclusions. However, there were four cases of 'Acute myocardial infarction' and five subjects with 'Cholecystitis acute' in the tirzepatide arms, and no cases of these AEs were reported in the semaglutide arm.

Table 26: Serious Adverse Events – Side by Side Comparisons of Phase 3 Trials (AS2)

	GPGK		GPGI		GPGM		GPGH		GPGO		GPGL		GPGP
System Organ Class MedDRA PT	PBO (N=115)	TZP ALL (N=363)	PBO (N=120)	TZP ALL (N=355)	Ins Glar (N=1000)	TZP ALL (N=995)	Ins Deg (N=360)	TZP ALL (N=1077)	Dula 0.75 mg (N=159)	TZP ALL (N=477)	Sema 1 mg (N=469)	TZP ALL (N=1409)	TZP ALL (443)
Subjects with ≥1 SAE— no. (%)	**3 (2.6)**	**8 (2.2)**	**10 (8.3)**	**31 (8.7)**	**193 (19.3)**	**143 (14.4)**	**22 (6.1)**	**75 (7.0)**	**14 (8.8)**	**25 (5.2)**	**13 (2.8)**	**85 (6.0)**	**24 (5.4)**
Cardiac disorders	**2 (1.7)**	**1 (0.3)**	**2 (1.7)**	**8 (2.3)**	**64 (6.4)**	**50 (5.0)**	**5 (1.4)**	**12 (1.1)**	**2 (1.3)**	**4 (0.8)**	**1 (0.2)**	**10 (0.7)**	**2 (0.5)**
Acute myocardial infarction	1 (0.9)	0 (0.0)	0 (0.0)	2 (0.6)	18 (1.8)	13 (1.3)	2 (0.6)	2 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)	4 (0.3)	0 (0.0)
Coronary artery disease	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.6)	15 (1.5)	11 (1.1)	1 (0.3)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Angina unstable	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	6 (0.6)	4 (0.4)	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.2)	0 (0.0)	1 (<0.1)	0 (0.0)
Atrial fibrillation	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	2 (0.2)	4 (0.4)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)
Cardiac failure	1 (0.9)	0 (0.0)	0 (0.0)	4 (1.1)	2 (0.2)	4 (0.4)	1 (0.3)	1 (<0.1)	1 (0.6)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Myocardial infarction	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)	4 (0.4)	4 (0.4)	0 (0.0)	3 (0.3)	0 (0.0)	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Cardio-respiratory arrest	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)
Acute coronary syndrome	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Angina pectoris	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	3 (0.3)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Aortic valve sclerosis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Arteriosclerosis coronary artery	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Atrial flutter	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Atrial tachycardia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Atrioventricular block second degree	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cardiac arrest	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.1)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cardiac failure acute	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cardiac failure chronic	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cardiomyopathy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Coronary artery stenosis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Ischaemic cardiomyopathy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Left ventricular failure	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Myocardial ischaemia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Myocarditis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Supraventricular extrasystoles	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Supraventricular tachycardia	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Ventricular dysfunction	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Ventricular extrasystoles	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Acute left ventricular failure	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

	GPGK		GPGI		GPGM		GPGH		GPGO		GPGL		GPGP
System Organ Class MedDRA PT	PBO (N=115)	TZP ALL (N=363)	PBO (N=120)	TZP ALL (N=355)	Ins Glar (N=1000)	TZP ALL (N=995)	Ins Deg (N=360)	TZP ALL (N=1077)	Dula 0.75 mg (N=159)	TZP ALL (N=477)	Sema 1 mg (N=469)	TZP ALL (N=1409)	TZP ALL (443)
Atrioventricular block	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Atrioventricular block complete	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Cardiac disorder	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cardiac failure congestive	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (0.5)	0 (0.0)	1 (0.3)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cardiogenic shock	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Tachycardia	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Ventricular tachycardia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
Infections and infestations	**0 (0.0)**	**2 (0.6)**	**1 (0.8)**	**6 (1.7)**	**52 (5.2)**	**36 (3.6)**	**8 (2.2)**	**16 (1.5)**	**4 (2.5)**	**5 (1.0)**	**6 (1.3)**	**25 (1.8)**	**3 (0.7)**
COVID-19 pneumonia	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)	15 (1.5)	11 (1.1)	0 (0.0)	3 (0.3)	2 (1.3)	0 (0.0)	4 (0.9)	6 (0.4)	0 (0.0)
COVID-19	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	10 (1.0)	6 (0.6)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	1 (0.2)	1 (<0.1)	0 (0.0)
Urosepsis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	5 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Pneumonia	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	10 (1.0)	4 (0.4)	2 (0.6)	2 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	2 (0.1)	0 (0.0)
Septic shock	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Appendicitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (<0.1)	1 (0.2)
Asymptomatic COVID-19	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cellulitis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	2 (0.2)	1 (0.1)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Diverticulitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.3)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Fournier's gangrene	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Gastroenteritis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	2 (0.2)	1 (0.1)	0 (0.0)	3 (0.3)	0 (0.0)	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Postoperative wound infection	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Sepsis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.4)	1 (0.1)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Urinary tract infection	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	3 (0.3)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)
Wound infection	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Atypical pneumonia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Bacteraemia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (<0.1)	0 (0.0)
Bronchitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cellulitis orbital	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cholecystitis infective	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Clostridium difficile infection	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Colon gangrene	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Complicated appendicitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Coronavirus infection	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Dengue fever	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)

	GPGK		GPGI		GPGM		GPGH		GPGO		GPGL		GPGP
System Organ Class MedDRA PT	PBO (N=115)	TZP ALL (N=363)	PBO (N=120)	TZP ALL (N=355)	Ins Glar (N=1000)	TZP ALL (N=995)	Ins Deg (N=360)	TZP ALL (N=1077)	Dula 0.75 mg (N=159)	TZP ALL (N=477)	Sema 1 mg (N=469)	TZP ALL (N=1409)	TZP ALL (443)
Device related infection	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Diabetic foot infection	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Diabetic gangrene	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Endocarditis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Epididymitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Erysipelas	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Escherichia bacteraemia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
HIV infection	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hepatitis E	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Infected skin ulcer	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Infection	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Infectious pleural effusion	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Intervertebral discitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Liver abscess	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Lower respiratory tract infection	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Nosocomial infection	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Osteomyelitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Periodontitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pharyngeal abscess	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Pneumonia bacterial	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pneumonia klebsiella	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pneumonia legionella	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Pyelitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Pyelonephritis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Pyelonephritis acute	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Respiratory tract infection	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Sinusitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Suspected COVID-19	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Systemic candida	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Nervous system disorders	**0 (0.0)**	**1 (0.3)**	**1 (0.8)**	**3 (0.8)**	**26 (2.6)**	**19 (1.9)**	**3 (0.8)**	**6 (0.6)**	**0 (0.0)**	**1 (0.2)**	**1 (0.2)**	**5 (0.4)**	**1 (0.2)**
Ischaemic stroke	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	6 (0.6)	7 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
Transient ischaemic attack	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.1)	3 (0.3)	0 (0.0)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cerebrovascular accident	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)

	GPGK		GPGI		GPGM		GPGH		GPGO		GPGL		GPGP
System Organ Class MedDRA PT	PBO (N=115)	TZP ALL (N=363)	PBO (N=120)	TZP ALL (N=355)	Ins Glar (N=1000)	TZP ALL (N=995)	Ins Deg (N=360)	TZP ALL (N=1077)	Dula 0.75 mg (N=159)	TZP ALL (N=477)	Sema 1 mg (N=469)	TZP ALL (N=1409)	TZP ALL (443)
Haemorrhagic stroke	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)	2 (0.2)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cerebellar stroke	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cognitive disorder	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cranial nerve disorder	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Guillain-Barre syndrome	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Headache	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Hemiplegia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hypoxic-ischaemic encephalopathy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Neuropathy peripheral	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Syncope	0 (0.0)	1 (0.3)	1 (0.8)	0 (0.0)	2 (0.2)	1 (0.1)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)
Carpal tunnel syndrome	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cerebellar infarction	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Coma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Diabetic neuropathy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Dizziness	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Encephalopathy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Facial paralysis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Hypoglycaemic unconsciousness	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Lacunar infarction	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Lacunar stroke	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Lumbar radiculopathy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Metabolic encephalopathy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Myelopathy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Orthostatic intolerance	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Presyncope	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Spinal cord compression	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Subarachnoid haemorrhage	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Thalamic infarction	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Vertebrobasilar insufficiency	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Neoplasms benign, malignant and unspecified	**1 (0.9)**	**1 (0.3)**	**1 (0.8)**	**3 (0.8)**	**17 (1.7)**	**12 (1.2)**	**1 (0.3)**	**11 (1.0)**	**3 (1.9)**	**6 (1.3)**	**1 (0.2)**	**9 (0.6)**	**5 (1.1)**
Adenocarcinoma of colon	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.1)	0 (0.0)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Breast cancer stage II	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

	GPGK		GPGI		GPGM		GPGH		GPGO		GPGL		GPGP
System Organ Class MedDRA PT	PBO (N=115)	TZP ALL (N=363)	PBO (N=120)	TZP ALL (N=355)	Ins Glar (N=1000)	TZP ALL (N=995)	Ins Deg (N=360)	TZP ALL (N=1077)	Dula 0.75 mg (N=159)	TZP ALL (N=477)	Sema 1 mg (N=469)	TZP ALL (N=1409)	TZP ALL (443)
Colon cancer metastatic	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Invasive lobular breast carcinoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Metastases to lymph nodes	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Metastatic squamous cell carcinoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Neoplasm malignant	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Ovarian cancer	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pancreatic carcinoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pancreatic neoplasm	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Papillary renal cell carcinoma	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Prostate cancer	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.3)	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.6)	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Renal cancer recurrent	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Renal cell carcinoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (<0.1)	0 (0.0)
Adenocarcinoma	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Basal cell carcinoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Bile duct adenocarcinoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Bladder cancer	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Bladder papilloma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Bladder transitional cell carcinoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cerebellopontine angle tumour	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Cholangiocarcinoma	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cholesteatoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Colon adenoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Colon cancer	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Endometrial adenocarcinoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Gastric neoplasm	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Glioblastoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Glioblastoma multiforme	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Invasive breast carcinoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Invasive ductal breast carcinoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Laryngeal squamous cell carcinoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Lung adenocarcinoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

	GPGK		GPGI		GPGM		GPGH		GPGO		GPGL		GPGP
System Organ Class MedDRA PT	PBO (N=115)	TZP ALL (N=363)	PBO (N=120)	TZP ALL (N=355)	Ins Glar (N=1000)	TZP ALL (N=995)	Ins Deg (N=360)	TZP ALL (N=1077)	Dula 0.75 mg (N=159)	TZP ALL (N=477)	Sema 1 mg (N=469)	TZP ALL (N=1409)	TZP ALL (443)
Lung adenocarcinoma stage IV	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Lung carcinoma cell type unspecified stage III	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Lung neoplasm malignant	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Meningioma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Metastases to liver	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Nasopharyngeal cancer	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Neoplasm skin	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Neuroendocrine carcinoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Non-Hodgkin's lymphoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
Pituitary tumour benign	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Renal neoplasm	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Squamous cell carcinoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Squamous cell carcinoma of lung	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Squamous cell carcinoma of skin	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Testicular neoplasm	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Transitional cell carcinoma	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Uterine cancer	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Uterine leiomyoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Uterine neoplasm	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
General disorders and administration site conditions	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**2 (0.6)**	**6 (0.6)**	**10 (1.0)**	**1 (0.3)**	**3 (0.3)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**4 (0.3)**	**0 (0.0)**
Asthenia	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Chest pain	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)
Necrosis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Non-cardiac chest pain	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pyrexia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Sudden cardiac death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Systemic inflammatory response syndrome	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Impaired healing	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

	GPGK		GPGI		GPGM		GPGH		GPGO		GPGL		GPGP
System Organ Class MedDRA PT	PBO (N=115)	TZP ALL (N=363)	PBO (N=120)	TZP ALL (N=355)	Ins Glar (N=1000)	TZP ALL (N=995)	Ins Deg (N=360)	TZP ALL (N=1077)	Dula 0.75 mg (N=159)	TZP ALL (N=477)	Sema 1 mg (N=469)	TZP ALL (N=1409)	TZP ALL (443)
Multiple organ dysfunction syndrome	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Sudden death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Renal and urinary disorders	**0 (0.0)**	**1 (0.3)**	**1 (0.8)**	**1 (0.3)**	**12 (1.2)**	**10 (1.0)**	**2 (0.6)**	**3 (0.3)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**5 (0.4)**	**2 (0.5)**
Acute kidney injury	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.3)	3 (0.3)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Renal cyst	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Ureterolithiasis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Bladder mass	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Haematuria	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hydronephrosis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Nephrolithiasis	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.1)	0 (0.0)	3 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	1 (0.2)
Renal failure	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Bladder disorder	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Calculus urinary	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Chronic kidney disease	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
End stage renal disease	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Renal colic	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Renal impairment	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Renal infarct	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Renal mass	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Urinary bladder polyp	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Urinary tract obstruction	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Gastrointestinal disorders	**0 (0.0)**	**1 (0.3)**	**2 (1.7)**	**1 (0.3)**	**6 (0.6)**	**9 (0.9)**	**0 (0.0)**	**11 (1.0)**	**1 (0.6)**	**5 (1.0)**	**0 (0.0)**	**11 (0.8)**	**1 (0.2)**
Pancreatitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Duodenal ulcer	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Gastric polyps	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Gastric ulcer	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Gastritis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Inguinal hernia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	1 (<0.1)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Obstructive pancreatitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pancreatitis acute	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Abdominal hernia	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Abdominal pain	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Abdominal pain upper	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)

	GPGK		GPGI		GPGM		GPGH		GPGO		GPGL		GPGP
System Organ Class MedDRA PT	PBO (N=115)	TZP ALL (N=363)	PBO (N=120)	TZP ALL (N=355)	Ins Glar (N=1000)	TZP ALL (N=995)	Ins Deg (N=360)	TZP ALL (N=1077)	Dula 0.75 mg (N=159)	TZP ALL (N=477)	Sema 1 mg (N=469)	TZP ALL (N=1409)	TZP ALL (443)
Abdominal wall haematoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Colitis ischaemic	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Colitis ulcerative	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Constipation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Diarrhoea	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Diverticulum intestinal haemorrhagic	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Dyspepsia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Dysphagia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Epiploic appendagitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Faecaloma	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Gastric ulcer haemorrhage	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Gastritis alcoholic	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Gastrointestinal haemorrhage	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Inguinal hernia, obstructive	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Irritable bowel syndrome	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Large intestine polyp	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Lower gastrointestinal haemorrhage	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Nausea	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Pancreatic disorder	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Peptic ulcer	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Rectal polyp	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Segmental diverticular colitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Strangulated umbilical hernia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Vomiting	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Injury, poisoning and procedural complications	**0 (0.0)**	**0 (0.0)**	**1 (0.8)**	**3 (0.8)**	**9 (0.9)**	**9 (0.9)**	**2 (0.6)**	**8 (0.7)**	**2 (1.3)**	**3 (0.6)**	**1 (0.2)**	**8 (0.6)**	**2 (0.5)**
Thoracic vertebral fracture	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Ankle fracture	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Concussion	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Femoral neck fracture	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hip fracture	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.1)	1 (0.1)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
Limb injury	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

	GPGK		GPGI		GPGM		GPGH		GPGO		GPGL		GPGP
System Organ Class MedDRA PT	PBO (N=115)	TZP ALL (N=363)	PBO (N=120)	TZP ALL (N=355)	Ins Glar (N=1000)	TZP ALL (N=995)	Ins Deg (N=360)	TZP ALL (N=1077)	Dula 0.75 mg (N=159)	TZP ALL (N=477)	Sema 1 mg (N=469)	TZP ALL (N=1409)	TZP ALL (443)
Nerve injury	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Spinal compression fracture	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Subdural haematoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Accident	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Acetabulum fracture	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Clavicle fracture	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Craniocerebral injury	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Fall	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Femur fracture	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Foot fracture	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hand fracture	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Head injury	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Humerus fracture	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Injury	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Intentional overdose	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Intestinal anastomosis complication	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Joint dislocation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Ligament injury	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Limb traumatic amputation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Lumbar vertebral fracture	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Maternal exposure during pregnancy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Meniscus injury	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Multiple injuries	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Pulmonary contusion	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Radius fracture	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Rib fracture	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Spinal column injury	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Tendon injury	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Tendon rupture	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Traumatic amputation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Upper limb fracture	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (<0.1)	0 (0.0)
Vascular injury	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Wrist fracture	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Vascular disorders	**0 (0.0)**	**1 (0.3)**	**1 (0.8)**	**2 (0.6)**	**10 (1.0)**	**9 (0.9)**	**0 (0.0)**	**2 (0.2)**	**0 (0.0)**	**0 (0.0)**	**2 (0.4)**	**2 (0.1)**	**0 (0.0)**

	GPGK		GPGI		GPGM		GPGH		GPGO		GPGL		GPGP
System Organ Class MedDRA PT	PBO (N=115)	TZP ALL (N=363)	PBO (N=120)	TZP ALL (N=355)	Ins Glar (N=1000)	TZP ALL (N=995)	Ins Deg (N=360)	TZP ALL (N=1077)	Dula 0.75 mg (N=159)	TZP ALL (N=477)	Sema 1 mg (N=469)	TZP ALL (N=1409)	TZP ALL (443)
Peripheral arterial occlusive disease	0 (0.0)	1 (0.3)	0 (0.0)	2 (0.6)	1 (0.1)	3 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Peripheral artery occlusion	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Aortic aneurysm	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Deep vein thrombosis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)	1 (0.1)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Hypertension	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
Peripheral ischaemia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Aortic aneurysm rupture	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Aortic stenosis	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Arteriosclerosis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Dry gangrene	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hypotension	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Iliac artery stenosis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Orthostatic hypotension	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Peripheral vascular disorder	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
Thrombophlebitis superficial	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Venous thrombosis limb	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
Metabolism and nutrition disorders	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**2 (0.6)**	**17 (1.7)**	**8 (0.8)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**4 (0.3)**	**0 (0.0)**
Hypoglycaemia	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.6)	12 (1.2)	4 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)
Dehydration	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Hyperkalaemia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Iron deficiency	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Diabetes mellitus inadequate control	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hypokalaemia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hyponatraemia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	**0 (0.0)**	**1 (0.3)**	**1 (0.8)**	**4 (1.1)**	**22 (2.2)**	**7 (0.7)**	**1 (0.3)**	**3 (0.3)**	**0 (0.0)**	**1 (0.2)**	**1 (0.2)**	**6 (0.4)**	**0 (0.0)**
Acute pulmonary oedema	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Acute respiratory failure	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.3)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Asthma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
Asthmatic crisis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Dyspnoea	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Hypoxia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pulmonary embolism	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)	3 (0.3)	1 (0.1)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)

	GPGK		GPGI		GPGM		GPGH		GPGO		GPGL		GPGP
System Organ Class MedDRA PT	PBO (N=115)	TZP ALL (N=363)	PBO (N=120)	TZP ALL (N=355)	Ins Glar (N=1000)	TZP ALL (N=995)	Ins Deg (N=360)	TZP ALL (N=1077)	Dula 0.75 mg (N=159)	TZP ALL (N=477)	Sema 1 mg (N=469)	TZP ALL (N=1409)	TZP ALL (443)
Acute respiratory distress syndrome	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Chronic obstructive pulmonary disease	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.6)	3 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Epistaxis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Interstitial lung disease	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pleural effusion	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)
Pneumothorax	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Pulmonary fibrosis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pulmonary mass	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Respiratory failure	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.3)	4 (0.4)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Sleep apnoea syndrome	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hepatobiliary disorders	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**6 (0.6)**	**5 (0.5)**	**0 (0.0)**	**5 (0.5)**	**0 (0.0)**	**2 (0.4)**	**0 (0.0)**	**5 (0.4)**	**1 (0.2)**
Cholecystitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)	1 (0.1)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cholecystitis acute	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (0.4)	0 (0.0)
Hepatic cirrhosis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hepatitis acute	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hepatotoxicity	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Biliary dilatation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cholangitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Cholangitis acute	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Cholelithiasis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.3)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Hepatic function abnormal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Malignant biliary obstruction	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Musculoskeletal and connective tissue disorders	**0 (0.0)**	**1 (0.3)**	**0 (0.0)**	**2 (0.6)**	**5 (0.5)**	**3 (0.3)**	**1 (0.3)**	**2 (0.2)**	**1 (0.6)**	**1 (0.2)**	**1 (0.2)**	**1 (<0.1)**	**2 (0.5)**
Intervertebral disc protrusion	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pain in extremity	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Systemic lupus erythematosus	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Arthralgia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Arthropathy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Back pain	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
Intervertebral disc disorder	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Jaw cyst	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Joint contracture	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Lumbar spinal stenosis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)

	GPGK		GPGI		GPGM		GPGH		GPGO		GPGL		GPGP
System Organ Class MedDRA PT	PBO (N=115)	TZP ALL (N=363)	PBO (N=120)	TZP ALL (N=355)	Ins Glar (N=1000)	TZP ALL (N=995)	Ins Deg (N=360)	TZP ALL (N=1077)	Dula 0.75 mg (N=159)	TZP ALL (N=477)	Sema 1 mg (N=469)	TZP ALL (N=1409)	TZP ALL (443)
Musculoskeletal chest pain	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Osteoarthritis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Rotator cuff syndrome	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Spinal ligament ossification	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Spinal osteoarthritis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Spinal stenosis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Synovial cyst	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Skin and subcutaneous tissue disorders	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**4 (0.4)**	**2 (0.2)**	**1 (0.3)**	**1 (<0.1)**	**1 (0.6)**	**0 (0.0)**	**0 (0.0)**	**1 (<0.1)**	**0 (0.0)**
Diabetic foot	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.3)	1 (0.1)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Skin necrosis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Dermatomyositis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Diabetic ulcer	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Skin ulcer	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Surgical and medical procedures	**0 (0.0)**	**0 (0.0)**	**1 (0.8)**	**1 (0.3)**	**1 (0.1)**	**2 (0.2)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**1 (0.2)**	**0 (0.0)**	**1 (<0.1)**	**2 (0.5)**
Coronary artery bypass	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Intervertebral disc operation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Abdominal hernia repair	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Cardiac ablation	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Intra-cerebral aneurysm operation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Pancreatic lesion excision	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Percutaneous coronary intervention	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Spinal fusion surgery	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Blood and lymphatic system disorders	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**5 (0.5)**	**1 (0.1)**	**1 (0.3)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**1 (<0.1)**	**0 (0.0)**
Anaemia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.3)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Bicytopenia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hypochromic anaemia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Neutropenia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Thrombocytopenia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Congenital, familial and genetic disorders	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**1 (0.1)**	**1 (0.3)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**
Phimosis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Arrhythmogenic right ventricular dysplasia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

	GPGK		GPGI		GPGM		GPGH		GPGO		GPGL		GPGP
System Organ Class MedDRA PT	PBO (N=115)	TZP ALL (N=363)	PBO (N=120)	TZP ALL (N=355)	Ins Glar (N=1000)	TZP ALL (N=995)	Ins Deg (N=360)	TZP ALL (N=1077)	Dula 0.75 mg (N=159)	TZP ALL (N=477)	Sema 1 mg (N=469)	TZP ALL (N=1409)	TZP ALL (443)
Ear and labyrinth disorders	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**1 (0.3)**	**0 (0.0)**	**1 (0.1)**	**1 (0.3)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**1 (0.2)**
Vertigo	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Deafness unilateral	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Vertigo positional	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Eye disorders	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**1 (0.1)**	**1 (0.1)**	**1 (0.3)**	**1 (<0.1)**	**1 (0.6)**	**0 (0.0)**	**0 (0.0)**	**1 (<0.1)**	**4 (0.9)**
Retinal vein occlusion	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Cataract	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.7)
Eyelid ptosis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Macular fibrosis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Retinal detachment	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Vitreous haemorrhage	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Investigations	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**3 (0.3)**	**1 (0.1)**	**0 (0.0)**	**1 (<0.1)**	**0 (0.0)**	**1 (0.2)**	**0 (0.0)**	**2 (0.1)**	**0 (0.0)**
Pancreatic enzymes increased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Amylase increased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Blood creatinine increased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Blood lactic acid increased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Coronavirus test positive	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Influenza A virus test positive	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Lipase increased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
SARS-CoV-2 test positive	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Psychiatric disorders	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**1 (0.3)**	**1 (0.1)**	**1 (0.1)**	**2 (0.6)**	**2 (0.2)**	**0 (0.0)**	**0 (0.0)**	**1 (0.2)**	**1 (<0.1)**	**0 (0.0)**
Disorientation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Alcohol abuse	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Anxiety	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Confusional state	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Depression suicidal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Major depression	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Post-traumatic stress disorder	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
Suicide attempt	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Endocrine disorders	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**1 (<0.1)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**1 (<0.1)**	**0 (0.0)**
Acromegaly	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Inappropriate antidiuretic hormone secretion	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

	GPGK		GPGI		GPGM		GPGH		GPGO		GPGL		GPGP
System Organ Class MedDRA PT	PBO (N=115)	TZP ALL (N=363)	PBO (N=120)	TZP ALL (N=355)	Ins Glar (N=1000)	TZP ALL (N=995)	Ins Deg (N=360)	TZP ALL (N=1077)	Dula 0.75 mg (N=159)	TZP ALL (N=477)	Sema 1 mg (N=469)	TZP ALL (N=1409)	TZP ALL (443)
Pregnancy, puerperium and perinatal conditions	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**1 (<0.1)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**
Abortion spontaneous	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Reproductive system and breast disorders	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**1 (0.1)**	**0 (0.0)**	**0 (0.0)**	**1 (<0.1)**	**0 (0.0)**	**0 (0.0)**	**1 (0.2)**	**1 (<0.1)**	**0 (0.0)**
Cervical dysplasia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Metrorrhagia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Ovarian cyst	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Uterine prolapse	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)

Source: Derived from the adsl.xpt and adae.xpt datasets, available at: \\CDSESUB1\evsprod\NDA215866\0001\m5\datasets
Abbreviation: AS1, Analysis Set 2 (pool of 7 phase 3 trials); Dula, dulaglutide; Ins Deg, insulin degludec; Ins Glar, insulin glargine; MedDRA, Medical Dictionary for Regulatory Activities; no., number; PBO, placebo; PT, preferred term; Sema, semaglutide; SOC, system organ class; TEAE, treatment-emergent adverse event; and TZP, tirzepatide.

In the 4MSU, SAEs were reported in 6.67% (908/13,603) of subjects across all treatment arms in the blinded ongoing phase 2/3 T2D clinical trials. For the unblinded T2D trials (N=2171), SAEs were reported in 4.5% (59/1317), 3.2% (20/634), and 7.7% (17/220) subjects in tirzepatide, insulin lispro, and insulin glargine treatment arms. The data from the Applicant's CVOT (GPGN) remain blinded.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

In total, 6 subjects (2.6%) in the placebo arm and 48 subjects (6.7%) in the pooled tirzepatide arm discontinued IP due to AEs (Table 27). Although event counts by individual PT were limited for determining meaningful differences, a numeric imbalance favoring the placebo arm was observed for discontinuations due to AEs in the 'Gastrointestinal disorders' SOC (i.e., 5% in tirzepatide-treated subjects vs. 0.4% in the placebo arm), for which there appeared to be a dose-response relationship.

Table 27: Discontinuations Due to Adverse Events – Phase 3 Placebo-Controlled Pool (AS1)

System Organ Class MedDRA PT	PBO (N=235)	TZP 5mg (N=237)	TZP 10mg (N=240)	TZP 15mg (N=241)	TZP ALL (N=718)
Subjects Discontinuing IP due to AEs — no. (%)	**6 (2.6)**	**11 (4.6)**	**16 (6.7)**	**21 (8.7)**	**48 (6.7)**
Gastrointestinal disorders	**1 (0.4)**	**7 (3.0)**	**13 (5.4)**	**16 (6.6)**	**36 (5.0)**
Nausea	1 (0.4)	1 (0.4)	4 (1.7)	5 (2.1)	10 (1.4)
Diarrhoea	0 (0.0)	1 (0.4)	3 (1.3)	3 (1.2)	7 (1.0)
Abdominal discomfort	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.8)	2 (0.3)
Gastrointestinal disorder	0 (0.0)	1 (0.4)	2 (0.8)	2 (0.8)	5 (0.7)
Vomiting	0 (0.0)	1 (0.4)	2 (0.8)	2 (0.8)	5 (0.7)
Dyspepsia	0 (0.0)	2 (0.8)	1 (0.4)	1 (0.4)	4 (0.6)
Gastrooesophageal reflux disease	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.1)
Abdominal pain upper	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.1)
Colitis ischaemic	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.1)
Infections and infestations	**1 (0.4)**	**0 (0.0)**	**0 (0.0)**	**2 (0.8)**	**2 (0.3)**
Gastrointestinal infection	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.8)	2 (0.3)
COVID-19 pneumonia	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Metabolism and nutrition disorders	**0 (0.0)**	**0 (0.0)**	**1 (0.4)**	**2 (0.8)**	**3 (0.4)**
Decreased appetite	0 (0.0)	0 (0.0)	1 (0.4)	2 (0.8)	3 (0.4)
General disorders and administration site conditions	**0 (0.0)**	**0 (0.0)**	**1 (0.4)**	**1 (0.4)**	**2 (0.3)**
Malaise	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.4)	2 (0.3)
Cardiac disorders	**1 (0.4)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**
Acute myocardial infarction	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Eye disorders	**1 (0.4)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**
Vision blurred	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Investigations	**1 (0.4)**	**2 (0.8)**	**0 (0.0)**	**0 (0.0)**	**2 (0.3)**
Blood calcitonin increased	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.1)
Blood glucose fluctuation	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Lipase increased	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.1)

System Organ Class MedDRA PT	PBO (N=235)	TZP 5mg (N=237)	TZP 10mg (N=240)	TZP 15mg (N=241)	TZP ALL (N=718)
Musculoskeletal and connective tissue disorders	**0 (0.0)**	**0 (0.0)**	**1 (0.4)**	**0 (0.0)**	**1 (0.1)**
Sarcopenia	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**1 (0.4)**	**2 (0.8)**	**0 (0.0)**	**0 (0.0)**	**2 (0.3)**
Papillary renal cell carcinoma	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.1)
Renal neoplasm	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.1)
Transitional cell carcinoma	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Source: Derived from the adsl.xpt and adae.xpt datasets, available at: \\CDSESUB1\evsprod\NDA215866\0001\m5\datasets
Abbreviation: AS1, Analysis Set 1 (pool of 2 placebo-controlled phase 3 trials); MedDRA, Medical Dictionary for Regulatory Activities; no., number; PBO, placebo; PT, preferred term; SOC, system organ class; TEAE, treatment-emergent adverse event; and TZP, tirzepatide.

Similarly, a dose-response relationship was observed across the phase 3 trials (AS2) for discontinuations due to AEs in the 'Gastrointestinal disorders' SOC for tirzepatide-treated subjects, with the most common PTs coded as 'Nausea', 'Diarrhoea', and 'Vomiting' (Table 28). Please note that the numbers of subjects that discontinued IP due to an AE in Table 28 differ from those in Table 22. The data in Table 28 are considered more reliable as they were collected closer to the time of the event. Refer to Table 59 (Appendix 13.6) for the side-by-side comparison of discontinuations due to AEs in the seven phase 3 trials.

Table 28: Discontinuations Due to Adverse Events (AS2)

System Organ Class MedDRA PT	PBO (N=235)	Ins Glar (N=1000)	Ins Deg (N=360)	Dula 0.75mg (N=159)	Sema 1 mg (N=469)	TZP 5mg (N=1701)	TZP 10mg (N=1702)	TZP 15mg (N=1716)
Subjects Discontinuing IP due to AEs — no. (%)	**6 (2.6)**	**54 (5.4)**	**5 (1.4)**	**9 (5.7)**	**19 (4.1)**	**121 (7.1)**	**145 (8.5)**	**169 (9.8)**
Gastrointestinal disorders	**1 (0.4)**	**0 (0.0)**	**1 (0.3)**	**1 (0.6)**	**15 (3.2)**	**55 (3.2)**	**74 (4.3)**	**88 (5.1)**
Nausea	1 (0.4)	0 (0.0)	1 (0.3)	0 (0.0)	4 (0.9)	18 (1.1)	24 (1.4)	27 (1.6)
Diarrhoea	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.2)	9 (0.5)	9 (0.5)	20 (1.2)
Vomiting	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.6)	7 (0.4)	17 (1.0)	14 (0.8)
Abdominal discomfort	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	1 (<0.1)	5 (0.3)
Dyspepsia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	7 (0.4)	6 (0.4)	5 (0.3)
Abdominal pain	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.9)	3 (0.2)	2 (0.1)	4 (0.2)
Gastrointestinal disorder	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	2 (0.1)	3 (0.2)
Abdominal pain upper	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	2 (0.1)	2 (0.1)
Gastrooesophageal reflux disease	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)
Colitis ulcerative	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Constipation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (<0.1)	4 (0.2)	1 (<0.1)
Epigastric discomfort	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	1 (<0.1)
Eructation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Gastric ulcer haemorrhage	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)

System Organ Class MedDRA PT	PBO (N=235)	Ins Glar (N=1000)	Ins Deg (N=360)	Dula 0.75mg (N=159)	Sema 1 mg (N=469)	TZP 5mg (N=1701)	TZP 10mg (N=1702)	TZP 15mg (N=1716)
Pancreatitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	1 (<0.1)
Abdominal distension	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	2 (0.1)	0 (0.0)
Colitis ischaemic	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)
Flatulence	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	2 (0.1)	0 (0.0)
Gastric disorder	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Obstructive pancreatitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)
Pancreatitis acute	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (<0.1)	0 (0.0)
Pancreatitis chronic	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Investigations	**1 (0.4)**	**1 (0.1)**	**0 (0.0)**	**1 (0.6)**	**1 (0.2)**	**9 (0.5)**	**13 (0.8)**	**18 (1.0)**
Weight decreased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	4 (0.2)	7 (0.4)
Amylase increased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)
Blood calcitonin increased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.2)	3 (0.2)	2 (0.1)
Pancreatic enzymes increased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	2 (0.1)	2 (0.1)
Blood pressure increased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Hepatic enzyme increased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Hepatitis C antibody positive	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Lipase increased	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.2)	2 (0.1)	3 (0.2)	1 (<0.1)
Liver function test increased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Blood glucose fluctuation	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Bone density decreased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)
Digestive enzyme increased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Weight increased	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
General disorders and administration site conditions	**0 (0.0)**	**4 (0.4)**	**1 (0.3)**	**1 (0.6)**	**1 (0.2)**	**8 (0.5)**	**11 (0.6)**	**15 (0.9)**
Malaise	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	4 (0.2)
Fatigue	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	2 (0.1)	2 (0.1)	3 (0.2)
Asthenia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.2)	0 (0.0)	2 (0.1)
Application site reaction	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Early satiety	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	1 (<0.1)	1 (<0.1)
General physical health deterioration	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Injection site reaction	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.2)	1 (<0.1)
Pain	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Sudden cardiac death	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Chills	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Death	0 (0.0)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)	0 (0.0)
Influenza like illness	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Injection site erythema	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Injection site hypersensitivity	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

System Organ Class MedDRA PT	PBO (N=235)	Ins Glar (N=1000)	Ins Deg (N=360)	Dula 0.75mg (N=159)	Sema 1 mg (N=469)	TZP 5mg (N=1701)	TZP 10mg (N=1702)	TZP 15mg (N=1716)
Sudden death	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Metabolism and nutrition disorders	**0 (0.0)**	**0 (0.0)**	**1 (0.3)**	**0 (0.0)**	**0 (0.0)**	**10 (0.6)**	**16 (0.9)**	**15 (0.9)**
Decreased appetite	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	9 (0.5)	13 (0.8)	13 (0.8)
Abnormal loss of weight	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	1 (<0.1)
Gout	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Food aversion	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Hyperglycaemia	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hyperlipasaemia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Latent autoimmune diabetes in adults	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)
Infections and infestations	**1 (0.4)**	**13 (1.3)**	**1 (0.3)**	**2 (1.3)**	**1 (0.2)**	**8 (0.5)**	**7 (0.4)**	**10 (0.6)**
COVID-19 pneumonia	1 (0.4)	4 (0.4)	0 (0.0)	1 (0.6)	1 (0.2)	2 (0.1)	2 (0.1)	2 (0.1)
Gastrointestinal infection	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)
Diabetic gangrene	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Diverticulitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Gastroenteritis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Herpes zoster	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	1 (<0.1)
Sepsis	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Septic shock	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Atypical pneumonia	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
COVID-19	0 (0.0)	6 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	2 (0.1)	0 (0.0)
Cellulitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)
Diabetic foot infection	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hepatitis E	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)
Intervertebral discitis	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Nosocomial infection	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pneumonia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Pyelonephritis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)
Urinary tract infection	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Urosepsis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)
Cardiac disorders	**1 (0.4)**	**12 (1.2)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**9 (0.5)**	**4 (0.2)**	**5 (0.3)**
Acute myocardial infarction	1 (0.4)	3 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	3 (0.2)	3 (0.2)
Cardiac failure	0 (0.0)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	1 (<0.1)
Cardio-respiratory arrest	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	1 (<0.1)	1 (<0.1)
Angina unstable	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cardiac arrest	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)
Cardiac disorder	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cardiac failure congestive	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

System Organ Class MedDRA PT	PBO (N=235)	Ins Glar (N=1000)	Ins Deg (N=360)	Dula 0.75mg (N=159)	Sema 1 mg (N=469)	TZP 5mg (N=1701)	TZP 10mg (N=1702)	TZP 15mg (N=1716)
Cardiogenic shock	0 (0.0)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Coronary artery disease	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)
Ischaemic cardiomyopathy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)
Myocardial infarction	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Tachycardia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)
Nervous system disorders	**0 (0.0)**	**1 (0.1)**	**0 (0.0)**	**1 (0.6)**	**0 (0.0)**	**3 (0.2)**	**2 (0.1)**	**5 (0.3)**
Cerebrovascular accident	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Dizziness	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	1 (<0.1)
Facial paralysis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Headache	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Lethargy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Amnesia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Coma	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Haemorrhagic stroke	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)
Multiple system atrophy	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Paraesthesia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Taste disorder	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**1 (0.4)**	**11 (1.1)**	**0 (0.0)**	**2 (1.3)**	**0 (0.0)**	**10 (0.6)**	**11 (0.6)**	**5 (0.3)**
Adenocarcinoma of colon	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	1 (<0.1)
Colon cancer	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Colon cancer metastatic	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Renal neoplasm	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	1 (<0.1)
Squamous cell carcinoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Transitional cell carcinoma	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Adenocarcinoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)
Bladder papilloma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Bladder transitional cell carcinoma	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Breast cancer stage II	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Cerebellopontine angle tumour	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Endometrial adenocarcinoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)
Invasive ductal breast carcinoma	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)
Invasive lobular breast carcinoma	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Laryngeal squamous cell carcinoma	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Lung adenocarcinoma	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

System Organ Class MedDRA PT	PBO (N=235)	Ins Glar (N=1000)	Ins Deg (N=360)	Dula 0.75mg (N=159)	Sema 1 mg (N=469)	TZP 5mg (N=1701)	TZP 10mg (N=1702)	TZP 15mg (N=1716)
Lung adenocarcinoma stage IV	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Lung carcinoma cell type unspecified stage III	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)
Lung neoplasm malignant	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Lymphoproliferative disorder	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Metastatic squamous cell carcinoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)
Nasopharyngeal cancer	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Non-Hodgkin's lymphoma	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Papillary renal cell carcinoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)
Penile squamous cell carcinoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)
Prostate cancer	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)
Renal cell carcinoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	1 (<0.1)	0 (0.0)
Squamous cell carcinoma of lung	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Testicular neoplasm	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)
Nervous system disorders	**0 (0.0)**	**2 (0.2)**	**0 (0.0)**	**1 (0.6)**	**1 (0.2)**	**3 (0.2)**	**2 (0.1)**	**5 (0.3)**
Cerebrovascular accident	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Dizziness	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (<0.1)	0 (0.0)	1 (<0.1)
Facial paralysis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Headache	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Lethargy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Amnesia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Coma	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Haemorrhagic stroke	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)
Multiple system atrophy	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Paraesthesia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Taste disorder	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)
Injury, poisoning and procedural complications	**0 (0.0)**	**1 (0.1)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**1 (<0.1)**	**1 (<0.1)**	**2 (0.1)**
Road traffic accident	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Thoracic vertebral fracture	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Fall	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)
Procedural headache	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Spinal column injury	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Skin and subcutaneous tissue disorders	**0 (0.0)**	**0 (0.0)**	**1 (0.3)**	**1 (0.6)**	**0 (0.0)**	**2 (0.1)**	**2 (0.1)**	**2 (0.1)**
Eczema	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Urticaria	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	1 (<0.1)
Chronic pigmented purpura	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)

System Organ Class MedDRA PT	PBO (N=235)	Ins Glar (N=1000)	Ins Deg (N=360)	Dula 0.75mg (N=159)	Sema 1 mg (N=469)	TZP 5mg (N=1701)	TZP 10mg (N=1702)	TZP 15mg (N=1716)
Dermatomyositis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Rash	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	1 (<0.1)	1 (<0.1)	0 (0.0)
Hepatobiliary disorders	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**1 (<0.1)**	**1 (<0.1)**	**1 (<0.1)**
Cholestasis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Cholangitis acute	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Hepatic cirrhosis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)
Immune system disorders	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**1 (<0.1)**
Hypersensitivity	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Musculoskeletal and connective tissue disorders	**0 (0.0)**	**1 (0.1)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**1 (<0.1)**	**1 (<0.1)**
Intervertebral disc protrusion	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Arthropathy	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Sarcopenia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Renal and urinary disorders	**0 (0.0)**	**1 (0.1)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**2 (0.1)**	**1 (<0.1)**	**1 (<0.1)**
Nephropathy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Chronic kidney disease	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)
End stage renal disease	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Renal impairment	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)
Blood and lymphatic system disorders	**0 (0.0)**	**1 (0.1)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**
Anaemia	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Ear and labyrinth disorders	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**1 (<0.1)**	**0 (0.0)**	**0 (0.0)**
Vertigo	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)
Endocrine disorders	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**1 (<0.1)**	**0 (0.0)**	**0 (0.0)**
Acromegaly	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)
Eye disorders	**1 (0.4)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**
Vision blurred	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	**0 (0.0)**	**7 (0.7)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**1 (<0.1)**	**0 (0.0)**	**0 (0.0)**
Acute pulmonary oedema	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Acute respiratory failure	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pulmonary embolism	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)
Respiratory failure	0 (0.0)	4 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Surgical and medical procedures	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**1 (<0.1)**	**0 (0.0)**
Gastric bypass	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)

Source: Derived from the adsl.xpt and adae.xpt datasets, available at: \\CDSESUB1\evsprod\NDA215866\0001\m5\datasets
Abbreviation: AS2, Analysis Set 2 (pool of 7 phase 3 trials); MedDRA, Medical Dictionary for Regulatory Activities; no., number; PBO, placebo; PT, preferred term; SOC, system organ class; TEAE, treatment-emergent adverse event; and TZP, tirzepatide.

8.4.4. Treatment-Emergent Adverse Events and Adverse Reactions

A summary of common TEAEs that were reported in ≥5% of tirzepatide-treated subjects are presented for the two phase 3 placebo-controlled trial pool (Table 29), the seven phase 3 trial pool (Table 30), and as a side-by-side comparison by phase 3 trial (Table 31). Compared to the pooled placebo arms, gastrointestinal (GI) disorders AEs were more frequent in tirzepatide-treated subjects, occurring in approximately 40% of subjects in the pooled tirzepatide arms vs. 20% of subjects in the placebo arms (Table 29). A dose-response was observed across the seven phase 3 trials, with GI AEs reported in 38%, 44%, and 49% of subjects in the tirzepatide 5, 10, and 15 mg arms, respectively (Table 30). Similarly, relatively high percentages of subjects randomized to GLP-1 RA active comparator arms (i.e., dulaglutide and semaglutide) also experienced GI-related AEs (i.e., 31% and 41%, respectively). However, across all phase 3 trials, higher proportions of tirzepatide-treated subjects experienced GI AEs compared to each control arm (Table 30). Other common AEs reported for tirzepatide-treated subjects included 'Nasopharyngitis', 'Decreased appetite', and 'Lipase increased'. No new safety concerns/issues were detected following the review of the entire listing of TEAEs.

Table 29: Summary of Common TEAEs (≥5%) – Phase 3 Placebo-Controlled Pool (AS1)

System Organ Class MedDRA PT	PBO (N=235)	TZP 5mg (N=237)	TZP 10mg (N=240)	TZP 15mg (N=241)	TZP ALL (N=718)
Subjects with ≥1 TEAE— no. (%)	**157 (66.8)**	**168 (70.9)**	**162 (67.5)**	**171 (71.0)**	**501 (69.8)**
Gastrointestinal disorders	**48 (20.4)**	**88 (37.1)**	**95 (39.6)**	**105 (43.6)**	**288 (40.1)**
Nausea	10 (4.3)	29 (12.2)	37 (15.4)	44 (18.3)	110 (15.3)
Diarrhoea	21 (8.9)	28 (11.8)	32 (13.3)	39 (16.2)	99 (13.8)
Dyspepsia	6 (2.6)	19 (8.0)	18 (7.5)	13 (5.4)	50 (7.0)
Vomiting	5 (2.1)	12 (5.1)	12 (5.0)	22 (9.1)	46 (6.4)
Constipation	3 (1.3)	14 (5.9)	14 (5.8)	16 (6.6)	44 (6.1)
Infections and infestations	***73 (31.1)***	***71 (30.0)***	***51 (21.3)***	***57 (23.7)***	***179 (24.9)***
Nasopharyngitis	33 (14.0)	25 (10.5)	16 (6.7)	23 (9.5)	64 (8.9)
Metabolism and nutrition disorders	**55 (23.4)**	**28 (11.8)**	**35 (14.6)**	**37 (15.4)**	**100 (13.9)**
Decreased appetite	3 (1.3)	13 (5.5)	23 (9.6)	27 (11.2)	63 (8.8)
Investigations	**10 (4.3)**	**18 (7.6)**	**17 (7.1)**	**22 (9.1)**	**57 (7.9)**
Lipase increased	6 (2.6)	7 (3.0)	3 (1.3)	13 (5.4)	23 (3.2)

Source: Derived from the adsl.xpt and adae.xpt datasets, available at:
\\CDSESUB1\evsprod\NDA215866\0001\m5\datasets
Abbreviation: AS1, Analysis Set 1 (pool of 2 placebo-controlled phase 3 trials); MedDRA, Medical Dictionary for Regulatory Activities; no., number; PBO, placebo; PT, preferred term; SOC, system organ class; TEAE, treatment-emergent adverse event; and TZP, tirzepatide.

Table 30: Summary of Common TEAEs (≥5%) – Phase 3 Pool (AS2)

System Organ Class MedDRA PT	PBO (N=235)	Ins Glar (N=1000)	Ins Deg (N=360)	Dula 0.75mg (N=159)	Sema 1 mg (N=469)	TZP 5mg (N=1701)	TZP 10mg (N=1702)	TZP 15mg (N=1716)
Subjects with ≥1 TEAE— no. (%)	**157 (66.8)**	**679 (67.9)**	**193 (53.6)**	**123 (77.4)**	**301 (64.2)**	**1158 (68.1)**	**1202 (70.6)**	**1276 (74.4)**
Gastrointestinal disorders	**48 (20.4)**	**146 (14.6)**	**32 (8.9)**	**50 (31.4)**	**193 (41.2)**	**647 (38.0)**	**746 (43.8)**	**837 (48.8)**
Nausea	10 (4.3)	23 (2.3)	6 (1.7)	12 (7.5)	84 (17.9)	224 (13.2)	312 (18.3)	381 (22.2)
Diarrhoea	21 (8.9)	44 (4.4)	14 (3.9)	11 (6.9)	54 (11.5)	224 (13.2)	268 (15.7)	272 (15.9)
Vomiting	5 (2.1)	16 (1.6)	4 (1.1)	2 (1.3)	39 (8.3)	93 (5.5)	132 (7.8)	167 (9.7)
Dyspepsia	6 (2.6)	13 (1.3)	0 (0.0)	2 (1.3)	31 (6.6)	101 (5.9)	125 (7.3)	115 (6.7)
Constipation	3 (1.3)	5 (0.5)	4 (1.1)	17 (10.7)	27 (5.8)	110 (6.5)	110 (6.5)	112 (6.5)
Infections and infestations	**73 (31.1)**	**342 (34.2)**	**85 (23.6)**	**53 (33.3)**	**81 (17.3)**	**430 (25.3)**	**392 (23.0)**	**401 (23.4)**
Nasopharyngitis	33 (14.0)	65 (6.5)	22 (6.1)	26 (16.4)	8 (1.7)	109 (6.4)	101 (5.9)	113 (6.6)
Metabolism and nutrition disorders	**55 (23.4)**	**102 (10.2)**	**27 (7.5)**	**16 (10.1)**	**73 (15.6)**	**236 (13.9)**	**270 (15.9)**	**291 (17.0)**
Decreased appetite	3 (1.3)	5 (0.5)	2 (0.6)	7 (4.4)	25 (5.3)	132 (7.8)	166 (9.8)	200 (11.7)
Investigations	**10 (4.3)**	**87 (8.7)**	**29 (8.1)**	**15 (9.4)**	**43 (9.2)**	**181 (10.6)**	**203 (11.9)**	**233 (13.6)**
Lipase increased	6 (2.6)	18 (1.8)	7 (1.9)	5 (3.1)	10 (2.1)	64 (3.8)	60 (3.5)	90 (5.2)

Source: Derived from the adsl.xpt and adae.xpt datasets, available at:
\\CDSESUB1\evsprod\NDA215866\0001\m5\datasets
Abbreviation: AS1, Analysis Set 2 (pool of 7 phase 3 trials); Dula, dulaglutide; Ins Deg, insulin degludec; Ins Glar, insulin glargine; MedDRA, Medical Dictionary for Regulatory Activities; no., number; PBO, placebo; PT, preferred term; Sema, semaglutide; SOC, system organ class; TEAE, treatment-emergent adverse event; and TZP, tirzepatide.

Table 31: Summary of Common TEAEs (≥5%) by Study – Phase 3 Trials (AS2)

	GPGK		GPGI		GPGM		GPGH		GPGO		GPGL		GPGP
System Organ Class MedDRA PT	**PBO (N=115)**	**TZP ALL (363)**	**PBO (N=120)**	**TZP ALL (355)**	**Ins Glar (N=1000)**	**TZP ALL (995)**	**Ins Deg (N=360)**	**TZP ALL (1077)**	**Dula 0.75mg (N=159)**	**TZP ALL (477)**	**Sema 1 mg (N=469)**	**TZP ALL (1409)**	**TZP ALL (443)**
Subjects with ≥1 TEAE — no. (%)	**76 (66.1)**	**241 (66.4)**	**81 (67.5)**	**260 (73.2)**	**679 (67.9)**	**732 (73.6)**	**193 (53.6)**	**730 (67.8)**	**123 (77.4)**	**385 (80.7)**	**301 (64.2)**	**945 (67.1)**	**343 (77.4)**
Gastrointestinal disorders	**22 (19.1)**	**146 (40.2)**	**26 (21.7)**	**142 (40.0)**	**146 (14.6)**	**426 (42.8)**	**32 (8.9)**	**448 (41.6)**	**50 (31.4)**	**243 (50.9)**	**193 (41.2)**	**615 (43.6)**	**210 (47.4)**
Diarrhoea	9 (7.8)	45 (12.4)	12 (10.0)	54 (15.2)	44 (4.4)	180 (18.1)	14 (3.9)	171 (15.9)	11 (6.9)	59 (12.4)	54 (11.5)	204 (14.5)	51 (11.5)
Nausea	7 (6.1)	52 (14.3)	3 (2.5)	58 (16.3)	23 (2.3)	168 (16.9)	6 (1.7)	207 (19.2)	12 (7.5)	82 (17.2)	84 (17.9)	276 (19.6)	74 (16.7)
Vomiting	2 (1.7)	14 (3.9)	3 (2.5)	32 (9.0)	16 (1.6)	72 (7.2)	4 (1.1)	91 (8.4)	2 (1.3)	40 (8.4)	39 (8.3)	113 (8.0)	30 (6.8)
Dyspepsia	4 (3.5)	26 (7.2)	2 (1.7)	24 (6.8)	13 (1.3)	71 (7.1)	0 (0.0)	65 (6.0)	2 (1.3)	27 (5.7)	31 (6.6)	106 (7.5)	22 (5.0)
Constipation	1 (0.9)	21 (5.8)	2 (1.7)	23 (6.5)	5 (0.5)	45 (4.5)	4 (1.1)	41 (3.8)	17 (10.7)	74 (15.5)	27 (5.8)	74 (5.3)	54 (12.2)
Abdominal discomfort	3 (2.6)	6 (1.7)	3 (2.5)	7 (2.0)	5 (0.5)	16 (1.6)	1 (0.3)	20 (1.9)	4 (2.5)	37 (7.8)	5 (1.1)	22 (1.6)	24 (5.4)
Infections and infestations	**33 (28.7)**	**71 (19.6)**	**40 (33.3)**	**108 (30.4)**	**342 (34.2)**	**295 (29.6)**	**85 (23.6)**	**205 (19.0)**	**53 (33.3)**	**162 (34.0)**	**81 (17.3)**	**253 (18.0)**	**129 (29.1)**
Nasopharyngitis	10 (8.7)	23 (6.3)	23 (19.2)	41 (11.5)	65 (6.5)	42 (4.2)	22 (6.1)	40 (3.7)	26 (16.4)	76 (15.9)	8 (1.7)	26 (1.8)	75 (16.9)
Metabolism and nutrition disorders	**35 (30.4)**	**45 (12.4)**	**20 (16.7)**	**55 (15.5)**	**102 (10.2)**	**182 (18.3)**	**27 (7.5)**	**161 (14.9)**	**16 (10.1)**	**88 (18.4)**	**73 (15.6)**	**209 (14.8)**	**57 (12.9)**
Decreased appetite	1 (0.9)	23 (6.3)	2 (1.7)	40 (11.3)	5 (0.5)	100 (10.1)	2 (0.6)	102 (9.5)	7 (4.4)	78 (16.4)	25 (5.3)	111 (7.9)	44 (9.9)
Investigations	**6 (5.2)**	**19 (5.2)**	**4 (3.3)**	**38 (10.7)**	**87 (8.7)**	**143 (14.4)**	**29 (8.1)**	**141 (13.1)**	**15 (9.4)**	**63 (13.2)**	**43 (9.2)**	**163 (11.6)**	**50 (11.3)**
Lipase increased	4 (3.5)	7 (1.9)	2 (1.7)	16 (4.5)	18 (1.8)	44 (4.4)	7 (1.9)	57 (5.3)	5 (3.1)	28 (5.9)	10 (2.1)	45 (3.2)	17 (3.8)

Source: Derived from the adsl.xpt and adae.xpt datasets, available at: \\CDSESUB1\evsprod\NDA215866\0001\m5\datasets
Abbreviation: AS2, Analysis Set 2 (pool of 7 phase 3 trials); Dula, dulaglutide; Ins Deg, insulin degludec; Ins Glar, insulin glargine; MedDRA, Medical Dictionary for Regulatory Activities; no., number; PBO, placebo; PT, preferred term; Sema, semaglutide; SOC, system organ class; TEAE, treatment-emergent adverse event; and TZP, tirzepatide.

8.4.5. **Laboratory Findings**

Changes in glycemic and lipid laboratory parameters were evaluated as efficacy endpoints and discussed in Section 6.1.2 and Section 7.2.2, respectively. Additionally, please refer to other relevant sections for information related to treatment-emergent changes in the following laboratory parameters: ADAs (Section 8.4.9), serum calcitonin (Section 8.5.1), pancreatic enzymes (Section 8.5.2), renal function (Section 8.5.6), and liver laboratory parameters (Section 8.5.13).

Additionally, in the phase 3 placebo-controlled trials (AS1), 16.3% (107/656) of tirzepatide-treated subjects and 9.2% (20/218) of subjects randomized to the placebo arms shifted from a baseline normal/high hemoglobin concentration to postbaseline low hemoglobin concentration. The mean change from baseline for the tirzepatide-treated subjects with downward shifts was -1.7 g/dL and for the placebo-treated subjects -1.5 g/dL. Across the entire study pool, the mean±SD minimum postbaseline hemoglobin concentrations were 13.46±1.42, 13.29±1.47, 13.52±1.52, and 13.25±1.61 g/dL for placebo, and tirzepatide 5, 10, and 15 mg arms, respectively, and changes from baseline were -0.69±0.89, -0.86±0.92, -0.70±1.04, and -0.96±1.18 g/dL, respectively. Thirteen tirzepatide treated subjects (1.9%; ↓ hemoglobin concentrations of 3.2-6.7 g/dL) and 9 placebo-treated subjects (3.9%; ↓ hemoglobin concentrations of 2.3-5.9 g/dL) were considered outliers (i.e., ↓ hemoglobin concentrations >1.5x the interquartile range). Additionally, anemia was reported in 1.1% (8/718) of tirzepatide-treated subjects, while no AEs of anemia were reported in the pooled placebo arm (i.e., 0/235 subjects). The Applicant felt that these data do not suggest that low hemoglobin or anemia are safety concerns with tirzepatide treatment. As an association of anemia and/or reductions in hemoglobin concentrations with GLP-1 RAs was not apparent based on a review of the literature and labeling of other GLP-1 RA products, we also assessed anemia AEs across the phase 3 trials (AS2) using the FMQ standardized grouping of MedDRA PTs for anemia (Table 32). No obvious imbalances in AEs were observed.

Based on the existing data, I do not feel that the observed shifts in hemoglobin concentrations and AEs of anemia reported in the pooled placebo-controlled trials (AS1) warrant inclusion in labeling at this time. The Applicant's ongoing CVOT (trial GPGN), which as of January 17, 2022, randomized (1:1 allocation) 12,861 at-risk subjects (approximately 9,146 PY of follow-up) to either maximally tolerated doses of tirzepatide up to 15 mg SC QW or dulaglutide 1.5 mg SC QW, will better inform the clinical relevance of hematologic abnormalities associated with tirzepatide.

Table 32: Anemia-Related Adverse Events (AS2)

FDA Medical Query MedDRA PT	Pooled Comparators (N=2223)	Pooled TZP (N=5119)
Subjects with ≥1 Anemia-Related TEAE — no. (%)	**55 (2.5)**	**113 (2.2)**
Anaemia	45 (2.0)	84 (1.6)
Iron deficiency anaemia	6 (0.3)	15 (0.3)
Haemoglobin decreased	1 (<0.1)	6 (0.1)
Microcytic anaemia	1 (<0.1)	4 (<0.1)
Blood loss anaemia	1 (<0.1)	2 (<0.1)
Anaemia of chronic disease	0 (0.0)	1 (<0.1)
Anaemia postoperative	0 (0.0)	1 (<0.1)
Normochromic normocytic anaemia	0 (0.0)	1 (<0.1)
Hypochromic anaemia	2 (<0.1)	0 (0.0)

Source: Derived from the adsl.xpt and adae.xpt datasets, available at: \\CDSESUB1\evsprod\NDA215866\0001\m5\datasets
Abbreviation: AS2, Analysis Set 2 (pool of 7 phase 3 trials); FDA, Food and Drug Administration; MedDRA, Medical Dictionary for Regulatory Activities; no., number; PT, preferred term; TEAE, treatment-emergent adverse event; and TZP, tirzepatide.

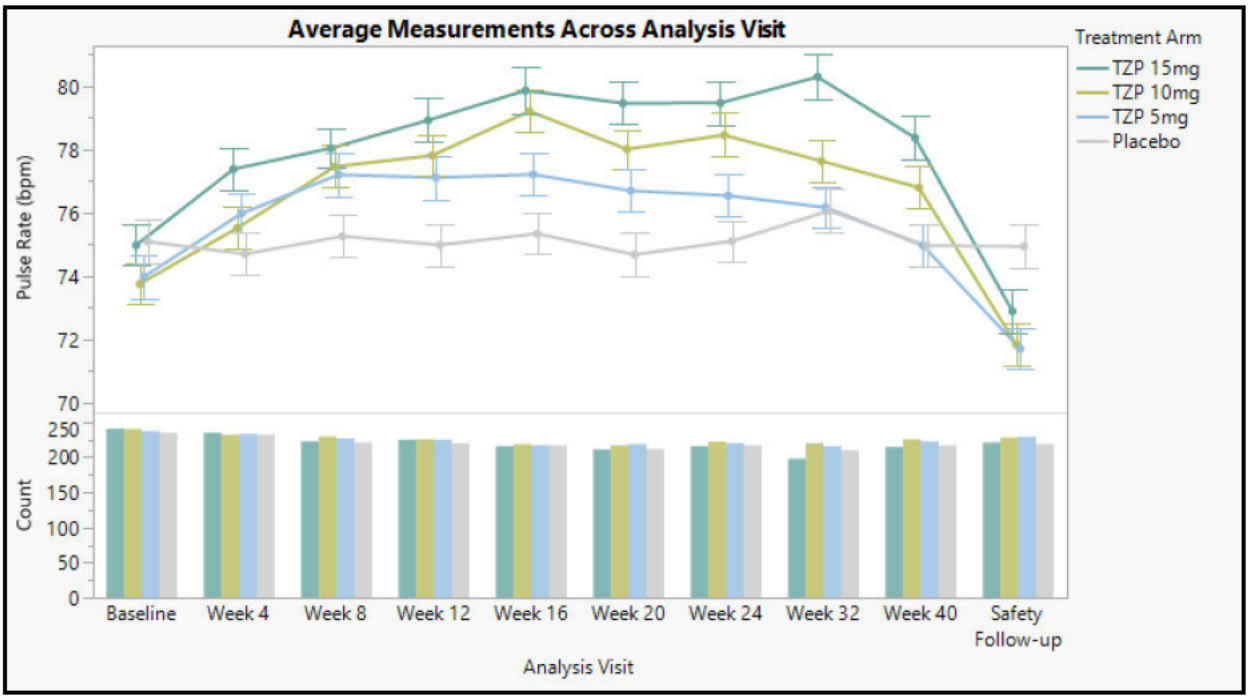
8.4.6. Vital Signs

An increase in heart rate[173-176] and reductions in blood pressure[173,174,176-182] and body weight[8,9,179,180,183-190] are recognized class effects of GLP-1 RAs and often reported in the labeling of these products.[2-6,8-11] Because of these known changes, assessments of vital signs were performed throughout the treatment periods in the tirzepatide clinical development program. Vital signs (sitting) were measured in triplicate for the phase 2 trials, and in duplicate for the phase 3 trials. The blood pressure was evaluated using an automated machine for all phase 3 trials.

Pulse Rate

In the Applicant's pooled placebo-controlled phase 3 trials (AS1), the average (mean±SD) pulse rate at baseline was 75.1±10.38, 74.0±10.81, 73.7±10.12, and 75.1±10.05 beats per minute (bpm) in the placebo, and tirzepatide 5, 10, and 15 mg arms, respectively. The mean (SE) changes from baseline over time are displayed in Figure 7. Using a mixed model repeated measures (MMRM) model, the Applicant reported mean increases from baseline in pulse rate at Week 40 of 0.1±0.57, 1.1±0.56, 2.8±0.56, and 3.4±0.57 bpm, respectively, with maximum mean increases of 1.0±0.57 bpm reported for the pooled placebo arm, and 3.3±0.50, 5.2±0.54, and 4.8±0.54 for the tirzepatide 5, 10, and 15 mg arms, respectively. Differences between the tirzepatide and placebo arms were observed throughout the treatment period but returned towards baseline at the 4-week safety follow-up.

Figure 7: Mean (SE) Change from Baseline in Pulse Rate Over Time (AS1)



Source: Derived from the Applicant's ISS adsl.xpt and advs.xpt datasets, available at: \\CDSESUB1\evsprod\NDA215866\0001\m5\datasets\integrated-database
Abbreviations: AS1, Analysis Set 1 (pool of 2 placebo-controlled phase 3 trials); bpm, beats per minute; SE, standard error; Sema, semaglutide; and TZP, tirzepatide.

Compared to placebo, the occurrence of sinus tachycardia (pulse rate >100 bpm) was more frequent in tirzepatide-treated subjects (11.1%) and appeared to be dose-related, with reported events in 6.8%, 7.2%, 9.7%, and 16.3% of subjects in the placebo, and tirzepatide 5, 10, and 15 mg arms, respectively (Table 33). Additionally, persistence of sinus tachycardia (recorded at ≥2 consecutive visits) was reported in 2.1%, 2.1%, 3.8% and 5% of subjects, respectively, and sinus tachycardia associated with a concomitant increase from baseline of ≥15 bpm, was reported in 4.3%, 4.6%, 5.9% and 10% of subjects, respectively. No subjects in any treatment arm had reported heart rates >130 bpm (i.e., the Applicant's threshold for abnormal pulse rate).

Table 33: Abnormal Pulse Rate Changes Postbaseline (AS1)

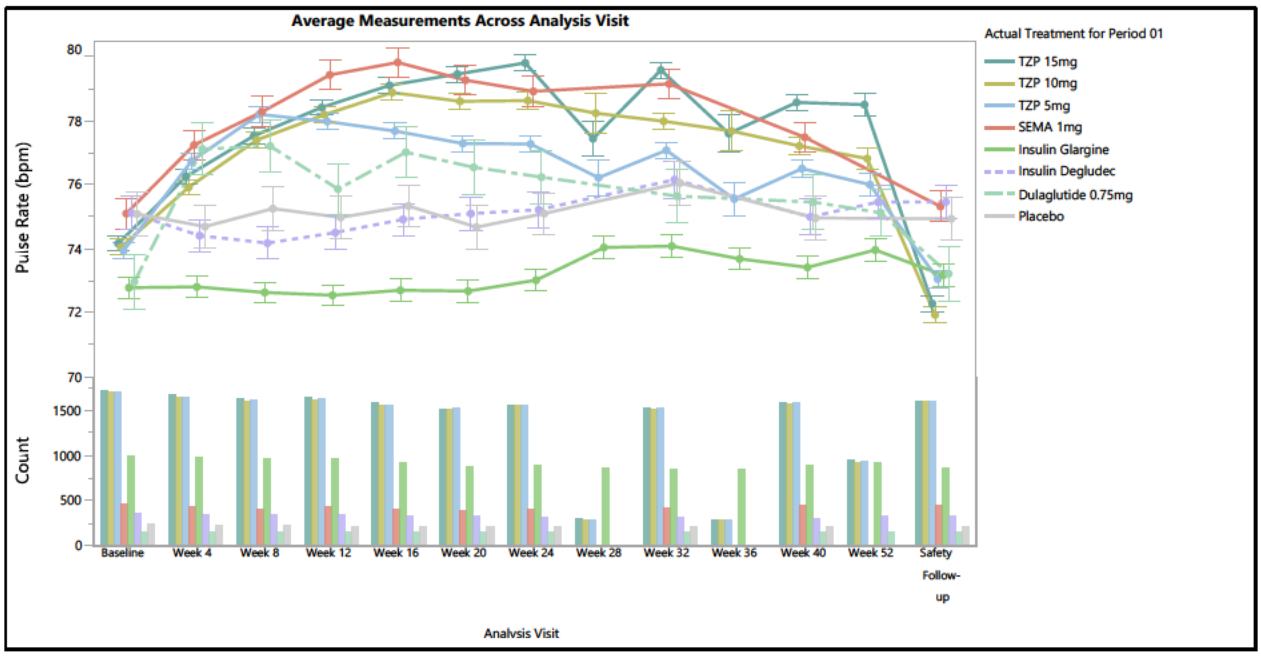
Abnormal Pulse Rate Changes	Placebo (N=235)	TZP 5mg (N=237)	TZP 10mg (N=240)	TZP 15mg (N=241)	TZP ALL (N=718)
Subjects at timepoint	**235**	**237**	**237**	**240**	**714**
Pulse rate criteria — no. (%)					
>100 bpm at any visit	16 (6.8)	17 (7.2)	23 (9.7)	39 (16.3)	79 (11.1)
>100 bpm at ≥2 consecutive visits	5 (2.1)	5 (2.1)	9 (3.8)	12 (5.0)	26 (3.6)
>100 bpm at ≥3 consecutive visits	4 (1.7)	5 (2.1)	6 (2.5)	13 (5.4)	24 (3.4)

Abnormal Pulse Rate Changes	Placebo (N=235)	TZP 5mg (N=237)	TZP 10mg (N=240)	TZP 15mg (N=241)	TZP ALL (N=718)
>130 bpm at any visit	0	0	0	0	0
CFB>20 bpm at any visit	15 (6.4)	23 (9.7)	29 (12.2)	36 (15.0)	88 (12.3)
CFB>20 bpm at ≥2 consecutive visits	5 (2.1)	5 (2.1)	9 (3.8)	7 (2.9)	21 (2.9)
CFB>20 bpm at ≥3 consecutive visits	1 (0.4)	4 (1.7)	6 (2.5)	7 (2.9)	17 (2.4)
>100 bpm and CFB>15 bpm	10 (4.3)	11 (4.6)	14 (5.9)	24 (10.0)	49 (6.9)

Source: Adapted from the Applicant's ISS, page 3448 of 7807, available at: \\CDSESUB1\evsprod\nda215866\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\type-2-diabetes-mellitus\5353-rep-analys-data-more-one-stud\iss\iss-46-integrated-sum-of-safety--t2dm-.pdf.
Abbreviation: AS1, Analysis Set 1 (pool of 2 placebo-controlled phase 3 trials); bpm, beats per minute; CFB, change from baseline; and TZP, tirzepatide.

Across the Applicant's seven phase 3 trials (AS2), dose-dependent increases in pulse rate were observed in tirzepatide-treated subjects, particularly during the titration phase (Figure 8). The maximum mean increases in pulse rate ranged from 4.3 to 5.7 bpm by tirzepatide dose. For the phase 3 trials that included a GLP-1 RA comparator, the reported mean maximum increase in pulse rate for semaglutide-treated subjects (1 mg SC QW) in trial GPGL was 4.6 bpm, while changes in pulse rate reported for subjects randomized to low dose dulaglutide 0.75 mg SC QW in trial GPGO were more limited.

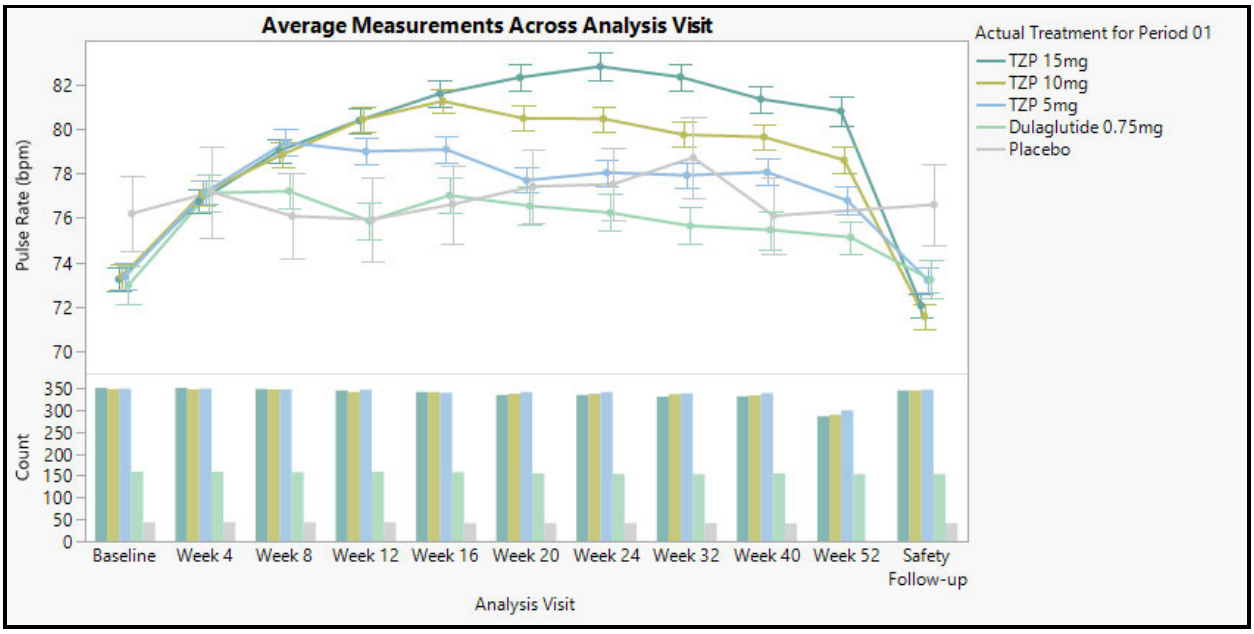
Figure 8: Mean (SE) Pulse Rate Changes from Baseline Over Time (AS2)



Source: Derived from the Applicant's ISS adsl.xpt and advs.xpt datasets, available at: \\CDSESUB1\evsprod\NDA215866\0001\m5\datasets\integrated-database
Abbreviations: AS2, Analysis Set 2 (pool of 7 phase 3 trials); bpm, beats per minute; SE, standard error; Sema, semaglutide; and TZP, tirzepatide.

In the Phase 3 trials (AS2) conducted in Japan (i.e., trials GPGI, GPGK, GPGO, GPGP), that randomized 1048 Japanese T2D subjects to tirzepatide 5 mg (349 subjects), 10 mg (348 subjects) and 15 mg (351 subjects), the observed increases in pulse rate again showed a dose-response pattern (Figure 9). Sinus tachycardia (>100 bpm) at any study visit was reported in 12.3%, 12.9%, and 18.2% of Japanese subjects randomized to the tirzepatide 5, 10, and 15 mg arms, respectively. A higher percentage of subjects in the tirzepatide 15 mg arm also experienced sinus tachycardia with a concomitant increase from baseline in heart rate of ≥15 beats per minute (13.7%) compared to the tirzepatide 5 mg (7.2%) and 10 mg (8.9%) arms. None of these subjects experienced heart rates >130 bpm. Across the subset of subjects from Japan for the four phase 3 trials, there were four tirzepatide-treated subjects (all randomized to the 5 mg arm) who experienced supraventricular arrhythmias, which included three subjects with atrial fibrillation (GPGO-125-12504, GPGO-160-16007, GPGP-205-20502) and a fourth subject with sinus tachycardia (GPGO-122-12201). All four events were reported as nonserious.

Figure 9: Mean (SE) Plus Rate Changes from Baseline Over Time – Japanese Subgroup (AS2)



Source: Derived from the Applicant's ISS adsl.xpt and advs.xpt datasets, available at: \\CDSESUB1\evsprod\NDA215866\0001\m5\datasets\integrated-database
Abbreviations: AS2, Analysis Set 2 (pool of 7 phase 3 trials); bpm, beats per minute; SE, standard error; Sema, semaglutide; and TZP, tirzepatide.

In the phase 3 trials (AS2), approximately 85% of the randomized Asian population were from clinical study sites in Japan. Higher proportions of Japanese subjects (Table 34) in all tirzepatide dose arms met prespecified abnormal pulse rate criteria (i.e., except for pulse rates of >130 bpm). Dose-related increases in heart rate in Japanese subjects have been observed with other GLP-1 RA products but these changes were not compared to other racial subgroups.[191-194] It is notable

that the average baseline BMI for subjects from Japan (i.e., trials GPGI, GPGK, GPGO, and GPGP) was approximately 28.1 kg/m^2 (mean body weight of 78 kg), while across all seven phase 3 trials (excluding these subjects), the average BMI at baseline was approximately 33.6 kg/m^2 (mean body weight 99 kg). Trials GPGK and GPGI randomized subjects with a BMI as low as 23 kg/m^2.

Of interest, in a published report of a subgroup analysis of phase 3 trials conducted with another GLP-1 RA (i.e., dulaglutide), increases in pulse rate at Week 26 were less in Japanese subjects with lower (<70kg) vs. higher (≥70 kg) body weights (-0.92 bpm, 95% CI: -1.84, -0.00; p=0.05).[195]

Table 34: Subjects Meeting Abnormal Pulse Rate Criteria in Phase 3 Trials (AS2)

Abnormal Pulse Rate Changes (bpm)	n (%)			
	TZP 5 mg (N=1701)	TZP 10 mg (N=1702)	TZP 15 mg (N=1716)	ALL TZP (N=5119)
Pulse rate criteria — no. (%)				
>100 at any visit	**136 (8.0)**	**140 (8.3)**	**183 (10.7)*,****	**459 (9.0)**
Japanese subjects†	43/349 (12.3)	45/348 (12.9)	64/351 (18.2)*	152/1048 (14.5)
Excluding Japanese subjects	93/1352 (6.9)	95/1354 (7.1)	119/1365 (8.7)	307/4071 (7.6)
>100 for ≥2 consecutive visits	**36 (2.1)**	**37 (2.2)**	**55 (3.2)**	**128 (2.5)**
Japanese subjects†	15/349 (4.3)	15/348 (4.3)	24/351 (6.8)	54/1048 (5.2)
Excluding Japanese subjects	21/1352 (1.6)	22/1354 (1.6)	31/1365 (2.3)	74/4071 (1.8)
>100 for ≥3 visits	**35 (2.1)**	**38 (2.2)**	**48 (2.8)**	**121 (2.4)**
Japanese subjects†	16/349 (4.6)	15/348 (4.3)	22/351 (6.3)	53/1048 (5.1)
Excluding Japanese subjects	19/1352 (1.4)	23/1354 (1.7)	26/1365 (1.9)	68/4071 (1.7)
>130 at any visit	**0**	**0**	**0**	**0**
Japanese subjects†	0/349	0/348	0/351	0/1048
Excluding Japanese subjects	0/1352	0/1354	0/1365	0/4071
CFB >20 at any visit	**164 (9.7)**	**183 (10.8)**	**257 (15.0)*,****	**604 (11.8)**
Japanese subjects†	45/349 (12.9)	56/348 (16.1)	92/351 (26.2)*,**	193/1048 (18.4)
Excluding Japanese subjects	119/1352 (8.9)	127/1354 (9.4)	165/1365 (12.1)*	411/4071 (10.1)
CFB >20 for ≥2 consecutive visits	**22 (1.3)**	**44 (2.6)***	**75 (4.4)*,****	**141 (2.8)**
Japanese subjects†	7/349 (2.0)	12/348 (3.5)	28/351 (8.0)*,**	47/1048 (4.5)
Excluding Japanese subjects	15/1352 (1.1)	32/1354 (2.4)*	47/1365 (3.5)*	94/4071 (2.3)
CFB >20 for ≥3 visits	**21 (1.2)**	**35 (2.1)**	**70 (4.1)*,****	**126 (2.5)**
Japanese subjects†	6/349 (1.7)	8/348 (2.3)	27/351 (7.7)*,**	41/1048 (3.9)
Excluding Japanese subjects	15/1352 (1.1)	27/1354 (2.0)	43/1365 (3.2)*	85/4071 (2.1)
>100 and CFB ≥15 at any visit	**85 (5.0)**	**78 (4.6)**	**121 (7.1)*,****	**284 (5.6)**
Japanese subjects†	25/349 (7.2)	31/348 (8.9)	48/351 (13.7)*,**	104/1048 (9.9)
Excluding Japanese subjects	60/1352 (4.5)	47/1354 (3.5)	73/1365 (5.4)**	180/4071 (4.4)

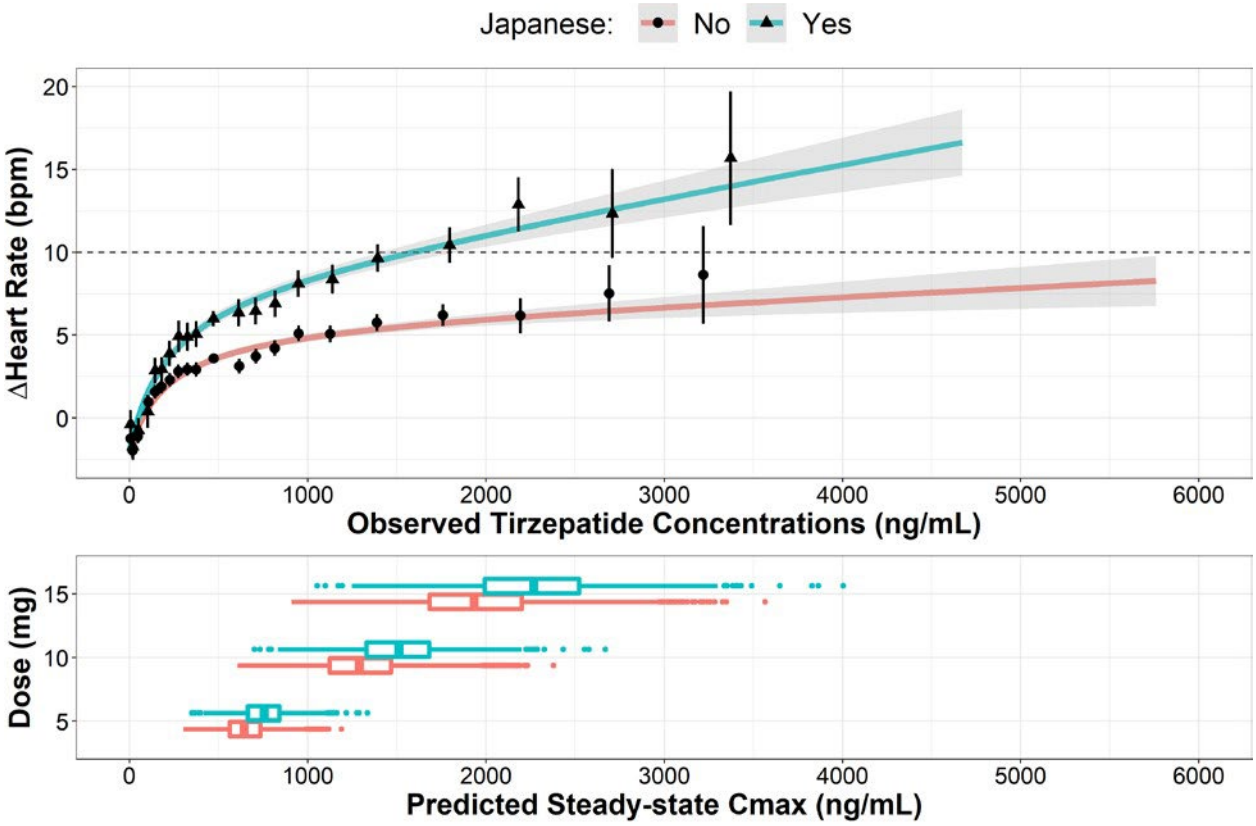
Source: Adapted from the Applicant's ISS, page 3452-3464 of 7807, available at: \\CDSESUB1\evsprod\nda215866\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\type-2-diabetes-mellitus\5353-rep-analys-data-more-one-stud\iss\iss-46-integrated-sum-of-safety--t2dm-.pdf.
Abbreviation: AS2, Analysis Set 2 (pool of 7 phase 3 trials); bpm, beats per minute; CFB, change from baseline; no., number; and TZP, tirzepatide.
*P-value <0.05 versus TZP 5 mg; and ** P-value <0.05 versus TZP 10 mg.
P-values derived by the Applicant using the Cochran-Mantel-Haenszel (CMH) test of general association stratified by study.
† Trials GPGO, GPGP, GPGK, GPGI.

To limit the effects of different trial designs (active comparators, exposure durations, and inclusion of only Japan or non-Japan study sites), we also reviewed the vital sign data from the placebo-controlled trials (AS1), which accrued subjects from both Japan and non-Japan study sites and included 40-week treatment durations. In these trials, post-randomization pulse rates of >100 bpm with changes from baseline of ≥15 bpm were reported in 7% (3/43), 7.1% (3/42), 9.3% (4/43) and 23.3% (10/43) of subjects from Japan randomized to the placebo, and tirzepatide 5, 10, and 15 mg treatment arms, respectively. At the non-Japan study sites, 3.6% (7/192), 4.1% (8/195), 5.1% (10/197), and 7.1% (14/198) of placebo-, and tirzepatide 5 mg-, 10 mg-, and 15 mg-treated subjects met this abnormal pulse rate criteria, respectively. Although a dose-response was observed regardless of whether the trials were conducted in Japan, higher proportions of subjects from Japan met this abnormal pulse rate criteria.

Since it was unclear whether the observed abnormal pulse rate changes in the subgroup of subjects from Japan may have been due to an enhanced pharmacodynamic response or increased drug exposure, Dr. Shanti Gomatam performed an exploratory analysis using a linear regression approach. The change in pulse rate at Week 24 was modeled as a function of dose, baseline BMI, baseline pulse, and interactions between dose and baseline BMI and between dose and baseline pulse rate for the Japan and non-Japan subgroups. Her results indicate that dose and pulse rate at baseline were significant predictors of change from baseline in pulse rate at Week 24 for the overall AS2 population, and for the Japan and non-Japan subgroups. The interaction of dose with baseline pulse was nominally statistically significant for overall AS2 and non-Japan subgroups ($p< 0.001$ in both cases), and the interaction of BMI with dose was nominally statistically significant (p-value=0.047) for the Japan subgroup. However, the coefficients estimated for these interactions were small, and therefore it does not appear that there are practically significant effects on change in pulse rate at Week 24 by these terms.

The Office of Clinical Pharmacology (OCP) review team also assessed the observed tirzepatide associated increases in pulse rate based on PK and PD time-matched observations (n=29,026) from the seven phase 3 trials (5066 subjects). A combined linear and Emax (maximum drug effect) mixed effects model best described the relationship between tirzepatide concentrations and the change from baseline in heart rate (ΔHR). The developed concentration-response model was used to evaluate differences in the changes in heart rate (ΔHR) between studies, populations, or demographic characteristics. These analyses showed that the Japanese subjects (representing 21% of the evaluated subjects) had a 17% higher tirzepatide exposure and steady-state Cmax (Cmax,ss) compared to non-Japanese subjects due to a lower median body weight (i.e., 76 kg vs. 90 kg). At the highest maintenance dose of 15 mg, the predicted median, 95th percentile, and maximum tirzepatide Cmax,ss in Japanese subjects were 2268, 2952, and 4006 ng/mL, which were associated with predicted mean ΔHR of 11.6, 13.1, and 15.3 bpm, respectively (Figure 10). At the same Cmax,ss of tirzepatide, the expected mean ΔHR in non-Japanese subjects were 5.9, 6.4, and 7 bpm, respectively.

Figure 10: Mean Predicted ΔHR versus Tirzepatide Concentrations (upper panel) and Distribution of Tirzepatide Steady-State Cmax Under Tirzepatide 5, 10, and 15 mg (lower panel)



Source: Excerpt from the Clinical Pharmacology Review (dated March 18, 2022), page 96 of 116.
Note: In the upper panel, the shared areas around the model-predicted mean ΔHR (solid blue and red line) represent the 90%CI around mean ΔHR. Model-predicted mean ΔHR for non-Japanese (solid red line) and for Japanese subjects (solid blue line). The black circles and triangles represent the mean of the observed ΔHR in non-Japanese and Japanese subjects, respectively. The vertical error bars represent the 90%CI around the mean of the observed ΔHR in each quantile of tirzepatide plasma concentrations. The lower panel shows the distribution of the expected tirzepatide steady-state Cmax (Cmax,ss) under a tirzepatide dose of 5 mg , 10 mg, and 15 mg in non-Japanese (red box plots) and Japanese (blue box plots), predicted using the individual PK parameters of phase 3 studies patients and derived from the Applicant's PK model.

Based on these data, the OCP review team concluded that the concentration-ΔHR analysis showed a positive effect of tirzepatide exposure on HR increase, with a non-linear relationship between tirzepatide concentrations and ΔHR. The Japanese subjects appear to be more sensitive to HR increases than non-Japanese subjects under similar tirzepatide exposures. The exposure-response analysis suggests that the Japanese patients may need closer monitoring of their pulse rate and the potential for associated cardiovascular events. However, a specific dose adjustment would not be necessary for this patient population, given that the proposed tirzepatide labeling recommends a gradual dose titration to an effective, tolerable dose, which may allow for control

of these potential adverse events. Refer to the Clinical Pharmacology review (dated March 18, 2022) for more detailed information.

To evaluate the relevance of the observed increase in pulse rates in their phase 3 program, the Applicant also provided an analysis (Table 35) of TEAEs associated with supraventricular tachyarrhythmias (using a narrow SMQ), as well as clinically meaningful AEs (i.e., subjects with fatal, or serious AEs, or resulting in permanent discontinuation of IP) across their seven phase 3 trials (AS2). A dose response for the occurrence of these AEs was not apparent. Although major imbalances in total events were not obvious in this population, AEs of atrial fibrillation and SAEs were numerically higher in the pooled tirzepatide arm. There were no deaths and no subjects permanently discontinued IP due to supraventricular tachyarrhythmias.

Table 35: Supraventricular Tachyarrhythmias AEs (Narrow SMQ) Across Phase 3 Trials (AS2)

Supraventricular tachyarrhythmias	TZP 5 mg (N=1701)	TZP 10 mg (N=1702)	TZP 15 mg (N=1716)	All TZP (N=5119)	All Comparators (N=2223)
Subjects with ≥1 AE – No. (%) [adj %]*	22 (1.29) [1.41]	16 (0.94) [1.13]	10 (0.58) [0.70]	48 (0.94)[1.08]	20 (0.90) [0.65]
Subjects with ≥1 fatal AE – No. (%) [adj %]*	0 (0.0) [0.0]	0 (0.0) [0.0]	0 (0.0) [0.0]	0 (0.0) [0.0]	0 (0.0) [0.0]
Subjects with ≥1 SAE – No. (%) [adj %]*	8 (0.47) [0.49]	5 (0.29) [0.41]	2 (0.12) [0.13]	15 (0.29) [0.35]	4 (0.18) [0.11]
Subjects discontinuing IP – No. (%) [adj %]*	0 (0.0) [0.0]	0 (0.0) [0.0]	0 (0.0) [0.0]	0 (0.0) [0.0]	0 (0.0) [0.0]
PT – No. (%)					
Atrial fibrillation	**15 (0.88)** [0.95]	**11 (0.65) [0.77]**	7 (0.41) [0.48]	**33 (0.64)[0.73]**	**9 (0.40) [0.24]**
Sinus tachycardia	**4** (0.24) [0.28]	1 (0.06) [0.05]	1 (0.06) [0.08]	6 (0.12) [0.14]	**4 (0.18) [0.14]**
Atrial flutter	1 (0.06) [0.08]	0 (0.0) [0.0]	2 (0.12) [0.13]	3 (0.06) [0.07]	**3 (0.13) [0.11]**
Atrial tachycardia	1 (0.06) [0.05]	1 (0.06) [0.08]	0 (0.0) [0.0]	2 (0.04) [0.05]	0 (0.0) [0.0]
Supraventricular extrasystoles	0 (0.0) [0.0]	**2 (0.12) [0.14]**	0 (0.0) [0.0]	2 (0.04) [0.05]	**3 (0.13) [0.14]**
Supraventricular tachycardia	**1 (0.06) [0.05]**	1 (0.06) [0.08]	0 (0.0) [0.0]	2 (0.04) [0.05]	1 (0.04) [0.03]
Arrhythmia supraventricular	1 (0.06) [0.08]	0 (0.0) [0.0]	0 (0.0) [0.0]	1 (0.02) [0.03]	1 (0.04) [0.03]

Source: Adapted from the Applicant's Regulatory Response (dated December 31, 2021), page 1269 of 1709, available at: \\CDSESUB1\evsprod\nda215866\0029\m1\us\regulatory-response--fda-midcycle-dec-2021-.pdf
Abbreviations: adj, adjusted for study size; AE, adverse event; AS2, Analysis Set 2 (pool of 7 phase 3 trials); IP, investigational product; MedDRA, Medical Dictionary for Regulatory Activities; No., number; SAE, serious adverse event; SMQ, standardized MedDRA queries; and TZP, tirzepatide.
*Study adjusted percentage provided in brackets is adjusted for study size.

(b) (4)

The mean increase in heart rate of 1.1-3.3 bpm in the placebo-controlled pool (AS1) is consistent with the changes reported in the labeling of other GLP-1 RAs approved for the treatment of T2D, all of which are reported in Section 6.1 (Clinical Trials Experience).[2,3,5,7-11] Based on the information described above, these data should be included in Section 6.1 of tirzepatide labeling (b) (4)

(b) (4)

Considering the observed reductions in HbA1c, body weight, and blood pressure in the tirzepatide phase 3 development program, the limited number of supraventricular tachyarrhythmias, as well as the results from the Applicant's CVMA (please refer to Section 8.5.11), I feel that the reported heart rate changes in the tirzepatide clinical development program may not warrant inclusion in Section 5. However, tirzepatide labeling should reflect the

potential for abnormal pharmacodynamic responses in the Japanese patient population for which the mechanisms behind these hemodynamic changes remain unknown.

Blood Pressure

In the Applicant's pool of placebo-controlled phase 3 trials (AS1), the least squares mean (LSmean) ± standard error (SE) reductions in systolic (SBP) and diastolic blood pressure (DBP) at Week 40 for placebo-treated subjects were -1.8±0.83 mmHg and -1.7±0.53 mmHg, respectively. Reductions in SBP of -5.5±0.82, -6.8±0.82, and -8.7±0.83 mmHg and DBP of -2.6±0.53, -3.2±0.52, -4±0.53 mmHg were reported for subjects randomized to the tirzepatide 5, 10, and 15 mg arms, respectively. These changes were initially placed in Section 12.2 (Pharmacodynamics) of proposed product labeling. Since blood pressure changes were not included as key secondary endpoints (i.e., not included in the hierarchical testing sequence) for any of the five global phase 3 trials, I feel that these data could suggest a BP efficacy claim and should not be included in product labeling.

Body Weight

Change from baseline in body weight was considered a key secondary endpoint for all five global phase 3 trials (GPGH, GPGI, GPGK, GPGL, and GPGM). In these trials, comparator-subtracted reductions in body weight ranged from -1.9 to -8.9 kg in the tirzepatide 5 mg arms, -3.6 to -11.5 kg in the tirzepatide 10 mg arm, and -5.5 to -13.2 kg in the tirzepatide 15 mg arms were reported. Please refer to Section 6.1.2 for additional information on changes in body weight reported in the global phase 3 trials.

8.4.7. **Electrocardiograms (ECGs)**

In the tirzepatide clinical development program, 12-lead ECGs were typically performed at baseline, at the time of the primary endpoint, and at the 4-week safety follow-up visit. Mean changes from baseline (screening visit) in ECG parameters (PR, QRS, and QT intervals) over time did not appear to be clinically meaningful between arms. The pulse rate changes from baseline at Week 40 measured by ECG (i.e., LSmean±SE increases of 1.8±0.6, 3.5±0.6, and 4.2±0.62 bpm in subjects randomized to the tirzepatide 5, 10, and 15 mg arms, respectively, compared with 0.7±0.62 bpm for subjects randomized to the placebo arm) for the placebo-controlled phase 3 pool (AS1) were consistent with those observed with routine vital sign assessments (please refer to Section 8.4.6 above).

8.4.8. **QT**

A Thorough QT (TQT) study was not conducted for this NDA. At the EOP2 meeting (dated September 6, 2018), the Agency acknowledged that a thorough QTc study would be challenging due to the long half-life (i.e., approximately 5 days) and titration schedule required to achieve

steady state concentrations with tirzepatide (e.g., approximately 24 weeks to achieve steady state with the 15 mg dose). The Applicant agreed to conduct in vitro evaluation (hERG assay), evaluate concentration-QTc analysis of data collected in their Phase 1 and Phase 2 clinical trials, and safety ECGs obtained in their phase 3 program.

In the nonclinical program, tirzepatide did not prolong the QTc in monkeys following single or multiple doses (1- and 6-month repeat dose toxicity studies). Additionally, tirzepatide did not inhibit hERG current at the highest concentration tested (i.e., 300 μM).

In the Applicant's clinical pharmacology program (i.e., phase 1 trial GPGA) and phase 2 trials (GPGB and GPGF), population PK model-based analyses were conducted utilizing data from healthy participants and subjects with T2D administered placebo or tirzepatide. ECG findings did not show QTc or PR interval prolongation with tirzepatide. Additionally, no clinically meaningful differences in QTc abnormalities between the placebo and tirzepatide arms for the two placebo-controlled phase 3 trials (AS1) or between three tirzepatide dose arms (5, 10, and 15 mg) in the seven phase 3 trials (AS2) were apparent, and no subjects experienced QTc prolongation of >500 msec or an increase in of >60 msec. Across the entire tirzepatide clinical program, there were no AEs of Torsades de pointes. In their phase 3 trials, the following AEs were reported: ECG QT prolonged (n=2 subjects; one in the tirzepatide 10 mg and one in the 15 mg arm); ventricular tachycardia (n=5 subjects; 2 in the 5 mg arm, 1 in the 10 mg arm, and 2 in the 15 mg arm), and ventricular arrhythmia (n=1 subject in the 5 mg arm). For seven of the eight subjects, the AEs were not serious, however, one subject (b) (6) randomized to the tirzepatide 15 mg arm experienced a SAE of ventricular tachycardia.

- **Subject (b) (6):** a 71-year-old White female with T2D randomized to the tirzepatide 15 mg treatment arm, experienced two SAE of ventricular tachycardia on Days 8 and 30. Besides T2D, she had a history of hyperlipidemia and hypertension, for which she was prescribed atorvastatin and lisinopril, respectively. She denied the use of tobacco products. Her baseline blood pressure, pulse rate and ECG were normal. On Day 7, she received a 2.5 mg dose of tirzepatide, and presented to the emergency room on Day 8 with palpitations and was hospitalized with severe ventricular tachycardia (CTC grade III). Atorvastatin and lisinopril were discontinued, and she was started on rosuvastatin and verapamil. A chest x-ray showed the heart size was normal and that the thoracic aorta was calcified. Her ECG showed normal sinus rhythm with nonspecific ST-segment changes. Her workup included a computerized tomography (CT) scan (showed left ventricular ejection fraction [EF] of 76%), pharmacologic stress testing (heart rate increased from 67 bpm to 90 bpm), myocardial perfusion scan (normal myocardial perfusion, wall motion and left ventricular systolic function), and magnetic resonance imaging (MRI; yielded no findings), and she started wearing a Holter monitor. The cause of the SAE was not determined. On Day 12, she was discharged from the hospital, and the Holter monitor showed ventricular tachycardia on Day 14. On Day 28, the subjects received a 5 mg dose of tirzepatide, and presented with recurrent dizziness and

> palpitations on Day 30 and was again diagnosed with severe ventricular tachycardia and frequent ventricular contractions. An ECG showed frequent episodes of nonsustained ventricular tachycardia. There was no apparent structural heart disease. Due to frequent episodes of non-sustained ventricular tachycardia associated with symptoms, the subject underwent cardiac ablation, recovered from the SAE of ventricular tachycardia, and was discharged from the hospital on Day 33. On Day 58, she experienced an AE of mild palpitations. Treatment with tizepatide was temporarily interrupted at the request of the subject on Day 72, and subsequently permanently discontinued by the investigator on Day 84. The subject received her last dose of IP on Day 77 and completed the trial on Day 383. The investigator classified the SAE of ventricular tachycardia as not related to IP based on electrical V-T indicated by electrophysiology.

Although the investigator did not feel that the SAEs of ventricular tachycardia in this 71-year-old subject were related to IP, it is not possible to rule out whether tirzepatide contributed to the occurrence/recurrence of these events based on the temporal relationship, medical history, and the decision by the investigator to prematurely discontinue IP.

The Interdisciplinary Review Team (IRT) for Cardiac Safety Studies was consulted to review the Applicant's clinical QT assessment and in vitro hERG study report. In their memorandum (dated February 16, 2022), Dr. Girish Bende noted that the Applicant did not propose QT labeling language in Section 12.2 (Cardiac Electrophysiology) and agreed that this is consistent with the Agency's labeling practices for peptides and large targeted proteins when a thorough QT study is not conducted. Additionally, based on historical clinical and nonclinical data, peptides comprised of naturally occurring amino acids have a low likelihood of direct ion channel interactions, and therefore, a thorough QT study is not necessary provided a proarrhythmic risk is not identified (e.g., mechanistically, or based on nonclinical or clinical data). However, although tirzepatide is a synthetic peptide with 39 amino acids, it is metabolized releasing a free linker (lysine residue at position 20 of drug substance) for which there is limited information on systemic exposure, the IRT reviewed the nonclinical and clinical data. Based on review of these data, the IRT felt that the submitted nonclinical and clinical data do not indicate any unexpected or important effects of tizepatide on the QTc interval at clinically relevant exposures. They agreed with not including QT labeling language in Section 12.2 of proposed tirzepatide labeling. Please refer to the IRT memorandum, dated February 16, 2022, for more detailed information.

I concur with the IRT's assessment that the data from the Applicant's nonclinical and clinical development programs do not indicate a potential safety signal of QTc prolongation with tirzepatide use.

8.4.9. **Immunogenicity**

Immunogenicity was assessed as an AESI in the tirzepatide clinical development program. For evaluating immunogenicity across the seven phase 3 trials (AS2), the Applicant used a multitiered

immunogenicity assessment strategy. This approach used ligand-binding assays to screen (Tier 1), confirm (Tier 2a), titer (Tier 3), and assess cross-reactive binding of anti-drug antibodies (ADA) against native GIP (nGIP; Tier 2b) or nGLP-1 (Tier 2c). Cell-based neutralizing antibody (NAb) assays were used to detect NAb against tirzepatide activity on the GIP receptor and GLP-1 receptor (Tiers 4a and 4b, respectively), and a model in-silico system was used to characterize the cross-reactivity of NAbs against endogenous nGIP (Tier 4c) and nGLP-1 (Tier 4d) peptide hormones. The validated disease-state cut points were 1.22 (Tier 1), 30.4% (Tier 2a), 14.5% (Tier 2b), and 18.1% (Tier 2c). Immunogenicity sampling timepoints for the phase 3 trials typically included baseline, and Weeks 4, 12, 24, 40, and safety follow-up visit for six of the trials, and for trial GPGM, baseline, and Weeks 4, 12, 24, 42, 52, 78, 104, and safety follow-up visit. Treatment-emergent ADA positivity was defined as subjects being ADA- at baseline with a postbaseline titer ≥2x MRD of the ADA assay. For subjects who were ADA+ at baseline, the postbaseline titer should be at least two dilutions (4-fold) greater than the baseline titer. Due to concerns that subjects with high ADA titers may reduce the efficacy and clearance of tirzepatide, the Office of Biotechnology Products (OBP) requested that the Applicant assess the effects of ADA titers ≥1:5120 on efficacy endpoints (e.g., changes from baseline in HbA1c and body weight).

In the phase 3 pool (AS2), 2,570 (51.1%) of 5,025 tirzepatide-treated subjects developed ADAs, with ADA positivity (ADA+) reported in 48.8%, 51.4%, and 53.2% of subjects randomized to the tirzepatide 5, 10, and 15 mg arms, respectively. Approximately 2403 (93.%) of the treatment-emergent ADA+ subjects were classified as treatment-induced, while 167 (6.5%) were considered as treatment boosted. ADA positivity appeared to increase by dose and duration of exposure. The maximum antibody titers ranged from 1:20 to 1:327,860 (median 1:160). Additionally, 1,705 (33.9% of 5025) and 716 (14.2% of 5025) ADA+ subjects showed cross-reactivity to nGIP and nGLP-1, respectively. Ninety-four (1.9% of 5025) subjects developed NAb against tirzepatide activity on the GIP receptor, and 107 (2.1% of 5025) against tirzepatide activity on the GLP-1 receptor. Cross-reactive NAb against native GIP (nGIP) and native GLP-1 (nGLP-1) were observed in 0.9% (43/5025) and 0.4% (18/5025) of tirzepatide-treated subjects, respectively.

Across the seven phase trials development of ADAs did not appear to impact the pharmacokinetics (clearance) or efficacy (reductions in HbA1c or body weight) of tirzepatide. ADA titers >1:160 (i.e., >the median titer) in 1168 subjects and the presence of NAb also did not appear to affect tirzepatide clearance, and the efficacy was not affected in a subgroup of 91 ADA+ subjects with elevated titers ≥1:5120. However, ADA positivity was associated with higher proportions of subjects experiencing TEAEs of hypersensitivity (i.e., 2.1% vs. 1.4% of ADA- subjects) and injection site reactions (2.3% vs. 0.4% of ADA- subjects). None of these AEs were coded as serious or severe (b) (4) the Applicant states that the development of ADA did not appear to alter the pharmacokinetics, efficacy, or safety of tirzepatide. However, of 179 tirzepatide-treated subjects that experienced hypersensitivity reactions, 106 (59.2%) were ADA+ and 73 (40.8%) were ADA-. Also, of the 137 tirzepatide-treated subjects who experienced injection site reactions, 119 (86.9%) were ADA+ and 18 (13.1%) were ADA-. Additionally, ADA+ subjects randomized from Japan sites experienced more

hypersensitivity and injection site reactions than ADA- subjects (i.e., 54 vs. 13 subjects of 67 events and 45 vs. 5 subjects of 50 events, respectively). The Applicant reported that there was no pattern detected between the time of the event reporting and ADA status, and most events were coded as mild in severity and resolved irrespective of ADA status. Please refer to Section 8.5.4 below for additional information on hypersensitivity reactions and Section 8.5.5 for information related to injection site reactions.

Dr. Faruk Sheikh, from OBP, reviewed the immunogenicity assessment data submitted to the Application. Although he noted that tirzepatide was highly immunogenic, he felt that no safety or efficacy concern(s) were correlated with ADA development in subjects participating in the clinical studies conducted under this NDA. From an immunogenicity perspective, he recommended approval of tirzepatide. I concur with his assessment. However, the effects of discontinuation of tirzepatide treatment on glycemic control in subjects who develop neutralizing antibodies against native GIP or GLP-1 is unknown, as the four-week safety follow-up period in the clinical trials may not have been adequate assess this risk. Please refer to Dr. Sheikh's review, dated February 15, 2022, for detailed discussion of the immunogenicity findings of this Application.

8.5. Analysis of Submission-Specific Safety Issues

This section will review AESI (Special Safety Topics) considered as potential or established GLP-1 RA class-related AEs. Please refer to Section 8.1 for a more complete list of AESI considered for this Application.

8.5.1. Thyroid Safety

Medullary thyroid carcinoma (MTC), a relatively rare neuroendocrine tumor of the parafollicular C-cells of the thyroid gland, accounts for 3% of all thyroid cancers.[196] Product labeling of long-acting glucagon-like peptide 1 receptor agonists (GLP-1 RAs) carry a boxed warning of the risk of thyroid C-cell tumors, and include statements that these products cause thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in rodents, and that the relevance of these findings in humans has not been determined.[2-11] Due to the nonclinical findings, long-acting GLP-1 RAs are contraindicated in patients with a personal or family history of MTC or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Similarly, proposed labeling for tirzepatide also includes a boxed warning and contraindications for use in patients with a personal or family history of MTC or in patients with MEN 2.

In a 2-year carcinogenicity study conducted in the tirzepatide nonclinical program, increases in thyroid C-cell hyperplasia and neoplasia were observed in male and female rats. The incidences of thyroid C-cell adenomas and/or carcinomas were increased in the tirzepatide 0.15, 0.5, and 1.5 mg/kg dose groups. The 1.5 mg/kg tirzepatide dose in rats is approximately equivalent to the

proposed maximum exposure in humans of 15 mg of tirzepatide SC QW. The Applicant noted that thyroid C-cell lesions have not been observed in published reports with GLP-1 RAs in monkeys.[129,197] However, cases of MTC have been previously reported for other GLP-1 RAs.[5,7,10,11,198]

In the tirzepatide clinical development program, the safety database included 5415 subjects who received tirzepatide in nine phase 2/3 clinical trials (AS3) and included 4833.1 patient-years of exposure (treatment durations of 12-106 weeks). In this populations, approximately 1.02% (55/5415) of tirzepatide-treated subjects and 1.36% (32/2354) across the pooled comparator arm experienced treatment-emergent malignancies (Table 36). However, there were no TEAEs of thyroid malignancies, including events of MTC or thyroid C-cell hyperplasia.

Table 36: Treatment-Emergent Adverse Events of Thyroid Malignancies (AS3)

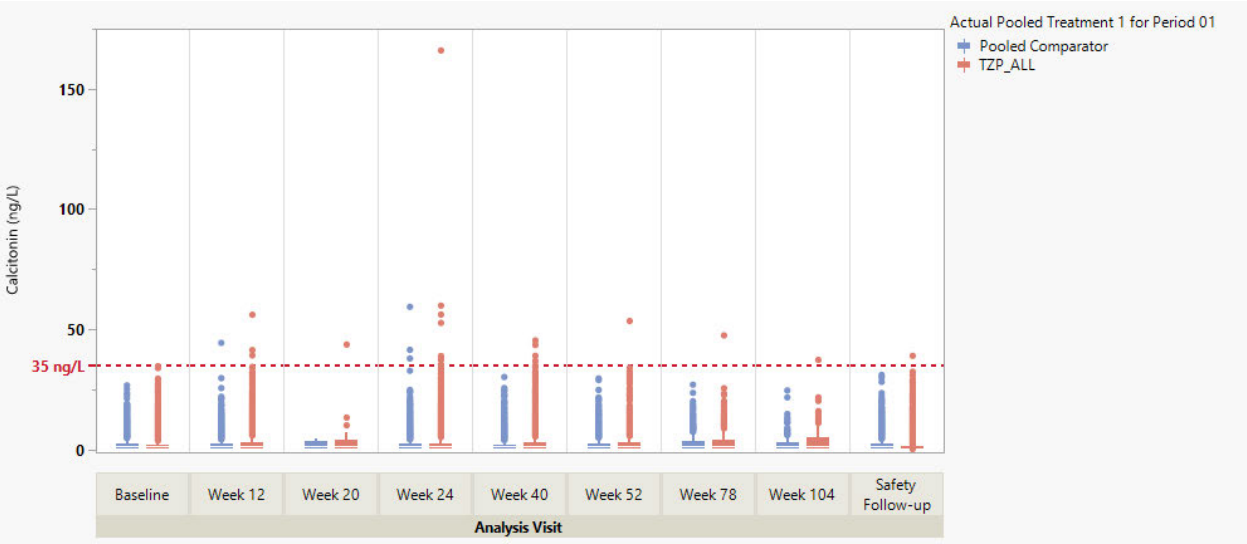
	TZP ALL (N=5415)	Rate per 100 PY	Pooled Comparator (N=2354)	Rate per 100 PY
Subjects with ≥1 TEAEs of Malignancy — No. (%)	**55 (1.02)**	~0.99*	**32 (1.36)**	~1.09*
Thyroid neoplasm malignant	0	—	0	—
Anaplastic thyroid cancer	0	—	0	—
Follicular thyroid cancer	0	—	0	—
Huerthle cell carcinoma	0	—	0	—
Medullary thyroid cancer	0	—	0	—
Papillary thyroid cancer	0	—	0	—
Poorly differentiated thyroid carcinoma	0	—	0	—
Thyroid cancer	0	—	0	—
Thyroid cancer metastatic	0	—	0	—
Thyroid cancer recurrent	0	—	0	—
Thyroid cancer stage 0	0	—	0	—
Thyroid cancer stage I	0	—	0	—
Thyroid cancer stage II	0	—	0	—
Thyroid cancer stage III	0	—	0	—
Thyroid cancer stage IV	0	—	0	—
Thyroid C-cell hyperplasia	0	—	0	—

Source: Derived from the adsl.xpt and adae.xpt datasets.
Abbreviations: AS3, Analysis Set 3 (pool of 9 phase 2/3 trials); PY, patient-year; and TZP, tirzepatide.
*Event rates to be confirmed with the Applicant.

Calcitonin

In the phase 2/3 trials (AS3), calcitonin serum concentrations were measured during the trials to assess whether tirzepatide affected C-cell function, potentially indicating the development of C-cell hyperplasia/neoplasms (Figure 11).

Figure 11: Serum Calcitonin Concentrations in Phase 2/3 Trials (AS3)



Source: Derived from the ISS adsl.xpt and adlb.xpt datasets.
Abbreviations: AS3, Analysis Set 3 (pool of 9 phase 2/3 trials); and TZP, tirzepatide.

Sixteen tirzepatide-treated subjects (Table 37) in these trials (none in the phase 2 trials) experienced an increase in serum calcitonin concentrations of ≥50% and an absolute value ≥35 ng/L (i.e., criteria for exclusion, discontinuing investigational product [IP], and consultation with a thyroidologist/endocrinologist and longer follow-up). These laboratory abnormalities were reported on study days 83 to 679. Tirzepatide was discontinued in eight of these subjects, and continued in the remaining eight subjects, . Calcitonin concentrations improved for 15 of the 16 subjects at the 4-week safety follow-up visit, while for one subject (b) (6), the calcitonin concentration peaked at the follow-up visit (i.e., increased from 13.3 ng/L at baseline to 39 ng/L on Day 481). This subject had permanently discontinued tirzepatide 5 mg on Day 29 due to gastrointestinal AEs. An additional subject (b) (6) had a postbaseline calcitonin of 166 ng/L (Day 170), but a repeat measurement five days later was 1.5 ng/L. Thyroid ultrasound performed for five of the 16 subjects were reported as normal for four subjects and revealed a benign thyroid nodule for the fifth. It also is acknowledged that 13 of the 16 subjects were male, nine used tobacco products, and five received concomitant proton pump inhibitor (PPI) medications, factors which may have influenced the elevated serum calcitonin measurements.[199-203] Additionally, 40 tirzepatide-treated subjects in the phase 2/3 clinical program had TEAEs of 'Blood calcitonin increased' (0.72 events/100 PY), which included: 9 subjects with postbaseline peak calcitonin concentrations ≥35 ng/L; 8 with concentrations of >20 ng/L to <35 ng/L; and 23 with concentrations ≤20 ng/L.

Table 37: Subjects with Postbaseline Calcitonin Increase ≥50% with Value ≥35 ng/dL in Phase 2/3 Trials (AS3)

Subject ID	Treatment	Subject Characteristics			Calcitonin (ng/L)				Thyroid-Related AE Reported		Treatment Discontinued due to Calcitonin	Comments
		Sex	Age (yr)	Tobacco use (Y/N)	Study Day	% CFB	PBL Peak Value	Safety Follow-up Value	Y/N	PT	Y/N	
(b) (6)	Tirzepatide 5 mg	F	29	Y	Day 281	66	43.4	22.6	Y	Blood calcitonin increased	Y	Subject reported concomitant use of PPI.
	Tirzepatide 5 mg	M	63	Y	Day 170	58	38.0	12.3	Y	Blood calcitonin increased, Thymus enlargement	Y	Subsequent thyroid ultrasound was normal
	Tirzepatide 5 mg	M	55	N	Day 100	133	51.4	28.0	Y	Blood calcitonin increased	Y	Subsequent thyroid ultrasound was normal
	Tirzepatide 5 mg	M	71	Y	Day 679	52	37.2	23.3	N		N	Subject reported concomitant use of PPI.
	Tirzepatide 5 mg	M	77	Y	Day 481	193	39.0	N/A	N		N	Subject discontinued study drug on Study Day 29 due to AE of flatulence. Peak calcitonin was at safety follow-up.
	Tirzepatide 10 mg	M	44	Y	Day 164	82	35.3	23.9	Y	Blood calcitonin increased	Y	Subsequent thyroid ultrasound was normal
	Tirzepatide 10 mg	M	55	N	Day 278	681	45.3	27.3	N		N	Calcitonin level returned to normal level (27.3 ng/L) after stopping PPI

Subject ID	Treatment	Subject Characteristics			Calcitonin (ng/L)				Thyroid-Related AE Reported		Treatment Discontinued due to Calcitonin	Comments
		Sex	Age (yr)	Tobacco use (Y/N)	Study Day	% CFB	PBL Peak Value	Safety Follow-up Value	Y/N	PT	Y/N	
(b) (6)	Tirzepatide 10 mg	M	54	Y	Day 85	66	39.1	21.0	Y	Blood calcitonin increased	Y	Subsequent thyroid ultrasound was normal
	Tirzepatide 10 mg	F	65	N	Day 275	179	36.8	25.2	N		N	Subject reported concomitant use of PPI.
	Tirzepatide 15 mg	M	52	N	Day 83	321	56.0	17.9	Y	Blood calcitonin increased	Y	
	Tirzepatide 15 mg	M	56	N	Day 169	126	38.8	19.9	Y	Blood calcitonin increased	N	Repeat calcitonin on Day 175, 6 days after the peak value was measured, was improved (32.1 ng/L).
	Tirzepatide 15 mg	M	71	N	Day 171	83	52.6	38.9	N		Y	Calcitonin returned to baseline levels of 29.7 ng/L on Day 284. No thyroid follow-up was performed. Subject reported concomitant use of PPI.
	Tirzepatide 15 mg	M	62	Y	Day 177	128	62.4	30.9	Y	Blood calcitonin increased, Thyroid mass	Y	Subsequent thyroid ultrasound showed left thyroid nodule. Imaging revealed a colloid nodular goiter
	Tirzepatide 15 mg	F	72	N	Day 170	1650 0	166.0	1.0	N		N	PI felt the calcitonin result (Day 170) was incorrect. The re-test from Day 175 result was

Subject ID	Treatment	Subject Characteristics			Calcitonin (ng/L)				Thyroid-Related AE Reported		Treatment Discontinued due to Calcitonin	Comments
		Sex	Age (yr)	Tobacco use (Y/N)	Study Day	% CFB	PBL Peak Value	Safety Follow-up Value	Y/N	PT	Y/N	
(b) (6)												1.5 ng/L. Due to this, PI did not perform additional follow-up.
	Tirzepatide 15 mg	M	67	Y	Day 367	775	53.4	10.6	N		N	Repeat calcitonin on Day 373 which was 6 days after the date of peak value measurement was normal at 6.9 ng/L.
	Tirzepatide 15 mg	M	47	Y	Day 175	237	67.0	29.0	Y	Blood calcitonin increased	N	Multiple repeat measures after the peak value trended down.

Source: Adapted from the Applicant's Summary of Clinical Safety, page 165 of 327, available at: \\CDSESUB1\evsprod\nda215866\0001\m2\27-clin-sum\clin-safety-sum--tzp-t2dm-.pdf
Abbreviations: AE, adverse event; AS3, Analysis Set 3 (pool of 9 phase 2/3 trials; CFB, change from baseline; eGFR, estimated glomerular filtration rate; F, female; ID, unique subject identifier; M, male; N, no; PBL, postbaseline; PPI, proton pump inhibitor; PT, preferred term; Y, yes; and yr, year;

The Applicant felt that there was no evidence of increased risk of MTC, C-cell hyperplasia, or persistently elevated calcitonin levels with the use of tirzepatide, and therefore they did not recommend routine monitoring of serum calcitonin or thyroid ultrasound in patients receiving tirzepatide. I concur with the Applicant's conclusion.

In the Applicant's 4-MSU, they reported three AEs of 'Papillary thyroid cancer' (0.23%; 3/1317 subjects) in tirzepatide-treated subjects in ongoing trial GPHO (Subjects (b) (6), and (b) (6)) being conducted in China. All three subjects had pre-existing thyroid nodules and the diagnosis of papillary thyroid cancer was made within 4.7 to 7.6 months following randomization. Based on the presence of preexisting nodules, the thyroid cancer subtype, normal serum calcitonin concentrations, and relatively short latency periods, it is unlikely that tirzepatide is causally associated with these events. However, whether tirzepatide could have contributed to disease progression in these subjects is unknown.

Since 2010, Sponsors of long-acting GLP-1 RAs have been required to participate in a MTC surveillance study (registry-based case series of at least 15 years in duration) as a postmarketing requirement (PMR) to systematically monitor the annual incidence of MTC in the United States (US), and to identify any increase in incidence related to the introduction of long-acting GLP-1 RAs into the US marketplace.[204] Considering the relatively short trial durations in the tirzepatide clinical development program, the latency of MTC, and in accordance with Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA), the Applicant will be asked to conduct a postmarketing study to assess a signal of a serious risk for medullary thyroid carcinoma.

8.5.2. Exocrine Pancreas Safety

Type 2 diabetes is a population at risk for pancreatitis.[205-213] Cases of acute pancreatitis also have been reported in the medical literature with the use of GLP-1 RAs in this population.[214-229] In March of 2013, the Agency issued a Drug Safety Communication of possible increased risk of pancreatitis and pre-cancerous findings of the pancreas from incretin mimetic drugs, including GLP-1 RAs, for T2D.[230] The risk of pancreatitis also is included in the Warnings and Precautions section of GLP-1 RA labeling.[2-11]

In the Applicant's nonclinical program, they did not find evidence of pancreatitis, pancreatic cancer or tirzepatide-related pancreas AEs in mice, rats, or monkeys. In the tirzepatide clinical development program, the Applicant assessed relevant AEs, primarily identified by SMQ and serial serum pancreatic enzyme measurements (amylase and lipase) to identify possible cases of pancreatitis. Suspected cases were then adjudicated by an independent, blinded CEC. The case definition for acute pancreatitis was an acute inflammatory process of the pancreas that may involve peri-pancreatic tissues and/or remote organ systems.[231] The diagnosis of acute pancreatitis included at least two of the following three criteria:

1) Abdominal pain characteristic of acute pancreatitis[231,232]
2) Serum lipase or amylase at least 3x UNL
3) Characteristic findings by computerized tomography (CT) or magnetic resonance imaging (MRI).

The diagnosis of chronic pancreatitis was based on the medical history and/or cross-sectional imaging.

Of 61 subjects with 64 AEs of suspected pancreatitis submitted for adjudication (data not shown) across the Applicant's phase 2/3 trials (AS3), there were 17 cases of confirmed pancreatitis (Table 38), of which 14 cases were adjudicated as acute pancreatitis in 13 tirzepatide-treated subjects (0.23 events/100 PY), three cases as acute pancreatitis (all receiving semaglutide 1 mg SC QW) in the pooled comparator arm (0.11 events/100 PY), and one case as chronic pancreatitis (trial GPGM, receiving insulin glargine) in the pooled comparator arm (0.04/100 PY). For six of the 13 tirzepatide-treated subjects (seven total pancreatitis AEs), the events were coded as serious (Table 39). Five of these six SAEs were reported in trial GPGM, which included subjects with the highest level of baseline comorbidities and longest treatment exposure. No adjudicated pancreatitis events in the comparator arms were coded as serious. There were no fatal outcomes, and events were reported as recovered/resolved or recovering/resolving for nine of the 13 subjects. Although a numeric imbalance in serious acute pancreatitis events was observed in trial GPGM (5/995 tirzepatide-treated subjects vs. 0/1000 insulin glargine-treated subjects), events of MACE-4 (HR 0.80, 95% CI: 0.57, 1.11) and all-cause mortality (HR 0.80, 95% CI: 0.51, 1.25) reported in the CVMA (for which trial GPGM contributed the majority of events) favored the pooled tirzepatide arm, and therefore would likely support a favorable benefit-risk profile in this at-risk population. Please refer to Section 8.5.11 for additional information on the CVMA.

Table 38: Adjudicated Cases of Pancreatitis (AS3)

Pancreatitis AEs Preferred Term	All Comparators (N=2354) PY=2761.6	TZP 5 mg (N=1756)	TZP 10 mg (N=1756)	TZP 15 mg (N=1825)	All TZP (N=5415)* PY=5582.4
SUBJECTS WITH ≥1 CONFIRMED PANCREATITIS EVENT— NO. (%)	**4 (0.17)**	**5 (0.28)†**	**4 (0.23)**	**4 (0.22)**	**13 (0.24)**
PYE / IR	2759.4 / 0.14				5575.0 / 0.23
Acute pancreatitis	3 (0.13)	5 (0.28)†	4 (0.23)	4 (0.22)	13 (0.24)
PYE / IR	2759.9 / 0.11				5575.0 / 0.23
Chronic pancreatitis	1 (0.04)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
PYE / IR	2761.1 / 0.04				0 (0.0)
Unknown	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Source: Adapted in part from the Applicant's ISS, page 2872 of 7807, available at:
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Abbreviations: AE, adverse event; AS3, Analysis Set 3 (pool of 9 phase 2/3 trials); IR, incidence rate per 100 PY; ISS, Integrated Summary of Safety; No., number: PY, total patient-years in study; PYE, total patient years at risk (sum of exposure time to the assessment date for subjects with the event and exposure time to end of the study for those without the event); and TZP, tirzepatide.
*The All TZP arm included trials that randomized subjects to other tirzepatide doses besides the 5 mg, 10 mg or 15 mg doses.
†Subject (b) (6), randomized to the tirzepatide 5 mg arm, experienced two SAEs adjudicated as acute pancreatitis.

Adjudicated pancreatitis AEs in the 13 tirzepatide-treated subjects (Table 39) occurred following approximately 19 to 511 (mean 212±163) days of exposure. The mean age of these subjects was 60.6±9.1 years, and nine were male, nine were White, and three listed cholelithiasis as a contributing factor. Based on a review of the clinical narratives and adjudication report, the adjudication appeared to be appropriate.

Table 39: Subjects in the Tirzepatide Arm with Adjudicated Acute Pancreatitis Events (AS3)

Subject ID	Dose/ Days on TZP*	Age/Race/Sex	MedDRA PT (SAE: Y/N)	Study Day	Contributing Risk Factors	CEC Adjudicated Event Type	Diagnostic Criteria (Outcome)
(b) (6)	TZP 15mg / 365 days	44/A/Male	Lipase increased (N)	358	None	Pancreatitis, Acute (mild severity)	• **Imaging** (pancreatic anomaly) • **Elevated enzymes** (amylase 75 IU/L [ULN 53] and lipase 282 IU/L [ULN 60 IU/L]) **(Not Recovered/Not Resolved)**
	TZP 5mg / 14 days	54/W/Male	Pancreatitis acute (N)	19	None	Pancreatitis, Acute (mild severity)	• **Symptoms** (abdominal pain, nausea, vomiting) • **Elevated enzymes** (amylase 142 [ULN 120 IU/L], lipase 323 IU/L [ULN 100]) **(Recovered/Resolved)**
	TZP 5mg / 84 days	61/W/Female	Pancreatitis acute (Y)	125	Cholelithiasis	Pancreatitis, Acute (mild severity)	• **Symptoms** (abdominal pain, and vomiting) • **Imaging** (acute pancreatitis with maximum involvement in the pancreatic body and tail, and infiltration in the surrounding area). **(Recovered/Resolved)**
			Pancreatitis acute (Y)	158	Cholelithiasis	Pancreatitis, Acute (moderate severity)	• **Symptoms** (abdominal pain and vomiting) • **Imaging** (acute edematous pancreatitis with reactive fluid in a small pelvis, and inflammatory irritation of the peripancreatic space / Balthazar C, score 2). **(Recovered/Resolved)**
	TZP 10mg / 169 days	63/A/Male	Digestive enzyme increased (N)	166	None	Pancreatitis, Acute (mild severity)	• **Symptoms** (epigastric pain and nausea) • **Elevated enzymes** (amylase 288 IU/L [ULN 53 IU/L] and lipase 518 IU/L [ULN 60 IU/L) **(Not Recovered/Not Resolved)**

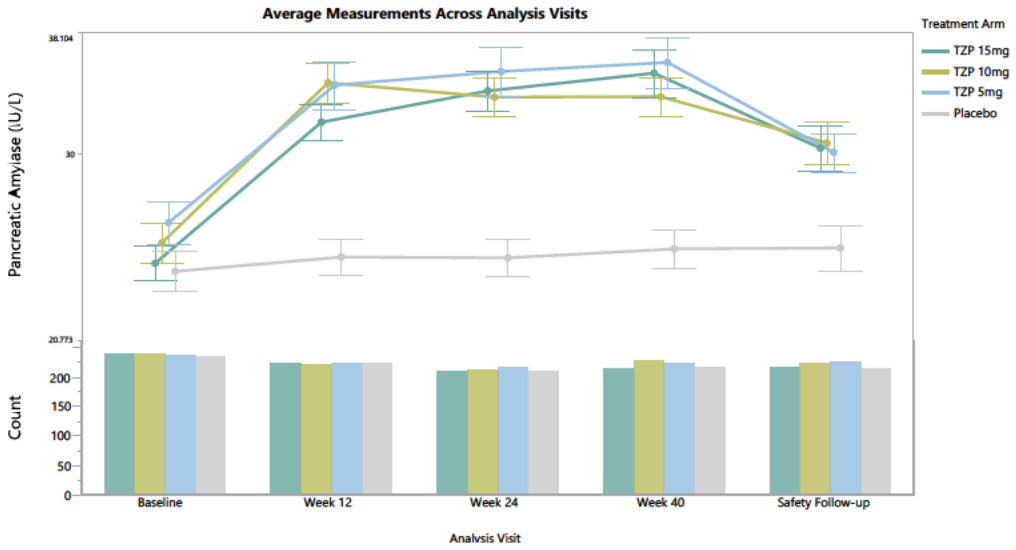
Subject ID	Dose/ Days on TZP*	Age/Race/Sex	MedDRA PT (SAE: Y/N)	Study Day	Contributing Risk Factors	CEC Adjudicated Event Type	Diagnostic Criteria (Outcome)
(b) (6)	TZP 15mg / 287 days	56/W/Female	Pancreatitis acute (N)	281	None	Pancreatitis, Acute (mild severity)	• **Symptoms** (abdominal pain and nausea) • **Elevated enzymes** (amylase 97 IU/L [ULN 53 IU/L] and lipase 180 IU/L [ULN 60 IU/L]) **(Not Recovered/Not Resolved)**
	TZP 15mg / 281 days	58/W/Male	Pancreatic enzymes increased (N)	86	NR	Pancreatitis, Acute	• **Symptoms** (abdominal pain, nausea, and vomiting) • **Elevated enzymes** (amylase 76 IU/L [ULN 53 IU/L] and lipase 185 IU/L [ULN 60 IU/L]) **(Recovered/Resolved)**
	TZP 10mg / 154 days	56/W/Male	Pancreatitis chronic (N)	85	Cholelithiasis	Pancreatitis, Acute (mild severity)	• **Imaging** (pancreatic calcification) • **Elevated enzymes** (amylase 329 IU/L [ULN 53 IU/L] and lipase 724 IU/L [ULN 60 IU/L]) **(Not Recovered/Not Resolved)**
	TZP 5mg / 91 days	54/W/Male	Pancreatitis (Y)	90	Drug-induced	Pancreatitis, Acute (mild severity)	• **Symptoms** (abdominal pain, anorexia, and nausea) • **Elevated enzymes** (amylase 221 IU/L [ULN 53 IU/L and lipase 362 IU/L [ULN 60 IU/L) **(Recovered/Resolved)**
	TZP 5mg / 35 days	74/W/Male	Pancreatitis (Y)	50	Drug-induced	Pancreatitis, Acute (moderate severity)	• **Symptoms** (epigastric abdominal pain, nausea, and vomiting) • **Imaging** (necrosis and irregular peripancreatic fluid collection) • **Elevated enzymes** (lipase 30,000 IU/L [ULN 393 IU/L], amylase [NR]) **(Recovered/Resolved)**
	TZP 10mg / 385 days	63/W/Female	Pancreatitis acute (Y)	395	NR	Pancreatitis, Acute (mild severity)	• **Symptoms** (abdominal pain) • **Elevated enzymes** (amylase 120 IU/L [ULN 53 IU/L] and lipase 202 IU/L [ULN 60 IU/L]) **(Recovered/Resolved)**
	TZP 5mg / 433 days	77/AIAN/Male	Obstructive pancreatitis (Y)	432	Cholelithiasis	Pancreatitis, Acute (mild severity)	• **Symptoms** (abdominal pain, nausea, and vomiting), imaging (pancreatitis, moderate, secondary to residual cholelithiasis) • **Elevated enzymes** (amylase 564 IU/L [ULN NR], lipase [NR]) **(Recovering/Resolving)**

Subject ID	Dose/ Days on TZP*	Age/Race/Sex	MedDRA PT (SAE: Y/N)	Study Day	Contributing Risk Factors	CEC Adjudicated Event Type	Diagnostic Criteria (Outcome)
(b) (6)	TZP 10mg / 511 days	67/W/Male	Pancreatitis (Y)	511	NR	Pancreatitis, Acute (moderate severity)	• Symptoms (abdominal pain, nausea) • **Imaging** (increase in diameter at the level of the cephalic portion of the pancreas and loss of the acinar pattern, as well as peripancreatic laminar fluid, compatible with an acute inflammatory process) • **Elevated enzymes** (amylase 393 IU/L [ULN 100 IU/L] and lipase 498 IU/L [ULN 60]) **(Recovered/Resolved)**
	TZP 15mg / 372 days	71/A/Female	Pancreatitis (N)	368	NR	Pancreatitis, Acute (moderate severity)	• **Imaging** (mildly swollen pancreatic body with no peripancreatic fluid collection) • **Elevated enzymes** (amylase 271 IU/L [ULN 53 IU/L] and lipase 521 IU/L [ULN 60 IU/L]) **(Recovered/Resolved)**

Source: Derived from the Applicant's:
Clinical Study Reports, available at:
\\CDSESUB1\evsprod\NDA215866\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\type-2-diabetes-mellitus\5351-stud-rep-contr
Integrated Summary of Safety, pages 2853-2858 of 7807, available at:
\\CDSESUB1\evsprod\nda215866\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\type-2-diabetes-mellitus\5353-rep-analys-data-more-one-stud\iss\iss-46-integrated-sum-of-safety--t2dm-.pdf
Table of Significant and Notable Patients – Phase 2 and Phase 3, available at:
\\CDSESUB1\evsprod\nda215866\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\type-2-diabetes-mellitus\5353-rep-analys-data-more-one-stud\iss\table-of-significant-and-notable-patients---phase-2-and-3.pdf
Abbreviations: A, Asian; AE, adverse event; AIAN, American Indian or Alaska Native; AS3, Analysis Set 3 (pool of 9 phase 2/3 trials); CEC, Clinical Event Committee; ID, identification; N, no; NR, not reported; SAE, serious adverse event; TZP, tirzepatide; ULN, upper limit of normal; W, white; and Y, yes.
*Note, the Applicant's on-treatment duration of exposure to TZP is equivalent to the day of the last dose plus 7 days.

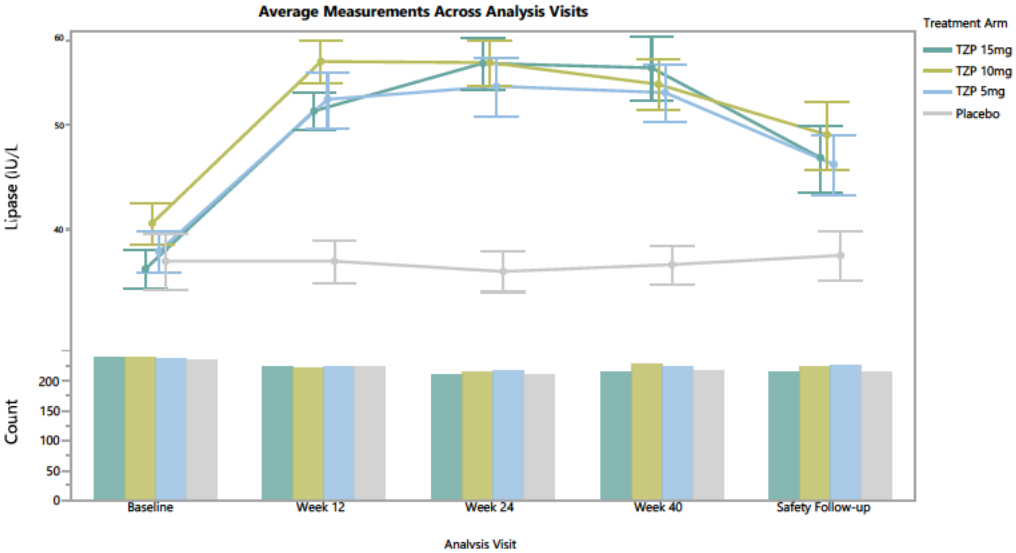
Changes from baseline in serum amylase (Figure 12) and lipase (Figure 13) in the pooled placebo-controlled population (AS1) are presented below. The mean increases in serum amylase (i.e., ↑32.5±3.1%, 33.8±3.11%, and 38.3±3.29% for tirzepatide 5, 10, and 15 mg arms, respectively) and lipase (↑31-42%) concentrations in tirzepatide-treated subjects was higher than that reported in the placebo-controlled arm (i.e., ↑4.3±2.47% and 0%, respectively).

Figure 12: Mean Changes in Serum Amylase Concentrations (AS1)



Each error bar is constructed using 1 standard error from the mean.
Source: Derived from the ISS adsl.xpt and adlb.xpt datasets.
Abbreviations: AS1, Analysis Set 1 (pool of 2 placebo-controlled phase 3 trials); ISS, Integrated Summary of Safety, TZP, tirzepatide.

Figure 13: Mean Changes in Serum Lipase Concentrations (AS1)



Each error bar is constructed using 1 standard error from the mean.
Source: Derived from the ISS adsl.xpt and adlb.xpt datasets.
Abbreviations: AS1, Analysis Set 1 (pool of 2 placebo-controlled phase 3 trials), ISS, Integrated Summary of Safety, TZP, tirzepatide.

Additionally, across the Applicant's phase 2/3 clinical program (AS3), postbaseline shifts in serum amylase and lipase from baseline concentrations of ≤1x ULN to >3x ULN were reported in 1.2% (62/5155) and 5.7% (268/4710) of tirzepatide-treated subjects, respectively (Table 40). Increases in serum lipase to >10x ULN were reported in 12 of these subjects.

Table 40: Maximum Baseline to Maximum Postbaseline Shifts in Serum Amylase and Lipase (AS3)

	Maximum Post-Baseline Result						
Treatment Max baseline result	**≤1x ULN n (%)**	**>1 to ≤3x ULN n (%)**	**>3 to ≤5x ULN n (%)**	**>5 to ≤10x ULN n (%)**	**>10x ULN n (%)**	**Missing n (%)**	**Total n (%)**
TZP ALL (N=5415)							
Amylase (IU/L)*							
≤1x ULN	3950 (72.95)	1087 (20.07)	55 (1.02)	7 (0.13)	0 (0.00)	56 (1.03)	5155 (95.20)
>1x ULN	38 (0.70)	175 (3.23)	25 (0.46)	12 (0.22)	0 (0.00)	4 (0.07)	254 (4.69)
Missing	5 (0.09)	1 (0.02)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	6 (0.11)
Total	3993 (73.74)	1263 (23.32)	80 (1.48)	19 (0.35)	0 (0.00)	60 (1.11)	5415 (100.00)
Lipase (IU/L)							
≤1x ULN	2660 (49.12)	1732 (31.99)	177 (3.27)	79 (1.46)	12 (0.22)	50 (0.92)	4710 (86.98)
>1x ULN	94 (1.74)	410 (7.57)	109 (2.01)	53 (0.98)	23 (0.42)	10 (0.18)	699 (12.91)
Missing	5 (0.09)	1 (0.02)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	6 (0.11)
Total	2759 (50.95)	2143 (39.58)	286 (5.28)	132 (2.44)	35 (0.65)	60 (1.11)	5415 (100.00)

Source: Adapted from the Applicant's Integrated Summary of Safety, pages 3008-3009 of 7807, available at: \\CDSESUB1\evsprod\nda215866\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\type-2-diabetes-mellitus\5353-rep-analys-data-more-one-stud\iss\iss-46-integrated-sum-of-safety--t2dm-.pdf
Abbreviations: AS3, Analysis Set 3 (pool of 9 phase 2/3 trials); Max, maximum; n, number of subjects in each shift category; N, number of subjects in the population in the specified treatment group; TZP, tirzepatide; ULN, upper limit of normal range.
*Serum amylase was collected for trials GPGB and GPGF, and p-amylase for all other trials.

The Applicant noted that serial measurements of pancreatic enzymes may have limited clinical value for predicting episodes of acute pancreatitis in asymptomatic subjects.[233-235] Therefore, they propose to describe these data in Section 12.2 (Pharmacodynamics) of tirzepatide product labeling. The proposed labeling also will include the risk of pancreatitis and the observed incidence rate reported from the phase 2/3 clinical trials in Section 5 (Warnings and Precautions). Considering that acute pancreatitis is a potentially life-threatening condition, an early onset of these events in several of the tirzepatide-treated subjects, and the relative lack of identifiable contributing factors in many of adjudicated cases, I concur that this risk and associated incidence rate should be conveyed to prescribers in Section 5 of product labeling. However, the observed changes in serum amylase and lipase concentrations should be considered abnormal laboratory findings and described in Section 6.1 (Clinical Trials Experience), and not Section 12.2 as proposed by the Applicant. This also is consistent with class labeling for other GLP-1 RA products. It is notable that confirmed acute pancreatitis AEs for 12 of the 13 tirzepatide-treated subjects with adjudicated events included elevated pancreatic enzymes as part of the diagnostic criteria (Table 39), and shifts in serum pancreatic amylase and lipase from <1x the upper limit of normal (ULN) to >5x ULN were reported in seven subjects (0.13%), and 91 subjects (1.68%), respectively, in the tirzepatide treatment arms.

8.5.3. Hypoglycemia

Events of hypoglycemia in tirzepatide clinical development program were defined and identified according to the following three categories:

- **Level 1 hypoglycemia:** Episodes associated with blood glucose concentrations <70 mg/dL and ≥54 mg/dL.
- **Level 2 hypoglycemia:** Episodes associated with blood glucose concentrations <54 mg/dL.
- **Level 3 (severe) hypoglycemia:** Episodes with severe cognitive impairment requiring the assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions.

The proportions of subjects experiencing clinically meaningful hypoglycemic events (i.e., Level 2 and Level 3) in the Applicant's phase 3 placebo-controlled pool (AS1) is presented in Table 41.

Table 41: Hypoglycemic Adverse Events (AS1)

Hypoglycemia AEs Preferred Term	Placebo	TZP 5 mg	TZP 10 mg	TZP 15 mg
Monotherapy (trial GPGK; 40 weeks) — no. (%)	**N=115**	**N=121**	**N=119**	**N=120**
Level 2†	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)
Level 3‡	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Add-on to Ins Glar ± Met (trial GPGI; 40 weeks) — no. (%)	**N=120**	**N=116**	**N=119**	**N=120**
Level 2†	15 (12.5)	18 (15.5)	22 (19)	17 (14.2)
Level 3‡	0 (0.0)	0 (0.0)	2 (1.7)	1 (0.8)

Source: Derived from the Applicant's Clinical Study Reports for:
Trial GPGK, pages of , available at: \\CDSESUB1\evsprod\NDA215866\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\type-2-diabetes-mellitus\5351-stud-rep-contr\i8f-mc-gpgk
Trial GPGI, page 82 of 182, available at: \\CDSESUB1\evsprod\NDA215866\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\type-2-diabetes-mellitus\5351-stud-rep-contr\i8f-mc-gpgi
Abbreviations: AE, adverse event; AS1, Analysis Set 1 (i.e., 2 phase 3 placebo-controlled trials); Ins Glar, insulin glargine; No., number; and TZP, tirzepatide.
† Episodes associated with a blood glucose <54 mg/dL.
‡ Episodes requiring the assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions.

In trial GPGI (i.e., add-on to insulin glargine ± metformin), three tirzepatide-subjects experienced severe hypoglycemic reactions, two subjects in the tirzepatide 10 mg arm (b) (6) and one subject in the 15 mg arm (b) (6) Additionally, clinically meaningful hypoglycemia events (i.e., ADA Level 2 and Level 3) also were reported more frequently with concomitant use of a sulfonylurea (SU) in trial GPGM. Of the subjects receiving a SU, Level 2 or Level 3 hypoglycemia occurred in 13.8% (26/189), 9.9% (18/181), and 12.9% (23/179) of subjects randomized to the tirzepatide 5, 10, and 15 mg arms, respectively, and severe hypoglycemia occurred in 0.5% (1/189), 0% (0/181), and 0.6% (1/179) of subjects (including the safety follow-up period), respectively. For subjects not receiving a SU, Level 2 or Level 3 hypoglycemia was

reported in 2.1% (3/140), 1.4% (2/147), and 2.5% (4/159) of the subjects randomized to the tirzepatide 5, 10, and 15 mg arms, respectively. The Applicant intends to show these data in Section 6.1 of proposed tirzepatide product labeling and to include the risk of hypoglycemia associated with concomitant administration of tirzepatide with an insulin secretagogue or insulin as a Warnings and Precautions. I concur with these labeling proposals.

8.5.4. **Hypersensitivity Reactions**

Hypersensitivity is listed in the Warnings and Precautions section of other products with GLP-1 inhibitor activity and as a contraindication for individuals with a history of a serious hypersensitivity reaction to the respective GLP-1 products.[2-11,24-26] Additionally, hypersensitivity reactions associated with GLP-1 RAs, including anaphylaxis, have been reported in the literature.[236-241]

In the tirzepatide clinical development program, hypersensitivity reactions were identified using a predefined SMQ search strategy and evaluated as immediate (occurring within 24 hours of administration of IP) or potential non-immediate hypersensitivity. For this review, immediate and non-immediate hypersensitivity AEs were combined to evaluate the overall risk of hypersensitivity reactions associated with the use of tirzepatide.

Across the Applicant's phase 2/3 trials (AS3), hypersensitivity reactions were reported in 193 tirzepatide-treated subjects (study size adjusted percentage [adj 3.5%]) and 62 subjects [adj 2.5%] in the pooled comparator arms (Table 42). The study size adjusted incidence rates[171,172] in tirzepatide-treated subjects were 3.25 events per 100 PY and 2.56 per 100 PY across the comparator arms for eight of the nine trials (i.e., excluding trial GPGP which did not include a comparator arm). No anaphylactic reactions were reported in these trials. The most common reported PTs in the tirzepatide arms included 'Rash' (33/5415 subjects and 15/2354 subjects in the comparator arms, and 'Urticaria' (30 subjects and 4 subjects, respectively). One of the urticaria AEs reported in a tirzepatide-treated subject was recorded as severe (Subject (b) (6)). This subject experienced six previous AEs of urticaria which were classified as mild to moderate in severity by the investigator prior to the severe event Day 186). Notable hypersensitivity reactions reported for three additional tirzepatide-treated subjects included severe allergic rhinitis (Subject (b) (6)), treatment-emergent eczema resulting in discontinuation of IP (Subject (b) (6), and skin necrosis (Subject (b) (6); described below). For Subject (b) (6), a 46-year-old white female subject with a preexisting history of drug hypersensitivity to antibiotics (i.e., penicillin, sulfonamides, and fluoroquinolones), the event was reported 49 days after the final tirzepatide 5 mg dose. ADAs were not detected at baseline or end of study (Day 363). Considering the onset of this AE, and a half-life of approximately 5 days, it is not likely the tirzepatide caused the severe allergic rhinitis experienced by this subject.

- **Subject** (b) (6)**:** a 77-year-old White male with T2D randomized to the tirzepatide 5 mg treatment arm, experienced an SAE of 'Skin necrosis' on Day 437 (necrotized ulcer on right foot), which was reported as moderate in intensity and resulted in hospitalization and treatment with antibiotics. No AEs of nausea, vomiting, or diarrhea were reported. Relevant medical history included coronary artery disease (CAD), acute myocardial infarction (MI), coronary arterial stent insertion, and cardiac failure. On Day 477 he had surgery (amputation of his right half foot due to gangrene) and was subsequently discharged from the hospital on antibiotics on Day 481. On Day 487, he experienced diarrhea, fever, and shortness of breath, and was diagnosed with COVID-19 (possibly exposed during hospitalization), which resulted in hospitalization and death on Day 493. The subject received his last dose of IP on Day 428. The investigator classified the SAE and death as not related to IP.

Due to pre-existing comorbidities, this AE did not appear to be associated with a hypersensitivity reaction. However, whether tirzepatide contributed to the SAE or COVID-19 related death is unknown.

The Applicant intends to include hypersensitivity in Sections 4 (Contraindications) and 5 (Warnings and Precautions) of the proposed tirzepatide labeling. As this is consistent with class GLP-1 RA product labeling, I concur. Additionally, an association of hypersensitivity reactions with tirzepatide ADA positivity was observed. This information would be informative to prescribers and should be included in proposed labeling. Please see Section 8.4.9 for further details.

Table 42: Hypersensitivity Adverse Events — Side-by-Side Comparison of Phase 2/3 Trials (AS3)

	GPGK		GPGI		GPGF		GPGM		GPGH		GPGO		GPGB			GPGL		GPGP
Hypersensitivity Adverse Events	**PBO (N=115)**	**TZP ALL (N=363)**	**PBO (N=120)**	**TZP ALL (N=355)**	**PBO (N=26)**	**TZP ALL (N=85)**	**Ins Glar (N=1000)**	**TZP ALL (N=995)**	**Ins Deg (N=360)**	**TZP ALL (N=1077)**	**Dula 0.75 mg (N=159)**	**TZP ALL (N=477)**	**PBO (N=51)**	**Dula 1.5 mg (N=54)**	**TZP ALL (N=211)**	**Sema 1 mg (N=469)**	**TZP ALL (N=1409)**	**TZP ALL (443)**
Subjects with Events Across Trials	**ALL Comparators: 62/2354 subjects (2.6%) [adj 2.51%] – TZP: 193/5415 subjects (3.6%) [adj 3.53%]**																	
Total Subjects — no. (%)	**1 (0.9)**	**6 (1.7)**	**3 (2.5)**	**17 (4.8)**	**1 (3.8)**	**3 (3.5)**	**24 (2.4)**	**35 (3.5)**	**6 (1.7)**	**31 (2.9)**	**11 (6.9)**	**43 (9.0)**	**5 (9.8)**	**0 (0.0)**	**6 (2.8)**	**11 (2.3)**	**30 (2.1)**	**22 (5.0)**
Total Events — no.	1	6	3	20	1	3	32	44	6	50	16	77	5	0	6	14	33	25
PY	92.2	292.7	100.9	290.4	7.2	24.5	1566.4	1590.8	376	1125.1	168	502.6	28.1	30.1	116.2	392.7	1179.7	460.4
PYE	91.5	289.7	99.2	280.4	7	23.8	1541	1551.1	372.1	1100.5	160	476.3	26.6	30.1	114.1	387.1	1162.8	446.1
IR per 100 PY	1.09	2.07	3.03	6.06	14.38	12.59	1.56	2.26	1.61	2.82	6.88	9.03	18.77	0	5.26	2.84	2.58	4.93
MedDRA PT																		
Rash	0 (0.0)	1 (0.3)	1 (0.8)	2 (0.6)	0 (0.0)	0 (0.0)	6 (0.6)	6 (0.6)	3 (0.8)	6 (0.6)	1 (0.6)	4 (0.8)	1 (2.0)	0 (0.0)	1 (0.5)	3 (0.6)	10 (0.7)	3 (0.7)
Dermatitis	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (0.5)	4 (0.4)	0 (0.0)	3 (0.3)	1 (0.6)	3 (0.6)	1 (2.0)	0 (0.0)	2 (0.9)	1 (0.2)	1 (<0.1)	1 (0.2)
Hypersensitivity	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.8)	0 (0.0)	1 (0.1)	3 (0.3)	0 (0.0)	4 (0.4)	0 (0.0)	1 (0.2)	2 (3.9)	0 (0.0)	1 (0.5)	0 (0.0)	3 (0.2)	0 (0.0)
Dermatitis contact	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.4)	2 (0.2)	3 (0.3)	0 (0.0)	3 (0.3)	1 (0.6)	6 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	3 (0.2)	1 (0.2)
Urticaria	0 (0.0)	1 (0.3)	0 (0.0)	3 (0.8)	0 (0.0)	0 (0.0)	2 (0.2)	3 (0.3)	1 (0.3)	6 (0.6)	0 (0.0)	11 (2.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	2 (0.1)	4 (0.9)
Drug hypersensitivity	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)	0 (0.0)	2 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Rhinitis allergic	0 (0.0)	2 (0.6)	1 (0.8)	3 (0.8)	0 (0.0)	0 (0.0)	4 (0.4)	2 (0.2)	1 (0.3)	0 (0.0)	0 (0.0)	4 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	4 (0.3)	2 (0.5)
Dermatitis allergic	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.1)	2 (0.2)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	2 (0.1)	0 (0.0)
Dermatitis atopic	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)
Eczema	1 (0.9)	0 (0.0)	1 (0.8)	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.1)	2 (0.2)	0 (0.0)	0 (0.0)	4 (2.5)	10 (2.1)	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.2)	1 (<0.1)	8 (1.8)
Eye allergy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Injection site dermatitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Injection site hypersensitivity	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	2 (0.2)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Injection site rash	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Allergic bronchitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

	GPGK		GPGI		GPGF		GPGM		GPGH		GPGO		GPGB			GPGL		GPGP
Hypersensitivity Adverse Events	**PBO (N=115)**	**TZP ALL (N=363)**	**PBO (N=120)**	**TZP ALL (N=355)**	**PBO (N=26)**	**TZP ALL (N=85)**	**Ins Glar (N=1000)**	**TZP ALL (N=995)**	**Ins Deg (N=360)**	**TZP ALL (N=1077)**	**Dula 0.75 mg (N=159)**	**TZP ALL (N=477)**	**PBO (N=51)**	**Dula 1.5 mg (N=54)**	**TZP ALL (N=211)**	**Sema 1 mg (N=469)**	**TZP ALL (N=1409)**	**TZP ALL (443)**
Drug eruption	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Skin necrosis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Conjunctivitis allergic	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)	2 (0.5)
Eye oedema	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Periorbital swelling	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
Swelling of eyelid	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Gingival swelling	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Injection site eczema	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Swelling face	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Allergy to vaccine	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Dermatitis infected	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Blood pressure decreased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Vulvovaginal rash	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Bronchospasm	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Throat tightness	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Angioedema	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Hand dermatitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Mucocutaneous rash	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Rash erythematous	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Rash macular	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Rash maculo-papular	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)
Rash pruritic	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.3)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)
Skin reaction	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Shock	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Source: Derived from the Applicant's ISS adsl.xpt and adae datasets, available at: \\CDSESUB1\evsprod\NDA215866\0001\m5\datasets\integrated-database\analysis\adam\datasets, and adapted from the Applicant's Regulatory Response (dated December 31, 2021), pages 1147-1151of 1709, available at: \\CDSESUB1\evsprod\nda215866\0029\m1\us\regulatory-response--fda-midcycle-dec-2021-.pdf
Abbreviations: adj, study size adjusted percentage; Dula, dulaglutide; Ins Deg, insulin degludec; Ins Glar, insulin glargine; IR, incidence rate (100 times the number of subjects experiencing the event divided by PYE); ISS, Integrated Summary of Safety; MedDRA, Medical Dictionary for Regulatory Activities; PBO, placebo; PY, patient-year (sum of time from date of first dose to end of the study); PYE, total patient years at risk (sum of time period from date of first dose to the onset of the event for subjects with the event, and time period from date of first dose to the end of the study for subjects without the even); Sema, semaglutide; and TZP, tirzepatide.

8.5.5. **Injection Site Reactions**

Injection site reactions are common with GLP-1 RA products administered by SC injection.[2,4-11,24-26,237] In the tirzepatide development program, these reactions were identified using a predefined MedDRA queries and review of the electronic case report forms (eCRFs).

In the phase 2/3 trials (AS3), injection site reactions were reported in 151 tirzepatide-treated subjects [adj 2.69%] and 45 subjects [adj 1.86%] in the pooled comparator arms (Table 43). The study size adjusted incidence rates[171,172] in tirzepatide-treated subjects were 2.5 events per 100 PY and 1.84 per 100 PY across the comparator arms for eight of the nine trials (i.e., excluding trial GPGP which did not include a comparator arm). The most common reported PTs in the tirzepatide arms included 'Injection site reaction' (92/5415 subjects [adj 1.57%] vs. 20/2354 subjects [adj 0.9%] in the comparator arms) 'Injection site bruising' (18 subjects [adj 0.33%] vs. 9 subjects [adj 0.38%]) and 'Injection site pruritus' (18 subjects [adj 0.33%] vs. 5 subjects [adj 0.21%]). None of the injection site reactions for tirzepatide-treated subjects were coded as severe or serious, and four subjects discontinued IP due to these events. However, review of the eCRFs revealed one subject (b) (6) who experienced a SAE of cellulitis at the injection site for which he was hospitalized and received antibiotics, and a second subject (b) (6) who discontinued IP due to application site pruritus. In the individual trials, the proportions of tirzepatide-treated subjects experiencing treatment-emergent injection site reactions were higher compared to placebo and semaglutide treatment arms, similar compared to insulin degludec and insulin glargine arms, and lower compared to dulaglutide arms (Table 43).

In the Applicant's pool of phase 3 trials (AS2), a dose-response relationship was observed, with injection site reactions reported in 1.9% (33/1701), 2.7% (46/1702), and 3.5% (60/1716) of tirzepatide-treated subjects randomized to the 5, 10, and 15 mg treatment arms, respectively. Reactions were typically coded as mild to moderate in severity, reported prior to subjects achieving the higher maintenance doses, and occurred approximately six hours to 14 days after an injection (~91% of subjects). Approximately 54% of subjects with injection site reactions had ≥2 events, with 30% experiencing >5 events.

The Applicant proposes to describe the injection site reactions reported in their placebo-controlled pool in Section 6 (Adverse Reactions) of proposed tirzepatide labeling. In these trials, injection site reactions were reported in 3.2% (23/718) of tirzepatide-treated subjects and 0.4% (1/235) of subjects randomized to the placebo arms. I agree with inclusion of this information in labeling as the placebo-controlled pool would reflect a drug effect. However, the observed association of injection site reactions with tirzepatide ADA positivity was not described. This information would be informative to prescribers and should be included in proposed labeling. Please see Section 8.4.9 for further details.

Table 43: Injection Site Reactions — Side-by-Side Comparison of Phase 2/3 Trials (AS3)

	GPGK		GPGI		GPGF		GPGM		GPGH		GPGO		GPGB			GPGL		GPGP
Injection Site Reactions	PBO (N=115)	TZP ALL (N=363)	PBO (N=120)	TZP ALL (N=355)	PBO (N=26)	TZP ALL (N=85)	Ins Glar (N=1000)	TZP ALL (N=995)	Ins Deg (N=360)	TZP ALL (N=1077)	Dula 0.75 mg (N=159)	TZP ALL (N=477)	PBO (N=51)	Dula 1.5 mg (N=54)	TZP ALL (N=211)	Sema 1 mg (N=469)	TZP ALL (N=1409)	TZP ALL (443)
Subjects with Events Across Trials	ALL Comparators: 45/2354 subjects (1.91%) [adj 1.86%] – TZP: 151/5415 subjects (2.79%) [adj 2.69%]																	
Total Subjects — no. (%)	0 (0.0)	11 (3.0)	1 (0.8)	12 (3.4)	1 (3.8)	6 (7.1)	16 (1.6)	17 (1.7)	6 (1.7)	15 (1.4)	16 (10.1)	28 (5.9)	0 (0.0)	4 (7.4)	6 (2.8)	1 (0.2)	43 (3.1)	13 (2.9)
Total Events — no.	0	52	1	162	1	7	31	30	6	52	166	385	0	8	7	1	185	107
PY	92.2	292.7	100.9	290.4	7.2	24.5	1566.4	1590.8	376	1125.1	168	502.6	28.1	30.1	116.2	392.7	1179.7	460.4
PYE	92.2	285.5	100.1	283	7	23.3	1544.7	1567.3	371.3	1112.8	157.2	479.4	28.1	28	113.5	392.2	1155.6	449.9
IR per 100 PY	0	3.85	1	4.24	14.27	25.72	1.04	1.08	1.62	1.35	10.18	5.84	0	14.28	5.28	0.25	3.72	2.89
MedDRA PT																		
Injection site bruising	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.8)	1 (1.2)	4 (0.4)	4 (0.4)	1 (0.3)	0 (0.0)	1 (0.6)	3 (0.6)	0 (0.0)	2 (3.7)	3 (1.4)	0 (0.0)	7 (0.5)	0 (0.0)
Injection site reaction	0 (0.0)	10 (2.8)	0 (0.0)	8 (2.3)	0 (0.0)	4 (4.7)	4 (0.4)	4 (0.4)	1 (0.3)	7 (0.6)	12 (7.5)	16 (3.4)	0 (0.0)	2 (3.7)	2 (0.9)	1 (0.2)	30 (2.1)	11 (2.5)
Injection site erythema	0 (0.0)	2 (0.6)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.3)	1 (0.3)	4 (0.4)	1 (0.6)	6 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.3)	0 (0.0)
Injection site pain	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)	1 (1.2)	3 (0.3)	3 (0.3)	2 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.9)	0 (0.0)	0 (0.0)	1 (0.2)
Injection site pruritus	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	2 (0.2)	3 (0.3)	0 (0.0)	3 (0.3)	3 (1.9)	7 (1.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.3)	0 (0.0)
Injection site dermatitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Injection site haemorrhage	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Injection site hypersensitivity	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	2 (0.2)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Injection site rash	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Administration site reaction	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Injection site atrophy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Injection site discomfort	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Injection site eczema	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Injection site haematoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

	GPGK		GPGI		GPGF		GPGM		GPGH		GPGO		GPGB			GPGL		GPGP
Injection Site Reactions	**PBO (N=115)**	**TZP ALL (N=363)**	**PBO (N=120)**	**TZP ALL (N=355)**	**PBO (N=26)**	**TZP ALL (N=85)**	**Ins Glar (N=1000)**	**TZP ALL (N=995)**	**Ins Deg (N=360)**	**TZP ALL (N=1077)**	**Dula 0.75 mg (N=159)**	**TZP ALL (N=477)**	**PBO (N=51)**	**Dula 1.5 mg (N=54)**	**TZP ALL (N=211)**	**Sema 1 mg (N=469)**	**TZP ALL (N=1409)**	**TZP ALL (443)**
Injection site induration	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Injection site irritation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)
Injection site mass	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Injection site oedema	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Injection site swelling	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Vessel puncture site reaction	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Source: Derived from the Applicant's ISS adsl.xpt and adae datasets, available at: \\CDSESUB1\evsprod\NDA215866\0001\m5\datasets\integrated-database\analysis\adam\datasets, and adapted from the Applicant's Regulatory Response (dated December 31, 2021), pages of 1709, available at: \\CDSESUB1\evsprod\nda215866\0029\m1\us\regulatory-response--fda-midcycle-dec-2021-.pdf
Abbreviations: adj, study size adjusted percentage; AS3, Analysis Set 3 (pool of 9 phase 2/3 trials); Dula, dulaglutide; Ins Deg, insulin degludec; Ins Glar, insulin glargine; IR, incidence rate (100 times the number of subjects experiencing the event divided by PYE); ISS, Integrated Summary of Safety; MedDRA, Medical Dictionary for Regulatory Activities; PBO, placebo; PY, patient-year (sum of time from date of first dose to end of the study); PYE, total patient years at risk (sum of time period from date of first dose to the onset of the event for subjects with the event, and time period from date of first dose to the end of the study for subjects without the even); Sema, semaglutide; and TZP, tirzepatide.

8.5.6. Renal Safety

Diabetes remains a leading cause of kidney failure,[48] and the prevalence of chronic kidney disease (CKD) among adults diagnosed with diabetes in the US is approximately 20%.[242] There have been postmarketing reports of acute kidney injury and worsening of chronic renal failure, sometimes requiring hemodialysis, and often associated with nausea, vomiting, diarrhea, or dehydration with the use of GLP-1 RAs products. Therefore, product labeling for most GLP-1 RAs includes a Warnings and Precautions of renal impairment[5,6] or acute kidney injury,[2-4,7-11,24-26] and prescribers are cautioned to monitor renal function in patients reporting severe adverse GI reactions with and without renal impairment.

The Applicant noted that their repeat-dose toxicology studies in rats and monkeys (with exposures up to six months) did not show that tirzepatide directly affected urinalysis parameters or kidney histopathology. Additionally, in humans, the PKs of tirzepatide did not appear to be altered based on the PK data from trial GPGG and the population PK data across the phase 3 trials.

In the placebo-controlled pool (AS1), mean reductions in eGFR from baseline at Week 40 were higher in the tirzepatide arms compared to the placebo arm, but these differences were not clinically meaningful. A dose-response relationship was not observed (Table 44). A graphical depiction of the eGFR changes in these trials over time is presented in Figure 14. The proportions of subjects who maintained their eGFR category (73.2% vs. 69.7%) or shifted to a lower eGFR category (24.2% vs. 27.8%) were similar between placebo and tirzepatide treatment arms, respectively.

Table 44: Mean Changes in eGFR (mL/min/1.73 m^2) from Baseline at Week 40 (AS1)

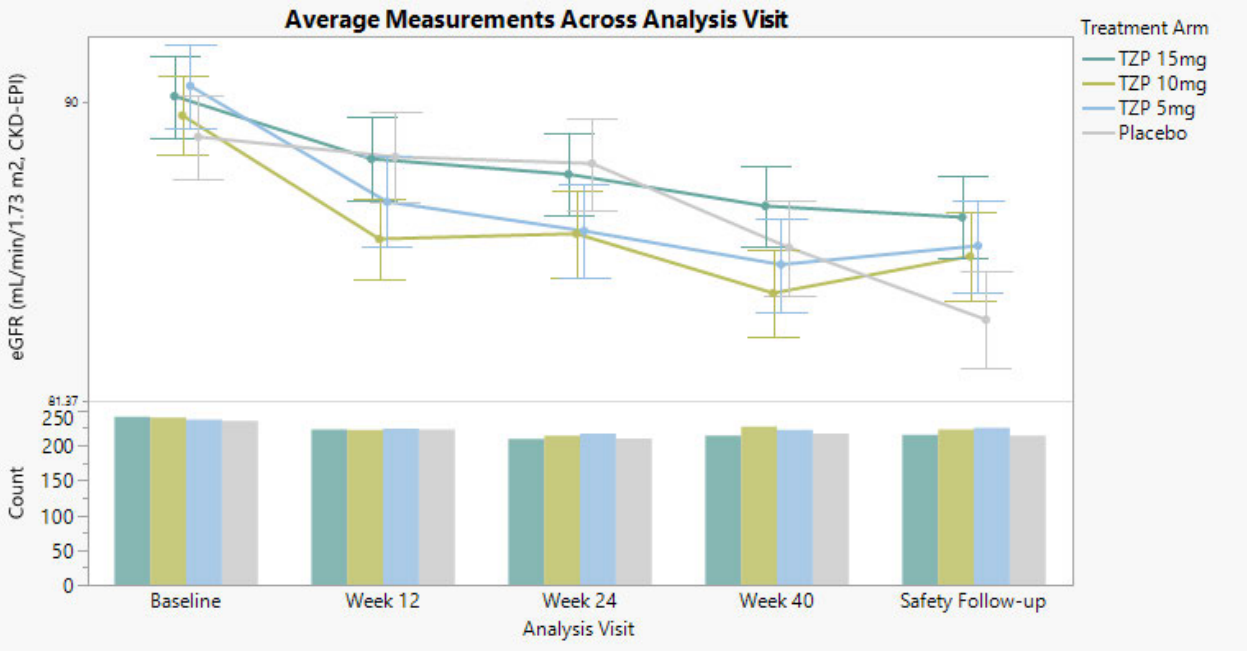
eGFR CKD-EPI	mL/min/1.73 m^2							
	TZP 5 mg (N=234)		TZP 10 mg (N=234)		TZP 15 mg (N=232)		Placebo (N=228)	
	40 Weeks	SFU	40 Weeks	SFU	40 Weeks	SFU	40 Weeks	SFU
Baseline – mean (SE)	90.1 (1.22)		89.3 (1.22)		90.1 (1.23)		88.7 (1.24)	
Change from baseline – mean (SE)	-4.9 (0.63)	-4.2 (0.63)	-4.9 (0.62)	-3.8 (0.63)	-3.5 (0.63)	-3.0 (0.64)	-3.2 (0.63)	-4.8 (0.64)
Change difference from placebo – mean (95% CI)	-1.6 (-3.4, 0.1)	0.6 (-1.1, 2.4)	-1.7 (-3.4, 0.1)	1.1 (-0.7, 2.8)	-0.3 (-2.0, 1.5)	1.9 (0.1, 3.6)	N/A	N/A

Source: Adapted from the Applicant's ISS, pages 2698, and 2701-2702 of 7807, available at: \\CDSESUB1\evsprod\nda215866\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\type-2-diabetes-mellitus\5353-rep-analys-data-more-one-stud\iss\iss-46-integrated-sum-of-safety--t2dm-.pdf

Abbreviations: CI, confidence interval; CKD-EPI, Chronic Kidney Disease-Epidemiology; eGFR, estimated glomerular filtration rate; MMRM, mixed-model repeated measures; N, number of subjects who were randomized and received at least 1 dose of study drug and with baseline and at least one postbaseline value; N/A = not applicable; SFU = safety follow-up; and TZP = tirzepatide.

Note: MMRM analysis. Only subjects with non-missing baseline value and at least 1 non-missing postbaseline value of the response variable were included in the analysis.
Note: Shown are the least-squares means.

Figure 14: Estimated Glomerular Filtration Rate Change Over Time (AS1)



Source: Derived from the ISS adsl.xpt and adlb.xpt datasets, available at: \\CDSESUB1\evsprod\NDA215866\0007\m5\datasets\integrated-database\analysis\adam\datasets
Abbreviations: AS1, Analysis Set 1 (pool of 2 placebo-controlled phase 3 trials); CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; ISS, Integrated Summary of Safety; and TZP, tirzepatide.
Each error bar is constructed using 1 standard error from the mean.

The Applicant also identified relevant renal AEs using the 'Acute renal failure' and 'Chronic kidney disease' SMQs (narrow). Across their phase 2/3 trials (AS3), renal AEs were reported in 45 subjects [adj 1.4%] in the comparator arms and 66 tirzepatide-treated subjects [adj 1.4%]. A dose-response relationship was not obvious (Table 45). The most common reported PTs in subjects randomized to the tirzepatide arms were 'Chronic kidney disease' (n=23), 'Acute kidney injury' (n=18), and 'Renal impairment' (n=18). These AEs were balanced between tirzepatide and comparator treatment arms. The study size adjusted incidence rates[171,172] of renal events in tirzepatide-treated subjects were 1.33 events per 100 PY and 1.41 per 100 PY across the comparator arms for eight of the nine trials (i.e., excluding trial GPGP which did not include a comparator arm). Serious renal AEs were reported in 7 tirzepatide-treated subjects [adj 0.16%] and 9 subjects [adj 0.26% adj] in the comparator arms, without imbalances between arms by individual reported PTs.

Proposed tirzepatide labeling includes AKI as a Warnings and Precautions (Section 5). Additionally, in Section 8.6 (Renal Impairment), it states that no dosage adjustment of tirzepatide is recommended for patients with renal impairment and that in subjects with renal impairment,

including end-stage renal disease (ESRD), no change in tirzepatide PKs was observed. The Clinical Pharmacology review team felt that this information was acceptable for labeling. I concur that this information is appropriate for Sections 5 and 8.6, respectively.

Table 45: Renal Adverse Events — Side-by-Side Comparison of Phase 2/3 Trials (AS3)

	GPGK		GPGI		GPGF		GPGM		GPGH		GPGO		GPGB			GPGL		GPGP
Renal Disorders SMQs	PBO (N=115)	TZP ALL (N=363)	PBO (N=120)	TZP ALL (N=355)	PBO (N=26)	TZP ALL (N=85)	Ins Glar (N=1000)	TZP ALL (N=995)	Ins Deg (N=360)	TZP ALL (N=1077)	Dula 0.75 mg (N=159)	TZP ALL (N=477)	PBO (N=51)	Dula 1.5 mg (N=54)	TZP ALL (N=211)	Sema 1 mg (N=469)	TZP ALL (N=1409)	TZP ALL (443)
Subjects with Events Across Trials	ALL Comparators: 45/2354 subjects (1.91%) [adj 1.41%] — TZP: 66/5415 subjects (1.22%) [adj 1.37%]																	
Total Subjects — no. (%)	0 (0.0)	1 (0.3)	1 (0.8)	7 (2.0)	0 (0.0)	0 (0.0)	35 (3.5)	28 (2.8)	5 (1.4)	14 (1.3)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	3 (0.6)	13 (0.9)	2 (0.5)
Total Events — no.	0	1	1	7	0	0	38	33	7	14	1	0	0	0	1	3	13	2
PY	92.2	292.7	100.9	290.4	7.2	24.5	1566.4	1590.8	376	1125.1	168	502.6	28.1	30.1	116.2	392.7	1179.7	460.4
PYE	92.2	292.7	100.9	288.2	7.2	24.5	1541	1566.5	373.4	1116.6	167.9	502.6	28.1	30.1	115.8	391.7	1174	459.4
IR per 100 PY	0	0.34	0.99	2.43	0	0	2.27	1.79	1.34	1.25	0.6	0	0	0	0.86	0.77	1.11	0.44
MedDRA PT																		
Chronic kidney disease	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.8)	0 (0.0)	0 (0.0)	10 (1.0)	12 (1.2)	4 (1.1)	5 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	3 (0.2)	0 (0.0)
Acute kidney injury	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	12 (1.2)	8 (0.8)	1 (0.3)	6 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	2 (0.1)	0 (0.0)
Renal impairment	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	10 (1.0)	7 (0.7)	0 (0.0)	1 (<0.1)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	6 (0.4)	2 (0.5)
Renal failure	0 (0.0)	0 (0.0)	1 (0.8)	2 (0.6)	0 (0.0)	0 (0.0)	3 (0.3)	3 (0.3)	1 (0.3)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Hyperparathyroidism secondary	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Nephrosclerosis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
End stage renal disease	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)

Source: Derived from the Applicant's ISS adsl.xpt and adae datasets, available at: \\CDSESUB1\evsprod\NDA215866\0001\m5\datasets\integrated-database\analysis\adam\datasets, and adapted from the Applicant's Regulatory Response (dated December 31, 2021), page 1139 of 1709, available at: \\CDSESUB1\evsprod\nda215866\0029\m1\us\regulatory-response--fda-midcycle-dec-2021-.pdf
Abbreviations: adj, study size adjusted percentage; Dula, dulaglutide; Ins Deg, insulin degludec; Ins Glar, insulin glargine; IR, incidence rate (100 times the number of subjects experiencing the event divided by PYE); ISS, Integrated Summary of Safety; MedDRA, Medical Dictionary for Regulatory Activities; PBO, placebo; PY, patient-year (sum of time from date of first dose to end of the study); PYE, total patient years at risk (sum of time period from date of first dose to the onset of the event for subjects with the event, and time period from date of first dose to the end of the study for subjects without the even); Sema, semaglutide; and TZP, tirzepatide.

8.5.7. Gastrointestinal Adverse Events

Gastrointestinal AEs are common with all GLP-1 RA products.[2-11,24-26] In both the phase 3 placebo-controlled pool (AS1; Table 29), and across the Applicant's phase 3 trials (AS2; Table 30), GI AEs occurred in ≥5% of tirzepatide-treated subjects, of which nausea diarrhea, dyspepsia, vomiting, and constipation were the most common reported events. These GI AEs occurred most often during the dose-escalation period. A dose-response relationship was observed for AEs of nausea, vomiting, and diarrhea, and temporary and permanent discontinuations of IP due to GI AEs, with approximately 2.1% (108/5119) of tirzepatide-treated subjects experiencing at least one serious or severe GI AE (Table 46). Additionally, 8.6%, 11.4%, and 14.5% of subjects randomized to the tirzepatide 5, 10, and 15 mg arms, respectively, required concomitant medication for treatment-emergent nausea, vomiting, or diarrhea. Proposed product labeling will include a Warnings and Precaution with the use of tirzepatide in patients with severe GI disease, and an association with severe or serious GI-related AEs. I agree with inclusion of this information in proposed labeling.

Table 46: Tirzepatide-Treated Subjects with Gastrointestinal Disorder-Related AEs (AS2)

	TZP 5 mg (N=1701)	TZP 10 mg (N=1702)	TZP 15 mg (N=1716)	All TZP (N=5119)
Subjects completing the trial — no. (%)	**1602 (94.2)**	**1592 (93.5)**	**1600 (93.2)**	**4794 (93.7)**
Subjects completing the trial and treatment — no. (%)[a]	1514 (89.0)	1466 (86.1)	1437 (83.7)	4417 (86.3)
Subjects completing the trial on the planned dose (including subjects who discontinued IP) — no. (%)[b]	1591 (93.5)	1418 (83.3)	1337 (77.9)	4346 (84.9)
Subjects completing the trial on the planned dose (excluding subjects who discontinued IP) — no. (%)[c]	1513 (88.9)	1361 (80.0)	1293 (75.3)	4167 (81.4)
Subjects experiencing GI disorder AEs — no. (%)	647 (38.0)	746 (43.8)	837 (48.8)	2230 (43.6)
Subjects experiencing severe/serious GI disorder AEs — no. (%)	40 (2.4)	39 (2.3)	29(1.7)	108 (2.1)
Subjects experiencing nausea, vomiting, or diarrhea — no. (%)	377 (22.2)	496 (29.1)	571 (33.3)	1444 (28.2)
Subjects not able to achieve the planned dose due to GI disorder AEs — no. (%)[d]	7 (0.4)	107 (6.3)	181 (10.6)	295 (5.8)
Subjects who permanently discontinue IP due to GI disorder AEs — no. (%)	55 (3.2)	74 (4.4)	88 (5.1)	217 (4.2)
Subjects who permanently discontinued IP due to GI disorder AEs prior to receiving planned dose — no. (%)	6 (0.4)	46 (2.7)	59 (3.4)	111 (2.2)
Subjects who permanently discontinued IP due to nausea, vomiting or diarrhea — no. (%)	34 (2.0)	50 (2.9)	61 (3.6)	145 (2.8)
Subjects who permanently discontinued IP due to nausea, vomiting or diarrhea prior to receiving planned dose — no. (%)	2 (0.1)	33 (1.9)	42 (2.5)	77 (1.5)
Subjects with dose interruptions due to GI disorder AEs — no. (%)[e]	54 (3.2)	77 (4.5)	92 (5.4)	223 (4.4)
Number of temporary dose interruptions due to GI disorder AEs — mean (SD)[f]	1.4 (1.4)	1.5 (1.9)	1.2 (1.1)	1.4 (1.5)
Number of temporary dose interruptions due to GI disorder AEs — median (IQR)[f]	1.0 (1, 1)	1.0 (1, 2)	1.0 (1, 1)	1.0 (1, 1)
Duration (weeks) of temporary dose interruptions for GI disorder AEs — mean (SD)[g]	1.8 (1.4)	2.3 (4.2)	2.7 (6.2)	2.3 (4.6)
Duration (weeks) of temporary dose interruptions for GI disorder AEs — median (IQR)[g]	1.0 (1, 2)	1.0 (1, 2)	1.0 (1, 2)	1.0 (1, 2)
Subjects unable to up-titrate IP as planned due to GI disorder AEs — no. (%)[h]	11 (0.7)	113 (6.6)	190 (11.1)	314 (6.1)
Subjects requiring dose de-escalations due to GI disorder AEs — no. (%)	0	105 (12.6)	131 (15.5)	236 (9.4)
Subjects requiring concomitant medication for treatment-emergent nausea, vomiting or diarrhea	146 (8.6)	194 (11.4)	249 (14.5)	589 (11.5)
Subjects requiring concomitant medication(s) for treatment-emergent diarrhea — no. (%)	79 (4.6)	88 (5.2)	92 (5.4)	259 (5.1)
Subjects requiring concomitant medication(s) for treatment-emergent nausea/vomiting — no. (%)	81 (4.8)	117 (6.9)	176 (10.3)	374 (7.3)

Source: Adapted from the Applicant's Regulatory Response (dated January 12, 2022), and derived from the ISS adsl.xpt, adae.xpt and adcm.xpt datasets, available at: \\CDSESUB1\evsprod\NDA215866\0033
\\CDSESUB1\evsprod\NDA215866\0001\m5\datasets
Abbreviations: AE, adverse event; AS2, Analysis Set 2 (pool of 7 phase 3 trials); eCRF, electronic case report form; GI, gastrointestinal; IP, investigational product; No., number; SD, standard deviation; and TZP, tirzepatide.

[a] Only included subjects who completed both IP and trial (including the safety follow-up visit).
[b] Subjects who prematurely discontinued IP and completed study with final administered dose same as planned dose were also included.
[c] Only included subjects who completed both IP and trial with final dose same as planned dose.
[d] Subject considered "not able to achieve the planned dose" if the max dose of IP received was less than the planned dose. Not able to achieve planned dose" was deemed to be "due to GI disorder AE" if any of the following 3 conditions was met: 1) Study treatment discontinued due to GI AE prior to reaching planned dose; 2) Study treatment de-escalated; or 3) GI AE occurred during escalation period with one of the following actions taken by the investigator: i) drug withdrawn, ii) drug interrupted, or iii) dose reduced, as reported in eCRF.
[e] "Subjects with dose interruptions due to GI disorder AEs" was defined as subjects with GI AE occurred with the action taken by the investigator of 'drug interrupted', as reported in eCRF.
[f] Number of dose interruptions for subjects included in Row # 8 was calculated. An interruption was defined as either missing a single dose or missing multiple doses consecutively. Multiple dose interruptions may be identified for the same patient.
[g] Duration (weeks) per interruptions included in Row # 9 is provided. Duration of interruption was calculated as the number of missing doses in an interruption since tirzepatide injections were administered weekly.
[h] "Unable to up-titrate as scheduled" was defined as subjects meeting either of the following criteria: 1) Subjects who never reached planned maintenance dose; or 2) Subjects for whom the actual dose (including missing) was less than the scheduled dose for the week when each dose escalation was scheduled to occur per protocol. Specifically, i) Subjects randomized to 5 mg – 5th dose, ii) Subjects randomized to 10 mg – 5th, 9th, and 13th dose, and iii) Subjects randomized to 15 mg – 5th, 9th, 13th, 17th, and 21st dose. The subjects "unable to up-titrate as scheduled" meeting any of the following were deemed to be related to GI disorder: 1) discontinuing IP due to GI AE during dose escalation period; 2) de-escalated IP during dose escalation period (applicable only to trials GPGH, GPGM, and GPGP); or 3) GI AE occurred during dose escalation period with one of the following actions taken by the investigator: i) drug withdrawn, ii) drug interrupted, or iii) dose reduced, as reported in eCRF.
[i] Dose de-escalation to a lower maintenance dose was only permitted in trial GPGH, GPGM, and GPGP. Subjects could de-escalate their dose only once and were not allowed to re-escalate. Percentages are reflective of the 3 trials that allowed de-escalation.

8.5.8. **Acute Gallbladder Disorders**

Patients with T2D have an increased risk for gallbladder-related disorders, including cholelithiasis and cholecystitis.[243,244] Additionally, diabetic patients undergoing cholecystectomy for acute cholecystitis may develop more severe complications and/or have longer hospital stays.[245,246] Rapid weight loss also is a risk factor for cholelithiasis,[247-249] and several GLP-1 RA products approved for chronic weight management also include a Warnings and Precautions of acute gallbladder disease (e.g., cholelithiasis and cholecystitis).[4,6] A meta-analysis that included 90 randomized controlled trials (RCTs) of T2D patients receiving GLP-1 RAs (17,232 GLP-1 RA-treated subjects vs. 14,872 subjects in the comparator arms) reported an increase risk of cholelithiasis (Mantel-Haenszel odds ratio [MH-OR] 1.30, 95% CI: 1.01, 1.68, p=0.041).[250] Similarly, a more recent meta-analysis of 76 randomized controlled trials (RCTs) involving 103,371 patients found that use of GLP-1 RAs was associated with increased risk of gallbladder (e.g., cholelithiasis, and cholecystitis) or biliary diseases (relative risk [RR] 1.37, 95% CI: 1.23, 1.52), especially when used at higher doses (RR 1.56, 95% CI: 1.36, 1.78), for longer durations (RR 1.40, 95% CI: 1.26, 1.56), and for weight loss (RR 2.29, 95% CI: 1.64, 3.18).[251]

In the placebo-controlled trials (AS1), treatment-emergent gallbladder disease was reported in 0.6% (4/718) of tirzepatide-treated subjects ('Cholelithiasis', n=2; 'Biliary colic', n=1; and 'Cholecystectomy', n=1), with no events reported in the 235 subjects in the placebo arm.

Across the Applicant's phase 2/3 trials (AS3), gallbladder-related AEs were reported in 55 tirzepatide-treated subjects [adj 1.1%] and 18 subjects [adj 0.6%] in the pooled comparator arms (Table 47). Seventeen of the 55 tirzepatide-treated subjects experienced severe/serious events.

The Applicant reported that AEs associated with weight loss were not associated with gallbladder-related events across these trials. Cholelithiasis was the most frequently reported event and occurred in 33 [adj 0.6%] and 6 [adj 0.2%] subjects in the pooled tirzepatide and comparator arms, respectively. The study size adjusted incidence rates[171,172] of gallbladder-related AEs in tirzepatide-treated subjects were 0.99 events per 100 patient-years (PY) and 0.58 per 100 PY across the comparator arms for eight of the nine trials (i.e., excluding trial GPGP which did not include a comparator arm). The Applicant felt that the results do not suggest tirzepatide increases the risk of gallbladder disease in patients with T2D. However, higher numbers of tirzepatide-treated subjects experienced these events. Additionally, across the five global phase 3 trials, tirzepatide was associated with significant comparator-subtracted reductions in body weight in T2D subjects for all treatment arms (i.e., 6.3-7.6 kg for the 5 mg, 7-9.6 kg for the 10 mg, and 7.8-12.2 kg for the 15 mg arms, respectively), with 15% reductions in total body weight reported in 6.9-13.7%, 15.7-25.4%, and 22.9%-25.8% of subjects randomized to the tirzepatide 5, 10, and 15 mg arms, respectively within 40-52 weeks.

Since acute gallbladder disease is included in the Warnings and Precautions section of labeling for GLP-1 RA product associated with substantial or relatively rapid weight loss,[4,6] and cases of acute gallbladder disorders have been identified in FAERs reports and published literature with the use of these products, the Division had decided to include acute gallbladder disease as a Warnings and Precautions for proposed tirzepatide and GLP-1 RA class-wide product labeling.

On March 28, 2022, a Safety Labeling Change (SLC) Notification was issued informing Sponsors of GLP-1 RA products that the Agency has become aware of postmarketing cases in FAERS and the medical literature of acute events of gallbladder disease, and that GLP-1 RAs represent a class of products that have the potential for the same serious risk of acute gallbladder disease. This information is considered “new safety information” as defined in section 505-1(b)(3) of the FDCA. Therefore, in accordance with Section 505(o)(4) of the FDCA, this safety information should be included in the labeling of GLP-1 RA products. Proposed tirzepatide labeling will conform with the recommended language included in the SLC Notification.

Table 47: Acute Gallbladder-Related Adverse Events — Side-by-Side Comparison of Phase 2/3 Trials (AS3)

	GPGK		GPGI		GPGF		GPGM		GPGH		GPGO		GPGB			GPGL		GPGP
Gallbladder Disorders SMQs	PBO (N=115)	TZP ALL (N=363)	PBO (N=120)	TZP ALL (N=355)	PBO (N=26)	TZP ALL (N=85)	Ins Glar (N=1000)	TZP ALL (N=995)	Ins Deg (N=360)	TZP ALL (N=1077)	Dula 0.75 mg (N=159)	TZP ALL (N=477)	PBO (N=51)	Dula 1.5 mg (N=54)	TZP ALL (N=211)	Sema 1 mg (N=469)	TZP ALL (N=1409)	TZP ALL (443)
Subjects with Events Across Trials	ALL Comparators: 18/2354 subjects (0.8%) [adj 0.6%] and TZP: 55/5415 subjects (1.0%) [adj 1.1%]																	
Total Subjects — no. (%)	0 (0.0)	2 (0.6)	0 (0.0)	2 (0.6)	0 (0.0)	0 (0.0)	13 (1.3)	14 (1.4)	1 (0.3)	10 (0.9)	0 (0.0)	4 (0.8)	0 (0.0)	1 (1.9)	4 (1.9)	3 (0.6)	15 (1.1)	4 (0.9)
Total Events — no.	0	2	0	2	0	0	17	16	1	11	0	6	0	1	4	4	20	4
PY	92.2	292.7	100.9	290.4	7.2	24.5	1566.4	1590.8	376	1125.1	168	502.6	28.1	30.1	116.2	392.7	1179.7	460.4
PYE	92.2	292.4	100.9	289.3	7.2	24.5	1553.6	1576.5	375.7	1119.3	168	500.4	28.1	29.9	115.6	391.6	1172.1	459
IR per 100 PY	0	0.68	0	0.69	0	0	0.84	0.89	0.27	0.89	0	0.8	0	3.35	3.46	0.77	1.28	0.87
MedDRA PT																		
Cholelithiasis	0 (0.0)	2 (0.6)	0 (0.0)	2 (0.6)	0 (0.0)	0 (0.0)	13 (1.3)	14 (1.4)	1 (0.3)	10 (0.9)	0 (0.0)	4 (0.8)	0 (0.0)	1 (1.9)	4 (1.9)	3 (0.6)	15 (1.1)	4 (0.9)
Cholecystitis	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	4 (0.4)	5 (0.5)	0 (0.0)	4 (0.4)	0 (0.0)	3 (0.6)	0 (0.0)	0 (0.0)	3 (1.4)	2 (0.4)	12 (0.9)	4 (0.9)
Cholecystitis acute	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	6 (0.6)	2 (0.2)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.9)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Bile duct stone	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.3)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	5 (0.4)	0 (0.0)
Biliary colic	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cholecystitis chronic	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (<0.1)	0 (0.0)
Cholestasis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.1)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hyperbilirubinaemia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.3)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Porcelain gallbladder	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.1)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Biliary dilatation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cholangitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cholangitis acute	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Malignant biliary obstruction	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Source: Derived from the Applicant's ISS adsl.xpt and adae.xpt datasets, available at: \\CDSESUB1\evsprod\NDA215866\0001\m5\datasets\integrated-database\analysis\adam\datasets and adapted from the Applicant's Regulatory Response (dated December 31, 2021), page 1158 of 1709, available at: \\CDSESUB1\evsprod\nda215866\0029\m1\us\regulatory-response--fda-midcycle-dec-2021-.pdf
Abbreviations: adj, study size adjusted percentage; Dula, dulaglutide; Ins Deg, insulin degludec; Ins Glar, insulin glargine; IR, incidence rate (100 times the number of subjects experiencing the event divided by PYE); ISS, Integrated Summary of Safety; MedDRA, Medical Dictionary for Regulatory Activities; PBO, placebo; PY, patient-year (sum of time from date of first dose to end of the study); PYE, total patient years at risk (sum of time period from date of first dose to the onset of the event for subjects with the event, and time period from date of first dose to the end of the study for subjects without the even); Sema, semaglutide; and TZP, tirzepatide.

8.5.9. **Dehydration-Related Adverse Events**

The labeling of GLP-1 RA products includes Warnings and Precautions of the risk of acute kidney injury/renal impairment associated with nausea, vomiting, diarrhea, or dehydration/ hypovolemia.[2-11,24-26] Some of these events have been reported in patients without known underlying renal disease. Prescribers are cautioned to advise patients of the potential risk of dehydration due to severe adverse GI reactions and take precautions to avoid fluid depletion (e.g., monitor renal function when initiating or escalating doses in patients reporting severe adverse GI reactions).

In the tirzepatide clinical development program, dehydration AEs were identified using the MedDRA 'Dehydration' SMQ (narrow). Across the Applicant's phase 2/3 trials (AS3), dehydration AEs (Table 48) were relatively limited and included six subjects [adj 0.21%], all coded as 'Dehydration' in the comparator arms and 18 tirzepatide-treated subjects [adj 0.35%]; 16 coded as 'Dehydration and 2 as 'Hypovolaemia'). The study size adjusted incidence rates[171,172] of dehydration-related AEs in tirzepatide-treated subjects were 0.32 events per 100 PY and 0.20 per 100 PY across the comparator arms for eight of the nine trials (i.e., excluding trial GPGP which did not include a comparator arm). Nine of the 18 tirzepatide-treated subjects were in the tirzepatide 15 mg arm, five in the 5 mg arm, three in the 10 mg arm, and one in the 12 mg arm (phase 2 trial GPGB). Three tirzepatide-treated subjects (two receiving 5 mg and one 15 mg) and one subject in the comparator arm (receiving insulin glargine) had AEs coded as serious (all reported as dehydration). Review of the clinical narratives for the three subjects randomized to tirzepatide (i.e., Subjects (b) (6) did not show that these SAEs were related to gastrointestinal AEs. Additionally, the Applicant reported that 12 of 16 subjects with dehydration-related AEs in their phase 3 trials (AS2) had chronic kidney disease at baseline, eight had acute infections prior to events, five acute renal failure AEs (identified by SMQ), and seven had GI AEs within 30 days (one of which also had an AE of AKI); Subject (b) (6)). A brief narrative of this subject is as follows:

- **Subject** (b) (6) a 71-year-old White female with T2D randomized to the tirzepatide 10 mg treatment arm, experienced an SAE of diarrhea on Day 373. On Day 372, she was hospitalized with symptoms of shortness of breath, fatigue, and loose diarrhea. While hospitalized (Day 377), she developed nonserious AEs of dehydration and AKI (identified by lab work which was not provided), both classified as moderate in severity. All three AEs were reported as resolved on Day 379, and she was discharged from the hospital that same day. Her relevant medical history included colon cancer and partial colectomy, and she had a preexisting history of intermittent diarrhea since 1980. Her eGFR at baseline was 72 mL/min/1.73 m^2. The etiology for the diarrhea was unknown but suspected to be viral. Ova and parasite screening were negative, while lactoferrin levels were positive (suggestive of an inflammatory cause for the diarrhea). The subject received her last dose of IP on Day 372 and completed the trial on Day 420. It was reported that the cause of AKI was due to dehydration, which was caused by diarrhea.

The investigator classified the SAE of diarrhea as not related to IP.

The subject's preexisting condition (chronic intermittent diarrhea) and limited laboratory data available at the time of hospitalization make it difficult to determine a causal association with tirzepatide with the AEs of diarrhea, dehydration, and AKI, but it is possible that tirzepatide may have contributed to these events.

The Applicant proposes to include severe GI disease AKI as Warnings and Precautions and include statements cautioning prescribers that GI adverse reactions (e.g., nausea, vomiting, and diarrhea) may lead to dehydration and cause renal impairment, including AKI. I concur that this information should be included in Section 5 of proposed labeling.

Table 48: Dehydration-Related Adverse Events — Side-by-Side Comparison of Phase 2/3 Trials (AS3)

	GPGK		GPGI		GPGF		GPGM		GPGH		GPGO		GPGB			GPGL		GPGP
Dehydration SMQ	**PBO (N=115)**	**TZP ALL (N=363)**	**PBO (N=120)**	**TZP ALL (N=355)**	**PBO (N=26)**	**TZP ALL (N=85)**	**Ins Glar (N=1000)**	**TZP ALL (N=995)**	**Ins Deg (N=360)**	**TZP ALL (N=1077)**	**Dula 0.75 mg (N=159)**	**TZP ALL (N=477)**	**PBO (N=51)**	**Dula 1.5 mg (N=54)**	**TZP ALL (N=211)**	**Sema 1 mg (N=469)**	**TZP ALL (N=1409)**	**TZP ALL (443)**
Subjects with Events Across Trials	**ALL Comparators: 6/2354 subjects (0.25%) [adj 0.21%] — TZP: 18/5415 subjects (0.33%) [adj 0.35%]**																	
Total Subjects — no. (%)	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**1 (1.2)**	**4 (0.4)**	**6 (0.6)**	**0 (0.0)**	**4 (0.4)**	**0 (0.0)**	**1 (0.2)**	**0 (0.0)**	**0 (0.0)**	**1 (0.5)**	**2 (0.4)**	**3 (0.2)**	**2 (0.5)**
Total Events — no.	**0**	**0**	**0**	**0**	**0**	1	4	6	**0**	4	**0**	1	**0**	**0**	1	2	3	2
PY	92.2	292.7	100.9	290.4	7.2	24.5	1566.4	1590.8	376.0	1125.1	168.0	502.6	28.1	30.1	116.2	392.7	1179.7	460.4
PYE	92.2	292.7	100.9	290.4	7.2	24.2	1564.2	1585.8	376.0	1122.6	168.0	501.6	28.1	30.1	115.8	391.4	1178.6	458.8
IR per 100 PY	0.00	0.00	0.00	0.00	0.00	4.12	0.26	0.38	0.00	0.36	0.00	0.20	0.00	0.00	0.86	0.51	0.25	0.44
MedDRA PT																		
Dehydration	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.2)	4 (0.4)	4 (0.4)	0 (0.0)	4 (0.4)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.5)	2 (0.4)	3 (0.2)	2 (0.5)
Hypovolaemia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Source: Derived from the Applicant's ISS adsl.xpt and adae datasets, available at: \\CDSESUB1\evsprod\NDA215866\0001\m5\datasets\integrated-database\analysis\adam\datasets, and adapted from the Applicant's Regulatory Response (dated December 31, 2021), pages 1155-1156 of 1709, available at: \\CDSESUB1\evsprod\nda215866\0029\m1\us\regulatory-response--fda-midcycle-dec-2021-.pdf
Abbreviations: adj, study size adjusted percentage; Dula, dulaglutide; Ins Deg, insulin degludec; Ins Glar, insulin glargine; IR, incidence rate (100 times the number of subjects experiencing the event divided by PYE); ISS, Integrated Summary of Safety; MedDRA, Medical Dictionary for Regulatory Activities; PBO, placebo; PY, patient-year (sum of time from date of first dose to end of the study); PYE, total patient years at risk (sum of time period from date of first dose to the onset of the event for subjects with the event, and time period from date of first dose to the end of the study for subjects without the even); Sema, semaglutide; and TZP, tirzepatide.

8.5.10. **Diabetic Retinopathy Complications**

Diabetes remains a leading cause of adult-onset blindness,[49,50] The ADA currently recommends that glycemic control should be optimized to reduce the risk or slow the progression of diabetic retinopathy.[27] However, due to concerns that rapid improvement in glycemic control may be associated with a temporary worsening of diabetic retinopathy[252] and an increase in diabetic retinopathy complications observed in GLP-1 RA CVOTs,[253] several GLP-1 RAs have a Warnings and Precautions of the risk of diabetic retinopathy complications.[2-4,11] In the Applicant's phase 2 trials, subjects with a proliferative retinopathy were excluded from study participation. In their phase 3 trials, subjects with a history of proliferative diabetic retinopathy, diabetic maculopathy, or nonproliferative diabetic retinopathy requiring acute treatment were excluded from participation based on a dilated fundoscopic examination. A follow-up dilated fundoscopic examination could be repeated if clinically indicated during the trial. The Applicant used a CMQ to identify AEs related to diabetic retinopathy complications.

In their phase 2/3 trials (AS3), 23 subjects [adj 0.8%] in the comparator arms and 40 tirzepatide-treated subjects [adj 0.8%] experienced potential AEs of diabetic retinopathy complications (Table 49). The study size adjusted incidence rates[171,172] of diabetic retinopathy complication AEs in tirzepatide-treated subjects were 0.73 events per 100 PY and 0.78 per 100 PY across the comparator arms for eight of the nine trials (i.e., excluding trial GPGP which did not include a comparator arm). AEs coded as 'Diabetic retinopathy' (16 tirzepatide-treated subjects and 2 subjects in the comparator arms) and 'Macular oedema' (9 subjects and 1 subject, respectively) occurred in more subjects randomized to the tirzepatide arms. Three AEs were coded as serious (all in the tirzepatide-treated subjects) and included 'Retinal vein occlusion' (n=2; Subjects (b) (6) both randomized to the tirzepatide 5 mg arm) and 'Retinal detachment' (n=1; Subject (b) (6) randomized to the tirzepatide 10 mg arm). Additionally, across the phase 3 trials (AS2), the Applicant reported worsening fundoscopic examinations in 18 tirzepatide-treated subjects (0.35%) and five subjects (0.22%) in the comparator arms.

The Applicant includes diabetic retinopathy complications as a Warnings and Precautions in proposed tirzepatide labeling. I concur with inclusion of this information in Section 5 of product labeling. They also are conducting a dedicated diabetic retinopathy substudy as part of their CVOT (i.e., trial GPGN), which will better inform the risk of new onset or worsening diabetic retinopathy with tirzepatide use.

Table 49: Diabetic Retinopathy Complications — Side-by-Side Comparison of Phase 2/3 Trials (AS3)

	GPGK		GPGI		GPGF		GPGM		GPGH		GPGO		GPGB			GPGL		GPGP
Diabetic Retinopathy Complications CMQ	**PBO (N=115)**	**TZP ALL (N=363)**	**PBO (N=120)**	**TZP ALL (N=355)**	**PBO (N=26)**	**TZP ALL (N=85)**	**Ins Glar (N=1000)**	**TZP ALL (N=995)**	**Ins Deg (N=360)**	**TZP ALL (N=1077)**	**Dula 0.75 mg (N=159)**	**TZP ALL (N=477)**	**PBO (N=51)**	**Dula 1.5 mg (N=54)**	**TZP ALL (N=211)**	**Sema 1 mg (N=469)**	**TZP ALL (N=1409)**	**TZP ALL (443)**
Subjects with Events Across Trials	**ALL Comparators: 23/2354 subjects (0.98%) [adj 0.79%] — TZP: 40/5415 subjects (0.74%) [adj 0.80%]**																	
Total Subjects — no. (%)	**1 (0.9)**	**0 (0.0)**	**1 (0.8)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**15 (1.5)**	**14 (1.4)**	**2 (0.6)**	**6 (0.6)**	**1 (0.6)**	**3 (0.6)**	**1 (2.0)**	**0 (0.0)**	**3 (1.4)**	**2 (0.4)**	**10 (0.7)**	**4 (0.9)**
Total Events — no.	1	0	1	0	0	0	16	15	2	10	1	3	1	0	3	2	14	6
PY	92.2	292.7	100.9	290.4	7.2	24.5	1566.4	1590.8	376.0	1125.1	168.0	502.6	28.1	30.1	116.2	392.7	1179.7	460.4
PYE	92.1	292.7	100.7	290.4	7.2	24.5	1552.7	1580.2	374.9	1121.4	167.5	501.1	28.1	30.1	114.7	391.6	1174.5	458.4
IR per 100 PY	1.09	0.00	0.99	0.00	0.00	0.00	0.97	0.89	0.53	0.54	0.60	0.60	3.56	0.00	2.61	0.51	0.85	0.87
MedDRA PT																		
Macular oedema	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	3 (0.3)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (0.4)	0 (0.0)
Vision blurred	1 (0.9)	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.4)	2 (0.2)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.4)	1 (0.2)	3 (0.2)	0 (0.0)
Visual impairment	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Diplopia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.1)	2 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Retinal detachment	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Retinal vein occlusion	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Visual acuity reduced	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Amaurosis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Amaurosis fugax	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Maculopathy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)
Retinal artery embolism	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Retinal haemorrhage	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Retinopathy hypertensive	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)
Vitrectomy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Source: Derived from the Applicant's ISS adsl.xpt and adae datasets, available at: \\CDSESUB1\evsprod\NDA215866\0001\m5\datasets\integrated-database\analysis\adam\datasets, and adapted from the Applicant's Regulatory Response (dated December 31, 2021), page 1153 of 1709, available at: \\CDSESUB1\evsprod\nda215866\0029\m1\us\regulatory-response--fda-midcycle-dec-2021-.pdf
Abbreviations: adj, study size adjusted percentage; Dula, dulaglutide; Ins Deg, insulin degludec; Ins Glar, insulin glargine; IR, incidence rate (100 times the number of subjects experiencing the event divided by PYE); ISS, Integrated Summary of Safety; MedDRA, Medical Dictionary for Regulatory Activities; PBO, placebo; PY, patient-year (sum of time from date of first dose to end of the study); PYE, total patient years at risk (sum of time period from date of first dose to the onset of the event for subjects with the event, and time period from date of first dose to the end of the study for subjects without the even); Sema, semaglutide; and TZP, tirzepatide.

8.5.11. Cardiovascular Safety

To show that tirzepatide was not associated with an excess CV risk, the Applicant conducted an interim (intended to discharge premarketing safety requirements once 100 accrued subjects experienced a major adverse cardiovascular event-4 (MACE-4) endpoint) and complete CV meta-analysis (CVMA) in accordance with previous FDA guidance (i.e., prior to the release of a new draft guidance for industry in 2020)[170] and requirements of the European Medicines Agency (EMA, Committee for Medicinal Products for Human Use [CHMP]).[254,255] The Applicant compared the incidence of important CV events between the tirzepatide (pooled 5, 10, and 15 mg arms) and control groups across a pool of phase 2/3 clinical trials to show that the upper bound of the two-sided 95 percent confidence interval for the estimated risk ratio was less than 1.8.

The interim and complete CVMAs included a total of seven trials, one phase 2 (GPGB) and six phase 3 (GPGH, GPGI, GPGK, GPGL, GPGO, and GPGM) trials (AS5). Descriptions of these trials are presented in Section 5.1 (Table 5) above. These trials randomized 7215 subjects (Table 50), and contributed 7781.8 PYs of exposure (i.e., 5064.45 PYs in the tirzepatide arms and 2717.35 PYs in the pooled comparator arms). Trials GPGF (that included only a 12-week treatment duration) and GPGP (that did not include a control arm) were excluded from these analyses. The primary objective of the CVMA was to compare the time to first occurrence of the adjudicated MACE-4 endpoint (i.e., a composite of CV death, MI, stroke, and hospitalization for unstable angina [HUA]) between the pooled tirzepatide and pooled comparator arms. The time-to-event was defined as the time between the date of the first dose and: 1) the onset date of the Clinical Events Committee (CEC)-confirmed MACE-4 endpoint plus one day for subjects experiencing an event on or before the 30-day safety follow-up visit or 2) the censoring date plus one day for subjects who did not experience an event on or before the 30-day safety follow-up visit or early study termination. The objective of the CVMA was considered met if the upper bound of the 2-sided 95% CI was <1.8. Blinded adjudication of all CV events, thromboembolic events, hospitalization for heart failure (HHF), and deaths was performed by independent CEC (the Duke Clinical Research Committee for phase 2 trials, and the Cleveland Clinic Coordinating Center for Clinical Research for the phase 3 trials), composed minimally of Cardiology Fellows who were board certified in Internal Medicine and completed at least one year of their fellowship training.

The primary analysis compared the distribution of time-to-event of MACE-4 (i.e., first occurrence) between the pooled tirzepatide and pooled comparator arms, and adjusted Kaplan-Meier estimates of the survival curve, and the HR and CI estimates from a stratified Cox proportional hazards regression model (with treatment as a fixed effect and stratified by study-level CV risk) were provided. Type 1 error rate was controlled for multiple testing (interim and final assessments). Dr. Shanti Gomatam from the Division of Biometrics VII (DBVII) was consulted to provide the statistical review of the CV safety of tirzepatide. Please refer to her review (dated April 21, 2022) for more detailed discussion of the statistical analysis plan (SAP) of the CVMA for this Application.

The interim analysis was conducted after 116 subjects experienced at least 1 component of the adjudication-confirmed MACE-4 endpoint (i.e., 60 events in 4410 subjects from the pooled tirzepatide arm, and 56 events in 2169 subjects from the pooled comparator arm). The results showed that treatment with tirzepatide was not associated with an excess CV risk (i.e., estimated hazard ratio [HR] 0.81, adjusted 97.85% confidence interval [CI]: 0.52, 1.26, p=0.276), with the point estimate favoring the tirzepatide arm. Dr. Gomatam reanalyzed these data and confirmed the point estimate and CI.

The analysis of the complete CVMA (Table 50) included 142 subjects (72 MACE-4 events in the pooled tirzepatide arm, and 70 events in the pooled comparator arm). Most of these events (i.e., 109 subjects) were reported in trial GPGM (a trial enriched with subjects at high CV risk). The results again favored the pooled tirzepatide arm (HR 0.80, 95% CI: 0.57, 1.11, p=0.183) and were consistent with those reported for the interim analysis. The adjusted Kaplan-Meier curves appeared to show a separation between treatment arms starting at approximately 48 weeks and continuing through the remainder of follow-up (Figure 15). The HR point estimates for the individual components of the composite MACE-4 endpoint also were all <1. Results from the reanalysis of these data by Dr. Gomatam were similar (please refer to the footnotes of Table 50).

Table 50: Time to First MACE-4 Endpoint and Individual Components (AS5)

Endpoint	Follow-up (PY)	N (%)	Event Rate per 100 PY*	Hazard Ratio vs. Placebo (95% CI; p-value)†
MACE-4 (CV death, MI, stroke, hospitalization for unstable angina)				
Pooled Comparator (N=2328)	**2717.35**	**70 (3.01)**	**2.58 [1.61]**	
All Tirzepatide (N=4887)	**5064.45**	**72 (1.47)**	**1.42 [1.35]**	**0.80 (0.57, 1.11; p=0.183)**
Components				
CV Death				
Pooled Comparator (N=2328)	2756.39	22 (0.64)	0.80 [0.43]	
All Tirzepatide (N=4887)	5099.16	25 (0.41)	0.49 [0.46]	0.90 (0.50, 1.61)[a]
Myocardial infarction				
Pooled Comparator (N=2328)	2730.91	30 (1.29)	1.10 [0.71]	
All Tirzepatide (N=4887)	5081.70	30 (0.61)	0.59 [0.56]	0.76 (0.45, 1.28)[b]
Stroke				
Pooled Comparator (N=2328)	2747.20	15 (0.64)	0.55 [0.35]	
All Tirzepatide (N=4887)	5087.03	15 (0.31)	0.29 [0.27]	0.81 (0.39, 1.68)[c]
Hospitalization for Unstable Angina				
Pooled Comparator (N=2328)	2749.71	9 (0.34)	0.33 [0.20]	
All Tirzepatide (N=4887)	5094.05	5 (0.10)	0.10 [0.09]	0.46 (0.15, 1.41)[d]

Source: Adapted from the Applicant's 5.3.5.3 Integrated Data Report, page 62 of 394, available at: \\CDSESUB1\evsprod\nda215866\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\type-2-diabetes-mellitus\5353-rep-analys-data-more-one-stud\integrated-database\multistudy-cv-meta-analysis--t2dm-.pdf

*The number in brackets indicates the adjusted estimate (i.e., accounting for different randomization ratios and differences in patient populations among strata). The strata are defined as study-level CV risk (i.e., GPGM is one stratum, and all other trials are one stratum).

†Cox proportional-hazards model with treatment as a fixed effect, stratified by study-level CV risk (GPGM as one stratum, and all other studies as one stratum), and p-value was derived using the Wald test.

Dr. Gomatam's reanalysis of the components of MACE-4 at the end of the meta-analysis are as follows:

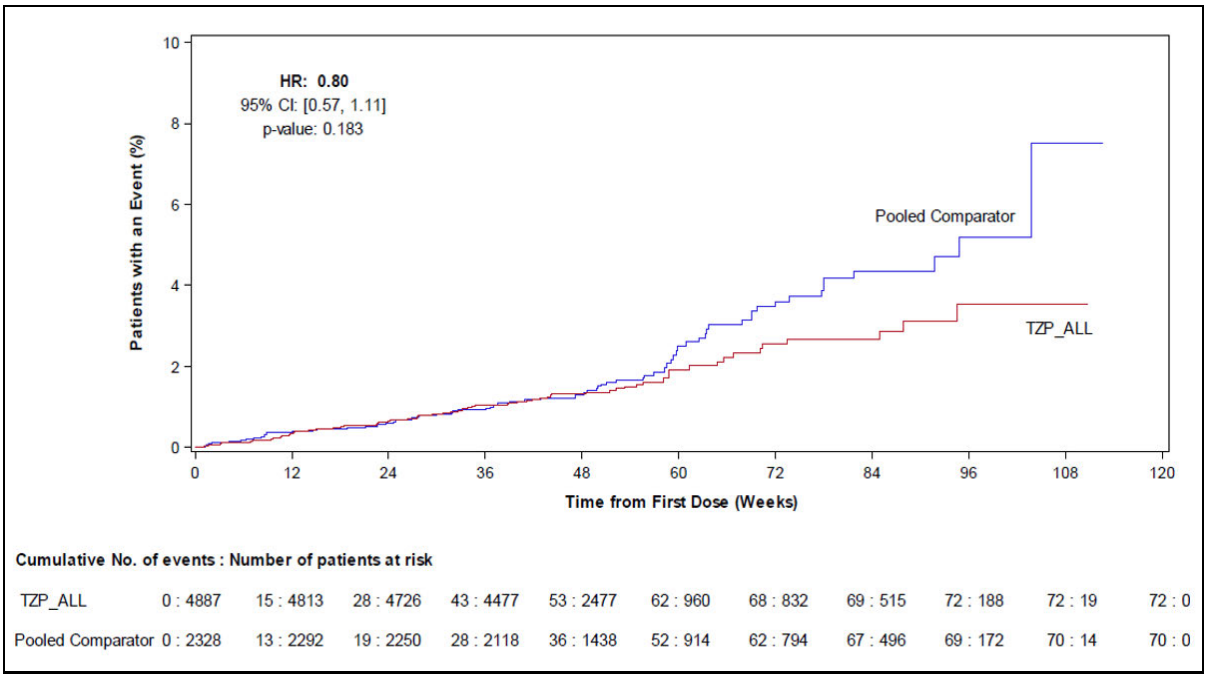
[a] CV death: HR 0.90 (95% CI: 0.45, 1.79)

[b] Myocardial infarction: HR 0.76 (95% CI: 0.41, 1.40)

[c] Stroke: HR 0.81 (95% CI: 0.34, 1.90)

[d] Hospitalization for unstable angina: HR 0.46 (95% CI 0.13, 1.71)

Figure 15: Time to First Occurrence of the Composite MACE-4 Endpoint (AS5)*



Source: Excerpt from the Applicant's 5.3.5.3 Integrated Data Report, page 63 of 394, available at: \\CDSESUB1\evsprod\nda215866\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\type-2-diabetes-mellitus\5353-rep-analys-data-more-one-stud\integrated-database\multistudy-cv-meta-analysis--t2dm-.pdf

Abbreviations: CI, confidence interval; HR, hazard ratio; No., number; and TZP, tirzepatide.

*The adjusted Kaplan-Meier was estimated by weighing with inverse probability of randomization for treatment within stratum, and the HR, CI and p-value were derived from a Cox proportional-hazards model with treatment as a fixed effect.

Dr. Gomatam also conducted an exploratory analysis of the primary MACE-4 endpoint by treatment arm (Table 51). Although this analysis suggests a possible risk reduction favoring the tirzepatide 15 mg arm (HR 0.59, 95% CI: 0.35, 0.99), event counts were limited, and this analysis should be considered exploratory/descriptive.

Table 51: Analysis of MACE-4 Endpoint by Treatment Arm (AS5)

	Tirzepatide					Comparator
	15 mg N=1621	10 mg N=1606	5 mg N= 1608	1 mg N=52	All N= 4887	N=2328
MACE-4 patient years of follow-up	1700.19	1669.13	1666.53	28.59	5064.45	2717.35
MACE-4 events (IR per 100 PY)	18 (1.06)	25 (1.50)	28 (1.68)	1 (3.50)	72 (1.42)	70 (2.58)
HR* (95% CI)	0.59 (0.35, 0.99)	0.84 (0.53, 1.34)	0.95 (0.61, 1.48)	4.73 (0.62, 35.86)	0.80 (0.57, 1.11)	-

Source: Reproduced from Dr. Shanti Gomatam's Statistical Review.
Abbreviations: HR, hazard ratio; IR, incidence rate; MACE-4, major adverse cardiovascular event-4 component composite endpoint (i.e., CV death, myocardial infarction, stroke, and hospitalization for unstable angina); and PY, patient-year.
*Hazard ratios computed using a Cox proportional hazards model with fixed effects for treatment and stratified by CV risk (GPGM versus others). mITT population (all randomized subjects who took at least one dose of IP), end-of-meta-analysis.

Additionally, there were 41 deaths (0.84% of 4887 subjects) in the pooled tirzepatide arm and 39 deaths (1.68% of 2328 subjects) in the pooled comparator arm. No difference was observed between treatment arms for all-cause death (HR 0.80, 95% CI: 0.51, 1.25). Although events were limited (10 events in tirzepatide-treated subjects and 9 events in pooled comparator arm), time to first occurrence of HHF also favored the tirzepatide arm (HR 0.67, 95% CI: 0.26, 1.70).

Since the upper limit of the CI for MACE-4 (i.e., 1.11) was less than 1.8, as previously defined by global regulatory agencies, the Applicant concluded that tirzepatide treatment was not associated with an excess CV risk. Similarly, Dr. Gomatam felt that the CVMA was successful in demonstrating CV safety of tirzepatide. However, she recommended caution in interpreting and generalizing the findings due to inclusion of open-label trials (which could introduce bias), different active comparators (e.g., semaglutide, insulin degludec, and insulin glargine), and limited MACE-4 events in several of the trials (e.g., a total of only 6 events were reported across trials GPGB, GPGI, and GPGK). Based on the Applicant's results and confirmatory analyses conducted by Dr. Gomatam, I concur that these data do not suggest an increased risk of major adverse CV events with the use of tirzepatide. Additionally, no CV safety concerns were identified following a review of the CV or cerebrovascular AEs submitted to this NDA, including the data from 4MSU. Please refer to Sections 8.4.1, 8.4.2, and 8.4.3 for a review of relevant deaths, SAEs, and discontinuations due to AEs, respectively, and to Sections 8.4.6, 8.4.7, and 8.4.8 for additional CV safety information pertaining to vital signs changes, ECG findings, and changes in the QTc interval, respectively.

To further inform the CV safety of tirzepatide, the Applicant also is conducting trial GPGN (SURPASS-CVOT), a cardiovascular outcomes trial (CVOT), which will compare tirzepatide to dulaglutide (1.5 mg SC QW) in a high CV risk patient population. This trial is ongoing, with an anticipated completion date by 2025. Several other GLP-1 RA products (i.e., dulaglutide,

liraglutide, and semaglutide) have a labeled indication to reduce the risk of MACE in adults with T2D and established CV disease or multiple CV risk factors based on the results of large, prospective CVOTs, enriched with high CV risk patient populations.[2,5,11] A fourth CVOT for a GLP-1 RA no longer available for clinical use (i.e., albiglutide) also reported CV benefit.[256] The ADA's 2022 Standards of Medical Care in Diabetes recommends the use of a GLP-1 RA with demonstrated CV benefit for adult T2D patients who have established atherosclerotic CV disease (ASCVD) or multiple risk factors for ASCVD (e.g., age ≥55 years with coronary, carotid, or lower-extremity artery stenosis >50% or left ventricular hypertrophy) to reduce the risk of major adverse CV events, independent of the HbA1c concentration.[17,30] Combination therapy with a GLP-1 RA and SGLT2i also has been recommended in this population for additive reduction in the risk of adverse CV and kidney events, especially if the HbA1c is above the glycemic target on either antihyperglycemic treatment alone.[17,30]

8.5.12. Amputations and Peripheral Revascularizations Procedures

Due to an increase in the incidence of peripheral vascular disease (PVD)[257-261] and peripheral neuropathy,[262-265] patients with T2D are at increased risk for lower limb amputations and peripheral revascularization procedures. According to the Centers for Disease Control and Prevention (CDC), diabetes remains the leading cause of lower limb amputations,[13] resulting in approximately 130,000 hospitalizations for a lower-extremity amputation each year (i.e., 5.6 per 1000 persons with diabetes).[12] Compared to nondiabetic individuals, patients with diabetics may have a 10-fold greater risk for lower extremity amputations, and diabetic amputees are more likely to be severely disabled, have an amputation at a younger age, progress to higher-level amputations, or die at a younger age.[266] Similarly, in individuals without coronary artery disease, the risk of lower limb revascularization has been reported to be 1.6-fold higher (95% CI: 1.16-2.05) among patients with T2D compared to nondiabetics.[260]

In the tirzepatide clinical development program, amputation and peripheral revascularization events were primarily identified through clinical narratives from the Applicant's Safety System (i.e., Lilly Safety System, LSS), since no TEAEs were identified through prespecified MedDRA searches.

In the Applicant's phase 2/3 trials (AS3), amputations were performed for 21 subjects, 13 tirzepatide-treated subjects, six subjects randomized to insulin glargine and two subjects randomized to insulin degludec. Of the 13 tirzepatide-treated subjects, four amputations were traumatic. Therefore, there 9/5215 subjects (0.17% [adj 0.2%]) in the combined tirzepatide arm and 8/2354 (0.34% [adj 0.26%]) subjects in the comparator arms experienced lower limb amputations. For the nine tirzepatide-treated subjects, five had a history of PVD, six used tobacco products, and amputations were typically associated with diabetic foot, peripheral ischemia/gangrene, or infection (e.g., osteomyelitis).

Additionally, peripheral revascularization procedures were performed on eight tirzepatide-treated subjects, two subjects receiving insulin glargine (trial GPGM), and one subject receiving semaglutide 1 mg (trial GPGL). The tirzepatide-treated subjects had preexisting risk factors (i.e., all seven had peripheral vascular disease (PVD), five used tobacco products, and the mean duration of T2D was approximately 16 years [range 3.8 to 35.1 years]).

In summary, tirzepatide did not appear to be associated with an increased risk of amputations or peripheral revascularization procedures. However, events were limited to determine meaningful differences. The risk of these AESI will be better assessed in the Applicant's CVOT (GPGN), which will expose at-risk subjects to tirzepatide for longer treatment durations. The Applicant does not intend to include the risk of lower limb amputations or peripheral revascularization procedures in proposed labeling. I agree that these AEs do not warrant inclusion in product labeling based on the existing data. Additionally, GLP-1 RAs do not appear to be associated with an increase of amputations,[267] and the risk of amputation and peripheral revascularization procedures are not included in labeling of these products.[2-11,24-26]

8.5.13. **Hepatobiliary Events**

Diabetes has been associated with liver disease, including nonalcoholic fatty liver disease (NAFLD), nonalcoholic steatohepatitis (NASH), and cirrhosis.[268-271] In the Applicant's phase 2/3 clinical development program, subjects were excluded from study participation if they had hepatitis (acute or chronic), symptoms of liver disease (individuals with nonalcoholic fatty liver disease [NAFLD] were eligible to participate) or had serum alanine aminotransferase (ALT) concentrations >2.5x ULN for phase 2 trials and >3x ULN for phase 3 trials at screening. The Applicant identified hepatobiliary events using the following MedDRA SMQs: 'Liver-related investigations, signs, and symptoms'; 'Cholestasis and jaundice of hepatic origin'; 'Hepatitis non-infectious'; 'Hepatic failure, fibrosis, and cirrhosis and other liver damage-related conditions': 'Liver-related coagulation and bleeding disturbances (narrow); 'Gallbladder-related disorders' (narrow); 'Biliary tract disorders' (narrow); and 'Gallstone-related disorders (narrow).

Across the Applicant's phase 2/3 trials (AS3), hepatobiliary disorder-related AEs were reported in 156 tirzepatide-treated subjects [adj 3%] and 63 subjects [adj 2.21%] in the pooled comparator arms (Table 53). The study size adjusted incidence rates[171,172] in tirzepatide-treated subjects were 2.85 events per 100 PY and 2.22 per 100 PY across the comparator arms for eight of the nine trials (i.e., excluding trial GPGP which did not include a comparator arm). The most common AEs in the tirzepatide arms included 'Hepatic steatosis' (40/5415 subjects vs. 19/2354 subjects in the comparator arms) and 'Cholelithiasis' (33 subjects vs. 6 subjects in the comparator arms). Nineteen [adj 0.37%] tirzepatide-treated subjects and 7 [adj 0.19%] from the comparator arms experienced SAEs, of which the most common reported SAEs in the tirzepatide treatment arms included 'Cholecystitis acute' (n=7) and 'Cholelithiasis' (n=5). No tirzepatide-treated subjects met the biochemical criteria for Hy's law.

In the Applicant's pool of phase 3 trials (AS2), which included the same tirzepatide doses and titration schedule, a dose-response relationship for hepatobiliary AEs was not apparent. In these trials, one subject each in the tirzepatide 10 mg (b) (6)) and 15 mg ((b) (6)) arms experienced maximum postbaseline elevations in serum ALT concentrations >10× ULN, while one subject ((b) (6)) randomized to the tirzepatide 15 mg arm had a maximum aspartate aminotransferase (AST) elevation >10× ULN (Table 52).

- **Subject** (b) (6) a 66-year-old White female with T2D randomized to the tirzepatide 10 mg treatment arm, had an ALT elevation of 653 U/L (19.8 x ULN) on Day 85 associated with an AST elevation of 300 U/L (9.7x ULN), and an alkaline phosphatase (ALP) 322 U/L (3.1x ULN). The total bilirubin (TBL) was within laboratory reference limits. These laboratory abnormalities were not associated with AEs. The subject had numerous comorbidities, including a history of chronic heart failure, cholecystitis, cholelithiasis, coronary artery disease, atherosclerosis, CKD/diabetic nephropathy/pyelonephritis, and dyslipidemia. Upon repeat testing one week later, the ALT was 73 U/L (2.2x ULN), ALP was 148 (1.4x ULN), and the ALT was within the normal laboratory range. The abnormal laboratory results on Day 85 were preceded by the addition rosuvastatin to her medication regimen 13 days earlier. Repeat liver laboratory test results were within normal reference limits for the remainder of the trial. The subject continued IP and completed the trial.

Limited additional information was provided in the clinical study report for this subject. The addition of a statin prior to the event,[272] with reductions in transaminase concentrations within the week and throughout the remainder of the trial, despite continuing administration of IP, make a causal association with tirzepatide less likely.

- **Subject** (b) (6) a 47-year-old White male with T2D randomized to the tirzepatide 15 mg treatment arm, experienced an ALT elevation of 1063 U/L (>10x ULN) on Day 166 associated with an AST of 363 U/L (>5x ULN), gamma-glutamyl transpeptidase (GGT) 340 U/L (>5x ULN), direct bilirubin (DBIL) 0.58 mg/dL (>2x ULN), and ALP 151 U/L (>1x ULN). On Day 168, he was seropositive for hepatitis E virus (HEV IgG and IgM antibody positive), which was reported as resolved by Day 184. On Day 181, the ALT was within normal reference limits, and the AST, DBIL and ALP returned to normal on Day 184. The subject continued IP and completed the trial.

A diagnosis of hepatitis E at the time of the elevated laboratory parameters with a relatively quick resolution while receiving IP make it unlikely that tirzepatide was causally related.

- **Subject** (b) (6) a 54-year-old White female with T2D randomized to the tirzepatide 15 mg treatment arm, had elevated AST (315 U/L; >10x ULN) and ALT (304 U/L, <10x ULN) concentrations reported on Day 384 during the safety follow-up period. Laboratory abnormalities resolved after completion of the trial. An ultrasound showed

fatty liver deposition which the investigator felt was not clinically significant. The subject completed IP on Day 358.

Although the Applicant felt that the elevated transaminase concentrations were acute, and occurred off IP, the relatively long half-life of tirzepatide (approximately five days), make it not possible to rule out an association with tirzepatide.

There were eight tirzepatide-treated subjects with TBL concentrations ≥2× ULN (2 subjects each in the 5 mg and 10 mg arms, and 3 in the 15 mg arm). These subjects had elevated TBL concentrations at baseline, and the abnormal findings were not associated with serum transaminase concentrations ≥3× ULN.

Table 52: Maximum Baseline to Maximum Postbaseline Transaminase Shift Table (AS2)

Treatment	Baseline Maximum	N	Postbaseline Maximum		
			≥3x ULN	≥5x ULN	≥10x ULN
Alanine Aminotransferase (IU/L)					
TZP ALL (N=5119)	**All subjects**	**5059**	**46 (0.91)**	**15 (0.30)**	**2 (0.04)**
	≤1×ULN	3979	24 (0.60)	8 (0.20)	1 (0.03)
	>1×ULN	1076	22 (2.04)	7 (0.65)	1 (0.09)
TZP 5 mg (N=1701)	All subjects	1679	14 (0.83)	3 (0.18)	0
	≤1×ULN	1331	7 (0.53)	2 (0.15)	0
	>1×ULN	348	7 (2.01)	1 (0.29)	0
TZP 10 mg (N=1702)	All subjects	1682	12 (0.71)	3 (0.18)	1 (0.06)
	≤1×ULN	1322	7 (0.53)	1 (0.08)	1 (0.08)
	>1×ULN	357	5 (1.40)	2 (0.56)	0
TZP 15 mg (N=1716)	All subjects	1698	20 (1.18)	9 (0.53)	1 (0.06)
	≤1×ULN	1326	10 (0.75)	5 (0.38)	0
	>1×ULN	371	10 (2.70)	4 (1.08)	1 (0.27)
Aspartate Aminotransferase (IU/L)					
TZP_ALL (N=5119)	**All subjects**	**5059**	**29 (0.57)**	**8 (0.16)**	**1 (0.02)**
	≤1×ULN	4409	21 (0.48)	7 (0.16)	1 (0.02)
	>1×ULN	647	8 (1.24)	1 (0.15)	0
TZP 5 mg (N=1701)	All subjects	1679	9 (0.54)	1 (0.06)	0
	≤1×ULN	1455	7 (0.48)	1 (0.07)	0
	>1×ULN	224	2 (0.89)	0	0
TZP 10 mg (N=1702)	All subjects	1682	8 (0.48)	2 (0.12)	0
	≤1×ULN	1463	4 (0.27)	1 (0.07)	0
	>1×ULN	216	4 (1.85)	1 (0.46)	0
TZP 15 mg (N=1716)	All subjects	1698	12 (0.71)	5 (0.29)	1 (0.06)
	≤1×ULN	1491	10 (0.67)	5 (0.34)	1 (0.07)
	>1×ULN	207	2 (0.97)	0	0

Source: Adapted from the Applicant's ISS, pages 2787-2789 of 7807, available at: \\CDSESUB1\evsprod\nda215866\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\type-2-diabetes-mellitus\5353-rep-analys-data-more-one-stud\iss\iss-46-integrated-sum-of-safety--t2dm-.pdf
Abbreviations: AS2, Analysis Set 2 (pool of 7 phase 3 trials); and TZP, tirzepatide; and ULN, upper limit of normal.

Additionally, based on the Applicant's dedicated hepatic impairment trial (GPGQ), the PKs of tirzepatide did not appear to be significantly altered by hepatic impairment (i.e., tirzepatide exposures based $AUC_{0\text{-tlast}}$, $AUC_{0\text{-}\infty}$ and C_{max} were similar across control and hepatic impairment arms). Therefore, proposed product includes the following statement: "No dosage adjustment is recommended for patients with hepatic impairment. In a clinical pharmacology study in subjects

with varying degrees of hepatic impairment, no change in tirzepatide PK was observed, (b) (4) ” The Clinical Pharmacology review team felt that this information was acceptable for inclusion in labeling. I concur with their assessment.

The Applicant also felt that the data in their clinical development program do not suggest that tirzepatide is hepatoxic. However, due to concerns of rapid weight loss in the intended patient population and the occurrence of severe or serious AEs, the Division has decided to include acute gallbladder disorders as a Warnings and Precautions in proposed tirzepatide labeling. Please refer to Section 8.5.8 for additional information on acute gallbladder disease-related AEs.

Table 53: Hepatobiliary Disorders — Side-by-Side Comparison of Phase 2/3 Trials (AS3)

	GPGK		GPGI		GPGF		GPGM		GPGH		GPGO		GPGB			GPGL		GPGP
Hepatobiliary Disorders SMQs	**PBO (N=115)**	**TZP ALL (N=363)**	**PBO (N=120)**	**TZP ALL (N=355)**	**PBO (N=26)**	**TZP ALL (N=85)**	**Ins Glar (N=1000)**	**TZP ALL (N=995)**	**Ins Deg (N=360)**	**TZP ALL (N=1077)**	**Dula 0.75 mg (N=159)**	**TZP ALL (N=477)**	**PBO (N=51)**	**Dula 1.5 mg (N=54)**	**TZP ALL (N=211)**	**Sema 1 mg (N=469)**	**TZP ALL (N=1409)**	**TZP ALL (443)**
Subjects with Events Across Trials	**ALL Comparators: 63/2354 subjects (2.7%) [adj 2.2%] — TZP: 156/5415 subjects (2.9%) [adj 3%]**																	
Total Subjects — no. (%)	**2 (1.7)**	**4 (1.1)**	**1 (0.8)**	**8 (2.3)**	**0 (0.0)**	**2 (2.4)**	**39 (3.9)**	**42 (4.2)**	**7 (1.9)**	**29 (2.7)**	**2 (1.3)**	**10 (2.1)**	**0 (0.0)**	**2 (3.7)**	**8 (3.8)**	**10 (2.1)**	**41 (2.9)**	**12 (2.7)**
Total Events — no.	2	4	1	10	0	2	47	54	9	35	2	12	0	2	13	12	54	19
PY	92.2	292.7	100.9	290.4	7.2	24.5	1566.4	1590.8	376	1125.1	168	502.6	28.1	30.1	116.2	392.7	1179.7	460.4
PYE	90.8	291.7	100.6	286.8	7.2	24.4	1534.2	1551.5	373.5	1112.1	167.3	497.4	28.1	29.3	113.9	387.6	1161.6	454.3
IR per 100 PY	2.2	1.37	0.99	2.79	0	8.18	2.54	2.71	1.87	2.61	1.2	2.01	0	6.82	7.03	2.58	3.53	2.64
MedDRA PT																		
Hepatic steatosis	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.8)	0 (0.0)	0 (0.0)	12 (1.2)	12 (1.2)	1 (0.3)	4 (0.4)	1 (0.6)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.5)	5 (1.1)	17 (1.2)	2 (0.5)
Cholelithiasis	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	4 (0.4)	5 (0.5)	0 (0.0)	4 (0.4)	0 (0.0)	3 (0.6)	0 (0.0)	0 (0.0)	3 (1.4)	2 (0.4)	12 (0.9)	4 (0.9)
Cholecystitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	6 (0.6)	2 (0.2)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.9)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Cholecystitis acute	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.3)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	5 (0.4)	0 (0.0)
Hepatic cirrhosis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	2 (0.2)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Hepatitis acute	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Aspartate aminotransferase increased	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	3 (0.3)	2 (0.2)	2 (0.6)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.9)	0 (0.0)	0 (0.0)	3 (0.7)
Hepatic enzyme increased	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.3)	0 (0.0)	1 (1.2)	2 (0.2)	2 (0.2)	0 (0.0)	5 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (0.4)	1 (0.2)
Ascites	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Varices oesophageal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Bile duct stone	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Biliary colic	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (<0.1)	0 (0.0)
Cholecystitis chronic	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.1)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cholestasis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.3)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hepatic calcification	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

	GPGK		GPGI		GPGF		GPGM		GPGH		GPGO		GPGB			GPGL		GPGP
Hepatobiliary Disorders SMQs	**PBO (N=115)**	**TZP ALL (N=363)**	**PBO (N=120)**	**TZP ALL (N=355)**	**PBO (N=26)**	**TZP ALL (N=85)**	**Ins Glar (N=1000)**	**TZP ALL (N=995)**	**Ins Deg (N=360)**	**TZP ALL (N=1077)**	**Dula 0.75 mg (N=159)**	**TZP ALL (N=477)**	**PBO (N=51)**	**Dula 1.5 mg (N=54)**	**TZP ALL (N=211)**	**Sema 1 mg (N=469)**	**TZP ALL (N=1409)**	**TZP ALL (443)**
Hepatic fibrosis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hepatic function abnormal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.5)
Hepatic lesion	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Hepatomegaly	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.2)	4 (0.3)	1 (0.2)
Hepatotoxicity	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hyperbilirubinaemia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.1)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Ischaemic hepatitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Liver disorder	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Liver injury	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Non-alcoholic steatohepatitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Nonalcoholic fatty liver disease	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Porcelain gallbladder	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Steatohepatitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Alanine aminotransferase increased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.4)	1 (0.1)	2 (0.6)	4 (0.4)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.9)	2 (0.4)	2 (0.1)	2 (0.5)
Bilirubin conjugated increased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)
Blood bilirubin increased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)
Gamma-glutamyltransferase abnormal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Autoimmune hepatitis	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Biliary dilatation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cholangitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cholangitis acute	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hepatic mass	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

	GPGK		GPGI		GPGF		GPGM		GPGH		GPGO		GPGB			GPGL		GPGP
Hepatobiliary Disorders SMQs	**PBO (N=115)**	**TZP ALL (N=363)**	**PBO (N=120)**	**TZP ALL (N=355)**	**PBO (N=26)**	**TZP ALL (N=85)**	**Ins Glar (N=1000)**	**TZP ALL (N=995)**	**Ins Deg (N=360)**	**TZP ALL (N=1077)**	**Dula 0.75 mg (N=159)**	**TZP ALL (N=477)**	**PBO (N=51)**	**Dula 1.5 mg (N=54)**	**TZP ALL (N=211)**	**Sema 1 mg (N=469)**	**TZP ALL (N=1409)**	**TZP ALL (443)**
Hepatocellular injury	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Malignant biliary obstruction	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Alanine aminotransferase abnormal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Blood alkaline phosphatase increased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.2)
Gamma-glutamyltransferase increased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.3)	3 (0.3)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Hepatic enzyme abnormal	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Liver function test abnormal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Liver function test increased	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (1.9)	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)
Transaminases increased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hyperammonaemia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cholecystectomy	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (<0.1)	0 (0.0)

Source: Derived from the Applicant's ISS adsl.xpt and adae datasets, available at: \\CDSESUB1\evsprod\NDA215866\0001\m5\datasets\integrated-database\analysis\adam\datasets, and adapted from the Applicant's Regulatory Response (dated December 31, 2021), pages 1154-1157 of 1709, available at: \\CDSESUB1\evsprod\nda215866\0029\m1\us\regulatory-response--fda-midcycle-dec-2021-.pdf

Abbreviations: adj, study size adjusted percentage; AS3, Analysis Set 3 (pool of 9 phase 2/3 trials); Dula, dulaglutide; Ins Deg, insulin degludec; Ins Glar, insulin glargine; IR, incidence rate (100 times the number of subjects experiencing the event divided by PYE); ISS, Integrated Summary of Safety; MedDRA, Medical Dictionary for Regulatory Activities; PBO, placebo; PY, patient-year (sum of time from date of first dose to end of the study); PYE, total patient years at risk (sum of time period from date of first dose to the onset of the event for subjects with the event, and time period from date of first dose to the end of the study for subjects without the even); Sema, semaglutide; and TZP, tirzepatide.

8.5.14. **Malignancy**

In this Application, AEs of malignancy were identified using the narrow SMQs 'Malignant tumours' and 'Tumours of unspecified malignancy'. Across the nine phase 2/3 trials (AS3), malignancies were reported in 55 tirzepatide-treated subjects [adj 1.1%] and 30 subjects [1%] in the comparator arms (Table 54). The study size adjusted incidence rates[171,172] in tirzepatide-treated subjects were 1.01 events per 100 PY and 1.02 per 100 PY across the comparator arms for eight of the nine trials (i.e., excluding trial GPGP which did not include a comparator arm). Malignancies reported in >2 tirzepatide-treated subjects included 'Basal cell carcinoma' (n=5), 'Squamous cell carcinoma' (n=, 'Adenocarcinoma of the colon' (n=3), 'Renal cell carcinoma' (n=3), 'Renal neoplasm' (n=3), and 'Prostate cancer' (n=3). As previously discussed in Section 8.5.1, there were no cases of thyroid malignancy or C-cell hyperplasia reported in these trials. Although there was a numeric imbalance in renal cancers (i.e., 8 malignancies, all in tirzepatide-treated subjects), only two of these subjects (both randomized to the tirzepatide 5 mg arm) were exposed for >180 days. The following are brief clinical summaries of these two subjects:

- **Subject** (b) (6) a 69-year-old White female with T2D randomized to the tirzepatide 5 mg treatment arm, experienced an SAE of 'Renal neoplasm' (kidney tumor on the right) on Day 192, which was reported as severe in intensity and resulted in hospitalization. The subject had a BMI of 27.8 kg/m^2 (body weight 74.7 kg) and her relevant medical history included acute kidney injury and tubulointerstitial nephritis. No tobacco use or relevant concomitant mediation were reported. She denied a history of tobacco use. Her eGFR decreased from 57 mL/min/1.73 m^2 at baseline to 37 mL/min/1.73 m^2 on Day 169. The subject declined to share details of diagnostic test results and no treatment was reported for the SAE. Additionally, the date she was discharged from the hospital was not specified. The subject received her last dose of IP on Day 176 and discontinued the trial on Day 192, the day of the SAE. The investigator classified the SAE as not related to IP.

- **Subject** (b) (6) a 69-year-old White (Hispanic or Latino ethnicity) male with T2D randomized to the tirzepatide 5 mg treatment arm, experienced an SAE of 'Papillary renal cell carcinoma' on Day 678, which was reported as moderate in intensity. The subject had a BMI of 31.8 kg/m^2 (body weight 96.3 kg) and his medical history included hypertension, benign prostatic hyperplasia, and chronic kidney disease. He denied a history of tobacco use. Relevant concomitant medications included amlodipine and losartan. On Day 483, the subject was seen by a hepatologist to evaluate possible NAFLD. Subsequent abdominal MRI on Day 575 showed the presence of a 9 mm solid nodule in the posterior cortex of the left kidney. The subject was diagnosed with moderate papillary renal cell carcinoma on Day 678 and hospitalized for surgery on that same day. No action was taken regarding IP, and he was discharged from the hospital on Day 679. The last dose of IP was on Day 673 and the subject completed the trial on Day 722. The

investigator classified the SAE as not related to IP.

For Subject (b) (6) the diagnosis of renal neoplasm after approximately six months makes it unlikely to be causally related to tirzepatide. Whether tirzepatide may have contributed to disease progression is unknown. Subject (b) (6) had preexisting risk factors that included his age, sex, obesity, T2D, and hypertension.[273-282] However, a diagnosis of papillary renal cell carcinoma was made following approximately 1.9 years of exposure, making it more difficult to rule out an association with tirzepatide.

In 2013, the FDA issued a Drug Safety Communication to inform health care professionals on possible increased risk of pancreatitis and pancreatic duct metaplasia in subjects with T2D treated with incretin mimetics, including the GLP-1 RA pharmacologic class.[230] In the tirzepatide phase 2/3 clinical program, two tirzepatide-treated subjects experienced pancreatic cancers and a third developed a pancreatic cyst:

> **Subject** (b) (6) a 64-year-old White male randomized to the tirzepatide 5 mg treatment arm, discontinued study drug on Day 79 due to vomiting and was subsequently diagnosed with 'Pancreatic carcinoma' on Study Day 102. A CT scan showed metastases to the liver and peritoneum. Besides T2D, he had no relevant medical history. The subject reported current tobacco use. At screening his serum amylase was 65 IU/L (reference range: 13-53 IU/L) and the serum lipase was 212 IU/L (reference range: 13-60 IU/L). On Day 135 the subject died.

Due to the limited treatment exposure, smoking history, and T2D, I feel that it is unlikely that this case was drug related.

> **Subject** (b) (6) a 55-year-old Black male randomized to tirzepatide 5 mg, experienced an SAE of 'Adenocarcinoma' (acinar cell carcinoma) on Day 296. The subject had a BMI of 35.3 kg/m^2 (body weight 117 kg). His medical history included throat cancer, and he reported tobacco use. At screening, the serum pancreatic amylase was 73 IU/L (reference range: 13-53) and lipase was 39 IU/L (reference range: 13-60 IU/L). On Day 264, the subject had a workup for moderate hematuria. A CT scan showed renal and pancreatic lesions along with kidney stones, and an MRI showed a pancreatic mass (dates of imaging not specified). On Day 279, the serum pancreatic amylase was 126 IU/L and lipase was 62 IU/L. The subject was diagnosed with nephrolithiasis and renal neoplasm (renal lesion). The final dose of IP was on Day 260. Since the diagnosis was made during the safety follow-up period, treatment was not interrupted. On Day 341, a fine needle biopsy confirmed the diagnosis of adenocarcinoma (acinar cell carcinoma). The investigator considered this SAE as not related to IP.

Preexisting risk factors for this subject (e.g., race, obesity, tobacco use, and T2D)[283-296] make it difficult to establish a causal relationship or determine whether tirzepatide may have contributed to disease progression (e.g., tumor promoting activity).

> **Subject** (b) (6) a 70-year-old Asian male (Subject (b) (6) randomized to the tirzepatide 10 mg arm experienced a SAE of 'Pancreatic neoplasm' (pancreatic cyst) on Day 103. His serum pancreatic amylase was 168 IU/L (reference range 13-53 IU/L) and the serum lipase was 157 IU/L (reference range 13-60 IU/L) at screening. An abdominal ultrasound was performed which showed "ill-defined hypoechoic avascular structure within the pancreatic head." On Day 41, a CT showed a tubular cystic pancreatic head. The serum pancreatic amylase was 89 IU/L and lipase was 101 IU/L on Day 89. An MRI performed on Day 103 showed a tubular cystic lesion (1.7 x 0.9 cm) in the pancreatic uncinate process. On Day 131, the tirzepatide dose was decreased to 5 mg/week, and on Day 582, the subject completed the trial. The investigator considered the SAE as not related to study drug.

Due to elevated pancreatic enzymes at screening, and abnormal imaging following a relatively short treatment exposure, I agree that a causal association of tirzepatide with this SAE is not likely.

Based on the existing data from the tirzepatide phase 2/3 development program and relatively short treatment exposures, preexisting risk factors, and comorbidities, a causal association of tirzepatide with any specific malignancy type was not obvious. The data from the Applicant's CVOT (trial GPGN) and routine postmarketing surveillance following longer treatment exposures will be more informative for assessing the carcinogenic potential of tirzepatide.

Table 54: Malignancies — Side-by-Side Comparison of Phase 2/3 Trials (AS3)

	GPGK		GPGI		GPGF		GPGM		GPGH		GPGO		GPGB			GPGL		GPGP
Malignancies SMQs	PBO (N=115)	TZP ALL (N=363)	PBO (N=120)	TZP ALL (N=355)	PBO (N=26)	TZP ALL (N=85)	Ins Glar (N=1000)	TZP ALL (N=995)	Ins Deg (N=360)	TZP ALL (N=1077)	Dula 0.75 mg (N=159)	TZP ALL (N=477)	PBO (N=51)	Dula 1.5 mg (N=54)	TZP ALL (N=211)	Sema 1 mg (N=469)	TZP ALL (N=1409)	TZP ALL (443)
Subjects with Events Across Trials	ALL Comparators: 30/2354 subjects (1.3 %) [adj 1%] — TZP: 55/5415 subjects (1%) [adj 1.1%]																	
Total Subjects — no. (%)	1 (0.9)	1 (0.3)	2 (1.7)	3 (0.8)	0 (0.0)	0 (0.0)	19 (1.9)	19 (1.9)	1 (0.3)	11 (1.0)	2 (1.3)	5 (1.0)	1 (2.0)	1 (1.9)	0 (0.0)	3 (0.6)	11 (0.8)	5 (1.1)
Total Events — no.	1	2	2	3	0	0	22	25	1	17	2	6	1	2	0	3	11	6
PY	92.2	292.7	100.9	290.4	7.2	24.5	1566.4	1590.8	376.0	1125.1	168.0	502.6	28.1	30.1	116.2	392.7	1179.7	460.4
PYE	92.0	292.6	99.7	289.3	7.2	24.5	1552.7	1571.9	375.1	1119.3	167.3	499.8	28.0	29.7	116.2	391.8	1174.5	456.9
IR per 100 PY	1.09	0.34	2.01	1.04	0.00	0.00	1.22	1.21	0.27	0.98	1.20	1.00	3.57	3.37	0.00	0.77	0.94	1.09
MedDRA PT																		
Basal cell carcinoma	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	4 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)
Adenocarcinoma of colon	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.1)	0 (0.0)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Breast cancer stage II	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Colon cancer metastatic	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Invasive lobular breast carcinoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Metastases to lymph nodes	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Metastatic squamous cell carcinoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Neoplasm malignant	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Ocular neoplasm	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Ovarian cancer	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pancreatic carcinoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pancreatic neoplasm	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Papillary renal cell carcinoma	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Penile squamous cell carcinoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

	GPGK		GPGI		GPGF		GPGM		GPGH		GPGO		GPGB			GPGL		GPGP
Malignancies SMQs	**PBO (N=115)**	**TZP ALL (N=363)**	**PBO (N=120)**	**TZP ALL (N=355)**	**PBO (N=26)**	**TZP ALL (N=85)**	**Ins Glar (N=1000)**	**TZP ALL (N=995)**	**Ins Deg (N=360)**	**TZP ALL (N=1077)**	**Dula 0.75 mg (N=159)**	**TZP ALL (N=477)**	**PBO (N=51)**	**Dula 1.5 mg (N=54)**	**TZP ALL (N=211)**	**Sema 1 mg (N=469)**	**TZP ALL (N=1409)**	**TZP ALL (443)**
Prostate cancer	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.3)	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.6)	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Queyrat erythroplasia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Renal cancer recurrent	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Renal cell carcinoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Skin cancer	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Squamous cell carcinoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (<0.1)	0 (0.0)
Adenocarcinoma	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Adrenal neoplasm	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Bile duct adenocarcinoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Bladder cancer	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Bladder neoplasm	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Bladder transitional cell carcinoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Bone neoplasm	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Bowen's disease	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Breast neoplasm	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cerebellopontine angle tumour	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cholangiocarcinoma	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Colon cancer	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Endometrial adenocarcinoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Gastric neoplasm	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Glioblastoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Glioblastoma multiforme	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Invasive breast carcinoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

	GPGK		GPGI		GPGF		GPGM		GPGH		GPGO		GPGB			GPGL		GPGP
Malignancies SMQs	**PBO (N=115)**	**TZP ALL (N=363)**	**PBO (N=120)**	**TZP ALL (N=355)**	**PBO (N=26)**	**TZP ALL (N=85)**	**Ins Glar (N=1000)**	**TZP ALL (N=995)**	**Ins Deg (N=360)**	**TZP ALL (N=1077)**	**Dula 0.75 mg (N=159)**	**TZP ALL (N=477)**	**PBO (N=51)**	**Dula 1.5 mg (N=54)**	**TZP ALL (N=211)**	**Sema 1 mg (N=469)**	**TZP ALL (N=1409)**	**TZP ALL (443)**
Invasive ductal breast carcinoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Laryngeal squamous cell carcinoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Lung adenocarcinoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Lung adenocarcinoma stage IV	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Lung carcinoma cell type unspecified stage III	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Lung neoplasm malignant	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Lymphoproliferative disorder	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Metastases to bone	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Metastases to liver	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Myeloproliferative neoplasm	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Nasopharyngeal cancer	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Neoplasm	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Neoplasm skin	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Neuroendocrine carcinoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Non-Hodgkin's lymphoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
Renal neoplasm	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Squamous cell carcinoma of lung	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Squamous cell carcinoma of skin	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Testicular neoplasm	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Transitional cell carcinoma	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Uterine cancer	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

	GPGK		GPGI		GPGF		GPGM		GPGH		GPGO		GPGB			GPGL		GPGP
Malignancies SMQs	**PBO (N=115)**	**TZP ALL (N=363)**	**PBO (N=120)**	**TZP ALL (N=355)**	**PBO (N=26)**	**TZP ALL (N=85)**	**Ins Glar (N=1000)**	**TZP ALL (N=995)**	**Ins Deg (N=360)**	**TZP ALL (N=1077)**	**Dula 0.75 mg (N=159)**	**TZP ALL (N=477)**	**PBO (N=51)**	**Dula 1.5 mg (N=54)**	**TZP ALL (N=211)**	**Sema 1 mg (N=469)**	**TZP ALL (N=1409)**	**TZP ALL (443)**
Uterine neoplasm	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)

Source: Derived from the Applicant's ISS adsl.xpt and adae datasets, available at: \\CDSESUB1\evsprod\NDA215866\0001\m5\datasets\integrated-database\analysis\adam\datasets, and adapted from the Applicant's Regulatory Response (dated December 31, 2021), pages 1159-1161 of 1709, available at: \\CDSESUB1\evsprod\nda215866\0029\m1\us\regulatory-response--fda-midcycle-dec-2021-.pdf
Abbreviations: adj, study size adjusted percentage; Dula, dulaglutide; Ins Deg, insulin degludec; Ins Glar, insulin glargine; IR, incidence rate (100 times the number of subjects experiencing the event divided by PYE); ISS, Integrated Summary of Safety; MedDRA, Medical Dictionary for Regulatory Activities; PBO, placebo; PY, patient-year (sum of time from date of first dose to end of the study); PYE, total patient years at risk (sum of time period from date of first dose to the onset of the event for subjects with the event, and time period from date of first dose to the end of the study for subjects without the even); Sema, semaglutide; and TZP, tirzepatide.

8.5.15. Major Depressive Disorders/Suicidal Ideation

Depression is a relatively common comorbidity in patients with T2D, affecting approximately 17-28% of these individuals.[297-299] Additionally, T2D patients who develop depression may have an increased risk of acute and chronic complications of diabetes and mortality.[298] Product labeling for several GLP-1 RAs approved for chronic weight management (CWM) includes a Warnings and Precautions of suicidal behavior and ideation, and cautions healthcare providers to monitor for depression or suicidal thoughts.[4,6]

In the tirzepatide development program, AEs of major depressive disorder or suicidal ideation were considered topics of interest. The Applicant identified these events using the MedDRA PTs from the following SMQs (narrow): 'Depression' (excluding suicide and self-injury) and 'Suicide/self-injury'.

Across the Applicant's phase 2/3 trials (AS3), AEs of depression or suicidal ideation were reported in 19 subjects [adj 0.7%] in the comparator arms and 41 [adj 0.8% adj] tirzepatide-treated subjects (Table 55). In the tirzepatide arms, 'Depression' was the most common PT, reported in 28 subjects [adj 0.53% adj] compared to 13 subjects [adj 0.44% adj] in the comparator arms. The study size adjusted incidence rates[171,172] of events in tirzepatide-treated subjects were 0.72 events per 100 PY and 0.67 per 100 PY across the comparator arms for eight of the nine trials (i.e., excluding trial GPGP which did not include a comparator arm). Four subjects (b) (6) and 1 subject in the comparator arms had serious events, of which one death (completed suicide) occurred in a subject randomized to the tirzepatide 15 mg arm (b) (6). One of the four subjects who attempted suicide on Day 220 (Subject (b) (6)) had no prior history of depression or suicidal ideation. A brief narrative summary of this subject who died is as follows:

- **Subject** (b) (6) a 40-year-old Native American/Alaskan Native female with T2D randomized to the tirzepatide 15 mg arm, attempted suicide (took 10 pills of clonazepam 2 mg) on Day 220 and was hospitalized. Relevant medical history included hypothyroidism, obesity (BMI 32 kg/m^2), and radiculopathy. Concomitant medications at the time of this SAE included levothyroxine, gabapentin, and metformin. Clonazepam was not prescribed for this subject. The subject did not have a history of depression, and no major life events were reported. On Day 185, she had experienced an AE of depression, associated with mood, change in weight and appetite, loss of energy, fatigue, worthlessness, and guilt, and was subsequently diagnosed with a major depressive disorder. Thyroid function tests were not available at the time of the SAE or AE. No action was taken regarding her study medication, and she received her last dose of IP on Day 275 and completed the trial on Day 309. The investigator classified the SAE as not related to IP.

As this subject did not have a history of depression or suicidal ideation, it is not possible to rule out an association with tirzepatide. Additionally, attempted suicide has been previously reported with a GLP-1RA.[300,301] Whether her pre-existing medical conditions (e.g., T2D,[302-308] hypothyroidism,[309-313] obesity,[314,315] and radiculopathy[316,317]) or concomitant medications (e.g., gabapentin[318,319]) may have contributed to this event is unknown.

Generally, major imbalances in AEs of depression and/or suicidal ideation between the tirzepatide and comparator arms were not obvious. Although this risk is included as Warnings and Precautions in GLP-1 RA products indicated for CWM,[4,6] I do not feel that these AEs warrant inclusion in proposed tirzepatide labeling based on the data submitted to this NDA.

Table 55: Major Depressive Disorder/Suicidal Ideation — Side-by-Side Comparison of Phase 2/3 Trials (AS3)

	GPGK		GPGI		GPGF		GPGM		GPGH		GPGO		GPGB			GPGL		GPGP
Major Depressive Disorder/Suicidal Ideation or Behavior SMQs	**PBO (N=115)**	**TZP ALL (N=363)**	**PBO (N=120)**	**TZP ALL (N=355)**	**PBO (N=26)**	**TZP ALL (N=85)**	**Ins Glar (N=1000)**	**TZP ALL (N=995)**	**Ins Deg (N=360)**	**TZP ALL (N=1077)**	**Dula 0.75 mg (N=159)**	**TZP ALL (N=477)**	**PBO (N=51)**	**Dula 1.5 mg (N=54)**	**TZP ALL (N=211)**	**Sema 1 mg (N=469)**	**TZP ALL (N=1409)**	**TZP ALL (443)**
Subjects with Events Across Trials	**ALL Comparators: 19/2354 subjects (0.8%) [adj 0.7%] — TZP: 41/5415 subjects (0.8%) [adj 0.8%]**																	
Total Subjects — no. (%)	**1 (0.9)**	**1 (0.3)**	**0 (0.0)**	**3 (0.8)**	**0 (0.0)**	**1 (1.2)**	**12 (1.2)**	**7 (0.7)**	**3 (0.8)**	**7 (0.6)**	**0 (0.0)**	**2 (0.4)**	**0 (0.0)**	**0 (0.0)**	**2 (0.9)**	**3 (0.6)**	**16 (1.1)**	**2 (0.5)**
Total Events — no.	1	1	0	3	0	1	13	7	4	7	0	2	0	0	2	3	16	2
PY	92.2	292.7	100.9	290.4	7.2	24.5	1566.4	1590.8	376.0	1125.1	168.0	502.6	28.1	30.1	116.2	392.7	1179.7	460.4
PYE	91.5	292.3	100.9	289.0	7.2	24.3	1557.4	1584.9	374.7	1121.3	168.0	501.3	28.1	30.1	115.9	390.4	1172.3	459.5
IR per 100 PY	1.09	0.34	0.00	1.04	0.00	4.12	0.77	0.44	0.80	0.62	0.00	0.40	0.00	0.00	1.73	0.77	1.36	0.44
MedDRA PT																		
Depression	0 (0.0)	1 (0.3)	0 (0.0)	2 (0.6)	0 (0.0)	1 (1.2)	9 (0.9)	6 (0.6)	2 (0.6)	5 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.9)	2 (0.4)	10 (0.7)	1 (0.2)
Major depression	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Intentional overdose	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Adjustment disorder with depressed mood	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Depressed mood	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.2)	0 (0.0)
Depression suicidal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Discouragement	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Mixed anxiety and depressive disorder	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Persistent depressive disorder	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
Suicide attempt	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)

Source: Derived from the Applicant's ISS adsl.xpt and adae datasets, available at: \\CDSESUB1\evsprod\NDA215866\0001\m5\datasets\integrated-database\analysis\adam\datasets, and adapted from the Applicant's Regulatory Response (dated December 31, 2021), page 1162 of 1709, available at: \\CDSESUB1\evsprod\nda215866\0029\m1\us\regulatory-response--fda-midcycle-dec-2021-.pdf
Abbreviations: adj, study size adjusted percentage; Dula, dulaglutide; Ins Deg, insulin degludec; Ins Glar, insulin glargine; IR, incidence rate (100 times the number of subjects experiencing the event divided by PYE); ISS, Integrated Summary of Safety; MedDRA, Medical Dictionary for Regulatory Activities; PBO, placebo; PY, patient-year (sum of time from date of first dose to end of the study); PYE, total patient years at risk (sum of time period from date of first dose to the onset of the event for subjects with the event, and time period from date of first dose to the end of the study for subjects without the even); Sema, semaglutide; and TZP, tirzepatide.

8.6. Safety Analyses by Demographic Subgroups

The Applicant also assessed frequent TEAEs (>5%) by the following subgroups for the placebo-controlled pool (AS1): age <65 and ≥65, sex, race (American Indian/Alaska Native, Asian, Black/African American, White, Multiple), BMI (<30, ≥30 and <35, ≥35 kg/m^2), eGFR (<60, ≥60 mL/min/1.73 m^2), and ethnicity (Hispanic or Latino, not Hispanic or Latino, not reported). In this analysis, all subgroup-by-treatment interactions p-values were ≥0.1, except for diarrhea (p=0.07), in which a treatment effect was versus placebo was seen for males, but not females.

For completeness, I also reviewed serious AEs by age (<65 and ≥65 years old), sex, race, region (US and outside the US), and baseline eGFR (<60 or ≥60 mL/min/1.73 m^2). Although an increase in SAEs were observed in older individuals and subjects with impaired renal function, differences in the proportions of subjects with events between the tirzepatide and comparator arms did not appear to be clinically meaningful. Additionally, increases in the proportions of subjects with abnormal pulse rate increases were reported in subjects from Japan. Please refer to Section 8.4.6 for additional information.

8.7. Specific Safety Studies/Clinical Trials

Not applicable for this submission.

8.8. Additional Safety Explorations

8.8.1. Human Carcinogenicity or Tumor Development

Please see Section 8.5.14 for discussion of malignancies observed in the tirzepatide development program, and to Section 4.4 for assessment of the carcinogenicity potential of tirzepatide in the nonclinical program.

8.8.2. Human Reproduction and Pregnancy

In the Applicant's nonclinical program, fetal growth reductions and abnormalities were reported in pregnant rats administered tirzepatide at clinically relevant exposures during organogenesis. Similarly, fetal growth reductions were in rabbits administered tirzepatide during organogenesis. The observed effects in animals were potentially attributed to the pharmacological effects of tirzepatide on maternal weight and food consumption. Based on these data, there may be risks to the fetus from tirzepatide exposure during pregnancy.

In the tirzepatide clinical development program, women who were pregnant or breastfeeding were excluded from study participation due to insufficient data to determine possible drug-associated risks. During the trials, women of childbearing potential also were to undergo pregnancy testing (serum and urine) and use an adequate method of contraception. In the event of a pregnancy, IP was to be stopped and the investigators were to collect data on the outcome for both mother and fetus. At the time of the submission of this Application, there were seven pregnancies (six maternal exposures during the first trimester, and one paternal exposure). The pregnancy outcomes for the six maternal exposures (five in subjects randomized to tirzepatide, and one in a semaglutide-treated subject) included one elective termination, one spontaneous abortion, one live birth (reported in "good condition"), and two pregnancies without outcomes reported (Table 56). The outcome of the female partner for a male subject randomized to the tirzepatide 10 mg arm was not reported.

Table 56: Pregnancies in Tirzepatide Completed Clinical Trials

Subject ID	Maternal Age (years)	Treatment	Estimated Exposure (weeks)	Pregnancy Outcome
(b) (6)	28	TZP 5 mg	7.9	Live birth (good condition)
	28	Sema 1 mg	9.1	NR
	35	TZP 15 mg	5.6	NR
	27	TZP 5 mg	8.9	NR
	39	TZP 10 mg	16.3	NR
	41	TZP 10 mg	5.1	Spontaneous abortion
	26	TZP 5 mg	1.7	Elective termination

Source: Adapted from the Applicant's Clinical Summary of Safety, pages 273-274 of 327, available at: \\CDSESUB1\evsprod\nda215866\0001\m2\27-clin-sum\clin-safety-sum--tzp-t2dm-.pdf
Abbreviations: NR, not reported; Sema, semaglutide; and TZP, tirzepatide.
* Partner of a male subject.

In the 4MSU the Applicant identified 18 additional pregnancies in their ongoing trials. Two pregnancies (paternal pregnancy and an ectopic pregnancy; treatment assignments remain blinded) occurred in their ongoing phase 3 T2D trials (GPHD, and GPHO), and one subject (ectopic pregnancy) received tirzepatide in GPHO. (b) (4) there were 15 pregnancies (treatment assignments remain blinded), of which there was one event each reported as: induced abortion, spontaneous abortion, early pregnancy and threatened abortion, ectopic pregnancy, and pregnant spouse.

Dr. Wenjie Sun, from the Division of Pediatric and Maternal Health (DPMH), was consulted to review proposed tirzepatide labeling for consistency with the Pregnancy and Lactation Labeling

Rule (PLLR). In her review she noted that currently there are no published reports on the use of tirzepatide during pregnancy or lactation. However, she acknowledged that GLP-1 is present in human milk and could potentially be important to infants for appetite and growth regulation.[320] Dr. Sun felt that the available human data regarding tirzepatide use during pregnancy were insufficient to assess potential drug-related risks (i.e., congenital malformations, miscarriage, or adverse maternal or fetal outcomes). Further, no data was provided by the Applicant on the presence of tirzepatide in either animal or human milk, and the effects of tirzepatide on breastfed infants or milk production were not assessed. Labeling of most GLP-1 RA products report the presence of drug substance in animal milk (mice or rats).[2-9,24-26] The molecular weights of these products (3751.2-4858.5) are large and similar to tirzepatide (i.e., 4813 Daltons).

As there are insufficient data regarding tirzepatide use in pregnancy, DPMH initially recommended a postmarketing descriptive pregnancy safety study to collect these data. However, upon further discussion with the Division, it was decided that a postmarketing pregnancy study would not be necessary. Additionally, since this product will be used in females of reproductive potential and there is a lack of human data regarding the use of tirzepatide during lactation, DPMH recommended a postmarketing clinical lactation study (milk only). Please refer to Dr. Sun's review (dated January 19, 2022) and to her Addendum (data March 24, 2022) for more detailed information on pregnancy and lactation risks associated with tirzepatide, labeling recommendations to address concerns that tirzepatide may reduce the efficacy of oral hormonal contraceptives due to delayed gastric emptying (please refer to Section 4.5.2), and recommendations for compliance of tirzepatide labeling with the PLLR format.

8.8.3. Pediatrics and Assessment of Effects on Growth

The clinical trials included in this Application did not enroll pediatric subjects (i.e., for eligibility subjects had to be ≥18 years of age). Please refer to Section 12 for information related to postmarketing requirements for pediatric assessments.

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

In the tirzepatide clinical development program, there was a single AE of intentional overdose (i.e., with amitriptyline 1120 mg) on Day 31 in a 36-year-old female subject (b) (6) with a history of depression who was randomized to the tirzepatide 5 mg arm, and no cases of drug withdrawal identified using the 'Drug withdrawal' SMQ. The concern for overdose, drug abuse, withdrawal, or rebound is low with the use of tirzepatide and GLP-1 RA products. Considering the mechanism of action of tirzepatide and other GLP-1 RA, and the extensive clinical experience worldwide with these products without evidence of abuse potential, I feel that an association of tirzepatide with this event is unlikely. Please refer to Section 8.5.15 for further discussion of depression/suicidality AEs reported in this Application.

8.9. Safety in the Postmarket Setting

8.9.1. Safety Concerns Identified Through Postmarket Experience

Since tirzepatide is not approved in any country, there is no postmarketing experience with this product. As with other products with GLP-1 RA properties, tirzepatide labeling also will include Warnings and Precautions of the risk of thyroid C-cell tumors, pancreatitis, hypoglycemia with concomitant use of insulin secretagogues or insulin, hypersensitivity reactions, acute kidney injury, severe gastrointestinal adverse events (including acute gallbladder disorder), and diabetic retinopathy complications. Additionally, the Applicant is conducting a CVOT (trial GPGN) to evaluate CV safety and will be required to evaluate the safety and efficacy of tirzepatide in pediatric subjects, conduct a lactation (i.e., milk only) study, and participate in a MTC registry based case series study to assess the long-term risk of MTC with tirzepatide. Please refer to Section 12 for additional information.

Following review of the 4-MSU, submitted on December 9, 2021, there were no new/important safety signals identified in the 15 ongoing clinical trials.

8.9.2. Expectations on Safety in the Postmarket Setting

The tirzepatide clinical development program provides a substantial amount of safety information/data to characterize the safety profile of tirzepatide in an adult T2D population. I believe that the observed safety concerns identified in these submissions can be adequately addressed with proposed product labeling and routine pharmacovigilance. In conclusion, no additional risk evaluation and mitigation strategy is recommended for this product.

8.9.3. Additional Safety Issues from Other Disciplines

Merkel cell carcinoma (MCC) is a rare, aggressive, cutaneous malignancy, with an incidence rate of approximately 0.7 cases/100,00 person years in the United States.[321] Typically, MCC affects sun-exposed skin of elderly fair-skinned individuals, and has been associated with high rates of recurrence, metastases, and mortality.[322,323] The Division of Pharmacovigilance (DPV) previously identified eight FDA Adverse Event Reporting System (FAERS) cases of MCC in postmarketing reports associated with the following GLP-1 RAs: dulaglutide (n=1), exenatide (n=1), and liraglutide (n=5; of which 2 cases reported previous exposure to exenatide). A Newly Identified Safety Signal (NISS) 495 was opened April 2018, but subsequently closed due to insufficient information. The Division of Epidemiology (DEPI) was asked to evaluate published observational studies and the potential for Sentinel Investigation. A review of published literature did not identify any observational studies of MCC associated with GLP-1 RA use. Following an evaluation of the Sentinel Distributed Database (January 1, 2008, to January 31, 2018), DEPI felt that the relatively short follow-up time of GLP-1 RA use (approximately 26.3 months) may not be

sufficient to identify an adequate number of MCC cases, which may take years to develop (e.g., <81 cases during 10 years of follow-up of 1,158,706 individuals in the Sentinel new user population). Additionally, due to concerns of misclassification/misdiagnosis, delays in the diagnosis, inability to assess unmeasured confounders (e.g., ultraviolet [UV] exposure and immunosuppression), and limitations in outcome identification/validation, DEPI felt that a Sentinel Investigation would not provide sufficient information on the relationship between GLP-1 RA and MCC.

The safety database in the phase 2/3 development program included 5415 subjects who received tirzepatide for 4833.1 patient-years of exposure (up to 106 weeks in trial GPGM). In these trials, there were 15 cases of cancer involving the skin in the tirzepatide arms, and four in the comparator arms. The reported TEAEs in the tirzepatide-treated subjects included 'Basal cell carcinoma' (n=5); 'Squamous cell carcinoma (n=3); 'Neoplasm skin' (n=2); Bowen's disease'; (n=1); 'Penile squamous cell carcinoma' (n=1); 'Queyrat erythroplasia' (n=1); 'Skin cancer' (n=1); and 'Squamous cell carcinoma of skin (n=1). No TEAEs were coded as 'Merkel cell carcinoma' or 'Neuroendocrine carcinoma of the skin', and review of the three cases involving skin neoplasms/cancer was not informative (all events occurring following ≤4 months of exposure):

- **Subject** (b) (6) a 72-year-old White male randomized to the tirzepatide 15 mg arm, with a TEAE of 'Neoplasm skin' subsequently diagnosed as basal cell carcinoma on Day 80
- **Subject** (b) (6) a 73-year-old White male randomized to the tirzepatide 15 mg arm, with a TEAE of 'Skin cancer' reported on Day 122
- **Subject** (b) (6) a 46-year-old Asian female randomized to the tirzepatide 5 mg arm, with a TEAE of 'Neoplasm skin' on Day 40

Although the data from the tirzepatide clinical development program do not indicate a safety signal for MCC, treatment exposures were limited to adequately rule out an association.

Integrated Assessment of Safety

This safety review primarily focused on safety database submitted from nine completed phase 2/3 trials (AS3) that randomized 5415 subjects to tirzepatide for a total treatment exposure of 4833.1 PYs. Overall, the safety findings reported in the tirzepatide clinical development program were consistent with the known safety profiles of other products with GLP-1 RA properties. Compared to placebo, higher proportions of subjects experienced the following common AEs (≥5% of subjects): nausea, diarrhea, decreased appetite, dyspepsia, vomiting, constipation, and abdominal pain. All these AEs are already described in proposed product labeling.

Of concern, there was an increased risk of pancreatitis associated with tirzepatide (i.e., 0.11 vs. 0.23 events/100 subject years in the placebo and tirzepatide treatment arms, respectively). This

risk is appropriately described in Section 5 (Warnings and Precautions) of proposed labeling. Additionally, acute gallbladder disorders will be included in Section 5 due to the relatively rapid and substantial weight loss (15% reductions) observed across the five global phase 3 trials, and higher numbers of tirzepatide-treated subjects experiencing these events.

Except for AEs common to injectable GLP-1 RAs (e.g., gastrointestinal disorders, hypersensitivity reactions, and injection site reactions), clinically meaningful imbalances were not observed for other AESI across the Applicant's phase 2/3 program. Additionally, review of the safety data (i.e., deaths, SAEs, and discontinuation due to AEs) using FMQs did not identify additional safety concerns.

In summary, taking into consideration the efficacy finding from the five global phase 3 trials, I conclude that the safety data submitted to this NDA show that the safety profile of tirzepatide is acceptable for approval of this product.

9. Advisory Committee Meeting and Other External Consultations

This Application was not discussed at an advisory committee (AC) meeting.

10.Labeling Recommendations

10.1. Prescription Drug Labeling

The Applicant has submitted proposed labeling for MOUNJARO, which included relevant clinical trial data from their five global phase 3 trials (GPGH, GPGI, GPGK, GPGL, and GPGM) to establish efficacy, as well supportive safety data from phase 2 (GPGB, and GPGF) and phase 3 (GPGO, and GPGP) clinical trials. The labeling of these products was reviewed for consistency with approved labeling for other GLP-1 RA products, including ADLYXIN (lixisenatide),[25] BYDUREON (exenatide extended-release; discontinued),[8] BYDUREON BCISE (exenatide extended-release),[9] BYETTA (exenatide),[24] OZEMPIC (semaglutide injection),[2] RYBELSUS (semaglutide tablets),[3] SAXENDA (liraglutide),[6] SOLIUA (insulin glargine and lixisenatide),[26] TANZEUM (albiglutide; discontinued),[10] TRULICITY (dulaglutide),[11] VICTOZA (liraglutide),[5] WEGOVY (semaglutide),[4] and XULTOPHY 100/3.6 (insulin degludec/liraglutide),[7] and to remove any reassuring language that might imply safety or efficacy claims. Proposed tirzepatide labeling conforms to the final rule governing the "Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products" released on January 24, 2006.[324] Relevant labeling issues identified that are the subject of this review include the following:

Section 1. INDICATIONS AND USAGE

- **Limitations of Use:** (b) (4)

  I disagree with this limitation of use. A numeric imbalance of subjects experiencing acute pancreatitis, favoring the comparator arms, was observed. Further, the data submitted in this Application do not support cautious use of tirzepatide in this patient population.

  Additionally, due to a boxed warning of nonclinical findings of thyroid C-cell tumors in rodents and an unknown risk of thyroid tumors (including MTC) in humans, the Division has previously recommended that labeling of GLP-1 RA products which have not demonstrated CVD benefit include the following limitation of use: (b) (4) owever, based on reassuring results from the Applicant's CVMA, and statistically and clinically meaningful reductions in HbA1c and body weight across the five global phase 3 trials, which included semaglutide and basal insulins as active comparators and at-risk patient populations (e.g., subjects with established CVD, or inadequate glycemic control on up to three antihyperglycemic products or basal insulin), this limitation of use was considered not necessary for tirzepatide labeling.

Section 2. DOSAGE AND ADMINISTRATION

Subsection 2.1. Dosage:

- Language related to dose titration of tirzepatide and missed doses revised for consistency with other GLP-1 RA products.

- To inform prescribers that the tirzepatide 2.5 mg dose is intended for initiation of therapy and is not effective for glycemic control, the following language was added:

  "The 2.5 mg dosage is for treatment initiation and is not intended for glycemic control."

- To inform prescribers of the timing between doses for dose changes the following language was added:

  "The day of weekly administration can be changed, if necessary, as long as the time between the two doses is at least 3 days (72 hours)."

Section 4. CONTRAINDICATIONS

- To replace serious hypersensitivity to tirzepatide or any of the (b) (4) to

"excipients in MOUNJARO."

Section 5. Warnings and Precautions

Subsection 5.2. Pancreatitis:

- The Applicant proposed cautious use of tirzepatide if patients had a history of pancreatitis. However, the data submitted in this Application do not support cautious use of tirzepatide in this patient population. Additionally, risk minimizing language was removed, and the Applicant was informed that the Warning and Precautions section should include the following: a succinct description of the adverse reaction (AR) and outcome; numerical estimate or AR rate; known risk factors for the AR; and steps to take to prevent, mitigate, monitor for, or manage the AR.

Subsection 5.4. Hypersensitivity Reactions:

- To describe reported severe or serious hypersensitivity reactions as follows:

> "Hypersensitivity reactions have been reported with MOUNJARO in clinical trials (e.g., urticaria and eczema) and were sometimes severe. If hypersensitivity reactions occur, discontinue use of MOUNJARO; treat promptly per standard of care, and monitor until signs and symptoms resolve. Do not use in patients with a previous serious hypersensitivity reaction to tirzepatide or any of the excipients in MOUNJARO *[see Contraindications (4)]*."

Subsection 5.6 Severe Gastrointestinal Disease:

- [redacted] (b) (4) se of tirzepatide has been associated with gastrointestinal adverse reactions, which were sometimes severe.

Subsection 5.7 Diabetic Retinopathy Complications in Patients with a History of Diabetic Retinopathy:

- [redacted] (b) (4)

"Rapid improvement in glucose control has been associated with a temporary

worsening of diabetic retinopathy. MOUNJARO has not been studied in patients with non-proliferative diabetic retinopathy requiring acute therapy, proliferative diabetic retinopathy, or diabetic macular edema. Patients with a history of diabetic retinopathy should be monitored for progression of diabetic retinopathy."

Subsection 5.8 Acute Gallbladder Disease

- To conform with a recent SLC Notification (please refer to Section 8.5.8), acute gallbladder disease was added to the Warnings and Precautions section to inform prescribers of the risk of acute gallbladder disease associated with GLP-1 RA products. Proposed language will include the following:

"Acute events of gallbladder disease such as such as cholelithiasis or cholecystitis have been reported in GLP-1 receptor agonist trials and postmarketing. In MOUNJARO placebo-controlled clinical trials, acute gallbladder disease (cholelithiasis, biliary colic, and cholecystectomy) was reported by 0.6% of MOUNJARO-treated patients and 0% of placebo-treated patients. If cholelithiasis is suspected, gallbladder diagnostic studies and appropriate clinical follow-up are indicated."

Section 6. ADVERSE REACTIONS

(b) (4)

Subsection 6.1 Clinical Trials Experience:

Gastrointestinal Adverse Reactions

- The language in this subsection was revised to better inform prescribers of frequency, severity, and management of gastrointestinal adverse reactions reported across their phase 3 program:

"In the pool of placebo-controlled trials, gastrointestinal adverse reactions occurred more frequently among patients receiving MOUNJARO than placebo (placebo 20.4%, MOUNJARO 5 mg 37.1%, MOUNJARO 10 mg 39.6%, MOUNJARO 15 mg 43.6%). More patients receiving MOUNJARO 5 mg (3.0%), MOUNJARO 10 mg (5.4%), and MOUNJARO 15 mg (6.6%) discontinued treatment due to gastrointestinal adverse reactions than patients receiving placebo (0.4%). The majority of reports of nausea, vomiting, and/or diarrhea occurred during dose escalation and decreased over time.

The following gastrointestinal adverse reactions were reported more frequently in MOUNJARO-treated patients than placebo-treated patients (frequencies listed, respectively, as: placebo; 5 mg; 10 mg; 15 mg): eructation (0.4%, 3.0%, 2.5%, 3.3%), flatulence (0%, 1.3%, 2.5%, 2.9%), gastroesophageal reflux disease (0.4%, 1.7%, 2.5%, 1.7%), abdominal distension (0.4%, 0.4%, 2.9%, 0.8%)."

Hypoglycemia

- The data in the table and text was revised to reflect (b) (4) hypoglycemia adverse reactions separately (b) (4)

Heart Rate Increase

- The Applicant originally proposed to report increases in pulse rate as a pharmacodynamic response in Section (b) (4) However, class labeling for GLP-1 RA products includes this information in Section 6.1. The proposed language is as follows:

"In the pool of (b) (4) placebo-controlled trials, treatment with MOUNJARO resulted in a mean increase in heart rate of 2 to 4 beats per minute compared to a mean increase of 1 beat per minute in placebo-treated patients. Episodes of sinus tachycardia, associated with a concomitant increase from baseline in heart rate of ≥15 beats per minute, also were reported in 4.3%, 4.6%, 5.9% and 10% of subjects treated with placebo, MOUNJARO 5 mg, 10 mg, and 15 mg, respectively. For patients enrolled in Japan, these episodes were reported in 7% (3/43), 7.1% (3/42), 9.3% (4/43), and 23% (10/43) of patients treated with placebo, MOUNJARO 5 mg, 10 mg, and 15 mg, respectively. The clinical relevance of heart rate increases is uncertain."

Hypersensitivity (b) (4) Reactions

- To inform prescribers of the occurrence of hypersensitivity (b) (4) reactions with tirzepatide, and association of these AEs with ADA positivity, the following language was added to these two subsections:

"*Hypersensitivity Reactions*
Hypersensitivity reactions have been reported with MOUNJARO in the pool of placebo-controlled trials, sometimes severe (e.g., urticaria and eczema); hypersensitivity reactions were reported in 3.2% of MOUNJARO-treated patients compared to 1.7% of placebo-treated patients.

In the pool of clinical trials, hypersensitivity reactions occurred in 106/2,570 (4.1%) of MOUNJARO-treated patients with anti-tirzepatide antibodies and in 73/2,455 (3.0%) of MOUNJARO-treated patients who did not develop anti-tirzepatide antibodies [see Clinical Pharmacology (12.6)]."

"Injection Site Reactions

In the pool of placebo-controlled trials, injection site reactions were reported in 3.2% of MOUNJARO-treated patients compared to 0.4% of placebo-treated patients.

In the pool of clinical trials, injection site reactions occurred in 119/2,570 (4.6%) of MOUNJARO-treated patients with anti-tirzepatide antibodies and in 18/2,455 (0.7%) of MOUNJARO-treated patients who did not develop anti-tirzepatide antibodies *[see Clinical Pharmacology (12.6)]*."

(b) (4)

Acute Gallbladder Disease

- The following text was added to describe adverse reactions of acute gallbladder disease reported in the placebo-controlled trials:

  (b) (4) placebo-controlled clinical trials, acute gallbladder disease (cholelithiasis, biliary colic and cholecystectomy) was reported by 0.6% of MOUNJARO-treated patients and 0% of placebo-treated patients."

Laboratory Abnormalities

- The Applicant proposes to report increases in serum amylase and lipase (b) (4) in Section 6.1 for other GLP-1 RA products. The revised language in this section will include the following:

  "In the pool of placebo-controlled clinical trials, treatment with MOUNJARO resulted in mean increases from baseline in serum pancreatic amylase concentrations of 33% to 38% and serum lipase concentrations of 31% to 42%. Placebo-treated patients had a mean increase from baseline in pancreatic amylase of 4% and no changes were observed in lipase. The clinical significance of elevations in lipase or amylase with MOUNJARO is unknown in the absence of other signs and symptoms of pancreatitis."

(b) (4)

(b) (4)

- In accordance with the content and format recommendations in the draft guidance for industry: Immunogenicity Information in Human Prescription Therapeutic Protein and Select Drug Product Labeling—Content and Format (February 2022),[(4)] the information in this section and proposed edits were placed in Section 12.6.

Section 7. DRUG INTERACTIONS

Subsection 7.1 Concomitant Use with an Insulin Secretagogue (e.g., Sulfonylurea) or Insulin:

- To inform prescribers of the risk of hyperglycemia when initiating tirzepatide with insulins secretagogues or insulins, the language in the subsection was revised as follow:

  "When initiating MOUNJARO, consider reducing the dose of concomitantly administered insulin secretagogues (e.g., sulfonylureas) or insulin to reduce the risk of hypoglycemia *[see Warnings and Precautions (5.3)].*

Subsection 7.2 Oral Medications:

(b) (4)

- To inform prescribers of the risk of a DDI associated with tirzepatide when co-administered with oral contraceptives (please refer to Section 4.5.2), the following language was added to the subsection:

  "Advise patients using oral hormonal contraceptives to switch to a non-oral contraceptive method, or add a barrier method of contraception for 4 weeks after initiation and for 4 weeks after each dose escalation with MOUNJARO. Hormonal contraceptives that are not administered orally should not be affected *[see Use in Specific Populations (8.3) and Clinical Pharmacology (12.2, 12.3)]*."

Section 8. USE IN SPECIFIC POPULATIONS

Subsection 8.1 Pregnancy:

- This section was edited to ensure compliance with PLLR labeling format.

Subsection 8.2 Lactation:

- This section also was edited for compliance with the PLLR format.

[(4)] The Agency updates guidances periodically. For the most recent version of the guidance, check the FDA Guidance Documents Database: https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

Subsection 8.3 Females and Males of Reproductive Potential:

- This section was edited for to correspond to Subsections 7.2 and 12.3:

  "Contraception
  Use of MOUNJARO may reduce the efficacy of oral hormonal contraceptives due to delayed gastric emptying. Advise patients using oral hormonal contraceptives to switch to a non-oral contraceptive method, or add a barrier method of contraception for 4 weeks after initiation and for 4 weeks after each dose escalation with MOUNJARO *[see Drug Interactions (7.2) and Clinical Pharmacology (12.2, 12.3)]*."

Subsection 8.6 Renal Impairment:

- The following information was added to be consistent with the language in GLP-1 RA product labeling.

  "Monitor renal function when initiating or escalating doses of MOUNJARO in patients with renal impairment reporting severe adverse gastrointestinal reactions *[see Warnings and Precautions (5.5)]."*

Section 10. OVERDOSAGE

- This section was revised to include language informing prescribers to contact the Poison Control in the event of an overdose.

Section 12. CLINICAL PHARMACOLOGY

Section 11. DESCRIPTION

- This section was revised to use the Established Pharmacologic Class (EPC) designation of tirzepatide, and to be consistent with approved GLP-1 RA product labeling:

  "MOUNJARO (tirzepatide) injection, for subcutaneous use, contains tirzepatide, a once weekly GIP receptor and GLP-1 receptor agonist. It is a 39-amino acid modified peptide based on the GIP sequence. Tirzepatide contains 2 non-coded amino acids (aminoisobutyric acid, Aib) in positions 2 and 13, a C-terminal amide, and Lys residue at position 20 that is attached to 1,20-eicosanedioic acid via a linker. The molecular weight is 4813.53 Da and the empirical formula is $C_{225}H_{348}N_{48}O_{68}$."

Subsection 12.1 Mechanism of Action:

- This section was revised to use the Established Pharmacologic Class (EPC) designation of tirzepatide, and to be consistent with approved GLP-1 RA product labeling:

  "Tirzepatide is a GIP receptor and GLP-1 receptor agonist. It is a 39-amino acid

modified peptide with a C20 fatty diacid moiety 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 and GLP-1.

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

Subsection 12.2 Pharmacodynamics:

- This section was revised for consistency with approved GLP-1RA product labeling, (b) (4)

(b) (4)

Subsection 12.3 Pharmacokinetics:

- This section was revised to inform prescribers that in vitro studies have shown a low potential for tirzepatide to inhibit or induce CYP enzymes or inhibit drug transporter. Additionally, the following language was included to caution prescribers of a potential DDI of tirzepatide with COC:

"*Potential for Tirzepatide to Influence the Pharmacokinetics of Other Drugs*
In vitro studies have shown low potential for tirzepatide to inhibit or induce 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 *[see Drug Interactions (7.2)].*

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 maximum concentration (Cmax) was reduced by 50%, and the median peak plasma concentration (tmax) occurred 1 hour later. After coadministration at week 4, there was no meaningful impact on acetaminophen Cmax and tmax. Overall acetaminophen exposure ($AUC_{0\text{-}24hr}$) 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 Cmax 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 tmax of 2.5 to 4.5 hours was observed."

Subsection 12.6 Immunogenicity:

- This section was moved from [redacted] (b) (4) in accordance with the content and format recommendations in the draft guidance for industry: Immunogenicity Information in Human Prescription Therapeutic Protein and Select Drug Product Labeling—Content and Format (February 2022).[5] The revised language included the following:

  "The observed incidence of anti-drug antibodies is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of anti-drug antibodies in the trials described below with the incidence of anti-drug antibodies in other trials, including those of tirzepatide or of GLP-1 receptor agonist products.

  During the 40- to 104-week treatment periods with ADA sampling conducted up to 44 to 108 weeks in seven clinical trials in adults with type 2 diabetes mellitus, 51% (2,570/5,025) of MOUNJARO-treated patients developed anti-tirzepatide antibodies. In these trials, anti-tirzepatide antibody formation in 34% and 14% of MOUNJARO-treated patients showed cross-reactivity to native GIP or native GLP-1, respectively.

  Of the 2,570 MOUNJARO-treated patients who developed anti-tirzepatide antibodies during the treatment periods of these seven trials, 2% and 2% developed neutralizing antibodies against tirzepatide activity on the GIP or GLP-1 receptors, respectively, and 0.9% and 0.4% developed neutralizing antibodies against native GIP or GLP-1, respectively.

  There was no identified clinically significant effect of [redacted] (b) (4) antibodies on pharmacokinetics or effectiveness of MOUNJARO. More MOUNJARO-treated patients who developed anti-tirzepatide antibodies experienced hypersensitivity reactions or injection site reactions than those who did not develop these antibodies [see Adverse Reactions (6.1)]."

Section 13. NONCLINICAL TOXICOLOGY

Subsection 13.1 Carcinogenesis, mutagenesis, impairment of fertility:

- The proposed language by the Applicant: [redacted] (b) (4) was revised for clarity as follows:

[5] The Agency updates guidances periodically. For the most recent version of the guidance, check the FDA Guidance Documents Database: https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

"A statistically significant increase in thyroid C-cell adenomas was observed in males (≥0.5 mg/kg) and females (≥ 0.15 mg/kg), and a statistically significant increase in thyroid C-cell adenomas and carcinomas combined was observed in males and females at all doses examined."

Section 14. CLINICAL STUDIES:

Subsection 14.2 Monotherapy Use of MOUNJARO in Patients with Type 2 Diabetes Mellitus:

- The description of the racial distributions for trial GPGI should include American Indians/Alaska Natives, which made up 25% of the population. American Indians/Alaska Natives are often underrepresented in antihyperglycemic clinical trials. These data are informative and should be described for respective clinical trials when appropriate. It is notable that for several of the five global phase 3 trials, the proportions of subjects were higher than those for several other subgroups described in Section 14.

- The Applicant was asked to specify the statistical methodology used to analyze the binary endpoint, "patients (%) achieving HbA1c <7%" and to provide additional clarification on the statistical methodology used.

Subsections 14.3: (b) (4)

- To help inform prescribers of the adequacy of the TTT insulin titration algorithms, the Applicant was asked to include the proportions of subjects who achieved the FSG targets of <90 mg/dL for trial GPGH and <100 mg/dL for trial GPGM.

Section 16. HOW SUPPLIED/STORAGE AND HANDLING

Subsection 16.2 Storage and Handling:

- The Agency recommended that storage temperatures in the prescribing information and container closure labeling be expressed in Celsius units first, with Fahrenheit units in parentheses, to maintain consistency with the current policy applied to drug products, including injectable dosage forms, and to comply with the USP requirement that storage temperatures be expressed in Celsius unit.

Section 17. PATIENT COUNSELING INFORMATION

- This section includes the following statements to inform patients of severe gastrointestinal disease, acute gallbladder disease, and pregnancy risk with oral hormonal contractive products:

"Severe Gastrointestinal Adverse Reactions

> Inform patients of the potential risk of severe gastrointestinal adverse reactions. Instruct patients to contact their healthcare provider if they have severe or persistent gastrointestinal symptoms *[see Warnings and Precautions (5.6)]*."
>
> "Acute Gallbladder Disease
> Inform patients of the risk of acute gallbladder disease. Instruct patients to contact their healthcare provider for appropriate clinical follow-up if gallbladder disease is suspected *[see Warnings and Precautions (5.8)]*."
>
> "Contraception
> Use of MOUNJARO may reduce the efficacy of oral hormonal contraceptives. Advise patients using oral hormonal contraceptives to switch to a non-oral contraceptive method or add a barrier method of contraception for 4 weeks after initiation and for 4 weeks after each dose escalation with MOUNJARO *[see Drug Interactions (7.2), Use in Specific Populations (8.3), and Clinical Pharmacology (12.3)]*."

Additionally, Dr. Ariane Conrad, from the Division of Medication Error Prevention and Analysis (DMEPA), performed a risk assessment of the proposed prescribing information (PI) for MOUNJARO to identify areas of vulnerability that could lead to medication errors. Based on the findings from her review, she felt that MOUNJARO labeling was acceptable from a medication error perspective. She provided recommendations to improve clarity in proposed labeling, as well as general comments to the Applicant for container and carton labeling. Please refer to Dr. Conrad's review (dated February 9, 2022) for additional information.

10.2. Nonprescription Drug Labeling

Not applicable for this submission.

11. Risk Evaluation and Mitigation Strategies (REMS)

A Risk Management Plan was not provided with this NDA. The Applicant's justification for not providing one was the following: "Upon review of the safety data included in this application, Lilly proposes that labeling will be adequate to communicate safety risks to patients and health care professionals. Therefore, Lilly has not proposed a Risk Evaluation and Mitigation Strategy."

12. Postmarketing Requirements and Commitments

The Applicant will be required to conduct the following three PMR studies:

1) A randomized, double-blind, placebo-controlled trial in pediatric T2D patients.
2) A milk-only lactation study
3) A medullary thyroid carcinoma registry-based case series study

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

The Division agreed to waiving the pediatric study requirement for ages 0 through 9 years (inclusive) because necessary studies are impossible or highly impracticable. This is because there are too few children in this age range with type 2 diabetes mellitus to study.

We agree to deferring submission of the Applicant's pediatric study for ages 10 to 17 years (inclusive) for this application because this product is ready for approval for use in adults and the pediatric study has not been completed.

The Applicant's deferred pediatric study required under section 505B(a) of the FDCA is a required postmarketing study. The status of this postmarketing study must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(C) of the FDCA. This required study is listed below.

1) Conduct a 30-week, randomized, double-blind, placebo-controlled, multicenter, parallel- arm study of the safety and efficacy of Mounjaro (tirzepatide) for the treatment of type 2 diabetes mellitus in pediatric patients ages 10 to 17 years (inclusive), followed by a 22- week open-label extension. Background therapy will consist of either metformin, insulin, or metformin plus insulin.

   Study Completion: 12/2027
   Final Report Submission: 09/2028

REQUIRED LACTATION STUDY

Additionally, the Applicant will be required to conduct the following lactation study:

2) Conduct a milk-only lactation study in lactating women who have received a dose of tirzepatide to assess concentrations of tirzepatide in breast milk using a validated assay.

Draft Protocol Submission:	January 2023
Final Protocol Submission:	July 2023
Study Completion:	July 2024
Final Report Submission:	July 2025

REQUIRED MEDULLARY THYROID CANCER SURVEILLANCE STUDY

Since 2010 (i.e., the approval of the first long-acting GLP-1 RA[118]), Sponsors of long-acting GLP-1 RAs have been required to participate in a MTC surveillance study (registry-based case series of at least 15 years in duration) as a postmarketing requirement (PMR) to systematically monitor the annual incidence of MTC in the United States (US), and to identify any increase in incidence related to the introduction of long-acting GLP-1 RAs into the US marketplace.[204] This registry aims to monitor the annual incidence and change in incidence of MTC; and document demographic, medical and risk factors related to the MTC diagnosis among MTC cases in the MTC participating State Cancer Registries. All MTC cases are clinically confirmed, and the MTC case series registry verifies GLP-1 RA treatment through treating physicians. Currently, the MTC case series registry covers 85% of the U.S. population from the 28 participating states. As of January 2022, there were a total of 5,190 eligible MTC cases reported to the registry and 4,781 finished study participation with completion of follow-up efforts.

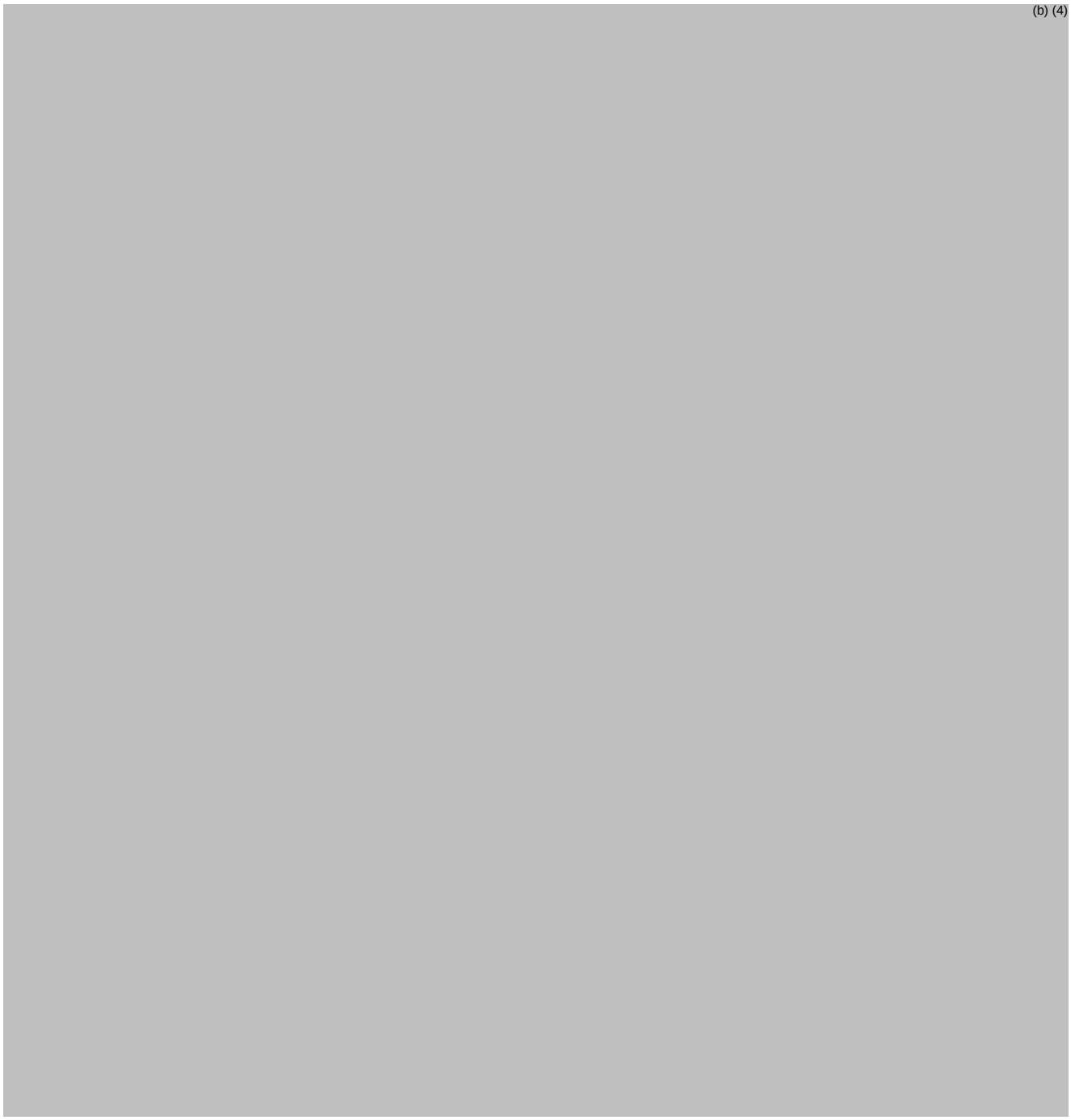
Given the challenges likely in obtaining a population with sufficient tirzepatide exposure, duration of follow-up, and number of events given the rarity of MTC, the use of an MTC registry design is sufficient. This study also is intended to establish a registry of incident cases of MTC and characterize the medical histories related to diabetes and GLP-1 RA use. Considering the relatively short trial durations in the tirzepatide clinical development program, the latency of MTC, and in accordance with Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA), the Agency requested (February 8, 2022) that the Applicant conduct the following postmarketing study to assess a signal of a serious risk for medullary thyroid carcinoma:

> Conduct a medullary thyroid carcinoma registry-based case series study of at least 15 years duration to systematically monitor the annual incidence of medullary thyroid carcinoma in the United States and to identify any increase related to the introduction of tirzepatide into the marketplace. This study will also establish a registry of incident cases of medullary thyroid carcinoma and characterize their medical histories related to diabetes and use of tirzepatide.

On February 15, 2022, the Applicant proposed an alternative to the MTC registry-based case series described above. They suggested a database study to monitor the annual incidence of MTC using nationally representative cancer registry data, which they felt would provide high quality population-based cancer information (e.g., demographic data) and be nationally representative real-world data of the United States population. They also felt that identification of exposure to tirzepatide using national real-world claims data would be more reliable than a case series design

that relies on self-reported patient exposure data. By linking pharmacy claims data to cancer registry data, details on drug exposures and MTC diagnosis information would be available. Further, they felt that cancer registry data would include additional details (e.g., histology and staging) that could be used to assess the magnitude of protopathic bias. They believe that the use of large administrative claims data could improve generalizability of the findings. The description of the proposed database study is as follows:

(b) (4)



On April 7, 2022, the Agency informed the Applicant that the following registry-based case series PMR would be required:

3) Conduct a medullary thyroid carcinoma registry-based case series study of at least 15 years duration to systematically monitor the annual incidence of medullary thyroid carcinoma in the United States and to identify any increase related to the introduction of tirzepatide into the marketplace. This study will also establish a registry of incident cases of medullary thyroid carcinoma and characterize their medical histories related to diabetes and use of tirzepatide.

Draft Protocol Submission:	November 2022
Final Protocol Submission:	May 2023
Interim Report Submission:	Yearly, March 2024 through March 2039
Study Completion:	July 2039
Final Report Submission:	July 2040

Since MTC is a rare, long latency disease, and there are no specific codes or validated algorithms to identify MTC, DEPII felt that the Sentinel Active Risk Identification and Analysis (ARIA) system was insufficient to assess MTC risk after tirzepatide exposure. Please refer to the ARIA Sufficiency Memorandum (dated May 2, 2022).

13.Appendices

13.1. References

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13.2. Glucagon-like Peptide-1 Receptor Agonists

Table 57: Summary Table of Approved GLP-1 RA Products

Trade Name (Established Name)	NDA/BLA # (Approval Date)*	Labeled Indication(s) Dosage and Administration	Dosing with Renal Impairment/Insufficiency†	Important Safety and Tolerability Issues‡
Albiglutide				
TANZEUM (albiglutide) **DISCONTINUED**	BLA 125431 (April 15, 2014)	**INDICATION:** • As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. **LIMITATIONS OF USE:** • Not recommended as first-line therapy for patients inadequately controlled on diet and exercise. • Has not been studied in patients with a history of pancreatitis. Consider other antidiabetic therapies in patients with a history of pancreatitis. • Not for treatment of type 1 diabetes mellitus or diabetic ketoacidosis. • Not for patients with preexisting severe gastrointestinal disease. • Has not been studied in combination with prandial insulin. **DOSAGE AND ADMINISTRATION:** • Administer once weekly at any time of day, without regard to meals. • Inject subcutaneously in the abdomen, thigh, or upper arm. • Initiate at 30 mg subcutaneously once weekly. Dose can be increased to 50 mg once weekly in patients requiring additional glycemic control.	**RENAL IMPAIRMENT:** **eGFR ≥15 to 89 mL/minute/1.73 m^2:** No dosage adjustment necessary; use caution when initiating or escalating doses in patients with renal impairment and/or in those reporting severe gastrointestinal symptoms. **eGFR <15 mL/minute/1.73 m^2:** No dosage adjustments provided in product labeling. • Albiglutide is a protein for which the expected metabolic pathway is degradation to small peptides and individual amino acids by ubiquitous proteolytic enzymes. Classical biotransformation studies have not been performed. Because albiglutide is an albumin fusion protein, it likely follows a metabolic pathway similar to native human serum albumin which is catabolized primarily in the vascular endothelium. The mean apparent clearance of albiglutide is 67 mL/h with an elimination half-life of approximately 5 days, making albiglutide suitable for once-weekly administration. • In a population pharmacokinetic analysis including a Phase 3 trial in patients with mild, moderate, and severe renal impairment, exposures were increased by approximately 30% to 40% in severe renal impairment compared with those observed in type 2 diabetes patients with normal renal function.	**BOXED WARNING:** • Carcinogenicity of albiglutide could not be assessed in rodents, but other GLP-1 receptor agonists have caused thyroid C-cell tumors in rodents at clinically relevant exposures. Human relevance of GLP-1 receptor agonist induced C-cell tumors in rodents has not been determined. It is unknown whether TANZEUM causes thyroid C-cell tumors, including MTC, in humans. Counsel patients regarding the potential risk of MTC and symptoms of thyroid tumors. • TANZEUM is contraindicated in patients with a personal or family history of MTC or in patients with MEN 2. **ADDITIONAL CONTRAINDICATIONS:** • Prior serious hypersensitivity reaction to albiglutide or any of the product components. **WARNINGS AND PRECAUTIONS:** • **Acute Pancreatitis:** Discontinue promptly if suspected. Do not restart if confirmed. Consider other antidiabetic therapies in patients with a history of pancreatitis.

Trade Name (Established Name)	NDA/BLA # (Approval Date)*	Labeled Indication(s) Dosage and Administration	Dosing with Renal Impairment/Insufficiency†	Important Safety and Tolerability Issues‡
		• If a dose is missed, administer within 3 days of missed dose. **DOSAGE FORMS AND STRENGTHS:** • **Injection:** 30 mg or 50 mg in a single-dose Pen		• **Hypoglycemia:** Can occur when used in combination with insulin secretagogues (e.g., sulfonylureas) or insulin. Consider lowering sulfonylurea or insulin dosage when starting TANZEUM. • **Hypersensitivity Reactions:** Serious hypersensitivity reactions (e.g., angioedema) have occurred. Discontinue TANZEUM and promptly seek medical advice. • **Acute Kidney Injury:** Postmarketing cases of worsening renal function and acute renal injury, some requiring hemodialysis, have occurred. Monitor renal function in patients with renal impairment reporting severe adverse gastrointestinal reactions and advise patients to avoid fluid depletion. • **Macrovascular Outcomes:** There have been no clinical trials establishing conclusive evidence of macrovascular risk reduction with TANZEUM. **COMMON ADVERSE EVENTS (≥10%):** • Upper respiratory tract infection, diarrhea, nausea, and injection site reaction.
Dulaglutide				
TRULICITY (dulaglutide)	BLA 125469 (September 18, 2014)	**INDICATION:** • As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.	**Renal Impairment:** • No dose adjustment is recommended in patients with renal impairment including end-stage renal disease (ESRD). Monitor renal function in patients with renal impairment reporting severe adverse gastrointestinal	**BOXED WARNING:** Dulaglutide • Dulaglutide causes thyroid C-cell tumors in rats. It is unknown whether TRULICITY causes thyroid

Trade Name (Established Name)	NDA/BLA # (Approval Date)*	Labeled Indication(s) Dosage and Administration	Dosing with Renal Impairment/Insufficiency†	Important Safety and Tolerability Issues‡
		• To reduce the risk of major adverse cardiovascular events in adults with type 2 diabetes mellitus who have established cardiovascular disease or multiple cardiovascular risk factors. **DOSAGE AND ADMINISTRATION:** • Initiate at 0.75 mg subcutaneously once weekly. Increase the dose to 1.5 mg once weekly for additional glycemic control. • If additional glycemic control is needed, increase the dose to 3 mg once weekly after at least 4 weeks on the 1.5 mg dose. • If additional glycemic control is needed, increase to the maximum dose of 4.5 mg once weekly after at least 4 weeks on the 3 mg dose. • If a dose is missed, administer the missed dose as soon as possible if there are at least 3 days (72 hours) until the next scheduled dose. • Administer once weekly at any time of day with or without food. • Inject subcutaneously in the abdomen, thigh, or upper arm. **LIMITATIONS OF USE:** • Has not been studied in patients with a history of pancreatitis. Consider other antidiabetic therapies in these patients. • Not for treatment of type 1 diabetes mellitus.	reactions. Use TRULICITY with caution in patients with ESRD. • Dulaglutide is presumed to be degraded into its component amino acids by general protein catabolism pathways. The apparent population mean clearance of dulaglutide was 0.142 L/h. The elimination half-life of dulaglutide was approximately 5 days. • Dulaglutide systemic exposure was increased by 20, 28, 14 and 12% for mild, moderate, severe, and ESRD renal impairment sub-groups, respectively, compared to subjects with normal renal function. The corresponding values for increase in Cmax were 13, 23, 20 and 11%, respectively. Additionally, in a 52 week clinical study in patients with type 2 diabetes and moderate to severe renal impairment, the pharmacokinetic (PK) behavior of TRULICITY 0.75 mg and 1.5 mg once weekly was similar to that demonstrated in previous clinical studies.	C-cell tumors, including medullary thyroid carcinoma (MTC), in humans as the human relevance of dulaglutide-induced rodent thyroid C-cell tumors has not been determined. • TRULICITY is contraindicated in patients with a personal or family history of MTC and in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Counsel patients regarding the potential risk of MTC and symptoms of thyroid tumors **ADDITIONAL CONTRAINDICATIONS:** • Prior serious hypersensitivity reaction to TRULICITY or any of the product components. **WARNINGS AND PRECAUTIONS:** • **Pancreatitis:** Has been reported in clinical trials. Discontinue promptly if pancreatitis is suspected. Do not restart if pancreatitis is confirmed • **Hypoglycemia:** Concomitant use with an insulin secretagogue or insulin may increase the risk of hypoglycemia, including severe hypoglycemia. Reducing the dose of insulin secretagogue or insulin may be necessary. • **Hypersensitivity Reactions:** Serious hypersensitivity reactions (e.g., anaphylactic reactions and angioedema) have occurred. Discontinue TRULICITY and promptly seek medical advice.

Trade Name (Established Name)	NDA/BLA # (Approval Date)*	Labeled Indication(s) Dosage and Administration	Dosing with Renal Impairment/Insufficiency†	Important Safety and Tolerability Issues‡
		• Not recommended in patients with severe gastrointestinal disease, including severe gastroparesis. **DOSAGE FORMS AND STRENGTHS:** • **Injection:** 0.75 mg/0.5 mL solution in a single-dose pen • **Injection:** 1.5 mg/0.5 mL solution in a single-dose pen • **Injection:** 3 mg/0.5 mL solution in a single-dose pen • **Injection:** 4.5 mg/0.5 mL solution in a single-dose pen		• **Acute Kidney Injury:** Monitor renal function in patients with renal impairment reporting severe adverse gastrointestinal reactions. • **Severe Gastrointestinal Disease:** Use may be associated with gastrointestinal adverse reactions, sometimes severe. Has not been studied in patients with severe gastrointestinal disease and is not recommended in these patients. • **Diabetic Retinopathy Complications:** Have been reported in a cardiovascular outcomes trial. Monitor patients with a history of diabetic retinopathy **COMMON ADVERSE EVENTS (≥5%):** • Nausea, diarrhea, vomiting, abdominal pain, and decreased appetite.
Exenatide				
BYDUREON (exenatide extended-release) **DISCONTINUED**	NDA 022200 (January 27, 2012)	**INDICATION:** • As an adjunct to diet and exercise to improve glycemic control in adults with T2D. **LIMITATIONS OF USE:** • Not recommended as first-line therapy for patients inadequately controlled on diet and exercise. • Should not be used to treat type 1 diabetes. • BYDUREON is an extended-release formulation of exenatide. Do not	**RENAL IMPAIRMENT:** **eGFR ≥45 mL/minute/1.73 m^2:** No dosage adjustment necessary; use caution, monitor for hypovolemia. **eGFR <45 mL/minute/1.73 m^2:** Use is not recommended. **ESRD:** Use is not recommended. • Nonclinical studies have shown that exenatide is predominantly eliminated by glomerular filtration with subsequent proteolytic degradation. The mean apparent clearance of exenatide in humans is 9.1 L/hour and is independent of the dose. Approximately 10 weeks after discontinuation of BYDUREON, plasma concentrations generally fall below the minimal detectable concentration of 10 pg/mL.	**BOXED WARNING:** • BYDUREON causes thyroid C-cell tumors at clinically relevant exposures in rats. It is unknown whether BYDUREON causes thyroid C-cell tumors, including MTC in humans, as the human relevance of exenatide extended-release-induced rodent thyroid C-cell tumors has not been determined. • BYDUREON is contraindicated in patients with a personal or family history of MTC or in patients with MEN 2.

Trade Name (Established Name)	NDA/BLA # (Approval Date)*	Labeled Indication(s) Dosage and Administration	Dosing with Renal Impairment/Insufficiency†	Important Safety and Tolerability Issues‡
		coadminister with other exenatide-containing products. • Has not been studied in patients with a history of pancreatitis. Consider other antidiabetic therapies in patients with a history of pancreatitis. **DOSAGE AND ADMINISTRATION:** • Administer 2 mg by subcutaneous injection once every seven days, at any time of day and with or without meals. • Administer immediately after the dose is prepared (powder is suspended). **DOSAGE FORMS AND STRENGTHS:** • **Extended-Release Injectable Suspension:** Single-dose tray containing 2 mg of exenatide in single-dose vial • **Extended-Release Injectable Suspension:** Single-dose pen containing 2 mg of exenatide	• BYDUREON has not been studied in patients with severe renal impairment (creatinine clearance <30 mL/min) or end-stage renal disease receiving dialysis. Population pharmacokinetic analysis of renally impaired patients receiving 2 mg exenatide extended-release indicate that there is a 62% and 33% increase in exposure in moderate (N=10) and mild (N=56) renally impaired patients, respectively, as compared to patients with normal renal function (N=84). • In a study of exenatide (BYETTA) in subjects with ESRD receiving dialysis, mean exenatide exposure increased by 3.4-fold compared to that of subjects with normal renal function.	**ADDITIONAL CONTRAINDICATIONS:** • Prior serious hypersensitivity reaction to exenatide or any of the product components. • History of drug-induced immune-mediated thrombocytopenia from exenatide products. **WARNINGS AND PRECAUTIONS:** • **Acute Pancreatitis:** Including fatal and non-fatal hemorrhagic or necrotizing pancreatitis has been reported. Discontinue promptly if pancreatitis is suspected. Do not restart if pancreatitis is confirmed. Consider other antidiabetic therapies if patient has history of pancreatitis. • **Hypoglycemia with Concomitant Use of Insulin Secretagogue or Insulin:** Patients taking an insulin secretagogue or insulin may have an increased risk of hypoglycemia, including severe hypoglycemia. Reduction in the dose of insulin secretagogue or insulin may be necessary. • **Acute Kidney Injury:** Postmarketing increased serum creatinine (SrCr), renal impairment, worsened chronic renal failure and acute renal failure, sometimes requiring hemodialysis or kidney transplantation. Not recommended for use in patients with eGFR below 45 mL/min/1.73 m^2.

Trade Name (Established Name)	NDA/BLA # (Approval Date)*	Labeled Indication(s) Dosage and Administration	Dosing with Renal Impairment/Insufficiency†	Important Safety and Tolerability Issues‡
				• **Gastrointestinal Disease:** Not recommended in patients with severe gastrointestinal disease (e.g., gastroparesis). • **Immunogenicity**: Patients may develop antibodies to exenatide. If there is worsening glycemic control or failure to achieve target glycemic control, consider alternative antidiabetic therapy. • **Hypersensitivity:** Serious hypersensitivity reactions (e.g., anaphylaxis and angioedema) have been reported. In such cases, patients are to discontinue BYDUREON and promptly seek medical advice. • **Drug-induced Immune-mediated Thrombocytopenia:** Serious bleeding which may be fatal has been reported. Discontinue BYDUREON promptly and avoid re-exposure to exenatide. • **Injection-site Reactions:** Serious injection-site reactions with or without subcutaneous nodules have been reported. • **Acute Gallbladder Disease:** If cholelithiasis or cholecystitis are suspected, gallbladder studies are indicated. **COMMON ADVERSE EVENTS (≥5%):** • Nausea, diarrhea, headache, vomiting, constipation, injection-site pruritus, injection-site nodule, and dyspepsia.

Trade Name (Established Name)	NDA/BLA # (Approval Date)*	Labeled Indication(s) Dosage and Administration	Dosing with Renal Impairment/Insufficiency†	Important Safety and Tolerability Issues‡
BYDUREON BCISE (exenatide extended-release)	NDA 209210 (October 20, 2017)	**INDICATION:** • As an adjunct to diet and exercise to improve glycemic control in adults with T2D. **LIMITATIONS OF USE:** • Not recommended as first-line therapy for patients inadequately controlled on diet and exercise. • Should not be used to treat type 1 diabetes. • BYDUREON BCISE is an extended-release formulation of exenatide. Do not coadminister with other exenatide-containing products. • Has not been studied in patients with a history of pancreatitis. Consider other antidiabetic therapies in patients with a history of pancreatitis. **DOSAGE AND ADMINISTRATION:** • Administer 2 mg by subcutaneous injection once every seven days, at any time of day and with or without meals. • Administer immediately after the dose is prepared. **DOSAGE FORMS AND STRENGTHS:** • **Extended-Release Injectable Suspension:** 2 mg of exenatide in a 0.85 mL single-dose autoinjector	**RENAL IMPAIRMENT:** **eGFR ≥45 mL/minute/1.73 m^2:** No dosage adjustment necessary; use caution, monitor for hypovolemia. **eGFR <45 mL/minute/1.73 m^2:** Use is not recommended. • Nonclinical studies have shown that exenatide is predominantly eliminated by glomerular filtration with subsequent proteolytic degradation. The mean apparent clearance of exenatide in humans is 9.1 L/hour and is independent of the dose. Approximately 10 weeks after discontinuation of BYDUREON BCISE therapy, plasma exenatide concentrations generally fall below the minimal quantifiable concentration of 20 pg/mL. • BYDUREON BCISE has not been studied in patients with severe renal impairment (CrCL <30 mL/min, eGFR <30 mL/min/1.73m^2) or end-stage renal disease receiving dialysis. Pharmacokinetic analysis of patients receiving 2 mg BYDUREON BCISE indicated that there was a 28% and 69% higher systemic exposure to exenatide in patients with mild (N=96) or moderate (N=24) renal impairment, respectively, as compared to patients with normal renal function (N=70)	**BOXED WARNING:** • Exenatide extended-release causes thyroid C-cell tumors at clinically relevant exposures in rats. It is unknown whether BYDUREON causes thyroid C-cell tumors, including MTC in humans, as the human relevance of exenatide extended-release-induced rodent thyroid C-cell tumors has not been determined. • BYDUREON BCISE is contraindicated in patients with a personal or family history of MTC or in patients with MEN 2. **ADDITIONAL CONTRAINDICATIONS:** • Prior serious hypersensitivity reaction to exenatide or any of the product components. **WARNINGS AND PRECAUTIONS:** • **Acute pancreatitis:** Including fatal and non-fatal hemorrhagic or necrotizing pancreatitis has been reported. Do not restart if pancreatitis is confirmed. Consider other antidiabetic therapies if patient has history of pancreatitis • **Hypoglycemia with Concomitant Use of Insulin Secretagogues or Insulin:** Patients taking an insulin secretagogue or insulin may have an increased risk of hypoglycemia, including severe hypoglycemia. Reduction in the dose of insulin secretagogues or insulin may be necessary.

Trade Name (Established Name)	NDA/BLA # (Approval Date)*	Labeled Indication(s) Dosage and Administration	Dosing with Renal Impairment/Insufficiency†	Important Safety and Tolerability Issues‡
				• **Acute kidney injury:** May induce nausea and vomiting with transient hypovolemia and may worsen renal functions. Postmarketing increased SrCr, renal impairment, worsened chronic renal failure and acute renal failure, sometimes requiring hemodialysis or kidney transplantation has been reported. Not recommended if patient with and eGFR <45 mL/min/1.73 m^2. • **Gastrointestinal disease:** Not recommended in patients with severe gastrointestinal disease (e.g., gastroparesis). • **Immunogenicity:** Patients may develop antibodies to exenatide. If there is worsening glycemic control or failure to achieve target glycemic control, consider alternative antidiabetic therapy. • **Hypersensitivity:** Serious hypersensitivity reactions (e.g., anaphylaxis and angioedema) have been reported. • **Drug-induced Immune-mediated Thrombocytopenia:** Serious bleeding which may be fatal has been reported. Discontinue BYDUREON BCISE promptly and avoid re-exposure to exenatide. • **Injection-Site Reactions:** Serious injection-site reactions with or without subcutaneous nodules have been reported.

Trade Name (Established Name)	NDA/BLA # (Approval Date)*	Labeled Indication(s) Dosage and Administration	Dosing with Renal Impairment/Insufficiency†	Important Safety and Tolerability Issues‡
				• **Acute Gallbladder Disease:** If cholelithiasis or cholecystitis are suspected, gallbladder studies are indicated. **COMMON ADVERSE EVENTS (≥5%):** • Injection-site nodule, and nausea.
BYETTA (exenatide)	NDA 021773 (April 28, 2005)	**BYETTA INDICATION:** • As an adjunct to diet and exercise to improve glycemic control in adults with T2D. **LIMITATIONS OF USE:** • Is not indicated for use in patients with type 1 diabetes. • Contains exenatide and should not be used with other products containing the active ingredient exenatide. • Has not been studied in patients with a history of pancreatitis. Consider other antidiabetic therapies in patients with a history of pancreatitis. **DOSAGE AND ADMINISTRATION:** • Inject subcutaneously within 60 minutes prior to morning and evening meals (or before the two main meals of the day, approximately six hours or more apart. • Initiate 5 mcg per dose twice daily; increase to 10 mcg twice daily after one month based on clinical response. **DOSAGE FORMS AND STRENGTHS:** • **Injection:** 5 mcg per dose, 60 doses, 1.2 mL single-patient-use prefilled pen • **Injection:** 10 mcg per dose, 60 doses, 2.4 mL single-patient-use prefilled pen	**RENAL IMPAIRMENT:** **CrCl ≥30 mL/minute:** No dosage adjustment necessary; use caution with initiation of therapy or when increasing the dose in patients with CrCl 30 to 50 mL/minute; monitor for hypovolemia. **CrCl <30 mL/minute:** Use is not recommended. **ESRD:** Use is not recommended. • Nonclinical studies have shown that exenatide is predominantly eliminated by glomerular filtration with subsequent proteolytic degradation. The mean apparent clearance of exenatide in humans is 9.1 L/hour and the mean terminal half-life is 2.4 hours. These pharmacokinetic characteristics of exenatide are independent of the dose. In most individuals, exenatide concentrations are measurable for approximately 10 hours post-dose. • In a study of exenatide in subjects with ESRD receiving dialysis, mean exenatide exposure increased by 3.37-fold compared to that of subjects with normal renal function.	**CONTRAINDICATIONS:** • History of severe hypersensitivity to exenatide or any of the excipients in BYETTA. • History of drug-induced immune-mediated thrombocytopenia from exenatide products **WARNINGS AND PRECAUTIONS:** • **Never share a BYETTA pen between patients**, even if the needle is changed. • **Acute Pancreatitis:** Postmarketing reports with exenatide, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis. Discontinue BYETTA promptly. BYETTA should not be restarted. Consider other antidiabetic therapies in patients with a history of pancreatitis. • **Hypoglycemia with Concomitant Use of Insulin Secretagogues or Insulin:** Patients taking an insulin secretagogue or insulin may have an increased risk of hypoglycemia, including severe hypoglycemia. Reduction in the dose of insulin secretagogues or insulin may be necessary. • **Acute Kidney Injury:** Postmarketing reports with exenatide, sometimes

Trade Name (Established Name)	NDA/BLA # (Approval Date)*	Labeled Indication(s) Dosage and Administration	Dosing with Renal Impairment/Insufficiency†	Important Safety and Tolerability Issues‡
				requiring hemodialysis and kidney transplantation. BYETTA should not be used in patients with severe renal impairment or end-stage renal disease and should be used with caution in patients with renal transplantation. Caution should be applied when initiating BYETTA or escalating the dose of BYETTA in patients with moderate renal failure. • **Severe Gastrointestinal Disease:** Use of BYETTA is not recommended in patients with severe gastrointestinal disease (e.g., gastroparesis). • **Immunogenicity:** Patients may develop antibodies to exenatide. If there is worsening glycemic control or failure to achieve target glycemic control, consider alternative antidiabetic therapy. • **Hypersensitivity:** Serious hypersensitivity reactions (e.g., anaphylaxis and angioedema) have been reported. Discontinue BYETTA and promptly seek medical advice. • **Drug-induced Immune-mediated Thrombocytopenia:** Serious bleeding which may be fatal has been reported. Discontinue BYETTA promptly and avoid re-exposure to exenatide. **COMMON ADVERSE EVENTS (≥5%):** • Nausea, hypoglycemia, vomiting, diarrhea, feeling jittery, dizziness, headache, dyspepsia, constipation,

Trade Name (Established Name)	NDA/BLA # (Approval Date)*	Labeled Indication(s) Dosage and Administration	Dosing with Renal Impairment/Insufficiency†	Important Safety and Tolerability Issues‡
				asthenia. Nausea usually decreases over time.
Liraglutide				
VICTOZA (liraglutide)	NDA 022341 (January 25, 2010)	**INDICATION:** • As an adjunct to diet and exercise to improve glycemic control in patients 10 years and older with type 2 diabetes mellitus. • To reduce the risk of major adverse cardiovascular events in adults with type 2 diabetes mellitus and established cardiovascular disease. **LIMITATIONS OF USE:** • Not for treatment of type 1 diabetes mellitus. • Should not be coadministered with other liraglutide-containing products. **DOSAGE AND ADMINISTRATION:** • Inspect visually prior to each injection. Only use if solution is clear, colorless, and contains no particles. • Inject VICTOZA subcutaneously once-daily at any time of day, independently of meals, in the abdomen, thigh or upper arm. • When using VICTOZA with insulin, administer as separate injections. Never mix. • **Adult Dosage:** Initiate at 0.6 mg daily for one week then increase to 1.2 mg daily. If additional glycemic control is required, increase the dose to 1.8 mg daily after one week of treatment with the 1.2 mg daily dose.	**RENAL IMPAIRMENT:** • No dose adjustment of VICTOZA is recommended for patients with renal impairment. • In the VICTOZA treatment arm of the LEADER trial [see Clinical Studies (14.3)], 1932 (41.4%) patients had mild renal impairment, 999 (21.4%) patients had moderate renal impairment and 117 (2.5%) patients had severe renal impairment at baseline. No overall differences in safety or efficacy were seen in these patients compared to patients with normal renal function. • There is limited experience with VICTOZA in patients with end stage renal disease. There have been postmarketing reports of acute renal failure and worsening of chronic renal failure, which may sometimes require hemodialysis. Use caution in patients who experience dehydration • The safety and efficacy of VICTOZA was evaluated in a 26-week clinical study that included patients with moderate renal impairment (eGFR 30 to 60 mL/min/1.73m^2). • During the initial 24 hours following administration of a single [^{3}H]-liraglutide dose to healthy subjects, the major component in plasma was intact liraglutide. Liraglutide is endogenously metabolized in a similar manner to large proteins without a specific organ as a major route of elimination. Following a [^{3}H]-liraglutide dose, intact liraglutide was not detected in urine or feces. Only a minor part of the administered radioactivity was excreted as liraglutide-related metabolites in urine or feces (6% and 5%, respectively). The majority of urine and feces radioactivity was excreted during the first 6-8 days. The mean apparent	**BOXED WARNING:** • Liraglutide causes thyroid C-cell tumors in rats and mice. It is unknown whether liraglutide causes thyroid C-cell tumors, including MTC, in humans as human relevance of liraglutide-induced rodent thyroid C-cell tumors has not been determined. • Liraglutide is contraindicated in patients with a personal or family history of MTC or in patients with MEN 2. **ADDITIONAL CONTRAINDICATIONS:** • Prior serious hypersensitivity reaction to liraglutide or any of the excipients in VICTOZA. **WARNINGS AND PRECAUTIONS:** • **Pancreatitis:** Postmarketing reports, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis. Discontinue promptly if pancreatitis is suspected. Do not restart if pancreatitis is confirmed. • **Never share a VICTOZA pen between patients**, even if the needle is changed. • **Hypoglycemia:** Adult patients taking an insulin secretagogue or insulin may have an increased risk of hypoglycemia, including severe hypoglycemia. In pediatric patients

Trade Name (Established Name)	NDA/BLA # (Approval Date)*	Labeled Indication(s) Dosage and Administration	Dosing with Renal Impairment/Insufficiency†	Important Safety and Tolerability Issues‡
		• **Pediatric Dosage:** Initiate at 0.6 mg daily for at least one week. If additional glycemic control is required increase the dose to 1.2 mg daily and if additional glycemic control is still required, increase the dose to 1.8 mg daily after at least one week of treatment with the 1.2 mg daily dose. **DOSAGE FORMS AND STRENGTHS:** • **Injection:** 6 mg/mL solution in a pre-filled, single-patient-use pen that delivers doses of 0.6 mg, 1.2 mg, 1.8 mg.	clearance following subcutaneous administration of a single dose of liraglutide is approximately 1.2 L/h with an elimination half-life of approximately 13 hours, making VICTOZA suitable for once daily administration. • The single-dose pharmacokinetics of VICTOZA were evaluated in patients with varying degrees of renal impairment. Patients with mild (estimated creatinine clearance 50-80 mL/min) to severe (estimated creatinine clearance <30 mL/min) renal impairment and subjects with end-stage renal disease requiring dialysis were included in the trial. Compared to healthy subjects, liraglutide AUC in mild, moderate, and severe renal impairment and in end-stage renal disease was on average 35%, 19%, 29% and 30% lower, respectively.	10 years of age and older, the risk of hypoglycemia was higher with VICTOZA regardless of insulin and/or metformin use. Reduction in the dose of insulin secretagogues or insulin may be necessary. • **Renal Impairment:** Postmarketing, usually in association with nausea, vomiting, diarrhea, or dehydration which may sometimes require hemodialysis. Use caution when initiating or escalating doses of VICTOZA in patients with renal impairment. • **Hypersensitivity:** Postmarketing reports of serious hypersensitivity reactions (e.g., anaphylactic reactions and angioedema). Discontinue VICTOZA and promptly seek medical advice . • **Acute Gallbladder Disease:** If cholelithiasis or cholecystitis are suspected, gallbladder studies are indicated. **COMMON ADVERSE EVENTS (≥5%):** • Nausea, diarrhea, vomiting, decreased appetite, dyspepsia, constipation. • Immunogenicity-related events, including urticaria, were more common in VICTOZA-treated patients (0.8%) than among comparator-treated patients (0.4%) in clinical trials.

Trade Name (Established Name)	NDA/BLA # (Approval Date)*	Labeled Indication(s) Dosage and Administration	Dosing with Renal Impairment/Insufficiency†	Important Safety and Tolerability Issues‡
SAXENDA (liraglutide)	NDA 206321 (December 23, 2014)	**INDICATION:** • As an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in: — Adult patients with an initial body mass index (BMI) of ○ 30 kg/m^2 or greater (obese), or ○ 27 kg/m^2 or greater (overweight) in the presence of at least one weight-related comorbid condition (e.g., hypertension, type 2 diabetes mellitus, or dyslipidemia). — Pediatric patients aged 12 years and older with: ○ Body weight above 60 kg and ○ An initial BMI corresponding to 30 kg/m2 for adults (obese) by international cut-offs **DOSAGE AND ADMINISTRATION:** • Inject SAXENDA subcutaneously in the abdomen, thigh, or upper arm once daily at any time of day, without regard to the timing of meals. • The recommended dose of SAXENDA is 3 mg daily. • Initiate at 0.6 mg per day for one week. In weekly intervals, increase the dose until a dose of 3 mg is reached. • If pediatric patients do not tolerate an increased dose during dose escalation, the dose may also be lowered to the previous level. Dose escalation for pediatric patients may take up to 8 weeks.	**RENAL IMPAIRMENT:** • There is limited experience with SAXENDA in patients with mild, moderate, and severe renal impairment, including end-stage renal disease. However, there have been postmarketing reports of acute renal failure and worsening of chronic renal failure with liraglutide, which may sometimes require hemodialysis. SAXENDA should be used with caution in this patient population. • In patients treated with GLP-1 receptor agonists, including SAXENDA, there have been reports of acute renal failure and worsening of chronic renal failure, sometimes requiring hemodialysis. Some of these events were reported in patients without known underlying renal disease. A majority of the reported events occurred in patients who had experienced nausea, vomiting, or diarrhea leading to volume depletion. Some of the reported events occurred in patients receiving one or more medications known to affect renal function or volume status. Altered renal function has been reversed in many of the reported cases with supportive treatment and discontinuation of potentially causative agents, including liraglutide. Use caution when initiating or escalating doses of SAXENDA in patients with renal impairment. • During the initial 24 hours following administration of a single [^{3}H]-liraglutide dose to healthy subjects, the major component in plasma was intact liraglutide. Liraglutide is endogenously metabolized in a similar manner to large proteins without a specific organ as a major route of elimination. Following a [^{3}H]-liraglutide dose, intact liraglutide was not detected in urine or feces. Only a minor part of the administered radioactivity was excreted as liraglutide-related metabolites in urine or feces (6% and 5%, respectively). The majority of urine and feces radioactivity was excreted during the first 6-8 days. The mean apparent clearance following subcutaneous administration of a	**BOXED WARNING:** • Liraglutide causes thyroid C-cell tumors in rats and mice. It is unknown whether liraglutide causes thyroid C-cell tumors, including MTC, in humans as human relevance of liraglutide-induced rodent thyroid C-cell tumors has not been determined. • Liraglutide is contraindicated in patients with a personal or family history of MTC or in patients with MEN 2. **ADDITIONAL CONTRAINDICATIONS:** • Personal or family history of medullary thyroid carcinoma or Multiple Endocrine Neoplasia syndrome type 2. • Hypersensitivity to liraglutide or any excipients in SAXENDA. • Pregnancy. **WARNINGS AND PRECAUTIONS:** . • **Acute Pancreatitis:** Discontinue promptly if pancreatitis is suspected. Do not restart if pancreatitis is confirmed. • **Acute Gallbladder Disease:** If cholelithiasis or cholecystitis are suspected, gallbladder studies are indicated. • **Hypoglycemia:** Can occur in adults when SAXENDA is used with an insulin secretagogue (e.g., a sulfonylurea) or insulin. The risk may be lowered by a reduction in the dose of concomitantly

Trade Name (Established Name)	NDA/BLA # (Approval Date)*	Labeled Indication(s) Dosage and Administration	Dosing with Renal Impairment/Insufficiency†	Important Safety and Tolerability Issues‡
		• Pediatric patients who do not tolerate 3 mg daily may have their dose reduced to 2.4 mg daily. • Adult patients with type 2 diabetes should monitor blood glucose prior to starting SAXENDA and during SAXENDA treatment. **LIMITATIONS OF USE:** • SAXENDA contains liraglutide and should not be coadministered with other liraglutide-containing products or with any other GLP-1 receptor agonist. • The safety and effectiveness of SAXENDA in pediatric patients with type 2 diabetes have not been established. • The safety and efficacy of SAXENDA in combination with other products intended for weight loss have not been established. **DOSAGE FORMS AND STRENGTHS:** • **Injection:** 6 mg/mL solution in a 3 mL pre-filled, single-patient-use pen that delivers doses of 0.6 mg, 1.2 mg, 1.8 mg, 2.4 mg, or 3 mg.	single dose of liraglutide is approximately 0.9-1.4 L/h with an elimination half-life of approximately 13 hours, making liraglutide suitable for once daily administration. • The single-dose pharmacokinetics of liraglutide were evaluated in patients with varying degrees of renal impairment. Patients with mild (estimated creatinine clearance 50-80 mL/min) to severe (estimated creatinine clearance less than 30 mL/min) renal impairment and patients with end-stage renal disease requiring dialysis were included in the trial. Compared to healthy subjects, liraglutide AUC in mild, moderate, and severe renal impairment and in end-stage renal disease was on average 35%, 19%, 29% and 30% lower, respectively.	administered insulin secretagogues or insulin. In the pediatric clinical trial, patients did not have type 2 diabetes. Hypoglycemia occurred in SAXENDA-treated pediatric patients. Inform all patients of the risk of hypoglycemia and educate them on the signs and symptoms of hypoglycemia. • **Heart Rate Increase:** Monitor heart rate at regular intervals. • **Renal Impairment:** Has been reported postmarketing, usually in association with nausea, vomiting, diarrhea, or dehydration which may sometimes require hemodialysis. Use caution when initiating or escalating doses of SAXENDA in patients with renal impairment. • **Hypersensitivity Reactions:** Postmarketing reports of serious hypersensitivity reactions (e.g., anaphylactic reactions and angioedema). Discontinue SAXENDA and other suspect medications and promptly seek medical advice. • **Suicidal Behavior and Ideation:** Monitor for depression or suicidal thoughts. Discontinue SAXENDA if symptoms develop **COMMON ADVERSE EVENTS (≥5%):** • Nausea, diarrhea, constipation, vomiting, injection site reactions, headache, hypoglycemia, dyspepsia, fatigue, dizziness, abdominal pain,

Trade Name (Established Name)	NDA/BLA # (Approval Date)*	Labeled Indication(s) Dosage and Administration	Dosing with Renal Impairment/Insufficiency†	Important Safety and Tolerability Issues‡
				increased lipase, upper abdominal pain, pyrexia, and gastroenteritis.
Combination Products **XULTOPHY** (insulin degludec/liraglutide)	BLA 208583 (November 21, 2016)	**INDICATION:** • As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. **LIMITATIONS OF USE:** • Not recommended as first-line therapy for patients inadequately controlled on diet and exercise. • Not recommended for use in combination with any other product containing liraglutide or another GLP-1 receptor agonist. • Not for treatment of type 1 diabetes mellitus or diabetic ketoacidosis. • Has not been studied in combination with prandial insulin. **DOSAGE AND ADMINISTRATION:** • Inject Discontinue therapy with liraglutide or basal insulin prior to initiation of XULTOPHY 100/3.6. • Recommended starting dose in patients naïve to basal insulin or GLP-1 receptor agonist is 10 units (10 units of insulin degludec and 0.36 mg of liraglutide) given subcutaneously once-daily. • Recommended starting dose in patients currently on basal insulin or GLP-1 receptor agonist is 16 units (16 units of insulin degludec and 0.58 mg of liraglutide) given subcutaneously once-daily.	**RENAL IMPAIRMENT:** *XULTOPHY 100/3.6* • There is limited experience with XULTOPHY 100/3.6 in patients with mild and moderate renal impairment and when used in these patients, additional glucose monitoring and XULTOPHY 100/3.6 dose adjustments may be required on an individual basis. XULTOPHY 100/3.6 has not been studied in patients with severe renal impairment. *Insulin degludec* • No clinically relevant difference in the pharmacokinetics of insulin degludec was identified in a study comparing healthy subjects and subjects with renal impairment including subjects with end stage renal disease. • Insulin degludec has been studied in a pharmacokinetic study in 32 subjects (n=6/group) with normal or impaired renal function/end-stage renal disease following administration of a single dose (0.4U/kg) of insulin degludec. Renal function was defined using creatinine clearance (CrCl) as follows: >80 mL/min (normal), 50-80 mL/min (mild), 30-50 mL/min (moderate) and <30 mL/min (severe). Subjects requiring dialysis were classified as having end-stage renal disease (ESRD). Total exposure (AUCIDeg,0-120h,SD) of insulin degludec was similar in subjects with normal and impaired renal function. No clinically relevant difference in the pharmacokinetics of insulin degludec was identified between healthy subjects and subjects with renal impairment. Hemodialysis did not affect clearance of insulin degludec ($CL/F_{IDeg,SD}$) in subjects with ESRD. *Liraglutide*	**BOXED WARNING:** • Liraglutide, one of the components of XULTOPHY 100/3.6, causes thyroid C-cell tumors at clinically relevant exposures in both genders of rats and mice. It is unknown whether XULTOPHY 100/3.6 causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans, as the human relevance of liraglutide-induced rodent thyroid C-cell tumors has not been determined. • XULTOPHY 100/3.6 is contraindicated in patients with a personal or family history of MTC or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Counsel patients regarding the potential risk of MTC and the symptoms of thyroid tumors. **ADDITIONAL CONTRAINDICATIONS:** • During episodes of hypoglycemia. • Patients with a prior serious hypersensitivity reaction to XULTOPHY 100/3.6 or either of the active substances or any of its excipients. **WARNINGS AND PRECAUTIONS:** • **Pancreatitis:** Pancreatitis: Postmarketing reports, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis have been reported for liraglutide. Discontinue

Trade Name (Established Name)	NDA/BLA # (Approval Date)*	Labeled Indication(s) Dosage and Administration	Dosing with Renal Impairment/Insufficiency†	Important Safety and Tolerability Issues‡
		• Administer once daily at same time each day with or without food. • Inject XULTOPHY 100/3.6 subcutaneously into the thigh, upper arm, or abdomen. • Rotate injection sites to reduce risk of lipodystrophy and localized cutaneous amyloidosis. • Maximum daily dosage is 50 units (50 units of insulin degludec and 1.8 mg of liraglutide). • XULTOPHY 100/3.6 pen delivers doses from 10 to 50 units with each injection; each XULTOPHY 100/3.6 dosage unit contains 1 unit of insulin degludec and 0.036 mg of liraglutide. • See Full Prescribing Information for titration recommendations. • Inject subcutaneously in thigh, upper arm, or abdomen. • Do not administer intravenously, intramuscularly, or by an infusion pump. • Do not dilute or mix with any other insulin products or solutions. **DOSAGE FORMS AND STRENGTHS:** • **Injection:** 100 units of insulin degludec per mL and 3.6 mg of liraglutide per mL in a 3 mL single-patient-use pen.	• The safety and efficacy of liraglutide was evaluated in a 26 week clinical study that included patients with moderate renal impairment (eGFR 30 to 60 mL/min/1.73 m2). In the liraglutide treatment arm of a cardiovascular outcomes trial (LEADER trial), 1932 (41.4%) patients had mild renal impairment, 999 (21.4%) patients had moderate renal impairment and 117 (2.5%) patients had severe renal impairment at baseline. No overall differences in safety or efficacy were seen in these patients compared to patients with normal renal function. There is limited experience with liraglutide in patients with end stage renal disease. There have been postmarketing reports of acute renal failure and worsening of chronic renal failure, which may sometimes require hemodialysis. • During the initial 24 hours following administration of a single [^{3}H]-liraglutide dose to healthy subjects, the major component in plasma was intact liraglutide. Liraglutide is endogenously metabolized in a similar manner to large proteins without a specific organ as a major route of elimination. The half-life of insulin degludec is approximately 25 hours and the half-life of liraglutide is approximately 13 hours. • The single-dose pharmacokinetics of liraglutide were evaluated in subjects with varying degrees of renal impairment. Subjects with mild (estimated creatinine clearance 50-80 mL/min) to severe (estimated creatinine clearance <30 mL/min) renal impairment and subjects with end-stage renal disease requiring dialysis were included in the trial. Compared to healthy subjects, liraglutide AUC in mild, moderate, and severe renal impairment and in end-stage renal disease was on average 35%, 19%, 29% and 30% lower, respectively.	promptly if pancreatitis is suspected. • **Never share a XULTOPHY 100/3.6 pen between patients**, even if the needle is changed. • **Hyperglycemia or hypoglycemia with changes in insulin regimen:** Make changes to a patient's insulin regimen (e.g., insulin strength, manufacturer, type, injection site or method of administration) under close medical supervision with increased frequency of blood glucose monitoring. • **Overdose due to medication errors:** XULTOPHY 100/3.6 contains two drugs. Instruct patients to check label before injection since accidental mix-ups with insulin containing products can occur. Do not exceed the maximum dose or administer with other GLP-1 receptor agonists. • Hypoglycemia: May be life-threatening. Increase monitoring with changes to: dosage, co-administered glucose lowering medications, meal pattern, physical activity; and in patients with renal impairment or hepatic impairment or hypoglycemia unawareness. • **Acute Kidney Injury:** Has been reported postmarketing for liraglutide, usually in association with nausea, vomiting, diarrhea, or dehydration, which may sometimes

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				require hemodialysis. Advise patients of the potential risk of dehydration due to gastrointestinal adverse reactions and take precautions to avoid fluid depletion. • **Hypersensitivity and Allergic Reactions:** Severe, life-threatening, generalized allergy, including anaphylaxis, angioedema, bronchospasm, hypotension, and shock can occur. If a hypersensitivity reaction occurs, discontinue and treat per standard of care. • **Acute Gallbladder Disease:** If cholelithiasis or cholecystitis are suspected, gallbladder studies are indicated. • **Hypokalemia:** May be life-threatening. Monitor potassium levels in patients at risk for hypokalemia and treat if indicated. • **Fluid retention and congestive heart failure (CHF) with use of thiazolidinediones (TZDs):** Observe for signs and symptoms of heart failure; consider dosage reduction or discontinuation if heart failure occurs. **COMMON ADVERSE EVENTS (≥5%):** • Nasopharyngitis, headache, nausea, diarrhea, increased lipase, and upper respiratory tract infection.
Lixisenatide				
ADLYXIN (lixisenatide)	BLA 208471 (July 27, 2016)	**INDICATION:**	**RENAL IMPAIRMENT:**	**CONTRAINDICATIONS:**

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		• As an adjunct to diet and exercise to improve glycemic control in adults with T2D. **LIMITATIONS OF USE:** • Has not been studied in patients with chronic pancreatitis or a history of unexplained pancreatitis. Consider other antidiabetic therapies in patients with a history of pancreatitis. • Not for treatment of type 1 diabetes. • Has not been studied in patients with gastroparesis and is not recommended in patients with gastroparesis. **DOSAGE AND ADMINISTRATION:** • Initiate at 10 mcg once daily for 14 days. On Day 15, increase dosage to 20 mcg once daily. • Administer once daily within one hour before the first meal of the day. • Inject subcutaneously in the abdomen, thigh, or upper arm. **DOSAGE FORMS AND STRENGTHS:** • **Injection:** 50 mcg/mL in a 3 mL single-patient-use prefilled pen (for 14 doses of 10 mcg per dose) • **Injection:** 100 mcg/mL in a 3 mL single patient-use prefilled pen (for 14 doses of 20 mcg per dose)	**eGFR ≥30 to 89 mL/min/1.73 m^2:** No dosage adjustment necessary; monitor closely for increased adverse GI effects (e.g., diarrhea, nausea, vomiting) which may lead to dehydration and worsening of renal function. **eGFR 15 to 29 mL/min/1.73 m^2:** There are no dosage adjustments provided in product labeling (limited data); exposure is increased in these patients. Monitor closely for increased adverse gastrointestinal (GI) effects (e.g., diarrhea, nausea, vomiting) which may lead to dehydration and worsening of renal function. **eGFR <15 mL/min/1.73 m^2:** Use is not recommended (has not been studied) • Lixisenatide is presumed to be eliminated through glomerular filtration, and proteolytic degradation. After multiple dose administration in patients with T2D, the mean terminal half-life was approximately 3 hours and the mean apparent clearance (CL/F) about 35 L/h. • Compared to healthy subjects [CrCl using Cockcroft-Gault ≥90 mL/min (N=4)], plasma Cmax of lixisenatide was increased by approximately 60%, 42%, and 83% in subjects with mild [CrCl 60–89 mL/min (N=9)], moderate [CrCl 30–59 mL/min (N=11)], and severe [CrCl 15–29 mL/min (N=8)] renal impairment. Plasma AUC was increased by approximately 34%, 69% and 124% with mild, moderate and severe renal impairment, respectively. • In patients with mild renal impairment (eGFR: 60–89 mL/min/1.73 m^2) no dose adjustment is required, but close monitoring for lixisenatide related adverse reactions and for changes in renal function is recommended because a higher incidence of hypoglycemia, nausea and vomiting were observed in these patients. • In a cardiovascular outcome study, 655 (22%) lixisenatide treated patients had moderate renal	• Severe hypersensitivity to lixisenatide or any component of ADLYXIN. **WARNINGS AND PRECAUTIONS:** • **Anaphylaxis and Serious Hypersensitivity Reactions:** Discontinue ADLYXIN and promptly seek medical advice. • **Pancreatitis:** Discontinue promptly if pancreatitis is suspected. Do not restart if pancreatitis is confirmed. Consider other antidiabetic therapies in patients with a history of pancreatitis. • **Never share ADLYXIN pen between patients**, even if the needle is changed. • **Hypoglycemia with Concomitant Use of Insulin Secretagogues or Insulin:** Patients taking an insulin secretagogue or insulin may have an increased risk of hypoglycemia, including severe hypoglycemia. Reduction in the dose of insulin secretagogues or insulin may be necessary. • **Acute Kidney Injury:** Monitor renal function in patients with renal impairment reporting severe adverse gastrointestinal reactions. ADLYXIN is not recommended in patients with end stage renal disease. • **Immunogenicity:** Patients may develop antibodies to lixisenatide. If there is worsening glycemic control

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			impairment (eGFR: 30 to less than 60 mL/min/1.73 m^2). No dosing adjustment is recommended in patients with moderate renal impairment, but close monitoring for lixisenatide related adverse gastrointestinal reactions and for changes in renal function is recommended because these may lead to dehydration and acute renal failure and worsening of chronic failure in these patients. • Clinical experience in patients with severe renal impairment is limited as there were only 5 patients with severe renal impairment (eGFR 15 to less than 30 mL/min/1.73 m^2) exposed to lixisenatide in all controlled studies. Lixisenatide exposure was higher in these patients. Patients with severe renal impairment exposed to lixisenatide should be closely monitored for occurrence of gastrointestinal adverse reactions and for changes in renal function. • There is no therapeutic experience in patients with end stage renal disease (eGFR <15 mL/min/1.73 m^2), and it is not recommended to use lixisenatide in this population.	or failure to achieve targeted glycemic control, significant injection site reactions or allergic reactions, alternative antidiabetic therapy should be considered. **COMMON ADVERSE EVENTS (≥5%):** • Nausea, vomiting, headache, diarrhea, dizziness, and hypoglycemia.
Combination Products **SOLIQUA 100/33** (insulin glargine + lixisenatide)	BLA 208673 (November 21, 2016)	**INDICATION:** • As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. **LIMITATIONS OF USE:** • Has not been studied in patients with chronic pancreatitis or a history of unexplained pancreatitis. Consider other antidiabetic therapies in patients with a history of pancreatitis. • Not recommended for use in combination with any other product containing a GLP-1 receptor agonist.	**RENAL IMPAIRMENT:** **FOR LIXISENATIDE MONOTHERAPY:** **eGFR ≥30 to 89 mL/min/1.73 m^2:** No dosage adjustment necessary; monitor closely for increased adverse gastrointestinal (GI) effects (e.g., diarrhea, nausea, vomiting) which may lead to dehydration and worsening of renal function. **eGFR 15 to 29 mL/min/1.73 m^2:** There are no dosage adjustments provided in product labeling (limited data); exposure is increased in these patients. Monitor closely for increased adverse GI effects (e.g., diarrhea, nausea, vomiting) which may lead to dehydration and worsening of renal function. **eGFR <15 mL/min/1.73 m^2:** Use is not recommended (has not been studied).	**CONTRAINDICATIONS:** • During episodes of hypoglycemia. • Serious hypersensitivity to insulin glargine, lixisenatide, or any of the excipients in SOLIQUA 100/33. **WARNINGS AND PRECAUTIONS:** • **Anaphylaxis and serious hypersensitivity reactions:** Severe, life- threatening, and generalized allergic reactions can occur. Instruct patients to discontinue use if a reaction occurs and promptly seek medical attention.

Trade Name (Established Name)	NDA/BLA # (Approval Date)*	Labeled Indication(s) Dosage and Administration	Dosing with Renal Impairment/Insufficiency†	Important Safety and Tolerability Issues‡
		• Not for treatment of type 1 diabetes mellitus or diabetic ketoacidosis. • Not recommended for use in patients with gastroparesis. • Has not been studied in combination with prandial insulin. **DOSAGE AND ADMINISTRATION:** • Inject once a day within the hour prior to the first meal of the day. • SOLIQUA 100/33 Pen delivers doses from 15 to 60 units with each injection. • Maximum daily dosage is 60 units (60 units of insulin glargine and 20 mcg of lixisenatide). • Discontinue basal insulin or GLP-1 receptor agonist prior to initiation. • In patients naïve to basal insulin or to a GLP-1 receptor agonist, inadequately controlled on less than 30 units of basal insulin or on a GLP-1 receptor agonist, the starting dosage is 15 units (15 units insulin glargine/5 mcg lixisenatide) given subcutaneously once daily. • In patients inadequately controlled on 30 to 60 units of basal insulin, the starting dosage is 30 units (30 units insulin glargine/10 mcg lixisenatide) given subcutaneously once daily. • Inject subcutaneously in thigh, upper arm, or abdomen. • Rotate injection sites within the same region from one injection to the next to reduce risk of lipodystrophy and localized cutaneous amyloidosis.	**FOR INSULIN MONOTHERAPY:** • Some studies with human insulin have shown increased circulating levels of insulin in patients with renal failure.	• **Pancreatitis:** Discontinue promptly if pancreatitis is suspected. Do not restart if pancreatitis is confirmed. • **Never share a SOLIQUA 100/33 prefilled pen between patients,** even if the needle is changed. (5.3) • **Hyperglycemia or hypoglycemia with changes in insulin regimen:** Make changes to a patient's insulin regimen (e.g., insulin strength, manufacturer, type, injection site or method of administration) under close medical supervision with increased frequency of blood glucose monitoring. • **Overdose due to medication errors:** SOLIQUA 100/33 contains two drugs. Instruct patients to always check the label before each injection since accidental mix-ups with insulin products can occur. Do not exceed the maximum dose or use with other GLP-1 receptor agonists. • **Hypoglycemia:** May be life-threatening. Increase frequency of glucose monitoring with changes to: insulin dosage, coadministered glucose lowering medications, meal pattern, physical activity; and in patients with renal or hepatic impairment and hypoglycemia unawareness. • **Acute kidney injury:** Monitor renal function in patients with renal impairment and in patients with

Trade Name (Established Name)	NDA/BLA # (Approval Date)*	Labeled Indication(s) Dosage and Administration	Dosing with Renal Impairment/Insufficiency†	Important Safety and Tolerability Issues‡
		• Do not administer intravenously, or via an infusion pump. • Do not dilute or mix with any other insulin products or solutions. **DOSAGE FORMS AND STRENGTHS:** • **Injection:** 100 units insulin glargine and 33 mcg lixisenatide per mL in a 3 mL single-patient-use pen		severe GI adverse reactions. Use is not recommended in patients with end-stage renal disease. • **Immunogenicity:** Patients may develop antibodies to insulin glargine and lixisenatide. If there is worsening glycemic control or failure to achieve targeted glycemic control, significant injection-site reactions or allergic reactions, alternative antidiabetic therapy should be considered. • **Hypokalemia:** May be life-threatening. Monitor potassium levels in patients at risk of hypokalemia and treat if indicated. • **Fluid retention and heart failure with use of thiazolidinediones (TZDs):** Observe for signs and symptoms of heart failure; consider dosage reduction or discontinuation if heart failure occurs. **COMMON ADVERSE EVENTS (≥5%):** • Hypoglycemia, nausea, nasopharyngitis, diarrhea, upper respiratory tract infection, and headache.
Semaglutide				
OZEMPIC (semaglutide)	NDA 209637 (December 5, 2017)	**INDICATIONS:** • As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. • To reduce the risk of major adverse cardiovascular events in adults with	**RENAL IMPAIRMENT:** • No dose adjustment of OZEMPIC is recommended for patients with renal impairment. In subjects with renal impairment including ESRD, no clinically relevant change in semaglutide PK was observed. • The apparent clearance of semaglutide in patients with type 2 diabetes is approximately 0.05 L/h. With an	**BOXED WARNING:** • In rodents, semaglutide causes thyroid C-cell tumors. It is unknown whether OZEMPIC causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans as the human relevance of

Trade Name (Established Name)	NDA/BLA # (Approval Date)*	Labeled Indication(s) Dosage and Administration	Dosing with Renal Impairment/Insufficiency†	Important Safety and Tolerability Issues‡
		type 2 diabetes mellitus and established cardiovascular disease. **LIMITATIONS OF USE:** • Has not been studied in patients with a history of pancreatitis. Consider another antidiabetic therapy. • Not for treatment of type 1 diabetes mellitus **DOSAGE AND ADMINISTRATION:** • Start at 0.25 mg once weekly. After 4 weeks, increase the dose to 0.5 mg once weekly. • If additional glycemic control is needed, increase the dose to 1 mg once weekly after at least 4 weeks on the 0.5 mg dose. • If additional glycemic control is needed, increase the dose to 2 mg once weekly after at least 4 weeks on the 1 mg dose. • Administer once weekly at any time of day, with or without meals. • If a dose is missed administer within 5 days of missed dose. • Inject subcutaneously in the abdomen, thigh, or upper arm. **DOSAGE FORMS AND STRENGTHS:** • **Injection:** 2 mg/1.5 mL (1.34 mg/mL) available in: — Single-patient-use pen that delivers 0.25 mg or 0.5 mg per injection. — Single-patient-use pen that delivers 1 mg per injection.	elimination half-life of approximately 1 week, semaglutide will be present in the circulation for about 5 weeks after the last dose. • Renal impairment does not impact the PK of semaglutide in a clinically relevant manner. This was shown in a study with a single dose of 0.5 mg semaglutide in patients with different degrees of renal impairment (mild, moderate, severe, ESRD) compared with subjects with normal renal function. This was also shown for subjects with both type 2 diabetes and renal impairment based on data from clinical studies. • The primary route of elimination for semaglutide is metabolism following proteolytic cleavage of the peptide backbone and sequential beta-oxidation of the fatty acid sidechain. The primary excretion routes of semaglutide-related material is via the urine and feces. • Approximately 3% of the dose is excreted in the urine as intact semaglutide.	semaglutide-induced rodent thyroid C-cell tumors has not been determined. • OZEMPIC is contraindicated in patients with a personal or family history of MTC or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Counsel patients regarding the potential risk of MTC and symptoms of thyroid tumors (e.g., a mass in the neck, dysphagia, dyspnea, persistent hoarseness). Routine monitoring of serum calcitonin or using thyroid ultrasound is of uncertain value for early detection of MTC in patients treated with OZEMPIC. **ADDITIONAL CONTRAINDICATIONS:** • A serious hypersensitivity reaction to semaglutide or to any of the excipients in OZEMPIC. Serious hypersensitivity reactions including anaphylaxis and angioedema have been reported with OZEMPIC. **WARNINGS AND PRECAUTIONS:** • **Pancreatitis:** Has been reported in clinical trials. Discontinue promptly if pancreatitis is suspected. Do not restart if pancreatitis is confirmed. • **Diabetic Retinopathy Complications:** Has been reported in a clinical trial. Patients with a history of diabetic retinopathy should be monitored.

Trade Name (Established Name)	NDA/BLA # (Approval Date)*	Labeled Indication(s) Dosage and Administration	Dosing with Renal Impairment/Insufficiency†	Important Safety and Tolerability Issues‡
		• **Injection:** 4 mg/3 mL (1.34 mg/mL) available in: — Single-patient-use pen that delivers 1 mg per injection • **Injection:** 8 mg/3 mL (2.68 mg/mL) available in: — Single-patient-use pen that delivers 2 mg per injection		• **Never share an OZEMPIC pen between patients**, even if the needle is changed. • **Hypoglycemia:** Concomitant use with an insulin secretagogue or insulin may increase the risk of hypoglycemia, including severe hypoglycemia. Reducing dose of insulin secretagogue or insulin may be necessary. • **Acute Kidney Injury:** Monitor renal function in patients with renal impairment reporting severe adverse gastrointestinal reactions. • **Hypersensitivity Reactions:** Serious hypersensitivity reactions (e.g., anaphylaxis and angioedema) have been reported. Discontinue OZEMPIC if suspected and promptly seek medical advice. • **Acute Gallbladder Disease:** If cholelithiasis or cholecystitis are suspected, gallbladder studies are indicated **COMMON ADVERSE EVENTS (≥5%):** • Nausea, vomiting, diarrhea, abdominal pain, and constipation.
RYBELSUS (semaglutide)	NDA 213051 (September 20, 2019)	**INDICATION:** • As an adjunct to diet and exercise to improve glycemic control in adults with T2D. **LIMITATIONS OF USE:** • Not recommended as first-line therapy for patients inadequately controlled on diet and exercise.	**RENAL IMPAIRMENT:** • No dose adjustment of RYBELSUS is recommended for patients with renal impairment. In patients with renal impairment including ESRD, no clinically relevant change in semaglutide PK was observed. • The primary excretion routes of semaglutide-related material are via the urine and feces. Approximately 3%	**BOXED WARNING:** • In rodents, semaglutide causes thyroid C-cell tumors. It is unknown whether RYBELSUS causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans as the human relevance of semaglutide-induced rodent thyroid

Trade Name (Established Name)	NDA/BLA # (Approval Date)*	Labeled Indication(s) Dosage and Administration	Dosing with Renal Impairment/Insufficiency†	Important Safety and Tolerability Issues‡
		• Has not been studied in patients with a history of pancreatitis. • Not for treatment of type 1 diabetes mellitus. **DOSAGE AND ADMINISTRATION:** • Instruct patients to take RYBELSUS at least 30 minutes before the first food, beverage, or other oral medications of the day with no more than 4 ounces of plain water only. Waiting less than 30 minutes, or taking with food, beverages (other than plain water) or other oral medications will lessen the effect of RYBELSUS. Waiting more than 30 minutes to eat may increase the absorption of RYBELSUS. • Swallow tablets whole. Do not cut, crush, or chew tablets. • Start RYBELSUS with 3 mg once daily for 30 days. After 30 days on the 3 mg dose, increase the dose to 7 mg once daily. • Dose may be increased to 14 mg once daily if additional glycemic control is needed after at least 30 days on the 7 mg dose. • See the Full Prescribing Information for instructions on switching between Ozempic and RYBELSUS. **DOSAGE FORMS AND STRENGTHS:** • **Tablets:** 3 mg, 7 mg, and 14 mg	of the absorbed dose is excreted in the urine as intact semaglutide. • Renal impairment does not impact the pharmacokinetics of semaglutide in a clinically relevant manner. This was shown in a study with 10 consecutive days of once daily oral doses of semaglutide in patients with different degrees of renal impairment (mild, moderate, severe, end staged renal disease) compared with subjects with normal renal function. This was also shown for subjects with both type 2 diabetes and renal impairment based on data from clinical studies. • Monitor renal function in patients with renal impairment reporting severe adverse gastrointestinal reactions.	C-cell tumors has not been determined. • RYBELSUS is contraindicated in patients with a personal or family history of MTC or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Counsel patients regarding the potential risk of MTC and symptoms of thyroid tumors. **ADDITIONAL CONTRAINDICATIONS:** • Prior serious hypersensitivity reaction to semaglutide or to any of the excipients in RYBELSUS. **WARNINGS AND PRECAUTIONS:** • **Pancreatitis:** Has been reported in clinical trials. Discontinue promptly if pancreatitis is suspected. Do not restart if pancreatitis is confirmed. • **Diabetic Retinopathy Complications:** Has been reported in a cardiovascular outcomes trial with semaglutide injection. Patients with a history of diabetic retinopathy should be monitored. • **Hypoglycemia:** Concomitant use with an insulin secretagogue or insulin may increase the risk of hypoglycemia, including severe hypoglycemia. Reducing dose of insulin secretagogue or insulin may be necessary. • **Acute Kidney Injury:** Monitor renal function in patients with renal

Trade Name (Established Name)	NDA/BLA # (Approval Date)*	Labeled Indication(s) Dosage and Administration	Dosing with Renal Impairment/Insufficiency†	Important Safety and Tolerability Issues‡
				impairment reporting severe adverse gastrointestinal reactions. • **Hypersensitivity Reactions:** Serious hypersensitivity reactions (e.g., anaphylaxis and angioedema) have been reported. Discontinue RYBELSUS if suspected and promptly seek medical advice. **COMMON ADVERSE EVENTS (≥5%):** • Nausea, abdominal pain, diarrhea, decreased appetite, vomiting and constipation.
WEGOVY (semaglutide)	NDA 215256 (June 4, 2021)	**INDICATIONS:** • As an adjunct to a reduced calorie diet and increased physical activity for chronic weight management in adult patients with an initial body mass index (BMI) of: — 30 kg/m2 or greater (obesity) or — 27 kg/m2 or greater (overweight) in the presence of at least one weight-related comorbid condition (e.g., hypertension, type 2 diabetes mellitus, or dyslipidemia) **LIMITATIONS OF USE:** • WEGOVY should not be used in combination with other semaglutide-containing products or any other GLP-1 receptor agonist. • The safety and efficacy of coadministration with other products for weight loss have not been established. • WEGOVY has not been studied in patients with a history of pancreatitis.	**RENAL IMPAIRMENT:** • No dose adjustment of WEGOVY is recommended for patients with renal impairment. In subjects with renal impairment including ESRD, no clinically relevant change in semaglutide PK was observed. • The apparent clearance of semaglutide in patients with obesity or overweight is approximately 0.05 L/h. With an elimination half-life of approximately 1 week, semaglutide will be present in the circulation for about 5 to 7 weeks after the last dose of 2.4 mg. • Renal impairment did not impact the exposure of semaglutide in a clinically relevant manner. The pharmacokinetics of semaglutide were evaluated following a single dose of 0.5 mg semaglutide in a study of patients with different degrees of renal impairment (mild, moderate, severe, or ESRD) compared with subjects with normal renal function. The pharmacokinetics were also assessed in subjects with overweight (BMI 27-29.9 kg/m^2) or obesity (BMI greater than or equal to 30 kg/m^2) and mild to moderate renal impairment, based on data from clinical trials • The primary route of elimination for semaglutide is metabolism following proteolytic cleavage of the	**BOXED WARNING:** • In rodents, semaglutide causes thyroid C-cell tumors. It is unknown whether WEGOVY causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans as the human relevance of semaglutide-induced rodent thyroid C-cell tumors has not been determined. • WEGOVY is contraindicated in patients with a personal or family history of MTC or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Counsel patients regarding the potential risk of MTC and symptoms of thyroid tumors. **ADDITIONAL CONTRAINDICATIONS:** • Known hypersensitivity reaction to semaglutide or to any of the excipients in WEGOVY. **WARNINGS AND PRECAUTIONS:**

Trade Name (Established Name)	NDA/BLA # (Approval Date)*	Labeled Indication(s) Dosage and Administration	Dosing with Renal Impairment/Insufficiency†	Important Safety and Tolerability Issues‡
		DOSAGE AND ADMINISTRATION: • Start at 0.25 mg once weekly. After 4 weeks, increase the dose to 0.5 mg once weekly. If after at least 4 weeks additional glycemic control is needed, increase to 1 mg once weekly. • Administer WEGOVY once weekly, on the same day each week, at any time of day, with or without meals. • Inject subcutaneously in the abdomen, thigh or upper arm. • Initiate at 0.25 mg once weekly for 4 weeks. In 4-week intervals, increase the dose until a dose of 2.4 mg is reached. • The maintenance dose of WEGOVY is 2.4 mg once weekly. • In patients with type 2 diabetes, monitor blood glucose prior to starting and during WEGOVY treatment. **DOSAGE FORMS AND STRENGTHS:** • **Injection:** 4 pre-filled, single-dose pen that delivers doses of 0.25 mg, 0.5 mg, 1 mg, 1.7 mg or 2.4 mg	peptide backbone and sequential beta-oxidation of the fatty acid sidechain. The primary excretion routes of semaglutide-related material are via the urine and feces. Approximately 3% of the dose is excreted in the urine as intact semaglutide.	• **Acute Pancreatitis:** Has occurred in clinical trials. Discontinue promptly if pancreatitis is suspected. Do not restart if pancreatitis is confirmed. • **Acute Gallbladder Disease:** Has occurred in clinical trials. If cholelithiasis is suspected, gallbladder studies and clinical follow-up are indicated. • **Hypoglycemia:** Concomitant use with an insulin secretagogue or insulin may increase the risk of hypoglycemia, including severe hypoglycemia. Reducing the dose of insulin secretagogue or insulin may be necessary. Inform all patients of the risk of hypoglycemia and educate them on the signs and symptoms of hypoglycemia. • **Acute Kidney Injury:** Has occurred. Monitor renal function when initiating or escalating doses of WEGOVY in patients reporting severe adverse gastrointestinal reactions or in those with renal impairment reporting severe adverse gastrointestinal reactions. • **Hypersensitivity:** Anaphylactic reactions and angioedema have been reported postmarketing. Discontinue WEGOVY if suspected and promptly seek medical advice. • **Diabetic Retinopathy Complications in Patients with Type 2 Diabetes:** Has been reported in trials with semaglutide. Patients

Trade Name (Established Name)	NDA/BLA # (Approval Date)*	Labeled Indication(s) Dosage and Administration	Dosing with Renal Impairment/Insufficiency†	Important Safety and Tolerability Issues‡
				with a history of diabetic retinopathy should be monitored. • **Heart Rate Increase:** Monitor heart rate at regular intervals. • **Suicidal Behavior and Ideation:** Monitor for depression or suicidal thoughts. Discontinue WEGOVY if symptoms develop. **COMMON ADVERSE EVENTS (≥5%):** • Hypoglycemia. nausea, diarrhea, vomiting, constipation, abdominal pain, headache, fatigue, dyspepsia, dizziness, abdominal distension, eructation, hypoglycemia in patients with type 2 diabetes, flatulence, gastroenteritis, and gastroesophageal reflux disease.

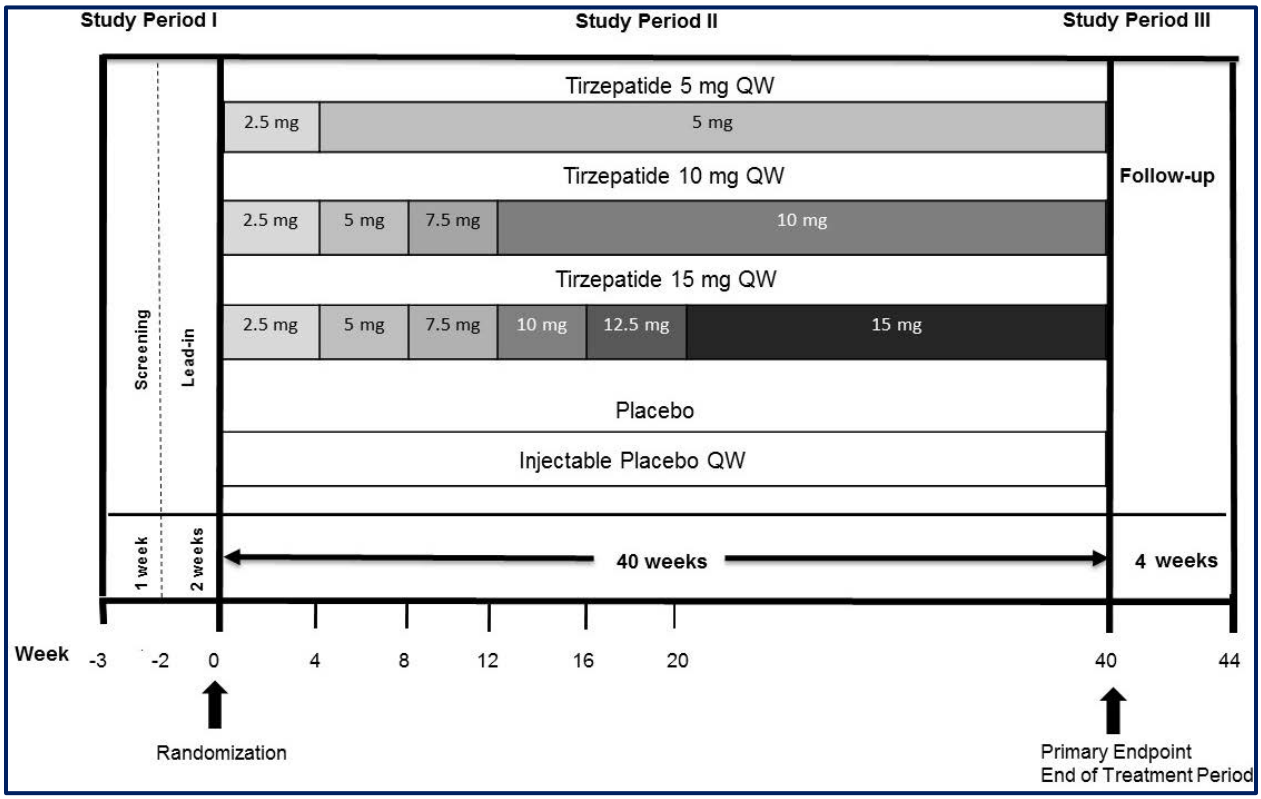
Sources: Product labeling, available at Drugs@FDA: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm; Facts & Comparisons eAnswers: http://online.factsandcomparisons.com/; UpToDate: http://www.uptodate.com.ezproxy.nihlibrary.nih.gov/contents/search; and selected literature (as referenced in the table).
Abbreviations: ADA, American Diabetes Association; AUC, area under the concentration-time curve; BLA, Biologics License Application; CL/F, apparent total clearance of the drug from plasma after oral administration; Cmax, maximum plasma concentration; CrCl, creatinine clearance; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; GI, gastrointestinal; GLP-1, glucagon-like peptide-1; h, hour; MEN 2, Multiple endocrine neoplasia syndrome type 2; min, minute; MTC, medullary thyroid carcinoma; NDA, New Drug Application; and PK, pharmacokinetic.

13.3. Study Designs of Relevant Phase 3 Trials

The study designs for the five global phase 3 clinical trials (GPGK, GPGL, GPGH, GPGM, and GPGI) used to demonstrate the efficacy of tirzepatide for the proposed indication (i.e., as an adjunct to diet and exercise to improve glycemic control in adults with T2D) are presented below.

Trial 18F-MC-GPGK (SURPASS-1): A multicenter, randomized, double-blind, parallel-group, placebo-controlled, phase 3 trial in subjects with T2D, naive to antihyperglycemic injectable therapy, inadequately controlled with diet and exercise alone, and had not been treated with any oral antihyperglycemic medication during the three months preceding to the start of the trial. This trial consisted of 3 periods: a 3-week screening/lead-in period, followed by a 40-week treatment period, and a 4-week safety follow-up period. Subjects were randomized in a 1:1:1:1 ratio (tirzepatide 5 , 10 , or 15 mg, or injectable placebo SC QW).

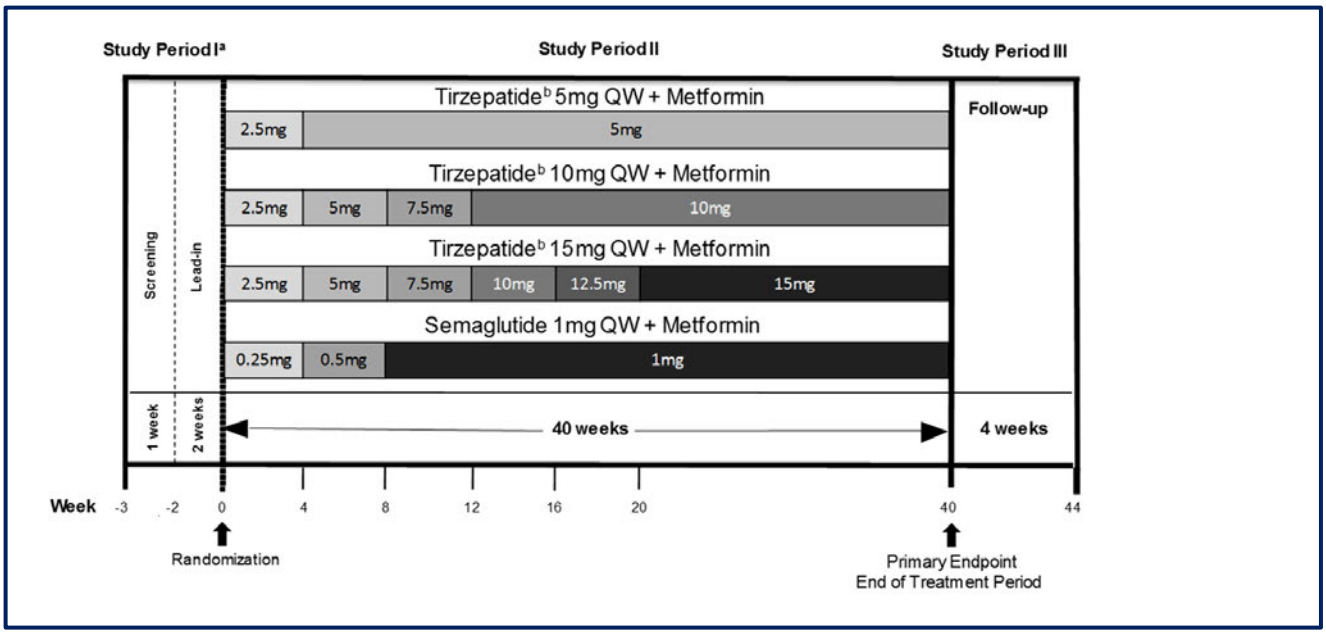
Figure 16: Study Design of Trial GPGK



Source: Reproduced from the Applicant's Clinical Study Report, Protocol 18F-MC-GPGK, labeled as Figure GPGK.1, page 25 of 90, available at: \\CDSESUB1\evsprod\nda215866\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\type-2-diabetes-mellitus\5351-stud-rep-contr\i8f-mc-gpgk\gpgk-05-protocol--b-.pdf

Trial 18F-MC-GPGL (SURPASS-2): A multicenter, randomized, open-label, parallel-group, active-controlled, phase 3 trial with subjects with T2D, inadequately controlled on ≥1500 mg/day of metformin alone during the three months preceding to the start of the trial. This trial consisted of 3 periods: a 3-week screening/lead-in period, followed by a 40-week treatment period, and a 4-week safety follow-up period. Subjects were randomized in a 1:1:1:1 ratio (tirzepatide 5 , 10, or 15 mg [doses double-blinded], or semaglutide 1 mg [not blinded] SC QW).

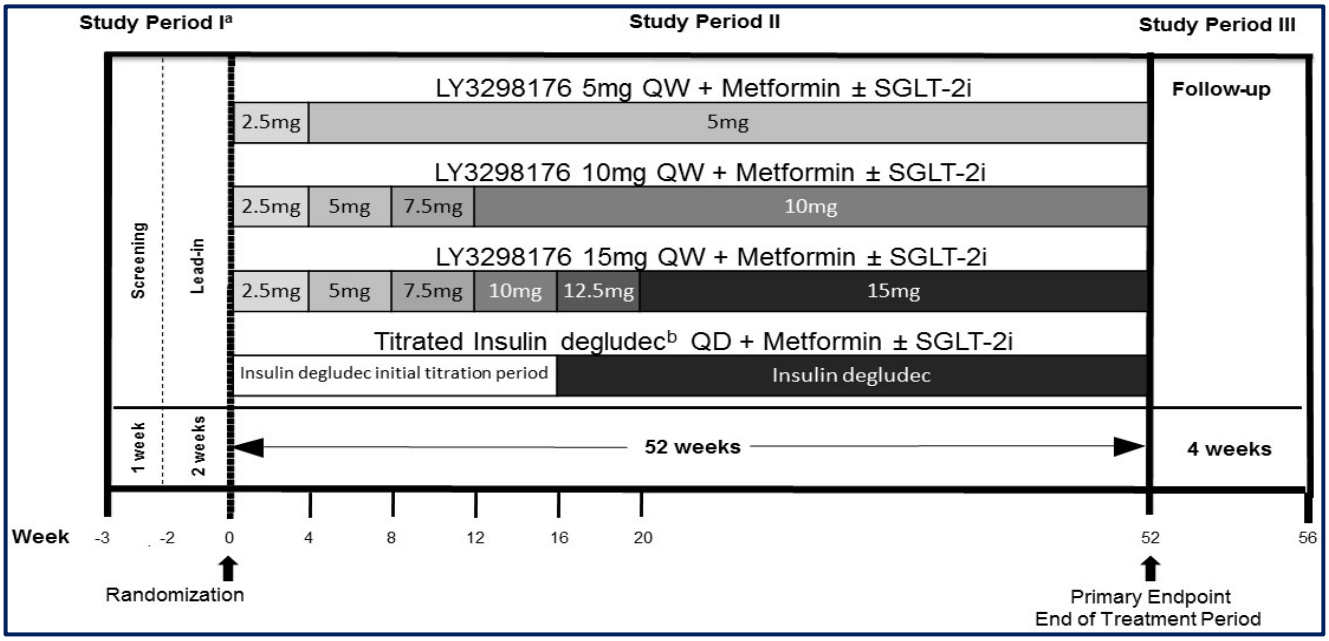
Figure 17: Study Design of Trial GPGL



Source: Reproduced from the Applicant's Clinical Study Report, Protocol 18F-MC-GPGL, labeled as Figure GPGL.1, page 27 of 98, available at: \\CDSESUB1\evsprod\nda215866\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\type-2-diabetes-mellitus\5351-stud-rep-contr\i8f-mc-gpgl\gpgl-05-protocol--b-.pdf
Abbreviations: QW, once weekly.
[a] Stable doses of metformin (≥1500 mg/day) for ≥3 months
[b] All tirzepatide doses were double-blinded.

Trial 18F-MC-GPGH (SURPASS-3): A multicenter, randomized, open-label, parallel-group phase 3 trial in subjects with T2D, inadequately controlled on stable doses of metformin (≥1500 mg/day) with or without a SGLT2i during the three months preceding to the start of the trial. This trial consisted of 3 periods: a 3-week screening/lead-in period, followed by a 52-week treatment period, and a 4-week safety follow-up period. Subjects were randomized in a 1:1:1:1 ratio (tirzepatide 5, 10, or 15 mg SC QW, or insulin degludec SC QD).

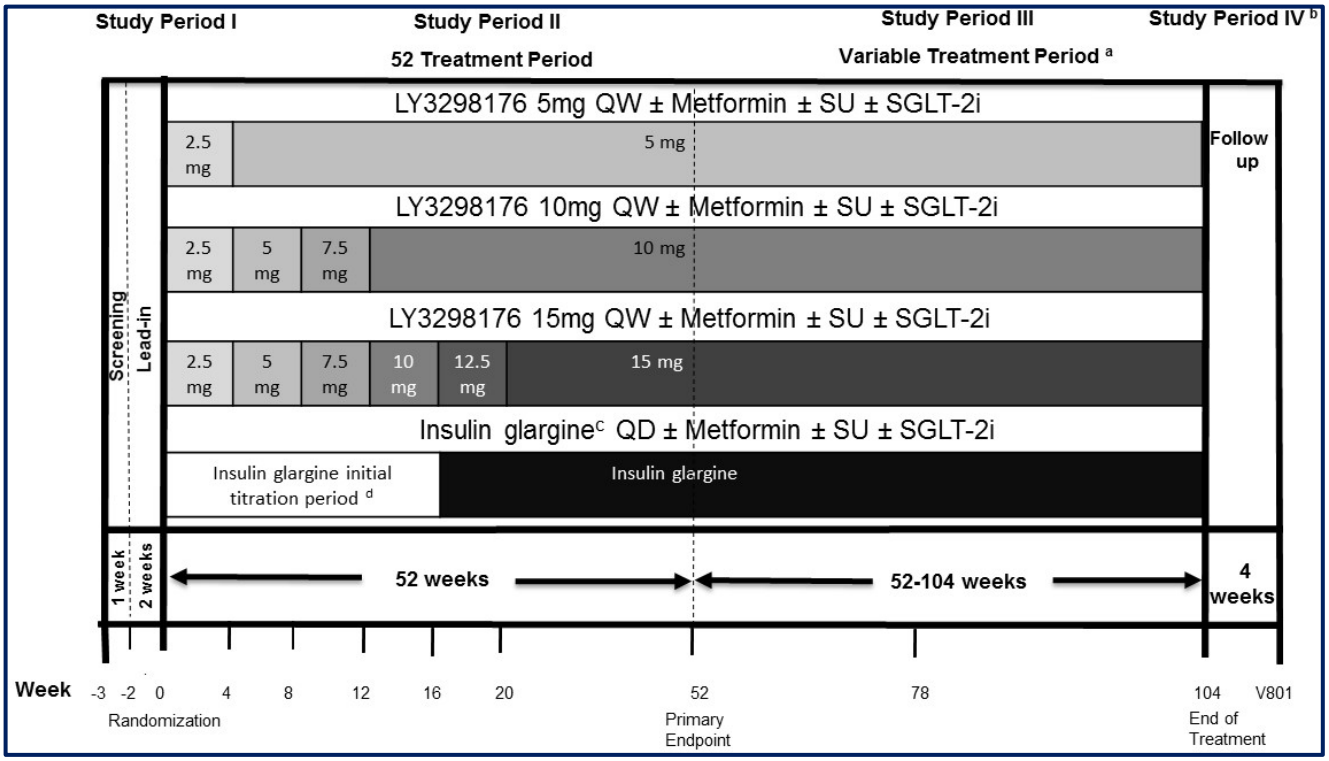
Figure 18: Study Design of Trial GPGH



Source: Reproduced from the Applicant's Clinical Study Report, Protocol 18F-MC-GPGH, labeled as Figure, page 28 of 94, available at: \\CDSESUB1\evsprod\nda215866\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\type-2-diabetes-mellitus\5351-stud-rep-contr\i8f-mc-gpgh\gpgh-05-protocol--c-.pdf
Abbreviations: QD, daily; and QW, once weekly; and SGLT-2i, sodium-glucose cotransporter-2 inhibitor.
[a] Stable doses of metformin (≥1500 mg/day) ± a SGLT-2i ≥3 months
[b] The starting dose of insulin degludec was 10 IU/day ideally at bedtime, titrated to a fasting blood glucose (FBG) <90 mg/dL, following a treat-to-target (TTT) algorithm.

Trial 18F-MC-GPGM (SURPASS-4): A multicenter, randomized, open-label, parallel-group, active-controlled, phase 3 trial in subjects with T2D with increased CV risk, inadequately controlled on stable doses of at least one and no more than three oral antihyperglycemic medications during the three months preceding to the start of the trial. This trial consisted of 3 periods: a 3-week screening/lead-in period, followed by a ≥52 to 104-week treatment period (i.e., treatment continued for ≥52 weeks from the time the last subject was randomized), and a 4-week safety follow-up period. Subjects were randomized in a 1:1:1:3 ratio (tirzepatide 5, 10, or 15 mg SC QW, or insulin glargine SC QD). The starting dose of insulin glargine was 10 units/day at bedtime, titrated to a FBG <100 mg/dL, following a TTT algorithm.

Figure 19: Study Design of Trial GPGM



Source: Reproduced from the Applicant's Clinical Study Report, Protocol 18F-MC-GPGM, labeled as Figure, page 28 of 93, available at: \\CDSESUB1\evsprod\nda215866\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\type-2-diabetes-mellitus\5351-stud-rep-contr\i8f-mc-gpgm\gpgm-05-protocol--b-.pdf

Abbreviations: QD, daily; and QW, once weekly; SGLT-2i, sodium-glucose cotransporter-2 inhibitor; and SU, sulfonylurea.

[a] Patients will be on IP for at ≥12 months.

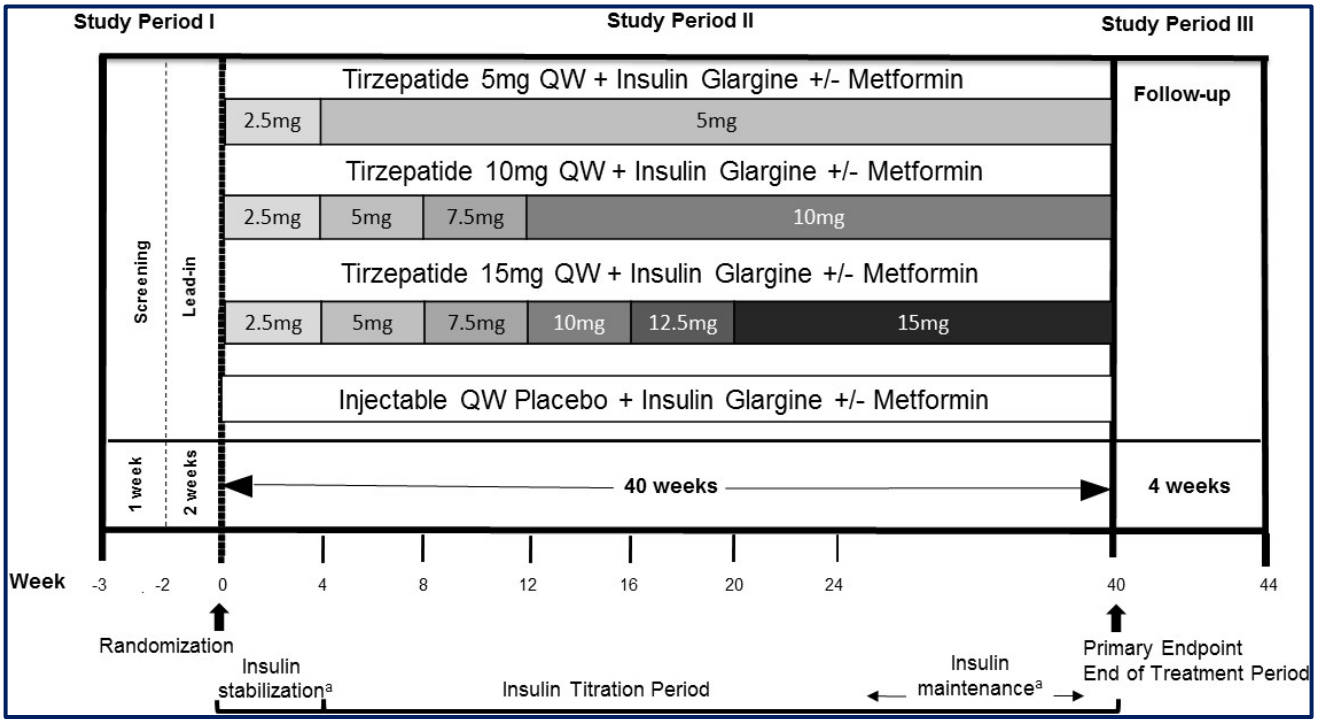
[b] All subjects will perform a Visit 801 4 weeks after their last treatment visit

[c] The starting dose of insulin glargine was 10 IU/day at bedtime, titrated to a fasting blood glucose (FBG) <100 mg/dL, following a TTT algorithm.

[d] Subjects will titrate insulin glargine dose in a weekly manner and will make the dose decision with the investigator for the first 8 weeks (phone or clinic visit). From Week 8 to Week 16, subjects will continue the titration by a phone consultation or clinic visit every other week, with 3 weeks between Visits 13 and 14.

Trial 18F-MC-GPGI (SURPASS-5): A multicenter, randomized, double-blind, parallel-group, placebo-controlled, phase 3 study with 3 study periods in subjects with T2D, inadequately controlled on stable doses of titrated basal insulin glargine (>0.25 units/kg/day or >20 units/day) with or without metformin during the three months preceding to the start of the trial. This trial consisted of 3 periods: a 3-week screening/lead-in period, followed by a 40-week treatment period, and a 4-week safety follow-up period. Subjects were randomized in a 1:1:1:1 ratio (tirzepatide 5, 10, or 15 mg, or injectable placebo SC QW).

Figure 20: Study Design of Trial GPGI



Source: Reproduced from the Applicant's Clinical Study Report, Protocol 18F-MC-GPGI, labeled as Figure, page 28 of 99, available at: \\CDSESUB1\evsprod\nda215866\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\type-2-diabetes-mellitus\5351-stud-rep-contr\i8f-mc-gpgi\gpgi-05-protocol--b-.pdf

Abbreviations: ±, with or without; and QW, once weekly.

[a] Insulin stabilization period is the first 4 weeks after randomization, with restricted insulin dose adjustments. Insulin glargine titration period Weeks 4 to 40 (end of treatment/end of study), with unrestricted insulin dose adjustments. Maintenance period is from Weeks 24 to 40 (end of treatment/end of study), the period when insulin glargine dose is expected to be stable.

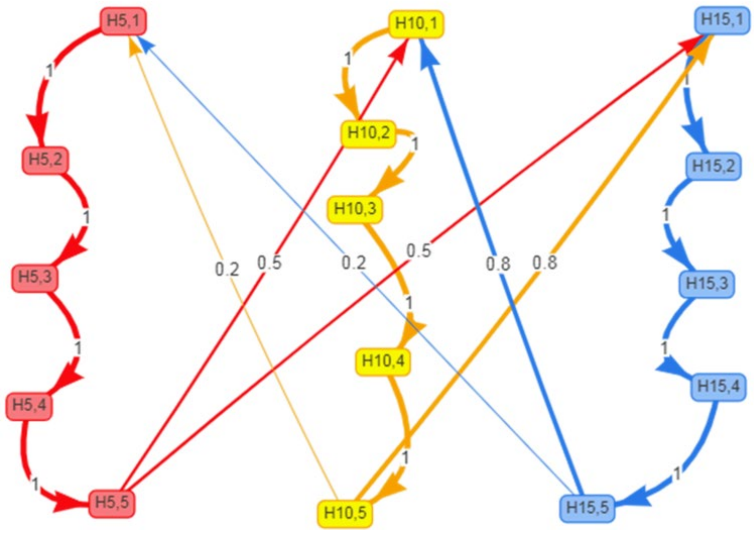
13.4. Graphical Multiple-Testing Procedures for Type I Error Control

The graphical multiple-testing procedures for the primary and key secondary objectives for the treatment-regimen estimand and the efficacy estimand are presented for the five global phase 3 clinical trials (GPGK, GPGL, GPGH, GPGM, and GPGI). These procedures controlled the family-wise type 1 error rate for individual estimands.

Trial 18F-MC-GPGK (SURPASS-1): The graphical testing scheme[325,326] used to control for type 1 error in trial GPGK is displayed in Figure 21. The primary and key secondary objective hypotheses were as follows:

- $H_{5,1}$, $H_{10,1}$, and $H_{15,1}$: Superiority test of tirzepatide 5 mg, 10 mg, 15 mg versus placebo in HbA1c change from baseline at 40 weeks, respectively (each initially tested at a 0.01667 significance level).
- $H_{5,2}$, $H_{10,2}$, and $H_{15,2}$: Superiority test of tirzepatide 5 mg, 10 mg, 15 mg versus placebo in body weight change from baseline at 40 weeks respectively.
- $H_{5,3}$, $H_{10,3}$, and $H_{15,3}$: Superiority test of tirzepatide 5 mg, 10 mg, 15 mg versus placebo in proportion of subjects achieve HbA1c <7% at 40 weeks respectively.
- $H_{5,4}$, $H_{10,4}$, and $H_{15,4}$: Superiority test of tirzepatide 5 mg, 10 mg, 15 mg versus placebo in fasting serum glucose (FSG) change from baseline at 40 weeks respectively.
- $H_{5,5}$, $H_{10,5}$, and $H_{15,5}$: Superiority test of tirzepatide 5 mg, 10 mg, 15 mg versus placebo in proportion of subjects achieve HbA1c <5.7% at 40 weeks respectively.

Figure 21: Type 1 Error Control Strategy (Primary & Key Secondary Endpoints)—Trial GPGK

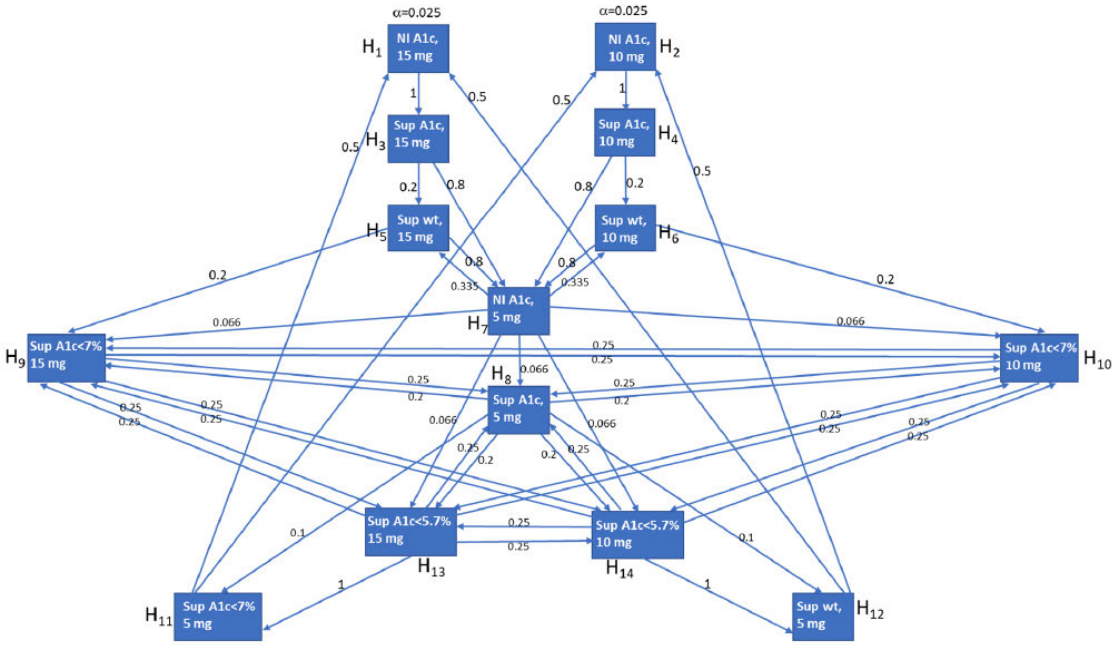


Source: Reproduced/Adapted from the Applicant's 18F-MC-GPGK Statistical Analysis Plan (Version 3), pages 19-20 of 80, available at: \\CDSESUB1\evsprod\NDA215866\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\type-2-diabetes-mellitus\5351-stud-rep-contr\i8f-mc-gpgk\gpgk-13-statistical-analysis-plan-v3-including-v2.pdf

Trial 18F-MC-GPGL (SURPASS-2): The graphical testing scheme[325] used to control for type 1 error in trial GPGL is displayed in Figure 22. The primary and key secondary objective hypotheses were as follows:

- H_1, and H_2: Noninferiority test of tirzepatide 10 mg and 15 mg versus semaglutide in HbA1c change from baseline at 40 weeks (each initially tested at a 0.025 significance level).
- H_3, and H_4: Superiority test of tirzepatide 10 mg, and 15 mg versus semaglutide in HbA1c change from baseline at 40 weeks.
- H_5, and H_6: Superiority test of tirzepatide 10 mg, and 15 mg versus semaglutide in body weight change from baseline at 40 weeks.
- H_7: Noninferiority test of tirzepatide 5 mg versus semaglutide in HbA1c change from baseline at 40 weeks.
- H_8: Superiority test of tirzepatide 5 mg versus semaglutide in HbA1c change from baseline at 40 weeks.
- H_9, H_{10}, and H_{11}: Superiority test of tirzepatide 10 mg, 15 mg, and 5 mg versus semaglutide in proportion of subjects achieving HbA1c <7% at 40 weeks.
- H_{12}: Superiority test of tirzepatide 5 mg versus semaglutide in body weight change from baseline at 40 weeks.
- H_{13}, and H_{14}: Superiority test of tirzepatide 10 mg, and 15 mg versus semaglutide in proportion of subjects achieving HbA1c < 5.7% at 40 weeks.

Figure 22: Type 1 Error Control Strategy (Primary & Key Secondary Endpoints)—Trial GPGL



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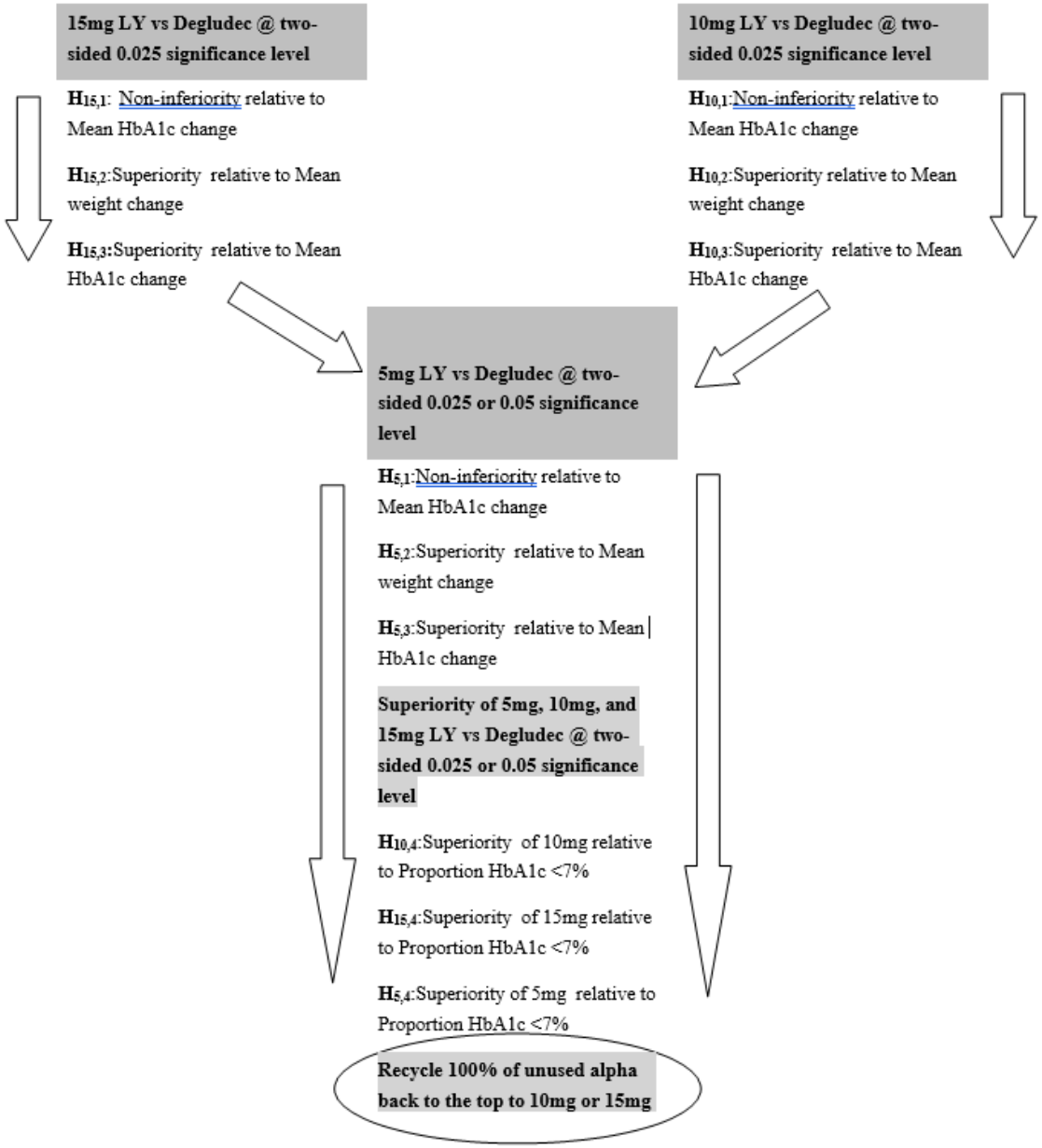
Abbreviations: A1c, hemoglobin A1c; NI, noninferiority; Sup, superiority; and wt, body weight.

Trial 18F-MC-GPGH (SURPASS-3): The graphical testing scheme used to control for type 1 error in trial GPGH is displayed in Figure 23. The primary and key secondary objective hypotheses were as follows:

1. $H_{15,1}$, $H_{15,2}$, and $H_{15,3}$ were evaluated hierarchically each at a 2-sided 0.025 significance level conditioned on successfully achieving the preceding objective. In parallel,
2. $H_{10,1}$, $H_{10,2}$, and $H_{10,3}$ were evaluated hierarchically each at a 2-sided 0.025 significance level conditioned on successfully achieving the preceding objective.
3.
    a. If all objectives in #1 and #2 above were successfully established, $H_{5,1}$, $H_{5,2}$, and $H_{5,3}$ were evaluated hierarchically, each at a 2-sided 0.05 significance level.
    b. If all objectives in only #1 or only #2 above were successfully established, $H_{5,1}$, $H_{5,2}$, and $H_{5,3}$ were evaluated hierarchically, each at a 2-sided 0.025 significance level.
4. If all objectives: $H_{5,1}$, $H_{5,2}$, and $H_{5,3}$ were successfully established and
    a. If all objectives in #1 and #2 above were successfully established, then $H_{10,4}$, $H_{15,4}$, and $H_{5,4}$ were evaluated hierarchically each at a 2-sided 0.05 significance level conditioned on successfully achieving the preceding objective.
    b. If all objectives in only #1 or only #2 above were successfully established, then $H_{10,4}$, $H_{15,4}$, and $H_{5,4}$ were evaluated hierarchically each at a 2-sided 0.025 significance level conditioned on successfully achieving the preceding objective.
5. If all objectives in #3 and #4 above were successfully established, and at least 1 objective from #1 or #2 above was not successfully established, 100% of the unused alpha was recycled back to #1 or #2 above.

Figure 23: Type 1 Error Control Strategy (Primary & Key Secondary Endpoints)—Trial GPGH



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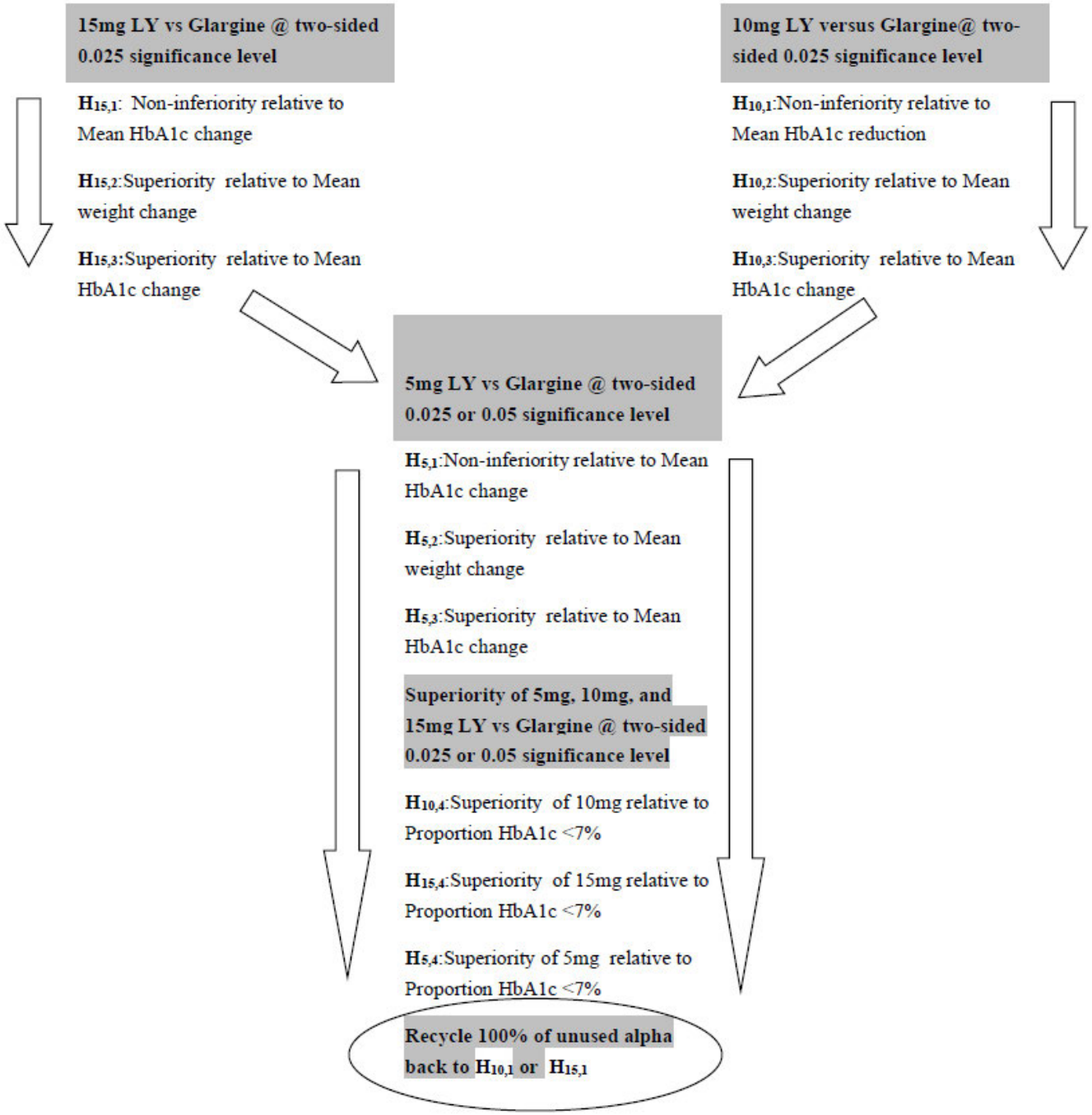
Abbreviations: HbA1c, hemoglobin A1c; LY, LY3298176 (tirzepatide); and vs, versus.

Trial 18F-MC-GPGM (SURPASS-4): The graphical testing scheme used to control for type 1 error in trial GPGM is displayed in Figure 24Figure 22. The primary and key secondary objective hypotheses were as follows:

1. $H_{15,1}$, $H_{15,2}$, and $H_{15,3}$ were evaluated hierarchically each at two-sided 0.025 significance level conditioned on the successfully achieving the preceding objective. In parallel,
2. $H_{10,1}$, $H_{10,2}$, and $H_{10,3}$ were evaluated hierarchically each at two-sided 0.025 significance level conditioned on the successfully achieving the preceding objective.
3.
    a) If all objectives in #1 and #2 above were successfully established, $H_{5,1}$, $H_{5,2}$, and $H_{5,3}$ were evaluated hierarchically, each at two-sided 0.05 significance level.
    b) If all objectives in only #1 or only #2 above were successfully established, $H_{5,1}$, $H_{5,2}$, and $H_{5,3}$ were evaluated hierarchically, each at two-sided 0.025 significance level.
4. If all objectives: $H_{5,1}$, $H_{5,2}$, and $H_{5,3}$ were successfully established and
    a) if all objectives in #1 and #2 above were successfully established, then $H_{10,4}$, $H_{15,4}$ and $H_{5,4}$ were evaluated hierarchically each at two-sided 0.05 significance level conditioned on the successfully achieving the preceding objective.
    b) if all objectives in only #1 or only #2 above were successfully established, then $H_{10,4}$, $H_{15,4}$ and $H_{5,4}$ were evaluated hierarchically each at two-sided 0.025 significance level conditioned on the successfully achieving the preceding objective.
5. If all objectives in #3 and #4 above were successfully established, and at least 1 objective from #1 or #2 above was not successfully established, 100% of the unused alpha recycled back to #1 or #2 above.

Figure 24: Type 1 Error Control Strategy (Primary & Key Secondary Endpoints)—Trial GPGM



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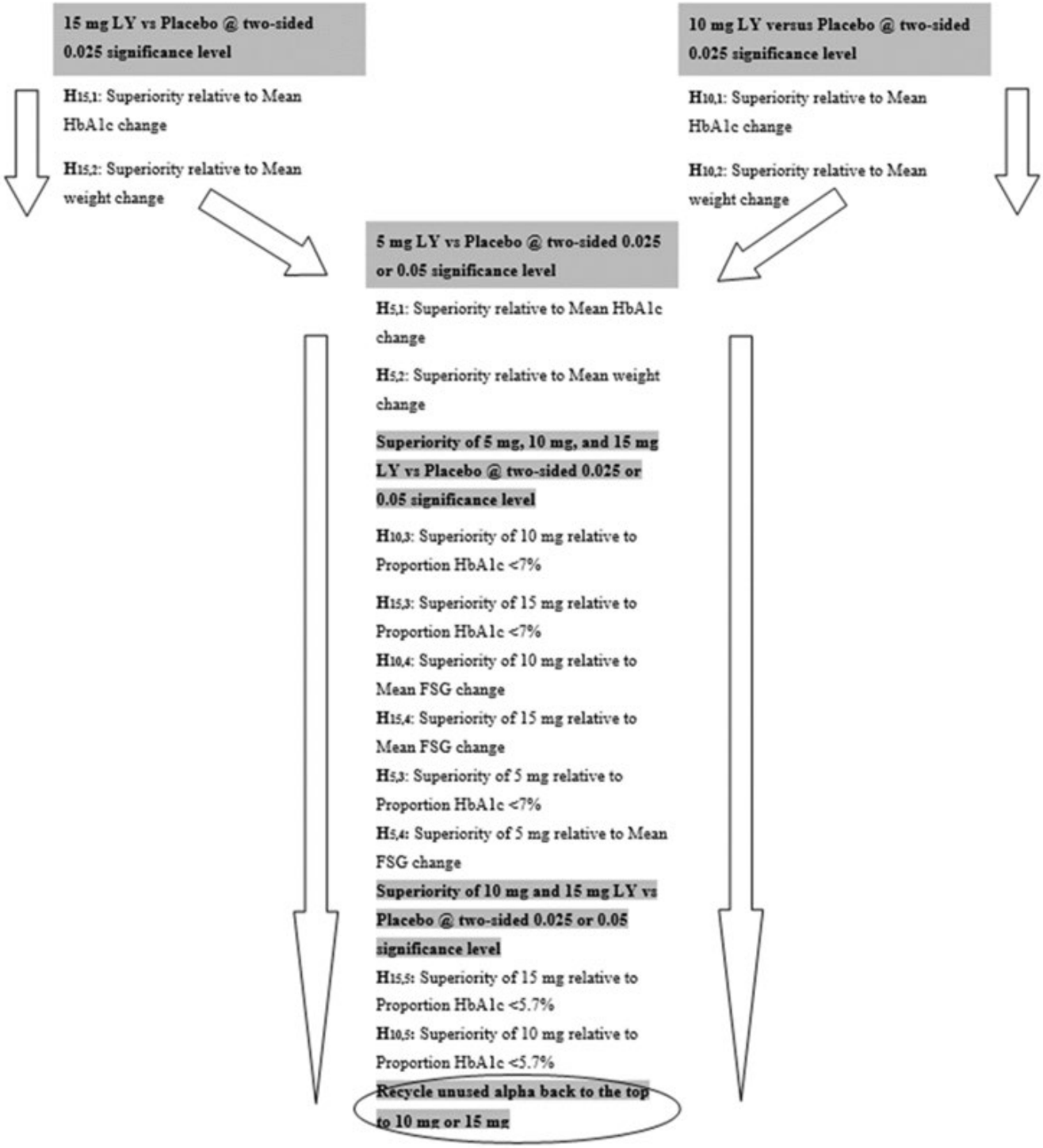
Abbreviations: HbA1c, hemoglobin A1c; LY, LY3298176 (tirzepatide); and vs, versus.

Trial 18F-MC-GPGI (SURPASS-5): The graphical testing scheme used to control for type 1 error in trial GPGI is displayed in Figure 25. The primary and key secondary objective hypotheses were as follows:

1. $H_{15,1}$ and $H_{15,2}$ were evaluated hierarchically each at a 2-sided 0.025 significance level conditioned on successfully achieving the preceding objective. In parallel,
2. $H_{10,1}$ and $H_{10,2}$ were evaluated hierarchically each at a 2-sided 0.025 significance level conditioned on successfully achieving the preceding objective.
3.
    a. If all objectives in #1 and #2 above were successfully established, $H_{5,1}$ and $H_{5,2}$ were evaluated hierarchically, each at a 2-sided 0.05 significance level.
    b. If all objectives in only #1 or only #2 above were successfully established, $H_{5,1}$ and $H_{5,2}$ were evaluated hierarchically, each at a 2-sided 0.025 significance level.
4. If both objectives: $H_{5,1}$ and $H_{5,2}$ were successfully established and
    a. If all objectives in #1 and #2 above were successfully established, then $H_{10,3}$, $H_{15,3}$, $H_{10,4}$, $H_{15,4}$, $H_{5,3}$, $H_{5,4}$, $H_{15,5}$, and $H_{10,5}$ were evaluated hierarchically each at a 2-sided 0.05 significance level conditioned on successfully achieving the preceding objective.
    b. If all objectives in only #1 or only #2 above were successfully established, then $H_{10,3}$, $H_{15,3}$, $H_{10,4}$, $H_{15,4}$, $H_{5,3}$, $H_{5,4}$, $H_{15,5}$, and $H_{10,5}$ were evaluated hierarchically each at a 2-sided 0.025 significance level conditioned on successfully achieving the preceding objective.
5. If all objectives in #3, #4, and #5 above were successfully established, and at least 1 objective from #1 or #2 above was not successfully established, 100% of the unused alpha was recycled back to #1 or #2 above.

Figure 25: Type 1 Error Control Strategy (Primary & Key Secondary Endpoints)—Trial GPGI



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Abbreviations: FSG, fasting serum glucose; HbA1c, hemoglobin A1c; LY, LY3298176 (tirzepatide); and vs, versus.

13.5. Financial Disclosure

The Applicant submitted a Form FDA 3454 for this NDA and provided a list of 2629 investigators, of which they certified the absence of financial interests and/or arrangements of 2605 investigators/sub-investigators (Table 58). A single investigator was not certified (no longer at study site). Please refer to Section 6.1.2 for further details.

Table 58: Covered Phase 2/3 Clinical Trials

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 2629		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): None		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 24 for 18 individual investigators.		
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: None reported. Significant payments of other sorts: 18 investigators for 24 Form FDA 3455 reports, involving $27,241.49 to $204,371.78. Proprietary interest in the product tested held by investigator: None reported Significant equity interest held by investigator in study: None reported Sponsor of covered study: Eli Lilly		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes[a] ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): 2629		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

[a] Note: Steps taken to minimize bias: While not specifically stated for the three investigators with disclosable financial interests, VERTIS CV was a large randomized, double-blinded trial, and the results were therefore unlikely to be driven by any single clinical site.

13.6. Discontinuations Due to Adverse Events — Phase 3 Trials (AS2)

Table 59: Discontinuations Due to Adverse Events by System Organ Class Across the Seven Phase 3 Trials

	GPGK		GPGI		GPGM		GPGH		GPGO		GPGL		GPGP
System Organ Class MedDRA PT	PBO (N=115)	TZP ALL (N=363)	PBO (N=120)	TZP ALL (N=355)	Ins Glar (N=1000)	TZP ALL (N=995)	Ins Deg (N=360)	TZP ALL (N=1077)	Dula 0.75 mg (N=159)	TZP ALL (N=477)	Sema 1 mg (N=469)	TZP ALL (N=1409)	TZP ALL (443)
Subjects Discontinuing IP due to AEs — no. (%)	**3 (2.6)**	**18 (5.0)**	**3 (2.5)**	**30 (8.5)**	**54 (5.4)**	**101 (10.2)**	**5 (1.4)**	**101 (9.4)**	**9 (5.7)**	**44 (9.2)**	**19 (4.1)**	**108 (7.7)**	**33 (7.4)**
Gastrointestinal disorders	**1 (0.9)**	**17 (4.7)**	**0 (0.0)**	**19 (5.4)**	**0 (0.0)**	**45 (4.5)**	**1 (0.3)**	**51 (4.7)**	**1 (0.6)**	**22 (4.6)**	**15 (3.2)**	**53 (3.8)**	**10 (2.3)**
Diarrhoea	0 (0.0)	4 (1.1)	0 (0.0)	3 (0.8)	0 (0.0)	11 (1.1)	0 (0.0)	8 (0.7)	1 (0.6)	2 (0.4)	1 (0.2)	10 (0.7)	0 (0.0)
Vomiting	0 (0.0)	0 (0.0)	0 (0.0)	5 (1.4)	0 (0.0)	9 (0.9)	0 (0.0)	12 (1.1)	0 (0.0)	3 (0.6)	3 (0.6)	9 (0.6)	0 (0.0)
Nausea	1 (0.9)	3 (0.8)	0 (0.0)	7 (2.0)	0 (0.0)	8 (0.8)	1 (0.3)	19 (1.8)	0 (0.0)	8 (1.7)	4 (0.9)	17 (1.2)	7 (1.6)
Dyspepsia	0 (0.0)	2 (0.6)	0 (0.0)	2 (0.6)	0 (0.0)	4 (0.4)	0 (0.0)	3 (0.3)	0 (0.0)	2 (0.4)	0 (0.0)	5 (0.4)	0 (0.0)
Abdominal pain	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	4 (0.9)	5 (0.4)	0 (0.0)
Constipation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)	0 (0.0)	1 (<0.1)	0 (0.0)	1 (0.2)	1 (0.2)	2 (0.1)	0 (0.0)
Flatulence	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)	0 (0.0)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pancreatitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Abdominal distension	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.5)
Eructation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Obstructive pancreatitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pancreatitis acute	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
Abdominal discomfort	0 (0.0)	2 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)	0 (0.0)	2 (0.4)	0 (0.0)	1 (<0.1)	0 (0.0)
Abdominal pain upper	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)
Colitis ischaemic	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Colitis ulcerative	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Epigastric discomfort	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Gastric disorder	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)

	GPGK		GPGI		GPGM		GPGH		GPGO		GPGL		GPGP
System Organ Class MedDRA PT	PBO (N=115)	TZP ALL (N=363)	PBO (N=120)	TZP ALL (N=355)	Ins Glar (N=1000)	TZP ALL (N=995)	Ins Deg (N=360)	TZP ALL (N=1077)	Dula 0.75 mg (N=159)	TZP ALL (N=477)	Sema 1 mg (N=469)	TZP ALL (N=1409)	TZP ALL (443)
Gastric ulcer haemorrhage	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Gastrointestinal disorder	0 (0.0)	5 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Gastrooesophageal reflux disease	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Pancreatitis chronic	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Cardiac disorders	**1 (0.9)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**12 (1.2)**	**11 (1.1)**	**0 (0.0)**	**1 (<0.1)**	**0 (0.0)**	**1 (0.2)**	**0 (0.0)**	**5 (0.4)**	**0 (0.0)**
Acute myocardial infarction	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.3)	5 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	2 (0.1)	0 (0.0)
Cardiac failure	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cardiac arrest	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cardio-respiratory arrest	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)
Coronary artery disease	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Ischaemic cardiomyopathy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Angina unstable	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cardiac disorder	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cardiac failure congestive	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cardiogenic shock	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Myocardial infarction	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Tachycardia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Infections and infestations	**0 (0.0)**	**0 (0.0)**	**1 (0.8)**	**2 (0.6)**	**13 (1.3)**	**10 (1.0)**	**1 (0.3)**	**5 (0.5)**	**2 (1.3)**	**0 (0.0)**	**1 (0.2)**	**7 (0.5)**	**1 (0.2)**
COVID-19	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	6 (0.6)	3 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
COVID-19 pneumonia	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)	4 (0.4)	3 (0.3)	0 (0.0)	1 (<0.1)	1 (0.6)	0 (0.0)	1 (0.2)	2 (0.1)	0 (0.0)
Cellulitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pneumonia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Septic shock	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Urosepsis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Atypical pneumonia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

	GPGK		GPGI		GPGM		GPGH		GPGO		GPGL		GPGP
System Organ Class MedDRA PT	PBO (N=115)	TZP ALL (N=363)	PBO (N=120)	TZP ALL (N=355)	Ins Glar (N=1000)	TZP ALL (N=995)	Ins Deg (N=360)	TZP ALL (N=1077)	Dula 0.75 mg (N=159)	TZP ALL (N=477)	Sema 1 mg (N=469)	TZP ALL (N=1409)	TZP ALL (443)
Diabetic foot infection	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Diabetic gangrene	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Diverticulitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Gastroenteritis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Gastrointestinal infection	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hepatitis E	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Herpes zoster	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Intervertebral discitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Nosocomial infection	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pyelonephritis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Sepsis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Urinary tract infection	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Investigations	**0 (0.0)**	**1 (0.3)**	**1 (0.8)**	**1 (0.3)**	**1 (0.1)**	**10 (1.0)**	**0 (0.0)**	**16 (1.5)**	**1 (0.6)**	**1 (0.2)**	**1 (0.2)**	**8 (0.6)**	**3 (0.7)**
Weight decreased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.3)	0 (0.0)	6 (0.6)	0 (0.0)	1 (0.2)	0 (0.0)	1 (<0.1)	2 (0.5)
Amylase increased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Blood calcitonin increased	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	3 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.2)	0 (0.0)
Bone density decreased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hepatitis C antibody positive	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Lipase increased	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.1)	0 (0.0)	4 (0.4)	1 (0.6)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
Pancreatic enzymes increased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)
Blood glucose fluctuation	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Blood pressure increased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Digestive enzyme increased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Hepatic enzyme increased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Liver function test increased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)

	GPGK		GPGI		GPGM		GPGH		GPGO		GPGL		GPGP
System Organ Class MedDRA PT	PBO (N=115)	TZP ALL (N=363)	PBO (N=120)	TZP ALL (N=355)	Ins Glar (N=1000)	TZP ALL (N=995)	Ins Deg (N=360)	TZP ALL (N=1077)	Dula 0.75 mg (N=159)	TZP ALL (N=477)	Sema 1 mg (N=469)	TZP ALL (N=1409)	TZP ALL (443)
Weight increased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Metabolism and nutrition disorders	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**3 (0.8)**	**0 (0.0)**	**8 (0.8)**	**1 (0.3)**	**8 (0.7)**	**0 (0.0)**	**9 (1.9)**	**0 (0.0)**	**6 (0.4)**	**7 (1.6)**
Decreased appetite	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.8)	0 (0.0)	5 (0.5)	0 (0.0)	6 (0.6)	0 (0.0)	9 (1.9)	0 (0.0)	5 (0.4)	7 (1.6)
Food aversion	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Gout	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Latent autoimmune diabetes in adults	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Abnormal loss of weight	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hyperglycaemia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hyperlipasaemia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**0 (0.0)**	**0 (0.0)**	**1 (0.8)**	**2 (0.6)**	**11 (1.1)**	**6 (0.6)**	**0 (0.0)**	**6 (0.6)**	**2 (1.3)**	**4 (0.8)**	**0 (0.0)**	**5 (0.4)**	**3 (0.7)**
Breast cancer stage II	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Colon cancer metastatic	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Invasive lobular breast carcinoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Metastatic squamous cell carcinoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Penile squamous cell carcinoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Renal cell carcinoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (<0.1)	0 (0.0)
Adenocarcinoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Adenocarcinoma of colon	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Bladder papilloma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Bladder transitional cell carcinoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cerebellopontine angle tumour	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Colon cancer	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Endometrial adenocarcinoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Invasive ductal breast carcinoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Laryngeal squamous cell carcinoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

	GPGK		GPGI		GPGM		GPGH		GPGO		GPGL		GPGP
System Organ Class MedDRA PT	PBO (N=115)	TZP ALL (N=363)	PBO (N=120)	TZP ALL (N=355)	Ins Glar (N=1000)	TZP ALL (N=995)	Ins Deg (N=360)	TZP ALL (N=1077)	Dula 0.75 mg (N=159)	TZP ALL (N=477)	Sema 1 mg (N=469)	TZP ALL (N=1409)	TZP ALL (443)
Lung adenocarcinoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Lung adenocarcinoma stage IV	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Lung carcinoma cell type unspecified stage III	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Lung neoplasm malignant	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Lymphoproliferative disorder	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Nasopharyngeal cancer	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Non-Hodgkin's lymphoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Papillary renal cell carcinoma	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Prostate cancer	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Renal neoplasm	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Squamous cell carcinoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Squamous cell carcinoma of lung	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Testicular neoplasm	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Transitional cell carcinoma	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
General disorders and administration site conditions	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**2 (0.6)**	**4 (0.4)**	**4 (0.4)**	**1 (0.3)**	**6 (0.6)**	**1 (0.6)**	**2 (0.4)**	**1 (0.2)**	**15 (1.1)**	**5 (1.1)**
Death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Early satiety	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)
Pain	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Sudden cardiac death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Application site reaction	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Asthenia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)
Chills	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Fatigue	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	3 (0.2)	2 (0.5)
General physical health deterioration	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)

	GPGK		GPGI		GPGM		GPGH		GPGO		GPGL		GPGP
System Organ Class MedDRA PT	PBO (N=115)	TZP ALL (N=363)	PBO (N=120)	TZP ALL (N=355)	Ins Glar (N=1000)	TZP ALL (N=995)	Ins Deg (N=360)	TZP ALL (N=1077)	Dula 0.75 mg (N=159)	TZP ALL (N=477)	Sema 1 mg (N=469)	TZP ALL (N=1409)	TZP ALL (443)
Influenza like illness	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Injection site erythema	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Injection site hypersensitivity	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Injection site reaction	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	3 (0.2)	0 (0.0)
Malaise	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	3 (0.7)
Sudden death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Nervous system disorders	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**2 (0.2)**	**2 (0.2)**	**0 (0.0)**	**2 (0.2)**	**1 (0.6)**	**2 (0.4)**	**1 (0.2)**	**3 (0.2)**	**1 (0.2)**
Amnesia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Haemorrhagic stroke	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cerebrovascular accident	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Coma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Dizziness	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	1 (0.2)	1 (<0.1)	0 (0.0)
Facial paralysis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Headache	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Lethargy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Multiple system atrophy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Paraesthesia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Taste disorder	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Hepatobiliary disorders	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**1 (0.1)**	**0 (0.0)**	**1 (<0.1)**	**0 (0.0)**	**1 (0.2)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**
Hepatic cirrhosis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cholangitis acute	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Cholestasis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Injury, poisoning and procedural complications	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**1 (0.1)**	**1 (0.1)**	**0 (0.0)**	**2 (0.2)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**1 (<0.1)**	**0 (0.0)**
Thoracic vertebral fracture	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Fall	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)

	GPGK		GPGI		GPGM		GPGH		GPGO		GPGL		GPGP
System Organ Class MedDRA PT	PBO (N=115)	TZP ALL (N=363)	PBO (N=120)	TZP ALL (N=355)	Ins Glar (N=1000)	TZP ALL (N=995)	Ins Deg (N=360)	TZP ALL (N=1077)	Dula 0.75 mg (N=159)	TZP ALL (N=477)	Sema 1 mg (N=469)	TZP ALL (N=1409)	TZP ALL (443)
Procedural headache	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Road traffic accident	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Spinal column injury	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Musculoskeletal and connective tissue disorders	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**1 (0.3)**	**1 (0.1)**	**1 (0.1)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**
Intervertebral disc protrusion	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Arthropathy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Sarcopenia	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Renal and urinary disorders	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**1 (0.1)**	**1 (0.1)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**2 (0.1)**	**1 (0.2)**
Nephropathy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Chronic kidney disease	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
End stage renal disease	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Renal impairment	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Respiratory, thoracic and mediastinal disorders	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**7 (0.7)**	**1 (0.1)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**
Pulmonary embolism	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Acute pulmonary oedema	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Acute respiratory failure	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Respiratory failure	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Blood and lymphatic system disorders	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**1 (0.1)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	0 (0.0)
Anaemia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Ear and labyrinth disorders	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**1 (<0.1)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**
Vertigo	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Endocrine disorders	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**1 (<0.1)**	**0 (0.0)**
Acromegaly	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Eye disorders	**1 (0.9)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**

	GPGK		GPGI		GPGM		GPGH		GPGO		GPGL		GPGP
System Organ Class MedDRA PT	PBO (N=115)	TZP ALL (N=363)	PBO (N=120)	TZP ALL (N=355)	Ins Glar (N=1000)	TZP ALL (N=995)	Ins Deg (N=360)	TZP ALL (N=1077)	Dula 0.75 mg (N=159)	TZP ALL (N=477)	Sema 1 mg (N=469)	TZP ALL (N=1409)	TZP ALL (443)
Vision blurred	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Immune system disorders	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**1 (<0.1)**	**0 (0.0)**
Hypersensitivity	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Skin and subcutaneous tissue disorders	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**1 (0.3)**	**1 (<0.1)**	**1 (0.6)**	**2 (0.4)**	**0 (0.0)**	**1 (<0.1)**	**2 (0.5)**
Chronic pigmented purpura	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Dermatomyositis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Eczema	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Rash	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Urticaria	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Surgical and medical procedures	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**1 (<0.1)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**
Gastric bypass	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Source: Derived from the adsl.xpt and adae.xpt datasets, available at: \\CDSESUB1\evsprod\NDA215866\0001\m5\datasets
Abbreviation: AS2, Analysis Set 2 (pool of 7 phase 3 trials); MedDRA, Medical Dictionary for Regulatory Activities; no., number; PBO, placebo; PT, preferred term; SOC, system organ class; TEAE, treatment-emergent adverse event; and TZP, tirzepatide.

13.7. Serious Adverse Events by System Organ Class — Phase 3 Trials

Table 60: Serious Adverse Events Across the Seven Phase 3 Trials (AS2)

SAEs by SOC MedDRA PT	PBO (N=235)	Ins Glar (N=1000)	Ins Deg (N=360)	Dula 0.75mg (N=159)	Sema 1 mg (N=469)	TZP 5mg (N=1701)	TZP 10mg (N=1702)	TZP 15mg (N=1716)
Subjects with ≥1 SAE— no. (%)	**13 (5.5)**	**193 (19.3)**	**22 (6.1)**	**14 (8.8)**	**13 (2.8)**	**134 (7.9)**	**135 (7.9)**	**122 (7.1)**
Infections and infestations	**1 (0.4)**	**52 (5.2)**	**8 (2.2)**	**4 (2.5)**	**6 (1.3)**	**30 (1.8)**	**32 (1.9)**	**31 (1.8)**
COVID-19 pneumonia	1 (0.4)	15 (1.5)	0 (0.0)	2 (1.3)	4 (0.9)	5 (0.3)	9 (0.5)	6 (0.3)
Pneumonia	0 (0.0)	10 (1.0)	2 (0.6)	0 (0.0)	1 (0.2)	2 (0.1)	2 (0.1)	5 (0.3)
Urosepsis	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	1 (<0.1)	3 (0.2)
COVID-19	0 (0.0)	10 (1.0)	0 (0.0)	0 (0.0)	1 (0.2)	3 (0.2)	3 (0.2)	2 (0.1)
Gastroenteritis	0 (0.0)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.2)	2 (0.1)	2 (0.1)
Sepsis	0 (0.0)	4 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	2 (0.1)
Urinary tract infection	0 (0.0)	3 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	2 (0.1)
Asymptomatic COVID-19	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Coronavirus infection	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	1 (<0.1)
Dengue fever	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Device related infection	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Diabetic gangrene	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Diverticulitis	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	1 (<0.1)	1 (<0.1)	1 (<0.1)
Infectious pleural effusion	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Lower respiratory tract infection	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Pyelonephritis	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	1 (<0.1)
Pyelonephritis acute	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Septic shock	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	1 (<0.1)
Suspected COVID-19	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Appendicitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	2 (0.1)	0 (0.0)
Atypical pneumonia	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Bacteraemia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (<0.1)	0 (0.0)
Bronchitis	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cellulitis	0 (0.0)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	2 (0.1)	0 (0.0)
Cellulitis orbital	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cholecystitis infective	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Clostridium difficile infection	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Colon gangrene	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Complicated appendicitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)
Diabetic foot infection	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Endocarditis	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Epididymitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)

SAEs by SOC MedDRA PT	PBO (N=235)	Ins Glar (N=1000)	Ins Deg (N=360)	Dula 0.75mg (N=159)	Sema 1 mg (N=469)	TZP 5mg (N=1701)	TZP 10mg (N=1702)	TZP 15mg (N=1716)
Erysipelas	0 (0.0)	3 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Escherichia bacteraemia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)
Fournier's gangrene	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
HIV infection	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hepatitis E	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)
Infected skin ulcer	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Infection	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Intervertebral discitis	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Liver abscess	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Nosocomial infection	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Osteomyelitis	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	1 (<0.1)	1 (<0.1)	0 (0.0)
Periodontitis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pharyngeal abscess	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Pneumonia bacterial	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pneumonia klebsiella	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pneumonia legionella	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)
Postoperative wound infection	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)
Pyelitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)
Respiratory tract infection	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Sinusitis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Systemic candida	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Wound infection	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Cardiac disorders	**4 (1.7)**	**64 (6.4)**	**5 (1.4)**	**2 (1.3)**	**1 (0.2)**	**37 (2.2)**	**27 (1.6)**	**23 (1.3)**
Acute myocardial infarction	1 (0.4)	18 (1.8)	2 (0.6)	0 (0.0)	0 (0.0)	7 (0.4)	9 (0.5)	6 (0.3)
Coronary artery disease	0 (0.0)	15 (1.5)	1 (0.3)	0 (0.0)	0 (0.0)	7 (0.4)	5 (0.3)	4 (0.2)
Myocardial infarction	1 (0.4)	4 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	5 (0.3)	1 (<0.1)	3 (0.2)
Cardiac failure	1 (0.4)	2 (0.2)	1 (0.3)	1 (0.6)	0 (0.0)	6 (0.4)	2 (0.1)	2 (0.1)
Angina pectoris	0 (0.0)	3 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	2 (0.1)
Cardio-respiratory arrest	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	1 (<0.1)	2 (0.1)
Acute coronary syndrome	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Angina unstable	0 (0.0)	6 (0.6)	0 (0.0)	1 (0.6)	0 (0.0)	1 (<0.1)	4 (0.2)	1 (<0.1)
Atrial fibrillation	0 (0.0)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	5 (0.3)	2 (0.1)	1 (<0.1)
Atrial flutter	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	1 (<0.1)
Cardiac failure acute	0 (0.0)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Myocardial ischaemia	0 (0.0)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Myocarditis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Ventricular tachycardia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (<0.1)
Tachycardia	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

SAEs by SOC MedDRA PT	PBO (N=235)	Ins Glar (N=1000)	Ins Deg (N=360)	Dula 0.75mg (N=159)	Sema 1 mg (N=469)	TZP 5mg (N=1701)	TZP 10mg (N=1702)	TZP 15mg (N=1716)
Acute left ventricular failure	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Aortic valve sclerosis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Arteriosclerosis coronary artery	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)
Atrial tachycardia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	1 (<0.1)	0 (0.0)
Atrioventricular block	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Atrioventricular block complete	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Atrioventricular block second degree	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)
Cardiac arrest	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)	0 (0.0)
Cardiac disorder	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cardiac failure chronic	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Cardiac failure congestive	0 (0.0)	5 (0.5)	1 (0.3)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)
Cardiogenic shock	0 (0.0)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cardiomyopathy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)
Coronary artery stenosis	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)
Ischaemic cardiomyopathy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)
Left ventricular failure	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)
Supraventricular extrasystoles	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Supraventricular tachycardia	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	1 (<0.1)	0 (0.0)
Ventricular dysfunction	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)
Ventricular extrasystoles	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**2 (0.9)**	**17 (1.7)**	**1 (0.3)**	**3 (1.9)**	**1 (0.2)**	**15 (0.9)**	**18 (1.1)**	**14 (0.8)**
Adenocarcinoma of colon	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	1 (<0.1)
Basal cell carcinoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Bladder cancer	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Colon cancer	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Colon cancer metastatic	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Glioblastoma multiforme	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Neoplasm malignant	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Neoplasm skin	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Neuroendocrine carcinoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Ovarian cancer	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Pituitary tumour benign	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Prostate cancer	0 (0.0)	3 (0.3)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	2 (0.1)	1 (<0.1)
Renal neoplasm	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	1 (<0.1)
Squamous cell carcinoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Uterine leiomyoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)

SAEs by SOC MedDRA PT	PBO (N=235)	Ins Glar (N=1000)	Ins Deg (N=360)	Dula 0.75mg (N=159)	Sema 1 mg (N=469)	TZP 5mg (N=1701)	TZP 10mg (N=1702)	TZP 15mg (N=1716)
Cholangiocarcinoma	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Transitional cell carcinoma	1 (0.4)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Adenocarcinoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)	0 (0.0)
Bile duct adenocarcinoma	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Bladder papilloma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Bladder transitional cell carcinoma	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Breast cancer stage II	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Cerebellopontine angle tumour	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Cholesteatoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Colon adenoma	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Endometrial adenocarcinoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)
Gastric neoplasm	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)
Glioblastoma	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Invasive breast carcinoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Invasive ductal breast carcinoma	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)
Invasive lobular breast carcinoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Laryngeal squamous cell carcinoma	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Lung adenocarcinoma	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Lung adenocarcinoma stage IV	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Lung carcinoma cell type unspecified stage III	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)
Lung neoplasm malignant	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Meningioma	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Metastases to liver	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)
Metastases to lymph nodes	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Metastatic squamous cell carcinoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)
Nasopharyngeal cancer	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Non-Hodgkin's lymphoma	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Pancreatic carcinoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)
Pancreatic neoplasm	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Papillary renal cell carcinoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)	0 (0.0)
Renal cancer recurrent	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)
Renal cell carcinoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	1 (<0.1)	0 (0.0)
Squamous cell carcinoma of lung	0 (0.0)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Squamous cell carcinoma of skin	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)

SAEs by SOC MedDRA PT	PBO (N=235)	Ins Glar (N=1000)	Ins Deg (N=360)	Dula 0.75mg (N=159)	Sema 1 mg (N=469)	TZP 5mg (N=1701)	TZP 10mg (N=1702)	TZP 15mg (N=1716)
Testicular neoplasm	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)
Uterine cancer	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Uterine neoplasm	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)
Nervous system disorders	**1 (0.4)**	**26 (2.6)**	**3 (0.8)**	**0 (0.0)**	**1 (0.2)**	**13 (0.8)**	**10 (0.6)**	**13 (0.8)**
Cerebrovascular accident	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	3 (0.2)
Syncope	1 (0.4)	2 (0.2)	1 (0.3)	0 (0.0)	0 (0.0)	1 (<0.1)	1 (<0.1)	2 (0.1)
Facial paralysis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	1 (<0.1)
Guillain-Barre syndrome	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Hypoglycaemic unconsciousness	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	1 (<0.1)
Hypoxic-ischaemic encephalopathy	0 (0.0)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Ischaemic stroke	0 (0.0)	6 (0.6)	0 (0.0)	0 (0.0)	1 (0.2)	2 (0.1)	4 (0.2)	1 (<0.1)
Orthostatic intolerance	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Subarachnoid haemorrhage	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Transient ischaemic attack	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	3 (0.2)	1 (<0.1)
Carpal tunnel syndrome	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cerebellar infarction	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)
Cerebellar stroke	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Cognitive disorder	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)
Coma	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cranial nerve disorder	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)
Diabetic neuropathy	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)
Dizziness	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Encephalopathy	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Haemorrhagic stroke	0 (0.0)	2 (0.2)	1 (0.3)	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)	0 (0.0)
Headache	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)	0 (0.0)
Hemiplegia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)
Lacunar infarction	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Lacunar stroke	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Lumbar radiculopathy	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Metabolic encephalopathy	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Myelopathy	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Neuropathy peripheral	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)
Presyncope	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Spinal cord compression	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Thalamic infarction	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Vertebrobasilar insufficiency	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)
Injury, poisoning and procedural complications	**1 (0.4)**	**9 (0.9)**	**2 (0.6)**	**2 (1.3)**	**1 (0.2)**	**9 (0.5)**	**13 (0.8)**	**11 (0.6)**

SAEs by SOC MedDRA PT	PBO (N=235)	Ins Glar (N=1000)	Ins Deg (N=360)	Dula 0.75mg (N=159)	Sema 1 mg (N=469)	TZP 5mg (N=1701)	TZP 10mg (N=1702)	TZP 15mg (N=1716)
Hip fracture	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	3 (0.2)
Acetabulum fracture	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Femur fracture	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	1 (<0.1)
Foot fracture	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Head injury	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Lumbar vertebral fracture	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Multiple injuries	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Nerve injury	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Spinal compression fracture	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	1 (<0.1)
Thoracic vertebral fracture	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	1 (<0.1)
Traumatic amputation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Vascular injury	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Intestinal anastomosis complication	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Accident	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)
Ankle fracture	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.2)	0 (0.0)
Clavicle fracture	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	1 (<0.1)	0 (0.0)
Concussion	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)
Craniocerebral injury	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)
Fall	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Femoral neck fracture	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)
Hand fracture	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Humerus fracture	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Injury	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Intentional overdose	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)
Joint dislocation	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Ligament injury	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Limb injury	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Limb traumatic amputation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)
Maternal exposure during pregnancy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Meniscus injury	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pulmonary contusion	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)
Radius fracture	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Rib fracture	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)
Spinal column injury	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Subdural haematoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)
Tendon injury	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Tendon rupture	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

SAEs by SOC MedDRA PT	PBO (N=235)	Ins Glar (N=1000)	Ins Deg (N=360)	Dula 0.75mg (N=159)	Sema 1 mg (N=469)	TZP 5mg (N=1701)	TZP 10mg (N=1702)	TZP 15mg (N=1716)
Upper limb fracture	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	1 (<0.1)	0 (0.0)
Wrist fracture	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	**1 (0.4)**	**22 (2.2)**	**1 (0.3)**	**0 (0.0)**	**1 (0.2)**	**9 (0.5)**	**4 (0.2)**	**9 (0.5)**
Asthma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	2 (0.1)
Chronic obstructive pulmonary disease	0 (0.0)	3 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	2 (0.1)
Dyspnoea	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	2 (0.1)
Pulmonary embolism	1 (0.4)	3 (0.3)	1 (0.3)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	1 (<0.1)
Hypoxia	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Pleural effusion	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	1 (<0.1)
Pneumothorax	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	1 (<0.1)
Respiratory failure	0 (0.0)	4 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.2)	0 (0.0)	1 (<0.1)
Acute pulmonary oedema	0 (0.0)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	1 (<0.1)	0 (0.0)
Acute respiratory distress syndrome	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Acute respiratory failure	0 (0.0)	3 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)
Asthmatic crisis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)
Epistaxis	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Interstitial lung disease	0 (0.0)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pulmonary fibrosis	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pulmonary mass	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Sleep apnoea syndrome	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)
General disorders and administration site conditions	**0 (0.0)**	**6 (0.6)**	**1 (0.3)**	**0 (0.0)**	**0 (0.0)**	**8 (0.5)**	**3 (0.2)**	**8 (0.5)**
Asthenia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	2 (0.1)
Pyrexia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)
Chest pain	0 (0.0)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	1 (<0.1)	1 (<0.1)
Death	0 (0.0)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)	1 (<0.1)
Impaired healing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Necrosis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	1 (<0.1)
Sudden cardiac death	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Multiple organ dysfunction syndrome	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Non-cardiac chest pain	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.2)	0 (0.0)	0 (0.0)
Sudden death	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Systemic inflammatory response syndrome	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)
Hepatobiliary disorders	**0 (0.0)**	**6 (0.6)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**3 (0.2)**	**8 (0.5)**	**7 (0.4)**
Cholecystitis acute	0 (0.0)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	3 (0.2)	2 (0.1)
Cholecystitis	0 (0.0)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	1 (<0.1)

SAEs by SOC MedDRA PT	PBO (N=235)	Ins Glar (N=1000)	Ins Deg (N=360)	Dula 0.75mg (N=159)	Sema 1 mg (N=469)	TZP 5mg (N=1701)	TZP 10mg (N=1702)	TZP 15mg (N=1716)
Cholelithiasis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	2 (0.1)	1 (<0.1)
Hepatic cirrhosis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Hepatitis acute	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Hepatotoxicity	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Biliary dilatation	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cholangitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Cholangitis acute	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Hepatic function abnormal	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Malignant biliary obstruction	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Metabolism and nutrition disorders	**0 (0.0)**	**17 (1.7)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**6 (0.4)**	**1 (<0.1)**	**7 (0.4)**
Hypoglycaemia	0 (0.0)	12 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	1 (<0.1)	5 (0.3)
Dehydration	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)	1 (<0.1)
Hyponatraemia	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Diabetes mellitus inadequate control	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hyperkalaemia	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)
Hypokalaemia	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Iron deficiency	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)
Renal and urinary disorders	**1 (0.4)**	**12 (1.2)**	**2 (0.6)**	**0 (0.0)**	**0 (0.0)**	**8 (0.5)**	**7 (0.4)**	**7 (0.4)**
Acute kidney injury	0 (0.0)	3 (0.3)	1 (0.3)	0 (0.0)	0 (0.0)	2 (0.1)	1 (<0.1)	1 (<0.1)
Calculus urinary	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Haematuria	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Nephrolithiasis	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.2)	3 (0.2)	1 (<0.1)
Renal cyst	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	1 (<0.1)
Ureterolithiasis	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	1 (<0.1)	1 (<0.1)
Urinary tract obstruction	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Bladder disorder	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Bladder mass	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)
Chronic kidney disease	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
End stage renal disease	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Hydronephrosis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)
Renal colic	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Renal failure	0 (0.0)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Renal impairment	0 (0.0)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Renal infarct	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Renal mass	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Urinary bladder polyp	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Gastrointestinal disorders	**2 (0.9)**	**6 (0.6)**	**0 (0.0)**	**1 (0.6)**	**0 (0.0)**	**17 (1.0)**	**16 (0.9)**	**6 (0.3)**

SAEs by SOC MedDRA PT	PBO (N=235)	Ins Glar (N=1000)	Ins Deg (N=360)	Dula 0.75mg (N=159)	Sema 1 mg (N=469)	TZP 5mg (N=1701)	TZP 10mg (N=1702)	TZP 15mg (N=1716)
Abdominal pain upper	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	1 (<0.1)
Colitis ulcerative	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Gastric ulcer haemorrhage	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	1 (<0.1)
Large intestine polyp	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Lower gastrointestinal haemorrhage	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	1 (<0.1)
Strangulated umbilical hernia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Abdominal hernia	1 (0.4)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pancreatic disorder	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Abdominal pain	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Abdominal wall haematoma	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Colitis ischaemic	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)
Constipation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	1 (<0.1)	0 (0.0)
Diarrhoea	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Diverticulum intestinal haemorrhagic	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)
Duodenal ulcer	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Dyspepsia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)
Dysphagia	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Epiploic appendagitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Faecaloma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)
Gastric polyps	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Gastric ulcer	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)
Gastritis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Gastritis alcoholic	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)
Gastrointestinal haemorrhage	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	1 (<0.1)	0 (0.0)
Inguinal hernia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.2)	0 (0.0)	0 (0.0)
Inguinal hernia, obstructive	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)
Irritable bowel syndrome	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Nausea	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Obstructive pancreatitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)
Pancreatitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	1 (<0.1)	0 (0.0)
Pancreatitis acute	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)
Peptic ulcer	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Rectal polyp	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)
Segmental diverticular colitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Vomiting	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Vascular disorders	**1 (0.4)**	**10 (1.0)**	**0 (0.0)**	**0 (0.0)**	**2 (0.4)**	**4 (0.2)**	**6 (0.4)**	**6 (0.3)**
Peripheral arterial occlusive disease	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	3 (0.2)	2 (0.1)

SAEs by SOC MedDRA PT	PBO (N=235)	Ins Glar (N=1000)	Ins Deg (N=360)	Dula 0.75mg (N=159)	Sema 1 mg (N=469)	TZP 5mg (N=1701)	TZP 10mg (N=1702)	TZP 15mg (N=1716)
Deep vein thrombosis	0 (0.0)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)	1 (<0.1)
Dry gangrene	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Orthostatic hypotension	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Peripheral ischaemia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Aortic stenosis	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Aortic aneurysm	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Aortic aneurysm rupture	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Arteriosclerosis	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hypertension	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (<0.1)	0 (0.0)
Hypotension	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Iliac artery stenosis	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Peripheral artery occlusion	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	1 (<0.1)	0 (0.0)
Peripheral vascular disorder	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Thrombophlebitis superficial	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Venous thrombosis limb	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Musculoskeletal and connective tissue disorders	**0 (0.0)**	**5 (0.5)**	**1 (0.3)**	**1 (0.6)**	**1 (0.2)**	**5 (0.3)**	**3 (0.2)**	**4 (0.2)**
Intervertebral disc protrusion	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Joint contracture	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Lumbar spinal stenosis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	1 (<0.1)
Musculoskeletal chest pain	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Arthralgia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)
Arthropathy	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Back pain	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Intervertebral disc disorder	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Jaw cyst	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Osteoarthritis	0 (0.0)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)
Pain in extremity	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Rotator cuff syndrome	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Spinal ligament ossification	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)
Spinal osteoarthritis	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Spinal stenosis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Synovial cyst	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Systemic lupus erythematosus	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)
Psychiatric disorders	**0 (0.0)**	**1 (0.1)**	**2 (0.6)**	**0 (0.0)**	**1 (0.2)**	**0 (0.0)**	**2 (0.1)**	**3 (0.2)**
Depression suicidal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Major depression	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Suicide attempt	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Alcohol abuse	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

SAEs by SOC MedDRA PT	PBO (N=235)	Ins Glar (N=1000)	Ins Deg (N=360)	Dula 0.75mg (N=159)	Sema 1 mg (N=469)	TZP 5mg (N=1701)	TZP 10mg (N=1702)	TZP 15mg (N=1716)
Anxiety	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Confusional state	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Disorientation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Post-traumatic stress disorder	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Ear and labyrinth disorders	**0 (0.0)**	**0 (0.0)**	**1 (0.3)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**1 (<0.1)**	**2 (0.1)**
Deafness unilateral	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Vertigo positional	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Vertigo	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Surgical and medical procedures	**1 (0.4)**	**1 (0.1)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**1 (<0.1)**	**4 (0.2)**	**2 (0.1)**
Coronary artery bypass	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)
Pancreatic lesion excision	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Abdominal hernia repair	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)
Cardiac ablation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Intervertebral disc operation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Intra-cerebral aneurysm operation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Percutaneous coronary intervention	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Spinal fusion surgery	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Endocrine disorders	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**1 (<0.1)**	**0 (0.0)**	**1 (<0.1)**
Inappropriate antidiuretic hormone secretion	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Acromegaly	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)
Eye disorders	**0 (0.0)**	**1 (0.1)**	**1 (0.3)**	**1 (0.6)**	**0 (0.0)**	**2 (0.1)**	**4 (0.2)**	**1 (<0.1)**
Cataract	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.6)	0 (0.0)	0 (0.0)	2 (0.1)	1 (<0.1)
Macular fibrosis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Eyelid ptosis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Retinal detachment	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Retinal vein occlusion	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)	0 (0.0)
Vitreous haemorrhage	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Investigations	**0 (0.0)**	**3 (0.3)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**2 (0.1)**	**2 (0.1)**	**1 (<0.1)**
SARS-CoV-2 test positive	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	1 (<0.1)
Amylase increased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Blood creatinine increased	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Blood lactic acid increased	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Coronavirus test positive	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)
Influenza A virus test positive	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Lipase increased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Pancreatic enzymes increased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)

SAEs by SOC MedDRA PT	PBO (N=235)	Ins Glar (N=1000)	Ins Deg (N=360)	Dula 0.75mg (N=159)	Sema 1 mg (N=469)	TZP 5mg (N=1701)	TZP 10mg (N=1702)	TZP 15mg (N=1716)
Reproductive system and breast disorders	**0 (0.0)**	**1 (0.1)**	**0 (0.0)**	**0 (0.0)**	**1 (0.2)**	**1 (<0.1)**	**0 (0.0)**	**1 (<0.1)**
Cervical dysplasia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Metrorrhagia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)
Ovarian cyst	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Uterine prolapse	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Blood and lymphatic system disorders	**0 (0.0)**	**5 (0.5)**	**1 (0.3)**	**0 (0.0)**	**0 (0.0)**	**1 (<0.1)**	**1 (<0.1)**	**0 (0.0)**
Anaemia	0 (0.0)	3 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	1 (<0.1)	0 (0.0)
Bicytopenia	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hypochromic anaemia	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Neutropenia	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Thrombocytopenia	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Congenital, familial and genetic disorders	**0 (0.0)**	**0 (0.0)**	**1 (0.3)**	**0 (0.0)**	**0 (0.0)**	**1 (<0.1)**	**0 (0.0)**	**0 (0.0)**
Arrhythmogenic right ventricular dysplasia	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Phimosis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)
Pregnancy, puerperium and perinatal conditions	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Abortion spontaneous	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Skin and subcutaneous tissue disorders	**0 (0.0)**	**4 (0.4)**	**1 (0.3)**	**1 (0.6)**	**0 (0.0)**	**3 (0.2)**	**1 (<0.1)**	**0 (0.0)**
Dermatomyositis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Diabetic foot	0 (0.0)	3 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	1 (<0.1)	0 (0.0)
Diabetic ulcer	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)
Skin necrosis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)
Skin ulcer	0 (0.0)	1 (0.1)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Source: Derived from the adsl.xpt and adae.xpt datasets, available at: \\CDSESUB1\evsprod\NDA215866\0001\m5\datasets
Abbreviation: AS2, Analysis Set 2 (pool of 7 phase 3 trials); Dula, dulaglutide; Ins Deg, insulin degludec; Ins Glar, insulin glargine; MedDRA, Medical Dictionary for Regulatory Activities; no., number; PBO, placebo; PT, preferred term; Sema, semaglutide; SOC, system organ class; TEAE, treatment-emergent adverse event; and TZP, tirzepatide

13.8. Adverse Events of Special Interest — Search Strategy (v23.1)

AMPUTATIONS

- Search case narratives from the Lilly Safety System (LSS) for lower limb and atraumatic amputations
- Medical Dictionary for Regulatory Activities (MedDRA) preferred term (PT): Amputation

ARRHYTHMIAS AND CARDIAC CONDUCTION DISORDERS

- Arrhythmia-related investigations, signs, and symptoms SMQ (broad and narrow terms [20000051])
- Supraventricular tachyarrhythmia SMQ (broad and narrow terms [20000057])
- Tachyarrhythmia terms, nonspecific SMQ (narrow terms [20000164])
- Ventricular tachyarrhythmia SMQ (narrow terms [20000058])
- Conduction defects SMQ (narrow terms [20000056])
- HLT of cardiac conduction disorders (10000032)

DEHYDRATION

- Dehydration SMQ (narrow terms [20000232]).

DIABETIC COMPLICATIONS

- Retinopathy PTs
- Neuropathy PTs (neuropathy peripheral, mononeuropathy, autonomic neuropathy, orthostatic hypotension, diabetic neuropathy, diabetic mononeuropathy)
- Nephropathy
    - Narrow terms in acute renal failure SMQ (20000003)
    - Narrow terms in chronic kidney disease SMQ (20000213)
    - Nephropathy PTs (diabetic nephropathy, nephropathy)

DIABETIC RETINOPATHY COMPLICATIONS

CUSTOM MEDDRA QUERY (CMQ)

- Amaurosis
- Amaurosis fugax
- Arteriosclerotic retinopathy
- Blindness
- Blindness transient
- Blindness unilateral
- Choroidal neovascularization
- Cystoid macular oedema
- Detachment of macular retinal
- pigment epithelium

- Detachment of retinal pigment
- epithelium
- Diabetic blindness
- Diabetic eye disease
- Diabetic retinal oedema
- Diabetic retinopathy
- Diabetic uveitis
- Diplopia
- Exudative retinopathy
- Eye laser surgery
- Fundoscopy
- Fundoscopy abnormal
- Intraocular injection
- Macular detachment
- Macular oedema
- Maculopathy
- Noninfective chorioretinitis
- Noninfective retinitis
- Phacotrabeculectomy
- Retinal aneurysm
- Retinal arteriovenous malformation
- Retinal artery embolism
- Retinal artery occlusion
- Retinal artery stenosis
- Retinal collateral vessels
- Retinal cryoablation
- Retinal detachment
- Retinal exudates
- Retinal haemorrhage
- Retinal laser coagulation
- Retinal neovascularization
- Retinal oedema
- Retinal operation
- Retinal thickening
- Retinal vascular disorder
- Retinal vascular occlusion
- Retinal vein occlusion
- Retinitis
- Retinopathy
- Retinopathy haemorrhagic

- Retinopathy hypertensive
- Retinopathy hyperviscosity
- Retinopathy proliferative
- Scintillating scotoma
- Sudden visual loss
- Venous stasis retinopathy
- Vision blurred
- Visual impairment
- Visual acuity reduced
- Visual acuity reduced transiently
- Vitrectomy

GALLBLADDER-RELATED DISEASE

- Gallbladder-related disorders SMQ (narrow terms [20000124])
- Biliary tract disorders SMQ (narrow terms [20000125])
- Gallstone-related disorders SMQ (narrow terms [20000127])

GASTROINTESTINAL ADVERSE EVENTS

- Gastrointestinal disorders SOC

HEPATOBILIARY DISORDERS

- Liver-related investigations, signs, and symptoms SMQ (broad and narrow terms
- [20000008])
- Cholestasis and jaundice of hepatic origin SMQ (broad and narrow terms [20000009])
- Hepatitis non-infections SMQ (broad and narrow terms [20000010])
- Hepatic failure, fibrosis and cirrhosis, and other liver damage-related conditions SMQ (broad and narrow terms [20000013])
- Liver-related coagulation and bleeding disturbances SMQ (narrow terms [20000015])
- Gallbladder-related disorders SMQ (narrow terms [20000124])
- Biliary tract disorders SMQ (narrow terms [20000125])
- Gallstone-related disorders SMQ (narrow terms [20000127])

HYPERSENSITIVITY REACTIONS

- Hypersensitivity SMQ (narrow terms [20000214])
- Anaphylactic Reactions SMQ (narrow and algorithm terms [20000021])
- Angioedema SMQ (narrow terms [20000024])
- Severe Cutaneous Adverse Reactions SMQ (narrow terms [20000020])

HYPOGLYCEMIA

- Hypoglycaemia SMQ (narrow terms [20000226])
- Blood Glucose <54 mg/dL or Severe Hypoglycemia

INJECTION SITE REACTIONS

- Injection site reaction HLT
- Administration site reaction HLT
- Infusion site reaction HLT

MAJOR DEPRESSIVE DISORDER, OR SUICIDAL IDEATION OR BEHAVIOR

- Depression, excluding suicide and self-injury SMQ (narrow terms [20000167])
- Suicide/self-injury SMQ (narrow terms [20000037])

MALIGNANCY

- Malignant tumours SMQ (narrow terms [20000194])
- Tumours of unspecified malignancy SMQ (narrow terms [20000195])

METABOLIC ACIDOSIS

CMQ

- Blood ketone body
- Blood ketone body increased
- Blood ketone body present
- Diabetic ketoacidosis
- Diabetic ketoacidotic hyperglycaemic coma
- Diabetic ketosis
- Euglycaemic diabetic ketoacidosis
- Ketoacidosis
- Ketonuria
- Ketosis
- Lactic acidosis
- Urine ketone body
- Urine ketone body present

PANCREATITIS

- Acute pancreatitis SMQ (narrow terms [20000022])
- Pancreatitis chronic PT search of the AE database

PERIPHERAL REVASCULARIZATIONS

- Search case narratives from the LSS
- MedDRA PT: Peripheral revascularization

RENAL DISORDERS

- Acute renal failure SMQ (narrow terms [20000003])
- Chronic kidney disease SMQ (narrow terms [20000213])

SEVERE PERSISTENT HYPERGLYCEMIA

- Prespecified criteria

THYROID SAFETY

- Thyroid neoplasms HLT
- MedDRA PT: Thyroid C-cell hyperplasia

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/s/

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05/13/2022 08:49:41 AM

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