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RESEARCH**

APPLICATION NUMBER:

217806Orig1s000

CLINICAL REVIEW(S)

Clinical Review
Raymond Soccio, MD, PhD
NDA 217806
Zepbound (tirzepatide)

CLINICAL REVIEW

Application Type	505(b)(1) New Drug Application (NDA)
Application Number(s)	NDA 217806
Priority or Standard	Priority
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Division/Office	Division of Diabetes, Lipid Disorders, and Obesity (DDLO) Office of Cardiology, Hematology, Endocrinology and Nephrology (OCHEN)
Reviewer Name(s)	Raymond Soccio, MD, PhD
Review Completion Date	November 7, 2023
Established/Proper Name	Tirzepatide
(Proposed) Trade Name	Zepbound
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 starting dosage of ZEPBOUND is 2.5 mg injected subcutaneously once weekly. After 4 weeks, increase the dosage to 5 mg injected subcutaneously once weekly. (b) (4) increase the dosage in 2.5 mg increments after at least 4 weeks on the current dose. The maximum dosage of ZEPBOUND is 15 mg injected subcutaneously once weekly.
Applicant Proposed Indication(s)/Population(s)	As an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adults 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, dyslipidemia, (b) (4), type 2 diabetes mellitus, obstructive sleep apnea or cardiovascular disease).
Recommendation on Regulatory Action	Approval
Recommended Dosing Regimen(s)	The recommended starting dosage of ZEPBOUND is 2.5 mg injected subcutaneously once weekly. The 2.5 mg dosage is for

	treatment initiation and is not intended for chronic weight management. After 4 weeks, increase the dosage to 5 mg injected subcutaneously once weekly. The dosage may be increased in 2.5 mg increments, after at least 4 weeks on the current dose. The recommended maintenance dosages of ZEPBOUND in adults are 5 mg, 10 mg, or 15 mg injected subcutaneously once weekly. Consider treatment response and tolerability when selecting the maintenance dosage. If patients do not tolerate a maintenance dosage, consider a lower maintenance dosage. The maximum dosage of ZEPBOUND is 15 mg injected subcutaneously once weekly.
Recommended Indication(s)/Population(s)	As an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adults 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, dyslipidemia, type 2 diabetes mellitus, obstructive sleep apnea, or cardiovascular disease).

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Glossary

ABPM	ambulatory blood pressure monitoring
ADA	antidrug antibody
AE	adverse event
AKI	acute kidney injury
ALP	alkaline phosphatase
ALT	alanine transaminase
ASCVD	atherosclerotic cardiovascular disease
AST	aspartate aminotransferase
BLA	biologics license application
BMI	Body Mass Index
BPCA	Best Pharmaceuticals for Children Act
CDC	Centers for Disease Control and Prevention
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CEC	clinical events committee
CFR	Code of Federal Regulations
CKD	chronic kidney disease
CMC	chemistry, manufacturing, and controls
COC	combination oral contraceptive
CRO	contract research organization
CSR	clinical study report
CSS	Controlled Substance Staff
C-SSRS	Columbia-Suicide Severity Rating Scale
CVOT	cardiovascular outcome trial
CWM	chronic weight management
DCEP	Division of Cardiometabolic and Endocrine Pharmacology
DCOA	Division of Clinical Outcome Assessments
DMC	data monitoring committee
DMEPA	Division of Medication Error Prevention and Analysis
DILI	drug-induced liver injury
DPM	Division of Pharmacometrics
DPMH	Division of Pediatric and Maternal Health
DXA	Dual-Energy X-ray Absorptiometry
ECG	electrocardiogram
eCDF	empirical cumulative distribution function
eCRF	electronic case report form
eCTD	electronic common technical document
eGFR	estimated glomerular filtration rate
eDISH	evaluation of drug-induced serious hepatotoxicity

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FDA	Food and Drug Administration
FMQ	FDA MedDRA query
GCP	good clinical practice
GI	gastrointestinal
GIP	glucose-dependent insulinotropic polypeptide
GLP-1	glucagon-like peptide-1
HR	heart rate
ICH	International Council for Harmonization
IND	Investigational New Drug Application
iPSP	initial Pediatric Study Plan
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
IWQOL	Impact of Weight on Quality of Life
MACE	major adverse cardiovascular events
MedDRA	Medical Dictionary for Regulatory Activities
MEN2	multiple endocrine neoplasia type 2
MTC	medullary thyroid cancer
mITT	modified intent to treat
MTD	maximum tolerated dose
NAb	neutralizing antibody
NAFLD	nonalcoholic fatty liver disease
NASH	nonalcoholic steatohepatitis
NDA	new drug application
OBP	Office of Biotechnology Products
OCp	Office of Clinical Pharmacology
OGTT	oral glucose tolerance test
OPQ	Office of Pharmaceutical Quality
OSA	obstructive sleep apnea
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PCOS	polycystic ovarian syndrome
PD	pharmacodynamics
PFSS	Patient-Focused Statistical Scientists
PGIS	Patient Global Impression of Severity
PHQ-9	Patient Health Questionnaire-9
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PREA	Pediatric Research Equity Act
PRO	patient reported outcome

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Zepbound (tirzepatide)

PT	preferred term
PTSD	post-traumatic stress disorder
RBC	red blood cell
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SCE	Summary of Clinical Efficacy
SCS	Summary of Clinical Safety
SF-36v2	36-item Short Form Health Survey version 2
SFU	safety follow-up
SLE	systemic lupus erythematosus
SMQ	standardized MedDRA query
T2D	type 2 diabetes mellitus
TBL	total bilirubin
TEAE	treatment emergent adverse event
UACR	urine albumin to creatinine ratio
URRA	use-related risk analysis
WHO	World Health Organization

1.1. Product Introduction

Tirzepatide (proposed proprietary name: Zepbound, also known as LY3298176) is a dual agonist of the glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) receptors. The Applicant, Eli Lilly and Company (Lilly), proposes an indication as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management (CWM) in adults 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, dyslipidemia, type 2 diabetes mellitus, obstructive sleep apnea [OSA], or cardiovascular disease).

Tirzepatide is intended for once-weekly subcutaneous (SC) injection at three maintenance dosages of 5, 10, or 15 mg. To reduce the likelihood of gastrointestinal (GI) adverse events, a dose-escalation regimen is proposed, with a starting dose of 2.5 mg once weekly for 4 weeks and then dose increases every 4 weeks to 5, 7.5, 10, 12.5, and 15 mg/week. Tirzepatide is a drug-device combination with each dose delivered in a single-dose pen-injector prefilled with one of the six doses in a 0.5 mL volume.

Tirzepatide SC injection at these same dosages via the same device and dose escalation schedule is currently approved in the U.S. for treatment of type 2 diabetes (T2D) under NDA 215866 (proprietary name Mounjaro). While tirzepatide is the first approved dual agonist for both incretin hormone receptors GLP-1R and GIPR, GLP-1R only agonists are approved and widely-used for T2D and CWM, so parts of this review will refer more generally to class effects of incretin drugs. For the CWM indication, the Division granted tirzepatide Fast Track Designation and Rolling Review (see Section 3.2), and this NDA was reviewed on a priority timeline.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The Applicant has demonstrated substantial evidence of effectiveness to support approval of tirzepatide for the proposed indication as an adjunct to diet and exercise for CWM in patients with obesity or with overweight and weight-related comorbidities. To support the efficacy and safety of tirzepatide for the proposed indication, the Applicant has provided clinical data from two adequate and well-controlled phase 3 trials in subjects with obesity/overweight: GPHK (SURMOUNT-1) in a trial population with obesity/overweight without type 2 diabetes (T2D) and GPHL (SURMOUNT-2) in a trial population with obesity/overweight and T2D. The weight loss achieved in these two trials is statistically significant and clinically meaningful. At maintenance

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dosages of tirzepatide 10 mg or 15 mg weekly, the placebo-corrected mean weight loss at one year in the intention-to-treat (ITT) population was -16.4 to -17.8% from baseline in subjects without T2D (trial GPHK) and -9.6 to -11.6% from baseline in subjects with T2D (trial GPHL), and -11.9% with the lowest maintenance dosage of 5 mg in subjects without T2D (trial GPHK). In both trials, weight loss with tirzepatide was associated with improvements in risk factors for cardiovascular disease (glycemia, blood pressure, and lipids).

1.3. **Benefit-Risk Assessment**

See table below.

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Benefit-Risk Integrated Assessment

Tirzepatide is a selective dual agonist of the receptors for glucagon-like peptide-1 (GLP-1) and glucose-dependent insulintropic polypeptide (GIP) and is currently approved in the U.S. as a subcutaneous (SC) injection at dosages up to 15 mg weekly for the treatment of type 2 diabetes (T2D). The Applicant now submits NDA 217806 to support marketing approval of tirzepatide for chronic weight management (CWM) in adults with obesity (body mass index [BMI] ≥ 30 kg/m²) or with overweight (BMI ≥ 27 kg/m²) and one or more weight-related comorbidities.

Obesity and overweight impact millions of Americans, and excess weight is a risk factor for many common health conditions including hypertension, dyslipidemia, T2D, coronary heart disease, stroke, gallbladder disease, osteoarthritis, sleep apnea and respiratory problems, and some cancers. Individuals with obesity report impaired physical functioning, mental health conditions such as depression, and a decreased quality of life. The standard-of-care for treatment is lifestyle therapy, such as reduced calorie intake, nutritionally complete diets, increased physical activity, and behavioral modification. Patients with morbid obesity (BMI ≥ 40 kg/m² or ≥ 35 kg/m² with weight-related comorbidities) may benefit from bariatric surgery, with weight loss, cardiometabolic improvements (including resolution of T2D), and prolonged life. Historically, pharmacologic treatments for CWM were not widely used, likely due to a combination of factors including lack of insurance coverage, limited weight loss efficacy, safety issues, and historical concerns about the benefit-risk balance that have led several obesity drugs to be removed from the U.S. market. However, there is now rapidly growing public acceptance and utilization of injectable GLP-1R agonists like semaglutide (proprietary name Wegovy), which is highly effective for weight loss with a well-established safety profile. There is an unmet need for additional CWM drugs achieving even greater degrees of weight loss, and for multiple marketed drugs to ensure availability and potentially reduce costs.

Tirzepatide was studied with dose escalation to maintenance dosages of 5, 10, and 15 mg by weekly SC injection, in a large phase 3 program that meets the Division's expectations for size and scope. At dosages of 5, 10, and 15 mg, tirzepatide was shown to be effective for CWM at one year in a trial of subjects without diabetes (placebo-corrected weight loss of -11.9%, -16.4%, and -17.8%, respectively). In another trial of tirzepatide exclusively in subjects with T2D, tirzepatide at dosages of 10 and 15 mg gave placebo-corrected weight loss -9.6 and -11.6%. Though the tirzepatide 5 mg weekly maintenance dosage was not studied for CWM in subjects with T2D (who can already use this approved dosage for glycemic control), this 5 mg dosage was studied in previous trials for T2D and showed significant weight loss in subjects with T2D. Furthermore, the 5 mg dosage consistently showed evidence of better tolerability compared to the higher maintenance dosages of 10 and 15 mg weekly, supporting approval of this 5 mg dosage as safe and effective for CWM in patients with or without T2D. On all three tirzepatide maintenance dosages, weight loss was achieved and maintained for up to 72 weeks of treatment in all populations studied (with and without T2D). The majority of subjects on any maintenance dosage of tirzepatide achieved at least 5% body weight loss, a clinically meaningful threshold, at 72

weeks. The treatment effects observed with tirzepatide in this program are clinically meaningful and larger in magnitude than has been seen with any currently approved drug for CWM. Weight loss with tirzepatide was associated with clinically meaningful improvements in glycemia, blood pressure, and lipids in most trials. There was also some evidence for improvements in patient-reported physical functioning with tirzepatide, but the clinical meaningfulness of these changes is uncertain.

GLP-1R agonists have a well-characterized safety profile, and the CWM and T2D development programs for tirzepatide (a GLP-1R agonist with dual agonism at the GIPR) have not identified any additional safety concerns. There is a boxed warning for thyroid C-cell tumors and medullary thyroid carcinoma based on nonclinical data. Other described or theoretical safety concerns include gastrointestinal adverse events, volume depletion leading to acute kidney injury, gallbladder disease, acute pancreatitis, hypersensitivity, hypoglycemia, worsening of diabetic retinopathy, and psychiatric disorders including suicidality.

In summary, the weight loss efficacy of tirzepatide appears substantial and could, in some patients, reach the >20-25% weight loss from baseline typically achieved after bariatric surgery. The safety concerns for tirzepatide are well-established for the class of incretin drugs and can be appropriately mitigated in the post-market setting mainly via labeling and routine pharmacovigilance. While there is no evidence for reduced efficacy or safety with long-term use, it is unavoidable that there remains uncertainty regarding longer-term use of tirzepatide (or other incretin drugs) beyond the periods studied in trials. On balance, the benefit-risk assessment for tirzepatide for the indication of CWM in adults with overweight/obesity appears favorable.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	42% of U.S. adults have obesity. - Obesity is a chronic, relapsing health condition. - Obesity is difficult to treat. - Obesity increases the risk of chronic health outcomes, including hypertension, dyslipidemia, T2D, coronary heart disease, stroke, gallbladder disease, osteoarthritis, sleep apnea and respiratory problems, and some cancers.	Patients at risk from excess weight who would benefit from weight loss medication include those with BMI ≥ 30 kg/m ² (obesity) and those with BMI ≥ 27 kg/m ² (overweight) with weight-related co-morbidities (such as hypertension, dyslipidemia, and T2D).

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	- Weight loss of 5-10% in patients with obesity is generally accepted as beneficial on cardiometabolic health biomarkers. - The cardiovascular benefit of drug-induced weight loss in patients has not yet been shown in clinical trials, though cardiovascular outcomes trials in subjects with obesity/overweight are underway or under FDA review.	
Current Treatment Options	- Standard-of-care is lifestyle treatment (reduced calorie diet, increased physical activity). - Bariatric surgery is effective but, given risks, it is reserved for patients with morbid obesity. - Historically, medications for weight management suffered from poor acceptance and limited use, though this is changing rapidly. - One of the most frequently used medications for weight loss is generic phentermine, which has very limited long-term data for safety or efficacy and is only approved for short-term use. - Another commonly used medication is semaglutide (approved for T2D as Ozempic and for CWM as Wegovy), which is currently the most effective approved CWM medication. - Tirzepatide is currently approved for diabetes (as Mounjaro).	There is rapidly growing public acceptance and utilization of drugs for weight loss, particularly the class of injectable incretin drugs like semaglutide. Historically, the effort to treat obesity with drugs has been plagued with safety concerns, leading some drugs to be removed from the U.S. market. Phentermine and other amphetamine class drugs were approved in the U.S. primarily in the 1950s and 60s with a short-term use limitation. However, this class continues to be frequently used for medical weight loss, despite a lack of long-term safety and efficacy data. Five drugs are currently approved in the U.S. for CWM in patients with obesity/overweight: orlistat, phentermine/topiramate, naltrexone/bupropion, liraglutide, and semaglutide. (Other drugs, such as setmelanotide, are used for rare genetic causes of obesity).

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• Placebo-subtracted weight loss from baseline after 1 year at the maintenance tirzepatide dosages of 10 and 15 mg was -16.4 to -17.8% in a trial population without diabetes and -9.6 to -11.6% in a trial population with T2D. The maintenance dosage of tirzepatide 5 mg gave -11.9% weight loss in the trial population without diabetes. • Weight loss on tirzepatide was statistically significant, clinically meaningful, and greater in magnitude than that observed for semaglutide 2.4 mg weekly in separate trials (-10.3 to -12.4% in those without diabetes and -6.2% in those with type 2 diabetes). • The majority (79.2-90.9%) of subjects randomized to any dosage of tirzepatide achieved at least 5% body weight loss at the end of the trials, and this was 2 to 3 times the proportions of subjects randomized to placebo. • Weight loss with tirzepatide was associated with improvements in blood pressure, blood glucose, lipids, and patient-reported measures of physical function. • Cardiovascular and other outcomes benefits of tirzepatide in patients with overweight/obesity, with or without type 2 diabetes, are unknown. • Long-term benefits (beyond 72 weeks) are unknown.	The CWM clinical development program for tirzepatide has demonstrated robust and durable weight loss in obese and overweight patients over the study period. The weight loss was associated with improvements in cardiometabolic parameters, and it is expected to occur in the post-market setting. Two ongoing cardiovascular outcome trials should clarify the long-term cardiovascular benefits of tirzepatide, one in a population with T2D and one in a population with overweight/obesity but without T2D.
Risk and Risk Management	• Known or theoretical adverse events with tirzepatide treatment include gastrointestinal events, volume depletion, acute kidney injury, gallbladder disease, acute pancreatitis, hypersensitivity and injection site reactions, hypoglycemia, worsening of diabetic retinopathy, psychiatric disorders including suicidality, increase in heart rate, and hair loss. ○ Suicidality has been observed with other obesity drugs and is labeled for the entire class, including GLP-1R agonists, but occurred rarely in this program.	The safety profile of tirzepatide is well-characterized and consistent with other available GLP-1R agonists, and most common adverse reactions are monitorable and can be mitigated with labeling. Studies are ongoing or planned that will help to understand some of these risks, including

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	○ All drugs in the GLP-1R agonist class include a boxed warning for the rare cancer medullary thyroid cancer (MTC) based on nonclinical data in rodents. ○ Pancreatitis is also a GLP-1R agonist class warning but was infrequently seen in this program. ○ Hypoglycemia is primarily a safety concern for patients with T2D especially those also taking sulfonylureas or insulin, but it may also occur in patients without T2D. ○ Worsening of diabetic retinopathy can occur with improvement in blood glucose but was seen infrequently in this program. ○ Acute gallbladder disease and hair loss have also been reported in patients with substantial weight loss by lifestyle, bariatric surgery, or other CWM drugs, and it unknown whether tirzepatide affects these risks through weight loss alone or by mechanisms independent of weight loss. ○ Since the observed increase in heart rate is well less than 10 beats per minute from baseline, it is unlikely to translate to increased cardiovascular risk. ● In clinical trials, there were a small number of pregnancies in patients exposed to tirzepatide, and tirzepatide is discontinued during pregnancy (when weight loss is not indicated). There was no evidence for fetal or maternal harm based on the small amount of available data, but the safety of tirzepatide in pregnancy is largely unknown.	cardiovascular outcome trials in CWM and diabetes, a 2-year treatment extension in a CWM trial, pediatric trials in CWM, an MTC registry, and post-marketing pregnancy studies.

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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	
☒	Patient reported outcome (PRO)	Section 6
☐	Observer reported outcome (ObsRO)	
☐	Clinician reported outcome (ClinRO)	
☐	Performance outcome (PerfO)	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
☐	Patient-focused drug development or other stakeholder meeting summary reports	
☐	Observational survey studies designed to capture patient experience data	
☐	Natural history studies	
☐	Patient preference studies (e.g., submitted studies or scientific publications)	
☐	Other: (Please specify)	
☐	Patient experience data that were not submitted in the application, but were considered in this review:	
☐	Input informed from participation in meetings with patient stakeholders	
☐	Patient-focused drug development or other stakeholder meeting summary reports	
☐	Observational survey studies designed to capture patient experience data	
☐	Other: (Please specify)	
☐	Patient experience data was not submitted as part of this application.	

FDA's Division of Clinical Outcome Assessments (DCOA) was consulted for review and interpretation of PRO data in this NDA.

2. Therapeutic Context

2.1. Analysis of Condition

According to the U.S. Centers for Disease Control and Prevention (CDC), obesity (defined as BMI ≥ 30 kg/m²) is a common, severe, and costly health condition.¹ The U.S. obesity prevalence in the three years prior to the COVID-19 pandemic (2017 to March 2020) was 41.9%, increased from 30.5% two decades earlier (1999 to 2000). During the same time, the prevalence of severe obesity (defined as BMI ≥ 40 kg/m²) increased from 4.7% to 9.2%.² Obesity-related conditions include heart disease, stroke, T2D and certain types of cancer, which are among the leading causes of preventable, premature death. According to the 2013 American Heart Association / American College of Cardiology (AHA/ACC) guidelines on the management of overweight and obesity, obesity raises the risk of morbidity and mortality from atherosclerotic cardiovascular disease (ASCVD), and is also associated with increased risk of all-cause mortality.³ The estimated annual medical cost of obesity in the U.S. was nearly \$173 billion in 2019 dollars, and annual medical costs for adults with obesity were \$1,861 higher than for people with healthy weights.⁴ Obesity is notoriously difficult to treat yet affects millions of American adults, reducing their overall health, lifespan, and quality-of-life, and is therefore a significant public health issue.

As described in the FDA draft guidance for developing CWM drugs,⁵ weight change is the primary endpoint of interest in clinical trials for the development of obesity drugs. Among individuals with overweight or obesity, weight is an easily measured surrogate for body adiposity, and long-term weight loss in the range of 5 to 10% is associated with improved glycemic control, blood pressure, and lipid parameters.⁶

It is presumed that salutary changes in cardiovascular and metabolic risk factors will translate into ASCVD benefit, such as reductions in the incidence of myocardial infarction and stroke. Although some, but not all, observational studies suggest that modest degrees of intentional

¹ <https://www.cdc.gov/obesity/data/adult.html>

² Stierman, Bryan et al. "National Health and Nutrition Examination Survey 2017–March 2020 Prepandemic Data Files Development of Files and Prevalence Estimates for Selected Health Outcomes", no. 158, 2021

³ Jensen MD, et al. Executive summary: Guidelines (2013) for the management of overweight and obesity in adults. A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and The Obesity Society. Obesity 2014. 22(S2): S5-39.

⁴ Ward ZJ, Bleich SN, Long MW, Gortmaker SL (2021) Association of body mass index with health care expenditures in the United States by age and sex. PLOS ONE 16(3): e0247307. <https://doi.org/10.1371/journal.pone.0247307>

⁵ FDA Draft Guidance for Industry: Developing Products for Weight Management. February 2007.

⁶ Van Gaal LF, et al. The beneficial effects of modest weight loss on cardiovascular risk factors. Int J Obes Relat Metab Disord 1997 Mar; 21 Suppl 1: S5-9.

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weight loss in overweight and obese individuals can reduce the incidence of some cancers, cardiovascular disease, and all-cause mortality, weight loss (at least at the magnitude seen in trials of most other CWM drugs; see Table 1) has not been established as a surrogate for ASCVD benefit. The Look AHEAD (Action for Health in Diabetes) trial⁷ was a randomized controlled trial in over 5000 patients with T2D comparing an intensive lifestyle intervention (including weight loss) to standard-of-care for a follow-up of 10 years. The trial was stopped early (9.6 years) for futility of the composite primary outcome (first occurrence of CV death, non-fatal MI, non-fatal stroke, or hospitalized angina); HR 0.95 (95% CI 0.83, 1.09). Weight loss was greater in the intervention group (8.6% at 1 year, 6.0% at study end) as compared to the control group (0.7% at 1 year, 3.5% at study end). Weight loss drugs with sympathomimetic effects may also cause CV harm.⁸

Although two GLP-1R agonists (weekly semaglutide and daily liraglutide) have been approved to reduce the risk of major adverse cardiovascular events (MACE: CV death, non-fatal myocardial infarction, or non-fatal stroke) in adults with T2D and established CV disease, cardiovascular outcomes in subjects with obesity, who receive pharmacologic treatment for weight loss, are unknown. A cardiovascular outcome trial (CVOT) with semaglutide in subjects with overweight/obesity and without T2D (SELECT) is recently completed, and a CVOT is ongoing for tirzepatide in populations with obesity. The results of these two CVOTs will help clarify the potential benefits of drug-induced weight loss on cardiovascular outcomes.

2.2. Analysis of Current Treatment Options

As of this writing there are 5 drugs approved in the U.S. for CWM in obesity: orlistat, phentermine/topiramate, naltrexone/bupropion, liraglutide, and semaglutide (see Table 1). (Note that setmelanotide is indicated only in patients with rare monogenic causes of obesity).

Phentermine and other amphetamine congeners were approved in the U.S. primarily in the 1950s and 60s with a short-term use limitation. However, this class continues to be frequently used for prescription weight loss, despite a lack of long-term safety and efficacy data.

⁷ The Look AHEAD Research Group. Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. *N Engl J Med* 2013; 369: 145-54.

⁸ James WPT, et al. Effect of sibutramine on cardiovascular outcomes in overweight and obese subjects. *N Engl J Med* 2010; 363:905-17.

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Table 1. Summary of Treatment Armamentarium Relevant to Proposed Indication (Chronic Weight Management)

Product Name	Relevant Indication	Approval Year	Route and Frequency	Efficacy	Important Safety and Tolerability Issues	Other Comments
FDA-Approved Treatments						
Xenical (orlistat)	Overweight with comorbidities or obesity, in conjunction with a reduced-calorie diet. Also indicated to reduce the risk for weight regain after prior weight loss.	1999	One 120-mg capsule three times a day with each main meal containing fat	3% placebo-corrected mean percent weight loss at one year.	Decreased absorption of fat-soluble drugs (cyclosporine) and vitamins, liver injury, cholelithiasis, increases in urinary oxalate, and prominent GI symptoms (oily stool)	Label also includes onset of type 2 diabetes data from 4-year study. Approved at a lower dosage for over-the-counter weight loss.
Qsymia (phentermine and topiramate XR)	Adults with overweight with comorbidities or obesity. Pediatric patients aged ≥12 years with BMI ≥95 th percentile standardized for age and sex. Adjunct to a reduced-calorie diet and increased physical activity.	2012	Start 3.75/23 mg daily for 14 days; then increase to 7.5/46 mg daily. After 12 weeks, if a patient has not lost ≥3% body weight, then discontinue or dose escalate (increase to 11.25/69 mg daily for 14 days; followed by 15/92 mg daily). After 12 weeks, if a patient has not lost ≥5% body weight, discontinue.	6.6-9.4% placebo-corrected mean percent weight loss at one year, depending on dosage and trial population.	Embryo-fetal toxicity, increase in HR, suicidal behavior and ideation, acute myopia and secondary angle closure glaucoma, mood and sleep disorders, cognitive impairment, metabolic acidosis, kidney injury, hypoglycemia in T2D on anti-diabetic therapy, hypotension in patients on antihypertensive medications, CNS depression with CNS depressants, potential seizures with abrupt withdrawal, kidney stones, oligohydrosis and hypothermia, hypokalemia	Product is approved with a REMS for embryo-fetal toxicity. Study 2 included patients with and without T2D. Dose adjustment in renal and hepatic impairment. Monitoring labs (bicarbonate, creatinine, potassium, glucose) Both components are approved drugs available as generics that are prescribed off-label for weight management.
Contrave (naltrexone HCl and bupropion HCl)	Adults with overweight with comorbidities or obesity. Adjunct to a reduced-calorie diet and increased physical activity.	2014	Start at one 8/90 mg tablet once daily for one week, and dose escalate weekly to reach at the start of Week 4 a total daily dosage of two 8/90 mg tablets twice daily (32/360 mg total daily).	3.2-4.1% placebo-corrected mean percent weight loss at one year in subjects without T2D, 2.0% in subjects with T2D.	Suicidal behavior and ideation, neuropsychiatric adverse events and suicide risk in smoking cessation treatment, seizures, vulnerability to opioid overdose and precipitated opioid withdrawal, increase in BP and HR, allergic reactions, hepatotoxicity, activation of mania,	Both components are approved drugs available as generics that are prescribed off-label for weight management.

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					angle-closure glaucoma, hypoglycemia in T2D on anti-diabetic therapy	
Saxenda (liraglutide)	Adults with overweight with comorbidities or obesity. Pediatric patients aged ≥ 12 years with body weight >60 kg and BMI corresponding to ≥ 30 kg/m ² for adults by international cut-offs. Adjunct to a reduced-calorie diet and increased physical activity	2014 (2010 for T2D)	Start at 0.6 mg SC daily for 1 week, dose escalate weekly for 4 weeks until maintenance dosage of 3 mg daily is reached.	4.5-5.2% placebo-corrected mean percent weight loss at one year in subjects without T2D, 3.7% in subjects with T2D.	Most common AEs are GI (nausea, vomiting, diarrhea). Also risk of thyroid C-cell tumors, acute pancreatitis, acute gallbladder disease, hypoglycemia, heart rate increase, dehydration and acute kidney injury, hypersensitivity reactions, suicidal behavior and ideation.	Also approved for glycemic control in T2D and decreased risk of MACE in T2D with established ASCVD.
Wegovy (semaglutide)	Adults with overweight with comorbidities or obesity. Pediatric patients aged ≥ 12 years with BMI $\geq 95^{\text{th}}$ percentile standardized for age and sex. Adjunct to a reduced-calorie diet and increased physical activity.	2021 (2017 for T2D)	Start at 0.25 mg SC weekly for 4 weeks, dose escalate every 4 weeks until the recommended maintenance dosage of 2.4 mg weekly is reached, or 1.7 mg weekly.	10.3-12.4% placebo-corrected mean percent weight loss at one year in subjects without T2D, 6.2% in subjects with T2D.	As above for liraglutide	Also approved for glycemic control in T2D.
Other Treatments						
Phentermine and other amphetamine congeners	Patients with overweight with comorbidities or obesity. Short-term (a few weeks) adjunct in a regimen of weight reduction based on exercise, behavioral modification, and caloric restriction.	1959	Depends on product: typical oral dosage is individualized to obtain an adequate response with the lowest effective dose	Unknown. In short term trials, placebo-corrected weight loss was only a fraction of a pound per week, greatest in the first weeks and then decreasing.	Coadministration with other weight loss products not recommended, primary pulmonary hypertension, valvular heart disease, development of tolerance, effect on the ability to engage in potentially hazardous tasks, risk of abuse and dependence. Caution for usage with alcohol or in patients with hypertension or T2D	These short-term products are a hold-over from before the era of chronic use treatment for obesity

					on insulin or oral antihyperglycemic medications.	
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The widespread use of semaglutide has drastically changed the pharmacological treatment of obesity in the U.S., but there remains an unmet need for drugs capable of achieving even greater degrees of weight loss, and for multiple marketed drugs to help ensure availability and potentially reduce costs.

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Tirzepatide was approved as Mounjaro on May 13, 2022, under NDA 215866, as an adjunct to diet and exercise to improve glycemic control in adults with T2D. There are 3 ongoing PMRs for Mounjaro:

- A randomized, double-blind, placebo-controlled trial in pediatric T2D patients (note that pediatric studies will also be required for CWM, see Section 12)
- A milk-only lactation study (see Section 8.8.2)
- A medullary thyroid carcinoma (MTC) registry-based case series study, as required for all incretin drugs (see Section 8.5.1).

Please refer to Section 8.9.1 for details on the post-marketing safety surveillance for tirzepatide.

(b) (4)



3.2. Summary of Presubmission/Submission Regulatory Activity

This section provides the most relevant regulatory history of tirzepatide for CWM under IND 139721. Note that the early development of tirzepatide occurred for the T2D indication under IND 128801, as detailed in the review of T2D NDA 215866.⁹ The CWM pre-IND 139721 was opened on May 18, 2018. An End-of-Phase 2 (EOP2) meeting was held on June 26, 2019, with agreements including a gastric emptying study in subjects with overweight/obesity and without T2D (study GPHU in this application) and phase 3 trial design, including an early SURMOUNT-1 Ambulatory Blood Pressure Monitoring (ABPM) substudy to inform heart rate effects, adding a 5 mg maintenance dosage, and having four phase 3 SURMOUNT trials in the initial NDA. The IND was submitted on October 30, 2019, with GPHK/SURMOUNT-1 as the IND-opening trial, and it was deemed safe-to-proceed on November 29, 2019.

The pre-NDA meeting was held on August 11, 2022. (b) (4)

FDA advised waiting until SURMOUNT-2 data were available to establish substantial evidence of effectiveness with two adequate and well-controlled trials meeting the Division's expectations for CWM trials. FDA agreed that SURMOUNT-3 and -4 were not necessary for the initial NDA, and that the safety database for SURMOUNT-1 and -2 could be acceptable. (b) (4)

FDA granted Fast Track designation on October 3, 2022, based on the justification that tirzepatide had the potential to address an unmet medical need. FDA granted rolling review of the NDA on November 4, 2022, and the Applicant submitted clinical data from SURMOUNT-1 in the initial NDA sequence on November 17, 2022, and SURMOUNT-2 in the final sequence on May 8, 2023. As detailed in an FDA memo from the Office of New Drug Policy, Division of Regulatory Policy, dated July 6, 2023, the (b) (4)

and priority review was granted on the merits of the application.

3.3. Foreign Regulatory Actions and Marketing History

Tirzepatide is approved and marketed in the U.S. and other countries for T2D, including the EU, Canada, Australia, Japan, and Switzerland. To my knowledge, tirzepatide has not been approved for a weight management indication anywhere in the world to date.

⁹ F. Pucino, clinical review of NDA 215866,
https://www.accessdata.fda.gov/drugsatfda_docs/nda/2022/215866Orig1s000MedR.pdf

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

4.1. Office of Scientific Investigations (OSI)

OSI was consulted to inspect 6 sites, 2 in Argentina, 3 in the continental U.S., and one in Puerto Rico. These sites accounted for 8.4% of the subjects enrolled in the two phase 3 CWM trials: 118 of 2539 (4.6%) in trial GPHK and for 178 of 938 (19.0%) in trial GPHL. Sites were selected in consultation with Dr. Ling Yang, OSI reviewer. The rationale for the six selected clinical sites for inspection was primarily based on high efficacy, financial disclosures, complaints, and lack of previous compliance inspection.

The following sites were inspected, and no significant deficiencies were identified:

- Drs. Federico Manghi (Argentina, GPHK Site #503 with 62 subjects enrolled and GPHL Site #54333 with 63 subjects enrolled)
- Dr. Diego Aizenberg (Argentina, GPHL Site #85301 with 81 subjects enrolled)
- Dr. Timothy Smith (Saint Peters, MO, GPHK Site #114 with 29 subjects enrolled)
- Dr. Seth Forman (Tampa, FL, transferred from Dr. Tanya Bogle; GPHK Site #111 with 27 subjects enrolled)
- Dr. Gregorio Cortes-Maisonet (San Juan, Puerto Rico, GPHL Site #92464 with 18 subjects enrolled)
- Dr. Joanna Van (Tustin, CA, GPHL Site #83971 with 16 subjects enrolled)

Please refer to Dr. Yang's OSI review dated September 12, 2023, for further details. She concluded that, based on the overall inspection results of these clinical investigators and the regulatory assessments, the data generated by these sites are verifiable. Per OSI, trials GPHK and GPHL appear to have been conducted adequately and the clinical data submitted by the Applicant appear acceptable in support of the respective indication, and I concur.

4.2. Product Quality

For all drug substance information, this NDA cross-references the approved NDA 215866, tirzepatide for T2D (Mounjaro), and no new chemistry, manufacturing, and controls (CMC) information was submitted. The integrated quality review for the current NDA by the Office of Pharmaceutical Quality (OPQ) was signed by application technical lead Dr. Theodore Carver on October 6, 2023. This integrated review notes that the drug products in this NDA, including the six strengths of tirzepatide, are identical to the equivalent pen injector drug products approved in NDA 215866.

Please refer to the OPQ integrated quality assessment for detailed reviews of manufacturing to

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confirm adequacy of process and facilities, microbiology to address a specific requirement for validation of analytical procedures, and quality aspects of the drug product labeling. Also, the Applicant claimed a Categorical Exclusion from the requirement for an environmental assessment, and this was granted. For all other reviews of CMC information, refer to the CMC review of the relevant information for NDA 215866.¹⁰ OPQ made the final overall recommendation to approve this NDA, in agreement with the individual subdiscipline recommendations for drug substance, drug product, quality labeling, manufacturing, and microbiology.

4.3. Clinical Microbiology

Tirzepatide is not an antimicrobial or antiviral. The microbiology review by Drs. Aditi Das and Yuansha Chen was part of the integrated quality review of this NDA dated October 6, 2023, and no deficiencies were found. Under the current NDA, an information request was conveyed to the Applicant regarding validation of endotoxin testing, and their reply was deemed adequate. Please refer to NDA 215866 and its microbiology review dated December 13, 2021, for the rest of the sterility assurance and microbiological quality of the drug product assessment.

4.4. Nonclinical Pharmacology/Toxicology

For all nonclinical information, this NDA cross-references the approved NDA 215866, tirzepatide for T2D (Mounjaro). No new toxicology studies were conducted to support the CWM indication, as a complete nonclinical program was conducted and reviewed to support the T2D indication (IND 128801 and NDA 215866). No new nonclinical studies were required by FDA as the dosage of tirzepatide (up to 15 mg once weekly) and the age group (adults) are identical to those in the approved indication.

Below is a summary of select nonclinical data from the application and nonclinical review:

- Nonclinical pharmacodynamic data included effects of tirzepatide on gastric emptying in mice, and effects on food intake and body weight in rats fed a high fat high sucrose diet and diet-induced obese mice. Studies were also performed in knockout mice and cells lacking the GLP-1R or GIPR. For instance, tirzepatide stimulated cAMP production and lipolysis in mature adipocytes that express the GIPR and not the GLP-1R, indicating an effect of GIPR agonism. Consistent with this, a published study (not part of this NDA) showed in mouse and human islets that both the GIPR and GLP-1R contribute to

¹⁰ OPQ integrated quality review of NDA 215866,
https://www.accessdata.fda.gov/drugsatfda_docs/nda/2022/215866Orig1s000ChemR.pdf

tirzepatide effects on insulin secretion.¹¹

- To test for QT prolongation potential, the Applicant performed *in vitro* human ether-a-go-go related gene (hERG) assays showing no inhibition at the highest concentration tested (300 µM) and ECGs in monkeys with single and repeat tirzepatide dosing, showing no QT_c prolongation (consistent with the human ECG data, see Section 8.4.9).
- To test for mutagenesis and carcinogenesis, the Applicant performed an *in vivo* micronucleus genotoxicity study was conducted in rats (no evidence of genotoxicity), a 26-week study in RasH2 transgenic mice (no C-cell hyperplasia or neoplasia), and a 2-year carcinogenicity study in rats (increases in C-cell adenomas and carcinomas in both sexes). Due to species differences in GLP-1 receptor expression and activation, the relevance of these findings to humans is unclear, as reflected in the class labeling for incretins.
- 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. Generally, most maternal and fetal effects were likely secondary to effects on food consumption and body weight, though increased incidences of malformations and developmental variations were observed at the highest 0.5 mg/kg dose in rats.

Dr. Elena Braithwaite, of the Division of Pharmacology-Toxicology for Cardiology, Hematology, Endocrinology and Nephrology (DPT-CHEN), reviewed the T2D NDA (dated March 16, 2022)¹² and the current NDA (dated October 14, 2023); refer to these for a detailed discussion of the nonclinical findings, which were generally consistent with other GLP-1R agonists. The nonclinical team recommends approval.

4.5. Clinical Pharmacology

The clinical pharmacology data for this Application were reviewed by Office of Clinical Pharmacology (OCP): Drs. Mohamad Kronfol and Edwin Chow from the Division of Cardiometaabolic and Endocrine Pharmacology (DCEP) and Drs. Justin Earp and Jiajun Liu from the Division of Pharmacometrics (DPM). The OCP/DCEP review 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 October 11, 2023) for more detailed information.

¹¹ El K, Douros JD, Willard FS, et al. The incretin co-agonist tirzepatide requires GIPR for hormone secretion from human islets. *Nat Metab.* 2023;5(6):945-954. doi:10.1038/s42255-023-00811-0

¹² Nonclinical review of NDA 215866,
https://www.accessdata.fda.gov/drugsatfda_docs/nda/2022/215866Orig1s000PharmR.pdf

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The clinical pharmacology of tirzepatide had been well-characterized in the development program for T2D and reviewed under NDA 215866 and cross-referenced for this CWM NDA. Note that the phase 3 trials for T2D and CWM used the identical formulation, route of administration, and dosage escalation regimen. Please refer to the clinical pharmacology team primary review of T2D NDA 215866 dated March 18, 2022, by Drs. Mohamad Kronfol, Elyes Dahmane, and Yuching Yang.¹³

The clinical pharmacology studies conducted under the T2DM NDA 215866 included relative bioavailability, single- and multiple-ascending dose, disposition of radioactivity, hepatic and renal impairment, drug-drug interaction, and pharmacodynamic studies. The Applicant submits three additional clinical pharmacology studies or reports that were reviewed as part of this NDA:

- a new gastric emptying study (GPHU)
- a mechanistic study on caloric intake (GPGT)
- a new population PK and pharmacokinetic-pharmacodynamic (PK/PD) report in the indicated population.

Below is a summary of information from the OCP review of tirzepatide.

Mechanism of Action/Pharmacodynamics

Tirzepatide is an agonist at the GIP and GLP-1 receptors. Tirzepatide is a 39 amino acid synthetic peptide engineered from the GIP sequence and includes a C20 fatty diacid moiety. Based on known physiology and pharmacology of GIP and GLP-1, dual signaling at both receptors is proposed to result in improved weight loss and changes in carbohydrate and lipid metabolism.

The Applicant constructed population body weight models for phase 3 CWM trials GPHK and GPHL, and the models adequately described tirzepatide dose-dependent body weight reductions over time. The Applicant also constructed a PK/PD model for safety, which reasonably described the occurrence of nausea, vomiting, and diarrhea adverse events.

In new trial GPHU and previously-reviewed trial GPGA, tirzepatide reduced gastric emptying in subjects with and without T2D. Trial GPHU enrolled 36 subjects (30 of whom completed the trial) with overweight or obesity, 18 without T2D and 18 with T2D, to measure the effect of tirzepatide on the PK of acetaminophen as a probe of gastric emptying. Acetaminophen PK was measured in each subject on Day -1 in the absence of tirzepatide, on Day 2 after receiving tirzepatide 5 mg on Day 1, and on Day 37 after a rapid 6-week dose escalation to tirzepatide 15 mg (5 mg on Day 8; 10 mg on Days 15, 22, and 29; 15 mg on Day 36). There was an observed delay in acetaminophen t_{max} of approximately 1 hour and a maximum decrease in C_{max} of approximately 55% on Day 1 after an initial 5 mg dose of tirzepatide, with no clinically relevant

¹³ Clinical pharmacology review of NDA 215866,
https://www.accessdata.fda.gov/drugsatfda_docs/nda/2022/215866Orig1s000ClinPharmR.pdf

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impact on AUC. On Day 37 with tirzepatide 15 mg (after the rapid dose escalation), the $C_{\max}$ of acetaminophen was decreased approximately 32% with no clinically relevant impact change on AUC. Consistent with trial GPGA (maximum decrease in acetaminophen $C_{\max}$ of 50%), the delay in gastric emptying was greatest following the first tirzepatide dose and the delay was less evident following repeated tirzepatide doses within the study duration. The effects on gastric emptying of the proposed clinical dose escalation (2.5 mg initially, increasing by 2.5 mg every 4 weeks to reach 15 mg) and of maintenance dosages at steady-state are unknown. These trials support the statement in Section 12.2 (Pharmacodynamics) of labeling on delayed gastric emptying. Pathological delay in gastric emptying (i.e., gastroparesis) is also addressed in this review, Section 8.5.17.

Phase 1 trial GPGT assessed insulin and glucagon secretion during a clamp, and also assessed *ad libitum* food intake showing reduced calorie and macronutrient intake after 28 weeks of tirzepatide treatment. The trial enrolled 117 subjects with T2D and BMI 25-45 kg/m², assessing *ad libitum* food intake during a 45-minute buffet meal at noon at baseline and after 28 weeks of treatment with tirzepatide (via phase 3 dose escalation to 15 mg), semaglutide, or placebo. The Applicant concludes that at Week 28 tirzepatide lowered food intake by -309.8 kcal (95%CI -423.0, -196.6) from baseline versus placebo. The Applicant concludes that at Week 28 tirzepatide lowered carbohydrate, protein, and fat intake by -117.8 kcal (95% CI -172.8, -62.9), -59.9 kcal (-84.0, -35.7), and -142.5 kcal (-207.2, -77.8) respectively from baseline versus placebo. This study supports the statement in Section 12.2 (Pharmacodynamics) of labeling on food and calorie intake.

Absorption

Tirzepatide is administered as a weekly SC injection into the abdomen, thigh, or upper arm (the last of which may require another person to inject). Following SC administration, approximately 80% of an administered dose is absorbed, with maximum plasma concentrations ($C_{\max}$) occurring between 8 to 72 hours ($t_{\max}$) with a median of approximately 24 hours. PK is dose proportional in the dose ranging from 5-15 mg based on the population PK analysis.

Distribution

The mean volume of distribution of tirzepatide at steady state is approximately 9.7 L, and it is extensively bound (99%) to plasma albumin. Due to a prolonged half-life ($t_{1/2}$), steady-state plasma concentrations are typically achieved following four weeks of weekly dosing.

Metabolism and Elimination

Tirzepatide is primarily eliminated by metabolism (i.e., proteolytic cleavage of the peptide backbone, beta-oxidation of the C20 fatty diacid moiety, and amide hydrolysis), with a mean clearance of 0.056 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 are 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. Renal excretion is the primary route of

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elimination, and intact parent is not detected in urine or feces. Approximately 70% of radiolabeled dose is recovered as metabolites in urine (50%) and feces (20%).

Intrinsic Factors

In the DPM review of the population PK model, it was noted that body weight was the only statistically significant covariate identified on tirzepatide PK. Yet, weight-based dose adjustment was not deemed as warranted due to the moderate impact on PK and the proposed titration dosing approach. Additionally, age, sex, race, renal impairment, hepatic impairment, antidrug antibody (ADA) status, or ADA titer were not found to significantly impact tirzepatide PK, and no dosing adjustment was deemed necessary based on these factors in obese or overweight subjects.

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, C_{max} , and $t_{1/2}$) were observed compared to subjects with normal renal and normal hepatic function, respectively. Based on data from study GPHI, the clinical pharmacology team felt that dose adjustments would not be necessary based on differences in 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 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 trials GPGA and GPHU, 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. The OCP team 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.

In study GPGR, coadministration of a single 5 mg 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,

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90% CI: 0.274, 0.436), respectively.

Due to the findings reported in study GPGR, the Clinical Pharmacology review team recommended that proposed labeling 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 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.

Other key points from the clinical pharmacology reviews were:

- The to-be-marketed formulation and device were used the phase 3 CWM trials, and are identical to the formulation and device currently approved for T2D under NDA 215866, so no bridging studies were necessary.
- The proposed tirzepatide dosing and dose escalation strategies for CWM (currently approved for T2D under NDA 215866) were supported by phase 2 trials GPGB and GPGF. The dose escalation strategy used in phase 3 (starting at 2.5 mg with titration every 4 weeks) reduced discontinuations due to GI adverse events compared to more rapid dose escalations.
- No dedicated thorough QT study was performed, as detailed in Section 8.4.9. Concentration-QT analyses using ECG readings from phase 1, 2, and 3 trials did not indicate any unexpected or important effects of tirzepatide on the QT_c interval at clinically relevant exposures associated with the proposed dosages (up to 15 mg once weekly).
- Immunogenicity (anti-drug antibody [ADA] status and titer) did not have apparent effect on the PK of tirzepatide (see Section 8.4.10).
- Handling of missed dose was assessed by the population PK analysis in cross-referenced data from T2D NDA 215866, supporting the Applicant's proposal to administer tirzepatide as soon as possible within 4 days (96 hours) of a missed dose, or otherwise to skip the dose (if more than 4 days has passed) before resuming the regular weekly regimen.

4.6. Devices and Companion Diagnostic Issues

FDA's Center for Devices and Radiological Health (CDRH) was not consulted for this application, since the tirzepatide auto-injector device is the same as approved under tirzepatide T2D NDA 215866, originally developed by the Applicant for its GLP-1R agonist dulaglutide (Trulicity, BLA

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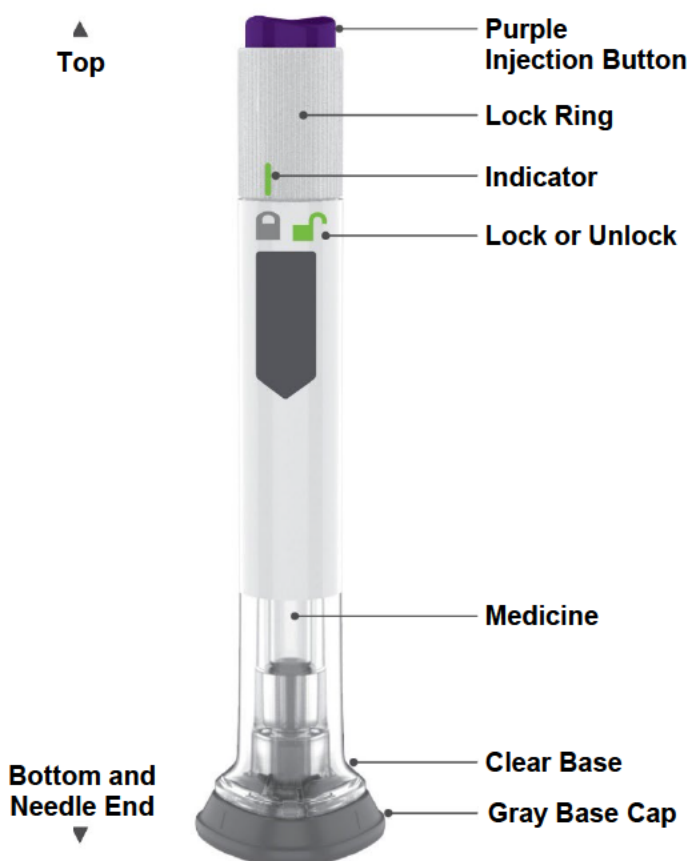
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125469). Under tirzepatide NDA 215866, Dr. Sreya Tarafdar, from the CDRH Division of Health Technology 3 C (Division of Drug Delivery, General Hospital & Human Factors) provided a consult review dated January 31, 2022.¹⁴ Overall, this CDRH review considered 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) under the T2D NDA 215866.

Briefly, the tirzepatide auto-injector (Figure 1) is a single-use needle-based injection system that automatically inserts the needle into the SC tissue and delivers 0.5 mL of tirzepatide drug product when activated.

Figure 1. Components of the Tirzepatide Auto-Injector



Source: Excerpt from the Applicant's Instructions for Use, in NDA module 1.14.1.3

¹⁴ Review of NDA 215866,
https://www.accessdata.fda.gov/drugsatfda_docs/nda/2022/215866Orig1s000OtherR.pdf

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The auto-injector safety features include a locking mechanism to prevent inadvertent activation, a first audible click when the button is pressed for activation, needle insertion to SC depth, automatic delivery of drug product, a retraction delay to ensure complete dose delivery, automatic needle retraction with a second audible click for injection completion, and a retraction lock to prevent re-activation. The instructions for use call for pressing and holding the injection button for up to 10 seconds, though they note that holding is not necessary except to help keep the auto-injector steady. Under NDA 215866, Dr. Tarafdar of CDRH felt that the device constituent parts of the combination product were approvable and recommended approval.

4.7. Consumer Study Reviews

For this tirzepatide NDA for CWM (Zepbound), the Applicant proposed to leverage human factors validation data from the currently approved tirzepatide for T2D (Mounjaro) under NDA 215866.¹⁵ Based on FDA feedback from the CWM pre-NDA meeting under IND 139721, the Applicant submitted with the NDA first sequence on November 17, 2022, a use-related risk analysis (URRA) and justification not to submit results of a human factors validation study. FDA's Division of Medication Error Prevention and Analysis 1 (DMEPA 1) provided a URRA review from the human factors evaluator Dr. Neha Kumar, dated May 9, 2023. This review agreed with the sponsor's justification, noting that:

- Physical characteristics did not differ between Zepbound and Mounjaro, with the same auto-injector pen, drug product, and strengths.
- User tasks did not differ between Zepbound and Mounjaro.
- Instructions for use did not differ between Zepbound and Mounjaro, except for the brand name text.
- No differences were identified between the user groups for Zepbound versus Mounjaro that would impact the proposed intended users' interactions with the user interface. Intended patient users of Zepbound did not differ meaningfully from Mounjaro users in characteristics of vision, hearing, physical strength, tactile sensitivity, cognitive abilities, mental and emotional state, handedness, dexterity characteristics, and comorbidities.
- The human factors study for Mounjaro included subjects with T2D and overweight or obesity.

Since these human factors studies were completed, post-marketing reports identified a potential user error with the auto-injector, in which some patients used the device upside down with the needle facing their thumb and the button facing the intended injection site. DMEPA recommended that the Applicant include a "Needle End" phrase on the pen container label for tirzepatide, and the Applicant agreed.

¹⁵ Review of NDA 215866,
https://www.accessdata.fda.gov/drugsatfda_docs/nda/2022/215866Orig1s000OtherR.pdf

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In conclusion, the DMEPA review of this NDA's URRA did not identify any new, differing, or unique risks for the proposed product, and agreed with the Applicant's justification for not submitting the results from another human factors validation study with their NDA for the proposed Zepbound (tirzepatide) auto-injector. Besides the labeling of the auto-injector pen as described above, DMEPA had no human factors recommendations for this marketing application.

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

Table 2 lists the tirzepatide trials conducted for CWM in support of this NDA. Please refer to Section 8.1 for a listing of trials conducted for T2D that contributed to the safety database for this NDA.

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Table 2. Listing of Clinical Trials Relevant to the Proposed Indication (Chronic Weight Management)

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
<i>Controlled Studies to Support Efficacy and Safety</i>								
18F-MC-GPHK SURMOUNT-1	NCT04184622	Randomized (1:1:1:1), double-blind, placebo-controlled, 4-arm, parallel group, multi-center, multinational trial assessing the efficacy and safety of tirzepatide 5, 10, or 15 mg weekly vs placebo as an adjunct to reduced calorie diet and increased physical activity. Included DXA and ABPM sub-studies.	Tirzepatide initiated at 2.5 mg SQ weekly for 4 weeks, increasing by 2.5 mg every 4 weeks to maintenance dosages of 5, 10, or 15 mg weekly	Co-primary: % change from baseline in body weight Subjects who achieve body weight reduction $\geq 5\%$ from baseline	72-week treatment, 4-week follow-up (Prediabetes extension ongoing)	2539	Adults with obesity (BMI ≥ 30 kg/m ²), or overweight (BMI ≥ 27 to <30 kg/m ²) and at least 1 weight-related comorbidity, excluding those with diabetes	118 centers, 9 countries (Argentina, Brazil, China, India, Japan, Mexico, Russian Federation, Taiwan, and U.S., including Puerto Rico)
18F-MC-GPHL SURMOUNT-2	NCT04657003	Randomized (1:1:1), double-blind, placebo-controlled, 3-arm, parallel group, multi-center, multinational trial assessing the efficacy and safety of tirzepatide 10 or 15 mg weekly vs placebo as an adjunct to reduced calorie diet and increased physical activity	Tirzepatide initiated at 2.5 mg SQ weekly for 4 weeks, increasing by 2.5 mg every 4 weeks to maintenance dosages of 5, 10, or 15 mg weekly	Co-primary: % change from baseline in body weight Subjects who achieve body weight reduction $\geq 5\%$ from baseline	72-week treatment, 4-week follow-up	938	Adults with T2D and obesity (BMI ≥ 30 kg/m ²), or overweight (BMI ≥ 27 to <30 kg/m ²)	77 centers, 7 countries (Argentina, Brazil, India, Japan, Russian Federation, Taiwan, and U.S. including Puerto Rico)

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		<i>Other studies pertinent to the review of efficacy or safety (e.g., clinical pharmacological studies)</i>						
18F-MC-GPHU	NCT04407234	Open-label fixed sequence study to assess the effect of tirzepatide on the PK profile of acetaminophen, a marker for gastric emptying	Tirzepatide SQ weekly, 5mg on Days 1 and 8, 10mg on Days 15, 22, and 29, 15mg on Day 36 Acetaminophen oral on Days -1, 2, and 37	PK profile of acetaminophen as a marker of gastric emptying	37 days	N=36 (18 with T2D, 18 without T2D)	Adults with overweight or obesity, with or without T2D	One U.S. center

5.2. Review Strategy

I reviewed all the information contained in this document.

I focused my efficacy assessment on the two phase 3 CWM clinical trials GPHK and GPHL. In this review, I mainly present the Applicant's efficacy results, noting where relevant when the FDA Office of Biostatistics (the primary statistical review by Dr. Kyunghhee Song dated October 10, 2023) confirmed or supplemented the analyses. To assess the weight loss of efficacy of the tirzepatide 5 mg weekly dosage in subjects with T2D (since this maintenance dosage was not evaluated in trial GPHL, see Section 6 below), I also reviewed the weight data in the T2D SURPASS 1-5 trials under NDA 215866. The efficacy review also references some analyses and assessments performed by reviewers from the DCOA staff. My review focused primarily on the prespecified primary and key secondary endpoints, trial endpoints that informed the assessment of benefit-risk, and those endpoints being considered for inclusion in product labeling.

My strategy for safety review is detailed in Section 8.1. Briefly, my primary focus for safety review was the two phase 3 CWM trials GPHK and GPHL, which were reviewed both individually and pooled. To confirm and expand upon the Applicant's safety results, I conducted safety analyses myself using the Applicant's datasets. I also considered the Applicant's data and results from subjects with BMI ≥ 27 kg/m² in their T2D phase 2/3 trials. Blinded data (including the Applicant's 120-day safety update) and post-marketing information were reviewed in selected sections of the safety review. In some cases, the safety review references analyses and assessments conducted by reviewers from other FDA offices and divisions, including OBP, OCP, Office of Surveillance and Epidemiology (OSE), DPT, and Division of Pediatrics and Maternal Health (DPMH).

6. Review of Relevant Individual Trials Used to Support Efficacy

This NDA includes two adequate and well-controlled trials intended to show substantial evidence of effectiveness of tirzepatide for CWM. Trials GPHK (SURMOUNT-1) and GPHL (SURMOUNT-2) are similar in design with two key differences:

- SURMOUNT-1 excluded subjects with diabetes and SURMOUNT-2 exclusively enrolled subjects with T2D.
- SURMOUNT-1 had four arms (placebo and tirzepatide 5, 10, and 15 mg weekly), while SURMOUNT-2 had three arms (placebo and tirzepatide 10 mg and 15 mg weekly), not studying the 5 mg dosage.

Since these two trials are otherwise similar in design, eligibility criteria, and endpoints, they will be described concurrently in Section 6.1, rather than in individual sections, to avoid unnecessary repetition.

6.1. Trials 18F-MC-GPHK and 18F-MC-GPHL (SURMOUNT-1 and -2)

6.1.1. Study Design

Overview and Objective

Trial GPHK

Full Title: Efficacy and Safety of Tirzepatide Once Weekly in Participants without Type 2 Diabetes Who Have Obesity or Are Overweight with Weight-Related Comorbidities: A Randomized, Double-Blind, Placebo-Controlled Trial (SURMOUNT-1)

Short Title: Efficacy and Safety of Tirzepatide Once Weekly Versus Placebo in Participants Who are either Obese or Overweight with Weight-Related Comorbidities (SURMOUNT-1)

Trial GPHK is the larger of the two phase 3 safety and efficacy trials in this NDA, designed to demonstrate that tirzepatide administered SC at dosages of 5 mg, 10 mg, or 15 mg once-weekly as an adjunct to reduced-calorie diet and increased physical activity, is effective (reduces body weight) and safe for the treatment of patients with overweight or obesity. Secondary objectives were to assess the effects of tirzepatide on cardiovascular risk factors (lipids, blood pressure, glucose metabolism), clinical outcome assessments, and other factors related to body weight.

Trial GPHL

Full Title: Efficacy and Safety of Tirzepatide Once Weekly in Participants with Type 2 Diabetes Who Have Obesity or Are Overweight: A Randomized, Double-Blind, Placebo-Controlled Trial (SURMOUNT-2)

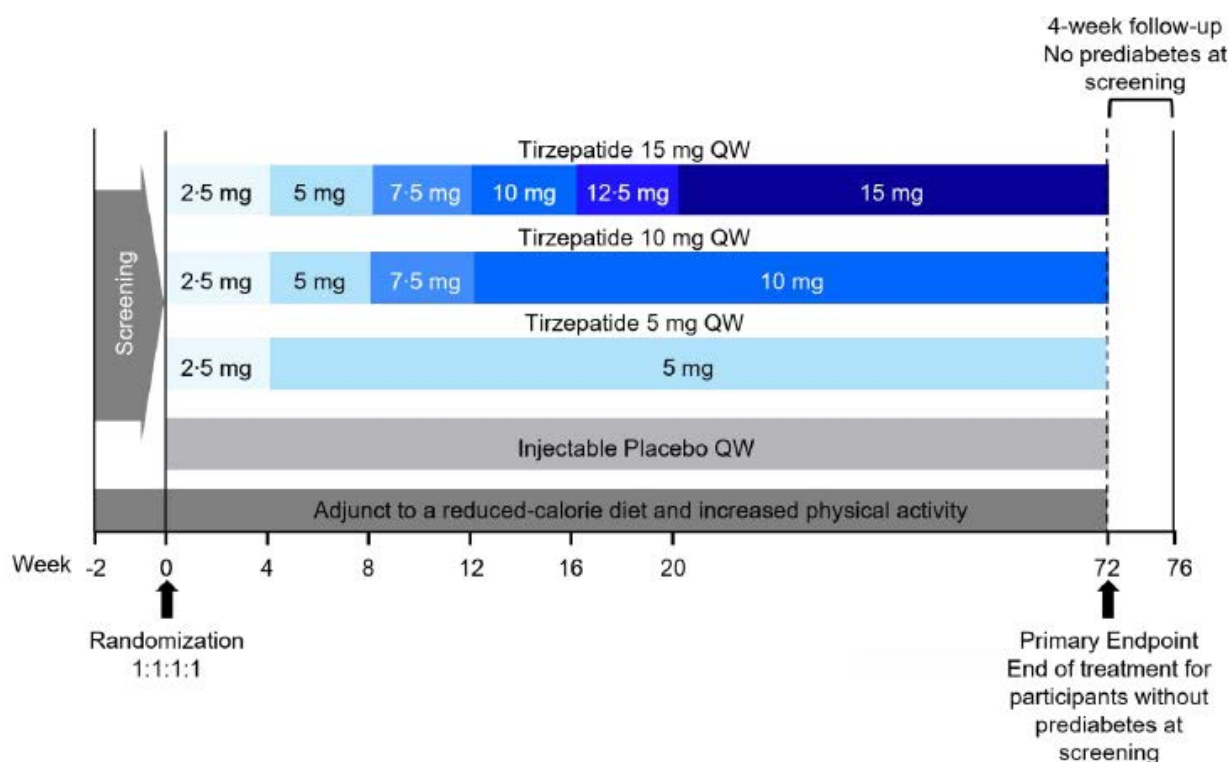
Short Title: Effect of Tirzepatide versus Placebo in Participants with Type 2 Diabetes Who Have Obesity or Are Overweight (SURMOUNT-2)

Trial GPHL shares objectives with GPHK, except in an overweight/obesity population exclusively with T2D, and not testing the tirzepatide 5 mg weekly dosage.

Trial Design

Basic study design: Trial GPHK included a 72-week randomized, double-blinded, four-arm, placebo-controlled main phase (Figure 2) and a 104-week treatment extension for subjects with prediabetes at baseline. Only the 72-week main phase was included in this NDA, as the extension phase is ongoing. The design of the 72-week main phase is typical for CWM trials (while the extension proposes to address progression of prediabetes to diabetes).

Figure 2. Study Design Diagram for Main Phase of Trial GPHK (SURMOUNT-1)



Abbreviations: QW = once weekly; T2DM = type 2 diabetes mellitus;
T2P = tirzepatide.

Note: All participants were randomized to at least 72 weeks of treatment to study the effects on body weight reduction. Participants who had prediabetes at randomization will be studied for a total of 176 weeks of treatment to provide sufficient follow-up time to detect potential differences in progression to T2DM.

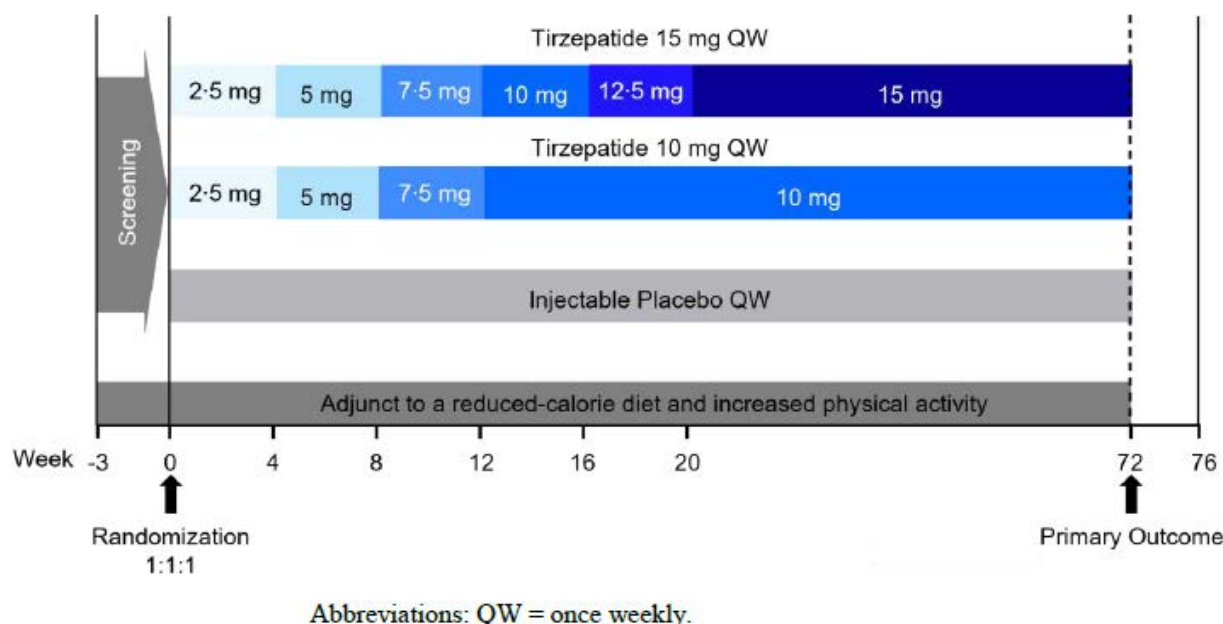
Source: Applicant SCE, Figure 2.7.3.1, page 21 of 123

Trial GPHK also included two sub-studies (reviewed in Section 8.7):

- The Dual-Energy X-ray Absorptiometry (DXA) Addendum involved body composition DXA scans performed at Baseline and Week 72 (or early termination) in a subset of subjects.
- The ABPM addendum involved 24-hour monitoring at Baseline and Week 36 in a subset of subjects.

Trial GPHL has a similar design (Figure 3) to the 72-week main phase of GPHK, without the sub-studies or 2-year treatment extension.

Figure 3. Study Design Diagram for Trial GPHL (SURMOUNT-2)



Source: Applicant SCE, Figure 2.7.3.15, page 50 of 123

Trial locations: Both trials GPHK and GPHL were multicenter, multinational trials with sites primarily in the United States (U.S.), Central and South America including Mexico, and Asia. Although some sites were outside the U.S., the results are applicable to the U.S. population as described in Section 6.1.2.

Choice of control group: In trials GPHK and GPHL, a placebo control arm is reasonable and typical for current CWM trials to support approval.

Diagnostic criteria: Both trials used standard definitions of obesity ($\text{BMI} \geq 30 \text{ kg/m}^2$) and overweight ($\text{BMI} \geq 27 \text{ kg/m}^2$) with weight-related complications for enrollment. In trial GPHL, the definition of T2D diagnosis for enrollment relies on World Health Organization (WHO) classification or other locally applicable standards.

Key inclusion/exclusion criteria: As noted above, the key difference between trials GPHK and GPHL is the exclusion or inclusion, respectively, of subjects with T2D: subjects with T2D were ineligible in GPHK (though subjects with prediabetes were allowed) and only subjects with T2D were eligible in GPHL. Both trials excluded subjects with type 1 or other forms of diabetes.

Both trials GPHK and GPHL enrolled subjects with obesity ($\text{BMI} \geq 30 \text{ kg/m}^2$). Trial GPHK also enrolled overweight ($\text{BMI} \geq 27$ and $< 30 \text{ kg/m}^2$) subjects with one or more weight-related comorbidities (hypertension, dyslipidemia, OSA, or cardiovascular disease), while any subject

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with BMI ≥ 27 kg/m² was eligible for trial GPLH since T2D is a weight-related comorbidity.

Trial GPLH included subjects with well-controlled T2D only (HbA1c 7-10%, inclusive, no recent severe hypoglycemia or hyperglycemia) treated by lifestyle alone or with any oral antihyperglycemic drugs, excluding DPP-4 inhibitors, insulin, and any oral or injectable GLP-1R agonist. A dilated fundoscopic exam was required during the screening period of trial GPLH to exclude those with proliferative diabetic retinopathy, diabetic macular edema, or nonproliferative diabetic retinopathy requiring acute treatment.

Both trials enrolled adult (age ≥ 18 years) subjects, with male and female subjects using defined and appropriate contraception as necessary to avoid pregnancy in women of child-bearing potential who are subjects or partners of male subjects.

Key exclusions in both trials were typical for CWM trials:

- secondary causes of obesity or weight gain (endocrine, monogenic, syndromic, certain medications, tetrahydrocannabinol [THC]), or abnormal TSH
- change in body weight >5 kg within 3 months of screening, or prior/planned surgical, endoscopic, or device treatment for obesity
- renal impairment (estimated glomerular filtration rate [eGFR] <30 mL/min/1.73m²)
- uncontrolled hypertension, congestive heart failure (NYHA class IV), heart attack or stroke within 3 months
- active or untreated malignancy (except for defined low-risk cancers), or remission for less than 5 years
- chronic hepatitis or abnormal liver chemistry (alanine transaminase [ALT] >3 x ULN, though NAFLD was allowed)
- active or unstable severe psychiatric disorder within 2 years, lifetime history of suicide attempt, abnormal scores on standard psychiatric screen instruments (detailed in Section 8.5.9 below), diagnosed eating disorder, or substance abuse
- hematologic conditions that could interfere with HbA1c measurement (such as hemolytic or sickle cell anemia)

Both trials also have typical exclusions for incretins based on known safety issues detailed in Section 8.5 below:

- severe GI disease including gastroparesis
- history of pancreatitis
- elevated calcitonin, or personal or family history of MTC or multiple endocrine neoplasia type 2 (MEN2, a rare familial cancer syndrome that includes MTC).

In general, these exclusions are appropriate and currently standard for CWM trials. A small minority of the treatment population for obesity in the U.S. is likely excluded from this trial population (for instance, due to the renal, psychiatric, liver, and pancreatic criteria).

Dose selection: The Applicant justifies dose selection in both trials based on exposure-response modeling in phase 1 and 2 studies to predict weight loss. In general, dose selection for incretins balances efficacy versus GI tolerability, and dose selection for tirzepatide in these trials appears reasonable, with a sufficiently broad ranges of dosages studied in early phase trials.

The 5 mg weekly dosage was studied in trial GPHK and in the development of tirzepatide for T2D, but not in trial GPHL, which the Applicant justifies since this dosage was considered unlikely to address the unmet need for >10% weight loss in patients with T2D (note also that patients with T2D can already take approved tirzepatide at this dosage for glycemic control).

Study treatments: In both trials, tirzepatide was administered SC once weekly, with dose-escalation for improved GI tolerability, starting at 2.5 mg weekly and increasing the dose by 2.5 mg every four weeks (to 5, 7.5, 10, 12.5, and 15 mg). Therefore, in the three treatment arms, the maintenance dosages of 5 mg, 10 mg, and 15 mg weekly were reached at Week 4, Week 12, and Week 20, respectively (Table 3). This dose escalation was developed in early phase studies of tirzepatide, notably phase 2 trial GPGF to investigate the impact of different starting doses and escalation regimens on tolerability. Subjects were also instructed at randomization on study drug administration via auto-injector device (single dose prefilled pen).

Table 3. Tirzepatide Dose Escalation Schedule in Trials GPHK and GPHL

Treatment Group	Treatment Period Intervals					
	Weeks 0 to 4	Weeks 4 to 8	Weeks 8 to 12	Weeks 12 to 16	Weeks 16 to 20	Week 20 through End of Treatment Period
TZP 5 mg ^a	2.5 mg	5 mg	5 mg	5 mg	5 mg	5 mg
TZP 10 mg	2.5 mg	5 mg	7.5 mg	10 mg	10 mg	10 mg
TZP 15 mg	2.5 mg	5 mg	7.5 mg	10 mg	12.5 mg	15 mg

Abbreviation: TZP = tirzepatide.

^a TZP 5 mg was a maintenance dose in SURMOUNT-1 but was not a maintenance dose in SURMOUNT-2.

Note 1: Bolded text indicates participants were taking their final assigned dose.

Source: Applicant SCE, Table 2.7.3.2, page 16 of 123

Reviewer comment: Note the 2.5, 7.5, and 12.5 mg dosages were only used for 4-week periods during dose escalation and were not used for maintenance, nor for dose reduction as described below. This trial design element has implications for Section 2 of labeling (Dosage and Administration), as described in Section 10 below.

Dietary restrictions/instructions: Tirzepatide was developed for CWM as an add-on treatment to a reduced calorie diet and increased physical activity. All subjects received an initial consultation with a qualified dietician to set lifestyle goals (hypocaloric diet with energy deficit of 500 kcal/day based on estimated total expenditure, physical activity ≥150 minutes per week)

that were reinforced by the dietician during study visits. For all study visits, subjects were to be fasting for approximately 8 hours without eating or drinking (except water), for accurate measurement of body weight and fasting laboratory values (such as lipids, glucose, insulin, and fatty acids). These dietary instructions are reasonable.

Assignment to treatment: Randomization procedures involved a computer-generated random sequence via an interactive web response system (IWRS). In trial GPHK, randomization was 1:1:1:1 to placebo or one of the three tirzepatide arms (5, 10, or 15 mg), stratified by country, sex, and prediabetes status. Trial GPHL randomized subjects 1:1:1 to placebo or tirzepatide 10 or 15 mg, stratified by country, sex, and types of medication(s) used for T2D (categorized by potential impact on weight):

- significant weight loss: SGLT2 inhibitor alone or combined with any except a sulfonylurea or thiazolidinedione (TZD)
- significant weight gain: sulfonylurea alone or combined with any except an SGLT2 inhibitor, or TZD alone or combined with any except an SGLT2 inhibitor
- weight neutral or others: lifestyle only, metformin monotherapy, or other combinations not above.

Reviewer comment: This stratification based on the anticipated weight effects of antihyperglycemic medications is reasonable to help ensure that background therapy is not confounding the weight effects of tirzepatide in subjects with T2D. There is still potential for confounding due to initiation of rescue therapy for hyperglycemia, as described below.

Blinding: Investigators, site staff, clinical monitors, and participants were blinded to the treatment assignments until the trial was complete. A limited number of Applicant individuals were unblinded to treatment assignments as needed for interim safety analyses provided to the external DMC, but this unblinded information was not communicated to study sites or the blinded study team unless necessary for subject safety.

Placebo was administered in the same auto-injector with a sham dose escalation to ensure blinding. There is potential for unblinding of subjects and investigators based on GI tolerability issues typical of tirzepatide and other incretin mimetic drugs, glycemic control in subjects with T2D (trial GPHL), and weight loss (which, unlike lab-based endpoints, may be directly observed by subjects). Nevertheless, because the primary endpoint of body weight reduction is based on objective scale-based measurements in clinic, any observed treatment effect is unlikely to be susceptible to bias from unblinding.

Dose modification or discontinuation: Both trial protocols pre-specified detailed procedures for dose interruption, reduction, and discontinuation.

For management of subjects with intolerable GI symptoms, prior to dose changes subjects were initially counselled on dietary behaviors (i.e., smaller meals) and could be prescribed

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symptomatic medications (antiemetic or antidiarrheal). Temporary interruptions of one dose were allowed for subjects who had taken the previous three weekly doses, with resumption of the assigned dose. If intolerable GI symptoms persisted, study drug could be resumed at the next-lowest maintenance dose (15 to 10 mg, 10 mg to 5 mg, 5 mg to placebo) in blinded manner, with only one such dose reduction allowed per subject in the entire study. These procedures are reasonable and justified by known GI tolerability issues for tirzepatide and incretin mimetics.

The trial protocol addressed other temporary interruptions (due to subject nonadherence, investigator judgement, or AEs), with resumption of the last administered dose (maintenance dose or per escalation schedule) if ≤ 2 doses were missed, and if ≥ 3 doses were missed restarting at 5 mg and repeating the blinded dose escalation.

The criteria for permanent study discontinuation were reasonable and included:

- diagnoses of drug hypersensitivity, type 1 diabetes, MTC, pancreatitis, malignancy, or pregnancy
- predefined elevations in serum calcitonin
- BMI ≤ 18.5 kg/m² reached during treatment
- Serious or significant AEs
- Suicidal ideation or behavior
- Liver events or blood test abnormalities (with detailed procedures for data collection and follow-up).

Administrative structure: Trial GPHK (but not GPHL) included an independent data monitoring committee (DMC) to review unblinded interim safety results. Both trials used a clinical events committee (CEC) to adjudicate deaths, MACE events, and pancreatitis.

Procedures and schedule: Trials GPHK (72-week main phase) and GPHL each included:

- a two-week screening period
- a 72-week primary treatment period, with in-person visits at Weeks 4, 8, 16, 20, 24, 36, 48, 60, and 72, and with early discontinuation if necessary. There were also telephone visits scheduled at Weeks 28, 32, 40, 44, 52, 56, 64, and 68.
- a 4-week treatment withdrawal period, with one safety follow-up visit 4 weeks after the last dose of study drug to account for the long half-life

In trial GPHK, subjects with prediabetes at baseline continued for an additional 2-year treatment period and this extension is ongoing, so 4-week safety follow-up for these subjects was not part of the current application.

Concurrent medications: As noted above, both trials excluded subjects on medications associated with weight gain (except for weight gain-associated medications for T2D allowed in trial GPHL but part of the stratification scheme), including systemic glucocorticoids and certain tricyclic antidepressants, atypical antipsychotics, and mood stabilizers used within 3 months of

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screening. Medications for weight loss (including other incretins, stimulants, orlistat, phentermine/topiramate, and bupropion/naltrexone) were also not permitted within 3 months of screening or during the study period.

In trial GPHK, metformin or any other glucose-lowering medications (even if used for other reasons) were not permitted, thus excluding other GLP-1R agonists, DPP4 inhibitors, and SGLT2 inhibitors.

Trial GPHL allowed oral glucose-lowering medications for T2D as detailed above in inclusions/exclusions, with insulin secretagogues like sulfonylureas having their doses halved at randomization (or discontinued if at the lowest dose) to minimize risk of hypoglycemia.

Treatment compliance: Compliance was assessed at each study in-person and telephone visit, with questioning and counting of unused study drug or empty cartons returned.

Rescue medication: Rescue medications for weight management were not permitted in either trial.

In trial GPHK, subjects who developed T2D during the study could initiate medications for glucose control with their usual care provider, including metformin but excluding GLP-1R agonists or DPP-4 inhibitors.

Since tirzepatide can cause hypoglycemia, all subjects in trial GPHL and those in GPHK who developed T2D during the trial were provided with a glucometer, glucose log, and device training, and educated on hypoglycemia signs, symptoms, and treatment.

In trial GPHL, new antihyperglycemic medications or dose adjustment of existing medication were rescue therapy for severe, persistent hyperglycemia, defined appropriately in the protocol depending on the time in the treatment period:

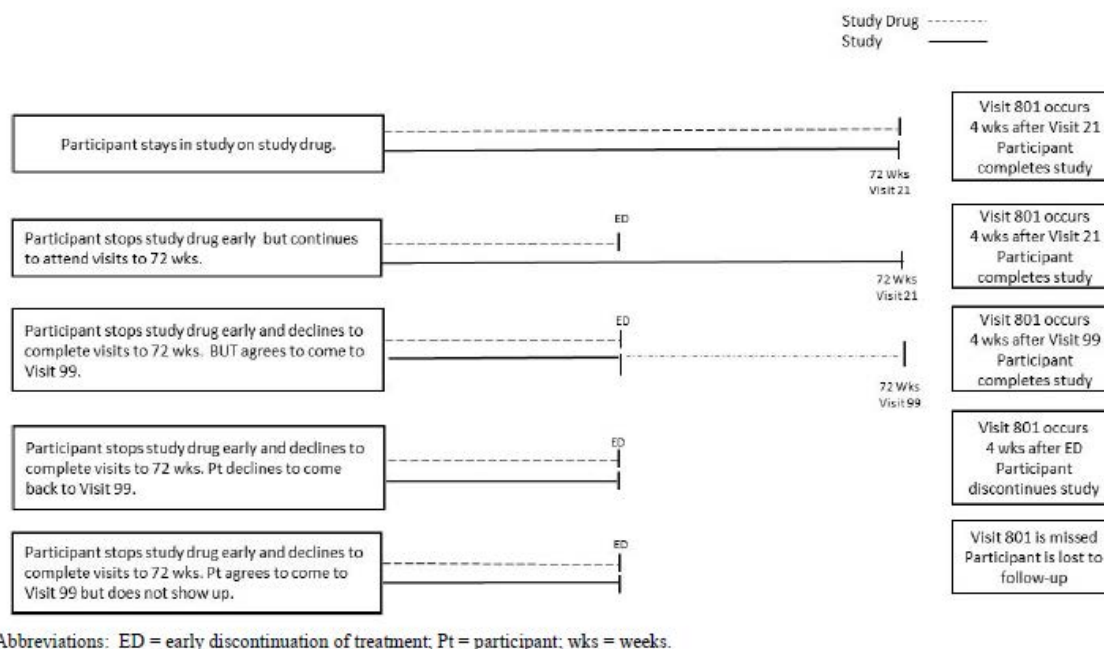
- 2 confirmed glucose values >270 mg/dl over 2 weeks during Weeks 0-8
- 2 confirmed glucose values >240 mg/dl over 2 weeks during Weeks 9-16
- 2 confirmed glucose values >200 mg/dl over 2 weeks during Week 16 or later
- HbA1c ≥ 8.5% during Week 24 or later.

Rescue therapy was at the discretion of the investigator or usual care provider (excluding GLP-1R agonists, DPP-4 inhibitors, or amylin analogues), with metformin recommended for subjects initially treated with lifestyle only and basal insulin considered for subjects already receiving ≥ 3 oral medications.

Subject completion, discontinuation, or withdrawal: The primary analysis in both trials was performed in a mITT population of all randomized subjects who receive at least one dose of study drug, regardless of whether there was discontinuation from the study drug or the study. Withdrawn subjects were not replaced. There were adequate procedures to assure safety

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follow-up and trial completion for subjects who discontinued study drug or study (Figure 4).

Figure 4. Trial Completion and Timing of Safety Follow-up for the Primary Endpoint (Trials GPHK and GPHL)



Source: Applicant GPHK protocol (b), page 65 of 131, and GPHL protocol, page 53 of 121

Reviewer comment: FDA recommends an ITT population rather than mITT. In trials GPHK and GPHL, the mITT populations were equivalent to ITT since they included all randomized subjects (see Table 7 below).

Study Design Conclusion: Overall, trials GPHK and GPHL were robustly designed, consistent with the Division's guidance and advice, to yield interpretable study results.

Study Endpoints

Table 4 summarizes the primary, key secondary, and secondary endpoints (abbreviated P, KS, and S, respectively) in trials GPHK and GPHL. The endpoints differ by tirzepatide dosage arms, with some endpoints tested in individual dosage arms and others in pooled dosage arms. These endpoints in the two individual trials are defined and further detailed below.

Table 4. Summary of Trial GPHK and GPHK Endpoints by Tirzepatide Dosage Arms

Trial Endpoints	Tirzepatide Dosage(s) compared to Placebo							
	GPHK /SURMOUNT-1					GPHL /SURMOUNT-2		
	5 mg	10 mg	15 mg	10, 15 mg	5, 10, 15 mg	10 mg	15 mg	10, 15 mg
Weight-related								
Percent change in body weight	KS	P	P			P	P	
Proportion achieving ≥5% reduction	KS	P	P			P	P	
Proportion achieving ≥10% reduction	S	KS	KS			KS	KS	
Proportion achieving ≥15% reduction	S	KS	KS			KS	KS	
Proportion achieving ≥20% reduction		KS	KS			KS	KS	
Waist circumference	S	KS	KS			KS	KS	
Percent change in body weight (week 20)				KS				
Body weight and BMI	S	S	S			S	S	
Patient-reported outcomes								
SF-36v2 Physical Functioning	S			KS		S	S	
IWQOL-Lite-CT Physical Function	S	S	S			S	S	
EQ-5D-5L utility and VAS scores						S	S	
Lipid-related								
TG, HDL-C, non-HDL-C					KS			KS
total cholesterol, LDL-C, VLDL-C, fatty acids					S			S
Blood-pressure related								
Systolic Blood Pressure					KS			KS
Diastolic Blood Pressure					S			S
Glycemia-related								
Fasting insulin					KS	S	S	
Fasting glucose	S	S	S			KS	KS	
HbA1c	S	S	S			KS	KS	
Proportion achieving HbA1c <7%, ≤6.5%, <5.7%						KS	KS	
7-point self-monitored blood glucose profiles						S	S	

Source: generated by reviewer from GPHK and GPHL CSRs

Abbreviations: P, primary; KS, key secondary; S, secondary

Note: all endpoints compare change from randomization to Week 72, except the noted Week 20 endpoint

Trial GPHK

In trial GPHK, the co-primary efficacy endpoints tested for superiority of tirzepatide 10 mg to placebo and/or tirzepatide 15 mg to placebo:

- Percent change in body weight from randomization to Week 72
- Proportion of subjects achieving a weight loss of ≥ 5% from randomization to Week 72.

Key secondary endpoints controlled for Type I error (for the primary 72-week treatment period) fell into 4 classes:

- Superiority of tirzepatide 5 mg to placebo for the two Week 72 endpoints above
- Superiority of tirzepatide 10 mg and/or 15 mg doses to placebo for:
 - Proportion of subjects achieving a weight loss of ≥10%, ≥15%, or ≥20% from randomization to Week 72

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- Change in waist circumference (cm) from randomization to Week 72
- Pooled dose analyses for tirzepatide 10 mg and 15 mg versus placebo:
 - Percent change in body weight from randomization to Week 20
 - Change in SF-36v2 acute form Physical Functioning domain score from randomization to Week 72
- Pooled dose analyses for all tirzepatide doses versus placebo, changes from randomization to Week 72 in:
 - Lipid parameters (mg/dL): triglycerides, non-HDL and HDL cholesterol
 - Systolic blood pressure (mmHg)
 - Fasting insulin (pmol/L)

Additional secondary endpoints not controlled for Type I error included:

- Superiority of tirzepatide 5 mg to placebo for other Week 72 endpoints not tested above:
 - Proportion of subjects achieving a weight loss of $\geq 10\%$ or $\geq 15\%$ (note that $\geq 20\%$ was not tested for this dosage)
 - Change in waist circumference
 - Change in SF-36v2 acute form Physical Functioning domain score
- Superiority of tirzepatide 5 mg, 10 mg and/or 15 mg doses to placebo for:
 - Body weight (kg) and BMI (kg/m^2)
 - HbA1c (%) and fasting glucose (mg/dL)
 - IWQOL-Lite-CT Physical Function composite score
- Pooled analyses of all tirzepatide doses versus placebo, changes from randomization to Week 72 in:
 - Diastolic blood pressure
 - Additional lipid parameters (mg/dL): free fatty acids; total, LDL, and VLDL cholesterol
- Population PK and PD parameters

Trial GPLH

In trial GPLH, all endpoints were from randomization to Week 72. The co-primary efficacy endpoints tested for superiority of tirzepatide 10 mg to placebo and/or tirzepatide 15 mg to placebo:

- Percent change in body weight
- Proportion of subjects achieving a weight loss of $\geq 5\%$.

Key secondary endpoints controlled for Type I error fell into 3 classes:

- Superiority of tirzepatide 10 mg and/or 15 mg doses to placebo for:
 - Proportion of subjects achieving a weight loss of $\geq 10\%$, $\geq 15\%$, or $\geq 20\%$
 - Change in waist circumference (cm)
 - Change in HbA1c (%) and fasting glucose (mg/dL)
 - Proportion of subjects achieving HbA1c $< 7\%$, $\leq 6.5\%$, or $< 5.7\%$

- Pooled dose analyses for tirzepatide 10 mg and 15 mg versus placebo, change in:
 - Lipid parameters (mg/dL): triglycerides, non-HDL and HDL cholesterol
 - Systolic blood pressure (mmHg)

Additional secondary endpoints not controlled for Type I error included changes in:

- Superiority of tirzepatide 10 mg and/or 15 mg doses to placebo for:
 - Body weight (kg) and BMI (kg/m²)
 - 7-point self-monitored blood glucose profiles
 - Fasting insulin (pmol/L)
 - SF-36v2 acute form Physical Functioning domain score
 - IWQOL-Lite-CT Physical Function composite score
 - EQ-5D-5L utility and VAS scores
- Pooled dose analyses for tirzepatide 10 mg and 15 mg versus placebo, changes in:
 - Diastolic blood pressure
 - Additional lipid parameters (mg/dL): free fatty acids; total, LDL, and VLDL cholesterol
- Population PK and PD parameters

Endpoints conclusion

The choice of endpoints and their timing at Week 72 (after 52 weeks at the highest 15 mg tirzepatide maintenance dosage) is consistent with FDA guidance¹⁶ and the Division's expectations. Body weight (reported as % change from baseline) has been used previously as a basis for full approval, and other endpoints on glycemia, lipids, blood pressure, and physical function are supportive.

The physical function endpoints were measured by patient-reported outcome (PRO) instruments (see details in Section 6.1.2 below), and the FDA DCOA was consulted to assist in review of these.

Reviewer comment: As discussed below in Section 10, there are potential labeling implications to the Applicant's choice to treat the 5 mg dosage differently from the 10 and 15 mg dosages for statistical testing of endpoints in trial GPHK, and to exclude this 5 mg dosage from trial GPHL.

Statistical Analysis Plan

The SAPs for both trials were finalized before results were known. In trial GPHK, the sample size calculation for 2,400 randomized subjects (600 each to the four arms) assumed ≥11% placebo-

¹⁶ FDA Guidance for Industry "Developing Products for Weight Management," 2007 draft guidance

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corrected body weight loss on tirzepatide 10 mg or 15 mg at Week 72, with a common standard deviation of 10% and dropout rate of 10%, giving >90% power to show superiority to placebo.

In trial GPHK, the sample size calculation for 900 subjects (randomized 300 each to the two arms) had the same assumptions, giving >90% power to show superiority to placebo.

In both trials, the Applicant conducted analyses for all primary and key secondary efficacy endpoints at Week 72 using two different estimands:

- For submission to FDA, the Applicant used a “hybrid” estimand, defined as the average treatment effect of tirzepatide relative to placebo at Week 72, as an adjunct to a reduced-calorie diet and increased physical for the randomized participants regardless of the adherence to study drug.
- For other regulatory agencies, publications, and other purposes, the Applicant also used an “efficacy” estimand, defined as the average treatment effect of tirzepatide relative to placebo at Week 72, as an adjunct to a reduced-calorie diet and increased physical activity, in the randomized participants had they remained on their randomized treatment for the entire planned 72-week treatment duration.

The hybrid estimand in an ITT population is consistent with FDA expectation that the analysis includes all randomized subjects without consideration of adherence or intercurrent events.

Please refer to the statistical review by Dr. Kyunghye Song dated October 10, 2023, for a detailed discussion of the Statistical Analysis Plans (SAPs), including the multiplicity correction and approaches to missing data.

Protocol Amendments

Trial GPHK had one protocol amendment, dated after the first subject visit (December 4, 2019), that was relevant to this submission. Amendment (b), dated October 4, 2021, modified the key and additional secondary endpoints, mainly changing the analyses by individual dosages versus by pooled dosages and adding the endpoint of $\geq 20\%$ body weight reduction (see Table 4 above, which reflects the final endpoints from this amendment). These minor changes to key secondary endpoints do not impact the integrity of the trial or my interpretation of results.

Trial GPHK had no protocol amendments, and the 3 addenda (to address local regulations at non-U.S. trial sites in India, Brazil, and Taiwan) were considered non-substantial by the Applicant and I agree. However, I noted that some secondary endpoints had minor differences in the trial GPHK CSR compared to the protocol, mainly to make trial GPHL endpoints align with those in GPHK (adding the $\geq 20\%$ weight loss responder analysis and allocating lipid parameters differently to key and additional secondary endpoints) and add diabetes-related endpoints (two lower HbA1c responder analysis thresholds and another PRO). As above for trial GPHK, these minor changes to secondary endpoints do not affect trial integrity or interpretation.

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6.1.2. Study Results

Compliance with Good Clinical Practices

The Applicant attests that trials GPHK and GPHL were conducted in accordance with the protocols, 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 International Council for Harmonisation (ICH) GCP guidelines, and applicable laws and regulations.

Two trials sites for GPHK and GPHL had known or potential GCP noncompliance:

- Site 708 in India had randomized 10 subjects in trial GPHK, and 2 were ongoing, presumably in the prediabetes extension study since the primary study period is completed. The site was closed due to GCP noncompliance, (b) (4), (b) (7)(A)
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- One site in Japan contracting with the contract research organization (b) (4)
(b) (4), (b) (7)(A) had suspected GCP violations (b) (4), (b) (7)(A) This site had 22 randomized subjects in trial GPHK (site 803) and 26 subjects in trial GPHL (site 23220).

The Applicant performed a sensitivity analysis of each trial's primary efficacy endpoints excluding the sites with GCP noncompliance, as detailed below (see below in Section 6.1.2, Data Quality and Integrity).

Financial Disclosure

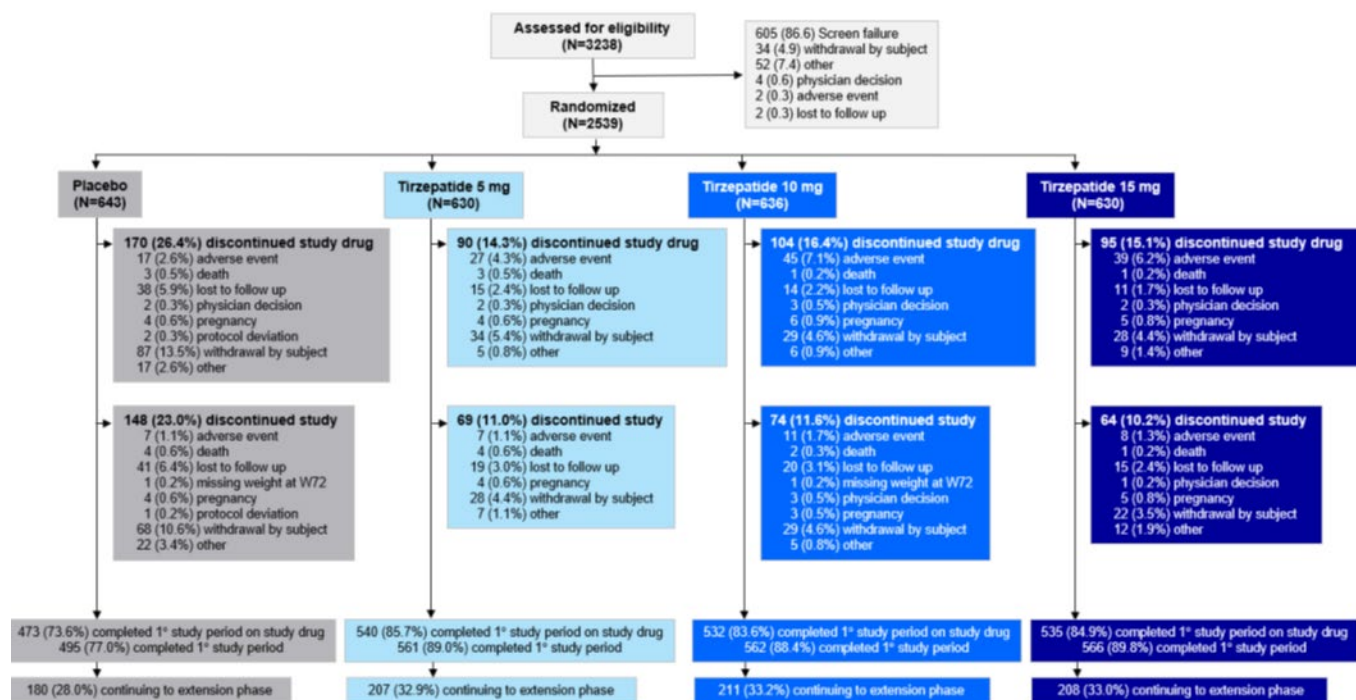
The Applicant submitted Form FDA 3455 reports as detailed in Appendix 13.2 below. For trial GPHK, 7 of 700 investigators (1.0%) reported financial interests/arrangements (mean \$98,194, ranging from \$36,619 to \$150,041), and these investigators enrolled 166 subjects out of 2539 randomized (4.8%). For trial GPHL, 3 of 410 investigators (0.7%) reported financial interests/arrangements (mean \$83,858, range \$40,000 to \$120,00), and these investigators enrolled 166 subjects out of 938 randomized (6.5%). These potential conflicts of interest do not raise significant concerns to me, since the contributions of the investigators with financial issues to overall study data was small, and the study design (randomized, blinded, with objective endpoints) minimized potential bias. There was no undue bias or influence that could affect the outcome of this trial or the review of this NDA.

¹⁷ Per correspondence under IND 139721, sequence number 0180 submitted on September 21, 2023

For trial GPHK, the Applicant's subject disposition flowchart is shown in Figure 5 and confirmed by my analysis of the demographic data (Table 5). 3,238 subjects were assessed for eligibility, and 2,539 were randomized, with 605/3238 (18.7%) not randomized due to screen failures.

Reviewer comment: *I did not review the reasons for screen failure to see which inclusion/exclusion criteria were not met, as this information was not provided in the demographic data in the Applicant's adsl.xpt dataset. However, since ~80% of potential subjects were eligible for enrollment and randomization, this suggests that the eligibility criteria discussed above were not excessively restrictive.*

Figure 5. Trial GPHK Subject Disposition Flowchart



Source: Trial GPHK CSR, Figure GPHK.4.1, page 58 of 2021

Table 5. Study and Treatment Discontinuations in Trial GPHK

	Placebo (N=643)	TZP 5mg (N=630)	TZP 10mg (N=636)	TZP 15mg (N=630)
Completed Study	495 (77.0)	561 (89.0)	562 (88.4)	566 (89.8)
Discontinued Study	148 (23.0)	69 (11.0)	74 (11.6)	64 (10.2)
Adverse event	7 (1.1)	7 (1.1)	11 (1.7)	8 (1.3)
Death	4 (0.6)	4 (0.6)	2 (0.3)	1 (0.2)
Lost to follow-up	41 (6.4)	19 (3.0)	20 (3.1)	15 (2.4)
Missing weight at Week 72	1 (0.2)	0	1 (0.2)	0
Other	22 (3.4)	7 (1.1)	5 (0.8)	12 (1.9)
Physician decision	0	0	3 (0.5)	1 (0.2)
Pregnancy	4 (0.6)	4 (0.6)	3 (0.5)	5 (0.8)
Protocol deviation	1 (0.2)	0	0	0
Withdrawal by subject	68 (10.6)	28 (4.4)	29 (4.6)	22 (3.5)
Completed Treatment	473 (73.6)	540 (85.7)	531 (83.5)	535 (84.9)
Discontinued Treatment	170 (26.4)	90 (14.3)	105 (16.5)	95 (15.1)
Adverse event	17 (2.6)	27 (4.3)	45 (7.1)	39 (6.2)
Death	3 (0.5)	3 (0.5)	1 (0.2)	1 (0.2)
Lost to follow-up	38 (5.9)	15 (2.4)	14 (2.2)	11 (1.7)
Other	17 (2.6)	5 (0.8)	6 (0.9)	9 (1.4)
Physician decision	2 (0.3)	2 (0.3)	3 (0.5)	2 (0.3)
Pregnancy	4 (0.6)	4 (0.6)	6 (0.9)	5 (0.8)
Protocol deviation	2 (0.3)	0	0	0
Withdrawal by subject	87 (13.5)	34 (5.4)	29 (4.6)	28 (4.4)

Source: Generated by Reviewer using data adsl.xpt in OCS Analysis Studio

Trial GPHL subject dispositions are presented below in Table 6. Overall in both trials GPHK and GPHL, treatment and study discontinuations were more common in the placebo arm compared to the tirzepatide arms. The most common reasons for discontinuation in placebo arms were lost to follow-up or withdrawal by subject, while tirzepatide-treated subjects were more likely to discontinue study or treatment due to adverse events.

Table 6. Study and Treatment Discontinuations in Trial GPLH

	Placebo (N=315)	TZP 10mg (N=312)	TZP 15mg (N=311)
Completed Study	281 (89.2)	296 (94.9)	282 (90.7)
Discontinued Study	34 (10.8)	16 (5.1)	29 (9.3)
Adverse Event	5 (1.6)	1 (0.3)	5 (1.6)
Death	0	2 (0.6)	0
Lost to follow-up	8 (2.5)	4 (1.3)	10 (3.2)
Other	3 (1.0)	2 (0.6)	1 (0.3)
Pregnancy	2 (0.6)	0	2 (0.6)
Withdrawal by subject	16 (5.1)	7 (2.2)	10 (3.2)
Completed Treatment	268 (85.1)	283 (90.7)	268 (86.2)
Discontinued Treatment	47 (14.9)	29 (9.3)	43 (13.8)
Adverse Event	12 (3.8)	12 (3.8)	23 (7.4)
Death	0	2 (0.6)	0
Lost to follow-up	7 (2.2)	3 (1.0)	9 (2.9)
Other	4 (1.3)	1 (0.3)	1 (0.3)
Physician decision	0	1 (0.3)	0
Pregnancy	1 (0.3)	0	2 (0.6)
Protocol deviation	2 (0.6)	0	0
Withdrawal by subject	21 (6.7)	10 (3.2)	8 (2.6)

Source: Generated by reviewer using OCS Analysis Studio, Custom Table Tool.

Reviewer comment: Overall discontinuations were fewer in trial GPLH (subjects with T2D) than in trial GPHK (subjects without T2D). Withdrawal by subjects in placebo arms of CWM trials is expected due to lack of efficacy, while discontinuations due to adverse events are expected in treatment arms for incretins due to GI intolerance (see Section 8.4.3 and 8.5.2 below). Overall discontinuation rates in these trials are less than the Applicant's estimate of 25% for power calculations, and less than that observed in most previous CWM trials, so the rates of discontinuation do not raise concerns about trial integrity.

For both trials GPHK and GPLH, all randomized subjects were included in each prespecified analysis set (Table 7). Therefore, no subjects were inappropriately excluded from analyses.

Table 7. Populations Analyzed in Trials GPHK and GPHL

	GPHK	GPHL
Entered subjects	3238	1514
Randomized subject	2539	938
Modified intent-to-treat	2539	938
Efficacy analysis set (EAS)	2539	938
Full analysis set (FAS)	2539	938
Safety analysis set	2539	938

Source: Applicant CSRs, Tables GPHK.4.3 and GPHL.4.2

Protocol Violations/Deviations

Important protocol deviations were assessed and captured in the Trial Issues Management Plan. For both trials GPHK and GPHL, important deviations appeared to be randomly distributed across treatment arms without any obvious or relevant trends. The Applicant concludes 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 detailed below are unlikely to have affected the overall conclusions for trials GPHK and GPHL.

Table 8 summarizes the important protocol deviations in trial GPHK.

Table 8. Important Protocol Deviations in Trial GPHK

	Placebo N=643	TZP 5mg N=630	TZP 10mg N=636	TZP 15mg N=630	Total N=2539
Subjects with ≥1 Important Protocol Deviation	99 (15.4)	82 (13.0)	84 (13.2)	90 (14.3)	355 (14.0)
Eligibility (inclusion/exclusion deviations)	16 (2.5)	17 (2.7)	24 (3.8)	27 (4.3)	84 (3.3)
Informed consent	3 (0.5)	0 (0.0)	1 (0.0)	1 (0.2)	4 (0.2)
Investigational Product	58 (9.0)	55 (8.7)	54 (8.5)	61 (9.7)	228 (9.0)
Safety	4 (0.6)	5 (0.8)	5 (0.8)	5 (0.8)	19 (0.7)
Study procedures	24 (3.7)	12 (1.9)	5 (0.8)	5 (0.8)	46 (1.8)

Source: Generated by reviewer based on Applicant GPHK CSR, Table GPHK.4.2, page 64 of 3021

These protocol violations in trial GPHK are divided into 5 categories:

- Eligibility: 84 subjects (3.3%) overall
 - 28 were related to the main study exclusion criteria, including diabetes at baseline (3), mental health exclusions (6), use of weight gain medications (5), and others not specified (10). 6 subjects reported for pregnancy exclusions in this category were not pregnant during the study, but instead they were not on

required contraception prior to randomization.

- o 56 were related to the ABPM substudy, which required BP <140/90 mmHg for enrollment, but these subjects were inadvertently enrolled based on the main trial eligibility (BP <160/100 mmHg). Thus, these subjects with SBP up to 20 mmHg higher than intended and/or DBP up to 10 mmHg higher than intended participated in the ABPM substudy. I agree with Applicant that this was unlikely to affect subject safety or results of the ABPM substudy.
- Informed consent: 4 subjects (0.2%) overall, with one having informed consent not obtained, requiring site re-training.
- Investigational Product: 228 subjects (9.0%) overall
 - o 151 subjects had incorrect stratification, 84 of them incorrectly stratified as having prediabetes and 39 as having normoglycemia at randomization. This error was corrected by changing the glycemic status, allowing subjects with prediabetes to proceed to the 2-year extension treatment period. 26 patients were incorrectly stratified in the ABPM study (for using or not using heart rate controlling medications), and this error was corrected for the analysis.
 - o 33 subjects had low compliance (<75% through 72 weeks)
 - o 38 subjects had dosing errors (two or more study drug injections within 24 hours, indicating potential overdose, see Section 8.8.4)
 - o Other deviations in this category were rare (3 dispensing error, 6 taking medication not fit for use)
- Safety: 19 subjects (0.7%) overall
 - o 17 subjects for pregnancy during the study, including 16 female subjects (who all discontinued study drug) and 1 female partner of a male subject. 3 additional pregnancies in the trial were not captured as protocol deviations.
 - o There was 1 delay in reporting a serious event (>24 hours) and 1 other unspecified deviation in this category.
- Study procedures: 46 subjects (1.8%) overall
 - o These mainly involved prohibited concomitant therapies: 6 subjects used metformin without a diagnosis of T2D, 14 subjects used weight gain-promoting medications, 4 subjects used weight-loss medications (3 in the placebo group and 1 in the tirzepatide 10 mg group), 6 subjects used GLP-1R agonists (liraglutide or semaglutide)
 - o 14 subjects had missing body weight at Week 72
 - o 4 subjects violated unspecified discontinuation criteria

For trial GPLH, Table 9 shows the important protocol violations. The Applicant's CSR for this trial provided fewer details than for trial GPHK, but the deviation categories are similar overall.

Table 9. Important Protocol Deviations in Trial GPLH

Protocol Deviation	Placebo (N=315)	T2P 10mg (N=312)	T2P 15mg (N=311)	Total (N=938)
Category	n (%)	n (%)	n (%)	n (%)
Subjects with ≥1 Important Protocol Deviation	65 (20.6)	40 (12.8)	60 (19.3)	165 (17.6)
Protocol Deviation	65 (20.6)	40 (12.8)	60 (19.3)	165 (17.6)
Concomitant Medication	6 (1.9)	4 (1.3)	3 (1.0)	13 (1.4)
Discontinuation Criteria	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.1)
Eligibility Criteria	4 (1.3)	5 (1.6)	13 (4.2)	22 (2.3)
Informed Consent	13 (4.1)	8 (2.6)	14 (4.5)	35 (3.7)
Investigational Medicinal Product and/or Investigational Device	9 (2.9)	4 (1.3)	5 (1.6)	18 (1.9)
Safety Reporting	4 (1.3)	1 (0.3)	4 (1.3)	9 (1.0)
Study Procedure Compliance	16 (5.1)	9 (2.9)	18 (5.8)	43 (4.6)
Treatment Assignment/Randomization	18 (5.7)	13 (4.2)	12 (3.9)	43 (4.6)

Abbreviations: N = number of subjects in analysis population; n = number of subjects in the specified category; IP = investigational product; T2P = tirzepatide.
Percentages are based on the treatment column denominator, N.

Source: Applicant GPLH CSR, Table GPLH.4.1, page 52 of 3056

The Applicant also reviewed the protocol deviations attributable to the COVID-19 pandemic, of which the great majority were minor. Two important deviations due to COVID-19 occurred in trial GPHK (one subject was missing Week 72 weight due to COVID-19, and one subject enrolled in another clinical trial [for a COVID-19 vaccine]), and none occurred in trial GPLH.

One serious trial breach was described by the Applicant for trial GPLH:

- “On (b) (6), Site 72763 confirmed that the study binder for Subject Number (b) (6) was missing. This finding was considered a serious breach, based on the impact to the rights of the trial participants and potential risk related to the integrity of this participant’s data. The site recreated the study binder to the best of their ability. The participant was reevaluated to confirm that they were medically appropriate to stay on study drug and any AEs were managed appropriately. Lilly offices for privacy and data protection were informed of the situation on (b) (6). Corrective and preventive action was developed and implemented. The participant was informed about the loss of information. The issue was determined to not have a significant impact to the trial data.”

In conclusion, the important protocol deviations, COVID-19 disruptions, and one trial breach were unlikely to affect the results of trials GPHK and GPLH.

Table of Demographic Characteristics

Table 10 shows the demographic characteristics in the phase 3 tirzepatide CWM trials GPHK and GPLH.

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NDA 217806
Zepbound (tirzepatide)

Table 10. Demographic Characteristics for the Primary Efficacy and Safety Analysis Populations (Trials GPHK and GPHL)

	GPHK / SURMOUNT-1		GPHL / SURMOUNT-2		Total	
	Placebo (N=643)	TZP All (N=1896)	Placebo (N=315)	TZP All (N=623)	Placebo (N=958)	TZP All (N=2519)
Sex						
Female	436 (67.8)	1278 (67.4)	159 (50.5)	317 (50.9)	595 (62.1)	1595 (63.3)
Male	207 (32.2)	618 (32.6)	156 (49.5)	306 (49.1)	363 (37.9)	924 (36.7)
Age, years						
Mean (SD)	44.4 (12.54)	45.0 (12.43)	54.7 (10.45)	54.0 (10.65)	47.8 (12.83)	47.3 (12.62)
Median (Min, Max)	44.0 (18, 78)	45.0 (18, 84)	55.0 (18, 80)	55.0 (22, 85)	49.0 (18, 80)	48.0 (18, 85)
Age Group, n (%)						
<65	609 (94.7)	1778 (93.8)	258 (81.9)	515 (82.7)	867 (90.5)	2293 (91.0)
>=65	34 (5.3)	118 (6.2)	57 (18.1)	108 (17.3)	91 (9.5)	226 (9.0)
Ethnicity, n (%)						
Hispanic or Latino	310 (48.2)	904 (47.7)	188 (59.7)	373 (59.9)	498 (52.0)	1277 (50.7)
Not Hispanic or Latino	281 (43.7)	842 (44.4)	122 (38.7)	236 (37.9)	403 (42.1)	1078 (42.8)
Not reported	52 (8.1)	150 (7.9)	5 (1.6)	14 (2.2)	57 (5.9)	164 (6.5)
Race, n (%)						
White	450 (70.0)	1342 (70.8)	248 (78.7)	462 (74.2)	698 (72.9)	1804 (71.6)
Asian	71 (11.0)	205 (10.8)	39 (12.4)	86 (13.8)	110 (11.5)	291 (11.6)
Black / African American	55 (8.6)	146 (7.7)	22 (7.0)	55 (8.8)	77 (8.0)	201 (8.0)
American Indian / Alaska Native	58 (9.0)	173 (9.1)	0 (0.0)	0 (0.0)	58 (6.1)	173 (6.9)
Multiple	7 (1.1)	23 (1.2)	5 (1.6)	18 (2.9)	12 (1.3)	41 (1.6)
Native Hawaiian / Pacific Islander	2 (0.3)	7 (0.4)	1 (0.3)	2 (0.3)	3 (0.3)	9 (0.4)
Geographic Region, n (%)						
U.S. (North America)	288 (44.8)	853 (45.0)	114 (36.2)	228 (36.6)	402 (42.0)	1081 (42.9)
Outside U.S.	355 (55.2)	1043 (55.0)	201 (63.8)	395 (63.4)	556 (58.0)	1438 (57.1)
Central/South America and Mexico	260 (40.4)	776 (40.9)	146 (46.3)	289 (46.4)	406 (42.4)	1065 (42.3)
Japan	33 (5.1)	91 (4.8)	21 (6.7)	46 (7.4)	54 (5.6)	137 (5.4)
Asia (excluding Japan)	30 (4.7)	90 (4.7)	17 (5.4)	34 (5.5)	47 (4.9)	124 (4.9)
Rest of World	32 (5.0)	86 (4.5)	17 (5.4)	26 (4.2)	49 (5.1)	112 (4.4)
Country, n (%)						
U.S. (excluding Puerto Rico)	251 (39.0)	780 (41.1)	114 (36.2)	228 (36.6)	365 (38.1)	1008 (40.0)
Argentina	93 (14.5)	271 (14.3)	116 (36.8)	230 (36.9)	209 (21.8)	501 (19.9)
Mexico	108 (16.8)	325 (17.1)	0 (0.0)	0 (0.0)	108 (11.3)	325 (12.9)
Brazil	59 (9.2)	180 (9.5)	30 (9.5)	59 (9.5)	89 (9.3)	239 (9.5)
Japan	33 (5.1)	91 (4.8)	21 (6.7)	46 (7.4)	54 (5.6)	137 (5.4)
Russian Federation	32 (5.0)	86 (4.5)	17 (5.4)	26 (4.2)	49 (5.1)	112 (4.4)
Puerto Rico	37 (5.8)	73 (3.9)	0 (0.0)	0 (0.0)	37 (3.9)	73 (2.9)
Taiwan	15 (2.3)	43 (2.3)	8 (2.5)	17 (2.7)	23 (2.4)	60 (2.4)
India	8 (1.2)	24 (1.3)	9 (2.9)	17 (2.7)	17 (1.8)	41 (1.6)
China	7 (1.1)	23 (1.2)	0 (0.0)	0 (0.0)	7 (0.7)	23 (0.9)

Source: Generated by reviewer using OCS Analysis Studio, Custom Table Tool

Clinical Review

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Zepbound (tirzepatide)

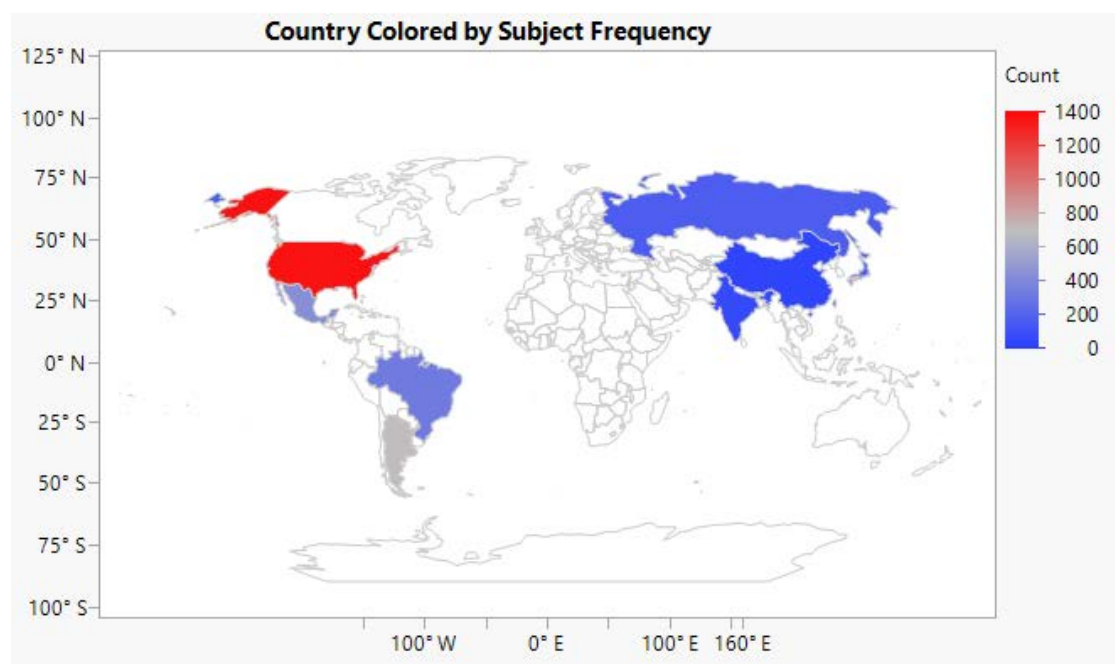
Within each trial, there are no meaningful imbalances in demographic characteristics across treatment groups.

There are several differences between trials:

- Trial GPHK enrolled approximately two-thirds female subjects, while GPHL is sex-balanced.
- Subjects are older in trial GPHL, based on the mean age about 10 years older and ~3 times more subjects aged ≥ 65 years or older compared to trial GPHK (~18% versus ~6%).
- Hispanic and Latino ethnicity is common in both trials but more so in trial GPHL than GPHK (~60% versus ~50%).
- American Indian or Alaska Native race is reported for 9% of subjects in GPHK and no subjects in GPHL.
- Trial GPHK had sites in Mexico, Puerto Rico, and China, while trial GPHL did not.

Across both trials, 43% of subjects were enrolled at sites in the United States (including Puerto Rico), with an additional 43% enrolled in Argentina, Mexico, and Brazil, and the remaining subjects in Asia and Russia (Figure 6).

Figure 6. Geographic Heat Map of Subject Enrollment by Country (Trials GPHK and GPHL)



Source: Generated by reviewer using JMP Clinical, demographics distribution

The Applicant's Clinical Overview document provides a rationale for applicability of foreign data, noting that:

- All trials were performed in accordance with GCP (and two foreign sites with GCP

noncompliance did not affect efficacy results, see Table 29 and Table 30 below)

- All trials met the conditions of 21 CFR 312.120 (Foreign Clinical Studies Not Conducted Under an Investigational New Drug Application)
- Each trial had the same eligibility criteria irrespective of region.

The Applicant concludes that data collected are applicable across geographies. I concur that non-U.S. data in this NDA is applicable to the U.S. population and U.S. medical practice.

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

Trials GPHK and GPHL were CWM trials enrolling subjects with overweight or obesity, so baseline weight-related characteristics are relevant in these trial populations (Table 11). Within each trial, there are no meaningful imbalances in these characteristics across treatment groups. Trial GPHL enrolled a trial population with less obesity than GPHK, as trial GPHL had with a lower mean body weight and more overweight subjects with BMI ≥ 27 to <30 kg/m².

Table 11. Baseline Weight-Related Characteristics (Trials GPHK and GPHL)

	GPHK / SURMOUNT-1		GPHL / SURMOUNT-2		Total	
	Placebo (N=643)	TZP All (N=1896)	Placebo (N=315)	TZP All (N=623)	Placebo (N=958)	TZP All (N=2519)
Weight, kg						
Mean (SD)	104.8 (21.37)	104.8 (22.38)	101.7 (22.26)	100.2 (20.49)	103.8 (21.71)	103.7 (22.01)
Median	101.0	100.6	96.7	97.3	100.0	99.7
Min, Max	67.6, 202.3	60.1, 214.3	55.1, 195.9	58.5, 219.8	55.1, 202.3	58.5, 219.8
Waist circumference, cm						
Mean (SD)	114.0 (14.92)	114.1 (15.24)	116.0 (15.72)	114.4 (13.58)	114.7 (15.21)	114.2 (14.84)
Median	112.0	112.2	113.5	113.0	113.0	112.5
Min, Max	80, 177.5	76.2, 191	83, 172	83, 173.5	80, 177.5	76.2, 191
BMI, kg/m²						
Mean (SD)	38.2 (6.89)	37.9 (6.79)	36.6 (7.27)	35.8 (6.26)	37.7 (7.05)	37.4 (6.72)
Median (Min, Max)	36.4	36.5	35.0	34.9	36.0	36.0
	26.9, 69.9	27.0, 68.9	26.3, 74.4	26.1, 66.1	26.3, 74.4	26.1, 68.9
BMI Group, n (%)						
<30	24 (3.7)	116 (6.1)	52 (16.5)	111 (17.8)	76 (7.9)	227 (9.0)
≥ 30 to <35	227 (35.3)	649 (34.2)	105 (33.3)	206 (33.1)	332 (34.7)	855 (33.9)
≥ 35	392 (61.0)	1131 (59.7)	158 (50.2)	306 (49.1)	550 (57.4)	1437 (57.0)

Source: Generated by reviewer using OCS Analysis Studio, Custom Table Tool

Trial GPHK enrolled subjects with normoglycemia or prediabetes, while trial GPHL enrolled subjects with T2D, so glycemia- or diabetes-related baseline characteristics are relevant to these trial populations (Table 12). Within each trial, there are no meaningful imbalances in these characteristics across treatment groups, while there are the expected differences between trials based on their respective enrollment criteria.

Table 12. Baseline Glycemia- and Diabetes-related Characteristics (Trials GPHK and GPHL)

	GPHK / SURMOUNT-1		GPHL / SURMOUNT-2		Total	
	Placebo (N=643)	TZP All (N=1896)	Placebo (N=315)	TZP All (N=623)	Placebo (N=958)	TZP All (N=2519)
Prediabetes, n (%)	270 (42.0)	762 (40.2)	0 (0.0)	0 (0.0)	270 (28.2)	762 (30.3)
Type 2 Diabetes, n (%)	0 (0.0)	0 (0.0)	315 (100.0)	623 (100.0)	315 (32.9)	623 (24.7)
HbA1c, %						
Mean (SD)	5.6 (0.37)	5.6 (0.38)	8.0 (0.84)	8.0 (0.92)	6.4 (1.27)	6.2 (1.21)
Median	5.6	5.5	7.8	7.9	5.8	5.7
Min, Max	4.5, 7.0	3.6, 8.9	6.0, 10.8	5.8, 11.7	4.5, 10.8	3.6, 11.7
HbA1c Group, n (%)						
<= 8.0%	643 (100.0)	1895 (99.9)	179 (56.8)	343 (55.1)	822 (85.8)	2238 (88.8)
> 8.0%	0 (0.0)	1 (0.1)	136 (43.2)	280 (44.9)	136 (14.2)	281 (11.2)
Fasting Serum Glucose, mg/dl						
Mean (SD)	95.7 (9.54)	95.4 (10.22)	158.5 (46.49)	159.8 (46.74)	116.3 (40.51)	111.3 (37.27)
Median	95.5	95.5	151.3	149.5	100.9	99.1
Duration of Diabetes, years						
Mean (SD)			8.8 (6.22)	8.4 (6.69)		
Median			7.6	6.6		
Min, Max			0.3, 33.7	0.2, 50.7		
Duration of Diabetes Group, n (%)						
<=5 years			97 (30.8)	232 (37.2)		
>10 years			114 (36.2)	211 (33.9)		
>5 to <=10 years			104 (33.0)	180 (28.9)		

Source: Generated by reviewer using OCS Analysis Studio, Custom Table Tool

Besides T2D, there are other relevant weight-related comorbidities in the GPHK and GPHL trial populations, based on baseline diagnoses (Table 13) or laboratory and vital sign criteria (Table 14, including blood pressure, lipids, and renal function). Within each trial, there are no meaningful imbalances in comorbidity diagnoses across treatment groups. There are several differences between trials:

- Baseline anxiety/depression and polycystic ovarian syndrome (PCOS) are more common in trial GPHK, which enrolled a younger and more predominantly female population.
- Baseline hypertension, dyslipidemia, NAFLD, and ASCVD (all considered metabolic comorbidities) were much more prevalent (~2-fold for each) in trial GPHL, which enrolled an older population with T2D.
- Baseline osteoarthritis, asthma/COPD, OSA, and gout appeared balanced between trials GPHK and GPHL.

Table 13. Baseline Subject Comorbidity Characteristics (Trials GPHK and GPHL)

n (%)	GPHK / SURMOUNT-1		GPHL / SURMOUNT-2		Total	
	Placebo (N=643)	TZP All (N=1896)	Placebo (N=315)	TZP All (N=623)	Placebo (N=958)	TZP All (N=2519)
Hypertension	199 (30.9)	620 (32.7)	217 (68.9)	403 (64.7)	416 (43.4)	1023 (40.6)
Dyslipidemia	186 (28.9)	571 (30.1)	210 (66.7)	363 (58.3)	396 (41.3)	934 (37.1)
Anxiety/Depression	108 (16.8)	314 (16.6)	34 (10.8)	77 (12.4)	142 (14.8)	391 (15.5)
Osteoarthritis	76 (11.8)	250 (13.2)	58 (18.4)	85 (13.6)	134 (14.0)	335 (13.3)
Asthma/COPD	78 (12.1)	189 (10.0)	30 (9.5)	48 (7.7)	108 (11.3)	237 (9.4)
NAFLD	46 (7.2)	134 (7.1)	54 (17.1)	108 (17.3)	100 (10.4)	242 (9.6)
Obstructive Sleep Apnea	59 (9.2)	138 (7.3)	29 (9.2)	49 (7.9)	88 (9.2)	187 (7.4)
Gout	35 (5.4)	101 (5.3)	19 (6.0)	35 (5.6)	54 (5.6)	136 (5.4)
ASCVD	21 (3.3)	57 (3.0)	44 (14.0)	53 (8.5)	65 (6.8)	110 (4.4)
PCOS	13 (2.0)	26 (1.4)	2 (0.6)	4 (0.6)	15 (1.6)	30 (1.2)

Source: Generated by reviewer using OCS Analysis Studio, Custom Table Tool

Table 14. Baseline Subject Laboratory and Vital Sign Characteristics (Trials GPHK and GPHL)

	GPHK / SURMOUNT-1		GPHL / SURMOUNT-2		Total	
	Placebo (N=643)	TZP All (N=1896)	Placebo (N=315)	TZP All (N=623)	Placebo (N=958)	TZP All (N=2519)
Pulse, bpm						
Mean (SD)	72.9 (9.27)	72.2 (9.71)	74.8 (9.89)	75.7 (9.93)	73.5 (9.51)	73.1 (9.88)
Median	72.3	72.0	75.0	75.5	72.7	73.0
SBP, mm Hg						
Mean (SD)	122.9 (12.77)	123.5 (12.72)	131.0 (11.87)	130.3 (12.22)	125.6 (13.04)	125.1 (12.93)
Median (Min, Max)	122.7	123.0	132.0	130.5	125.3	125.0
DBP, mm Hg						
Mean (SD)	79.6 (7.95)	79.5 (8.23)	79.4 (8.43)	80.0 (8.38)	79.5 (8.11)	79.6 (8.27)
Median	80.0	79.7	79.0	80.5	80.0	80.0
Triglycerides, mg/dL						
Mean (SD)	146.8 (82.03)	144.9 (110.02)	189.0 (116.43)	182.1 (133.40)	160.7 (96.72)	154.1 (117.31)
Median	126.7	125.8	159.4	155.0	139.9	132.0
Total cholesterol, mg/dL						
Mean (SD)	191.4 (39.23)	192.2 (38.79)	179.5 (41.09)	175.4 (42.35)	187.5 (40.22)	188.0 (40.35)
Median	187.9	187.9	179.0	172.9	184.8	184.8
LDL-C, mg/dL						
Mean (SD)	114.3 (33.75)	114.7 (32.50)	98.5 (33.27)	95.5 (35.30)	109.1 (34.38)	110.0 (34.23)
Median	110.2	112.1	98.2	94.0	106.0	107.9
HDL-C, mg/dL						
Mean (SD)	48.3 (13.02)	49.2 (13.06)	44.1 (11.31)	44.4 (11.58)	46.9 (12.63)	48.0 (12.88)
Median	46.4	47.2	42.9	42.9	44.9	46.0
eGFR, mL/min/1.73m²						
Mean (SD)	98.1 (18.28)	98.0 (17.93)	93.5 (19.07)	96.1 (17.64)	96.6 (18.66)	97.5 (17.88)
Median	99.0	99.0	96.0	98.0	98.0	99.0
eGFR Group, n (%)						
<60	7 (1.1)	37 (2.0)	18 (5.7)	17 (2.7)	25 (2.6)	54 (2.1)
>=30 to <45	1 (0.2)	4 (0.2)	2 (0.6)	7 (1.1)	3 (0.3)	11 (0.4)
>=45 to <60	6 (0.9)	33 (1.7)	16 (5.1)	10 (1.6)	22 (2.3)	43 (1.7)
>=60	636 (98.9)	1859 (98.0)	297 (94.3)	606 (97.3)	933 (97.4)	2465 (97.9)
>=60 to <90	194 (30.2)	579 (30.5)	100 (31.7)	172 (27.6)	294 (30.7)	751 (29.8)
>=90	442 (68.7)	1280 (67.5)	197 (62.5)	434 (69.7)	639 (66.7)	1714 (68.0)

Source: Generated by reviewer using OCS Analysis Studio, Custom Table Tool

The older T2D population in trial GPHL also has higher mean blood pressure, lower mean eGFR, more subjects with renal impairment, and higher mean triglycerides and lower mean HDL-C (consistent with the lipid abnormalities defining the metabolic syndrome). LDL-C is lower in trial GPHL than trial GPHK, likely attributable to more baseline statin use in the older T2D population with higher ASCVD risk in trial GPHL (see below).

Table 15 shows baseline use of medications for dyslipidemia and hypertension in each trial, with high use of both in trial GPHL. At baseline, the most common antihypertensive medications were angiotensin II receptor blockers, angiotensin-converting enzyme inhibitors, thiazides, and dihydropyridine derivatives, and the most common lipid lowering medications

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were 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) and fibrates.¹⁸ Antihyperglycemic medications were excluded in trial GPHK, and their use in trial GPHL is shown in Table 16.

Table 15. Baseline Subject Use of Medications for Hypertension and Dyslipidemia (Trials GPHK and GPHL)

Subjects with baseline medication use, n (%)	GPHK / SURMOUNT-1		GPHL / SURMOUNT-2		Total	
	Placebo (N=643)	TZP All (N=1896)	Placebo (N=315)	TZP All (N=623)	Placebo (N=958)	TZP All (N=2519)
≥1 medication for hypertension	181 (28.1)	576 (30.4)	206 (65.4)	392 (62.9)	387 (40.4)	968 (38.4)
≥1 medication for dyslipidemia	115 (17.9)	314 (16.6)	176 (55.9)	310 (49.8)	291 (30.4)	624 (24.7)

Source: Generated by reviewer from Applicant CSRs, Tables GPHK.8.13, GPHK.8.15, GPHL.8.9, and GPHL.8.11

Table 16. Baseline Subject Use of Antihyperglycemic Medications for T2D (Trial GPHL)

Attribute	Placebo (N=315)	TZP 10 mg (N=312)	TZP 15 mg (N=311)
Participants without AHM, n (%)	24 (7.6)	16 (5.1)	23 (7.4)
Participants with 1 AHM, n (%)	158 (50.2)	177 (56.7)	170 (54.7)
Participants with 2 AHM, n (%)	108 (34.3)	99 (31.7)	95 (30.5)
Participants with ≥3 AHM, n (%)	25 (7.9)	20 (6.4)	23 (7.4)
Metformin ^a , n (%)	274 (87.0%)	282 (90.4)	276 (88.7)
SU ^a , n (%)	94 (29.8)	78 (25.0)	78 (25.1)
SGLT-2i ^a , n (%)	66 (21.0)	63 (20.2)	62 (19.9)
TZD ^a , n (%)	11 (3.5)	11 (3.5)	11 (3.5)
Other ^a , n (%)	5 (1.6)	2 (0.6)	3 (1.0)

Abbreviations: AHM = antihyperglycemic medication; mITT = modified intent-to-treat; n = number of participants in the specified category; N = number of participants who were randomly assigned and received ≥1 dose of the study drug; SGLT-2i = sodium-glucose co-transporter 2 inhibitors; SU = sulfonylurea; TZD = thiazolidinediones; TZP = tirzepatide.

^a Indicates that rows are not mutually exclusive.

Note 1: Baseline refers to Visit 3 or Randomization Visit.

Note 2: The category “Other” includes voglibose, acarbose, insulin human (1 inadvertently enrolled participant), and repaglinide.

Source: Applicant GPHL CSR, Table GPHL.4.9

In conclusion, trials GPHK and GPHL have no apparent imbalances in baseline characteristics between placebo and tirzepatide treatment groups that could potentially impact the interpretation of efficacy or safety in the target population and for the proposed indication. The observed differences in baseline characteristics between trials GPHK and GPHL are consistent with trial GPHL enrolling an older sex-balanced population with T2D and more comorbidities,

¹⁸ Not shown, see referenced Applicant table for details.

compared to the GPHK trial population. Overall, baseline characteristics in these trials seem congruent with the to-be-marketed U.S. populations for CWM in patients with and without T2D.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment Compliance: In both trials, treatment compliance was defined as taking at least 75% of the required doses of study drug, and compliance for the entire treatment period was high (>95%) and did not differ between placebo and tirzepatide groups (Table 17). If needed, investigators were allowed to temporarily interrupt study drug for any reason. In both trials, subjects missing 3 or consecutive doses were rare (<6%) and not different between placebo and tirzepatide groups. A single dose reduction was allowed for intolerable GI adverse events, and in both trials this was rare, though much more frequent in the tirzepatide arms (5.4%) than placebo (0.1%) as expected given known GI tolerability issues. These compliance measures (in Table 17) did not differ meaningfully among tirzepatide dosages in the two trials (not shown), and subjects were included in all safety and efficacy analysis populations regardless of compliance.

Table 17. Compliance with Study Treatment in Trials GPHK and GPHL

Subjects, n (%)	GPHK / SURMOUNT-1		GPHL / SURMOUNT-2		Total	
	Placebo	TZP All	Placebo	TZP All	Placebo	TZP All
	(N=643)	(N=1896)	(N=315)	(N=623)	(N=958)	(N=2519)
Overall compliance (≥75% doses taken)	624 (97.0)	1849 (97.5)	302 (95.9)	605 (97.1)	926 (96.7)	2454 (97.4)
Subjects missing ≥3 consecutive doses	35 (5.4)	104 (5.5)	12 (3.8)	36 (5.8)	47 (4.9)	140 (5.6)
Subjects with dose reduction	1 (0.2)	96 (5.1)	0 (0.0)	39 (6.3)	1 (0.1)	135 (5.4)

Source: Generated by reviewer from Applicant CSRs, Tables GPHK.8.16 and GPHL.8.17

Concomitant Medications: Other weight management medications were not allowed at baseline, so there are no issues with such medications affecting the primary and secondary weight-related endpoints. There were secondary endpoints related to blood pressure, lipids, and glycemia, and compliance with medications for these was not formally measured in the trials. However, the Applicant reports changes in use and dosages for these medications:

- Lipid-lowering medications were not meaningfully changed in either trial (Table 18, Table 20). This is consistent with general clinical practice and guidelines, as statins are generally not discontinued or dose-reduced in the absence of adverse reactions. Therefore, secondary lipid-related endpoints were unlikely to be affected by compliance with lipid-lowering medications.
- In both trials, there were notably more reductions in baseline antihypertensive medications in the tirzepatide 10 mg and 15 mg arms compared to the placebo arms (Table 19, Table 20). Since the secondary endpoint results (see below) showed a

decrease in blood pressure in tirzepatide arms, this reduction in antihypertensive medications in the tirzepatide arm could be consistent with tirzepatide's effect on lowering blood pressure (i.e., blood pressure was at goal with fewer medications needed and/or there was reduction of antihypertensive medications for safety). The treatment effect of tirzepatide on blood pressure compared to placebo could theoretically have been larger if these antihypertensive medications were not reduced.

- Baseline antihyperglycemic medications were excluded in trial GPHK, and in trial GPHL there were notable dose reductions in these medications in the tirzepatide 10 mg and 15 mg arms compared to the placebo arm (Table 20). As above for hypertension, this is consistent with tirzepatide's efficacy for glycemic control, making other medications for diabetes unnecessary or unsafe, and these medication changes are predicted to reduce the observed treatment effect of tirzepatide versus placebo on glycemia-related secondary endpoints.

Table 18. Changes in Baseline Lipid-lowering Medications (Trial GPHK)

Change Status	n (%)			
	Placebo (N = 643)	TZP 5 mg (N = 630)	TZP 10 mg (N = 636)	TZP 15 mg (N = 630)
No use at both baseline and postbaseline period	503 (78.2)	500 (79.4)	529 (83.2)	522 (82.9)
Increased	10 (1.6)	8 (1.3)	8 (1.3)	5 (0.8)
Not changed	58 (9.0)	46 (7.3)	27 (4.2)	34 (5.4)
Decreased	7 (1.1)	9 (1.4)	10 (1.6)	8 (1.3)
Cannot be determined	65 (10.1)	67 (10.6)	62 (9.7)	61 (9.7)

Source: Applicant GPHK CSR, Table GPHK.4.8

Table 19. Changes in Baseline Antihypertensive Medications (Trial GPHK)

Change Status	n (%)			
	Placebo (N = 643)	TZP 5 mg (N = 630)	TZP 10 mg (N = 636)	TZP 15 mg (N = 630)
No use at both baseline and postbaseline period	441 (68.6)	429 (68.1)	437 (68.7)	430 (68.3)
Increased	15 (2.3)	14 (2.2)	7 (1.1)	10 (1.6)
Not changed	74 (11.5)	69 (11.0)	61 (9.6)	71 (11.3)
Decreased	13 (2.0)	18 (2.9)	33 (5.2)	31 (4.9)
Cannot be determined	100 (15.6)	100 (15.9)	98 (15.4)	88 (14.0)

Source: Applicant GPHK CSR, Table GPHK.4.7

Table 20. Changes in Baseline Lipid-lowering, Antihypertensive, and Antihyperglycemic Medications (Trial GPHL)

Category	Change Status	Placebo (N=315) n (%)	TEP 10mg (N=312) n (%)	TEP 15mg (N=311) n (%)
Lipid Lowering Therapy	No use during the trial	167 (53.0)	186 (59.6)	173 (55.6)
	Decreased	2 (0.6)	8 (2.6)	11 (3.5)
	Increased	12 (3.8)	11 (3.5)	4 (1.3)
	Not changed	130 (41.3)	107 (34.3)	117 (37.6)
	Cannot be determined	3 (1.0)	0	3 (1.0)
	Missing	1 (0.3)	0	3 (1.0)
Antihypertensive Therapy	No use during the trial	130 (41.3)	134 (42.9)	139 (44.7)
	Decreased	9 (2.9)	33 (10.6)	25 (8.0)
	Increased	16 (5.1)	10 (3.2)	10 (3.2)
	Not changed	159 (50.5)	134 (42.9)	134 (43.1)
	Cannot be determined	0	1 (0.3)	0
	Missing	1 (0.3)	0	3 (1.0)
Antihyperglycemic Therapy	No use during the trial	49 (15.6)	58 (18.6)	71 (22.8)
	Decreased	33 (10.5)	64 (20.5)	52 (16.7)
	Increased	83 (26.3)	14 (4.5)	15 (4.8)
	Not changed	146 (46.3)	176 (56.4)	166 (53.4)
	Cannot be determined	3 (1.0)	0	4 (1.3)
	Missing	1 (0.3)	0	3 (1.0)

Source: Applicant GPHL CSR, Table GPHL.8.10

Rescue therapy: Rescue therapy for weight management was not allowed during either trial, so there are no issues about such rescue medications affecting the primary and secondary weight-related endpoints. Rescue therapy for hypertension and dyslipidemia was not defined in this trial, so changes in medications for blood pressure and lipids would only occur as part of the subjects' usual care. Given that tirzepatide resulted in reduction in baseline use of antihypertensive and lipid-lowering medications (see above), it is possible that new treatment of lipids and blood pressure occurred more in placebo than tirzepatide arms, thus potentially reducing the treatment effects of tirzepatide versus placebo on blood pressure and lipid endpoint (see below).

Rescue therapy for hyperglycemia was defined in both trials. In trial GPHK, 5 subjects were diagnosed with T2D during the trial (3 with prediabetes at baseline) and started metformin (n=4) or semaglutide (n=1, a protocol violation included above). Notably, 4 subjects with new T2D were in the placebo arm (0.62%) compared to 1 in the tirzepatide 10 mg arm (0.05% of all tirzepatide-treated subjects). 15 subjects in trial GPHK received antihyperglycemic medications without a diagnosis of T2D:

- 9 received metformin (n = 7) or dapagliflozin (n = 2) to treat prediabetes, glucose intolerance, insulin resistance, or PCOS.
- 1 received insulin lispro to treat postoperative hyperglycemia.
- 5 received semaglutide (n = 2) or liraglutide (n = 3) to treat obesity or overweight, after having discontinued study drug.

In 12 cases, these were captured as important protocol violations (prohibited medication use). Overall in trial GPHK, subjects receiving post-baseline antihyperglycemic medications were unlikely to have affected glycemia-related endpoints, due to their small number and

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distribution among placebo and tirzepatide arms.

Rescue therapy for persistent hyperglycemia was well-defined in trial GPLH (see above), enrolling subjects with T2D at baseline. As expected given the glucose-lowering efficacy of tirzepatide, rescue therapy was >10-fold more common in the placebo arm (101/315, 32.1%) compared to the tirzepatide 10 mg (9/312, 2.9%) and 15 mg (8/311, 2.6%) arms.¹⁹ Antihyperglycemic rescue therapy predominantly in the placebo arm would tend to reduce the treatment effect of tirzepatide versus placebo on glycemia-related trial endpoints.

Conclusion on compliance, concomitant and rescue medications:

Overall, compliance with study drug was excellent in both trials. Baseline and rescue use of medications for hypertension, lipids, and glucose-lowering was unlikely to alter conclusions regarding the related secondary endpoints.

Efficacy Results – Primary Endpoint

For substantial evidence of effectiveness for the indication of CWM, the Division considers the primary endpoint of placebo-corrected mean percent change in body weight from baseline in the intention-to-treat population after at least one year on the maintenance dosage. Trials GPHK and GPLH both include this primary endpoint with appropriate protocol-specified statistical analyses, placebo controls, and durations of maintenance dosage tirzepatide treatment (Week 72 represents 52 weeks of maintenance for 15 mg, 60 weeks for 10 mg, and 68 weeks for 5 mg). For FDA review, the more conservative “treatment-regimen” estimand (in the ITT population) is considered rather than the “efficacy estimand” (in randomized subjects had they remained on their randomized treatment for the entire planned 72-week treatment duration).

For a detailed review of the statistical analyses for the primary endpoints, please refer to the FDA statistical review dated October 10, 2023, by Drs. Kyunghye Song and Feng Li (Office of Biostatistics, Division of Biometrics II). The co-primary endpoints in both trials were percent change in body weight and proportion of subject achieving ≥5% weight loss, with the difference from placebo for the tirzepatide 10 mg and 15 mg arms. For both trials GPHK and GPLH (SURMOUNT-1 and -2), FDA statistical review confirmed the Applicant’s primary efficacy analyses (Table 21).

¹⁹ Applicant GPLH CSR, Table.8.16, page 538 of 3056

Table 21. FDA Statistical Analysis of Primary Endpoints (Trials GPHK and GPHL)

	Tirzepatide 10 mg N=636	Tirzepatide 15 mg N=630	Placebo N=643
SURMOUNT-1			
%Change in body weight			
Baseline body weight (kg), mean (SD)	105.8 (23.3)	105.6 (22.9)	104.8 (21.4)
Estimate, LSMean (SE) ¹	-19.5 (0.5)	-20.9 (0.5)	-3.1 (0.6)
Difference from placebo, (95% CI)	-16.4 (-17.9, -14.8)	-17.8 (-19.3, -16.3)	
P-value	<0.001	<0.001	
Missing, n(%)	67 (10.5)	59 (9.4)	139 (21.6)
5% Body weight loss			
Proportion estimate ²	89.6	91.4	34.0
Difference from placebo (95% CI)	55.6 (50.0, 61.2)	57.4 (51.9, 62.9)	
P-value	<0.001	<0.001	
Missing, n(%)	67 (10.5)	59 (9.4)	139 (21.6)
SURMOUNT-2			
	N=312	N=311	N=315
%Change in body weight			
Baseline body weight (kg), mean (SD)	100.9 (20.9)	99.6 (20.1)	101.7 (22.3)
Estimate, LSMean (SE) ¹	-12.8 (0.6)	-14.7 (0.5)	-3.2 (0.5)
Difference from placebo, (95% CI)	-9.6 (-11.1, -8.1)	-11.6 (-13.0, -10.1)	
P-value	<0.001	<0.001	
Missing, n(%)	15 (4.8)	26 (8.4)	35 (11.1)
5% Body weight loss			
Proportion estimate ²	79.6	83.2	32.0
Difference from placebo (95% CI)	47.6 (40.2, 55.0)	51.2 (43.9, 58.4)	
P-value	<0.001	<0.001	
Missing, n(%)	15 (4.8)	26 (8.4)	35 (11.1)

Abbreviations: N = number of subjects randomized; SD=standard deviation; LSMean=least squares mean; SE=standard error; CI=confidence interval; ¹Model based estimates and standard error, the ANCOVA model included treatment and stratification group as factors and baseline body weight (kg) as a covariate; ²Estimates based on a logistic regression using treatment and stratification group as factors and baseline body weight (kg) as a covariate; Missing observations were imputed using hybrid imputation (refer to Section 3.2.2 of this review for details); [Source: Statistical Reviewer Analysis; adsl.xpt, advs.xpt, adcovid.xpt, adds.xpt]

In trial GPHK, the comparison of tirzepatide 5 mg to placebo for these endpoints was a key secondary endpoint, also confirmed by the FDA statistical review (Table 22).

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Table 22. FDA Statistical Analysis of a Key Secondary Endpoint (Weight Loss on Tirzepatide 5 mg in Trial GPHK)

	Tirzepatide 5 mg N=630	Placebo N=643
SURMOUNT-1		
%Change in body weight		
Baseline body weight (kg), mean (SD)	102.9 (20.7)	104.8 (21.4)
Estimate, LSMean (SE) ¹	-15.0 (0.4)	-3.1 (0.6)
Difference from placebo (95% CI)	-11.9 (-13.4, -10.4)	
P-value	<0.001	
Missing, n(%)	64 (10.2)	139 (21.6)
5% Body weight loss		
Proportion estimate ²	85.5	34.0
Difference from placebo (95% CI)	51.5 (45.7, 57.4)	
P-value	<0.001	
Missing, n(%)	64 (10.2)	139 (21.6)

Abbreviations: N = number of subjects randomized; SD=standard deviation; LSMean=least squares mean; SE=standard error; CI=confidence interval; ¹Model based estimates and standard error, the ANCOVA model included treatment and stratification group as factors and baseline value as a covariate; ²Estimates based on a logistic regression using treatment and stratification group as factors and baseline value as a covariate; Missing observations were imputed using hybrid imputation (refer to Section 3.2.2 of this review for details); [Source: Statistical Reviewer Analysis; adsl.xpt, advs.xpt, adcovid.xpt, adds.xpt]

Table 23 and Figure 7 show the Applicant's primary efficacy results of trial GPHK (SURMOUNT-1), in subjects without T2D.

Table 23. Primary Efficacy Analysis in Trial GPHK (Placebo-Corrected Mean Percent Change in Body Weight from Baseline)

Parameters	Placebo (N = 643)	TZP 5 mg ^a (N = 630)	TZP 10 mg (N = 636)	TZP 15 mg (N = 630)
Treatment-regimen Estimand^b				
Baseline (kg)	104.8	102.9	105.8	105.6
Percent change from baseline at 72 weeks (%)	-3.1 ^{†††}	-15.0 ^{†††}	-19.5 ^{†††}	-20.9 ^{†††}
Percent change difference from placebo at 72 weeks (%) (95% CI)	N/A	-11.9 ^{***} (-13.4, -10.4)	-16.4 ^{***} (-17.9, -14.8)	-17.8 ^{***} (-19.3, -16.3)
Efficacy Estimand^c				
Baseline (kg)	104.8	102.9	105.9	105.5
Percent change from baseline at 72 weeks (%)	-2.4 ^{†††}	-16.0 ^{†††}	-21.4 ^{†††}	-22.5 ^{†††}
Percent change difference from placebo at 72 weeks (%) (95% CI)	N/A	-13.5 ^{***} (-14.6, -12.5)	-18.9 ^{***} (-20.0, -17.8)	-20.1 ^{***} (-21.2, -19.0)

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; mITT population = modified intent-to-treat population; MMRM = mixed model for repeated measures; N = number of participants who were randomly assigned and received at least 1 dose of study drug; N/A = not applicable; TZP = tirzepatide.

^a For the tirzepatide 5-mg group, percent change in body weight at Week 72 is a key secondary objective.

Section 5.1.3.1 discusses the results for the tirzepatide 5-mg group.

^b ANCOVA with hybrid imputations for missing body weight at 72 weeks. Section 3.7.1 defines hybrid imputation.

^c MMRM analysis.

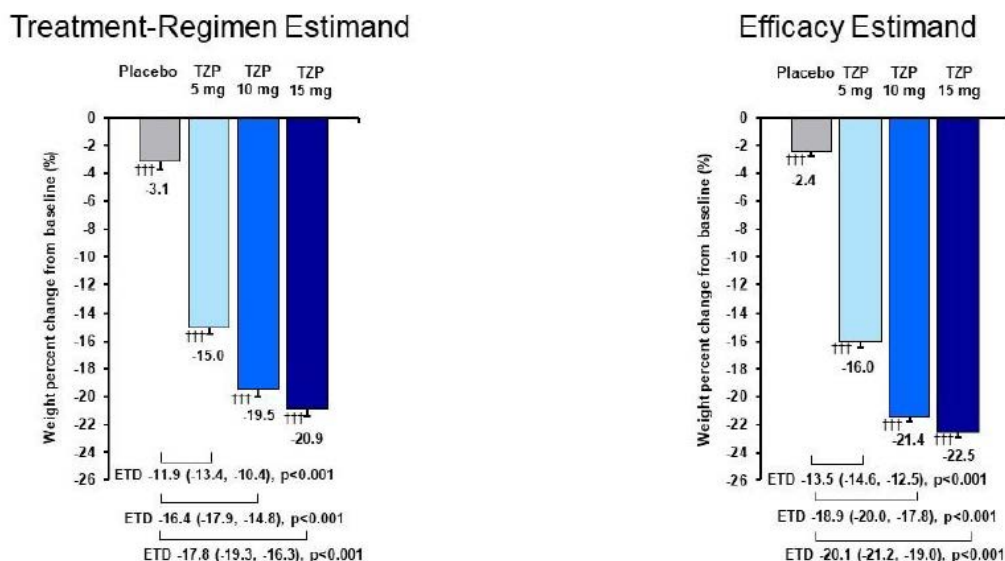
Note: Shown are least squares means.

***p-Value <0.001 versus placebo for superiority.

†††p-Value <0.001 versus baseline.

Source: Applicant GPHK CSR, Table GPHK.5.1, page 87 of 3021

Figure 7. Bar Graphs of Primary Efficacy Results in Trial GPHK (Mean Percent Change in Body Weight from Baseline)



Abbreviations: ANCOVA = analysis of covariance; CSR = clinical study report; ETD = estimated treatment difference; mITT = modified intent-to-treat; MMRM = mixed model for repeated measures; TZP = tirzepatide.

Note 1: ANCOVA analysis for treatment-regimen estimand; MMRM analysis for efficacy estimand.

Note 2: Shown are the least squares means $\pm$ standard errors.

†††p-Value <.001 versus baseline within each treatment group.

Source: Applicant SCE, Figure 2.7.3.2, page 26 of 123

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Table 24 and Figure 8 show the Applicant's primary efficacy results in trial GPLH (SURMOUNT-2), subjects with T2D.

Table 24. Primary Efficacy Analysis in Trial GPLH (Placebo-Corrected Mean Percent Change in Body Weight from Baseline)

Parameters	Placebo (N=315)	TZP 10mg (N=312)	TZP 15mg (N=311)
Percent Change in Body Weight (%)			
Baseline	101.65	100.86	99.60
Week 72: Percent Change from baseline	-3.17	-12.77	-14.71
Within-treatment p-value	<.001	<.001	<.001
Difference from Placebo (95% CI)	-	-9.61 (-11.08, -8.14)	-11.55 (-12.96, -10.13)
Between-treatment p-value	-	<.001	<.001

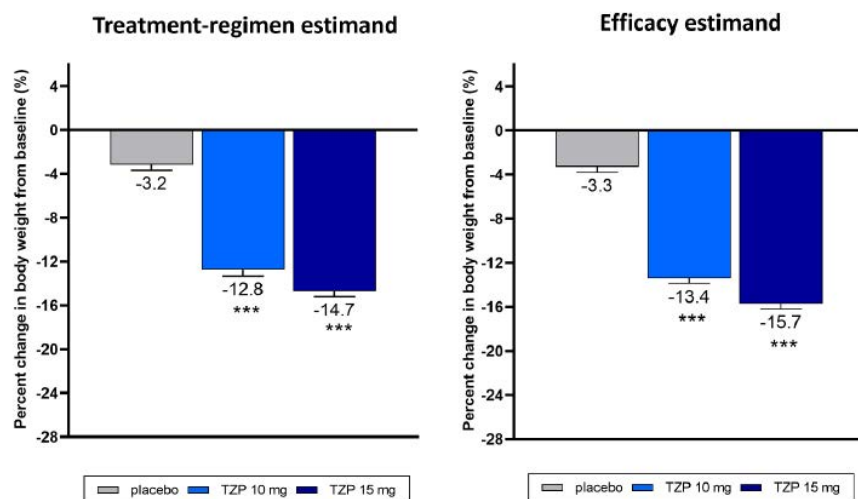
Abbreviations: - = not applicable; ANCOVA = analysis of covariance; CI = confidence interval; N = number of participants randomly assigned and received at least 1 dose of study drug; TZP = tirzepatide

Note: Shown are least squares means.

Source: Applicant GPHK CSR, Table GPHK.5.1, page 87 of 3021

Note 2: Only the treatment-regimen (mITT) estimand is shown

Figure 8. Bar Graphs of Primary Efficacy Results in Trial GPLH (Mean Percent Change in Body Weight from Baseline)



Abbreviations: ANCOVA = analysis of covariance; CSR = clinical study report; mITT = modified intent-to-treat; MMRM = mixed model for repeated measures; TZP = tirzepatide.

Note 1: ANCOVA analysis for treatment-regimen estimand; MMRM analysis for efficacy estimand.

Note 2: Shown are the least squares means $\pm$ standard errors.

***p-Value <.001 versus placebo for objectives controlled for type 1 error.

Source: Applicant SCE, Figure 2.7.3.16, page 55 of 123

Analysis by population: The data above show in both trials that the treatment effects of tirzepatide for weight loss were slightly greater in the Applicant's "efficacy" population (in randomized subjects had they remained on their randomized treatment for the entire planned 72-week treatment duration) than in the more conservative "treatment-regimen" (ITT) population used by FDA.

Handling missing data: As detailed above, the Applicant used a "hybrid imputation" (missing at random for exceptional circumstances [COVID-19], retrieved dropouts for other intercurrent events). For trial GPHK, the Applicant also presents (Table 25) a sensitivity analysis showing nearly identical results if imputed data was imputed solely by retrieved dropouts, showing little effect on the overall results for exceptional circumstances in the "hybrid imputation."

Table 25. Sensitivity Analysis for Primary Efficacy Endpoint in Trial GPHK

Parameters	Placebo (N = 643)	TZP 5 mg ^a (N = 630)	TZP 10 mg (N = 636)	TZP 15 mg (N = 630)
Primary analysis: Treatment-regimen estimand – Hybrid^b				
Baseline (kg)	104.8	102.9	105.8	105.6
Percent change from baseline at 72 weeks	-3.1 ^{†††}	-15.0 ^{†††}	-19.5 ^{†††}	-20.9 ^{†††}
Percent change difference from placebo at 72 weeks (%) (95% CI)	N/A	-11.9*** (-13.4, -10.4)	-16.4*** (-17.9, -14.8)	-17.8*** (-19.3, -16.3)
Sensitivity analysis: Treatment-regimen estimand – Retrieved dropout^c				
Baseline (kg)	104.8	102.9	105.8	105.6
Percent change from baseline at 72 weeks	-3.2 ^{†††}	-15.0 ^{†††}	-19.5 ^{†††}	-20.8 ^{†††}
Percent change difference from placebo at 72 weeks (%) (95% CI)	N/A	-11.8*** (-13.2, -10.3)	-16.2*** (-17.7, -14.7)	-17.5*** (-19.0, -16.1)

Abbreviations: CI = confidence interval; mITT population = modified intent-to-treat population; MMRM = mixed model for repeated measures; N = number of participants who were randomly assigned and received at least 1 dose of study drug; N/A = not applicable; TZP = tirzepatide.

- ^a For the tirzepatide 5-mg group, percent change in body weight at Week 72 is a key secondary objective. Section 5.1.3.1 discusses the results for the tirzepatide 5-mg group.
- ^b Logistic regression with missing value imputed by MMRM analysis for efficacy estimand; logistic regression with hybrid imputation analysis for treatment-regimen estimand. Section 3.7.1 defines hybrid imputation.
- ^c Logistic regression with missing data imputed based on retrieved dropouts.

***p-Value <0.001 versus placebo for superiority.

†††p-Value <0.001 versus baseline.

Source: Applicant GPHK CSR, Table GPHK.5.2, page 94 of 3021

Similarly for trial GPHL, the Applicant presents a sensitivity analysis (Table 26) showing nearly identical results if imputed data were imputed solely by retrieved dropouts, placebo imputation, or return to baseline multiple imputation.

Table 26. Sensitivity Analysis for Primary Efficacy Endpoint in Trial GPHL

Parameters	Placebo (N=315)	TZP 10 mg (N=312)	TZP 15 mg (N=311)
Primary analysis: treatment-regimen estimand – hybrid^a			
Baseline (kg)	101.7	100.9	99.6
Percent change from baseline at 72 weeks	-3.2†††	-12.8†††	-14.7†††
Percent change difference from placebo at 72 weeks (%) (95% CI)	-	-9.6*** (-11.1, -8.1)	-11.6*** (-13.0, -10.1)
Sensitivity analysis: treatment-regimen estimand – retrieved dropout^b			
Baseline (kg)	101.7	100.9	99.6
Percent change from baseline at 72 weeks	-3.2†††	-12.8†††	-14.7†††
Percent change difference from placebo at 72 weeks (%) (95% CI)	-	-9.6*** (-11.1, -8.1)	-11.5*** (-13.0, -10.1)
Sensitivity analysis: treatment-regimen estimand – placebo^c			
Baseline (kg)	101.7	100.9	99.6
Percent change from baseline at 72 weeks	-3.4†††	-12.5†††	-14.3†††
Percent change difference from placebo at 72 weeks (%) (95% CI)	-	-9.2*** (-10.5, -7.8)	-11.0*** (-12.3, -9.6)
Sensitivity analysis: treatment-regimen estimand – return to baseline^d			
Baseline (kg)	101.7	100.9	99.6
Percent change from baseline at 72 weeks	-3.0†††	-12.4†††	-13.6†††
Percent change difference from placebo at 72 weeks (%) (95% CI)	-	-9.4*** (-10.8, -7.9)	-10.5*** (-12.0, -9.1)

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; mITT population = modified intent-to-treat population; MMRM = mixed model for repeated measures; N = number of participants who were randomly assigned and received ≥1 dose of the study drug; TZP = tirzepatide.

a ANCOVA with hybrid imputation analysis for the treatment-regimen estimand. Section 3.7.1 defines hybrid imputation.

b ANCOVA with missing data imputed based on retrieved dropout imputation.

c ANCOVA with missing data imputed based on placebo imputation.

d ANCOVA with missing data imputed based on return to baseline multiple imputation.

***p-Value <.001 versus placebo for superiority.

†††p-Value <.001 versus baseline.

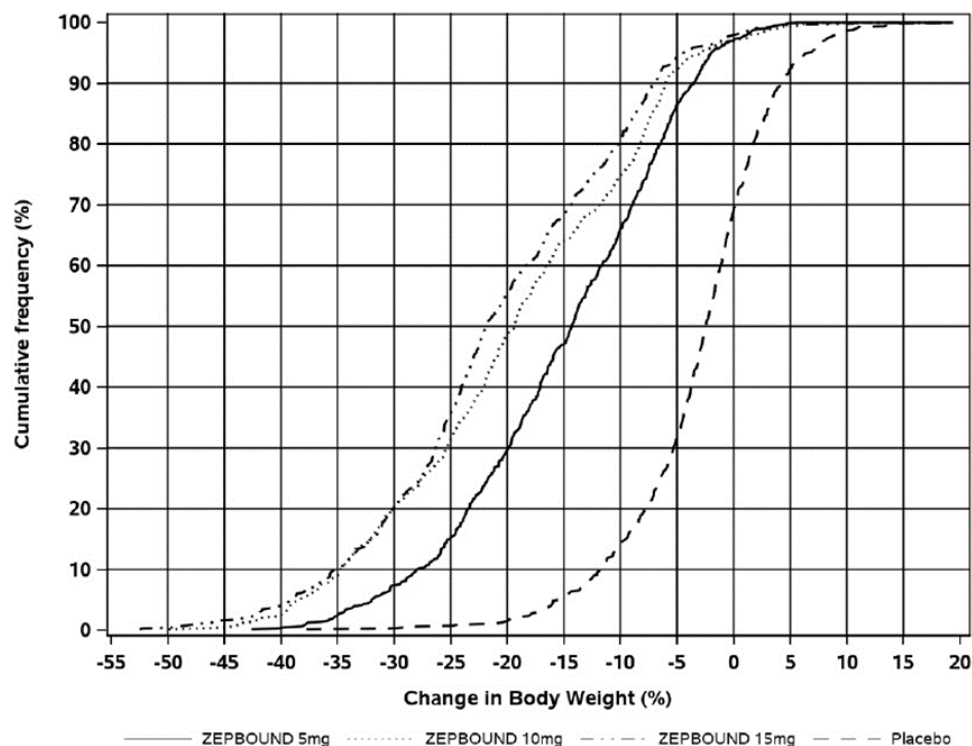
Source: Applicant GPHL CSR, Table GPHK.5.3, page 77 of 3056

Dr. Song’s statistical review notes: “Pre-specified sensitivity analyses using different imputation approaches were conducted to evaluate the robustness of the conclusions based on the primary analyses. All sensitivity analyses yielded results that were consistent with the primary analyses results.” She concluded that “Sensitivity analyses supported the robustness of the primary efficacy results.”

Distribution of effect size:

For trial GPHK, Figure 9 shows the cumulative proportion of subjects reaching percent changes in body weight.

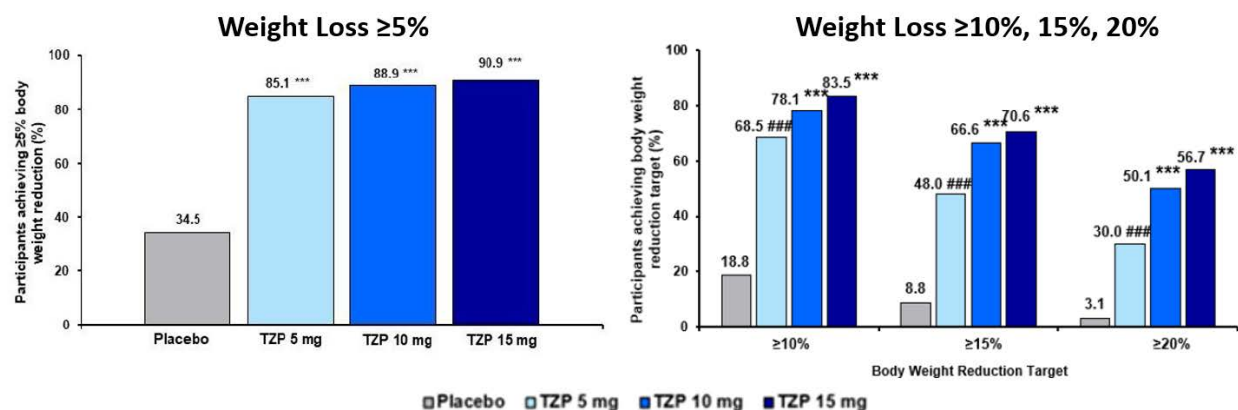
Figure 9. Cumulative Frequency Distribution of Body Weight Changes (Trial GPHK)



Source: Applicant's proposed prescribing information, similar to GPHK CSR, Figure GPHK.5.4

As detailed above in the endpoints description in Section 6.1.1, the Applicant also prespecified primary, key secondary, and other endpoints that were responder analyses of the proportion of subjects achieving specified weight loss thresholds ($\geq 5\%$, $\geq 10\%$, $\geq 15\%$, and $\geq 20\%$). These results were consistent with the distribution above, showed statistical significance, and will be tabulated in label Section 14 (Figure 10 summarizes these responder analyses using the treatment-regimen estimand). $\geq 25\%$ weight loss was not a prespecified endpoint, but this occurred in 15.3%, 32.3%, and 36.2% of trial GPHK subjects with tirzepatide 5 mg, 10 mg, and 15 mg, compared to 1.5% of subjects with placebo (treatment-regimen estimand, each $P < 0.001$ compared to placebo and not corrected for Type I error).

Figure 10. Responder Analyses of Body Weight Changes (Trial GPHK)



Source: Applicant SCE, Figures 2.7.3.3-4, page 27 of 123

Note 1: Logistic regression with missing value imputed by MMRM analysis for efficacy estimand; logistic regression with hybrid imputation analysis for treatment-regimen estimand.

Note 2: For the 10- and 15-mg groups, the percentage achieving ≥5% is a coprimary objective. For the 5-mg group, the percentage achieving ≥5% is a key secondary objective.

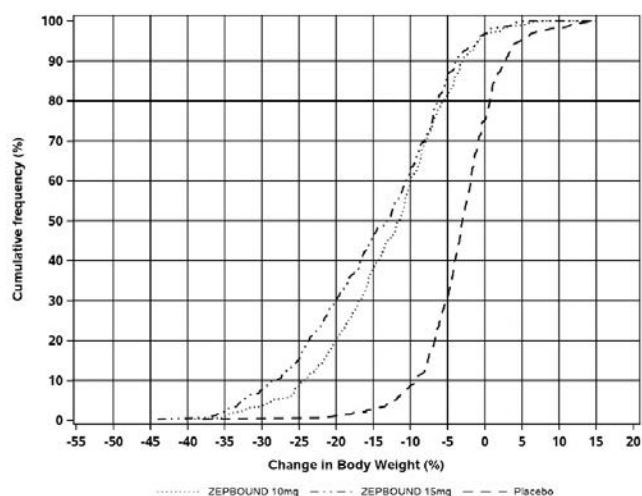
Note 3: For the 10- and 15-mg groups, the percentage achieving ≥10%, ≥15%, and ≥20% are key secondary objectives. For the 5-mg group, the percentage achieving ≥10% or ≥15% is an additional secondary objective, ≥20% is an additional prespecified objective, not controlled for type 1 error.

***p-Value <.001 versus placebo for objectives controlled for type 1 error.

###p-Value <.001 versus placebo for objectives not controlled for type 1 error

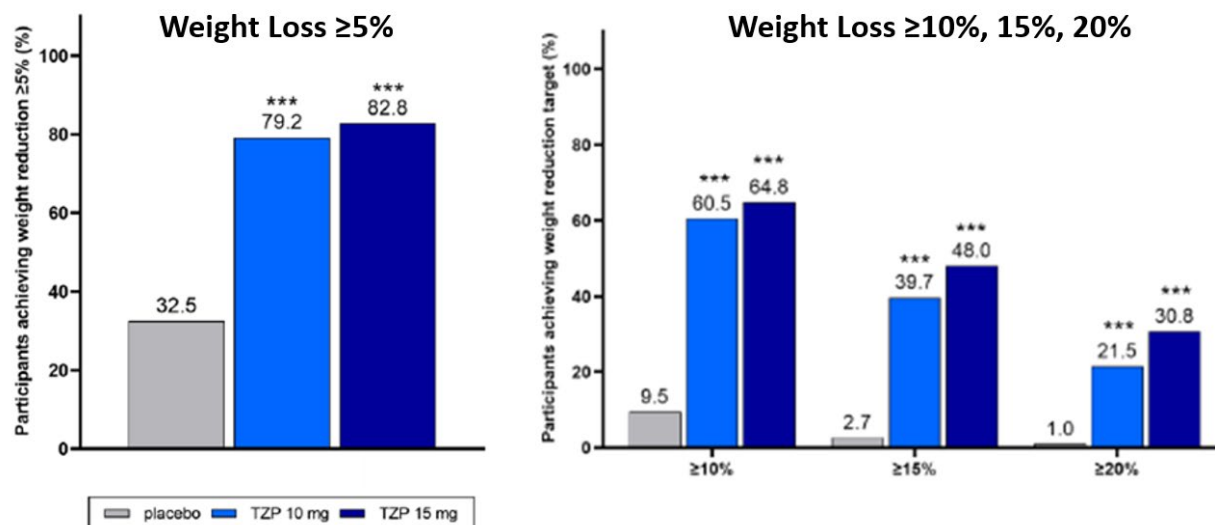
Similarly, for trial GPHL the Applicant presents cumulative frequency distributions (Figure 11) and responder analyses (Figure 12). ≥25% weight loss was not a prespecified endpoint, but this occurred in 9.0% and 15.5% of trial GPHL subjects with tirzepatide 10 mg and 15 mg, compared to 0.3% of subjects with placebo (treatment-regimen estimand, each $P < 0.001$ compared to placebo not corrected for Type I error).

Figure 11. Cumulative Frequency Distribution of Body Weight Changes (Trial GPLH)



Source: Applicant's proposed prescribing information, similar to GPLH CSR, Figure GPLH.5.4

Figure 12. Responder Analyses of Body Weight Changes (Trial GPLH)



Source: Applicant SCE, Figures 2.7.3.17-18, page 56 of 123

Note 1: Logistic regression with missing value imputed by MMRM analysis for efficacy estimand; logistic regression with hybrid imputation analysis for treatment-regimen estimand.

Note 2: For the 10- and 15-mg groups, the percentage achieving ≥5% is a coprimary objective. For the 5-mg group, the percentage achieving ≥5% is a key secondary objective.

Note 3: For the 10- and 15-mg groups, the percentage achieving ≥10%, ≥15%, and ≥20% are key secondary objectives. For the 5-mg group, the percentage achieving ≥10% or ≥15% is an additional secondary objective, ≥20% is an additional prespecified objective, not controlled for type 1 error.

***p-Value <.001 versus placebo for objectives controlled for type 1 error.

###p-Value <.001 versus placebo for objectives not controlled for type 1 error

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Since it can be challenging to interpret responder analyses to quantitatively assess benefit of investigational drugs for continuous interval outcomes,²⁰ the Division does not weigh these endpoints heavily in considering efficacy.

Effects in demographic and other subpopulations: The Applicant performed subgroup analyses for the following subject characteristics:

- age group (<65, ≥65 years), example graphical data for trial GPHK in Table 27
- race
- sex
- ethnicity
- region of enrollment (US, outside the US)
- baseline BMI category (<30, ≥30 and <35, ≥35 and <40, ≥40 kg/m²)
- glycemic status at randomization (normoglycemia versus prediabetes; applicable to GPHK/SURMOUNT-1 only)
- baseline HbA1c category (≤8.5%, >8.5%; applicable to GPHL/SURMOUNT-2 only)
- type of antihyperglycemic medications used at randomization (weight loss, weight gain, or weight neutral; applicable to GPHL/SURMOUNT-2 only)

For the primary endpoint of percent change in body weight, all subgroups showed significantly better weight reduction in the tirzepatide groups compared with the placebo group (using the treatment-regimen estimand, Table 28).

Table 27. Example Subgroup Analysis: Weight Loss by Age in Trial GPHK

Summary and Analysis of Percent Change in Body Weight (%) by Subgroup
MMRM By Treatment and Visit from Baseline to 72 Weeks
Modified Intent-to-Treat - Efficacy Analysis Set
I8F-MC-GPHK Primary Study Period
Variable Analyzed: Weight (kg)
[At Week 72 (Visit 21)]

Subgroup Category	Treatment	No. of Participants		LSM Difference (95% CI)	Interaction p-value
Pooled Age Group 1					0.724
<65	Placebo	449			
	TZP 5mg	496		-13.8 (-15.2, -12.5)	
	TZP 10mg	504		-19.2 (-20.5, -17.8)	
	TZP 15mg	507		-20.3 (-21.6, -19.0)	
≥65	Placebo	22			
	TZP 5mg	43		-11.6 (-15.4, -7.9)	
	TZP 10mg	27		-15.4 (-19.5, -11.2)	
	TZP 15mg	28		-19.1 (-23.2, -15.1)	

Source: Applicant GPHK CSR, Figure GPHK.5.25, page 197 of 3021

²⁰ Abugov R, Clark J, Higginbotham L, Li F, Nie L, Reasner D, Rothmann M, Yuan X, Sharretts J. Should responder analyses be conducted on continuous outcomes? Pharm Stat. 2023 Mar;22(2):312-327. doi: 10.1002/pst.2273. Epub 2022 Nov 23. PMID: 36418046.

Table 28. Summary of Subgroup Analyses for Change in Body Weight (Trials GPHK and GPHL)

Subgroup	p-Value for Treatment		p-Value for Treatment-by-Subgroup Interaction	
	SURMOUNT-1	SURMOUNT-2	SURMOUNT-1	SURMOUNT-2
N	2539	938	2539	938
Age (<65 , ≥ 65 years)	<0.001	<0.001	NS	NS
Race	<0.001	<0.001	NS	NS
Sex	<0.001	<0.001	0.010	NS
Ethnicity	<0.001	<0.001	0.022	NS
Geographic Region (US, OUS)	<0.001	<0.001	NS	NS
Baseline BMI Group (<30 , ≥ 30 to <35 , ≥ 35 to <40 , and ≥ 40 kg/m ²)	<0.001	<0.001	0.016	NS
Glycemic Status at Randomization (normoglycemia or prediabetes)	<0.001	-	NS	-
Baseline HbA1c Group ($\leq 8.5\%$, $>8.5\%$)	-	<0.001	-	0.025
Type of AHM used at Randomization (weight loss, weight gain, or weight neutral)	-	<0.001	-	NS

Abbreviations: - = not applicable; AHM = antihyperglycemic medication; ANCOVA = analysis of covariance; BMI = body mass index; CSR = clinical study report; HbA1c = glycosylated hemoglobin A1c; mITT = modified intent-to-treat; N = number of randomly assigned participants with obesity or overweight; NS = treatment-by-subgroup interaction p-value not considered significant ($p \geq 1$); OUS = outside the US.

Note 1: ANCOVA with hybrid imputation for missing body weight at the primary endpoint.

Note 2: Only treatment-by-subgroup interaction p-value $< .10$ is considered significant and presented in the table.

Note 3: Definitions of which types of AHM are considered weight loss, weight gain, or weight neutral are included in Section 6.3 of the SURMOUNT-2 protocol.

Sources: SURMOUNT-1 CSR Table GPHK.8.56 through Table GPHK.8.62 and SURMOUNT-2 CSR Table GPHL.8.71 through Table GPHL.8.78

Source: Applicant ISE, Table ISE.8.1, page 185 of 192

There are some statistically significant treatment-by-subgroup interactions in the table above (sex, ethnicity, and BMI category in GPHK and HbA1c category in GPHL), which the Applicant states have no obvious clinical relevance. These same interactions were identified by the FDA statistical review and are discussed below.

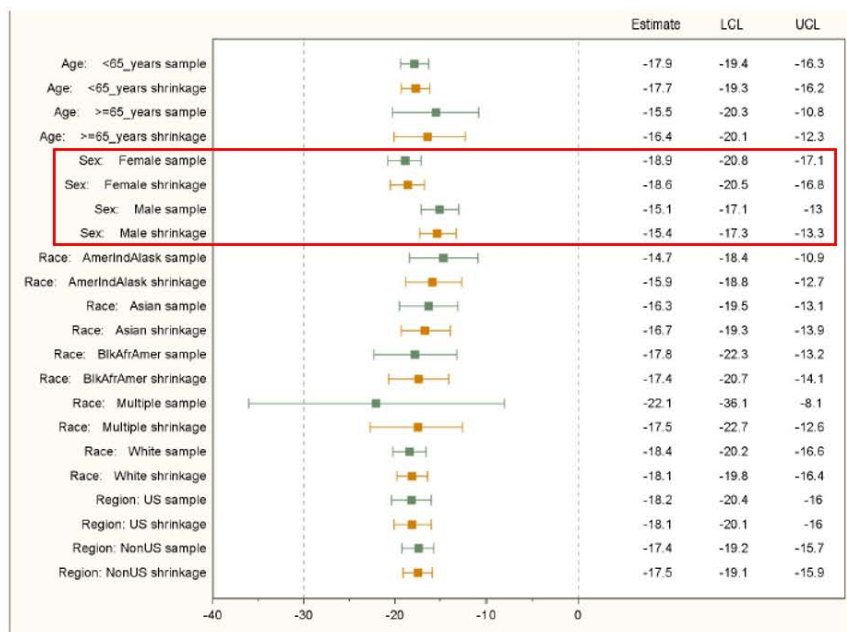
The Applicant presented the same subgroup analyses (not shown) for the co-primary endpoints of proportion achieving $\geq 5\%$ weight loss on tirzepatide 10 mg and 15 mg, with a similar lack of significant or relevant subgroup effects.

The FDA statistical reviewer Dr. Song also calculated shrinkage estimates of subgroup treatment effects using a Bayesian hierarchical model based on summary sample estimates; for details please see her review dated October 10, 2023. Briefly, for both trials the percent change from baseline in body weight at Week 72, all subgroups (sex, age, race, ethnicity, geographic region, baseline BMI, baseline prediabetes status in GPHK/SURMOUNT-1, and baseline HbA1c in GPHL/SURMOUNT-2) reported the upper limit of the 95% confidence interval less than zero, in favor of both tirzepatide 10 mg and 15 mg groups. With shrinkage estimates, the upper limits of the 95% credible intervals were also less than zero, in favor of tirzepatide (see examples below in Figure 13 and Figure 15).

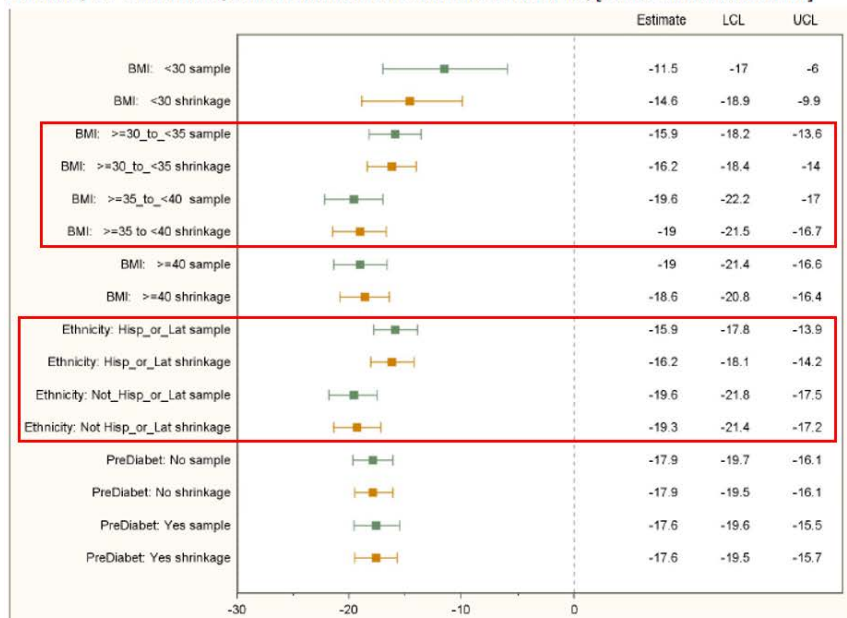
Of note, there were significant interaction effects between subgroups and tirzepatide treatment in trial GPHK/SURMOUNT-1 (Figure 13, red boxes), with weight reduction apparently more favorable:

- for females than for males
- for high baseline BMI than low baseline BMI
- for not Hispanic/Latino than Hispanic/Latino ethnicity

Figure 13. Selected Subgroup Analysis Results for Tirzepatide 15 mg Versus Placebo (Trial GPHK)



Note: Subgroup analysis results are shown for the %change from baseline at Week 72 in body weight; Sample estimates are shown with the corresponding 95% confidence interval (in green) and shrinkage estimates are shown with the corresponding 95% credible interval (in orange); LCL: lower confidence (or credible) limit; UCL: upper confidence (or credible) limit; AmerIndAlask=American Indian or Alaskan Native; BlkAfrAmer=Black or African American; US=United States; Dotted vertical lines are drawn at zero and at -30; [Source: Statistical Reviewer]



Note: Subgroup analysis results are shown for the %change from baseline at Week 72 in body weight; Sample estimates are shown with the corresponding 95% confidence interval (in green) and shrinkage estimates are shown with the corresponding 95% credible interval (in orange); LCL: lower confidence (or credible) limit; UCL: upper confidence (or credible) limit; BMI=body mass index (in kg/m²); Hisp_or_Lat=Hispanic or Latino; PreDiabet=prediabetes status at baseline; Dotted vertical line indicates zero; [Source: Statistical Reviewer]

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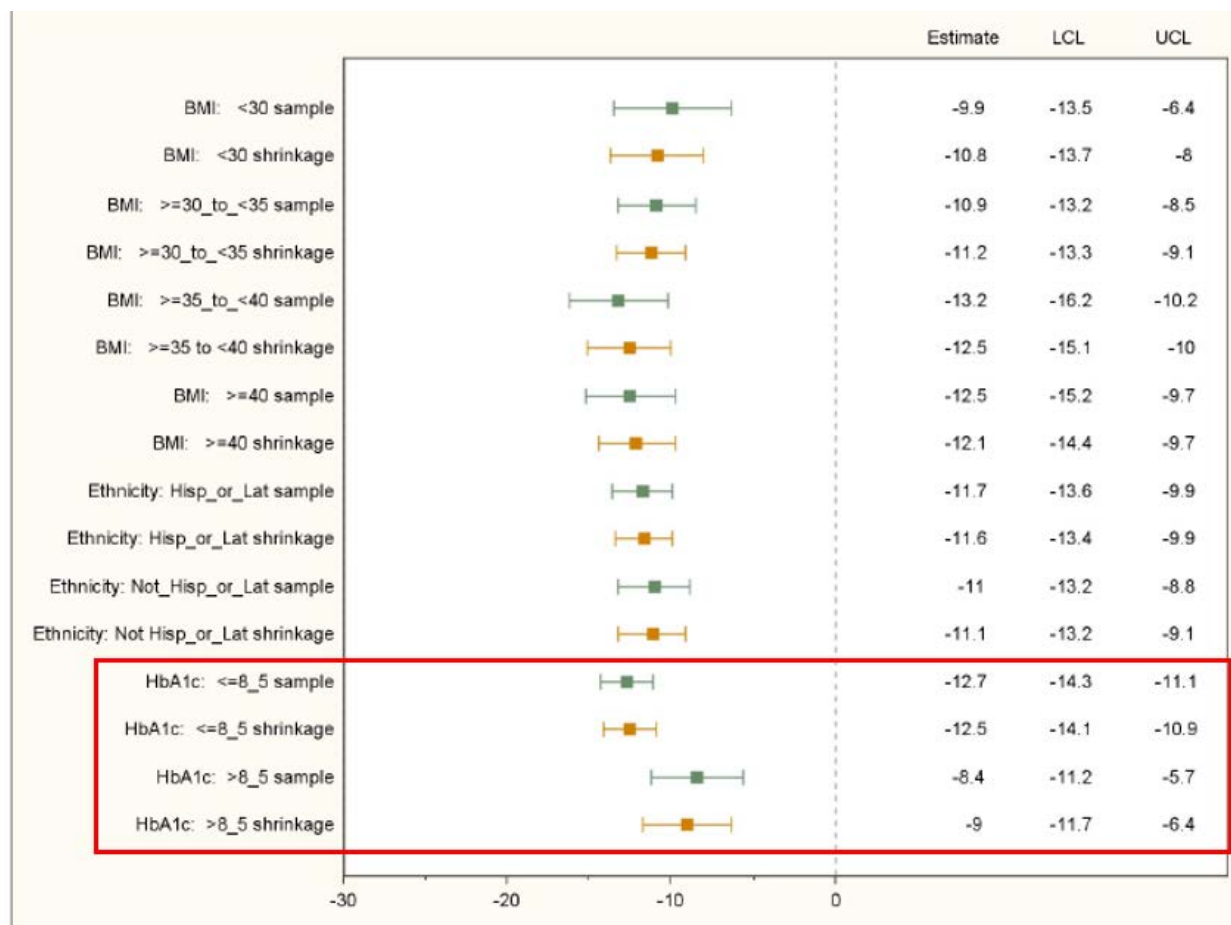
Raymond Soccio, MD, PhD

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In trial GPLH, weight reduction was apparently more favorable for those with lower versus higher baseline HbA1c values (Figure 14, red box).

Figure 14. Selected Subgroup Analysis Results for Tirzepatide 15 mg Versus Placebo (Trial GPLH)



Note: Subgroup analysis results are shown for the %change from baseline at Week 72 in body weight; Sample estimates are shown with the corresponding 95% confidence interval (in green) and shrinkage estimates are shown with the corresponding 95% credible interval (in orange); LCL: lower confidence (or credible) limit; UCL: upper confidence (or credible) limit; BMI=body mass index (in kg/m²); Hisp_or_Lat=Hispanic or Latino; HbA1c:<=8_5=baseline HbA1c ≤8.5%; HbA1c: >8_5=baseline HbA1c>8.5%; Dotted vertical line indicates zero; [Source: Statistical Reviewer]

Per Dr. Song's statistical review, these interactions were quantitative and not qualitative as the study drug was superior to placebo in all subgroups, but further investigation is necessary to understand the observed differences in treatment effects between subgroups.

Reviewer comment: There were four identified interaction terms with a significant p-value for the primary endpoint: sex, ethnicity, baseline BMI, and baseline HbA1c. Although statistically more weight loss was observed in females than in males, in those with BMI ≥ 35 kg/m² than

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those with lower BMIs, in those not identified as Hispanic/Latino ethnicity, and in those with T2D and HbA1c $\leq$ 8.5%, the 95% confidence intervals between subgroups overlapped. Further, despite these statistical findings, from a clinical perspective the weight loss was clinically meaningful in all subgroups (including men, those with BMI <35 kg/m², those identified as Hispanic/Latino ethnicity, and those with T2D and HbA1c $>$ 8.5%). For example, the difference in mean weight loss between females and males was -18.9% vs. -15.1%. An approximately 15% reduction in baseline weight is clinically meaningful and larger than the average treatment effect of lifestyle intervention and most approved CWM drugs (although cross-trial comparisons should be made with caution). Therefore, even with evidence of statistical differences in weight loss in some subgroups, the difference is not considered clinically meaningful and labeling should not reflect subgroup-specific efficacy.

Analysis by site: I compared efficacy for the primary endpoints at different trial sites, and no anomalies were identified.

Data Quality and Integrity

OSI inspected 6 trial sites for GPHK and found no significant issues at these sites (Section 4.1).

The Applicant did not analyze efficacy excluding the small number of sites (see Section 6.1.2, Financial Disclosures heading above) where investigators received significant financial compensation, but this was not considered necessary given the trial design (blinding and objective measure of body weight as the primary endpoint).

Two trial sites had known or suspected GCP noncompliance (see Section 6.1.2, Compliance with Good Clinical Practices heading above). Subjects at these two sites represented 1.3% of the total randomized in trial GPHK and 2.8% of the total randomized in trial GPHL. In response to an information request, the Applicant provided sensitivity analyses of the primary endpoints excluding these two sites. The results in the two trials were not meaningfully different, as there was slightly more weight loss efficacy when these sites with GCP noncompliance were excluded (Table 29 and Table 30).

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Table 29. Sensitivity Analysis of Primary Endpoints Excluding Sites with GCP noncompliance (Trial GPHK)

Modified Intent-to-Treat (mITT) Population ^a	SURMOUNT-1 (All Sites)				SURMOUNT-1 (Excluding Sites 708 and 803) ^{c,e}			
	Placebo N = 643	Tirzepatide 5 mg ^b N = 630	Tirzepatide 10 mg N = 636	Tirzepatide 15 mg N = 630	Placebo N = 635	Tirzepatide 5 mg N = 621	Tirzepatide 10 mg N = 626	Tirzepatide 15 mg N = 625
Body Weight								
Baseline mean (kg)	104.8	102.9	105.8	105.6	104.9	103.1	106.2	105.6
% change from baseline at Week 72 ^c	-3.1	-15.0	-19.5	-20.9	-3.2	-15.1	-19.6	-20.9
% change difference from placebo ^c (95% CI)		-11.9 (-13.4, -10.4) ^d	-16.4 (-17.9, -14.8) ^d	-17.8 (-19.3, -16.3) ^d		-12.0 (-13.5, -10.4) ^d	-16.4 (-18.0, -14.8) ^d	-17.8 (-19.2, -16.3) ^d
% of participants losing ≥5% body weight at Week 72	34.5	85.1	88.9	90.9	34.7	85.3	89.1	90.8
Odds ratio (95% CI)		11.5 (8.0, 16.4) ^{d,e}	16.7 (11.5, 24.3) ^{d,e}	20.6 (13.6, 31.3) ^{d,e}		11.6 (8.1, 16.7) ^{d,e}	17.0 (11.5, 25.2) ^{d,e}	20.2 (13.6, 29.9) ^{d,e}

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; COVID-19 = coronavirus disease 2019; N = number of participants randomly assigned to study drug.

- ^a The modified intent-to-treat population includes all randomly assigned participants who were exposed to at least 1 dose of study drug. The missing values were imputed based on retrieved dropouts from the same treatment group (if missing not due to COVID-19) or using all non-missing data assuming missing at random (for missing solely due to COVID-19).
- ^b Assessments of the tirzepatide 5-mg dose on these efficacy endpoints were considered key secondary objectives.
- ^c Least-squares mean from ANCOVA adjusted for baseline value and other stratification factors.
- ^d p-value<0.001 (unadjusted 2-sided).
- ^e Analyzed using logistic regression adjusted for baseline value and other stratification factors.

Note: Red font shows the differences between the summary excluding Sites 708 and 803 and the summary of all sites.

Source: Applicant Regulatory Response dated October 6, 2023, to FDA information request

Table 30. Sensitivity Analysis of Primary Endpoints Excluding Sites with GCP noncompliance (Trial GPHL)

Modified Intent-to-Treat (mITT) Population ^a	SURMOUNT-2 (All Sites)			SURMOUNT-2 (Excluding Site 23220)		
	Placebo N = 315	Tirzepatide 10 mg N = 312	Tirzepatide 15 mg N = 311	Placebo N = 307	Tirzepatide 10 mg N = 302	Tirzepatide 15 mg N = 303
Body Weight						
Baseline mean (kg)	101.7	100.9	99.6	102.0	101.5	99.9
% change from baseline at Week 72 ^b	-3.2	-12.8	-14.7	-3.2	-13.0	-14.9
% difference from placebo ^b (95% CI)		-9.6 (-11.1, -8.1) ^c	-11.6 (-13.0, -10.1) ^c		-9.8 (-11.4, -8.3) ^c	-11.7 (-13.2, -10.2) ^c
% of participants losing ≥5% body weight at Week 72	32.5	79.2	82.8	33.0	80.3	83.2
Odds ratio (95% CI)		8.3 (5.6, 12.3) ^{c,d}	10.5 (6.8, 16.1) ^{c,d}		8.6 (5.7, 12.8) ^{c,d}	10.5 (6.8, 16.3) ^{c,d}

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; COVID-19 = coronavirus disease 2019; N = number of participants randomly assigned to study drug.

- ^a The modified intent-to-treat population includes all randomly assigned participants who were exposed to at least 1 dose of study drug. The missing values were imputed by a hybrid approach using retrieved dropouts from the same treatment group (if missing not due to COVID-19) or using all non-missing data assuming missing at random (for missing solely due to COVID-19).
- ^b Least-squares mean from ANCOVA adjusted for baseline value and other stratification factors.
- ^c p-value<0.001 (unadjusted 2-sided).
- ^d Analyzed using logistic regression adjusted for baseline value and other stratification factors.

Note: Red font shows the differences between the summary excluding Site 23220 and the summary of all sites.

Source: Applicant Regulatory Response dated October 6, 2023, to FDA information request

Based on these results, no potential data quality or integrity issues in trials GPHK and GPHL were identified that could have affected the overall efficacy results or conclusions.

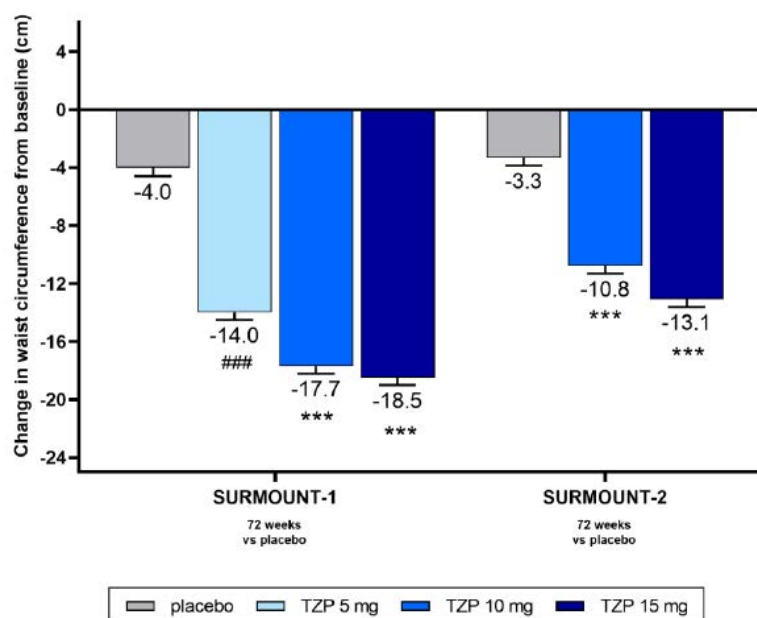
(b) (4)

The Division recommends the following secondary efficacy endpoints in CWM trials:²¹

- Waist circumference
- Lipid parameters
- Blood Pressure and pulse (pulse is considered separately in Section 8.4.6 below)
- Fasting glucose and insulin
- HbA1c (in subjects with T2D)

Results for these endpoints are shown in the Figures below. The FDA statistical reviewer Dr. Song was able to confirm all key secondary endpoint analyses; for details please see her review dated October 10, 2023.

Figure 15. Mean Changes from Baseline in Waist Circumference (Trials GPHK and GPHL)



Source: Applicant SCE, Figure 2.7.3.35, page 92 of 123

Note: least squares means $\pm$ standard errors using treatment regimen estimand

***p-Value <.001 versus placebo, controlled for type 1 error.

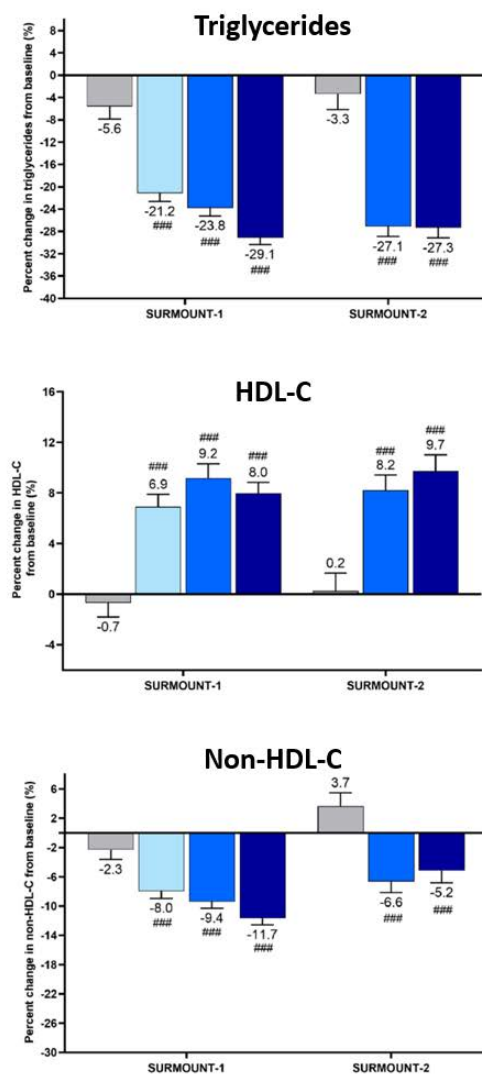
###p-Value <.001 versus placebo, not controlled for type 1 error.

Reviewer comment: As noted in the Division's guidance, waist circumference is an indirect measure of visceral fat content that should be measured not to show weight loss efficacy, but to confirm that reductions in weight are associated with expected improvements in other weight-related metabolic parameters.

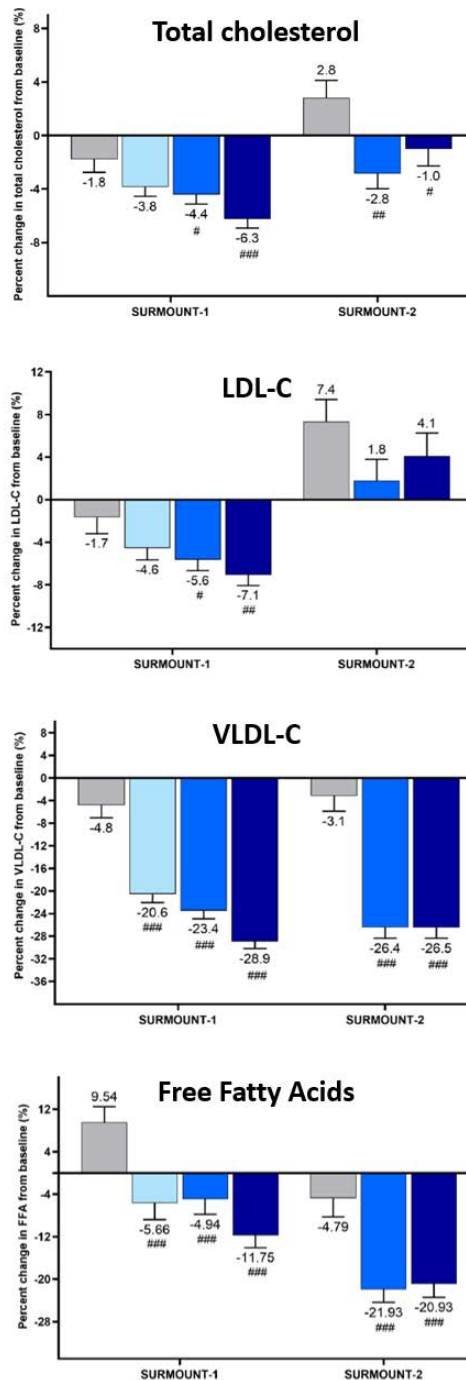
²¹ FDA GFI "Developing Products for Weight Management"

Figure 16. Mean Changes from Baseline in Lipid Parameters (Trials GPHK and GPHL)

Key Secondary



Secondary



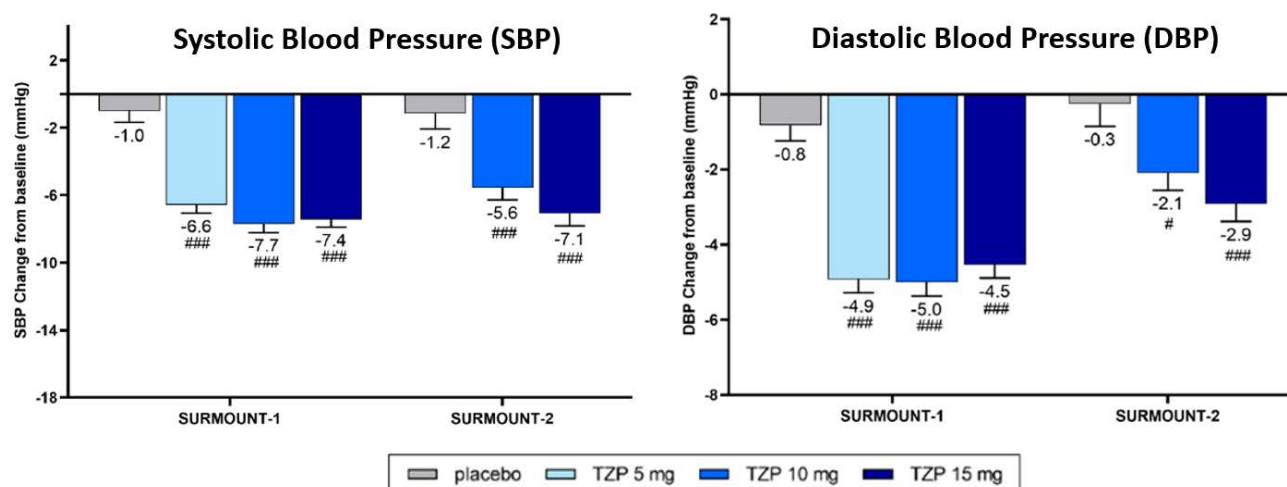
Source: Applicant SCE, Figure 2.7.3.36-43, page 94 of 123

Note: estimated means $\pm$ standard errors using treatment-regimen estimand

###p-Value <.001 versus placebo, not controlled for type 1 error.

Reviewer comment: Tirzepatide lowers triglycerides and raises HDL-C. Other cholesterol values (non-HDL, total, LDL-C, and VLDL-C) correlate with increased ASCVD risk, and tirzepatide generally reduced these measurements from baseline. In trial GPHL (subjects with T2D), tirzepatide did not lower LDL-C and had minimal effects on total cholesterol, likely attributable to the high baseline statin use and relatively low mean baseline LDL-C values in this trial (<100 mg/dL, see above).

Figure 17. Mean Changes from Baseline in Blood Pressure (Trials GPHK and GPHL)



Source: Applicant SCE, Figures 2.7.3.43-44, page 102 of 123

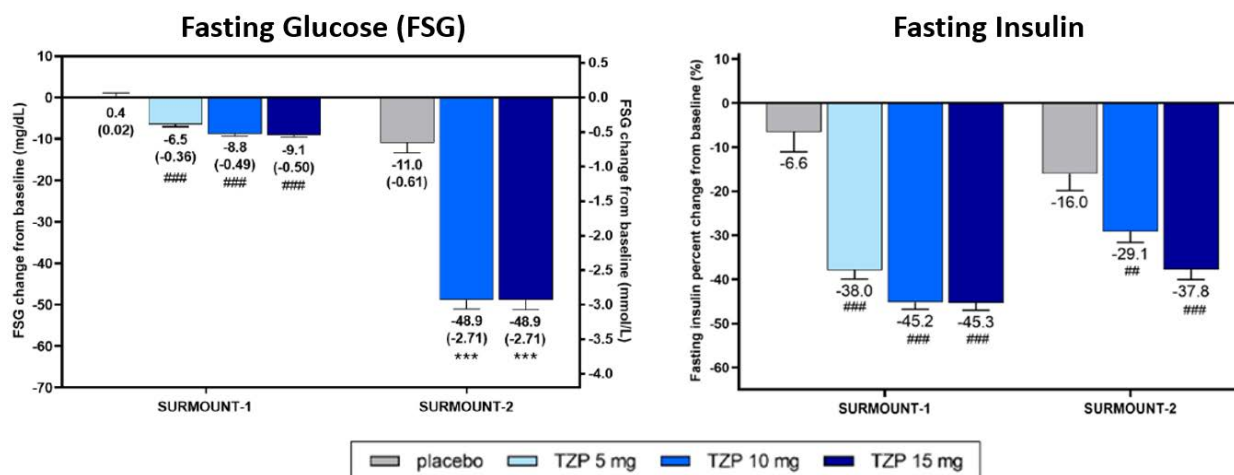
Note: least squares means $\pm$ standard errors using treatment regimen estimand

***p-Value < .001 versus placebo, controlled for type 1 error.

###p-Value < .001 versus placebo, not controlled for type 1 error.

Reviewer comment: Tirzepatide lowered systolic and diastolic blood pressure at all studied maintenance dosages. This reduction in blood pressure was observed despite the reduced use of antihypertensive medications in the tirzepatide arms (see Table 19 and Table 20 above). These reductions in blood pressure are clinically meaningful and would be predicted to improve cardiovascular outcomes.

Figure 18. Mean Changes from Baseline in Fasting Glucose and Insulin (Trials GPHK and GPHL)



Source: Applicant SCE, Figure 2.7.3.46-47, page 108 of 123

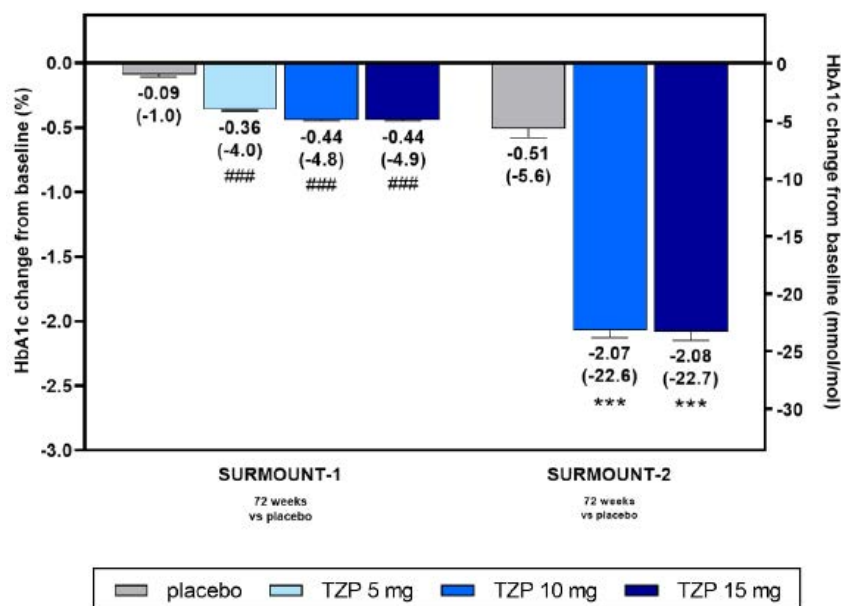
Note: least squares means $\pm$ standard errors for glucose and estimated means $\pm$ standard errors for insulin, both using treatment-regimen estimand

***p-Value <.001 versus placebo, controlled for type 1 error.

###p-Value <.001 versus placebo, not controlled for type 1 error.

Reviewer comment: *The reductions in both fasting insulin and glucose suggest that tirzepatide-treated subjects have become more insulin-sensitive (consistent with weight loss). The Division's guidance recommends glucose and insulin as secondary endpoints, but it is important to note* (b) (4)

Figure 19. Mean Changes from Baseline in HbA1c (Trials GPHK and GPHL)



Source: Applicant SCE, Figure 2.7.3.45, page 106 of 123

Note: least squares means $\pm$ standard errors using treatment-regimen estimand

***p-Value <.001 versus placebo, controlled for type 1 error.

###p-Value <.001 versus placebo, not controlled for type 1 error.

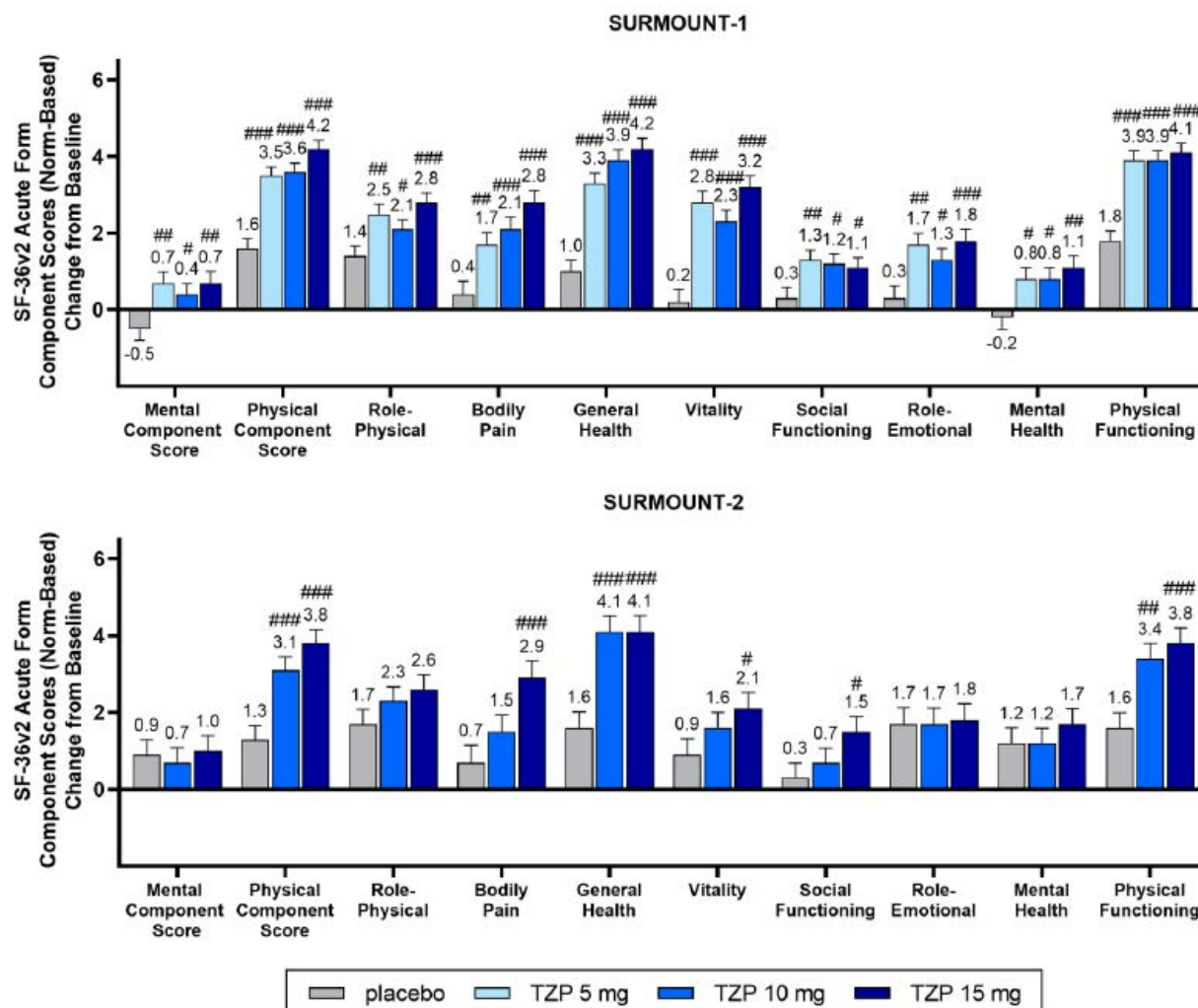
Reviewer comment: *The reductions in HbA1c in trial GPHL (>2% with tirzepatide and >1.5% more than placebo comparator) are consistent with those observed in the SURPASS trials for T2D, reviewed in NDA 215866.*

The Division's guidance notes that effective CWM is expected to improve these metabolic parameters (waist circumference, blood pressure, lipids, and glycemia), and the results above confirm this for tirzepatide. The guidance also notes that many trial subjects will be taking baseline concomitant medications for hypertension or T2D, and that an additional important endpoint is those subjects who have meaningful dose-reduction or complete withdrawal of these medications. In trials GPHK and GPHL, tirzepatide-treated subjects reduced these medications more than placebo-treated subjects (see Table 18, Table 19, and Table 20 above, under concomitant medications).

The Applicant also presents data from two patient-reported outcomes (PRO) instruments in trials GPHK and GPHL: the 36-item Short Form Health Survey version 2 (SF-36v2) Acute Form (Figure 20) and the Impact of Weight on Quality of Life-Lite (IWQOL-Lite, Figure 21). Change from baseline in SF-36v2 Physical Functioning Domain Score was a multiplicity-controlled key secondary endpoint in trial GPHK (comparing the pooled 10 mg and 15 mg weekly dosages to placebo), while this was a secondary endpoint in trial GPHL, and all other PRO-related endpoints were secondary or exploratory.

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Figure 20. Mean Changes from Baseline in SF-36v2 Acute Form Domains and Component Summary Scores (Trials GPHK and GPHL)

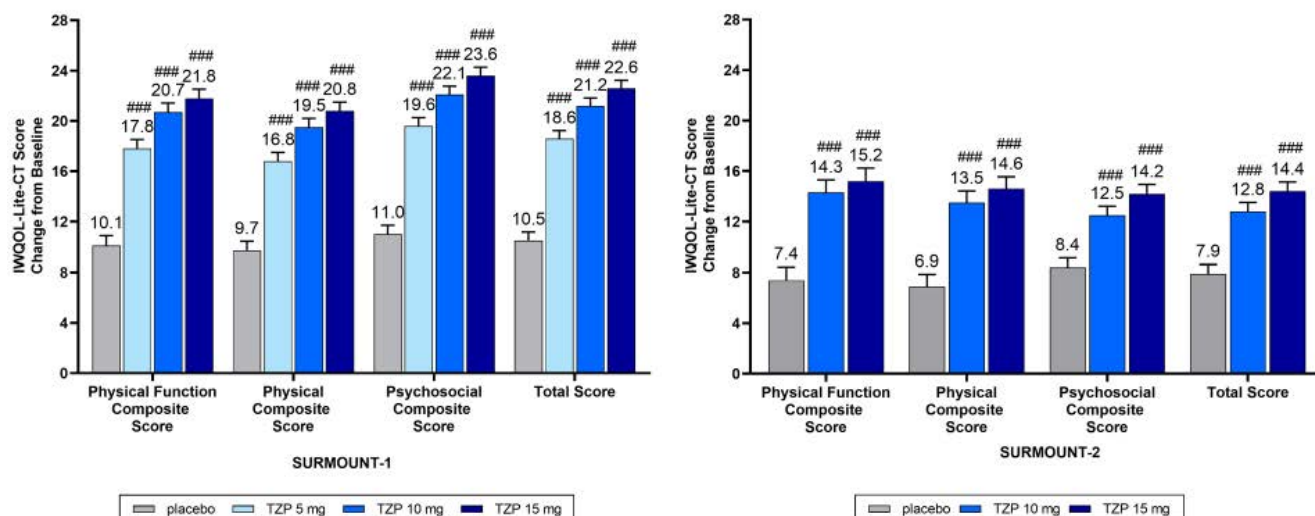


Source: Applicant SCE, Figure 2.7.3.48, page 113 of 123

Note 1: ANCOVA (LOCF). Only the non-missing postbaseline observation prior to study treatment discontinuation was carried forward. Least squares means $\pm$ standard errors of norm-based scores.

#p-Value <.05, ##p-value <.01, ###p-value <.001 versus placebo, not controlled for type 1 error.

Figure 21. Mean Changes from Baseline in IWQOL-Lite-CT (Trials GPHK and GPHL)



Source: Applicant SCE, Figure 2.7.3.49, page 115 of 123

Note 1: ANCOVA (LOCF). Only the nonmissing postbaseline observation prior to study treatment discontinuation was carried forward. Least squares means $\pm$ standard errors of norm-based scores.

#p-Value <.05, ##p-value <.01, ###p-value <.001 versus placebo, not controlled for type 1 error.

Since only physical functioning PROs (b) (4) only this aspect is discussed here, as jointly reviewed by Drs. Qing Xie and Selena Daniels of DCOA and Drs. Xin Yuan and Lili Garrard of the Patient-Focused Statistical Scientists (PFSS). Please see the joint DCOA/PFSS review dated October 18, 2023, for details on the physical functioning endpoints, with the key results and conclusions summarized below.

The data from trial GPHK showed a statistically significant improvement in SF-36v2 Physical Functioning Domain Scores, with similar increases in trial GPHL that were nominally improved but not significant due to lack of multiplicity control (Table 31). The DCOA/PFSS review noted the following issues with this result, despite achievement of statistical significance:

- The differences between treatment and placebo means were small and of uncertain clinical meaningfulness.
- Measurement at only two time points (Baseline and Week 72 or early discontinuation) could have missed information.
- The baseline scores of 47.9-49.6 in the treatment arms are similar to the general population mean of 50, such that subjects were not sufficiently limited in physical functioning at baseline for an adequate assessment of improvement.
- There were minimal to no observed changes in median raw scores for the item- and domain-level data.
- The changes observed in the normalized scores were also minimal as evidenced by lack of clear separation between the treatment arms in the empirical cumulative distribution function (eCDF) curves (Figure 22).

Table 31. Mean Change from Baseline in SF-36v2 Physical Functioning Domain Scores, Overall Trial Populations in GPHK and GPHL

Parameters	SURMOUNT-1		SURMOUNT-2		
	Placebo (N = 643)	Pooled TZP 10/15 mg (N = 1266)	Placebo (N=315)	TZP 10 mg (N=312)	TZP 15 mg (N=311)
Treatment-regimen estimand					
n	643	1264	270	281	270
Baseline	49.6	49.5	47.9	48.5	48.1
Change from baseline at Week 72	1.7	3.6	1.6	3.4	3.8
Change difference from placebo at Week 72 (95% CI)	N/A	1.9*** (1.0, 2.9)	N/A	1.8 (0.7, 2.9)	2.3 (1.1, 3.4)

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; mITT = modified intent-to-treat; N = number of participants who were randomly assigned and received at least 1 dose of study drug; n = number of participants in the mITT analysis set with baseline and at least 1 postbaseline value; N/A = not applicable; SF-36v2 = Short-Form-36 Health Survey, Version 2; TZP = tirzepatide.

Note: ANCOVA with hybrid imputation for missing values at 72 weeks.

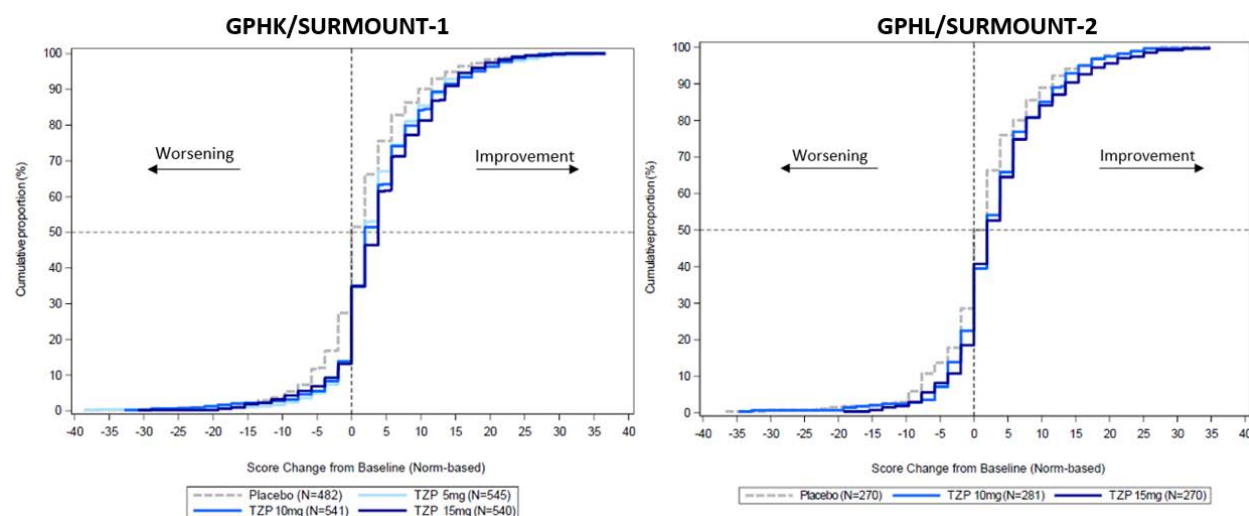
Shown are least-squares means.

***p-Value <0.001 versus placebo for superiority.

Source: Tables GPHK.5.9 of the SURMOUNT-1 Clinical Study Report and Table GPHL.5.25 of the SURMOUNT-2 Clinical Study Report.

Source: DCOA/PFSS review dated October 18, 2023.

Figure 22. Cumulative Distribution of Changes from Baseline in SF-26v2 Physical Functioning Domain Scores, Whole Trial Populations in GPHK and GPHL



Source: DCOA/PFSS review dated October 18, 2023, modified from Applicant Regulatory Response dated August 11, 2023.

(b) (4)

A subgroup analysis of those subjects

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with impaired function at baseline could be more informative; based on earlier FDA comments the Applicant proposed such exploratory analyses in the SAPs for both trials. The Patient Global Impression of Status for Physical Activity (PGIS) has a 5-point scale: “not limited at all,” “a little limited,” “moderately limited,” “very much limited,” and “extremely limited.” The Applicant defined impairment at baseline as PGIS “moderately limited” or worse, which appears reasonable and correlates with lower mean SF-36v2 physical function domain scores. By this definition, in trials GPHK and GPHL, 526/2539 (20.7%) and 216/938 (23.0%) of subjects had impaired physical functioning at baseline. In this impaired at baseline subgroup, the improvements from baseline mean SF-36v2 physical functioning domain scores were nominally greater than in the overall population (approximately 3 units in Table 32 below compared to approximately 2 units in Table 31 above).

Table 32. Mean Change from Baseline in SF-36v2 Physical Functioning Domain Scores, Impaired at Baseline Trial Populations in GPHK and GPHL

Parameters	SURMOUNT-1		SURMOUNT-2		
	Placebo (N = 643)	Pooled TZP 10/15 mg (N = 1266)	Placebo (N = 315)	TZP 10 mg (N = 312)	TZP 15 mg (N = 311)
Treatment-regimen estimand					
n	130	265	59	64	64
Baseline	43.0	43.1	643	48.3	48.2
Change from baseline at 72 weeks	3.9	7.0	0.5	3.3	3.4
Change difference from placebo at 72 weeks (95% CI)	N/A	3.1 (1.2, 5.0)	N/A	2.8 (1.4, 4.3)	3.0 (1.6, 4.4)

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; mITT = modified intent-to-treat; N = number of participants who were randomly assigned and received at least 1 dose of study drug; n = number of participants in the mITT analysis set with baseline and at least 1 postbaseline value; N/A = not applicable; SF-36v2 = Short-Form-36 Health Survey, Version 2; TZP = tirzepatide.

Note: ANCOVA with hybrid imputation for missing values at 72 weeks.

Shown are least-squares means.

Source: Table GPHK.5.10 of the SURMOUNT-1 Clinical Study Report and Table 4.1 of the applicant response to FDA IR dated September 25, 2023.

Source: DCOA/PFSS review dated October 18, 2023.

Reviewer comment: In the table above, there are apparent errors in the baseline SF-36v2 physical function domain scores for trial GPHL/SURMOUNT-2. Based on the DCOA/PFSS review, the means for this trial subgroup range from 43.0-43.1 consistent with impairment at baseline. This is likely a typographical error that does not affect the overall results or conclusions.

Furthermore, the eCDF curves for the impaired at baseline subgroup show separation of tirzepatide from placebo curves (though not as clearly for the tirzepatide 10 mg dosage in trial

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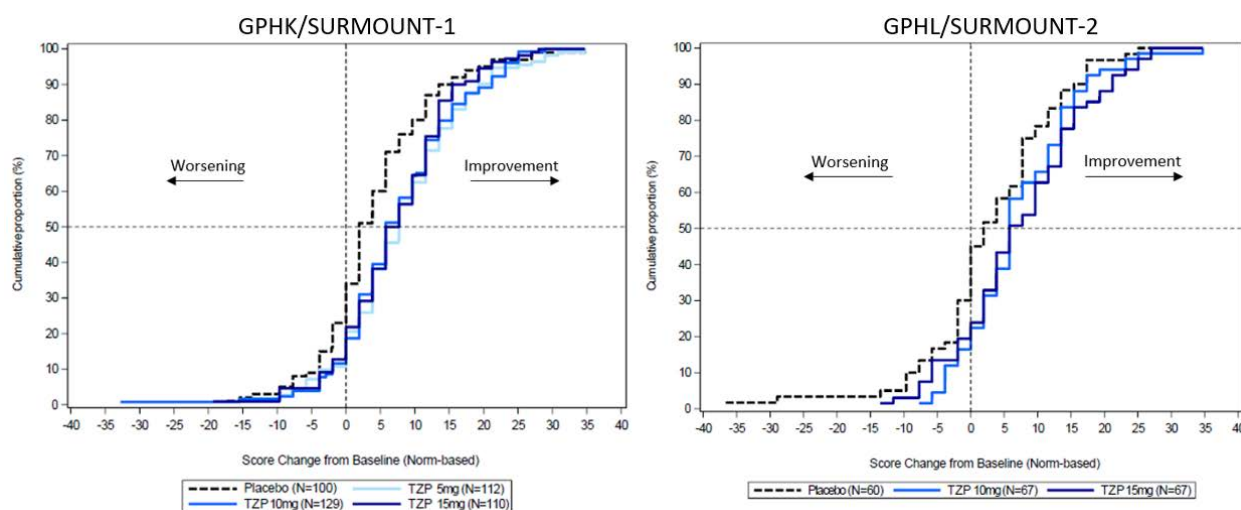
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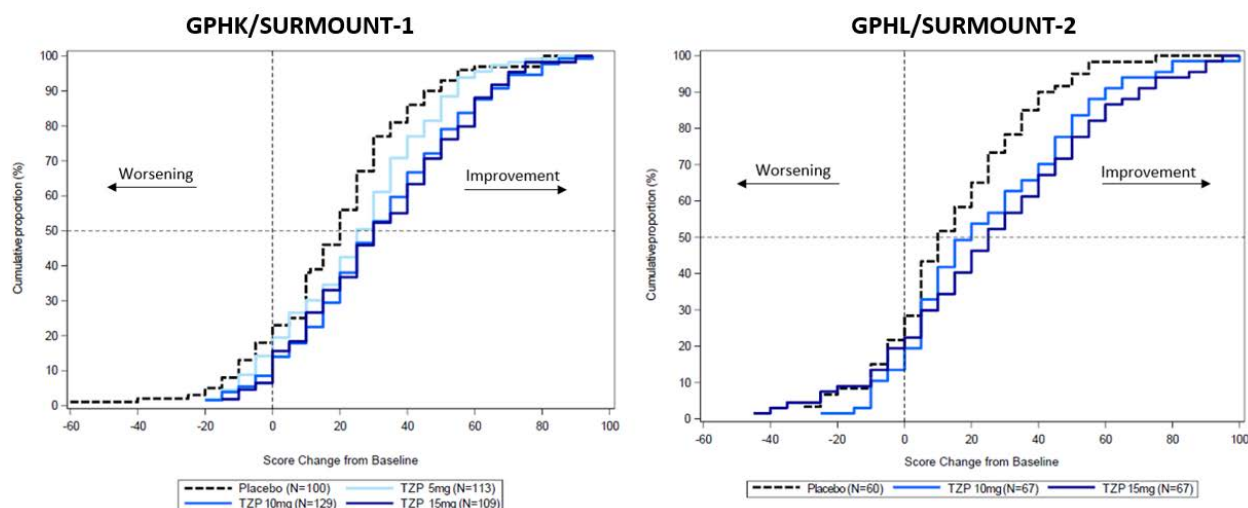
GPHL, Figure 23). Supporting this result with an independent PRO for physical function, the Applicant also provided eCDF curves showing separation for IWQOL-Lite-CT Physical Functioning domain scores in the impaired at baseline subgroup (Figure 24).

Figure 23. Distribution of Changes from Baseline in SF-26v2 Physical Functioning Domain Scores, Impaired at Baseline Trial Populations in GPHK and GPHL



Source: DCOA/PFSS review dated October 18, 2023, modified from Applicant Regulatory Response dated September 29, 2023.

Figure 24. Distribution of Changes from Baseline in IWQOL-Lite-CT Physical Functioning Domain score, Impaired at Baseline Trial Populations in GPHK and GPHL



Source: DCOA/PFSS review dated October 18, 2023, modified from Applicant Regulatory Response dated September 29, 2023.

The Applicant used both anchor-based analyses and qualitative methods (cognitive interviews) to support the proposed threshold(s) for meaningful within-patient change in the SF-36v2

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Physical Functioning domain score. As detailed in the DCOA/PFSS review, there were limitations to the anchor-based analysis (PGIS was not an ideal anchor since it was also used to define the impaired at baseline subgroup) and the cognitive interviews (querying the smallest meaningful improvement in only one item using a hypothetical approach, rather than a clinically meaningful improvements in multiple items using actual responses). Therefore, the DCOA/PFSS review concluded it was uncertain whether the observed changes in physical functioning scores, ranging from 2-3, were clinically meaningful.

Reviewer comment: The discussion above identifies three major limitations to the physical functioning results in trials GPHK and GPHL:

- ***There was no convincing treatment difference in the overall trial populations.***
- ***There was some evidence of treatment difference in the impaired at baseline subgroup that was prespecified, but this analysis was exploratory and not multiplicity-controlled.***
- ***There remains major uncertainty that the observed change of 2-3 on physical function scores represents a clinically meaningful difference.***

These issues were discussed with leadership of DDLO and DCOA.

(b) (4)

(b) (4)

Dose/Dose Response

See Section 7.1.4 below.

Trial GPHK included percent weight change at Week 20 as a key secondary endpoint controlled for Type I error, and there was significant and meaningful weight loss in the pooled tirzepatide 10 mg and 15 mg groups. This Week 20 time point mainly reflects weight loss during dosage titration: subjects following the planned dosage escalation would have been on the tirzepatide 10 mg maintenance dosage for 8 weeks, and in the tirzepatide 15 mg arm they would be in the process of increasing from 12.5 mg to the 15 mg maintenance dosage. >10% placebo-corrected statistically-significant weight loss was observed at Week 20 (Table 33).

Table 33. Change in Body Weight at Week 20 (Trial GPHK)

Parameters (kg)	Placebo (N = 643)	TZP 10/15 mg (N = 1266)
Treatment-regimen estimand^a		
Baseline	104.8	105.7
Change from baseline at 20 weeks	-2.7 ^{†††}	-12.8 ^{†††}
Change difference from placebo at 20 weeks (95% CI)	N/A	-10.1 ^{***} (-10.7, -9.6)
Efficacy Estimand^b		
Baseline	104.8	105.7
Change from baseline at 20 weeks	-2.5 ^{†††}	-13.2 ^{†††}
Change difference from placebo at 20 weeks (95% CI)	N/A	-10.7 ^{***} (-11.2, -10.1)

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; mITT = modified intent-to-treat; MMRM = mixed model for repeated measures; N = number of participants who were randomly assigned and received at least 1 dose of study drug; N/A = not applicable; TZP = tirzepatide.

^a ANCOVA with hybrid imputations for missing body weight at 20 weeks. Section 3.7.1 defines hybrid imputation.

^b MMRM analysis.

Note: Shown are the least squares means.

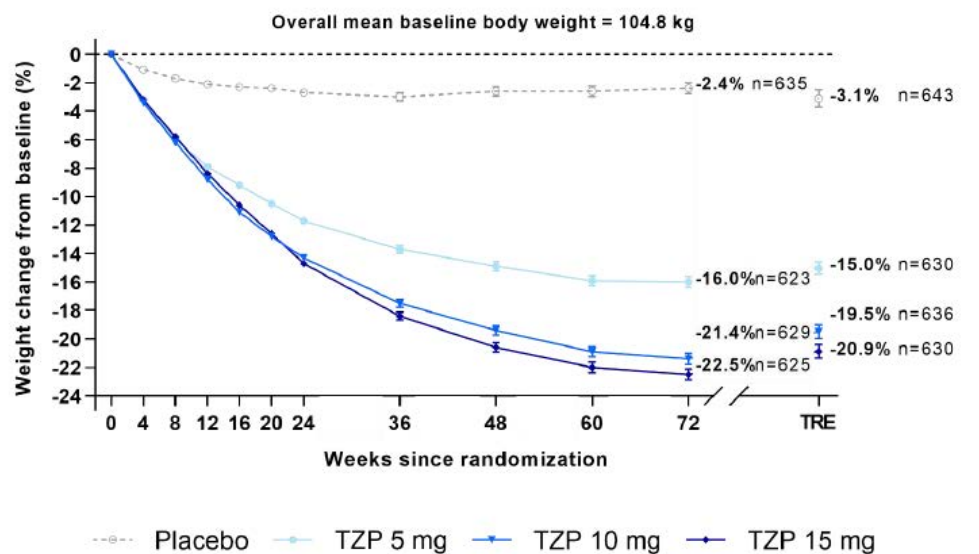
***p-Value <0.001 versus placebo for superiority.

†††p-Value <0.001 versus baseline.

Source: Applicant GPHK CSR, Table GPHK.5.4, page 98 of 3021

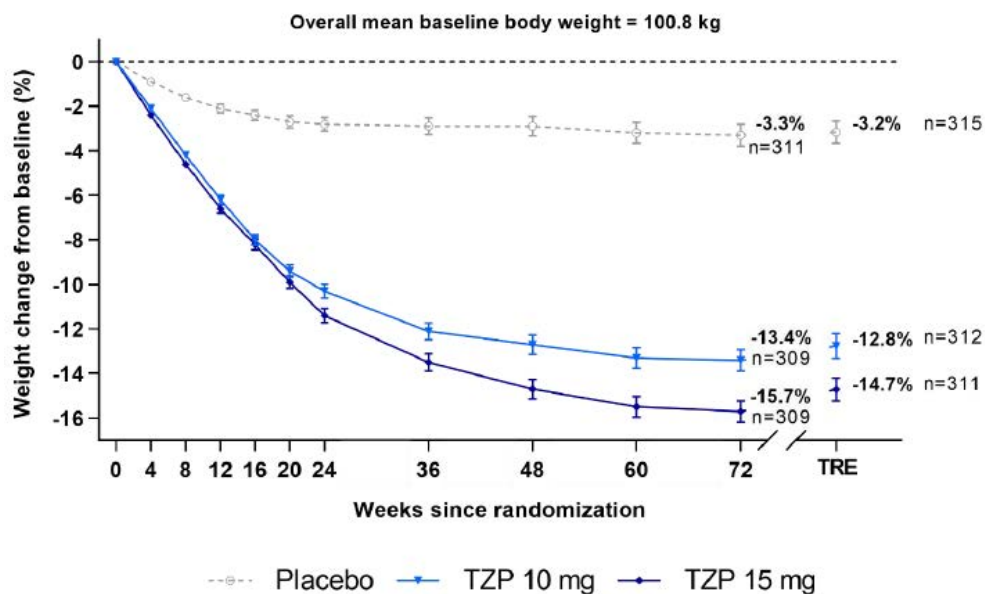
In trials GPHK and GPHL, the Applicant was able to demonstrate durability of effect throughout the intended 72-week planned treatment durations (Figure 25 and Figure 26). Separation of the weight curves is apparent as early as Week 4. Plateau in the curve in the tirzepatide arms occurs around Week 60, whereas the plateau occurs in the placebo group around Week 20.

Figure 25. Mean Percent Change in Body Weight Over Time (Trial GPHK)



Source: Applicant SCE, Figure 2.7.3.50, Page 122 of 123

Figure 26. Mean Percent Change in Body Weight Over Time (Trial GPHL)



Source: Applicant SCE, Figure 2.7.3.51, Page 123 of 123

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For CWM clinical development programs, 52-week treatment at the intended maintenance dosage is considered adequate to support durability of response, showing both the initial weight loss and its maintenance over time.

Reviewer comment: Weight loss maintenance beyond one year on tirzepatide is a question that will be addressed by future trials, including the prediabetes two-year extension in GPHK/SURMOUNT-1 and the phase 3b clinical outcomes trial SURMOUNT-MMO.

The Applicant also presents data showing the durability over 72 weeks for the improvements in secondary endpoints related to blood pressure, lipids, and glycemic parameters (not shown). Overall, I concur that the durability of tirzepatide response was demonstrated for the primary and secondary endpoints in trials GPHK and GPHL.

Persistence of Effect

Persistence of effect is not applicable for the two trials in this NDA, which did not test for persistence since they only included a four-week (off-treatment) safety follow-up period.

Reviewer comment: The Applicant has completed the SURMOUNT-4 randomized withdrawal trial. Based on results from a similar trial for semaglutide, this trial is likely to show weight regain in tirzepatide-treated subjects who are randomized to switch to placebo versus continuing tirzepatide. Therefore, it is unlikely that there will be persistence of the weight loss effect off-drug.

Additional Analyses Conducted on the Individual Trials

The two substudies in trial GPHK (DXA and ABPM) are primarily reviewed from a safety rather than efficacy perspective, so these are detailed in Section 8.7.

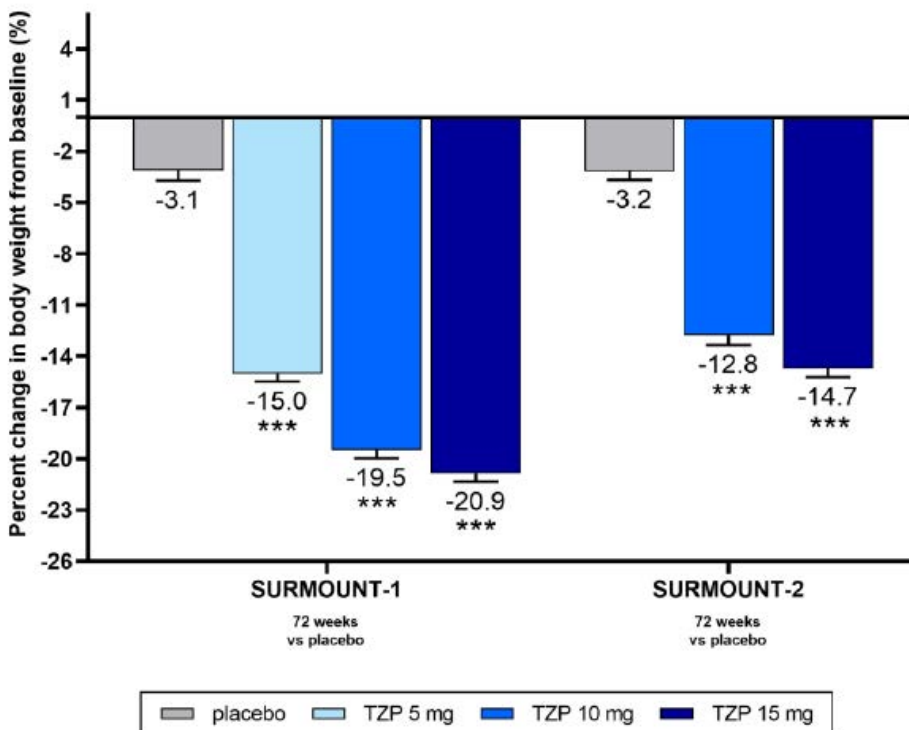
7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

7.1.1. Primary Endpoints

Figure 27 compares in trials GPHK (SURMOUNT-1) and GPHL (SURMOUNT-2) the primary efficacy endpoint of percent change in body weight from Baseline to Week 72.

Figure 27. Primary Efficacy Endpoint (Percent Weight Loss) Comparing Trials GPHK and GPHL



Source: Applicant SCE, Figure 2.7.3.30, page 85 of 123

Note: least squares means $\pm$ standard errors using treatment-regimen (mITT) estimand

***p-Value $< .001$ versus placebo, controlled for type 1 error

This primary endpoint is consistent with Division's expectations and guidelines, and the placebo-corrected effect size for tirzepatide is substantial and clinically meaningful. The effect size distribution in each trial (see above in Section 6.1.2) shows that the great majority of tirzepatide-treated subjects achieve clinically meaningful weight loss.

It is typical for CWM clinical trials to show higher efficacy in subjects without diabetes compared to subjects with diabetes, and this was the case for tirzepatide comparing trials GPHK and GPHL. Given this differential effect in populations based on T2D status, the separate efficacy analyses of the two trials above in Section 6.1.2 are preferred, as a pooled efficacy analysis for weight loss is not relevant.

The Applicant also presents evidence supportive of weight loss in the tirzepatide trials conducted for the indication of T2D, the phase 3 trials SURPASS 1-5, which for this NDA submission were limited to the subset of subjects with BMI ≥ 27 kg/m² at baseline. Of note, all five of these trials of subjects with T2D included the tirzepatide 5, 10, 15 mg weekly dosages, as opposed to GPHL/SURMOUNT-2 which did not include a 5 mg treatment arm. These SURPASS trials also contribute to the overall safety database and are described in more detail below in

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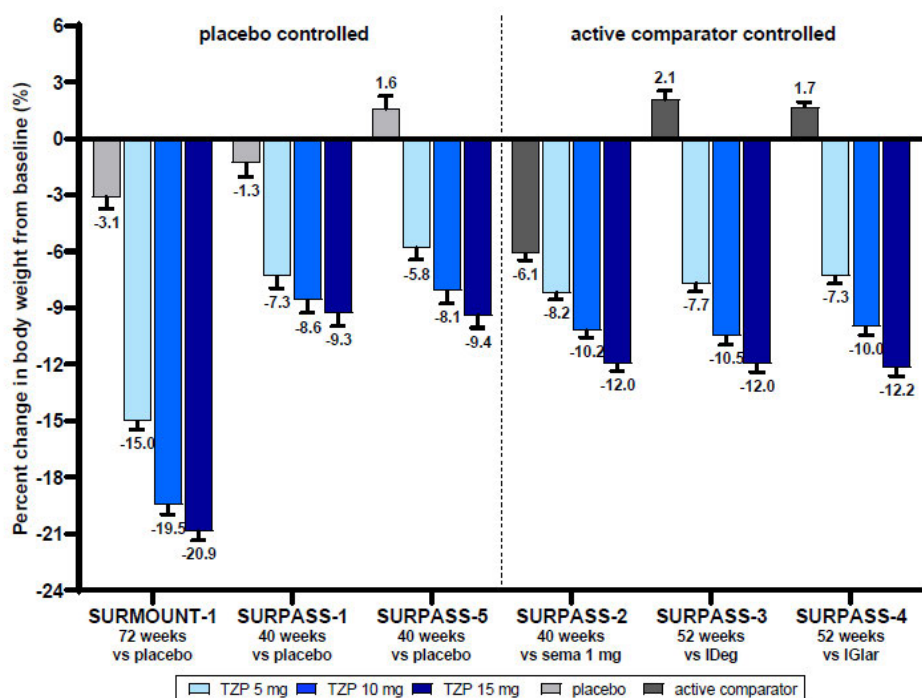
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Section 8.1. SURPASS-1 and -5 were placebo-controlled trials with 40-week treatment durations, SURPASS-2 had an active control of the GLP-1R agonist semaglutide 1 mg weekly which caused weight loss, while SURPASS-3 and -4 had long-acting insulin active controls which caused weight gain.

Weight loss in these SURPASS trials in overweight or obese subjects with T2D was substantial, though as expected, less than that achieved in subjects without diabetes treated for longer duration in trial GPHK/SURMOUNT-1 (shown for comparison in Figure 28 and Figure 29). Weight loss on the tirzepatide 10 mg and 15 mg dosages in the SURPASS trials was also consistent with the weight loss in GPHL/SURMOUNT-2.

Figure 28. Percent Change from Baseline in Weight at Primary Endpoint in SURPASS 1-5 Subjects with BMI ≥ 27 kg/m² at Baseline



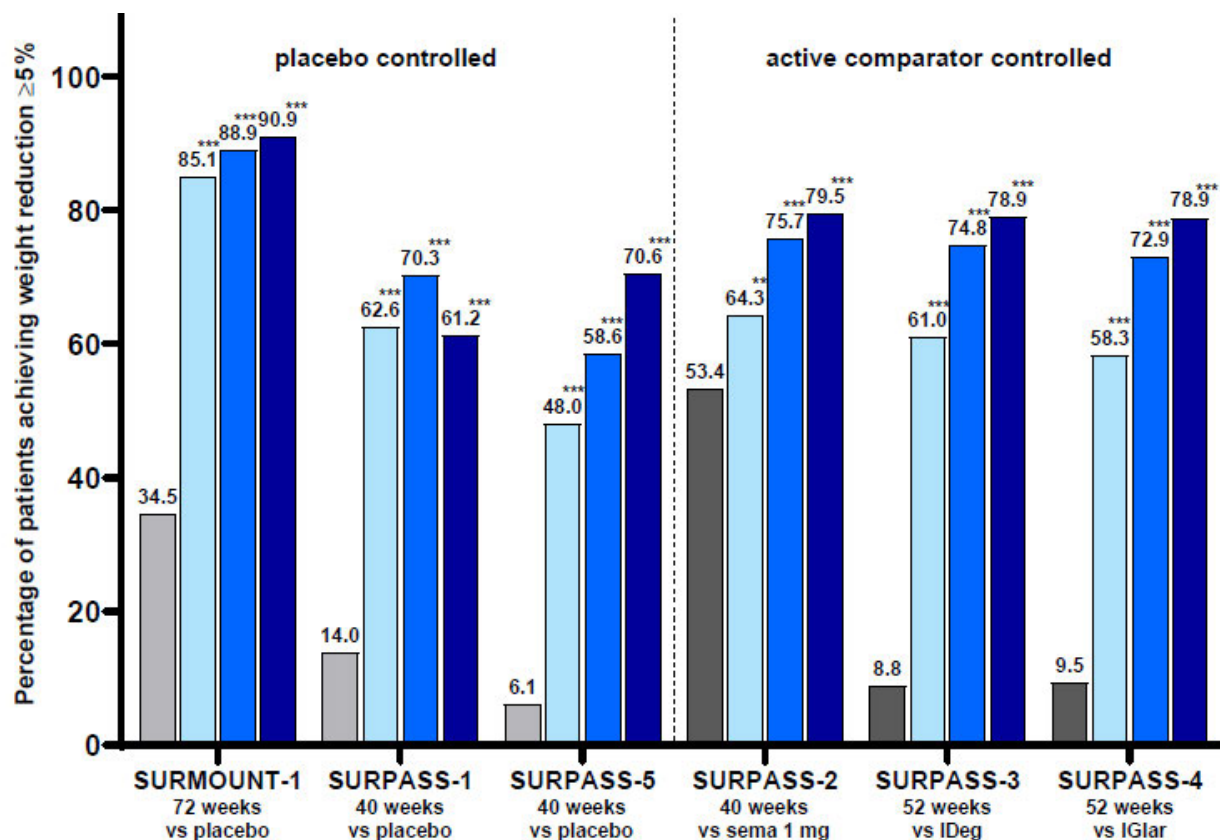
Abbreviations: BMI = body mass index; IDeg = insulin degludec; IGlar = insulin glargine; mITT = modified intent to treat; sema = semaglutide; TzP = tirzepatide.

Note: Shown are the estimated means $\pm$ standard errors.

Note: p-value < 0.001 compared with placebo/active comparator for all doses in all studies.

Source: Applicant pre-NDA briefing document for meeting on August 11, 2022, submitted under IND 139721.

Figure 29. Subject in SURPASS 1-5 with BMI ≥ 27 kg/m² at Baseline Achieving $\geq 5\%$ Weight Reduction at Primary Endpoint



Source: Applicant pre-NDA briefing document for meeting on August 11, 2022, submitted under IND 139721.

The SURPASS-4 trial with the insulin glargine active comparator had its primary endpoint at 52 weeks, but per the trial design a majority of subjects were treated for 78 weeks (and some for 104 weeks, data in Table 34 is for all subjects of whom 85% had BMI ≥ 27 kg/m²). In the SURPASS-4 subjects with T2D and BMI ≥ 27 kg/m², weight loss was maintained over the 72 weeks in all 3 tirzepatide dosage arms, including 5 mg (Figure 30).

Table 34. Percent Change from Baseline in Body Weight at Weeks 78 and 104 (Trial GPGM/SURPASS-4)

Parameter	kg							
	TZP 5 mg (N=328)		TZP 10 mg (N=326)		TZP 15 mg (N=337)		Insulin Glargine (N=998)	
	78 weeks	104 weeks	78 weeks	104 weeks	78 weeks	104 weeks	78 weeks	104 weeks
N1	196	38	193	32	194	35	600	97
Baseline	90.3		90.7		90.0		90.3	
Change from baseline	-8.3†††	-8.6†††	-10.8†††	-10.8†††	-13.0†††	-12.8†††	2.6†††	2.3†††
Change difference from insulin glargine (95% CI)	-10.9*** (-11.7, -10.1)	-10.9*** (-12.3, -9.4)	-13.4*** (-14.2, -12.6)	-13.1*** (-14.6, -11.5)	-15.6*** (-16.4, -14.8)	-15.1*** (-16.6, -13.6)	N/A	N/A

Abbreviations: CI = confidence interval; mITT = modified intent-to-treat; N = number of patients who were randomized and received at least 1 dose of study drug, excluding patients who discontinued study drug due to inadvertent enrollment; N1 = number of patients with baseline and postbaseline values at the specified time point; N/A = not applicable; TZP = tirzepatide.

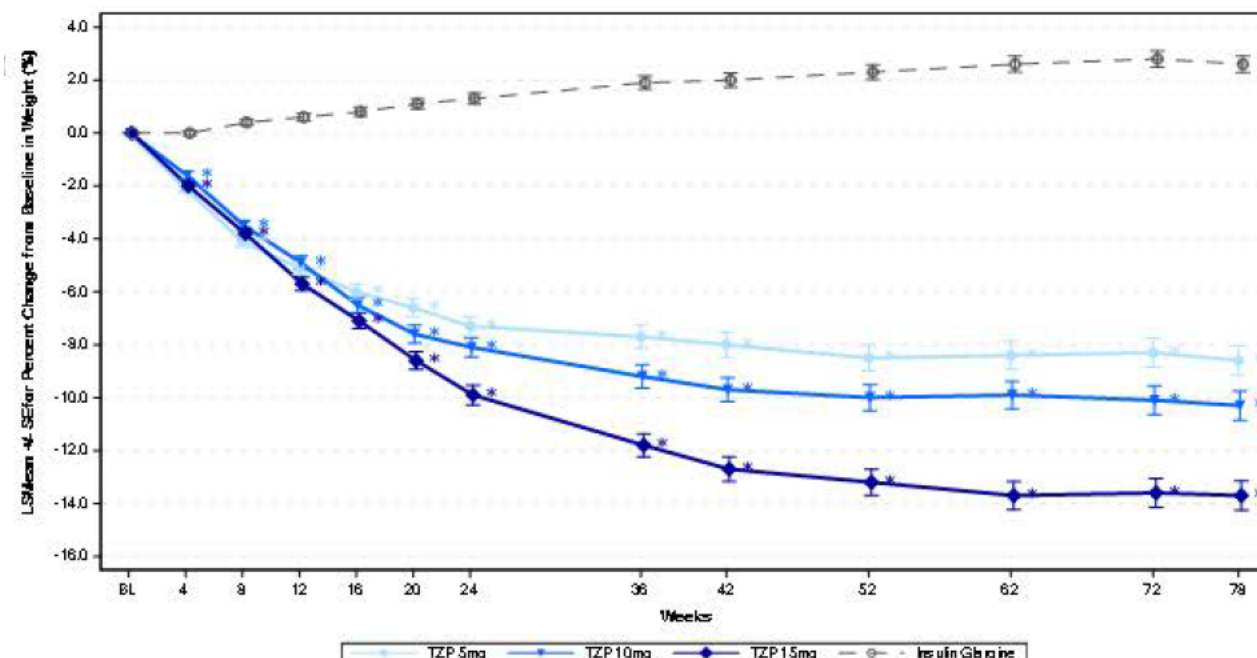
Notes: Shown are the least-squares means. Mixed model repeated measures analysis was performed.

†††p<0.001 versus baseline.

***p<0.001 versus insulin glargine.

Source: Applicant CSR for SURPASS-4, Table GPGM.5.12, page 150 of 5827, submitted under NDA 215866

Figure 30. Percent Change in Body Weight Over Time (Trial GPGM/SURPASS-4)



Source: Applicant pre-NDA response to FDA comments for meeting on August 11, 2022, submitted under IND 139721.

Reviewer Comment: In the SURPASS trials, it is clear that overweight or obese subjects with T2D achieved substantial weight loss on all 3 dosages of tirzepatide, including the 5 mg dosage that was not studied in GPHL/SURMOUNT-2. While these SURPASS trials do not meet

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the Division's expectations for CWM trials (i.e., trial design was for glycemic control, weight was not a primary endpoint, the BMI ≥ 27 kg/m² subgroup was not prespecified, the duration was too short, not all were placebo-controlled), they nonetheless contribute to the assessment of efficacy. While the tirzepatide 5 mg weekly dosage was not studied in subjects with T2D in CWM trial GPHL/SURMOUNT-2, the SURPASS data supports it as a maintenance dosage for use for CWM in subjects with T2D.

7.1.2. Secondary and Other Endpoints

See Section 6.1.2 above for Figures comparing secondary endpoints side-by-side for trials GPHK and GPHL. In general, the secondary endpoints related to blood pressure, lipids, glycemia, and patient-reported outcomes were consistent between the two trials and showed statistical significance. These secondary endpoints support the clinical relevance of the weight loss achieved with tirzepatide, as it is associated with improvements in cardiovascular risk factors. I agree with the Applicant that some of these endpoints are appropriate for inclusion in label Section 14, consistent with the labels for other CWM medications, as discussed further in Section 10.1.

7.1.3. Subpopulations

See Section 6.1.2 above for the subgroup analyses performed in trials GPHK and GPHL. In general for each trial, the primary efficacy results were similar in various subpopulations, and there were no subpopulations in which results showed clinically meaningful differences.

7.1.4. Dose and Dose-Response

Although subjects were randomized to tirzepatide 5, 10, or 15 mg weekly dosage arms, the phase 3 trials GPHK and GPHL were not intended to compare differences between tirzepatide dosages, but rather to compare each individual dosage to the placebo comparator. In each trial, all dosages were superior to placebo for the primary endpoint (percent change from baseline in body weight) and most of the secondary endpoints.

Reviewer comment: There does appear to be evidence of a dose-response for efficacy since placebo-correct weight loss with at Week 72 in trial GPHK was nominally greater at higher doses: -11.9%, -16.4%, and -17.8%, respectively, with tirzepatide 5, 10, or 15 mg weekly.

Based on the totality of evidence, the dose selection in these trials was adequate, as were the dosing recommendations for starting dose (2.5 mg), dose escalation schedule (by 2.5 mg every 4 weeks), and maintenance dosages (5, 10, and 15 mg). In trial GPHK, the lowest 5 mg tirzepatide dosage showed meaningfully less weight loss efficacy than the 10 mg and 15 mg

doses (though these dosages were not directly compared as above). This lowest dosage of 5 mg was not investigated in the population with T2D in trial GPHL (a limitation of the trial), and the 10 mg and 15 mg dosages showed relatively similar weight loss efficacy.

7.1.5. Onset, Duration, and Durability of Efficacy Effects

See Section 6.1.2 above for the time course of weight loss efficacy in trials GPHK and GPHL.

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Postmarket Setting

Overall, the two trial populations support that the observed effect of tirzepatide on weight loss is generalizable to the broader population of patients with obesity/overweight that might receive tirzepatide for CWM in the postmarketing setting, and that the benefit can reasonably be expected to be seen in the postmarket setting. Weight loss with tirzepatide and related salutary effects in the postmarket setting will depend on a number of factors, including compliance with adjunct diet and exercise recommendations and compliance with the drug long-term. Although more subjects discontinued tirzepatide due to GI adverse events (AEs) as compared to placebo (Section 8.4.3), mean weight loss was only minimally less with the treatment regimen estimand (mITT population) compared to the efficacy estimand (assuming all subjects completed treatment for 72 weeks). Though not studied in trials supporting this NDA, weight regain can be expected upon tirzepatide discontinuation, based on experience with other incretins and the anticipated results of the tirzepatide SURMOUNT-4 trial with randomized withdrawal. The optimal dosing of tirzepatide beyond one year remains uncertain but may be addressed by future trials.

7.2.2. Other Relevant Benefits

Compared to the most effective currently-marketed weight loss medication (semaglutide 2.4 mg weekly), tirzepatide offers the same once weekly SC injection with dosage escalation, so tirzepatide does not offer a more convenient dosing schedule or route of administration. While semaglutide is a selective GLP-1R agonist, tirzepatide is a dual agonist at the GLP-1R and GIP-R. While dual agonism may offer theoretical benefits in efficacy and safety as discussed elsewhere, these are mostly speculative and should not be considered in the overall assessment of tirzepatide's benefit.

7.3. Integrated Assessment of Effectiveness

The evidentiary standard of substantial evidence of effectiveness has been met by two adequate and well-controlled trials, GPHK and GPHL. The weight loss achieved in these two trials is statistically significant and clinically meaningful - and greater in magnitude than that observed in trials of other drugs previously approved for CWM. The statistical reviewer Dr. Song concluded "The collective evidence from the submitted data demonstrated efficacy of tirzepatide in the study population. We recommend approval for the proposed indication based on findings from the submitted results." – and I concur.

At dosages of tirzepatide 10 mg and 15 mg weekly, a mean weight loss at one year in the ITT population of -19.5 and -20.9% was achieved in subjects without T2D (trial GPHK, compared to -3.1% with placebo) and -12.8 and -14.7% in subjects with T2D (trial GPHL, compared to -3.2% with placebo). Furthermore, with the lowest maintenance dosage of 5 mg, -15.0% weight loss was achieved in subjects without T2D in trial GPHK - and this 5 mg maintenance dosage showed apparent weight loss in shorter duration SURPASS trials for glycemic control in subjects with T2D. Across populations in the two phase 3 CWM trials, >79% and up to 90.9% of tirzepatide-treated trial subjects achieved $\geq 5\%$ weight loss, a threshold the Division has considered for clinical meaningfulness (compared to 32.5-34.5% of placebo-treated subjects).

On tirzepatide 15 mg, mean weight reduction of $\geq 25\%$ was found in 36.2% of subjects without T2D and 15.5% of subjects with T2D (this degree of weight loss was negligible in placebo-treated subjects, 1.5% without T2D and 0.3% with T2D). Therefore, a substantial number of tirzepatide-treated patients could achieve degrees of weight loss >25%, comparable to that achieved after bariatric surgery. Importantly, maintenance of weight loss on tirzepatide is likely to require chronic therapy, and it unknown whether weight regain occurs during long-term therapy. Consistent with the observed weight loss having clinically meaningful benefits, in both trials weight loss with tirzepatide was associated with improvements in risk factors for cardiovascular disease (glycemia, blood pressure, and lipids). Overall, these two trials have generated efficacy data that are robust, interpretable, and persuasive in supporting the proposed indication of CWM in adults.

8. Review of Safety

8.1. Safety Review Approach

This safety review is primarily based on the two phase 3 CWM trials GPHK and GPHL (SURMOUNT-1 and -2), which were analyzed individually and pooled. The Applicant submitted safety data from these two trials, both of which include at least 52 weeks of placebo-controlled exposure to the intended maintenance dosage of tirzepatide (72-week treatment duration,

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with 20 weeks of dose escalation required to reach the highest dose of tirzepatide 15 mg weekly). These two trials allow an indication-specific review for CWM.

In addition to the data from these two phase 3 CWM trials, the Applicant's safety package to support the use of tirzepatide for CWM includes supportive data from nine other phase 3 trials and two phase 2 trials, primarily conducted in subjects with T2D, for a total of 13 trials (Table 35).

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Table 35. Phase 2 and 3 Trials Contributing to the Safety Database

Trial	Trial Type	Comparator/ Blinding	TZP doses (mg)	Duration (weeks) ^a	Overweight or Obese Subjects ^b	T2D NDA ^c	Primary Analysis	Analysis Set			
								1	2	3	4
GPHK/ SURMOUNT- 1	CWM	Placebo/DB	5/10/15	72	2539/2539 (100%)		x	x	x	x	x
GPHL/ SURMOUNT- 2 ^d	CWM	Placebo/DB	10/15	72	938/938 (100%)		x				
GPHN/ SURMOUNT- 4 ^e	CWM	None/OL	MTD (10/15)	36	782/782 (100%)					x	
GPGB	Phase 2, dose finding/escalation	Placebo/DB	1/5/10/15	26	267/316 (84%)	x				x	x
GPGF	Phase 2, dose finding/escalation	Placebo/DB	12/15	12	89/111 (80%)	x				x	x
GPGK/ SURPASS-1	T2D, no background therapy	Placebo/DB	5/10/15	40	371/478 (78%)	x		x	x	x	x
GPGL/ SURPASS-2	T2D, background metformin	Semaglutide/ OL	5/10/15	40	1670/1878 (89%)	x			x	x	x
GPGH/ SURPASS-3	T2D, background metformin ± SGLT2i	Insulin degludec/OL	5/10/15	52	1255/1437 (87%)	x			x	x	x
GPGM/ SURPASS-4	T2D, high CV risk, background 1-3 OAMs	Insulin glargine/OL	5/10/15	52	1689/1995 (85%)	x			x	x	x
GPGL/ SURPASS-5	T2D, background insulin glargine	Placebo/DB	5/10/15	40	407/475 (86%)	x		x	x	x	x
GPGO/ SURPASS-J Mono	T2D, Japan, no background therapy	Dulaglutide/ DB	5/10/15	52	319/636 (50%)	x			x	x	x
GPGP/ SURPASS-J Combo	T2D, Japan, background one OAM	None/OL	5/10/15	52	200/443 (45%)	x			x	x	
GPHO/ SURPASS-AP Combo	T2D, Asia Pacific, background metformin ± SU	Insulin glargine/OL	5/10/15	40	477/907 (53%)				x	x	x

Source: Adapted from the Applicant's Summary of Clinical Safety, Table 2.7.4.1, page 30 of 293

Abbreviations: BMI, body mass index; CV, cardiovascular; DB, double-blinded; CWM, chronic weight management; OAM, oral antihyperglycemic medication; MTD, maximum tolerated dose; OL, open-label; SGLT2i, sodium-glucose co-transporter 2 inhibitor; SU, sulfonylurea, T2D, type 2 diabetes; TZP, tirzepatide

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^a Exposure to maintenance TZP dosages is less than total trial duration due to dosage escalation periods; up to 20 weeks are necessary to reach the maximum maintenance dosage of TZP 15 mg weekly.

^b n/N (%); n, subjects with overweight or obesity (BMI ≥ 27 kg/m²); N, total subjects in trial; %, percentage of subjects in trial with overweight or obesity

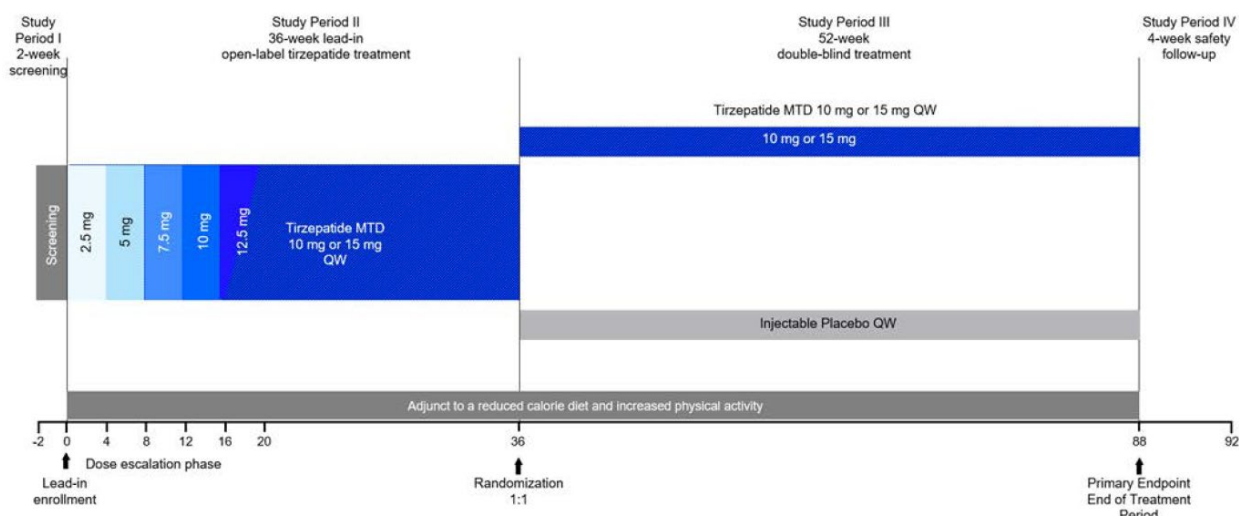
^c Trials that were in the initial submission for NDA 215866, tirzepatide for T2D.

^d Trial GPHL/SURMOUNT-2 was submitted in the second part of a rolling submission and is thus not included in the Applicant's pooled safety analysis sets.

^e Trial GPHN/SURMOUNT-4 includes a randomized, double-blinded placebo-controlled period that is not part of this analysis.

One other tirzepatide phase 3 CWM trial, GPHN (SURMOUNT-4), is included in the Applicant's safety package; only safety data from the 36-week open-label lead-in tirzepatide treatment period without a placebo comparator is included (this trial also included a subsequent randomized double-blinded placebo-controlled treatment period that is not included in this NDA submission, Figure 31). Since the available GPHN data is short duration (36 weeks total, thus 16 weeks at tirzepatide 15 mg weekly) and not placebo-controlled, it is of limited use for the safety review and only considered in the Applicant's pooled analysis set 3.

Figure 31. Study Design Diagram for Trial GPHN (SURMOUNT-4)



Abbreviations: MTD = maximum tolerated dose; QW = once weekly.

Source: Applicant SCE, Figure 2.7.3.29, page 77 of 123

Ten trials in the safety database (eight phase 3 SURPASS trials and both phase 2 trials) are from the tirzepatide development program for T2D. Nine of the T2D trials were included the original submission for NDA 215866 (tirzepatide for T2D), and one other T2D phase 3 trial (GPHO) has completed since that NDA submission. For these ten T2D trials included in the safety database for the current CWM NDA, the Applicant analyzed data only from subjects with overweight or obesity (BMI ≥ 27 kg/m²). In the T2D phase 2 and global phase 3 trials, 78-89% of trial subjects had overweight or obesity, and in the three regional phase 3 trials limited to Japan or the Asia-Pacific, 45-53% of subjects had overweight or obesity (see above, Table 35).

The Applicant has submitted four pooled analysis sets of trial safety data (see Table 35 above and Table 36 below); trial GPHL (SURMOUNT-2) was not included in the Applicant's pools as it was submitted in the second sequence of the rolling review:

- Analysis Set 1 (phase 3 Placebo-controlled): This pool includes three phase 3 trials with placebo-controlled exposure to tirzepatide. The duration of exposure differs between the CWM trial GPHK (72 weeks total, thus 52 weeks at the maximum 15 mg maintenance dose) and the T2D trials GPGK and GPGI (40 weeks total, thus 20 weeks at the 15 mg maintenance dose). 76.5% of subjects in this pool are from trial GPHK.
- Analysis Set 2 (phase 3 dose effect): This pool integrates data from nine phase 3 trials that randomized subjects equally to treatment arms with tirzepatide 5 mg, 10 mg, or 15 mg, thus allowing assessment of dose effect for adverse events. The pooled trials differ in population, duration, blinding, and comparators (see Table 35), and this applies to the next two pooled analysis sets as well.
- Analysis Set 3 (phase 2/3): This pool includes twelve phase 2 and 3 trials, pooling tirzepatide doses without regard to comparators.
- Analysis Set 4 (phase 2/3 Comparator-controlled): This pool includes ten phase 2 and 3 trials, pooling all tirzepatide doses and pooling all comparators (placebo and active).

Reviewer comment: The descriptions of the four pooled analysis sets above identify important issues with each, including differences among the pooled trials in treatment duration, comparators, blinding, trial design, and dosages. For these reasons, the primary focus of my safety review (and the Applicant's) was the two similar phase 3 CWM trials GPHK and GPHL, with the pooled analysis sets including T2D trial data used for further analysis of specific safety issues when relevant.

Table 36. Safety Analysis Sets Submitted by the Applicant

Analysis Set	Trials ^a	Description	Treatment Groups (Subjects with overweight or obesity / Total subjects)	Subjects from Trial GPHK
AS1: Phase 3 Placebo- Controlled	GPHK/SURMOUNT-1 GPGK/SURPASS-1 GPGI/SURPASS-5	Integrated data of fixed dose phase 3 studies compared to placebo for studies with placebo group and same dose-escalation schedule proposed for the label	Placebo (N=827/878) TZP 5 mg (N=830/867) TZP 10 mg (N=876) TZP 15 mg (N=871) TZP All (N=2490/2614) Total (N=3317/3492)	76.5%
AS2: Phase 3 Dose Effect	GPHK/SURMOUNT-1 GPGK/SURPASS-1 GPGI/SURPASS-5 GPGH/SURPASS-3 GPGM/SURPASS-4 GPGO/SURPASS-J Mono GPGP/SURPASS-J Combo GPHO/SURPASS-AP Combo	Integrated data from TZP-treated participants in all phase 3 fixed-dose studies with the same dose- escalation schedule for dose comparison	TZP 5 mg (N=2109/2561) TZP 10 mg (N=2095/2566) TZP 15 mg (N=2122/2575) Total (N=6326/7702)	30.0%
AS3: Phase 2/3	GPHK/SURMOUNT-1 GPHN/SURMOUNT-4 ^b GPGB (phase 2) GPGF (phase 2) GPGK/SURPASS-1 GPGI/SURPASS-5 GPGH/SURPASS-3 GPGM/SURPASS-4 GPGO/SURPASS-J Mono GPGP/SURPASS-J Combo GPHO/SURPASS-AP Combo	Integrated data from TZP-treated participants for pooled TZP doses. Includes all phase 2 and 3 studies and all TZP doses. It is created to facilitate identification of rare events that require further scrutiny through case reviews. All TZP doses are pooled.	TZP all (N=7354/8780)	36.4%
AS4: Phase 2/3 Comparator- Controlled	GPHK/SURMOUNT-1 GPGB (phase 2) GPGF (phase 2) GPGK/SURPASS-1 GPGI/SURPASS-5 GPGH/SURPASS-3 GPGM/SURPASS-4 GPGO/SURPASS-J Mono GPGP/SURPASS-J Combo GPHO/SURPASS-AP Combo	Integrated data for all phase 2 and 3 studies including comparator. All tirzepatide doses are pooled. All comparators (placebo and active comparators) are pooled.	Comparators (N=2711/3217) TZP All (N=6372/7555) Total (N=9083/10772)	28.0%

Source: Adapted from the Applicant's SCS, Table 2.7.4.2, page 36 of 293

Abbreviations: AS, analysis set; N, number of subjects; TZP, tirzepatide

^a Time for adverse events is from first dose of treatment to end of safety follow-up visit or date of withdrawal.

^b Trial GPHN/SURMOUNT-4 data from are from the 36-week open-label tirzepatide treatment period only.

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The safety evaluation for this NDA was primarily based on the Applicant's submitted datasets (analysis and tabulation) for trials GPHK/SURMOUNT-1 and GPHL/SURMOUNT-2 and information requests to the Applicant. Data from the Applicant's pooled analysis sets described above were reviewed in a supportive fashion or to clarify safety signals that arose in the CWM trials.

I also reviewed the Applicant's 120-day safety update submitted on August 8, 2023 (Table 37), which included safety data from:

- 20 ongoing studies (four phase 1, two phase 2, thirteen phase 3, and three phase 4), 19 of which contributed safety data since GPHJ/SURMOUNT-5 had not randomized subjects at the data cutoff
- 2 recently completed studies (phase 3 GPHD and phase 1 GPGU)
- Postmarketing data through May 13, 2023 (see Section 8.9.1).

The Applicant concludes that new data from completed trials and mostly blinded data from ongoing trials is consistent with that described for tirzepatide in the CWM NDA, and I concur. This additional information provided in the 4-month safety update does not significantly affect the safety review below or key safety information included in proposed labeling.

Table 37. Trials Contributing Safety Data in the 120-Day Safety Update Report

Phase <i>Disease State</i> Study	Completed ^a	Ongoing	Blinded	Unblinded	Presented Individually	Pooled
Phase 2, 3, and 4 studies						
<i>CWM</i>						
GPHK ^b						
GPHM						
GPHN ^c		X	X			X
GPHZ						
GPIA						
<i>T2DM</i>						
GPHD	X			X	X	
GPHE		X		X	X	
GPIH		X		X	X	
GPII		X		X	X	
GPII		X		X	X	
GPII		X	X		X	
GPII		X	X		X	
<i>CVOT</i>						
GPGN		X	X		X	
<i>HFpEF</i>						
GPID		X	X		X	
<i>OSA</i>						
GPIF master protocol		X	X			X
GPI1						
GPI2						
<i>MMO</i>						
GPIJ		X	X		X	
<i>NASH</i>						
GPHR		X	X		X	
<i>CKD</i>						
GPIG		X	X		X	
Phase 1 studies						
GPGU	X			X	X	
GPHH		X	X		X	
GPHV ^d		X		X	X	
GPIP		X		X	X	

Abbreviations: CKD = chronic kidney disease; CWM = chronic weight management; CVOT = cardiovascular outcome trial; HFpEF = heart failure with preserved ejection fraction; MMO = morbidity and mortality in obesity; NASH = nonalcoholic steatohepatitis; OSA = obstructive sleep apnea; T2DM = type 2 diabetes mellitus.

^a Completed studies are defined as having an approved clinical study report.

^b The data include only the ongoing additional 2-year treatment period (including the 17-week safety follow-up) for participants with prediabetes at randomization.

^c The data include only the 52-week double-blind treatment period and 4-week safety follow-up.

^d Study GPHV is investigator- and participant-blinded, but not sponsor-blinded. Therefore, it is treated as unblinded for purposes of the safety update report.

Note: Phase 3 CWM Study GPHJ is considered ongoing, but contributed no safety data because no participants had been randomized to treatment as of 28 April 2023.

Source: Applicant Safety Update Report, Table 5.2, page 27 of 1081

8.2. Review of the Safety Database

8.2.1. Overall Exposure

The overall safety database submitted for this NDA is presented in Table 38.

Table 38. Safety Database for Tirzepatide

Safety Database for Tirzepatide N=11,001 Individuals exposed to any treatment (N is the sum of all available numbers from the columns below)			
Clinical Trial Groups	New Drug (n=7,977)	Active Control (n=1,821)	Placebo (n=1,203)
Healthy volunteers	0	0	0
Controlled trials conducted for this indication ¹	2,519	0	958
All other trials conducted for this indication ²	782	0	0
Controlled trials conducted for other indications ³	5,458	1,821	245

Source: Generated by reviewer using Applicant adsl.xpt datasets for pooled analysis set 3 (12 trials) and trial GPLH (SURMOUNT-2)

¹ Trials GPHK and GPLH (SURMOUNT-1 and -2)

² Trial GPHN (SURMOUNT-4) open-label treatment lead-in period

³ Ten trials for T2D, two phase 2 trials and eight phase 3 SURPASS trials, limited to trial subjects with BMI ≥ 27 kg/m²

Per the Applicant, in analysis set 3 with twelve phase 2/3 trials of differing durations (not including GPLH/SURMOUNT-2), 7354 subjects received tirzepatide for 7,071 patient-years of exposure, and 2,711 subjects received placebo or active control for 2,905 patient-years of exposure.

The main safety analysis considers the two placebo-controlled phase 3 CWM trials (GPHK and GPLH). Per the Applicant, in these two trials:

- 2,519 subjects received at least one dose of tirzepatide, for 3201.7 patient-years of exposure, with a mean exposure duration of 66.3 weeks, and 88.8% of subject exposed for ≥52 weeks and 76.5% for ≥72 weeks
- 958 subjects received at least one dose of placebo, with a mean exposure duration of 62.9 weeks, and 80.3% of subject exposed for ≥52 weeks and 68.4% for ≥72 weeks.

The relevant durations of subject exposure to tirzepatide at different planned dosages in the three treatments arms is shown in Table 39.

Table 39. Duration of Tirzepatide Exposure in Trials GPHK and GPHL

Trial Arm	Number of patients exposed to the study drug:				
	≥1 dose	≥12 weeks	≥24 weeks	≥52 weeks	≥72 weeks
TZP 5 mg	N=630	N=608	N=599	N=562	N=491
TZP 10 mg	N=948	N=914	N=880	N=842	N=735
TZP 15 mg	N=941	N=912	N=886	N=832	N=700

Source: Adapted from Applicant SCS Addendum, Table 2.7.4.3, page 15 of 73

8.2.2. Relevant characteristics of the safety population:

For the two phase 3 placebo-controlled CWM trials GPHK and GPHL (SURMOUNT-1 and -2), the safety population is identical to the efficacy population as shown above in Table 7.

The additional 11 trials in the pooled safety analysis sets (limited to BMI ≥27 kg/m²) differ in baseline characteristics as shown in Table 40, with trial GPHK (SURMOUNT-1) shown for comparison. The CWM population in SURMOUNT-4 is similar to SURMOUNT-1, while the T2D populations in the other ten trials (5 global SURPASS trials, 3 regional SURPASS trials in Asia, and 2 phase 2 trials) differ in age, sex distribution, and BMI from SURMOUNT-1. These T2D populations are more similar to the trial population in CWM trial GPHL (SURMOUNT-2, see Table 10 above). Overall, the safety population is diverse reflecting an adequate number of subjects differing in sex, race, ethnicity, and BMI. A sufficient number of subjects were enrolled at trial sites in the U.S.

Table 40. Selected Baseline Characteristics of Subjects in the Phase 2/3 Analysis Pool 3

	SURMOUNT-1 (N=2537)	SURMOUNT-4 (N=782)	SURPASS-global (N=5392)	SURPASS-regional (N=996)	T2D Phase 2 (N=356)
Age, years					
Mean (SD)	44.9 (12.46)	47.6 (12.86)	58.7 (10.39)	52.8 (11.10)	57.0 (8.85)
Median (Min, Max)	45.0 (18, 84)	48.0 (18, 80)	59.0 (18, 87)	53.0 (20, 81)	58.0 (31, 75)
Age Group, n (%)					
<65 years	2385 (94.0)	700 (89.5)	3704 (68.7)	832 (83.5)	285 (80.1)
≥65 years	152 (6.0)	82 (10.5)	1688 (31.3)	164 (16.5)	71 (19.9)
Sex, n (%)					
Female	1714 (67.6)	546 (69.8)	2481 (46.0)	371 (37.2)	162 (45.5)
Male	823 (32.4)	236 (30.2)	2911 (54.0)	625 (62.8)	194 (54.5)
Race, n (%)					
White	1792 (70.6)	628 (80.3)	4490 (83.3)	10 (1.0)	288 (80.9)
Asian	274 (10.8)	57 (7.3)	255 (4.7)	982 (98.6)	6 (1.7)

	SURMOUNT-1 (N=2537)	SURMOUNT-4 (N=782)	SURPASS-global (N=5392)	SURPASS-regional (N=996)	T2D Phase 2 (N=356)
Black or African American	201 (7.9)	87 (11.1)	192 (3.6)	0	38 (10.7)
Other	270 (10.6)	10 (1.3)	452 (8.4)	4 (0.4)	23 (6.5)
Not Reported	0	0	3 (0.1)	0	1 (0.3)
Ethnicity, n (%)					
Hispanic or Latino	1214 (47.9)	343 (43.9)	2513 (46.6)	0	154 (43.3)
Not Hispanic or Latino	1122 (44.2)	438 (56.0)	2764 (51.3)	0	169 (47.5)
Not Reported	201 (7.9)	1 (0.1)	115 (2.1)	996 (100.0)	33 (9.3)
Region, n (%)					
US	1141 (45.0)	509 (65.1)	1193 (22.1)	0	295 (82.9)
Outside US	1396 (55.0)	273 (34.9)	4199 (77.9)	996 (100.0)	61 (17.1)
Central/South America and Mexico	1036 (40.8)	229 (29.3)	2067 (38.3)	0	0
EU, UK, Ukraine	0	0	1602 (29.7)	0	61 (17.1)
Japan	123 (4.8)	0	89 (1.7)	519 (52.1)	0
Asia (excluding Japan)	119 (4.7)	44 (5.6)	110 (2.0)	463 (46.5)	0
North America	0	0	83 (1.5)	0	0
Rest of World	118 (4.7)	0	248 (4.6)	14 (1.4)	0
BMI, kg/m²					
Mean (SD)	38.0 (6.81)	38.3 (6.57)	34.5 (5.87)	31.1 (4.09)	33.8 (5.12)
Median	36.5	37.1	33.3	29.9	32.6
BMI group, n (%)					
>=27 to <30 kg/m ²	138 (5.4)	23 (2.9)	1221 (22.6)	505 (50.7)	97 (27.2)
>=30 to <35 kg/m ²	876 (34.5)	254 (32.5)	2119 (39.3)	359 (36.0)	138 (38.8)
>=35 to <40 kg/m ²	720 (28.4)	250 (32.0)	1243 (23.1)	94 (9.4)	77 (21.6)
>=40 kg/m ²	803 (31.7)	255 (32.6)	809 (15.0)	38 (3.8)	44 (12.4)

Source: Generated by reviewer using OCS Analysis Studio, Custom Table Tool, and Applicant adsl.xpt dataset for pooled analysis set 3, limited to BMI ≥ 27 kg/m²

8.2.3. Adequacy of the safety database:

The adequacy of the safety database is based primarily on the phase 3 placebo-controlled CWM trials GPHK and GPHL (SURMOUNT-1 and -2). The Division generally expects a safety database of ≥3000 subjects exposed to drug for one year at the maintenance dose, with ≥1500 exposed to placebo in parallel groups. I find the safety database to be adequate with respect to three key features:

- **Duration:** Both trials are of sufficient duration to meet the Division's expectation, since

the 72-week total treatment duration gives 52 weeks after dosage escalation to the highest dose of tirzepatide 15 mg weekly.

- **Size:** The two trials include 2,519 subjects exposed to tirzepatide and 958 subjects exposed to placebo. Given the large amount of additional safety data in the NDA submission, primarily from the T2D development program and in the pooled analysis sets detailed above, I find the size of the safety database to be adequate.
- **Demographics:** The sex and age of the trial population generally reflect those who might seek CWM care in a primary care setting. Trial GPHL has a T2D population including more males, older subjects, and subjects with weight-related comorbidities. While the trials were somewhat over-representative of Hispanic or Latino ethnicity and under-representative of the Black or African American and Asian race in the U.S., overall these trials enrolled a population with adequate diversity by race and ethnicity.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

In general, the submission and data quality were very good. Trials GPHK and GPHL were analyzed to identify any data quality issues, and no significant issues were identified. I also compared site-specific efficacy and safety data for potential data integrity issues at specific sites. The findings from OSI inspections of selected sites are consistent with no meaningful site-specific issues (see Section 4.1).

The Applicant's data were consistent across datasets, and tabulations could be cross-referenced to case report forms and patient narratives. All clinical items requested in meetings with FDA leading up to and after submission were provided and easy to locate. As detailed below, I was able to confirm all key safety results from clinical trial reports and safety summaries with the provided analysis datasets.

8.3.2. Categorization of Adverse Events

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The Applicant performed safety analyses using a modified intention-to-treat (mITT) population (i.e., all subjects randomized who received at least one dose of IP) and all data (on or off study drug) from the start of treatment to the end of the 4-week safety follow-up. AE information obtained and documented in the eCRF included: the onset and duration, the seriousness and severity, relatedness to study drug, actions taken with respect to study treatment, and outcome.

The Applicant used the following definitions in their protocols and/or safety analyses:

- AE: 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 AEs (TEAEs): AEs that first occurred after baseline or worsened in severity after baseline. All analyses below focus on TEAEs.
- Serious AE: any untoward medical occurrence that either 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, or was an important medical event

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 25.1. 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.

This Applicant's package includes routine safety assessments and "Special Safety Topics Including Adverse Events of Interest." The latter are potential or established incretin class-related safety concerns, and these will be referred to as adverse events of special interest (AESI) throughout this review. The Applicant's AESI were:

- GI AEs
- dehydration-related AEs
- renal safety
- hepatobiliary disorders (including acute gallbladder disorders)
- major depressive disorders/suicidal ideation
- exocrine pancreas safety
- cardiovascular safety
- malignancy
- thyroid safety
- hypoglycemia
- injection site reactions
- immunogenicity (including hypersensitivity reactions).

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Four other AESI are only applicable to trial subjects with T2D, so these were assessed in CWM trial GPLH (SURMOUNT-2) but not GPHK (SURMOUNT-1):

- metabolic acidosis
- hyperglycemia requiring rescue therapy
- diabetic retinopathy complications
- amputation or peripheral revascularization.

The Applicant identified AESI primarily by searching the AE datasets using standardized MedDRA queries (SMQs) and customized MedDRA queries. The Applicant's search strategies for AESI appeared reasonable. All deaths, AEs of acute or chronic pancreatitis, and MACE, were adjudicated by an independent CEC. In my review, I also used FDA MedDRA queries (FMQs) for selected AEs and AESI, and cross-checked selected events with those provided with the NDA safety documents, with excellent agreement overall.

In conclusion, the Applicant's safety definitions, coding, and approach to AESI are all acceptable.

8.3.3. Routine Clinical Tests

Routine clinical testing in phase 3 CWM trials GPHK and GPLH was reasonable for the size and scope of the clinical development program.

The trials included routine clinical laboratory testing of blood and urine at baseline, every 12 weeks during the treatment period (Weeks 12, 24, 36, 48, and 60), at the end of treatment (Week 72) or early termination, and at the 4-week safety follow-up. Blood specimens for evaluation of lipid and glycemic parameters were collected under fasted conditions.

The vital signs pulse, blood pressure, and weight were collected at the visits above for laboratory tests, and also at scheduled visits every four weeks at the start of the treatment period (Weeks 4, 8, 12, 16, and 20). Pulse and blood pressure were measured in triplicate in the sitting position using an automated machine. 12-lead ECGs were obtained at baseline, Week 24, Week 72, and safety follow-up. Physical examination was conducted at baseline, with only targeted physical examinations as needed at subsequent study visits.

The Applicant analyzed laboratory, vital sign, and ECG data using central tendency measures and categorical shifts (e.g., from normal or high to low, and from normal or low to high).

8.4. Safety Results

Table 41 shows the safety results for deaths, SAEs, discontinuation, and TEAEs in trials GPHK and GPLH.

Table 41. Deaths, SAEs, Discontinuations, and TEAEs (Trials GPHK and GPHL)

	GPHK / SURMOUNT-1				GPHL / SURMOUNT-2			Total			
	Placebo (N=643)	TZP 5mg (N=630)	TZP 10mg (N=636)	TZP 15mg (N=630)	Placebo (N=315)	TZP 10mg (N=312)	TZP 15mg (N=311)	Placebo (N=958)	TZP 5mg (N=630)	TZP 10mg (N=948)	TZP 15mg (N=941)
Deaths	4 (0.6)	4 (0.6)	2 (0.3)	1 (0.2)	0	2 (0.6)	0	4 (0.4)	4 (0.6)	4 (0.4)	1 (0.1)
Serious Adverse Events	44 (6.8)	40 (6.3)	44 (6.9)	32 (5.1)	23 (7.3)	18 (5.8)	27 (8.7)	67 (7.0)	40 (6.3)	62 (6.5)	59 (6.3)
Discontinuations from Study due to Adverse Event	17 (2.6)	16 (2.5)	18 (2.8)	21 (3.3)	5 (1.6)	3 (1.0)	5 (1.6)	22 (2.3)	16 (2.5)	21 (2.2)	26 (2.8)
Discontinuations from Study Treatment due to Adverse Event	21 (3.3)	30 (4.8)	46 (7.2)	40 (6.3)	12 (3.8)	14 (4.5)	23 (7.4)	33 (3.4)	30 (4.8)	60 (6.3)	63 (6.7)
Treatment-Emergent Adverse Events	463 (72.0)	510 (81.0)	520 (81.8)	497 (78.9)	239 (75.9)	242 (77.6)	222 (71.4)	702 (73.3)	510 (81.0)	762 (80.4)	719 (76.4)

Source: Generated by reviewer using applicant adsl.xpt and adae.xpt datasets

Notes: Agrees with Applicant CSR Tables GPHK.5.33 and GPHL.5.39, deaths are also counted as SAEs and discontinuations.

8.4.1. Deaths

In CWM trials of tirzepatide submitted with this NDA, 13 deaths occurred in phase 3 trials GPHK and GPHL, and no deaths occurred in the phase 1 trial gastric emptying study GPHU. There was no apparent imbalance in deaths between the tirzepatide and placebo arms, with 9 deaths in tirzepatide arms (0.36%) and 4 in placebo arms (0.42%). There were no apparent trends in the causes of death, which appeared consistent with the expected morbidity and mortality in the trial population (Table 42).

Table 42. Listing of Deaths in Tirzepatide Weight Management Trials

Study Arm	Trial-Subject ID	Age / Sex	Dosing Duration (Days)	Study Day of Death	Primary Cause of Death
Placebo	(b) (6)	47 / M	287	312	Pulmonary embolism
Placebo		59 / M	184	183	Cardiac failure acute
Placebo		45 / F	77	370	Intestinal obstruction
Placebo		76 / F	448	480	Ischemic stroke
TZP 5mg		45 / F	310	318	Hepatic failure
TZP 5mg		59 / M	175	263	COVID-19 pneumonia
TZP 5mg		62 / M	56	94	COVID-19 pneumonia

Study Arm	Trial-Subject ID	Age / Sex	Dosing Duration (Days)	Study Day of Death	Primary Cause of Death
TZP 5mg	(b) (6)	38 / M	35	29	Multiple injuries
TZP 10mg	(b) (6)	36 / M	262	260	Homicide
TZP 10mg	(b) (6)	68 / M	36	325	Cerebrovascular accident
TZP 10mg	(b) (6)	64 / M	140	158	Respiratory fume inhalation disorder
TZP 10mg	(b) (6)	60 / M	63	85	Cardio-respiratory arrest
TZP 15mg	(b) (6)	61 / M	84	96	SARS-CoV-2 test positive

Source: Pooled GPHK and GPHL datasets (adae, adsl) analyzed by reviewer in OCS Analysis Studio, Listing Table Tool

Abbreviations: ARDS, Acute Respiratory Distress Syndrome

Nine deaths occurred in subjects receiving tirzepatide:

- Three deaths were attributed to COVID-19 pneumonia and respiratory failure.
- Three deaths were due to accident or trauma:
 - Subject (b) (6) was a passenger in a taxi that had a road traffic accident, and he died from multiple injuries.
 - Subject (b) (6) was the victim of a homicide.
 - Subject (b) (6) was in a house fire and found dead and burned by firefighters.

Reviewer comment: I agree with the Applicant's assessment that these six deaths due to COVID-19, accidents, or trauma are likely unrelated to tirzepatide.

- Two deaths were likely due to cardiovascular events:
 - The listed cause of death for subject (b) (6) is stroke. He was a 68-year-old Asian man with baseline BMI 28.5 kg/m² and history of hypertension, dyslipidemia, and smoking. He was randomized to tirzepatide 10 mg, but on Day 30 he received his last dose tirzepatide 5 mg which was then permanently discontinued due to the adverse event of nausea. On study Day 325 (295 days after the last tirzepatide dose), the subject suffered a suspected stroke (as adjudicated by the CEC) and died.
 - The listed cause of death for subject (b) (6) is cardiorespiratory arrest. He was 60-year-old Hispanic man with baseline BMI 36.9 kg/m² and a history of T2D, hypertension, and COPD due to past smoking. He was randomized to tirzepatide 10 mg, but on Day 57 he received his last dose tirzepatide 7.5 mg. On Day 85, he died from presumed cardiorespiratory arrest which was adjudicated by the CEC as an undetermined death.

Reviewer comment: Obesity and diabetes raise the risk of ASCVD, and both subjects were men aged ≥ 60 years with multiple risk factors. It is unlikely that tirzepatide caused these two events, which occurred 28 and 295 days after the last doses of tirzepatide. The Applicant is conducting phase 3b trial GPIJ (SURMOUNT-MMO) which will evaluate whether tirzepatide reduces ASCVD events.

- One death was attributed to hepatic failure. The listed cause of death for subject (b) (6) is hepatic failure, but her case was complicated by alcohol and polysubstance abuse and COVID-19 infection, and acute respiratory failure. She was a 45-year-old African American woman with a baseline BMI of 60.9 kg/m² and a history of cholecystectomy, hypertension, and prediabetes. Her liver laboratory tests were normal at baseline and at her last in-person visit on study Day 253, when she had lost 1.1% of her body weight taking tirzepatide 5 mg weekly. Prior to the events leading to death, the only adverse event she reported was arthralgia. Routine telephone visits on study Days 279 and 309 did not identify safety issues, but on Day 315 she was found unresponsive in her home by daughter and transported to the Emergency Department (ED) by ambulance. Per her daughter, in the days leading up to this event the subject had been drinking alcohol and taking increased amounts of ibuprofen and cannabidiol (CBD) for joint pain; in the ED, her blood alcohol content was 54 mg/dl (upper limit 10 mg/dl), and her urine drug screen was positive for cocaine and opiates. Her transaminases were markedly elevated (ALT 4185 U/L and aspartate aminotransferase [AST] 4772 U/L), with a normal bilirubin and mildly elevated INR of 1.7. She was intubated and mechanically ventilated, then admitted to the intensive care unit (ICU) with the diagnosis of acute liver failure with hepatic encephalopathy, shock, and acute kidney injury in the setting of a positive COVID-19 test and evidence of alcohol and drug abuse. Despite aggressive ICU care, she died on study Day 319 and no autopsy was performed.

Reviewer comment: This is a complicated case. Although it cannot be ruled out that this event was due to drug-induced liver injury (DILI) caused by tirzepatide, there are multiple confounding factors including alcohol abuse. Furthermore, the subject's low 5 mg dosage and lack of weight loss suggests potentially low exposure to drug, also making DILI unlikely. Liver safety of tirzepatide is addressed in detail below in Section 8.5.14.

Deaths in Ongoing Trials (Blinded)

The Applicant submitted a 4-month safety report update that reports 5 additional deaths in the CWM development program for tirzepatide, all of which remain blinded to treatment arm with no narratives provided:

- Subject (b) (6) in trial GPHK (SURMOUNT-1 extension study in subjects with prediabetes at baseline) died with adverse events of cardiac arrest, hypovolemic shock,

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and multiple traumas.

- Subject (b) (6) in trial GPHM (SURMOUNT-3 for CWM after intensive lifestyle modification) died with acute myocardial infarction.
- Subject (b) (6) also in trial GPHM died with heart attack and pulmonary thrombosis.
- Subject (b) (6) in trial GPHN (SURMOUNT-4 for CWM after randomized withdrawal from tirzepatide) died with decompensated congestive heart failure.
- Subject (b) (6) also in trial GPHN died with metastatic colon adenocarcinoma.

Reviewer comment: Cardiovascular and cancer deaths are not unexpected in CWM trials, so these deaths in subjects on blinded tirzepatide or placebo do not change my safety assessment of tirzepatide.

The 4-month safety update also lists other deaths in ongoing trials for other indications:

- In open-label T2D trial GPHD (comparing tirzepatide weekly to rapid-acting insulin 3 times daily in subjects already on basal insulin), there were 7 deaths on tirzepatide (1.0%) compared to 11 deaths on insulin lispro (1.6%).
- In the blinded T2D CVOT GPGN, there were 561 deaths (4.2%) as anticipated for the population with established CV disease and thus elevated risk. Likewise, there has been one death to date in trial GPIJ (SURMOUNT-MMO) which is enrolling a population with established CV disease or at high CV risk.
- In the blinded heart failure trial GPID, there have been 15 deaths (2.3%) in a high-risk population with chronic heart failure (NYHA class II to IV) with preserved ejection fraction.

Reviewer comment: Blinded cases are very difficult to interpret. Event rates will be calculated, and causality assessments will be conducted when the trials are complete. Unblinded safety data from the ongoing CVOTs is being monitored by DMCs.

8.4.2. Serious Adverse Events

In the phase 3 CWM trials GPHK and GPHL, serious treatment-emergent adverse events (SAEs) were balanced between placebo and tirzepatide groups, and there was no apparent dose effect of tirzepatide (6.3%, 6.5%, and 6.3% for tirzepatide 5, 10, and 15 mg compared to 7.0% for placebo, see Table 41 above). SAEs by SOC are shown in Table 43.

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Table 43. Serious TEAEs by SOC (Trials GPHK and GPHL)

System Organ Class	TZP All N = 2519	Placebo N = 958	Relative Risk	
	n (%)	n (%)	RR (95% CI)	Forest Plot
Any SAE	160 (6.4)	66 (6.9)	0.92 (0.70, 1.22)	
Infections and infestations	51 (2.0)	19 (2.0)	1.02 (0.61, 1.72)	
Hepatobiliary disorders	26 (1.0)	8 (0.8)	1.24 (0.56, 2.72)	
Gastrointestinal disorders	17 (0.7)	7 (0.7)	0.92 (0.38, 2.22)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	15 (0.6)	13 (1.4)	0.44 (0.21, 0.92)	
Injury, poisoning and procedural complications	14 (0.6)	3 (0.3)	1.77 (0.51, 6.16)	
Cardiac disorders	11 (0.4)	6 (0.6)	0.70 (0.26, 1.88)	
Nervous system disorders	11 (0.4)	5 (0.5)	0.84 (0.29, 2.40)	
Renal and urinary disorders	11 (0.4)	3 (0.3)	1.39 (0.39, 4.99)	
Respiratory, thoracic and mediastinal disorders	7 (0.3)	3 (0.3)	0.89 (0.23, 3.42)	
Vascular disorders	7 (0.3)	3 (0.3)	0.89 (0.23, 3.42)	
Psychiatric disorders	6 (0.2)	0 (0.0)	4.95 (0.28, 87.71)	
Metabolism and nutrition disorders	4 (0.2)	0 (0.0)	3.42 (0.18, 63.54)	
General disorders and administration site conditions	3 (0.1)	2 (0.2)	0.57 (0.10, 3.41)	
Investigations	2 (0.1)	0 (0.0)	1.90 (0.09, 39.59)	
Pregnancy, puerperium and perinatal conditions	2 (0.1)	0 (0.0)	1.90 (0.09, 39.59)	
Reproductive system and breast disorders	2 (0.1)	1 (0.1)	0.76 (0.07, 8.38)	
Ear and labyrinth disorders	1 (0.0)	0 (0.0)	1.14 (0.05, 27.99)	
Musculoskeletal and connective tissue disorders	1 (0.0)	4 (0.4)	0.10 (0.01, 0.85)	
Product issues	1 (0.0)	0 (0.0)	1.14 (0.05, 27.99)	
Social circumstances	1 (0.0)	0 (0.0)	1.14 (0.05, 27.99)	
Surgical and medical procedures	1 (0.0)	0 (0.0)	1.14 (0.05, 27.99)	
Blood and lymphatic system disorders	0 (0.0)	1 (0.1)	0.13 (0.01, 3.11)	
Skin and subcutaneous tissue disorders	0 (0.0)	1 (0.1)	0.13 (0.01, 3.11)	

System Organ Class	TZP All N = 2519 n (%)	Placebo N = 958 n (%)	Relative Risk	
			RR (95% CI)	Forest Plot
Any SAE	160 (6.4)	66 (6.9)	0.92 (0.70, 1.22)	

Source: Generated by reviewer with Applicant's pooled datasets for GPHK and GPHL (adsl, adae) using OCS Analysis Studio, Safety Explorer, and treatment emergent events in the safety population.

Relative Risk is calculated by comparing the TZP All to Placebo. A continuity correction of 0.5 (Yates, 1934) is used to calculate relative risk if any treatment arm has zero subjects.

The most common SOC with SAEs occurring in >0.5% of subjects on tirzepatide were:

- "Infections and infestations" were balanced between the tirzepatide and placebo groups, with most common PTs being COVID-19 related.
- "Hepatobiliary disorders" were balanced and are discussed below in Sections 8.5.4 and 8.5.14.
- GI disorders were balanced and are discussed below as in Section 8.5.2.
- Neoplasms occurred more frequently in the placebo group and are discussed below in Section 8.5.15. An exploratory endpoint in the phase 3b trial GPIJ (SURMOUNT-MMO) will evaluate whether tirzepatide reduces the incidence of obesity-associated malignancies.
- Injury, poisoning and procedural complications occurred more often in the tirzepatide group, but there was no meaningful pattern to the PTs for these events as shown below in Table 44.

Four SAE SOC occurred more than once in tirzepatide groups and not in placebo groups:

- Psychiatric disorders included anxiety, depression, substance abuse, and suicide attempt, as discussed below in Section 8.5.9.
- Metabolism and nutrition disorders included electrolyte abnormalities and dehydration, as discussed below in sections 8.4.6 and 8.5.3, respectively.
- The investigations were both COVID-19 testing and positivity, thus likely unrelated to tirzepatide.
- Pregnancy-related SAEs were an ectopic pregnancy and a spontaneous abortion, discussed below in Section 8.8.2.

All treatment emergent SAEs are enumerated in Table 44. My review of these 160 SAEs in tirzepatide-treated subjects by PTs did not reveal meaningful differences between arms.

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Table 44. All Serious TEAEs by PT (Trials GPHK and GPHL)

System Organ Class Preferred Term	TZP All N = 2519 n (%)	Placebo N = 958 n (%)
Any SAE	160 (6.4)	66 (6.9)
Blood and lymphatic system disorders	0 (0.0)	1 (0.1)
Anemia	0 (0.0)	1 (0.1)
Cardiac disorders	11 (0.4)	6 (0.6)
Acute coronary syndrome	1 (0.0)	0 (0.0)
Acute myocardial infarction	1 (0.0)	1 (0.1)
Angina unstable	3 (0.1)	0 (0.0)
Atrial fibrillation	1 (0.0)	1 (0.1)
Atrial flutter	1 (0.0)	0 (0.0)
Cardiac failure	1 (0.0)	0 (0.0)
Cardiac failure acute	0 (0.0)	1 (0.1)
Cardiac failure congestive	0 (0.0)	1 (0.1)
Cardio-respiratory arrest	1 (0.0)	0 (0.0)
Coronary artery disease	0 (0.0)	2 (0.2)
Coronary artery occlusion	1 (0.0)	0 (0.0)
Myocardial infarction	1 (0.0)	0 (0.0)
Ventricular arrhythmia	1 (0.0)	0 (0.0)
Ventricular extrasystoles	1 (0.0)	0 (0.0)
Ear and labyrinth disorders	1 (0.0)	0 (0.0)
Vertigo	1 (0.0)	0 (0.0)
Gastrointestinal disorders	17 (0.7)	7 (0.7)
Chronic gastritis	1 (0.0)	0 (0.0)
Colitis	1 (0.0)	0 (0.0)
Colitis ulcerative	1 (0.0)	0 (0.0)
Constipation	1 (0.0)	0 (0.0)
Diarrhea	1 (0.0)	0 (0.0)
Diverticulum intestinal hemorrhagic	0 (0.0)	1 (0.1)
Duodenal ulcer	0 (0.0)	1 (0.1)
Enteritis	1 (0.0)	0 (0.0)
Gastric antral vascular ectasia	1 (0.0)	0 (0.0)
Hernial eventration	1 (0.0)	0 (0.0)
Ileus paralytic	1 (0.0)	0 (0.0)
Inguinal hernia strangulated	1 (0.0)	0 (0.0)
Intestinal obstruction	0 (0.0)	1 (0.1)
Obstructive pancreatitis	0 (0.0)	2 (0.2)
Esophagitis ulcerative	1 (0.0)	0 (0.0)

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System Organ Class Preferred Term	TZP All N = 2519 n (%)	Placebo N = 958 n (%)
Any SAE	160 (6.4)	66 (6.9)
Pancreatitis	1 (0.0)	0 (0.0)
Pancreatitis acute	3 (0.1)	0 (0.0)
Proctitis	1 (0.0)	0 (0.0)
Retroperitoneal hematoma	0 (0.0)	1 (0.1)
Upper gastrointestinal hemorrhage	1 (0.0)	1 (0.1)
Vomiting	3 (0.1)	0 (0.0)
General disorders and administration site conditions	3 (0.1)	2 (0.2)
Chest pain	1 (0.0)	0 (0.0)
Non-cardiac chest pain	2 (0.1)	1 (0.1)
Pyrexia	0 (0.0)	1 (0.1)
Hepatobiliary disorders	26 (1.0)	8 (0.8)
Bile duct stone	1 (0.0)	0 (0.0)
Biliary colic	1 (0.0)	0 (0.0)
Biliary obstruction	1 (0.0)	0 (0.0)
Cholangitis acute	1 (0.0)	0 (0.0)
Cholecystitis	3 (0.1)	0 (0.0)
Cholecystitis acute	7 (0.3)	2 (0.2)
Cholecystitis chronic	2 (0.1)	3 (0.3)
Cholelithiasis	12 (0.5)	4 (0.4)
Hepatic failure	1 (0.0)	0 (0.0)
Sphincter of Oddi dysfunction	1 (0.0)	0 (0.0)
Infections and infestations	51 (2.0)	19 (2.0)
Abdominal abscess	1 (0.0)	0 (0.0)
Anal abscess	1 (0.0)	0 (0.0)
Appendicitis	7 (0.3)	3 (0.3)
Appendicitis perforated	0 (0.0)	1 (0.1)
Bacterial colitis	1 (0.0)	0 (0.0)
Cellulitis	3 (0.1)	0 (0.0)
Coronavirus infection	1 (0.0)	0 (0.0)
Coronavirus pneumonia	1 (0.0)	0 (0.0)
Covid-19	9 (0.4)	6 (0.6)
Covid-19 pneumonia	13 (0.5)	6 (0.6)
Diverticulitis	1 (0.0)	1 (0.1)
Gangrene	0 (0.0)	1 (0.1)
Gastroenteritis	3 (0.1)	0 (0.0)
Influenza	1 (0.0)	0 (0.0)

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System Organ Class Preferred Term	TZP All N = 2519 n (%)	Placebo N = 958 n (%)
Any SAE	160 (6.4)	66 (6.9)
Osteomyelitis	0 (0.0)	1 (0.1)
Pelvic inflammatory disease	1 (0.0)	0 (0.0)
Peritoneal tuberculosis	1 (0.0)	0 (0.0)
Peritonsillar abscess	1 (0.0)	0 (0.0)
Pneumonia	3 (0.1)	0 (0.0)
Pneumonia aspiration	1 (0.0)	0 (0.0)
Pneumonia bacterial	1 (0.0)	0 (0.0)
Pyelonephritis	2 (0.1)	0 (0.0)
Septic shock	1 (0.0)	0 (0.0)
Urinary tract infection	2 (0.1)	0 (0.0)
Injury, poisoning and procedural complications	14 (0.6)	3 (0.3)
Ankle fracture	1 (0.0)	1 (0.1)
Clavicle fracture	1 (0.0)	0 (0.0)
Contusion	2 (0.1)	0 (0.0)
Facial bones fracture	1 (0.0)	0 (0.0)
Femur fracture	1 (0.0)	0 (0.0)
Foot fracture	1 (0.0)	0 (0.0)
Limb traumatic amputation	1 (0.0)	0 (0.0)
Lumbar vertebral fracture	1 (0.0)	0 (0.0)
Multiple injuries	1 (0.0)	0 (0.0)
Post procedural hematuria	0 (0.0)	1 (0.1)
Procedural pain	1 (0.0)	0 (0.0)
Respiratory fume inhalation disorder	1 (0.0)	0 (0.0)
Road traffic accident	1 (0.0)	0 (0.0)
Shunt thrombosis	1 (0.0)	0 (0.0)
Tendon rupture	1 (0.0)	0 (0.0)
Tibia fracture	1 (0.0)	0 (0.0)
Vascular pseudoaneurysm	1 (0.0)	0 (0.0)
Wound	0 (0.0)	1 (0.1)
Investigations	2 (0.1)	0 (0.0)
Sars-cov-2 test positive	2 (0.1)	0 (0.0)
Metabolism and nutrition disorders	4 (0.2)	0 (0.0)
Dehydration	2 (0.1)	0 (0.0)
Hyponatremia	2 (0.1)	0 (0.0)
Musculoskeletal and connective tissue disorders	1 (0.0)	4 (0.4)
Osteoarthritis	1 (0.0)	3 (0.3)

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System Organ Class Preferred Term	TZP All N = 2519 n (%)	Placebo N = 958 n (%)
Any SAE	160 (6.4)	66 (6.9)
Spondylolisthesis	0 (0.0)	1 (0.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	15 (0.6)	13 (1.4)
Adenocarcinoma of colon	0 (0.0)	1 (0.1)
Adenocarcinoma of the cervix	0 (0.0)	1 (0.1)
Adenosquamous carcinoma of the cervix	1 (0.0)	0 (0.0)
Breast cancer	1 (0.0)	0 (0.0)
Colon cancer	0 (0.0)	1 (0.1)
Endometrial cancer	2 (0.1)	0 (0.0)
Gastric neoplasm	1 (0.0)	0 (0.0)
Intraductal proliferative breast lesion	1 (0.0)	1 (0.1)
Invasive breast carcinoma	0 (0.0)	1 (0.1)
Leiomyoma	1 (0.0)	0 (0.0)
Leukemia	0 (0.0)	1 (0.1)
Lung adenocarcinoma	1 (0.0)	0 (0.0)
Malignant melanoma	2 (0.1)	0 (0.0)
Mantle cell lymphoma	0 (0.0)	1 (0.1)
Meningioma	2 (0.1)	1 (0.1)
Ovarian cancer	0 (0.0)	1 (0.1)
Ovarian germ cell endodermal sinus tumor stage i	1 (0.0)	0 (0.0)
Pancreatic carcinoma metastatic	0 (0.0)	1 (0.1)
Papillary thyroid cancer	0 (0.0)	1 (0.1)
Plasma cell myeloma	0 (0.0)	1 (0.1)
Prostate cancer	2 (0.1)	1 (0.1)
Renal cancer	0 (0.0)	1 (0.1)
Uterine leiomyoma	1 (0.0)	0 (0.0)
Nervous system disorders	11 (0.4)	5 (0.5)
Brain oedema	1 (0.0)	0 (0.0)
Cerebrovascular accident	1 (0.0)	0 (0.0)
Dizziness	0 (0.0)	1 (0.1)
Encephalopathy	1 (0.0)	0 (0.0)
Hemorrhagic stroke	1 (0.0)	0 (0.0)
Hypoaesthesia	0 (0.0)	1 (0.1)
Idiopathic generalized epilepsy	0 (0.0)	1 (0.1)
Ischemic stroke	3 (0.1)	1 (0.1)
Multiple sclerosis relapse	1 (0.0)	0 (0.0)
Thalamus hemorrhage	1 (0.0)	0 (0.0)

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	TZP All	Placebo
System Organ Class	N = 2519	N = 958
Preferred Term	n (%)	n (%)
Any SAE	160 (6.4)	66 (6.9)
Transient ischemic attack	1 (0.0)	1 (0.1)
Vertebrobasilar stroke	1 (0.0)	0 (0.0)
Pregnancy, puerperium and perinatal conditions	2 (0.1)	0 (0.0)
Abortion spontaneous	1 (0.0)	0 (0.0)
Ectopic pregnancy	1 (0.0)	0 (0.0)
Product issues	1 (0.0)	0 (0.0)
Device dislocation	1 (0.0)	0 (0.0)
Psychiatric disorders	6 (0.2)	0 (0.0)
Adjustment disorder with mixed anxiety and depressed mood	1 (0.0)	0 (0.0)
Anxiety disorder	1 (0.0)	0 (0.0)
Bulimia nervosa	1 (0.0)	0 (0.0)
Major depression	1 (0.0)	0 (0.0)
Substance abuse	1 (0.0)	0 (0.0)
Suicide attempt	2 (0.1)	0 (0.0)
Renal and urinary disorders	11 (0.4)	3 (0.3)
Acute kidney injury	6 (0.2)	2 (0.2)
Calculus bladder	0 (0.0)	1 (0.1)
Nephrolithiasis	2 (0.1)	0 (0.0)
Renal failure	1 (0.0)	0 (0.0)
Renal injury	1 (0.0)	0 (0.0)
Renal mass	1 (0.0)	0 (0.0)
Reproductive system and breast disorders	2 (0.1)	1 (0.1)
Adenomyosis	1 (0.0)	0 (0.0)
Endometrial hyperplasia	1 (0.0)	0 (0.0)
Vaginal hemorrhage	0 (0.0)	1 (0.1)
Respiratory, thoracic and mediastinal disorders	7 (0.3)	3 (0.3)
Acute respiratory failure	2 (0.1)	0 (0.0)
Aspiration	1 (0.0)	0 (0.0)
Asthma	1 (0.0)	0 (0.0)
Chronic obstructive pulmonary disease	1 (0.0)	0 (0.0)
Dyspnea	1 (0.0)	0 (0.0)
Pneumonitis	1 (0.0)	0 (0.0)
Pulmonary embolism	1 (0.0)	3 (0.3)
Skin and subcutaneous tissue disorders	0 (0.0)	1 (0.1)
Diabetic foot	0 (0.0)	1 (0.1)
Social circumstances	1 (0.0)	0 (0.0)

System Organ Class Preferred Term	TZP All N = 2519 n (%)	Placebo N = 958 n (%)
Any SAE	160 (6.4)	66 (6.9)
Homicide	1 (0.0)	0 (0.0)
Surgical and medical procedures	1 (0.0)	0 (0.0)
Thyroidectomy	1 (0.0)	0 (0.0)
Vascular disorders	7 (0.3)	3 (0.3)
Deep vein thrombosis	1 (0.0)	0 (0.0)
Hematoma	1 (0.0)	0 (0.0)
Hypertension	0 (0.0)	2 (0.2)
Hypertensive urgency	1 (0.0)	0 (0.0)
Hypotension	3 (0.1)	0 (0.0)
Peripheral venous disease	1 (0.0)	0 (0.0)
Thrombophlebitis	0 (0.0)	1 (0.1)

Source: Generated by reviewer using OCS Analysis Studio, Safety Explorer.

I reviewed SAEs in other trials from the tirzepatide development program, and these did not raise additional safety concerns:

- No SAEs occurred in the 36 subjects in the phase 1 CWM trial GPHU.
- The Applicant's Summary of Clinical Safety and Integrated Summary of Safety provide tabulations of SAEs in analysis sets pooling CWM and T2D phase 2/3 trials.
- The Applicant's 4-month Safety Update describes SAEs in blinded CWM trials, blinded and unblinded T2D trials, blinded outcomes trials, phase 1 trials, and trials for heart failure, OSA, NASH, and CKD.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

In the phase 3 CWM trials GPHK and GPHL (SURMOUNT-1 and -2), TEAEs leading to discontinuation from study treatment occurred more often in tirzepatide than placebo arms, with an apparent dose effect of tirzepatide (4.8%, 6.3%, and 6.7% for tirzepatide 5, 10, and 15 mg, compared to 3.4% for placebo, see Table 41 above). TEAEs leading to discontinuation by SOC are shown in Table 45.

Table 45. TEAEs Leading to Study Drug Discontinuation by SOC (Trials GPHK and GPHL)

System Organ Class	TZP all N = 2519	Placebo N = 958	Relative Risk	
	n (%)	n (%)	RR (95% CI)	Forest Plot
Any AE	152 (6.0)	33 (3.4)	1.75 (1.21, 2.53)	
Gastrointestinal disorders	83 (3.3)	5 (0.5)	6.31 (2.57, 15.52)	
Investigations	12 (0.5)	2 (0.2)	2.28 (0.51, 10.18)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	10 (0.4)	9 (0.9)	0.42 (0.17, 1.04)	
General disorders and administration site conditions	6 (0.2)	1 (0.1)	2.28 (0.28, 18.93)	
Infections and infestations	5 (0.2)	2 (0.2)	0.95 (0.18, 4.89)	
Nervous system disorders	5 (0.2)	3 (0.3)	0.63 (0.15, 2.65)	
Psychiatric disorders	4 (0.2)	2 (0.2)	0.76 (0.14, 4.15)	
Hepatobiliary disorders	3 (0.1)	1 (0.1)	1.14 (0.12, 10.96)	
Metabolism and nutrition disorders	3 (0.1)	2 (0.2)	0.57 (0.10, 3.41)	
Musculoskeletal and connective tissue disorders	3 (0.1)	0 (0.0)	2.66 (0.14, 51.51)	
Skin and subcutaneous tissue disorders	3 (0.1)	1 (0.1)	1.14 (0.12, 10.96)	
Vascular disorders	3 (0.1)	0 (0.0)	2.66 (0.14, 51.51)	
Eye disorders	2 (0.1)	0 (0.0)	1.90 (0.09, 39.59)	
Injury, poisoning and procedural complications	2 (0.1)	0 (0.0)	1.90 (0.09, 39.59)	
Respiratory, thoracic and mediastinal disorders	2 (0.1)	2 (0.2)	0.38 (0.05, 2.70)	
Surgical and medical procedures	2 (0.1)	1 (0.1)	0.76 (0.07, 8.38)	
Cardiac disorders	1 (0.0)	1 (0.1)	0.38 (0.02, 6.07)	
Ear and labyrinth disorders	1 (0.0)	0 (0.0)	1.14 (0.05, 27.99)	
Renal and urinary disorders	1 (0.0)	0 (0.0)	1.14 (0.05, 27.99)	
Social circumstances	1 (0.0)	0 (0.0)	1.14 (0.05, 27.99)	
Immune system disorders	0 (0.0)	1 (0.1)	0.13 (0.01, 3.11)	

Source: Generated by reviewed using OCS Analysis Studio, Safety Explorer.

Relative Risk calculated by comparing the left column (Group 1) to the right column (Group 2). A continuity correction of 0.5 (Yates, 1934) is used to calculate relative risk if any treatment arm has zero subjects.

In summary, AEs leading to permanent discontinuation of trial product were higher with tirzepatide than with placebo, mostly due to GI AEs which are discussed below in Section 8.5.2.

8.4.4. Significant Adverse Events

Table 46 summarizes significant TEAE categories of interest in the two pooled phase 3 CWM trials: events reported as severe, events reported as not recovered, and events leading to changes in study drug. The proportion of subjects with any AE was slightly greater in the tirzepatide than placebo groups (see Section 8.4.5), and events without recovery noted were balanced between tirzepatide and placebo arms. More subjects on tirzepatide than placebo had TEAEs leading to permanent and temporary treatment discontinuation and dose reduction, as expected given known common adverse reactions to incretin drugs described below (see Sections 8.4.5 and 8.5.2).

Table 46. Overview of Selected Significant TEAEs (Trials GPHK and GPHL)

	TZP All (N=2519)	Placebo (N=958)
All events	1991 (79.0)	702 (73.3)
Serious events	160 (6.4)	66 (6.9)
Severe events	183 (7.3)	55 (5.7)
Outcome - Not recovered	749 (29.7)	264 (27.6)
Leading to		
Permanent discontinuation	143 (5.7)	28 (2.9)
Temporary interruption	236 (9.4)	62 (6.5)
Dose reduction	123 (4.9)	1 (0.1)

Source: Generated by reviewer using OCS Analysis Studio, Custom Table Tool.

Investigator-graded severity is a way to potentially assess significant events, and AEs graded as severe had slightly higher incidence in the tirzepatide (7.3%) than placebo (5.7%) groups.

Though grading is subjective, my review of selected case narratives agreed with the investigator-graded severity in a majority of cases. Table 47 shows all severe TEAEs by SOC.

Table 47. TEAEs Graded as Severe by SOC (Trials GPHK and GPHL)

System Organ Class	TZP All N = 2519	Placebo N = 958	Relative Risk	
	n (%)	n (%)	RR (95% CI)	Forest Plot
Any AE	183 (7.3)	55 (5.7)	1.27 (0.94, 1.69)	
Gastrointestinal disorders	64 (2.5)	10 (1.0)	2.43 (1.26, 4.72)	
Infections and infestations	37 (1.5)	12 (1.3)	1.17 (0.61, 2.24)	

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System Organ Class	TZP All N = 2519	Placebo N = 958	Relative Risk	
	n (%)	n (%)	RR (95% CI)	Forest Plot
Any AE	183 (7.3)	55 (5.7)	1.27 (0.94, 1.69)	
Nervous system disorders	20 (0.8)	6 (0.6)	1.27 (0.51, 3.15)	
Hepatobiliary disorders	16 (0.6)	2 (0.2)	3.04 (0.70, 13.21)	
Injury, poisoning and procedural complications	15 (0.6)	2 (0.2)	2.85 (0.65, 12.45)	
Musculoskeletal and connective tissue disorders	14 (0.6)	4 (0.4)	1.33 (0.44, 4.03)	
Metabolism and nutrition disorders	12 (0.5)	7 (0.7)	0.65 (0.26, 1.65)	
General disorders and administration site conditions	10 (0.4)	1 (0.1)	3.80 (0.49, 29.67)	
Psychiatric disorders	9 (0.4)	2 (0.2)	1.71 (0.37, 7.91)	
Renal and urinary disorders	9 (0.4)	3 (0.3)	1.14 (0.31, 4.21)	
Respiratory, thoracic and mediastinal disorders	9 (0.4)	6 (0.6)	0.57 (0.20, 1.60)	
Cardiac disorders	8 (0.3)	3 (0.3)	1.01 (0.27, 3.81)	
Investigations	7 (0.3)	0 (0.0)	5.71 (0.33, 99.82)	
Surgical and medical procedures	6 (0.2)	1 (0.1)	2.28 (0.28, 18.93)	
Vascular disorders	6 (0.2)	3 (0.3)	0.76 (0.19, 3.04)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	4 (0.2)	7 (0.7)	0.22 (0.06, 0.74)	
Reproductive system and breast disorders	3 (0.1)	0 (0.0)	2.66 (0.14, 51.51)	
Skin and subcutaneous tissue disorders	3 (0.1)	1 (0.1)	1.14 (0.12, 10.96)	
Ear and labyrinth disorders	2 (0.1)	0 (0.0)	1.90 (0.09, 39.59)	
Pregnancy, puerperium and perinatal conditions	2 (0.1)	0 (0.0)	1.90 (0.09, 39.59)	
Eye disorders	1 (0.0)	1 (0.1)	0.38 (0.02, 6.07)	
Immune system disorders	1 (0.0)	0 (0.0)	1.14 (0.05, 27.99)	
Social circumstances	1 (0.0)	0 (0.0)	1.14 (0.05, 27.99)	
Blood and lymphatic system disorders	0 (0.0)	2 (0.2)	0.08 (0.00, 1.58)	

Source: Generated by reviewer using OCS Analysis Studio, Safety Explorer.

Note: Relative Risk calculated by comparing the left column (Group 1) to the right column (Group 2). A continuity correction of 0.5 (Yates, 1934) is used to calculate relative risk if any treatment arm has zero subjects.

Two SOC's showed statistically significant differences in severe AEs between tirzepatide and placebo arms: severe GI AEs were more common with tirzepatide, while severe neoplasm AEs were less common with tirzepatide. Severe hepatobiliary and administration site AEs also showed apparent imbalances, and these and other severe or otherwise significant AESI are reviewed in depth in their respective subsections of Section 8.5, Analysis of Submission-Specific Safety Issues.

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

Table 48 presents all TEAEs in trials GPHK and GPHL by SOC. The most frequently observed AEs were in the "Gastrointestinal disorders" SOC, with 55.7% of tirzepatide- versus 29.6% of placebo-treated subjects reporting at least 1 event. GI disorders are described in more detail in Section 8.5.2. Four other SOC's showed significant risk differences in the tirzepatide versus placebo groups:

- "Infection and Infestations" were less common in the tirzepatide groups.
- "General disorders and administration site conditions" were higher in the tirzepatide group, with the difference driven primarily by injection site reaction AEs (see Section 8.5.11).
- "Nervous system disorders" were higher in the tirzepatide group, with the difference driven primarily by dizziness AEs. Dizziness and nausea are related AEs that may be difficult to distinguish for some subjects, or occur concurrently, so TEAEs reports of dizziness could also reflect GI AEs.
- "Skin and subcutaneous tissue disorders" were higher in the tirzepatide group, with the difference driven primarily by hair loss AEs (see Section 8.5.12).

Table 48. TEAEs by SOC Occurring in ≥1% of Tirzepatide-Treated Subjects (Trials GPHK and GPHL)

System Organ Class	TZP All N = 2519 n (%)	Placebo N = 958 n (%)	Risk Difference	
			RD (95% CI)	Forest Plot
Any AE	1991 (79.0)	702 (73.3)	5.76 (2.54, 8.98)	
Gastrointestinal disorders	1402 (55.7)	284 (29.6)	26.01 (22.53, 29.49)	
Infections and infestations	850 (33.7)	363 (37.9)	-4.15 (-7.73, -0.56)	
General disorders and administration site conditions	468 (18.6)	98 (10.2)	8.35 (5.90, 10.80)	
Nervous system disorders	390 (15.5)	122 (12.7)	2.75 (0.21, 5.29)	
Musculoskeletal and connective tissue disorders	366 (14.5)	127 (13.3)	1.27 (-1.28, 3.82)	

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System Organ Class	TZP All N = 2519 n (%)	Placebo N = 958 n (%)	Risk Difference	
			RD (95% CI)	Forest Plot
Any AE	1991 (79.0)	702 (73.3)	5.76 (2.54, 8.98)	
Metabolism and nutrition disorders	364 (14.5)	144 (15.0)	-0.58 (-3.23, 2.07)	
Skin and subcutaneous tissue disorders	260 (10.3)	51 (5.3)	5.00 (3.15, 6.85)	
Investigations	231 (9.2)	76 (7.9)	1.24 (-0.81, 3.29)	
Injury, poisoning and procedural complications	224 (8.9)	91 (9.5)	-0.61 (-2.77, 1.56)	
Psychiatric disorders	164 (6.5)	68 (7.1)	-0.59 (-2.48, 1.30)	
Respiratory, thoracic and mediastinal disorders	118 (4.7)	61 (6.4)	-1.68 (-3.44, 0.07)	
Cardiac disorders	106 (4.2)	37 (3.9)	0.35 (-1.10, 1.80)	
Vascular disorders	103 (4.1)	39 (4.1)	0.02 (-1.45, 1.49)	
Surgical and medical procedures	82 (3.3)	21 (2.2)	1.06 (-0.09, 2.22)	
Reproductive system and breast disorders	74 (2.9)	28 (2.9)	0.01 (-1.24, 1.27)	
Renal and urinary disorders	73 (2.9)	28 (2.9)	-0.02 (-1.28, 1.23)	
Hepatobiliary disorders	68 (2.7)	25 (2.6)	0.09 (-1.10, 1.28)	
Blood and lymphatic system disorders	61 (2.4)	19 (2.0)	0.44 (-0.63, 1.51)	
Eye disorders	52 (2.1)	12 (1.3)	0.81 (-0.09, 1.71)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	51 (2.0)	22 (2.3)	-0.27 (-1.37, 0.82)	
Immune system disorders	50 (2.0)	19 (2.0)	0.00 (-1.04, 1.04)	
Ear and labyrinth disorders	35 (1.4)	14 (1.5)	-0.07 (-0.96, 0.81)	

Source: Generated by Reviewer, OCS Analysis Studio, Safety Explorer.

Table 49 enumerates the most common TEAEs by PT.

Table 49. Common TEAEs, Occurrence $\geq 3\%$ in Tirzepatide-Treated Subjects and $\geq 1\%$ Higher than in Placebo-Treated Subjects (Trials GPHK and GPHL)

Preferred Term	TZP All (N=2519)		Placebo (N=958)		Risk Difference	
	n	(%)	n	(%)	RD	(95% CI)
Nausea	693	(27.5)	81	(8.5)	19.06	(16.58, 21.53)
Diarrhea	527	(20.9)	75	(7.8)	13.09	(10.76, 15.42)
Constipation	342	(13.6)	50	(5.2)	8.36	(6.42, 10.30)
Vomiting	272	(10.8)	21	(2.2)	8.61	(7.08, 10.13)
Decreased appetite	247	(9.8)	28	(2.9)	6.88	(5.31, 8.46)
Dyspepsia	234	(9.3)	37	(3.9)	5.43	(3.76, 7.09)
Abdominal pain	131	(5.2)	28	(2.9)	2.28	(0.90, 3.65)
Eructation	124	(4.9)	6	(0.6)	4.30	(3.31, 5.28)
Alopecia	118	(4.7)	8	(0.8)	3.85	(2.84, 4.86)
Dizziness	112	(4.4)	20	(2.1)	2.36	(1.15, 3.57)
Gastroesophageal reflux disease	107	(4.2)	20	(2.1)	2.16	(0.96, 3.36)
Injection site reaction	99	(3.9)	2	(0.2)	3.72	(2.91, 4.53)
Abdominal distension	92	(3.7)	21	(2.2)	1.46	(0.28, 2.64)
Flatulence	89	(3.5)	15	(1.6)	1.97	(0.90, 3.03)
Abdominal pain upper	83	(3.3)	15	(1.6)	1.73	(0.68, 2.78)

Source: Generated by Reviewer, OCS Analysis Studio, Safety Explorer.

Table 50 shows an exploratory analysis to assess whether any common TEAEs differ meaningfully in occurrence in trial subjects with T2D (GPHL, SURMOUNT-2) compared to those without diabetes (GPHK, SURMOUNT-1). Subjects in trial GPHK (without T2D) were more likely to report any AE in tirzepatide arms (80.5%) than in placebo arm (72.0%), while subjects in trial GPHL (with T2D) were more likely to report any AE in placebo arms (75.9%) than in tirzepatide arms (74.5%). Some AEs appeared more common in subjects with or without T2D, based on differences in the risk difference of $\geq 1\%$ between trials GPHK and GPHL. For instance, tirzepatide-treated subjects in trial GPHK (without T2D) were 6-9% more likely to report AEs of nausea and constipation, but these differences do not meaningfully affect the overall safety profile.

Table 50. Exploratory Analysis of Common TEAEs in Trial GPHK versus GPHL

Preferred Term	Tirzepatide					Placebo					Risk Difference		
	GPHK		GPHL		Delta GPHK- GPHL (%)	GPHK		GPHL		Delta GPHK- GPHL (%)	(TZP-Placebo)		Delta GPHK- GPHL (%)
	N = 1896		N = 623			N = 643		N=315			GPHK	GPHL	
	n	(%)	n	(%)		n	(%)	n	(%)		(%)	(%)	
Any AE	1527	(80.5)	464	(74.5)	6.0	463	(72.0)	239	(75.9)	-3.9	8.5	-1.4	9.9
More common without T2D													
Nausea	562	(29.6)	131	(21.0)	8.6	61	(9.5)	20	(6.3)	3.2	20.1	14.7	5.4
Constipation	289	(15.2)	53	(8.5)	6.7	37	(5.8)	13	(4.1)	1.7	9.4	4.4	5.0
Diarrhea	398	(21.0)	129	(20.7)	0.3	47	(7.3)	28	(8.9)	-1.6	13.7	11.8	1.9
Dyspepsia	189	(10.0)	45	(7.2)	2.8	27	(4.2)	10	(3.2)	1.0	5.8	4.00	1.8
Alopecia	99	(5.2)	19	(3.0)	2.2	6	(0.9)	2	(0.6)	0.3	4.3	2.4	1.9
*Injection site reaction	83	(4.4)	16	(2.6)	1.8	2	(0.3)	0	(0.0)	0.3	4.1	2.6	1.5
More common with T2D													
*Pyrexia	28	(1.5)	27	(4.3)	-2.8	9	(1.4)	4	(1.3)	0.1	0.1	3.0	-2.9
*Headache	125	(6.6)	31	(5.0)	1.6	42	(6.5)	9	(2.9)	3.6	0.1	2.1	-2.0
Flatulence	65	(3.4)	24	(3.9)	-0.5	13	(2.0)	2	(0.6)	1.4	1.4	3.3	-1.9
*Back pain	74	(3.9)	26	(4.2)	-0.3	23	(3.6)	9	(2.9)	0.7	0.3	1.3	-1.0
Abdominal pain	96	(5.1)	35	(5.6)	-0.5	21	(3.3)	7	(2.2)	1.1	1.8	3.4	-1.6
Decreased appetite	186	(9.8)	61	(9.8)	0	21	(3.3)	7	(2.2)	1.1	6.5	7.6	-1.1
Similar occurrence													
*Abdominal pain upper	65	(3.4)	18	(2.9)	0.5	10	(1.6)	5	(1.6)	0	1.8	1.3	0.5
Abdominal distension	64	(3.4)	28	(4.5)	-1.1	11	(1.7)	10	(3.2)	-1.5	1.7	1.3	0.4
Gastroesophageal reflux	83	(4.4)	24	(3.9)	0.5	14	(2.2)	6	(1.9)	0.3	2.2	2.0	0.2
Dizziness	87	(4.6)	25	(4.0)	0.6	15	(2.3)	5	(1.6)	0.7	2.3	2.4	-0.1
Vomiting	197	(10.4)	75	(12.0)	-1.6	11	(1.7)	10	(3.2)	-1.5	8.7	8.8	-0.1
Eructation	92	(4.9)	32	(5.1)	-0.2	4	(0.6)	2	(0.6)	0	4.3	4.5	-0.2

Source: Generated by Reviewer

*AEs that would differ in inclusion in Table 49 if this table were based on only trial GPHL (in subjects with T2D)

If the common TEAEs (from Table 49, informing the adverse reactions table in Section 6.1 of labeling) were based on either individual trial rather than the pooled data from trials GPHL and GPHK, there would be few minor differences as noted in Table 50. The only notable difference was that in trial GPHL, pyrexia TEAEs were reported in 27/623 (4.3%) of tirzepatide- compared to 4/315 (1.3%) placebo-treated subjects. Pyrexia (fever) is not addressed elsewhere in the labeling, and it is typically due to infection. However, common infections (with TEAE occurrence $\geq 3\%$ in any arm) generally occurred less frequently in tirzepatide-treated subjects than placebo-treated subjects, even in trial GPHL where pyrexia occurred more frequently (Table 51).

Table 51. Common Infection TEAEs in Trial GPHK versus GPHL

Preferred Term	Tirzepatide					Placebo					Risk Difference		
	GPHK		GPHL		Delta GPHK- GPHL (%)	GPHK		GPHL		Delta GPHK- GPHL (%)	(TZP-Placebo)		Delta GPHK- GPHL (%)
	N = 1896		N = 623			N = 643		N = 315			GPHK	GPHL	
	n	(%)	n	(%)		n	(%)	n	(%)		(%)	(%)	(%)
Covid-19	274	(14.5)	86	(13.8)	0.7	90	(14.0)	53	(16.8)	-2.8	0.5	-3.0	3.5
Upper respiratory tract infection	63	(3.3)	22	(3.5)	-0.2	24	(3.7)	21	(6.7)	-3	-0.4	-3.2	2.8
Urinary tract infection	78	(4.1)	19	(3.0)	1.1	31	(4.8)	10	(3.2)	1.6	-0.7	-0.2	-0.5
Nasopharyngitis	35	(1.8)	19	(3.0)	-1.2	16	(2.5)	17	(5.4)	-2.9	-0.7	-2.4	1.7
Bronchitis	14	(0.7)	5	(0.8)	-0.1	3	(0.5)	11	(3.5)	-3	0.2	-2.7	2.9
Influenza	40	(2.1)	17	(2.7)	-0.6	21	(3.3)	10	(3.2)	0.1	-1.2	-0.5	-0.7

Source: Generated by Reviewer

Reviewer comment: While pyrexia was imbalanced in tirzepatide-treated subjects in trial GPHL, there was not a corresponding imbalance in common infections (which were less frequent in tirzepatide-treated subjects). Imbalanced pyrexia TEAEs were not observed in the larger GPHK trial for CWM, nor in the development of tirzepatide for treatment of T2D under NDA 215866. Therefore, the observed imbalance of pyrexia in trial GPHL is likely spurious and it is appropriate to exclude pyrexia from the labeled adverse reactions.

Common Adverse Reactions for Labeling

For Section 6.1 of labeling, the applicant proposes a table of common adverse reactions that occur in ≥2% of tirzepatide-treated subjects and more often than in placebo-treated subjects (Table 52). I agree with the proposed thresholds for inclusion of reactions, and my independent analysis of the safety database (see above) confirms the Applicant's incidence numbers in this table. My analysis above shows no meaningful differences in common TEAEs between trials GPHK and GPHL (i.e., subjects without and with T2D), so I also agree with having a single table with pooled results from both trials (as opposed to separate tables).

Table 52. Applicant's Proposed Table of Common Adverse Reactions in Label Section 6.1

Adverse Reaction	Placebo (N=958) %	ZEPBOUND 5 mg (N=630) %	ZEPBOUND 10 mg (N=948) %	ZEPBOUND 15 mg (N=941) %
Nausea	8	25	29	28
Diarrhea ^a	8	19	21	23
Vomiting	2	8	11	13
Constipation ^b	5	17	14	11
Abdominal Pain ^c	5	9	9	10
Dyspepsia	4	9	9	10

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Injection Site Reactions ^d	2	6	8	8
Fatigue ^e	3	5	6	7
Hypersensitivity Reactions	3	5	5	5
Eructation	1	4	5	5
Hair Loss	1	5	4	5
Gastroesophageal Reflux Disease	2	4	4	5
Flatulence	2	3	3	4
Abdominal Distension	2	3	3	4
Dizziness	2	4	5	4
Hypotension ^f	0	1	1	2

Source: Applicant's proposed US package insert.

The footnotes for the proposed table include the following groupings, and I agree with them all:

- Diarrhea includes diarrhea, frequent bowel movements.
- Constipation includes constipation, feces hard.
- Abdominal pain includes abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, abdominal tenderness.
- Injection site reactions includes multiple related adverse event terms, such as injection site bruising, injection site erythema, injection site pruritus, injection site pain, injection site rash, injection site reaction.
- Fatigue includes asthenia, fatigue, lethargy, malaise.
- Hypotension includes blood pressure decreased, hypotension, orthostatic hypotension.

Reviewer comment: *I considered one other potential grouping of terms in this table: hair loss could include alopecia, alopecia areata, and androgenetic alopecia. As discussed below in Section 8.5.12, the latter two PTs (which suggest mechanisms of hair loss) were reported only once each, so including these events in addition to the PT "alopecia" does not change the reported numbers in the table, which are rounded to the nearest whole number. A footnote noting these two specific types of alopecia would suggest incorrectly that these contribute meaningfully to the AE reports of hair loss. Therefore, I agree with including only the general term "Hair loss" (synonymous with "alopecia;" these two accounting for the great majority of verbatim-reported terms) in this table without grouping multiple PTs.*

Overall, my review and analysis of common AEs agrees with the Applicant's. I agree with the proposed common adverse reactions for labeling in the Section 6.1 table.

Reviewer comment: *The common PT of "decreased appetite" (see Table 49) met the incidence threshold for inclusion in the label's adverse reactions table, and it is labeled in this table for the tirzepatide for T2D. However, decreased appetite is not considered an adverse reaction*

8.4.6. Laboratory Findings

Changes in glycemic and lipid laboratory parameters were evaluated as efficacy endpoints and discussed in Section 6.1.2. Additionally, please refer to other relevant sections for information related to treatment-emergent changes in the following laboratory parameters: ADAs (Section 8.4.10), serum calcitonin (Section 8.5.1), pancreatic enzymes (Section 8.5.5), renal function (Section 8.5.3), and liver laboratory parameters (Section 8.5.14).

Electrolytes

Table 53 summarizes shifts to abnormally high or low sodium, potassium, and calcium values in trials GPHK and GPHL. Shifts to low or high sodium values were balanced between tirzepatide and placebo groups, as were shifts to high potassium or calcium. Shifts to low potassium or calcium were significantly imbalanced (risk difference 95% CI not crossing 0) with more in subjects on tirzepatide than placebo:

- Those subjects with downward shifts in calcium had similar mean ($\pm$ SD) and percentage declines from baseline in the tirzepatide group (-0.39 ± 0.23 mmol/L, -16.6%) compared to the placebo group (-0.39 ± 0.17 mmol/L, -16.4%). Two tirzepatide-treated subjects had postbaseline calcium values <1.5 mmol/L, and upon review both appeared to be laboratory errors given undetectable calcium values at the visit but normal values at the visits before and after.
- Those subjects with downward shifts in potassium had similar mean ($\pm$ SD) and percentage declines from baseline in the tirzepatide group (-0.63 ± 0.30 mmol/L, -15.8%) compared to the placebo group (-0.66 ± 0.32 mmol/L, -16.2%). No subjects had postbaseline potassium values <2.8 mmol/L.

Table 53. Shifts in Electrolyte Laboratory Values (Trials GPHK and GPHL)

		TZP All N=2519		Placebo N=958		Risk Difference (%)	
		n/N1	(%)	n/N1	(%)	RD	(95% CI)
Sodium	Shift to Low	36/2469	(1.5)	11/930	(1.2)	0.28	(-0.57, 1.12)
	Shift to High	117/2459	(4.8)	42/926	(4.5)	0.22	(-1.36, 1.80)
Potassium	Shift to Low	86/2463	(3.5)	16/928	(1.7)	1.77	(0.66, 2.88)
	Shift to High	149/2404	(6.2)	49/901	(5.4)	0.76	(-1.01, 2.53)
Calcium	Shift to Low	66/2467	(2.7)	15/932	(1.6)	1.07	(0.04, 2.09)
	Shift to High	39/2447	(1.6)	11/920	(1.2)	0.40	(-0.46, 1.26)

Source: Adapted by reviewer from Applicant ISS addendum, Table ISS.4.17, page 1329 of 2079

Reviewer comment: *In addition to these shifts to low values, there were also nominally more*

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shifts to high values for sodium, potassium, and calcium with tirzepatide than placebo. The fact that the changes go in both directions argues against biological plausibility for a specific causal effect of drug.

TEAEs related to electrolyte disturbances were numerically greater in tirzepatide than placebo groups (Table 54).

Table 54. Selected Electrolyte-Related TEAEs (Trials GPHK and GPHL)

System Organ Class Preferred Term	TZP All N = 2519		Placebo N = 958	
	n	(%)	n	(%)
Metabolism and nutrition disorders				
Hyponatremia	3	(0.1)	0	(0.0)
Hypernatremia	2	(0.1)	0	(0.0)
Hypokalemia	8	(0.3)	1	(0.1)
Hyperkalemia	5	(0.2)	0	(0.0)
Hypocalcemia	1	(0.0)	0	(0.0)
Hypercalcemia	3	(0.1)	1	(0.1)
Investigations				
Blood potassium decreased	3	(0.1)	1	(0.1)
Blood potassium increased	3	(0.1)	0	(0.0)
Blood calcium decreased	1	(0.0)	0	(0.0)
Blood electrolytes decreased	1	(0.0)	0	(0.0)

Source: Generated by reviewer

In conclusion, electrolyte changes and TEAEs related to abnormal electrolytes in subjects on tirzepatide were rare but appeared more common than on placebo. However, mean values for calcium, potassium, and sodium at end of treatment (Visit 21, Week 72) and their changes from Baseline did not differ meaningfully between tirzepatide and placebo arms.²² Therefore, I do not think that electrolyte changes should be labelled for tirzepatide. AEs of vomiting and volume depletion will be labeled, and these can lead to electrolyte abnormalities that are clinically meaningful, so prescribers will already be alerted to this safety concern.

Hematology

In trials GPHK and GPHL, reductions in red and white blood cell concentrations were more common in tirzepatide- than placebo-treated subjects. Table 55 enumerates for selected hematology tests those trial subjects with shifts from baseline normal/high values to postbaseline low values.

²² SURMOUNT-1 CSR, Table GPHK.8.115, page 2633 of 3021; SURMOUNT-2 CSR, Table GPHL.8.136, page 2505 of 3056.

Table 55. Shifts to Low Values for Selected Hematology Values (Trials GPHK and GPHL)

	TZP 5mg N=630		TZP 10mg N=948		TZP 15mg N=941		TZP All N=2519		Placebo N=958		Risk Difference (%)	
	n/N1	(%)	n/N1	(%)	n/N1	(%)	n/N1	(%)	n/N1	(%)	RD	(95% CI)
Hemoglobin	75/597	(12.6)	130/878	(14.8)	117/872	(13.4)	322/2347	(13.7)	71/878	(8.1)	5.63	(3.36, 7.91)
Hematocrit	26/593	(4.4)	74/884	(8.4)	68/882	(7.7)	168/2359	(7.1)	53/885	(6.0)	1.13	(-0.74, 3.01)
Erythrocytes	102/585	(17.4)	179/890	(20.1)	185/878	(21.1)	466/2353	(19.8)	90/880	(10.2)	9.58	(7.01, 12.15)
Leukocytes	57/609	(9.4)	74/905	(8.2)	74/903	(8.2)	205/2417	(8.5)	43/912	(4.7)	3.77	(2.00, 5.53)
Neutrophils	57/602	(9.5)	77/904	(8.5)	79/900	(8.8)	213/2406	(8.9)	43/907	(4.7)	4.11	(2.32, 5.90)
Lymphocytes	21/613	(3.4)	27/917	(2.9)	28/910	(3.1)	76/2440	(3.1)	14/921	(1.5)	1.59	(0.55, 2.64)
Monocytes	24/610	(3.9)	14/920	(1.5)	35/911	(3.8)	73/2441	(3.0)	23/923	(2.5)	0.50	(-0.71, 1.71)
Basophils	0/616		0/922		0/916		0/2454		0/926		0.00	(0.00, 0.00)
Eosinophils	0/616		0/922		0/916		0/2454		0/926		0.00	(0.00, 0.00)
Platelets	16/604	(2.6)	15/907	(1.7)	17/897	(1.9)	48/2408	(2.0)	18/910	(2.0)	0.02	(-1.05, 1.08)

Source: Adapted by reviewer from Applicant ISS addendum, Table ISS.4.17, page 1329 of 2079

For these subjects with downward shifts in hemoglobin, the mean minimum hemoglobin ($\pm$ SD) was 11.16 g/dL in the placebo group and 11.14 g/dL in the tirzepatide group, with a mean decline from baseline of -1.70 g/dL in the placebo group and -1.93 g/dL in the tirzepatide groups. The difference of 0.23 g/dL is these changes in not clinically meaningful.

I reviewed other red blood cell (RBC) indices to investigate potential mechanisms of reduced hemoglobin. Shifts in mean corpuscular hemoglobin concentration are balanced between tirzepatide and placebo groups, suggesting no change in hemoglobin concentration per RBC. There is an imbalance in shifts to high mean corpuscular volumes (MCV), with more such shifts in the tirzepatide groups (Table 56). In all subjects at Week 72 (end of treatment), the mean MCV ($\pm$ SD) was 89.4 $\pm$ 6.3 fl in the placebo groups (mean difference of -0.25% from baseline) and 90.2 $\pm$ 5.6 fl in the tirzepatide groups (mean difference of +0.5% from baseline). Tirzepatide is also more associated more with shifts to low erythrocytes counts than with shifts to low hematocrits (see Table 55). Taken together, these data suggest that tirzepatide reduces the number of RBCs (erythrocyte count) and total blood hemoglobin concentration, with slightly larger RBCs (MCV) leading to a lesser decline in hematocrit, and unchanged hemoglobin concentration within RBCs (MCH).

Table 56. Shifts to High or Low Values for Selected RBC indices (Trials GPHK and GPHL)

		TZP All N=2519		Placebo N=958		Risk Difference (%)	
		n/N1	(%)	n/N1	(%)	RD	(95% CI)
Mean corpuscular volume	Shift to High	210/2272	(9.2)	53/848	(6.3)	2.99	(0.97, 5.01)
	Shift to Low	66/2322	(2.8)	35/873	(4.0)	-1.17	(-2.63, 0.30)
Mean corpuscular hemoglobin	Shift to High	0/2407		0/899		0.00	(0.00, 0.00)
	Shift to Low	281/2265	(12.4)	108/849	(12.7)	-0.31	(-2.94, 2.31)

Source: Adapted by reviewer from Applicant ISS addendum, Table ISS.4.17, page 1329 of 2079

In all subjects in phase 3 CWM trials GPHK and GPHL, the mean postbaseline minimum hemoglobin (g/dL) was 13.21 ± 1.44 in the placebo group compared to 13.06 ± 1.36 , 12.97 ± 1.46 , and 12.97 ± 1.44 in the tirzepatide 5, 10, and 15 mg groups. This difference in mean hemoglobin of 0.15-0.24 g/dL is not clinically meaningful.

Reviewer comment: *These small decreases in hemoglobin and shifts to low hemoglobin values with tirzepatide are consistent across trials, as similar shift was observed in trials of tirzepatide for T2D as reviewed in NDA 215866. There is also an apparent dose dependence, with tirzepatide 5 mg having less of an effect on hemoglobin compared to 10 mg and 15 mg. The mechanism of this effect of tirzepatide on hemoglobin is unknown, but the small effect size (0.23 mg/dL) is unlikely to be clinically meaningful.*

Downward shifts imbalanced in the tirzepatide over placebo groups are also noted for white blood cell (WBC) counts, including total leukocytes, lymphocytes, and neutrophils (but not monocytes, basophils, or eosinophils, Table 57). Similar to the results for hemoglobin in all subjects in trials GPHK and GPHL, the mean postbaseline minimum values for all WBC counts were lower in tirzepatide groups compared to placebo group, but the differences were small in magnitude (5-13%) and not likely to be clinically meaningful.

Table 57. Mean Postbaseline Minimum Values for Selected Hematology Parameters (Trials GPHK and GPHL)

x10 ⁹ /L, mean (SD)	Difference, x10 ⁹ /L (%)				
	Placebo	TZP 5 mg	TZP 10 mg	TZP 15mg	TZP 15mg vs Placebo
Leukocytes	5.99 (1.55)	5.55 (1.51)	5.68 (1.50)	5.69 (1.62)	-0.30 (5.1%)
Lymphocytes	1.78 (0.53)	1.64 (0.49)	1.69 (0.49)	1.68 (0.51)	-0.10 (5.7%)
Neutrophils	3.55 (1.17)	3.29 (1.17)	3.34 (1.15)	3.36 (1.23)	-0.19 (5.3%)
Basophils	0.041 (0.026)	0.036 (0.023)	0.038 (0.022)	0.037 (0.022)	-0.004 (9.0%)
Eosinophils	0.108 (0.070)	0.095 (0.060)	0.101 (0.071)	0.094 (0.070)	-0.014 (13.0%)
Monocytes	0.282 (0.113)	0.257 (0.099)	0.265 (0.101)	0.262 (0.109)	-0.02 (7.1%)
Platelets	244 (62)	238 (58)	241 (61)	240 (61)	-3.93 (1.6%)

Source: Generated by reviewer using JMP and adlb.xpt dataset from trials GPHK and GPHL

Reviewer comment: *Unlike the effects of tirzepatide on RBC parameters, the effects on WBC counts did not appear to be dose-dependent. The small changes in WBC counts (~5% reduction in lymphocytes and neutrophils) are unlikely to be clinically meaningful. Low WBC counts could predispose to infections, so it is reassuring that tirzepatide-treated trial subjects had significantly fewer TEAEs in the SOC “infections and infestations” compared to placebo-treat subjects (risk difference -4.5%, see Table 48) and fewer common infections (see Table 51). Changes in RBC and WBC counts on tirzepatide merit further evaluation in the phase 3b development, in particular the ongoing long term outcomes trial GPII (SURMOUNT-MMO). To assess whether hematology parameters return to baseline after withdrawal of tirzepatide, the CSR for the completed randomized withdrawal trial GPHN (SURMOUNT-4) will also be relevant.*

I also reviewed TEAEs in the SOC Blood and Lymphatic System disorders, none of which were serious or graded as severe in tirzepatide-treated subjects. There were numerically more TEAEs of anemia, leukopenia, and thrombocytopenia in tirzepatide than placebo groups (Table 58). Neutropenia TEAEs were rare and not imbalanced.

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Table 58. TEAEs in SOC Blood and Lymphatic System Disorders (Trials GPHK and GPHL)

Preferred Term	TZP All N = 2519		Placebo N = 958		Risk Difference	
	n	(%)	n	(%)	RD	(95% CI)
Any AE	61	(2.4)	19	(2.0)	0.44	(-0.63, 1.51)
Anemia	36	(1.4)	10	(1.0)	0.39	(-0.41, 1.18)
Leukocytosis	6	(0.2)	1	(0.1)	0.13	(-0.15, 0.41)
Leukopenia	5	(0.2)	0	(0.0)	0.20	(0.02, 0.37)
Thrombocytopenia	5	(0.2)	0	(0.0)	0.20	(0.02, 0.37)
Thrombocytosis	4	(0.2)	0	(0.0)	0.16	(0.00, 0.31)
Iron deficiency anemia	3	(0.1)	0	(0.0)	0.12	(-0.02, 0.25)
Lymphadenopathy	2	(0.1)	2	(0.2)	-0.13	(-0.44, 0.18)
Neutropenia	2	(0.1)	1	(0.1)	-0.02	(-0.26, 0.21)
Mast cell activation syndrome	1	(0.0)	0	(0.0)	0.04	(-0.04, 0.12)
Microcytic anemia	1	(0.0)	0	(0.0)	0.04	(-0.04, 0.12)
Microcytosis	1	(0.0)	0	(0.0)	0.04	(-0.04, 0.12)
Neutrophilia	1	(0.0)	0	(0.0)	0.04	(-0.04, 0.12)
Pancytopenia	1	(0.0)	0	(0.0)	0.04	(-0.04, 0.12)
Polycythemia	1	(0.0)	0	(0.0)	0.04	(-0.04, 0.12)
Splenic lesion	1	(0.0)	0	(0.0)	0.04	(-0.04, 0.12)
Eosinophilia	0	(0.0)	1	(0.1)	-0.10	(-0.31, 0.10)
Hypochromic anemia	0	(0.0)	1	(0.1)	-0.10	(-0.31, 0.10)

Source: Generated by reviewer

In conclusion, this review of hematology laboratory findings suggests that tirzepatide is associated with lower minimal values for RBC, WBC, and platelet counts. For RBC and some WBC counts, this led to shifts from normal to low values more frequently on tirzepatide than placebo, though no tirzepatide-treated subjects had serious or severe AEs corresponding to low blood counts. The apparent reductions in blood counts are small and unlikely to be clinically meaningful. Based on this existing data, I do not feel that the observed reductions in hematology laboratory values warrant inclusion in the tirzepatide labeling at this time.

Creatine kinase

High levels of serum creatine kinase (CK) can indicate muscle damage or rhabdomyolysis. There was no imbalance in subjects with shifts to high CK values on tirzepatide (322/2181, 14.8%) compared to placebo (138/825, 16.7%). Table 59 shows the tirzepatide and placebo groups were balanced for subjects with maximum post-baseline CK >ULN (20.6% on tirzepatide versus 22.5% on placebo), but there was numerical imbalance for post-baseline CK ≥5x ULN (2.1% tirzepatide versus 1.2% placebo) or CK ≥10x ULN (1.0% tirzepatide versus 0.4% placebo). The TEAE “blood creatine phosphokinase increased” was balanced: 28/2519 (1.1%) tirzepatide versus 10/958 (1.0%) on placebo. The AE PT of “rhabdomyolysis” does not occur in the safety

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database, though two cases of markedly elevated CK due to apparent exertional rhabdomyolysis are noted below (see Section 8.5.14 on liver safety, regarding the etiology of transaminase elevations in two subjects).

Table 59. Maximum Post-baseline Creatine Kinase Values in Trials GPHK and GPHL

	TZP 5mg N=621		TZP 10mg N=929		TZP 15mg N=926		TZP All N=2476		Placebo N=935		Risk Difference (%)	
	N	(%)	n	(%)	n	(%)	n	(%)	n	(%)	RD	(95% CI)
>ULN	137	(22.1)	208	(22.4)	164	(17.7)	509	(20.6)	210	(22.5)	-1.90	(-5.02, 1.21)
≥5x ULN	23	(3.7)	18	(1.9)	10	(1.1)	51	(2.1)	11	(1.2)	0.88	(-0.01, 1.77)
≥10x ULN	11	(1.8)	8	(0.9)	5	(0.5)	24	(1.0)	4	(0.4)	0.54	(-0.03, 1.11)

Source: Generated by Reviewer

In conclusion, while CK elevations to ≥5x and ≥10x ULN were more frequent in subjects treated with tirzepatide compared to placebo, these elevations were rare, not dose-dependent (occurring more at lower tirzepatide dosages, yet similarly in the tirzepatide 15 mg and placebo arms), and not clearly clinically meaningful, and thus do not merit inclusion in labeling.

8.4.7. Vital Signs

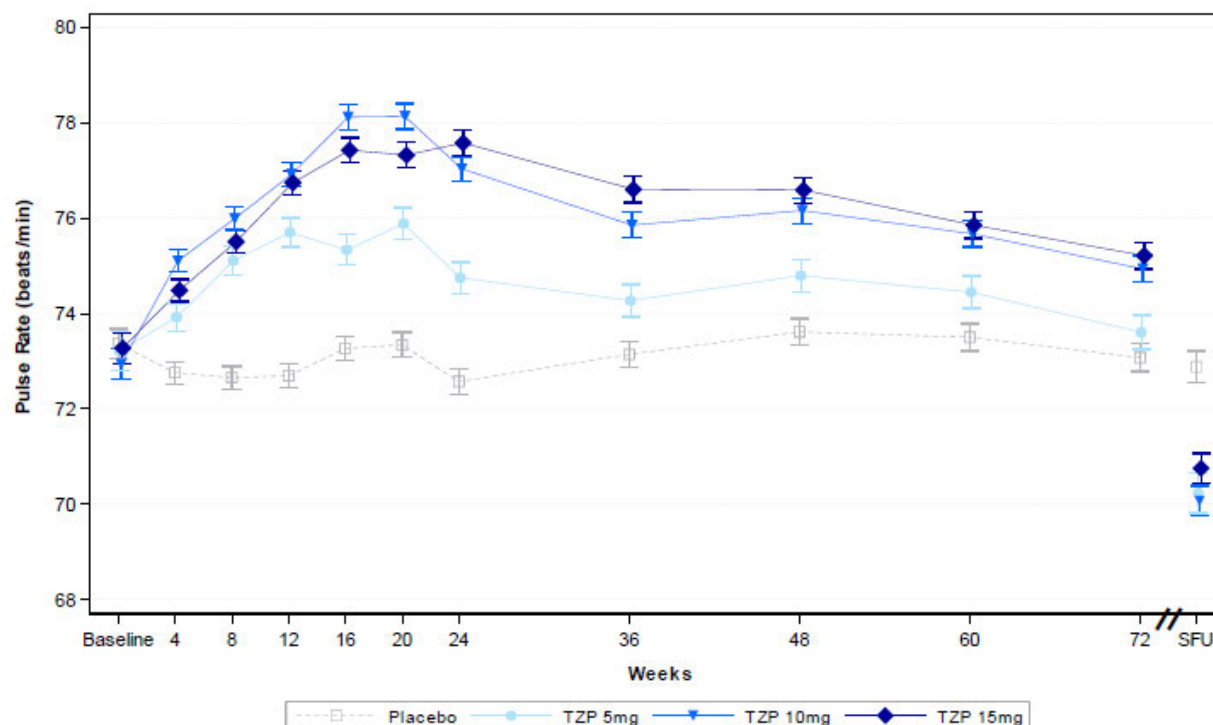
Tirzepatide is associated with reductions in blood pressure, which is an efficacy assessment described in Sections 6 and 7. This Section focuses on the increases in heart rate (HR) on tirzepatide, a known class effect of GLP-1R agonists. In the phase 3 trials GPHK and GPHL, at scheduled visits HR was measured in triplicate in a sitting position using an automated machine.

The tirzepatide-treated groups in trials GPHK and GPHL showed the following changes in HR (Figure 32):²³

- Increases in HR over the first 20 weeks of treatment (dose escalation period), with mean changes at Week 20 of 2.8, 5.1, and 4.1 bpm for tirzepatide 5, 10, and 15 mg, compared to 0.1 bpm for placebo.
- Reductions in the degree of increased HR during the remaining treatment period (dose maintenance period), with mean changes from baseline at end of treatment Week 72 of 0.7, 1.9, and 2.0 bpm for tirzepatide 5, 10, and 15 mg, compared to -0.3 bpm for placebo.
- Reductions of HR to below baseline at the safety follow-up, 4 weeks after treatment discontinuation, with mean changes from baseline of -2.5, -3.1, and -2.3 bpm for tirzepatide 5, 10, and 15 mg, compared to -0.3 bpm for placebo.

²³ Per the Applicant's ISS addendum, Table ISS.4.53, page 1756 of 2079

Figure 32. Changes in Heart Rate in Trials GPHK and GPHL



Source: Applicant ISS addendum, Figure ISS.4.8, page 1792 of 2079

Abbreviation: SFU, safety follow-up

Note: The Applicant used a mixed model of repeated measures, graphing the least squared means and standard deviations

Compared to placebo, the occurrence of sinus tachycardia (defined as HR >100 bpm at any post-baseline visit) was more frequent in tirzepatide-treated subjects (5.1%, compared to 3.2% for placebo) and appeared to be dose-related (1.9%, 6.3%, and 6.0% on tirzepatide 5, 10, and 15 mg, Table 60). Likewise, there were dose-related increases in the proportion of subjects with changes in HR from baseline >20 bpm at any visit (10.0% for tirzepatide versus 3.4% for placebo), at two or more consecutive visits (2.6% versus 0.4%), or at three or more visits (1.4% versus 0.1%). However, persistent sinus tachycardia was rare and not meaningfully imbalanced between tirzepatide and placebo groups:

- HR >100 bpm at two or more consecutive visits: 1.2% versus 0.8%
- HR >100 bpm at three or more visits: 1.1% vs 0.9%

Table 60. Subjects with Selected Abnormal Heart Rate Categories (Trials GPHK and GPHL)

Timepoint Variable Threshold	Placebo (N=958) n (%)	TSP 5mg (N=630) n (%)	TSP 10mg (N=948) n (%)	TSP 15mg (N=941) n (%)	TSP_ALL (N=2519) n (%)
Postbaseline					
Pulse Rate (bpm), N1	954	627	943	936	2506
>100 at any visit	31 (3.25)	12 (1.91)	59 (6.26)	56 (5.98)	127 (5.07)
>100 for ≥2 consecutive visits	8 (0.84)	1 (0.16)	15 (1.59)	11 (1.18)	27 (1.08)
>100 for ≥3 visits	9 (0.94)	3 (0.48)	15 (1.59)	10 (1.07)	28 (1.12)
>130 at any visit	0	1 (0.16)	0	0	1 (0.04)
Pulse Rate Change from baseline (bpm), N2	954	627	943	936	2506
CFB>20 at any visit	32 (3.35)	46 (7.34)	102 (10.82)	102 (10.90)	250 (9.98)
CFB>20 for ≥2 consecutive visits	4 (0.42)	5 (0.80)	14 (1.48)	24 (2.56)	43 (1.72)
CFB>20 for ≥3 visits	1 (0.10)	3 (0.48)	13 (1.38)	13 (1.39)	29 (1.16)

Source: Applicant ISS Addendum, Table ISS.4.54, page 1798 of 2079

One subject in the tirzepatide 5 mg group had a post-baseline HR >130 bpm, but this value of 139 bpm was an outlier measured at the off-treatment safety follow-up (SFU) visit, whereas values at previous visits were consistently normal (<100 bpm).

These tirzepatide-related increases in HR measured by routine vitals were confirmed by two other methods:

- Both trials GPHK and GPHL included routine ECG monitoring as detailed below in Section 8.4.8.
- Trial GPHK included ABPM substudy, which randomized 600 subjects 1:1:1:1 among placebo and the three tirzepatide dosages, with 24-hr ABPM conducted at baseline and Week 36. A primary endpoint was the mean change in 24-hour mean HR from baseline at Week 36, and these results (Table 61) were consistent with the increased HR measured by routine vital signs around this timepoint during the treatment period (see Figure 32).

Table 61. Changes from Baseline in Mean 24-hour Heart Rate (Trial GPHK ABPM substudy)

Parameters	Placebo (N = 131)	TZP 5 mg (N = 116)	TZP 10 mg (N = 123)	TZP 15 mg (N = 124)
Mean 24-hour Heart Rate (bpm)				
Baseline	76.8	77.8	77.2	78.0
Change from baseline at 36 weeks	-1.8 ^{††}	0.3	0.5	3.6 ^{†††}
Change difference from placebo at 36 weeks (95% CI)	N/A	2.1* (0.3, 3.9)	2.3* (0.6, 4.1)	5.4*** (3.6, 7.1)

Abbreviations: ABPM = ambulatory blood pressure monitoring; CI = confidence interval; DBP = diastolic blood pressure; mITT population = modified intent-to-treat population; N = number of participants with baseline and postbaseline values; N/A = not applicable; SBP = systolic blood pressure; TZP = tirzepatide.

Note: Least squares means are shown.

*p-Value <0.05, ***p-value <0.001 versus placebo.

[†]p-Value <0.05, ^{††}p-value <0.01, ^{†††}p-value <0.001 versus baseline.

Source: Applicant CSR for trial GPHK, Table GPHK.5.109, page 411 of 3021

TEAEs for trials GPHK and GPHL were reviewed for events related to increased HR. More subjects on tirzepatide (23/2519, 0.9%) than placebo (5/958, 0.5%) had TEAEs in the narrow FMQ “Tachycardia” (Table 62).

Table 62. FMQ Analysis for Tachycardia TEAEs in Trials GPHK and GPHL

FDA Medical Query	TZP 15mg (N = 941)	TZP 10mg (N = 948)	TZP 5mg (N = 630)	Placebo (N = 958)
Tachycardia	14 (1.5%)	8 (0.8%)	1 (0.2%)	5 (0.5%)
Tachycardia	10 (1.1%)	6 (0.6%)	1 (0.2%)	3 (0.3%)
Sinus tachycardia	2 (0.2%)	1 (0.1%)	0 (0%)	0 (0%)
Supraventricular tachycardia	1 (0.1%)	0 (0%)	0 (0%)	0 (0%)
Heart rate increased	2 (0.2%)	1 (0.1%)	0 (0%)	1 (0.1%)
Ventricular tachycardia	0 (0%)	0 (0%)	0 (0%)	1 (0.1%)

Source: Generated by reviewer using JMP Clinical, FMQ reports

The “Arrhythmia” narrow FMQ (Table 63) showed a similar small imbalance with slightly more subjects with events on tirzepatide (67/2519, 2.7%) than placebo (22/958, 2.3%).

Table 63. FMQ Analysis for Arrhythmia TEAEs in Trials GPHK and GPHL

FDA Medical Query	TZP 15mg (N = 941)	TZP 10mg (N = 948)	TZP 5mg (N = 630)	Placebo (N = 958)
Arrhythmia	27 (2.9%)	28 (3%)	12 (1.9%)	22 (2.3%)
Tachycardia	10 (1.1%)	6 (0.6%)	1 (0.2%)	3 (0.3%)
Sinus arrhythmia	1 (0.1%)	0 (0%)	3 (0.5%)	0 (0%)
Arrhythmia	1 (0.1%)	2 (0.2%)	1 (0.2%)	0 (0%)
Supraventricular extrasystoles	2 (0.2%)	3 (0.3%)	1 (0.2%)	1 (0.1%)
Sinus tachycardia	2 (0.2%)	1 (0.1%)	0 (0%)	0 (0%)
Ventricular arrhythmia	1 (0.1%)	0 (0%)	1 (0.2%)	0 (0%)
Sinus bradycardia	7 (0.7%)	6 (0.6%)	2 (0.3%)	5 (0.5%)
Bradycardia	1 (0.1%)	0 (0%)	2 (0.3%)	1 (0.1%)
Supraventricular tachycardia	1 (0.1%)	0 (0%)	0 (0%)	0 (0%)
Atrial fibrillation	3 (0.3%)	6 (0.6%)	0 (0%)	4 (0.4%)
Ventricular tachycardia	0 (0%)	0 (0%)	0 (0%)	1 (0.1%)
Arrhythmia supraventricular	0 (0%)	0 (0%)	0 (0%)	2 (0.2%)
Atrial flutter	0 (0%)	2 (0.2%)	0 (0%)	3 (0.3%)
Ventricular extrasystoles	1 (0.1%)	3 (0.3%)	2 (0.3%)	5 (0.5%)

Source: Generated by reviewer using JMP Clinical, FMQ reports

These tachycardia and arrhythmia events are rare, the differences between tirzepatide and placebo groups are small, and there is apparent dose-dependence with lower incidence in the tirzepatide 5 mg arm.

This review sought to assess the clinical meaningfulness of increased heart rate. The TEAE of “palpitations” was balanced between tirzepatide (12/2519, 0.5%) and placebo (4/958, 0.4%), suggesting that tirzepatide does not affect subjects’ reporting of this symptom. More importantly, increased HR could contribute to MACE, but these were not increased by tirzepatide as detailed below in Section 8.5.13. It is also highly relevant whether tirzepatide increases the risk of supraventricular tachyarrhythmias like atrial fibrillation and flutter, and these events were rare in trials GPHK and GPHL with no increase in risk in tirzepatide compared to placebo groups (Table 64).

Table 64. Supraventricular Arrhythmia TEAEs in Trials GPHK and GPHL

Preferred Term	TZP All N = 2519	Placebo N = 958	Relative Risk	
	n (%)	n (%)	RR (95% CI)	Forest Plot
Any AE	9 (0.4)	7 (0.7)	0.49 (0.18, 1.31)	
Atrial flutter	2 (0.1)	3 (0.3)	0.25 (0.04, 1.52)	
Atrial fibrillation	8 (0.3)	3 (0.3)	1.01 (0.27, 3.81)	
Arrhythmia supraventricular	0 (0.0)	2 (0.2)	0.08 (0.00, 1.58)	

Source: Generated by reviewer using OCS Analysis Studio, Safety Explorer.

Of these supraventricular arrhythmia events, one tirzepatide-treated subject had two serious TEAEs of atrial fibrillation and atrial flutter on tirzepatide (compared to one placebo-treated subject with one serious event):

- Subject (b) (6) was 30-year-old man in Argentina randomized to tirzepatide 10 mg, who discontinued tirzepatide after study Day 249 due to the AE of depression. On study Days 353 and 375, he had two separate hospitalizations for atrial flutter and fibrillation, with an ablation procedure leading to recovery. Given that these events occurred over 14 weeks after stopping tirzepatide (and, as noted above, in trials mean HR returned to baseline or below at the 4-week safety follow-up), I agree with the Applicant's assessment that the serious atrial fibrillation and flutter TEAEs were likely unrelated to tirzepatide.

In the review of tirzepatide for T2D under NDA 215866, it was noted that the dose-related increases in HR were greater in magnitude in subjects enrolled at Japanese sites compared to sites elsewhere in the world. This same pattern was also observed in CWM trials GPHK and GPHL, with the greatest apparent increases in HR compared to baseline at relevant study visits (Weeks 20 and 72) observed in Japan, with lesser increases in the rest of Asia and the rest of the world (Table 65). Likewise, tirzepatide treated subjects in Japan were more likely to meet the selected abnormal HR criteria.

Table 65. Mean Change in Heart Rate from Baseline by Region (Trials GPHK and GPHL)

mean change, bpm	Japan	Rest of Asia	Rest of World
Week 20			
Placebo	1.1	-0.7	0.1
TZP 5mg	3.4	-0.2	3
TZP 10mg	8.2	4.8	4.9
TZP 15mg	5.9	5.4	3.9
Week 72			
Placebo	1.5	-1.5	-0.3
TZP 5mg	2.5	-0.6	0.6
TZP 10mg	6.7	0.6	1.6
TZP 15mg	5.7	3.7	1.6
Safety Follow-up			
Placebo	1.1	-0.7	-0.4
TZP 5mg	-3.4	-5.5	-2.3
TZP 10mg	-3.8	-5.6	-2.9
TZP 15mg	-1.5	0.2	-2.5

Source: Adapted from Applicant regulatory response, Table 5.11

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Of note, subjects in trials GPHK and GPHL in Japan had lower mean baseline BMIs compared to subjects from the rest of Asia or the non-Asian regions (Table 66).

Table 66. Mean Baseline BMI in Japan Compared to Other Regions (Trials GPHK and GPHL)

kg/m ² , mean (SD)	TZP All	Placebo
Japan	31.5 (3.76)	31.5 (3.61)
Rest of Asia	34.1 (5.00)	35.0 (5.52)
non-Asia Rest of World	37.9 (6.72)	38.2 (7.07)

Source: Generated by reviewer

This suggests the potential for higher tirzepatide exposure in Japanese subjects based on body weight or other intrinsic or extrinsic factors. The same pattern in Japanese subjects (lower BMIs and greater HR increases) was observed in the tirzepatide trials for T2D reviewed in NDA 215866. As detailed in that review, the Office of Clinical Pharmacology (OCP) review team assessed the tirzepatide-associated HR increases based on PK and PD time-matched observations from seven phase 3 T2D trials. 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 HR and the potential for associated cardiovascular events. However, a specific dose adjustment was not deemed 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 potential AEs.

In conclusion, the observed dose-dependent elevations in HR on tirzepatide are consistent with other incretin drugs, and this merits inclusion in the label. The Applicant proposes labeling in section 6.1 on under the subheading “Other adverse reactions,” consistent with the labeling of tirzepatide for T2D, and I agree.

Reviewer comment: There is no evidence that incretin-mediated increases in HR are clinically meaningful (symptomatic or leading to arrhythmias or CV events), so I agree that these do not rise to the importance of label Section 5 (Warnings and Precautions) for tirzepatide. A cardiovascular outcomes trial with tirzepatide in subjects with obesity is ongoing.

8.4.8. Electrocardiograms (ECGs)

In trials GPHK and GPHL, 12-lead ECGs were performed at baseline, at Week 24, at Week 72

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(the time of the primary endpoint), and at the 4-week safety follow-up visit.²⁴ The tirzepatide dose-related pulse rate changes from baseline measured by ECG at Weeks 24, 72, and safety follow-up were consistent with the changes measured by routine vital sign assessment (see Section 8.4.7 above).

Mean changes from baseline in other ECG parameters (PR, QRS, and QT intervals) over time did not appear to be clinically meaningful between arms. Similarly, there was no meaningful imbalance in the proportion of subjects on tirzepatide versus placebo with abnormal PR (≥ 220 ms or < 120 ms), QRS (≥ 120 ms), or QT_c intervals (> 450 ms in males or > 470 ms in females).

The “Cardiac Conduction Disorders” narrow FMQ includes TEAEs related to ECG abnormalities (Table 67), and these were balanced with similar occurrence in subjects randomized to tirzepatide (36/2519, 1.4%) or placebo (14/958, 1.5%).

Table 67. Cardiac Conduction Disorder FDA Medical Query in Trials GPHK and GPHL

FDA Medical Query	TZP 15mg (N = 941)	TZP 10mg (N = 948)	TZP 5mg (N = 630)	Placebo (N = 958)
Cardiac Conduction Disturbance	16 (1.7%)	9 (0.9%)	11 (1.7%)	14 (1.5%)
Electrocardiogram PR prolongation	0 (0%)	1 (0.1%)	4 (0.6%)	1 (0.1%)
Electrocardiogram QT prolonged	3 (0.3%)	0 (0%)	4 (0.6%)	2 (0.2%)
Bundle branch block left	3 (0.3%)	2 (0.2%)	0 (0%)	1 (0.1%)
Electrocardiogram QRS complex abnormal	1 (0.1%)	0 (0%)	0 (0%)	0 (0%)
Bundle branch block right	1 (0.1%)	5 (0.5%)	2 (0.3%)	3 (0.3%)
Electrocardiogram PR shortened	2 (0.2%)	1 (0.1%)	0 (0%)	1 (0.1%)
Atrioventricular block first degree	5 (0.5%)	0 (0%)	2 (0.3%)	3 (0.3%)
Bundle branch block	0 (0%)	0 (0%)	0 (0%)	1 (0.1%)
Defect conduction intraventricular	2 (0.2%)	1 (0.1%)	0 (0%)	3 (0.3%)

Source: Generated by reviewer using JMP Clinical, FMQ Reports

In conclusion, ECGs confirmed the increase in HR on tirzepatide but did not identify other safety concerns.

8.4.9. QT

There were no events of Torsades de Points in tirzepatide trials for CWM, nor in the entire development program to date. A thorough QT study was not conducted for this CWM NDA, which relies on the QT assessment for tirzepatide under T2D NDA 215866, for which the Applicant performed *in vitro* evaluations and a concentration-QT_c analysis of ECG data. The results of these analyses are discussed in the review of NDA 215866. Briefly, the Interdisciplinary Review Team (IRT) for Cardiac Safety Studies review (dated February 16,

²⁴ Detailed ECG data from trials GPHK and GPHL are not shown here, but can be found in the Applicant’s ISS addendum, Table ISS.4.56, page 1806 of 2079

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2022)²⁵ noted that the submitted nonclinical and clinical data do not indicate any unexpected or important effects of tirzepatide on the QT_c interval at clinically relevant exposures.

Therefore, according to IRT, not including QT language in Section 12.2 of the label (Cardiac Electrophysiology) is consistent with the Agency's labeling practices for peptides and large targeted proteins when a thorough QT study is not conducted.

8.4.10. Immunogenicity

Tirzepatide is a peptide product that is highly immunogenic, based on its intrinsic potential as a peptide (based on endogenous GIP, and also sharing sequence homology with GLP-1), various quality parameters, and its SC administration route. This application was reviewed for immunogenicity by Drs. Faruk Sheikh and Harold Dickensheets from the FDA Office of Biotechnology Products (OBP), Division of Biotechnology Review & Research-2. The Applicant's immunogenicity data is summarized below, and please see the OBP review dated October 10, 2023, for further details. Overall, the OBP review recommended approval of this product from an immunogenicity perspective.

The Applicant had validated tirzepatide immunogenicity assays in a tiered system under T2D NDA 215866 but determined new assay "disease-specific cut points" in the CWM subjects, which the OBP review found acceptable. In phase 3 CWM trials GPHK and GPHL, treatment emergent ADAs were evaluable in 2467 tirzepatide-treated subjects; 1591 (64.5%) developed anti-tirzepatide ADAs, 1477 (59.9%) with treatment-induced ADAs and 114 (4.6%) with treatment-boosted ADAs (higher titers than baseline). The incidence of ADAs was slightly higher in trial GPHK (i.e., in subjects without T2D, 66.0%) compared to GPHL (i.e., in an older trial population with T2D, 59.9%) and to the shorter duration SURPASS trials for T2D (56.4%), but these differences are unlikely to be clinically meaningful and ADA development was high across all trials. ADAs also occurred similarly across tirzepatide dose groups but were consistently slightly higher at the higher tirzepatide doses (for instance, in GPHK/SURMOUNT-1 the treatment-induced ADA+ incidence was 60.1%, 61.1% and 63.7% with tirzepatide 5, 10, and 15 mg).

The OBP review found the sampling times for measurement of ADA to be adequately designed. In all phase 3 trials for CWM or T2D, the development of ADA+ titer followed similar profiles increasing over the treatment and follow-up period), with majority of ADA+ participants developing an ADA titer within 24 weeks and the number of participants developing an ADA titer almost doubling within 52 weeks. The median ADA titer was 1:160 for all studies, with a range of 1:20 to 1:20,480 in trials GPHK and GPHL (and up to 1:81,920 in the SURPASS trials). ADA titers peaked at Week 24, plateaued up to Week 48-52, and declined thereafter. High titers ≥1:5120 occurred similarly in ADA+ subjects in trial GPHK (60/1858, 3.2%) and trial GPHL

²⁵ Review of NDA 215866,
https://www.accessdata.fda.gov/drugsatfda_docs/nda/2022/215866Orig1s000OtherR.pdf

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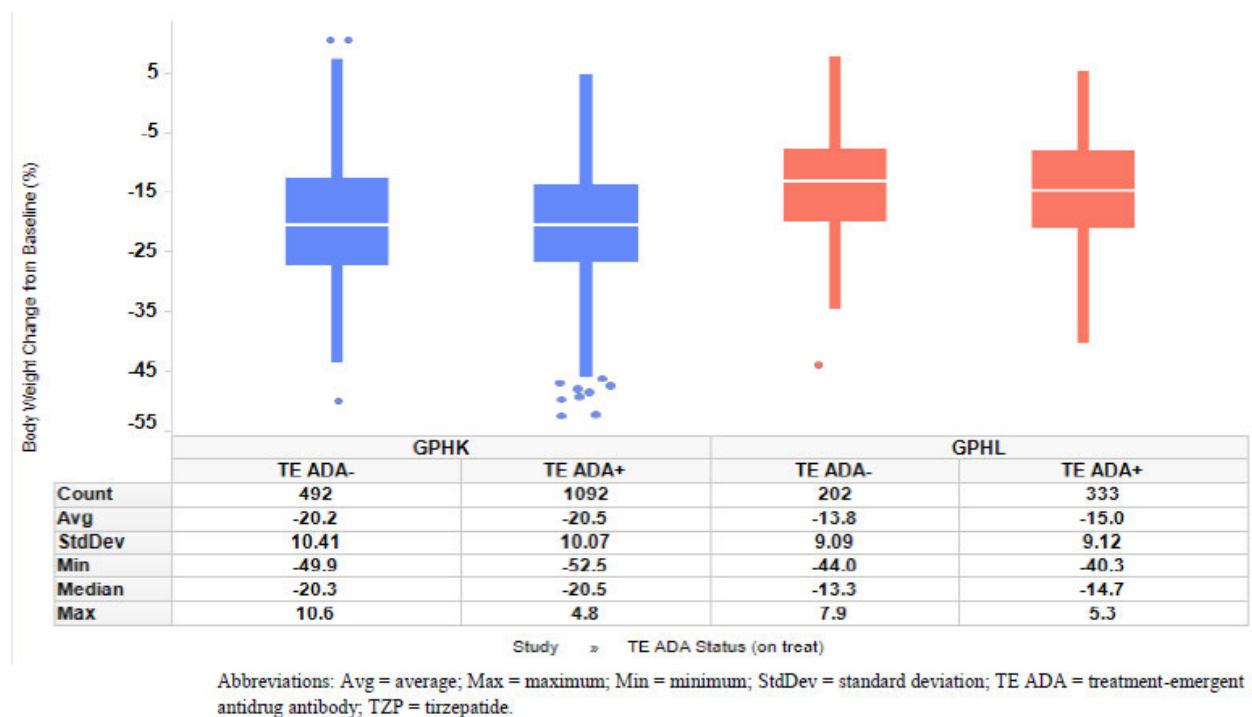
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(19/609, 3.1%), and slightly less than in the SURPASS trials (137/3484, 3.9%).

Neutralizing antibodies (NAb) could not be assessed at sites in China, leaving 2444 subjects evaluable for NAb. Cross-reactive binding of tirzepatide ADAs to endogenous GIP and GLP-1 occurred in 40.3% and 16.5% of these subjects, respectively, while cross-reactive NAb against endogenous GIP and GLP-1 occurred in 0.8% and 0.1% of subjects, both consistent with the greater homology of tirzepatide to GIP than GLP-1. NAb against tirzepatide activity at the GIPR and GLP-1R occurred in 2.8% and 2.7% of subjects, respectively.

There was no apparent effect of ADA or NAb on efficacy of tirzepatide for CWM. In trial GPHK of subjects without T2D, ADA-positive subjects lost a mean -20.5% of body weight on any dose of tirzepatide compared to -20.2% in ADA-negative subjects. Likewise, in trial GPHK of subjects with T2D, ADA-positive subjects lost a mean -15.0% compared to -13.8% in ADA-negative subjects (Figure 33).

Figure 33. Percent Change in Body Weight from Baseline by ADA Status in Tirzepatide-Treated Subjects (Trials GPHK and GPHL)



Source: Applicant ISI Addendum, Figure ISI.8.6, page 39 of 46

For those subjects on tirzepatide with the highest ADA titers ($\geq 1:5120$), the mean weight loss in trial GPHK was -20.4% in 53 subjects (versus -20.4% in 1531 other subjects) and in trial GPHL -15.3% in 18 subjects (versus -14.5% in 517 other subjects). Tirzepatide-treated subjects with NAb against the GIPR or GLP-1R likewise showed similar weight loss to subjects without such antibodies. Per the Applicant's data, ADA presence, ADA titer, and NAb presence also did not

affect the PK of tirzepatide (refer to the Clinical Pharmacology review for further details) or the percentage of subject achieving $\geq 5\%$ body weight reduction.²⁶

Reviewer comment: High-titer ADAs or NABs did not apparently affect the weight loss efficacy of tirzepatide. It remains unknown whether subjects who develop NABs will have differences in weight regain (or glycemic control) after discontinuation of tirzepatide, as the 4-week safety follow-up in trials GPHK and GPHL is too short in duration to address this question. The completed trial GPHN (SURMOUNT-4) involves randomized withdrawal of tirzepatide for one year, so review of ADA data in this trial may help address this question.

A greater proportion of ADA-positive subjects than ADA-negative subjects reported TEAEs of hypersensitivity (6.2% versus 3.0%, see Section 8.5.6) or injection site reactions (11.3% vs 1.0%, see Section 8.5.11). These events occurred in subjects with ADA titers across the entire range, yet the 79 subjects with highest ADA titers ($\geq 1:5120$) appeared to experience slightly more hypersensitivity (7/79, 8.9%) or injection site reactions (16/79, 20.3%) than subjects with lower ADA titers. There were no severe or serious injection site reactions. Three tirzepatide-treated subjects experienced severe but non-serious hypersensitivity reactions, and one with severe rash was ADA-positive while the other two were ADA-negative. The Applicant reports no pattern to the temporal relationship between ADA status or titer and these hypersensitivity or injection site reaction AEs.

In conclusion, no clinically meaningful association was observed between immunogenicity and tirzepatide drug exposure or weight loss efficacy. Immunogenicity was associated with the increased AEs of hypersensitivity and injection site reactions, and these will be addressed in the product label Section 6.1.

8.5. Analysis of Submission-Specific Safety Issues

8.5.1. Thyroid Safety

Medullary Thyroid Cancer and C-cell hyperplasia

MTC is a relatively rare neuroendocrine tumor of the parafollicular C-cells of the thyroid gland, accounting for ~3% of all thyroid cancers.²⁷ Product labeling of long-acting incretin drugs include a boxed warning of the risk of thyroid C-cell tumors, and include statements that these products cause in rodents thyroid C-cell tumors, including MTC, and that the relevance of these findings in humans has not been determined. Due to the nonclinical findings, long-acting incretin drugs are contraindicated in patients with a personal or family history of MTC or MEN2. Similarly, the tirzepatide labeling for T2D and proposed labeling for CWM include this boxed warning and contraindication.

²⁶ Applicant ISI Addendum, pages 35-42 of 46

²⁷ Jaber T, Dadu R, Hu MI. Medullary thyroid carcinoma. Curr Opin Endocrinol Diabetes Obes 2021; 28:540-6.

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 weekly.

In the tirzepatide phase 3 CWM trials GPHK and GPHL, there no events of MTC or C-cell hyperplasia. Furthermore, no such events have been reported to date across the entire tirzepatide clinical development program.

Other Thyroid Cancers or Neoplasms

There were two TEAEs of papillary thyroid cancer in the two trials, both in trial GPHK (SURMOUNT-1), one on tirzepatide (0.04%) and one on placebo (0.10%), and this more common thyroid cancer is not associated with incretins. No other malignant thyroid cancers (follicular, anaplastic, Huerthle cell, or poorly differentiated) were reported in these trials, and events related to benign thyroid nodules were rare and balanced between tirzepatide and placebo groups (Table 68).

Table 68. Thyroid Neoplasm TEAEs (Trials GPHK and GPHL)

Preferred Term	TZP All N = 2519 n (%)	Placebo N = 958 n (%)	Relative Risk	
			RR (95% CI)	Forest Plot
Any AE	8 (0.3)	4 (0.4)	0.76 (0.23, 2.52)	
Thyroid mass	6 (0.2)	2 (0.2)	1.14 (0.23, 5.64)	
Benign neoplasm of thyroid gland	1 (0.0)	1 (0.1)	0.38 (0.02, 6.07)	
Papillary thyroid cancer	1 (0.0)	1 (0.1)	0.38 (0.02, 6.07)	

Source: Generated by reviewer using OCS Analysis Studio, Safety Explorer.

Calcitonin

Serum calcitonin concentrations were monitored during trials GPHK and GPHL to assess whether tirzepatide affects C-cell function, potentially indicating the development of C-cell hyperplasia or MTC.

For both trials GPHK and GPHL, subjects were excluded for elevated calcitonin values at baseline, and significant elevations in calcitonin during the trial were defined based on eGFR:

- if eGFR ≥ 60 mL/min/1.73 m²
 - subjects were excluded for calcitonin ≥ 20 ng/L at Visit 1
 - in-trial calcitonin value ≥ 20 ng/L and < 35 ng/L AND $\geq 50\%$ increase from the

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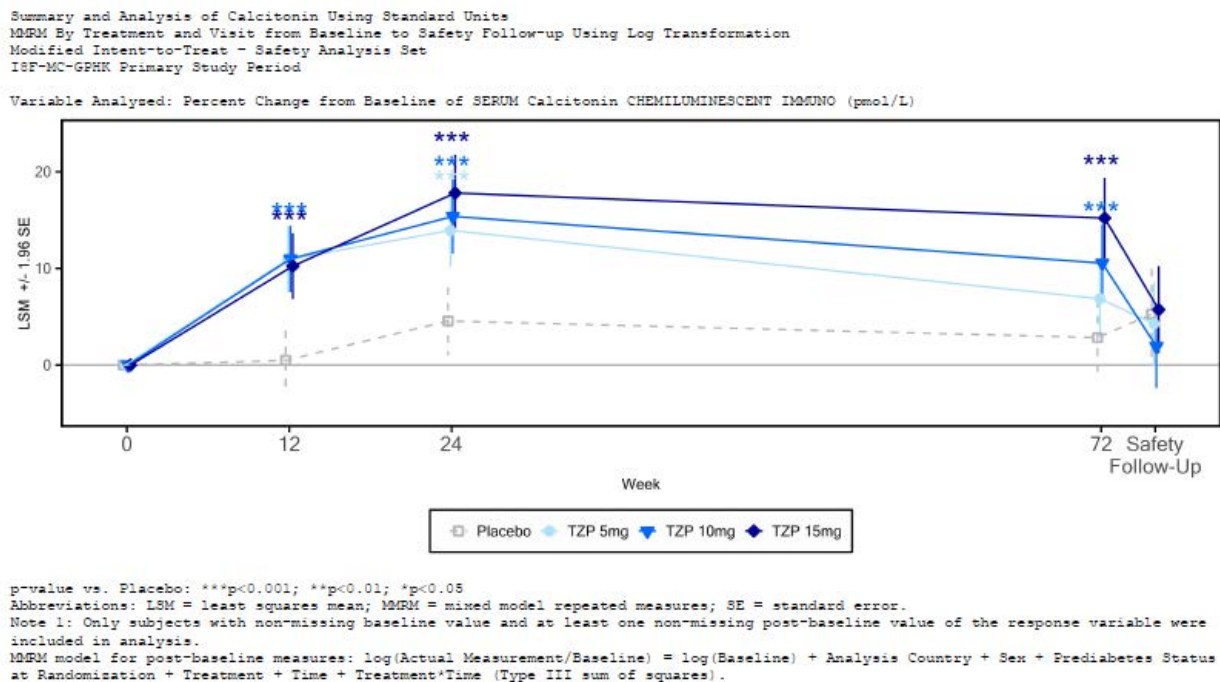
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screening value leads to repeat measurement in one month, and study drug discontinuation and endocrine follow-up if the calcitonin values showed a $\geq 10\%$ increase

- in-trial calcitonin value ≥ 35 ng/L AND $\geq 50\%$ over the screening value leads to study drug discontinuation and endocrine follow-up
- if eGFR < 60 mL/min/1.73 m²
 - subjects were excluded for calcitonin ≥ 35 ng/L at Visit 1
 - in-trial calcitonin value ≥ 35 ng/L AND $\geq 50\%$ over the screening value leads to study drug discontinuation and endocrine follow-up.

The Applicant presents data showing statistically significant increases in serum calcitonin upon tirzepatide treatment, with up to 20% increases at the end of treatment (72 weeks) which decline towards baseline 4 week later at safety follow-up. Figure 34 shows the percent change from baseline in serum calcitonin in trial GPHK, while Figure 35 shows the same data in trial GPHL.

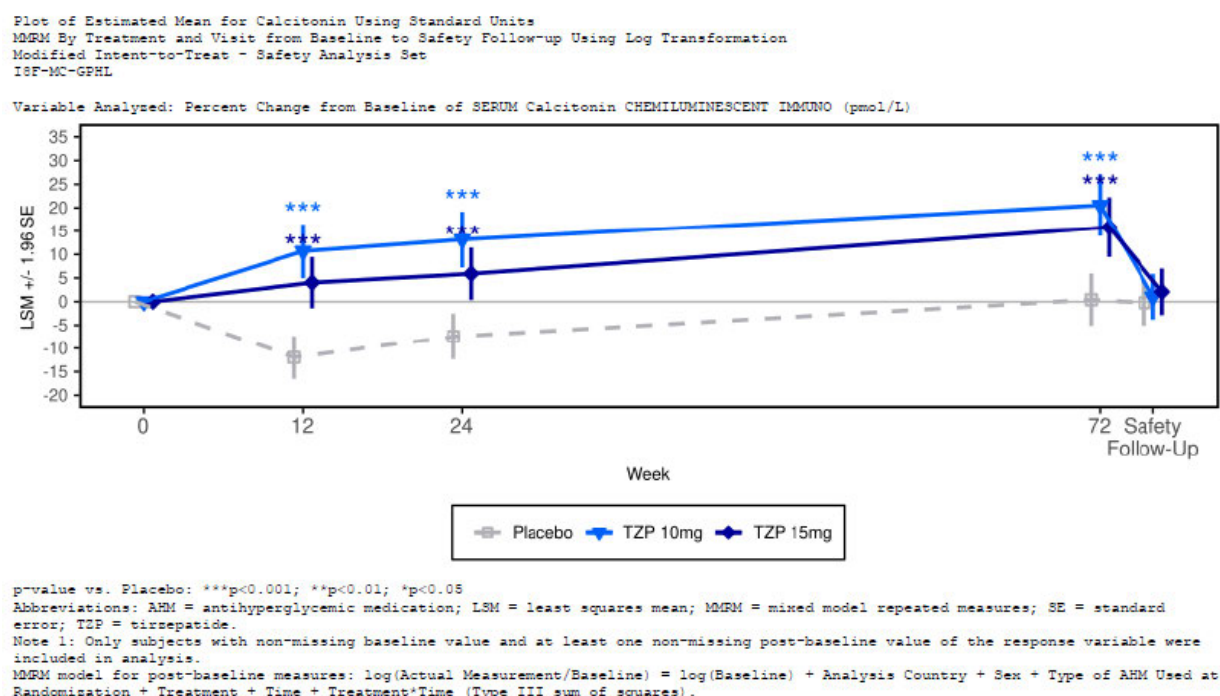
Figure 34. Percent Change in Serum Calcitonin Over Time in Trial GPHK



Source: Applicant GPHK CSR, Figure GPHK.5.34, page 347 of 3021

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Figure 35. Percent Change in Serum Calcitonin Over Time in Trial GPHL

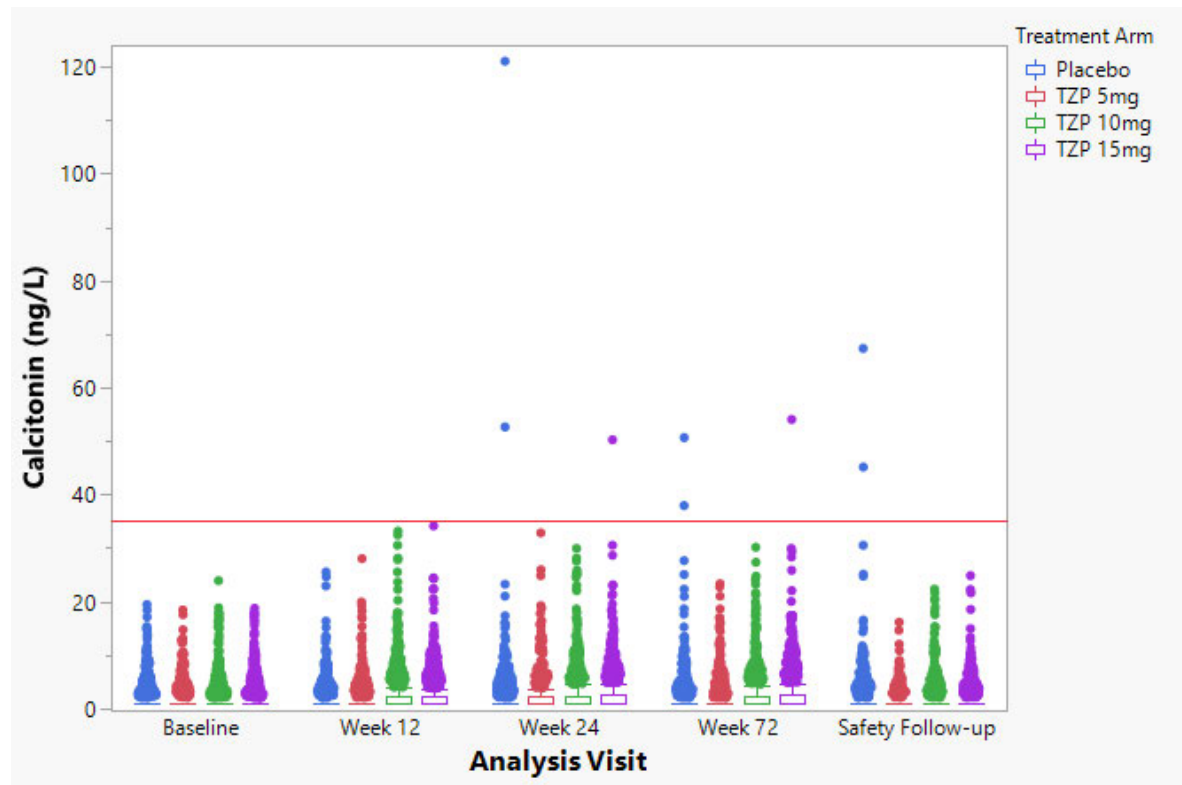


Source: Applicant GPHL CSR, Figure GPHL.5.31, page 356 of 3056

Reviewer comment: These data strongly indicate that tirzepatide, similar to other GLP-1R agonists, has direct effects on human C-cells to raise serum calcitonin levels. However, a normal calcitonin value is <5 ng/L and concerning values for C-cell hyperplasia or MTC are >50 or >100 ng/L, so it unlikely that the 10-20% increase in calcitonin on tirzepatide is clinically meaningful.

Serum calcitonin values at the scheduled safety measurement are shown in Figure 36. Calcitonin elevations to >35 ng/L (red line) were rare in the trial.

Figure 36. Serum Calcitonin Values at Scheduled Measurements (Trials GPHK and GPHL)



Source: Generated by reviewer in JMP using pooled GPHK and GPHL adlb dataset.

Note: Calcitonin values were converted from pmol/L to ng/L by multiplying by the conversion factor 3.42.

The Applicant presents analyses of shifts in serum calcitonin values during the trial. All baseline calcitonin values were ≤ 20 ng/L except for one subject in trial GPHL whose baseline value was 23.9 ng/L. Maximum postbaseline calcitonin levels were:

- >35 ng/L to ≤ 50 ng/L in 3 subjects: 2 on tirzepatide and 1 on placebo
- >50 ng/L to ≤ 100 ng/L in 5 subjects: 3 on tirzepatide and 2 on placebo
- >100 ng/L in one subject on placebo

There was no imbalance between tirzepatide and placebo groups in the number of subjects reaching these calcitonin thresholds.

An exploratory analysis of AEs was conducted, identifying the TEAE “blood calcitonin increased” in 33 subjects in Trials GPHK and GPHL, without imbalance between the tirzepatide and placebo groups (Table 69). None of these events were considered severe or serious, and 4 subjects on tirzepatide had drug withdrawn due to this AE.

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Table 69. TEAEs of Elevated Calcitonin (Trials GPHK and GPHL)

	TZP all (N=2519)	Placebo (N=958)
Blood Calcitonin Increased	24 (1.0)	9 (0.9)
Action Taken		
Dose not changed	11 (0.4)	4 (0.4)
Drug interrupted	2 (0.1)	1 (0.1)
Drug withdrawn	4 (0.2)	0
Not applicable	8 (0.3)	4 (0.4)
Outcome		
Not resolved	12 (0.5)	6 (0.6)
Resolved	9 (0.4)	3 (0.3)
Resolving	4 (0.2)	0

Source: Generated by reviewer using Applicant dataset (adae and adsl) in OCS Analysis Studio, Custom Table Tool.

The Applicant identified 9 subjects in trials GPHK and GPHL who met the prespecified criteria of calcitonin ≥ 35 ng/L and 50% increase from baseline, 4 on placebo and 5 on tirzepatide. For the 5 patients meeting this calcitonin criteria (Table 70), 4 had elevated calcitonin values of ≥ 10 ng/L at baseline, 2 discontinued study drug due to the calcitonin elevation, and 4 had follow-up calcitonin values that were lower or near baseline.

Table 70. Tirzepatide-Treated Subjects with Calcitonin ≥ 35 ng/L and 50% increase from baseline (Trials GPHK and GPHK)

Trial	Subject (b) (6)	Arm	Calcitonin (ng/L)		Study Day	Discontinued for Calcitonin	Follow-up Calcitonin values
			Baseline	Elevated			
GPHK		TZP 10mg	15.2	47.9	217	Day 253	Day 337 higher at 96.4 ng/L, day 512 (Week 72) 14.9 ng/L similar to baseline
GPHK		TZP 10mg	13.8	47.2	114	Day 127	Day 330 (Week 48) 21.5 ng/L trending down to baseline
GPHK		TZP 15mg	13.6	37.6	141	no	Day 224 30.9 ng/L
GPHK		TZP 15mg	1.0	54.0	510	no	retest 9 days later was 1 ng/L
GPHL		TZP 15mg	10.0	50.2	169	no	retest 5 days later was 11.8 ng/L, safety follow-up 11.3 ng/L, both near baseline

Source: Adapted from Applicant's ISS Addendum (Table ISS4.64, page 1858 of 2079), SCS (Table 2.7.4.87, page 229 of 293), and SCS Addendum (page 51 of 73)

Thyroid Safety Conclusion

There was no evidence of increased risk of MTC, C-cell hyperplasia, or persistently elevated calcitonin levels with the use of tirzepatide based on the clinical data submitted. Therefore,

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routine monitoring of serum calcitonin or thyroid ultrasound in patients receiving tirzepatide is unnecessary.

Since 2010, Sponsors of long-acting GLP-1R agonists 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-1R agonists into the U.S. marketplace. 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. Gastrointestinal Disorders

GI TEAEs are common with all incretin drugs, which typically employ dose escalation strategies to improve GI tolerability. Tirzepatide is started at 2.5 mg weekly and increased by 2.5 mg every 4 weeks, thus taking 8, 16, and 20 weeks to reach maintenance doses of 5, 10, 15 mg weekly. Tirzepatide phase 3 trials include strategies to mitigate and manage GI symptoms, including advice on small meals, temporary use of symptomatic antidiarrheal or antiemetic medications, and study drug interruption, dose reduction, or discontinuation. Across trials GPHK and GPHL, antiemetics were used in 419/2519 (16.6%) of tirzepatide- and 62/958 (6.5%) of placebo-treated subjects, and antidiarrheals were used in 168/2519 (6.7%) tirzepatide- and 15/958 (1.6%) placebo-treated subjects.²⁸

For tirzepatide CWM phase 3 trials GPHK and GPHL, TEAEs in the SOC “Gastrointestinal Disorders” occurred in 55.7% of tirzepatide- versus 29.6% of placebo-treated subjects (see Section 8.4.5, Table 48). Common TEAEs in this SOC include the PTs of nausea, diarrhea, constipation, dyspepsia, vomiting, abdominal pain, reflux, eructation, abdominal distension, and flatulence (see Section 8.4.5, Table 49). The occurrence of all GI AEs was not dose-related, but their maximum severity was dose-related: mild GI AEs were more common in the tirzepatide 5 mg arm while moderate and severe events were more common in the 10 and 15 mg arms (Table 71).

²⁸ Calculated from CSRs, Tables GPHK.4.9-10 (page 74 of 3021) and Tables GPHL.8.12-13 (page 530 of 3056)

Table 71. Severe and Serious Gastrointestinal Disorder SOC AEs (Trials GPHK and GPHL)

	TZP 5mg (N=630)	TZP 10mg (N=948)	TZP 15mg (N=941)	Placebo (N=958)
Any AE in SOC	350 (55.6)	529 (55.8)	523 (55.6)	284 (29.6)
Maximum Severity/Intensity				
Mild	236 (37.5)	317 (33.4)	303 (32.2)	206 (21.5)
Moderate	103 (17.8)	188 (19.8)	191 (20.3)	68 (7.1)
Severe	11 (1.7)	24 (2.5)	29 (3.1)	10 (1.0)
Serious	2 (0.3)	6 (0.6)	9 (1.0)	7 (0.7)

Source: OCS Analysis Studio, Custom Table Tool.

Serious GI AEs in the tirzepatide arms appeared dose-related (Table 71), but overall serious GI AEs were balanced between tirzepatide- and placebo-treated subjects (0.7% each, Table 43). Serious AEs of vomiting and pancreatitis occurred in multiple tirzepatide-treated subjects (Table 72): vomiting is a common AE while pancreatitis is addressed in Section 8.5.5 on exocrine pancreas safety.

Table 72. All Serious TEAEs in Gastrointestinal Disorders SOC (Trials GPHK and GPHL)

Preferred Term	TZP All N = 2519 n (%)	Placebo N = 958 n (%)
Any SAE	17 (0.7)	7 (0.7)
Pancreatitis acute	3 (0.1)	0 (0.0)
Vomiting	3 (0.1)	0 (0.0)
Chronic gastritis	1 (0.0)	0 (0.0)
Colitis	1 (0.0)	0 (0.0)
Colitis ulcerative	1 (0.0)	0 (0.0)
Constipation	1 (0.0)	0 (0.0)
Diarrhea	1 (0.0)	0 (0.0)
Enteritis	1 (0.0)	0 (0.0)
Gastric antral vascular ectasia	1 (0.0)	0 (0.0)
Hernial eventration	1 (0.0)	0 (0.0)
Ileus paralytic	1 (0.0)	0 (0.0)
Inguinal hernia strangulated	1 (0.0)	0 (0.0)
Esophagitis ulcerative	1 (0.0)	0 (0.0)
Pancreatitis	1 (0.0)	0 (0.0)
Proctitis	1 (0.0)	0 (0.0)
Upper gastrointestinal hemorrhage	1 (0.0)	1 (0.1)
Diverticulum intestinal hemorrhagic	0 (0.0)	1 (0.1)
Duodenal ulcer	0 (0.0)	1 (0.1)
Intestinal obstruction	0 (0.0)	1 (0.1)
Obstructive pancreatitis	0 (0.0)	2 (0.2)
Retroperitoneal hematoma	0 (0.0)	1 (0.1)

Source: OCS Analysis Studio, Safety Explorer.

Filters: TRT01A = "TZP 5mg" or "TZP 10mg" or "TZP 15mg" and SAFFL = "Y" (TZP All);
TRT01A = "Placebo" and SAFFL = "Y" (Placebo); TRTEMFL = "Y" and AESOC =
"Gastrointestinal disorders" and AESER = "Y" (Adverse Events).

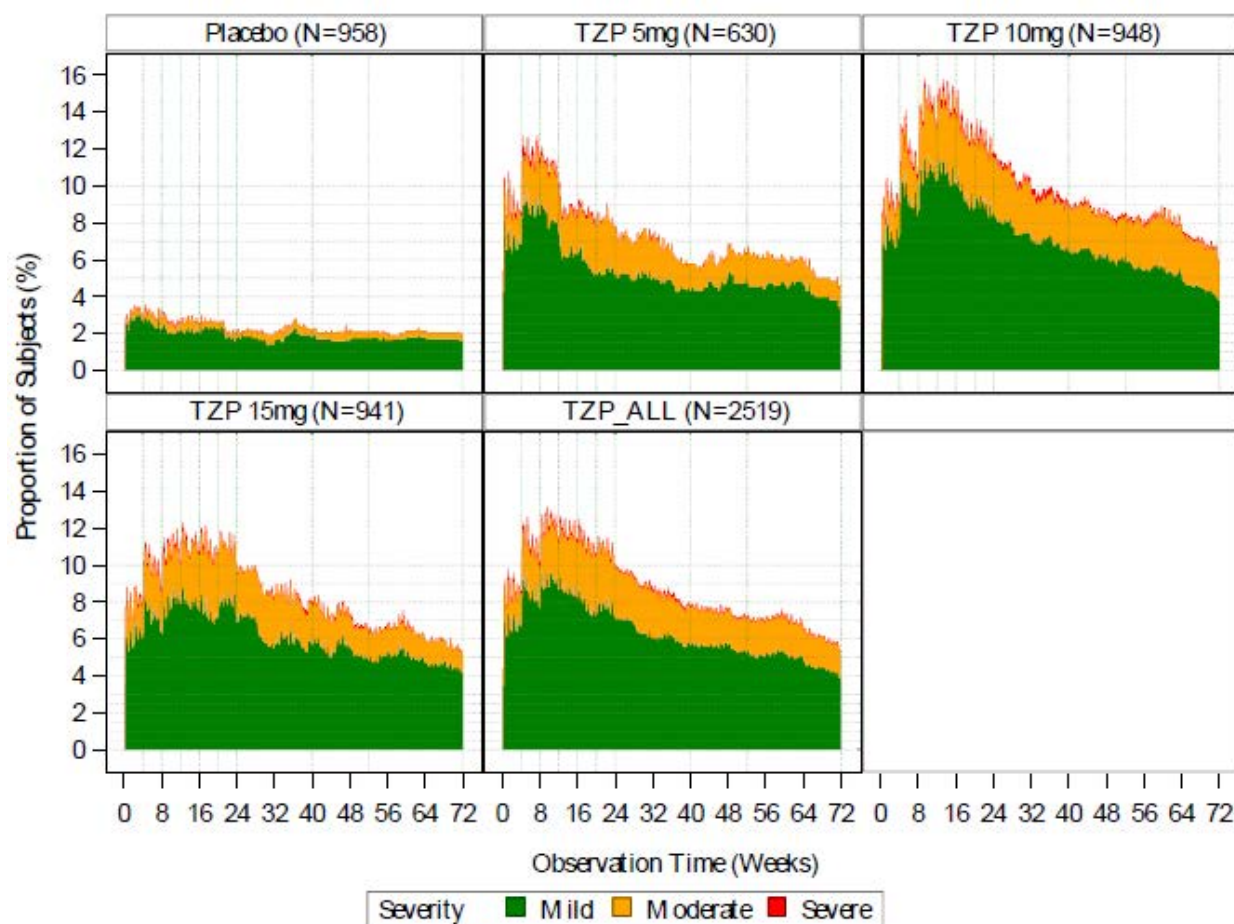
To capture other related TEAEs, I analyzed the Applicant's database using broad and narrow FMQs for nausea, vomiting, diarrhea, constipation, abdominal pain, and dyspepsia (Table 73). All showed a significant risk difference for tirzepatide over placebo, and all except constipation showed a dose effect with more events on tirzepatide 10 and 15 mg compared to 5 mg. Constipation showed the opposite dose effect, with more events on lower tirzepatide dosages.

Table 73. FMQs for Gastrointestinal Adverse Events (Trials GPHK and GPHL)

FMQ	Scope	TZP 5mg N=630 n (%)	TZP 10mg N=948 n (%)	TZP 15mg N=941 n (%)	TZP All N=2519 n (%)	Placebo N=958 n (%)	Risk Difference RD (95% CI)
Nausea	Narrow	155 (24.6)	277 (29.2)	265 (28.2)	697 (27.7)	81 (8.5)	19.21 (16.73, 21.70)
	Broad	175 (27.8)	306 (32.3)	298 (31.7)	779 (30.9)	92 (9.6)	21.32 (18.73, 23.92)
Vomiting	Narrow	52 (8.3)	102 (10.8)	118 (12.5)	272 (10.8)	21 (2.2)	8.61 (7.08, 10.13)
	Broad	176 (27.9)	310 (32.7)	298 (31.7)	784 (31.1)	96 (10.0)	21.10 (18.48, 23.73)
Diarrhea	Narrow	119 (18.9)	200 (21.1)	212 (22.5)	531 (21.1)	77 (8.0)	13.04 (10.70, 15.39)
	Broad	135 (21.4)	231 (24.4)	231 (24.5)	597 (23.7)	104 (10.9)	12.84 (10.27, 15.42)
Constipation	Narrow	106 (16.8)	134 (14.1)	103 (10.9)	343 (13.6)	50 (5.2)	8.40 (6.45, 10.34)
	Broad	106 (16.8)	135 (14.2)	105 (11.2)	346 (13.7)	50 (5.2)	8.52 (6.57, 10.46)
Abdominal Pain	Narrow	57 (9.0)	89 (9.4)	98 (10.4)	244 (9.7)	49 (5.1)	4.57 (2.76, 6.38)
	Broad	58 (9.2)	91 (9.6)	101 (10.7)	250 (9.9)	51 (5.3)	4.60 (2.76, 6.44)
Dyspepsia	Narrow	91 (14.4)	154 (16.2)	152 (16.2)	397 (15.8)	56 (5.8)	9.91 (7.86, 11.97)
	Broad	166 (26.3)	245 (25.8)	232 (24.7)	643 (25.5)	123 (12.8)	12.69 (9.97, 15.40)

The Applicant presents analyses showing that GI adverse events of nausea, vomiting, and diarrhea are most common early in the treatment period during dose escalation. For instance, Figure 37 shows the prevalence of a composite of nausea, vomiting, and diarrhea AE over time in Trials GPHK and GPHL, and similar results were found for the individual AEs and their prevalence and incidence, and in the individual trials.

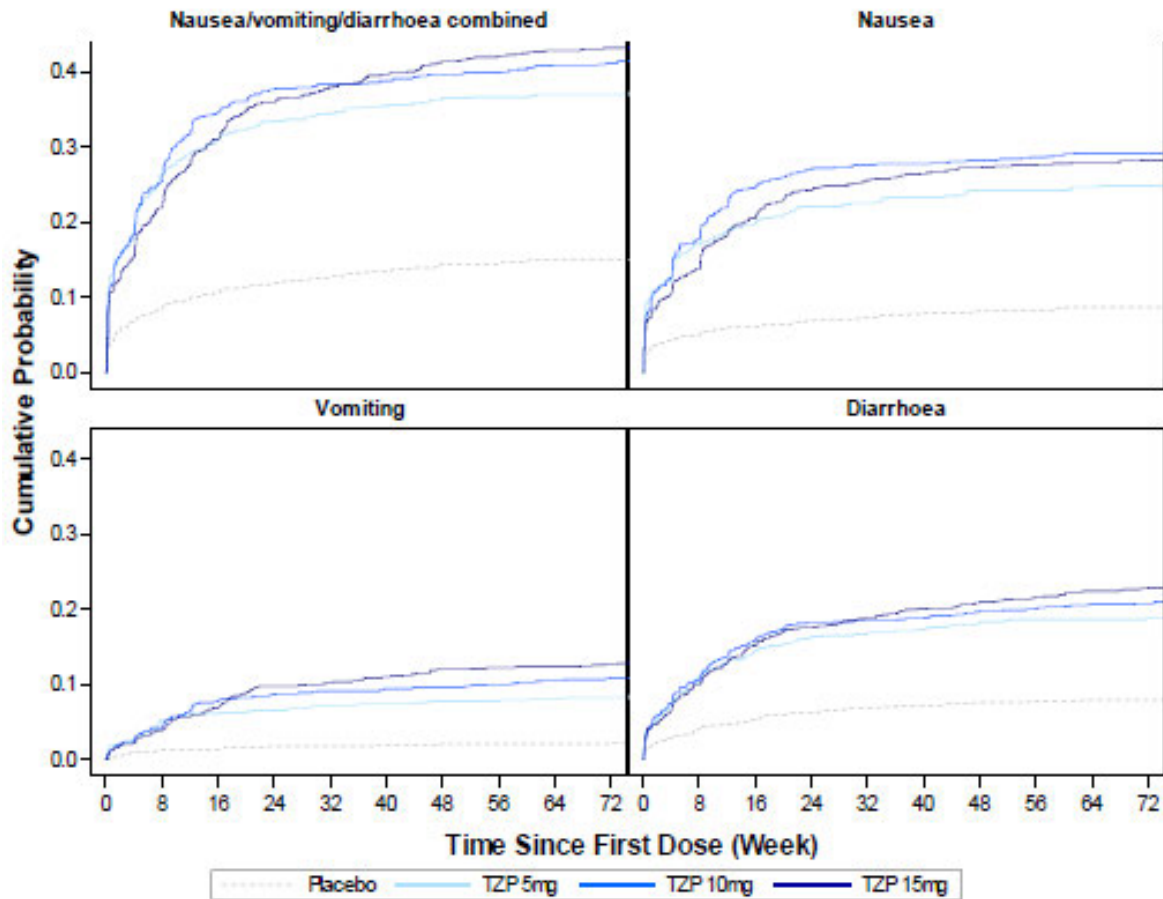
Figure 37. Prevalence of Nausea, Vomiting, Diarrhea Over Time (Trials GPHK and GPHL)



Source: ISS addendum, Figure ISS.4.6, page 1407 of 2079

The Applicant also presented the time to first onset for these common GI AEs, demonstrating highest onset during the first 24 weeks of tirzepatide treatment (Figure 38).

Figure 38. Time to Onset of Nausea, Vomiting, or Diarrhea (Trials GPHK and GPHL)



TEAEs in the SOC “Gastrointestinal disorders” were the most common TEAEs leading to study drug discontinuation (see Table 45), in 80/2515 (3.2%) tirzepatide- versus 4/958 (0.4%) of placebo-treated subjects. These GI TEAEs were also the most common reason for study drug dose reductions (Table 74), contributing to 115/124 (92.7%) of subjects with dose reductions.

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Table 74. Subjects with TEAEs Leading to Dose Reduction (Trials GPHK and GPHL)

	Placebo (N=958)	TZP 5mg (N=630)	TZP 10mg (N=948)	TZP 15mg (N=941)
All, n (%)	1 (0.1)	14 (2.2)	44 (4.6)	65 (6.9)
System Order Class, n (%)				
Gastrointestinal disorders	1 (0.1)	13 (2.1)	38 (4.0)	63 (6.7)
General disorders and administration site conditions	0	1 (0.2)	2 (0.2)	4 (0.4)
Infections and infestations	0	0	1 (0.1)	0
Investigations	0	0	2 (0.2)	0
Metabolism and nutrition disorders	0	0	4 (0.4)	7 (0.7)
Nervous system disorders	0	2 (0.3)	2 (0.2)	3 (0.3)
Psychiatric disorders	0	0	0	1 (0.1)

Source: OCS Analysis Studio, Custom Table Tool.

Columns - Dataset: Demographics; Filter: SAFFL = "Y".

All, n (%) - Dataset: Adverse Events; Filter: TRTEMFL = "Y", AEACN = "DOSE REDUCED".

Reviewer comment: *There is animal data that GIP agonists exert anti-nausea effects, suggesting the possibility that tirzepatide's dual agonism at the GIP and GLP-1 receptors might allow better GI tolerability than GLP-1 only agonists.²⁹ This hypothesis is difficult to test since tirzepatide is a single molecule with both agonist activities. Potential differences in GI AEs between the GIP/GLP-1 dual agonist tirzepatide and GLP-1 only agonists are difficult to compare across trials, but future CWM trials with head-to-head comparisons in parallel arms could address this question.*

Gastrointestinal Disorders Conclusion

The prevalence, severity, and seriousness of GI TEAEs with tirzepatide are consistent with the extensive clinical experience with GLP-1R agonists, are monitorable and reversible, and severe and common GI adverse reactions will be clearly addressed in Sections 5 and 6 of labeling of tirzepatide for CWM.

8.5.3. Acute Kidney Injury

Acute kidney injury (AKI) and worsening of CKD may occur as a result of dehydration or hypovolemia due to drug-related GI adverse effects (e.g., nausea, vomiting, diarrhea) which can lead fluid losses and potentially reduced intake.

Dehydration

I analyzed the Applicant's safety database for trials GPHK and GPHL using the narrow FMQ for "volume depletion," which includes the PTs "dehydration" and "hypovolemia." These AEs were

²⁹ Borner, Tito et al. "GIP Receptor Agonism Attenuates GLP-1 Receptor Agonist-Induced Nausea and Emesis in Preclinical Models." *Diabetes* vol. 70,11 (2021): 2545-2553. doi:10.2337/db21-0459

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rare, occurring in 15/2519 (0.60%) tirzepatide-treated subjects compared to 1/958 (0.10%) of placebo-treated subjects, for a 0.49% risk difference that was significant (95% CI 0.13 to 0.85). The Applicant's SMQ-based analysis gave identical results. The Applicant reviewed case narratives³⁰ for the 15 tirzepatide-treated subjects with dehydration:

- 5 reported GI AEs of diarrhea and/or vomiting shortly before or at the time of dehydration AE. 3 of the 5 subjects had a medical history of CKD, and 1 also had concomitant medications of hydrochlorothiazide and empagliflozin.
- 3 reported GI AEs of nausea only.
- 4 reported other concurrent medical conditions shortly before or at the time of dehydration AE (pyelonephritis, pneumonia, acute gastroenteritis caused by food poisoning, and upper GI bleeding/peptic ulcer).
- 1 had CKD at baseline as the only identifiable risk factor for dehydration.
- 2 did not report any GI TEAEs and did not have known risk factors for dehydration.

3 tirzepatide-treated subjects had serious or severe dehydration AEs:

- Subject (b) (6) was a 56-year-old female randomized to tirzepatide 15 mg with a severe but not serious dehydration AE with vomiting at the time of onset, who recovered with dose reduction.
- Subject (b) (6) was a 55-year-old male randomized to tirzepatide 10 mg with a severe and serious dehydration AE in the setting of gastroenteritis due to food poisoning and AKI, who recovered in two days with a dose interruption.
- Subject (b) (6) was a 60-year-old male randomized to tirzepatide 15 mg with a serious dehydration event of moderate severity, in the setting of nausea and vomiting, CKD, empagliflozin and hydrochlorothiazide use. Study drug was interrupted, and he recovered in 2 days.

Only one subject (b) (6) discontinued study drug due to dehydration, a 62-year-old female randomized to tirzepatide 10 mg who also had vomiting and AKI at the time of moderate dehydration, who recovered in one day.

Acute Kidney Injury

I analyzed the Applicant's safety database for trials GPHK and GPHL using the narrow FMQ for "acute kidney injury," which includes the PTs "acute kidney injury" and "renal injury." The "renal injury" TEAE was apparently a physical injury ("left kidney injury" occurring along with contusion/left chest bruise") and should not be included. "Acute kidney injury" TEAEs were rare, occurring in 13/2519 (0.52%) tirzepatide-treated subjects compared to 2/958 (0.21%) of placebo-treated subjects, for a 0.31% risk difference of that was not significant. The Applicant's SMQ-based analysis gave similar results using the narrow SMQ "acute renal failure": 0.64% and 0.31% for tirzepatide and placebo groups, respectively.³¹

³⁰ Details are in the SCS addendum, Table 2.7.4.6, page 30 of 73

³¹ ISS addendum, Table ISS.4.24, page 1417 of 2079

The Applicant identified 11 subjects in trials GPHK and GPHL with serious or severe “acute kidney injury” or “renal failure” events, 9 (0.36%) in tirzepatide groups and 2 (0.21%) in placebo groups. Case narratives were reviewed for the 9 tirzepatide-treated subjects:

- 5 subjects had concurrent serious medical conditions leading to acute kidney injury:
 - Subject (b) (6) had AKI (severe/serious) in the setting of acute liver failure and multiorgan failure which led to death, as discussed in Section 8.4.1.
 - Subject (b) (6) had AKI (severe/nonserious) in the setting of COVID-19 pneumonia which led to death.
 - Subject (b) (6) had AKI (moderate/serious) in the setting of septic shock and acute respiratory failure.
 - Subject (b) (6) had AKI (moderate/serious) in the setting of acute pancreatitis and pneumonia.
 - Subject (b) (6) had AKI (severe/nonserious) in the setting of the severe AE of ulcerative esophagitis, which likely led to dehydration.
- 2 subjects had nausea and vomiting leading to dehydration:
 - Subject (b) (6) had AKI (severe/serious) in the setting of food poisoning, gastroenteritis, and dehydration (discussed above), who recovered in 14 days with drug interruption.
 - Subject (b) (6) had AKI (severe/serious) in the setting of nausea, vomiting, and diarrhea, and recovered in 11 days with drug interruption.
- 2 subjects had renal injury unlikely related to tirzepatide:
 - Subject (b) (6) had renal failure (moderate/serious) and was diagnosed with granulomatous tubulointerstitial nephritis, which not associated with dehydration or with tirzepatide or other incretin drugs.
 - Subject (b) (6) had AKI (severe/serious) over one year after having discontinued study drug.

Limiting the analysis to serious adverse events (thus excluding the two events above graded as severe but non-serious), these occurred with slight imbalance in:

- Trial GPHK, in 4/1896 (0.21%) tirzepatide-treated versus 1/643 (0.16%) placebo-treated.
- Trial GPHL, in 3/623 (0.48%) tirzepatide-treated versus 1/315 (0.31%) placebo-treated.
- Both trials, in 7/2519 (0.27%) tirzepatide-treated versus 2/958 (0.21%) placebo-treated.

Five tirzepatide-treated subjects (all in trial GPHK) had non-serious mild or moderate severity acute kidney injury events:

- Three had GI AEs as likely contributors to kidney injury:
 - Subject (b) (6) reported moderate vomiting on Day 62, and on Day 71 reported severe vomiting, dehydration, AKI, metabolic acidosis, and hypokalemia, leading to study drug discontinuation due to severe vomiting.
 - (b) (6) reported nausea and hypotension on study Day 28, renal impairment on study Day 29, and discontinued study drug on Day 29 due to

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nausea. eGFR (mL/min/1.73 m²) was 62 at baseline, minimum 47 at Week 4, and near baseline 61 at Week 36.

- o Subject (b) (6) reported vomiting on study Days 71-80, then hypotension and AKI on Day 92, all recovered without change to study drug dose.
- One had dehydration without reported GI AEs:
 - o Subject (b) (6) reported on Day 154 AKI, dehydration, hypotension, and hypokalemia. All were mild-to-moderate and recovered without change to study drug dose.
- One had confounding baseline renal insufficiency and ibuprofen use:
 - o Subject (b) (6) had baseline renal insufficiency (eGFR 49 mL/min/1.73 m²) and ibuprofen use, with AKI reported on Day 113 and ibuprofen stopped on Day 162. Minimum eGFR (26 mL/min/1.73 m²) was on Day 175, it returned to near baseline at the safety follow-up (44 mL/min/1.73 m²). Study drug dose was not changed.

Considering the serious and non-serious TEAEs potentially related to AKI, I also pooled the PTs “acute kidney injury,” “renal impairment,” and “renal failure,” showing:

- Imbalance in trial GPHK, occurring in 12/1896 (0.63%) tirzepatide-treated versus 1/643 (0.16%) placebo-treated.
- No imbalance in trial GPHL, occurring in 4/623 (0.64%) tirzepatide-treated versus 2/315 (0.63%) placebo-treated.
- Small imbalance in both trials pooled, in 16/2519 (0.63%) tirzepatide-treated versus 3/958 (0.31%) placebo-treated.

Reviewer comment: Given that serious AKI events were rare (<0.5%) with minimal imbalance between tirzepatide and placebo arms (0.27% vs. 0.21%), and all such events were also rare (<0.7%) and imbalanced only in trial GPHK but not trial GPHL, these numerical incidences do not merit inclusion in label section 5 (Warnings and Precautions). This label section will include a general warning about risk of AKI, likely secondary to GI AEs and dehydration.

Renal Safety

The Applicant also assessed renal TEAEs more broadly with the SMQs “acute renal failure” and “chronic kidney disease,” identifying such AEs in 19 (0.75%) tirzepatide-treated and 6 (0.63%) placebo-treated subjects. These events were more common in subjects with impaired renal function based on eGFR category at baseline, in both the placebo and tirzepatide arms (Table 75).

Table 75. Renal TEAEs by Baseline eGFR category (Trials GPHK and GPHL)

eGFR category	Placebo		TZP ALL	
	N	n (%)	N	n (%)
≥90 mL/min/1.73m ²	639	3 (0.47)	1714	5 (0.29)
≥60 to <90 mL/min/1.73m ²	294	2 (0.68)	751	12 (1.60)
≥30 to <60 mL/min/1.73m ²	25	1 (4.00)	54	2 (3.70)

Abbreviations: eGFR = estimated glomerular filtration rate; N = number of participants in specified treatment arm; n = number of participants with at least 1 treatment-emergent renal event.

Source: Applicant ISS addendum, Table 2.7.4.7, page 34 of 73

The Applicant also assessed renal function by laboratory measurement of eGFR and urine albumin to creatinine ratio (UACR), analyzing changes from baseline and categorial shifts. These laboratory results in trials GPHK and GPHL did not raise concerns about renal safety, as summarized by the Applicant:³²

- Mean reductions from baseline in eGFR to Week 72 were small, with no clinically meaningful difference between tirzepatide groups (range: -0.1 to -1.1 mL/min/1.73 m²) and placebo (-0.4 mL/min/1.73 m²).
- The percentages of participants shifting to higher eGFR categories were comparable in the tirzepatide (3.3%) and placebo groups (3.6%). The percentage of participants shifting to lower eGFR categories was 22.9% for tirzepatide and 19.8% for placebo.
- The percent reduction in mean UACR from baseline at Week 72 was significantly greater in tirzepatide groups (range 19.1-24.7%), compared to placebo (6.6%).
- The percentage of participants who shifted to a higher UACR category was numerically smaller with tirzepatide (7.0%) compared to placebo (10.3%), while the percentage of participants that shifted to a lower UACR category was numerically greater with tirzepatide (7.5%) compared to placebo (4.7%).

Reviewer comment: I reviewed the Applicant's data on renal laboratory assessments in trials GPHK and GPHL, as well as the pooled analysis set in the Summary of Clinical Safety, and I agree with the Applicant's conclusions. The data for eGFR show no evidence of renal harm from tirzepatide, and the data for UACR suggest that tirzepatide may have a renal protective effect reducing microalbuminuria. The Applicant has renal endpoints in the ongoing phase 3b trial GPII (SURMOUNT-MMO), to test the hypothesis that tirzepatide improves renal outcomes.

Conclusion on Renal Safety

Events of dehydration and AKI were rare but occurred more often in tirzepatide compared to placebo groups, and renal TEAEs occurred more often in subjects with renal impairment at baseline. Case narratives for severe and serious events support the correlation with GI adverse events like nausea, vomiting, and diarrhea. Therefore, a labeled warning for AKI, already

³² Detailed results are ISS addendum, Tables ISS.4.27-30, page 1429 oof 2079

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labeled for tirzepatide for T2D, is appropriate for tirzepatide for CWM. This risk of AKI can be mitigated by monitoring, so the label will advise providers to monitor renal function in patients reporting adverse reactions to tirzepatide that could lead to volume depletion.

8.5.4. Acute Gallbladder Disease

Obesity and rapid weight loss are associated with an increased risk for gallstone formation.³³ The Applicant notes that the most common historical illness in the GPHK and GPHL trial population was cholecystectomy (11.6%). Incretin drugs have also been associated with gallstone formation and related disorders, including cholelithiasis and cholecystitis, though it remains uncertain whether there are weight-independent effects. For one GLP-1R agonist (liraglutide for CWM), the label notes that “the incidence of acute gallbladder disease was greater in SAXENDA-treated patients than in placebo-treated patients even after accounting for the degree of weight loss.”³⁴

The Applicant identified gallbladder-related PTs and note some imbalances with higher incidence in tirzepatide- than placebo-treated subjects. For instance, combining the PTs “cholecystitis” and “acute cholecystitis,” the incidence was 0.67% for tirzepatide and 0.21% for placebo. To capture a broader range of PTs that could indicate acute gallbladder disease, I queried the AE database with the broad FMQ “cholecystitis” (Table 76).

³³ Stinton LM, et al. Epidemiology of gallstones. *Gastroenterol Clin North Am* 2010 Jun; 39(2): 157-69, vii.

³⁴ Saxenda (liraglutide) prescribing information

Table 76. Cholecystitis FMQ TEAEs in Trials GPHK and GPHL

	TZP 5mg N=630 n (%)	TZP 10mg N=948 n (%)	TZP 15mg N=941 n (%)	TZP All N=2519 n (%)	Placebo N=958 n (%)	Risk Difference RD (95% CI)
Cholecystitis (FMQ Broad)	13 (2.1)	20 (2.1)	16 (1.7)	49 (1.9)	15 (1.6)	0.38 (-0.57, 1.33)
Cholelithiasis	8 (1.3)	11 (1.2)	11 (1.2)	30 (1.2)	10 (1.0)	0.15 (-0.62, 0.92)
Cholecystitis acute	1 (0.2)	5 (0.5)	4 (0.4)	10 (0.4)	2 (0.2)	0.19 (-0.19, 0.57)
Cholecystitis	4 (0.6)	3 (0.3)	0	7 (0.3)	0	0.28 (0.07, 0.48)
Cholecystitis chronic	1 (0.2)	1 (0.1)	3 (0.3)	5 (0.2)	3 (0.3)	-0.11 (-0.51, 0.28)
Cholecystectomy	2 (0.3)	2 (0.2)	0	4 (0.2)	0	0.16 (0.00, 0.31)
Bile duct stone	0	0	1 (0.1)	1 (0.0)	0	0.04 (-0.04, 0.12)
Cholangitis acute	0	0	1 (0.1)	1 (0.0)	0	0.04 (-0.04, 0.12)
Post cholecystectomy syndrome	0	0	1 (0.1)	1 (0.0)	0	0.04 (-0.04, 0.12)
Biliary colic	0	1 (0.1)	0	1 (0.0)	0	0.04 (-0.04, 0.12)
Sphincter of Oddi dysfunction	0	1 (0.1)	0	1 (0.0)	0	0.04 (-0.04, 0.12)
Biliary dyskinesia	0	0	0	0	1 (0.1)	-0.10 (-0.31, 0.10)

Source: Generated by reviewer in JMP Clinical FMQ Explorer

There was no apparent dose-effect of tirzepatide for these gallbladder events, and this FMQ showed no statistically significant or clinically meaningful imbalance (1.95% tirzepatide versus 1.57% placebo). The Applicant's analysis³⁵ found a very similar result (1.98% tirzepatide versus 1.67% placebo) defining acute gallbladder disease by the narrow SMQs "gallbladder-related disorders," "gallstone-related disorders," and "biliary tract disorders."

However, both my FMQ and the applicant's SMQ analyses include two frequent PTs that may be problematic for defining acute gallbladder disease: "chronic cholecystitis" is inconsistent with acute disease and "cholelithiasis" could, in the absence of other AEs, represent asymptomatic gallstones. Therefore, I generated a custom MedDRA query for acute gallbladder disease with the other terms from the "cholecystitis" broad FMQ excluding "cholelithiasis" and "chronic cholecystitis," and these AEs occurred in 23/2519 (0.91%) of tirzepatide-treated subjects and 2/958 (0.21%) of placebo-treated subjects, for a significant risk difference of 0.70% (Table 77).

³⁵ ISS Addendum, Table ISS.4.37, page 1640 of 2079

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Table 77. Custom Query for Acute Gallbladder Disease TEAEs (Trials GPHK and GPHL)

Custom MedDRA Query Preferred Term	TZP All N = 2519 n (%)	Placebo N = 958 n (%)	Risk Difference	
			RD (95% CI)	Forest Plot
Acute Gallbladder Disease	23 (0.9)	2 (0.2)	0.70 (0.23, 1.17)	
Cholecystitis acute	10 (0.4)	2 (0.2)	0.19 (-0.19, 0.57)	
Cholecystitis	7 (0.3)	0 (0.0)	0.28 (0.07, 0.48)	
Cholecystectomy	4 (0.2)	0 (0.0)	0.16 (0.00, 0.31)	
Bile duct stone	1 (0.0)	0 (0.0)	0.04 (-0.04, 0.12)	
Biliary colic	1 (0.0)	0 (0.0)	0.04 (-0.04, 0.12)	
Biliary obstruction	1 (0.0)	0 (0.0)	0.04 (-0.04, 0.12)	
Cholangitis acute	1 (0.0)	0 (0.0)	0.04 (-0.04, 0.12)	
Post cholecystectomy syndrome	1 (0.0)	0 (0.0)	0.04 (-0.04, 0.12)	
Sphincter of Oddi dysfunction	1 (0.0)	0 (0.0)	0.04 (-0.04, 0.12)	

Source: Generated by reviewer.

Serious (Table 78) and severe (Table 79) acute gallbladder disease events in this custom query were also more common in tirzepatide- than placebo-treated subjects.

Table 78. Serious Acute Gallbladder Disease TEAEs (Trials GPHK and GPHL)

Custom MedDRA Query Preferred Term	TZP All N = 2519 n (%)	Placebo N = 958 n (%)
Acute Gallbladder Disease	13 (0.5)	2 (0.2)
Cholecystitis acute	7 (0.3)	2 (0.2)
Cholecystitis	3 (0.1)	0 (0.0)
Bile duct stone	1 (0.0)	0 (0.0)
Biliary colic	1 (0.0)	0 (0.0)
Biliary obstruction	1 (0.0)	0 (0.0)
Cholangitis acute	1 (0.0)	0 (0.0)
Sphincter of Oddi dysfunction	1 (0.0)	0 (0.0)

Source: Generated by Reviewer, OCS Analysis Studio, Safety Explorer.

Table 79. Severe Acute Gallbladder Disease TEAEs (Trials GPHK and GPHL)

	TZP All	Placebo
Custom MedDRA Query	N = 2519	N = 958
Preferred Term	n (%)	n (%)
Acute Gallbladder Disease	10 (0.4)	0 (0.0)
Cholecystitis acute	7 (0.3)	0 (0.0)
Bile duct stone	1 (0.0)	0 (0.0)
Biliary colic	1 (0.0)	0 (0.0)
Biliary obstruction	1 (0.0)	0 (0.0)
Cholecystectomy	1 (0.0)	0 (0.0)
Sphincter of Oddi dysfunction	1 (0.0)	0 (0.0)

Source: Generated by Reviewer, OCS Analysis Studio, Safety Explorer.

The Applicant also conducted an analysis of acute gallbladder disease by maximum weight loss achieved.³⁶ 144 placebo-treated subjects achieved a weight loss from baseline of $\geq 10\%$ to $< 20\%$, and events of “cholecystitis” or “cholecystitis acute” occurred in 1/144 (0.69%), compared to 5/897 (0.56%) of tirzepatide-treated subjects with the same degree of weight loss. No placebo-treated subjects lost $\geq 20\%$ of body weight, and these cholecystitis AEs occurred in 10/1114 (0.89%) of tirzepatide-treated subjects with $\geq 20\%$ weight loss.

Reviewer comment: These results do not indicate a weight-independent effect of tirzepatide on acute cholecystitis, as the incidence was similar in placebo- and tirzepatide-treated subjects with 10-20% weight loss. Therefore, a labeling statement about potential weight-independent effects on acute gallbladder disease (like for liraglutide above) is not justified, and I agree with excluding such a statement from the tirzepatide label. The Applicant proposes a labeling statement that acute gallbladder disease is correlated with degree of weight loss, and, based on the data above, I agree that this statement is relevant to labeling.

In the review of semaglutide for CWM (NDA 215256), in a randomized withdrawal trial after a semaglutide run-in, it was noted that gallbladder TEAEs occurred more frequently in the placebo than the semaglutide group, suggesting the possibility of a drug withdrawal effect. Tirzepatide trial GPHN (SURMOUNT-4) has a similar design, so when submitted the data from this trial will be reviewed for this potential withdrawal effect on gallbladder-related events.

Acute Gallbladder Disease Conclusion

Acute gallbladder disease is a labeled warning (in Section 5) for most incretin drugs including tirzepatide for T2D, and I agree with the Applicant that it should be labeled here for tirzepatide for CWM. The caveats above about which PTs to include a combined query for acute gallbladder disease are beyond what can be included in the label, so I recommend that the label states incidences of the PTs cholelithiasis, acute cholecystitis (including, as the applicant

³⁶ ISS Addendum, Table ISS.4.39, page 1648 of 2079

8.5.5. Exocrine Pancreas Safety (including Acute Pancreatitis)

Pancreas safety, including concerns about acute pancreatitis, has historically been an area of interest with incretin drugs. However, as the Applicant notes, both obesity and T2D raise the risk of acute pancreatitis, and it remains uncertain whether incretin therapy affects this risk. Post-marketing reports of acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis with incretin drugs have led to Section 5 warnings in labeling regarding pancreatitis for the class. An imbalance in acute pancreatitis was reported in clinical trials (T2D and CWM) for liraglutide, but not for semaglutide.

An imbalance in acute pancreatitis is also noted in the labeling of tirzepatide for T2D.³⁷ In the trials for T2D reviewed under NDA 215866, 14 events of acute pancreatitis were confirmed by adjudication in 13 tirzepatide-treated patients (0.23 patients per 100 years of exposure) versus 3 events in 3 comparator-treated patients (0.11 patients per 100 years of exposure).

The Applicant’s nonclinical program did not find evidence of pancreatitis, pancreatic cancer or tirzepatide-related pancreas pathology in mice, rats, or monkeys. Subjects with a history of pancreatitis were excluded from clinical trials of tirzepatide for CWM and T2D, so it is unknown whether a history of pancreatitis raises the risk of future events on tirzepatide. Trial subjects with diagnoses of acute or chronic pancreatitis were also required to discontinue study drug.

To maximally capture cases of acute pancreatitis in the tirzepatide clinical development program for CWM, the Applicant had broad criteria to send cases for adjudication of pancreatitis:

- all suspected cases of acute or chronic pancreatitis
- AEs of severe or serious abdominal pain of unknown etiology
- cases of pancreatic amylase or lipase values $\geq 3 \times \text{ULN}$ with symptoms
- asymptomatic cases of amylase or lipase values $\geq 3 \times \text{ULN}$ that underwent additional diagnostic follow-up.

Suspected cases were then adjudicated by an independent, blinded CEC, and the diagnosis of acute pancreatitis included at least two of the following three criteria:

- abdominal pain characteristic of acute pancreatitis
- serum amylase or lipase at least $3 \times \text{ULN}$
- characteristic finding by cross-sectional imaging by computerized tomography (CT) or magnetic resonance imaging (MRI).

³⁷ Mounjaro (tirzepatide) prescribing information

In trials GPHK and GPHL, 31 potential cases of pancreatitis were sent for adjudication, and 7 cases were positively adjudicated, 5/27 in tirzepatide-treated subjects and 2/4 in placebo-treated subjects.³⁸ More subjects in tirzepatide than placebo arms were sent for adjudication due to AEs of abdominal pain and elevations in pancreatic enzymes. No cases were adjudicated as chronic pancreatitis or unknown (unable to determine), and no cases of acute pancreatitis were adjudicated as severe or critical. There was no imbalance in adjudication-confirmed pancreatitis, as 5/2519 (0.20%) tirzepatide- and 2/958 (0.21%) in placebo-treated subjects were each confirmed to have 1 event of acute pancreatitis. The Applicant also calculated the exposure-controlled incidence rates for adjudication-confirmed acute pancreatitis as 0.14 per 100 patient-years for tirzepatide versus 0.15 per 100 patient-years for placebo.

Reviewer comment: It is notable that an imbalance in adjudicated pancreatitis was noted in the tirzepatide phase 3 T2D trials under NDA 215866, but not for the phase 3 CWM trials GPHK and GPHL here. The balanced exposure-controlled rates of adjudication-confirmed acute pancreatitis in trials GPHK and GPHL are similar to those calculated by the Applicant using analysis set 4 of comparator-controlled phase 2/3 trials for T2D and CWM (including GPHK but not GPHL): 0.18 per 100 patient-years for tirzepatide compared to 0.19 per 100 patient-years for all comparators. Nonetheless, since an imbalance in acute pancreatitis events is noted in tirzepatide's label for T2D, it is reasonable to include the imbalanced T2D data in the proposed label for CWM since patients with T2D are contained within the indicated population.

I conducted a narrow FMQ for pancreatitis in the TEAE database, and found similar results, with 5 tirzepatide-treated and 1 placebo-treated subjects with TEAEs of “acute pancreatitis” or “pancreatitis.” The FMQ also identified the TEAE “obstructive pancreatitis” reported in two placebo-treated subjects, and this TEAE is more relevant to the hepatobiliary disorders in Section 8.5.4 above. This analysis confirms that investigator-assigned pancreatitis TEAEs largely agreed with the CEC adjudication, though there were 3 differences.

Table 80. Pancreatitis in Trials GPHK and GPHL by Adjudication or FDA MedDRA Query

	TZP 5mg N=630 n (%)	TZP 10mg N=948 n (%)	TZP 15mg N=941 n (%)	TZP All N=2519 n (%)	Placebo N=958 n (%)	Risk Difference RD (95% CI)
CEC adjudicated Pancreatitis	1 (0.2)	1 (0.1)	3 (0.3)	5 (0.2)	2 (0.2)	-0.01 (-0.35, 0.33)
Pancreatitis (FMQ Narrow)	2 (0.3)	0	3 (0.3)	5 (0.2)	3 (0.3)	-0.11 (-0.51, 0.28)
Pancreatitis Acute	2 (0.3)	0	2 (0.2)	4 (0.2)	1 (0.1)	0.05 (-0.20, 0.31)
Pancreatitis	0	0	1 (0.1)	1 (0.0)	0	0.04 (-0.04, 0.12)
Obstructive Pancreatitis	0	0	0	0	2 (0.2)	-0.21 (-0.50, 0.08)

³⁸ Adjudicated pancreatitis events are detailed the Applicant's ISS addendum, Table ISS.4.47, page 1710 of 2079

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I reviewed case narratives for the 7 CEC-adjudicated cases of pancreatitis, which did not raise concerns and the adjudications appeared appropriate.

Changes in Amylase and Lipase

GLP-1R agonists increase amylase and lipase as a class effect, and in the development of tirzepatide for T2D under NDA 215966 it increased these by approximately 30-40%. In CWM trials GPHK and GPHHL, the results were similar, with increases noted by the first post-baseline measurement at Week 12 that were maintained until Week 72 (end of treatment), declining towards baseline at the 4-week safety follow-up. The increases were dose-dependent with greater increases in tirzepatide 10 mg and 15 mg arms compared to tirzepatide 5 mg. Table 81 shows the mean values and percent changes in pancreatic enzymes at Week 72, and Figure 39 shows their time profiles:

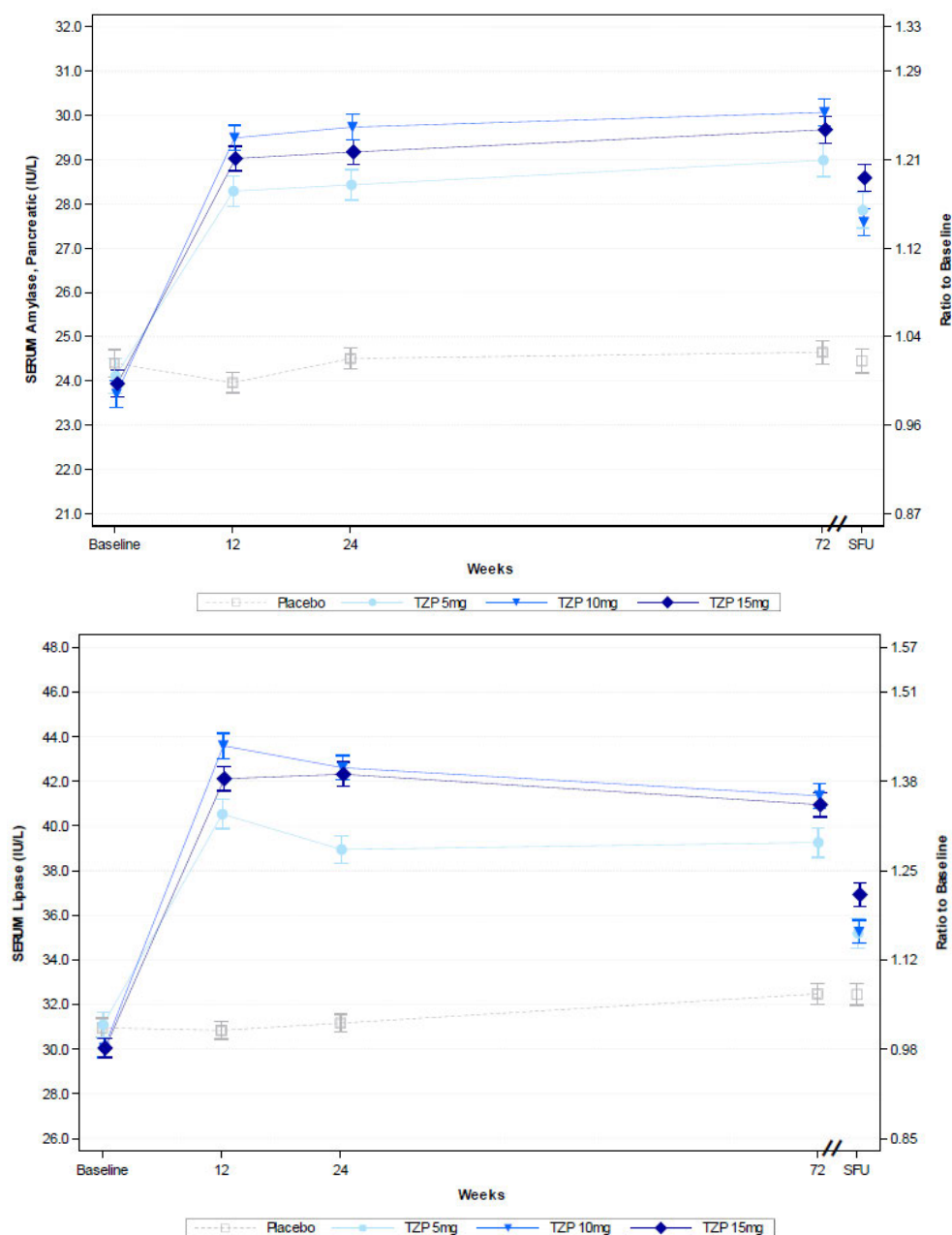
Table 81. Pancreatic Enzymes at End of Treatment (Week 72, Trials GPHK and GPHL)

IU/L	TZP 5mg		TZP 10mg		TZP 15mg		Placebo	
	mean (SD)	% CFB	mean (SD)	% CFB	mean (SD)	% CFB	mean (SD)	% CFB
Amylase	31.0 (14.2)	23.6	33.3 (18.6)	34.1	32.8 (20.3)	31.2	27.9 (17.7)	7.9
Lipase	41.9 (26.0)	40.7	48.8 (38.0)	52.9	48.2 (52.1)	49.7	38.8 (35.4)	15.3

Source: Adapted from Applicant ISS addendum, Table ISS.4.52, page 1721 of 2079

Abbreviations: CFB, change from baseline

Figure 39. Changes in Pancreatic Enzymes Over Time (Trials GPHK and GPHL)



Source: Applicant ISS Addendum, Figure ISS.4.7, Page 1751 of 2079

Note: Least square means and standard errors were calculated on a log scale from the MMRM model and back transformed to the original scale.

The mean amylase and lipase values remained in the normal range for all treatment groups, but tirzepatide-treated subjects had a dose-related increase in shifts to high amylase and lipase values (>ULN) compared to placebo-treated subjects (Table 82).

Table 82. Shifts to High Values for Pancreatic Enzymes (Trials GPHK and GPHL)

	TZP 5mg N=630 n/N1 (%)	TZP 10mg N=948 n/N1 (%)	TZP 15mg N=941 n/N1 (%)	TZP All N=2519 n/N1 (%)	Placebo N=958 n/N1 (%)	Risk Difference RD (95% CI)
Amylase	82/591 (13.9)	181/869 (20.8)	153/860 (17.8)	416/2320 (17.9)	56/860 (6.5)	11.42 (9.15, 13.69)
Lipase	41/609 (6.7)	94/905 (10.4)	90/905 (9.9)	225/2419 (9.3)	37/908 (4.1)	5.23 (3.50, 6.96)

Source: Adapted by reviewer from Applicant ISS addendum, Table ISS.4.17, page 1329 of 2079

The Applicant pre-specified increase in pancreatic enzyme >3x ULN for additional diagnostic follow-up (mandated if symptomatic and by investigator judgement if asymptomatic).

- In Trial GPHK, 15 subjects (all tirzepatide-treated, no placebo-treated) had amylase >3x ULN, and 3 cases were sent for adjudication. One case was positively-adjudicated as acute pancreatitis (subject (b) (6) in the tirzepatide 10 mg group had amylase >3x and ≤5x ULN and was also symptomatic with abdominal pain), while the other two were negatively-adjudicated.
- In Trial GPHK, 21 subjects (20 tirzepatide-treated, 1 placebo-treated) had lipase >3x ULN and 5 cases were sent for adjudication. Three of these are discussed above with amylase elevations: subject (b) (6) with lipase >3x and ≤5x ULN was positively-adjudicated, and two others were negatively adjudicated. Another subject was negatively adjudicated, and subject (b) (6) (in the tirzepatide 15 mg group, symptomatic with abdominal pain and nausea) was positively adjudicated.
- In trial GPHL, 28 subjects (20 tirzepatide-treated, 8 placebo-treated) had amylase >3x ULN, 5 cases were sent for adjudication, and all were negatively adjudicated. 27 subjects (19 tirzepatide-treated, 8 placebo-treated) had lipase >3x ULN, 4 cases were sent for adjudication, and all were negatively adjudicated.
- In both trials, only subject (b) (6) had either amylase or lipase post-baseline maximum of >10x ULN (both met this threshold), but this subject was negatively adjudicated for pancreatitis.

Pancreatic Cancer

In trials GPHK and GPHL, there was one case of pancreatic cancer in a placebo-treated subject.

Pancreas Safety Conclusion

Since acute pancreatitis is a potentially life-threatening event that is labeled for the incretin drug class, I agree with the Applicant that it should be listed in label Section 5 (Warnings and Precautions). Elevations in pancreatic enzymes are of uncertain significance, so I agree with the Applicant that this should be included in the label Section 6.1 (Clinical Trials Experience) as a subheading under laboratory abnormalities. In tirzepatide CWM trials GPHK and GPHL, screening for elevations in amylase and lipase was of limited utility for identifying cases of acute pancreatitis, and positively-adjudicated cases all had other symptoms in addition to pancreatic enzyme elevations. Therefore, the labeling language for tirzepatide for T2D and for incretin

drugs (i.e., the clinical significance of elevations in amylase or lipase is unknown in the absence of other signs and symptoms of pancreatitis) is also appropriate for tirzepatide for CWM.

8.5.6. Hypersensitivity

Hypersensitivity is generally included in Section 5 (Warnings and Precaution) of labeling for other incretin drugs, with a Section 4 contraindication for individuals with a history of a serious hypersensitivity reaction to the respective incretin drugs. Additionally, hypersensitivity reactions associated with incretin drugs, including anaphylaxis, have been reported in the literature.

In the tirzepatide clinical development program, the Applicant identified hypersensitivity cases by the following SMQs:

- Anaphylactic reaction (narrow and algorithm terms)
- Angioedema (narrow terms)
- Severe cutaneous adverse reactions (narrow terms)
- Hypersensitivity (narrow terms)
- Vasculitis (narrow terms).

Hypersensitivity was also classified as immediate (within 24 hours of study drug administration) or non-immediate (occurring more than 24 hours after study drug administration, but prior to the next administration).

By these definitions, in trials GPHK and GPHL,³⁹ 54/2519 (2.14%) tirzepatide- versus 4/958 (0.42%) placebo-treated subjects experienced one or more immediate hypersensitivity reactions. There was less imbalance for non-immediate hypersensitivity reactions (3.49% tirzepatide versus 2.71% placebo). There was not an apparent dose-related effect of tirzepatide on these immediate (1.75%, 2.43%, and 2.13% for 5, 10, and 15 mg) or non-immediate (3.49%, 3.16%, 3.83% for 5, 10, and 15 mg) hypersensitivity reactions. Pooling immediate and non-immediate reactions (5.12% with tirzepatide versus 3.13% with placebo), the most common PTs were cutaneous (e.g., rash, dermatitis, urticaria, eczema). These PTs could reflect generalized skin reactions, or they may indicate local reactions at the injection site (see Section 8.5.11 below). Non-cutaneous hypersensitivity PTs identified by this analysis (clearly indicating systemic rather than local reactions) were rare and not meaningfully imbalanced (with percentages shown for tirzepatide versus placebo arms):

- rhinitis (0.23% vs 0.63%) or conjunctivitis (0.04% vs 0.21%)
- angioedema (0.04% versus 0%)
- bronchospasm (0% tirzepatide versus 0.10% placebo)
- eye swelling or eyelid edema (0.08% vs 0%)
- lip swelling, mouth swelling, face swelling, or perioral dermatitis (0.08% vs 0.20%)

³⁹ These results are summarized from the Applicant's ISS addendum, Tables ISS.4.65-67, Page 1860 of 2079

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- mast cell activation syndrome (0.04% vs 0%).

No hypersensitivity reaction TEAEs were considered serious, and 3 were graded as severe (all in trial GPHK/SURMOUNT-1), one immediate and two non-immediate:

- Subject (b) (6) randomized to tirzepatide 10 mg, had an immediate reaction of severe hypersensitivity on Day 114 (no further details of the reaction are provided) which resolved the same day. The same subject reported a separate moderate severity anaphylactic reaction on Day 505. Neither event led to treatment interruption or discontinuation, and the subject completed the trial on study drug.
- Subject (b) (6), randomized to tirzepatide 10 mg, had a non-immediate reaction of severe rash, starting on study Day 80 and resolving 15 days later. Study drug was discontinued due to this rash (with last dose on Day 72). There was no rechallenge of study drug to test causality.
- Subject (b) (6), randomized to tirzepatide 15 mg, had a non-immediate reaction of severe dermatitis on Day 74, progressive from mild dermatitis initially reported on Day 70, with study drug interrupted then discontinued with last dose on Day 64. The severe dermatitis resolved by Day 81, and there was no rechallenge of study drug to test causality.

There were no treatment discontinuations due to immediate hypersensitivity reactions, and there were 4 discontinuations due to non-immediate hypersensitivity (2 for severe rash and severe dermatitis as above, plus 2 others for mild rash and mild injection site rash).

Hypersensitivity conclusions

In CWM trials GPHK and GPHL, TEAEs consistent with immediate and non-immediate hypersensitivity occurred more frequently in tirzepatide than placebo arms, consistent with the results in the tirzepatide development program for T2D (reviewed in NDA 215866). Most AEs were cutaneous, few clearly indicated systemic hypersensitivity reactions, and none were serious. Overall, 3/2519 tirzepatide-treated subjects (0.13%) and no placebo-treated subjects in trials GPHK and GPHL had hypersensitivity reactions graded as severe, with one immediate reaction of hypersensitivity resolving the same day with no dose adjustment, and two non-immediate reactions of rash or dermatitis resulting in study drug discontinuation.

Hypersensitivity will be labeled in Sections 4 (Contraindications), 5 (Warnings and Precautions), and 6.1 (under Common Adverse Reactions). The latter Section of labeling will report incidences of immediate and non-immediate hypersensitivity reactions as this information is relevant to prescribers, and it will describe the association of hypersensitivity reactions with tirzepatide ADA positivity (see Section 8.4.10 on Immunogenicity).

8.5.7. Hypoglycemia

GLP-1R agonists were originally developed as anti-hyperglycemic drugs to treat T2D. The Applicant cites references on incretin physiology, noting that both GLP-1 and GIP increase glucose-stimulated insulin release, but not in the setting of hypoglycemia. Furthermore, GIP is reported to stimulate glucagon release in the setting of hypoglycemia,⁴⁰ suggesting that the dual GIP and GLP-1 agonist tirzepatide may have less risk of hypoglycemia compared to pure GLP-1 agonists. For GLP-1 agonists, the risk of hypoglycemia is higher in subjects with T2D taking insulin or insulin secretagogues, and the same was seen in tirzepatide's development for T2D reviewed in NDA 215866. Based on such findings, there is class label warning for hypoglycemia in T2D for incretin drugs.

Hypoglycemia is reviewed separately for trial GPHK (SURMOUNT-1) in subjects without T2D and trial GPHL (SURMOUNT-2) in subjects with T2D. To minimize the risk for hypoglycemia in trial GPHL, subjects taking insulin were excluded and those taking insulin secretagogues (like sulfonylureas [SUs]) at baseline were to have their dose halved (or stopped if already on the lowest dose) at randomization.

In both trials, the Applicant defined two categories of hypoglycemia:

- Severe hypoglycemia: an episode with severe cognitive impairment requiring the assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions. These episodes may have been associated with sufficient neuroglycopenia to induce seizure or coma. Blood glucose (BG) measurements may not have been available during such an event, but neurological recovery attributable to the restoration of BG to normal was considered sufficient evidence that the event was induced by a low BG concentration.
- Hypoglycemia with BG <54 mg/dL (<3.0 mmol/L): primary analyses exclude any episodes that occurred after the initiation of a new anti-hyperglycemic therapy.

Reviewer comment: Rescue therapy for persistent hyperglycemia was much more common in placebo-treated (32.1%) than tirzepatide-treated (2.7%) subjects in trial GPHL (see Section 8.5.16 below), so excluding episodes after rescue therapy initiation is appropriate to accurately compare the tirzepatide and placebo arms. Including such episodes would increase hypoglycemic events in the placebo group and thus reduce the signal for imbalance compared to the tirzepatide group.

Severe hypoglycemia occurred in one subject without T2D in trial GPHK: subject (b) (6) who had hypoglycemia in the hospital while experiencing hepatic and multiorgan failure, resulting in ICU admission and death (see detailed case narrative in Section 8.4.1 on deaths). Severe

⁴⁰ Christensen MB, Calanna S, Holst JJ, et al. Glucose-dependent insulintropic polypeptide: blood glucose stabilizing effects in patients with type 2 diabetes. J Clin Endocrinol Metab. 2014;99(3): E418-E426. <https://doi.org/10.1210/jc.2013-3644>

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hypoglycemia did not occur in any subjects with T2D in trial GPHL.

Table 83 shows that hypoglycemia with BG<54 mg/dl occurred:

- In placebo-treated subjects: rarely in those without T2D (0.16%) and more frequently in those with T2D (1.27%), mainly in those with T2D on SUs (3.19%) versus not on SUs (0.45%).
- In subjects without T2D: more in tirzepatide-treated subjects than placebo-treated subjects (1.53% versus 0.16%), with no dose-effect.
- In subjects with T2D: more in those tirzepatide-treated than placebo-treated (4.17% versus 1.27%), with a potential dose-effect (4.82% with 15 mg versus 3.53% with 10 mg).
- In tirzepatide-treated subjects: more in subjects with T2D (4.17%) than without T2D (1.53%), and most frequently in those with T2D on SUs (10.26%), much more than those with T2D not on SUs (2.14%, more similar to those without T2D [1.53%]).

Table 83. Summary of Hypoglycemia (Glucose <54 mg/dL) Incidence in Trials GPHK and GPHL

	TZP 5mg	TZP 10mg	TZP 15mg	TZP All	Placebo
n/N1 (%); episodes	N=630	N=948	N=941	N=2519	N=958
GPHK (no T2D), all subjects	9/630 (1.43); 10	10/636 (1.57); 13	10/630 (1.59); 11	29/1896 (1.53); 34	1/643 (0.16); 1
GPHL (T2D), all subjects		11/312 (3.53); 17	15/311 (4.82); 24	26/623 (4.17); 31	4/315 (1.27); 31
GPHL (T2D), without SU		4/234 (1.71); 8	6/233 (2.58); 7	10/467 (2.14); 15	1/221 (0.45); 1
GPHL (T2D), with SU		7/78 (8.97); 9	9/78 (11.54); 17	16/156 (10.26); 26	3/94 (3.19); 30

Source: Adapted by reviewer from SCS (Table 2.7.4.88, page 234 of 293) and GPHL CSR (Tables GPHL.5.48-51, page 240 of 2056)
Abbreviations: SU, sulfonylurea

Reviewer comment: *In trial GPHL, 2 additional placebo-treated subjects had hypoglycemia events after initiation of new antihyperglycemic rescue therapy, so including these would increase the incidence in this group to 6/315 (1.9%) and not meaningfully change the results. The Applicant also calculated aggregated annual rates of hypoglycemia, but these were not informative in trial GPHL since 3 placebo-treated subjects on SUs had 30 hypoglycemic events, skewing the event rate in the placebo group, and minimizing the difference from the tirzepatide group.*

While Table 83 shows the overall incidence of glucose <54 mg/dL, the Applicant provided additional context for the hypoglycemia occurring in subjects without T2D in trial GPHK, which did not include the routine use of glucometers, glucose diaries, and case report forms to systematically capture and report hypoglycemia as done in studies for T2D. In trial GPHK, 29 tirzepatide-treated patients reported 34 episodes of blood glucose <54 mg/dL and 1 placebo-treated patient reported 1 episode. 25/34 recorded episodes with tirzepatide (73.5%) occurred during oral glucose tolerance tests (OGTTs), with all 25 low glucose values reported at post-load timepoints. The placebo-treated patient reported the 1 episode of low blood glucose during

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OGTT, also at a post-load timepoint. The 9 remaining reports of glucose <54 mg/dL were reported for 6 tirzepatide-treated patients outside of the OGTT setting.

Reviewer comment: The final Section 6.1 of labeling will describe the incidences of hypoglycemia in subjects without T2D in trial GPHK under “Other Adverse Reactions”. Episodes of reactive hypoglycemia post-load during OGTTs are not considered clinically meaningful, as they occur commonly in healthy individuals⁴¹ and lack of specificity and sensitivity for diagnosis of hypoglycemia.⁴² Therefore, this section of labeling will report trial GPHK hypoglycemia outside of OGTTs: 6/1896 (0.3%) with tirzepatide versus none with placebo.

Hypoglycemia conclusion

Section 5 (Warning and Precautions) of labeling will include a subsection on “Hypoglycemia,” describing the risks in patients with and without T2D. For patients with T2D, the label will note the increased risk of hypoglycemia in patients taking insulin secretagogues (based on the data above from trial GPHL) or insulin (since this combination was well-studied in the development program for T2D, and is and labeled for tirzepatide for T2D). For patients without T2D, Section 5 of labeling will include a general statement: “Hypoglycemia has also been associated with ZEPBOUND and GLP-1 receptor agonists in adults without type 2 diabetes mellitus,” with the incidences of hypoglycemia (outside OGTTs as noted above) in subjects without T2D reported in Section 6.1 of labeling. The risk of hypoglycemia is clearly greater in subjects with T2D, but the potential risk in those without T2D will also be addressed in Sections 5 and 6 of the label.

8.5.8. Diabetic Retinopathy

In patients with T2D, rapid improvements in glycemic control may be associated with temporary worsening of diabetic retinopathy. Increases in diabetic retinopathy complications were observed in a CVOT (SUSTAIN-6) of the GLP-1R agonist semaglutide, leading to Section 5 labeling (Warnings and Precautions) about diabetic retinopathy complications for most incretin drugs.

In the phase 3 CWM trial GPHL (SURMOUNT-2) in subjects with T2D (as well phase 3 trials for T2D reviewed under NDA 215866), subjects with a history of proliferative diabetic retinopathy, diabetic macular edema, or nonproliferative diabetic retinopathy that required acute treatment were excluded based on a dilated fundoscopic examination performed by a qualified eye care professional during screening. Follow-up dilated fundoscopic examination was performed when

⁴¹ Parekh S et al. Clinical characteristics of people experiencing biochemical hypoglycaemia during an oral glucose tolerance test: Cross-sectional analyses from a UK multi-ethnic population. *Diabetes Research and Clinical Practice*. 2014;104(3):427-434. doi.org/10.1016/j.diabres.2014.02.013.

⁴² Hall M et al. Metabolic parameters in patients with suspected reactive hypoglycemia. *Journal of Personalized Medicine*. 2021;11(4):276. doi: 10.3390/jpm11040276

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clinically indicated by any AE suspected of worsening retinopathy. The applicant used a customized MedDRA search for potential diabetic retinopathy complications (Table 84).

Table 84. Applicant's Custom MedDRA Search for Potential Diabetic Retinopathy Complications

Amaurosis	Fundoscopy abnormal	Retinal oedema
Amaurosis fugax	Intraocular injection	Retinal operation
Arteriosclerotic retinopathy	Macular detachment	Retinal thickening
Blindness	Macular oedema	Retinal vascular disorder
Blindness transient	Maculopathy	Retinal vascular occlusion
Blindness unilateral	Noninfective chorioretinitis	Retinal vein occlusion
Choroidal neovascularization	Noninfective retinitis	Retinitis
Cystoid macular oedema	Phacotrabeculectomy	Retinopathy
Detachment of macular retinal pigment epithelium	Retinal aneurysm	Retinopathy haemorrhagic
Detachment of retinal pigment epithelium	Retinal arteriovenous malformation	Retinopathy hypertensive
Diabetic blindness	Retinal artery embolism	Retinopathy hyperviscosity
Diabetic eye disease	Retinal artery occlusion	Retinopathy proliferative
Diabetic retinal oedema	Retinal artery stenosis	Scintillating scotoma
Diabetic retinopathy	Retinal collateral vessels	Sudden visual loss
Diabetic uveitis	Retinal cryoablation	Venous stasis retinopathy
Diplopia	Retinal detachment	Vision blurred
Exudative retinopathy	Retinal exudates	Visual impairment
Eye laser surgery	Retinal haemorrhage	Visual acuity reduced
Fundoscopy	Retinal laser coagulation	Visual acuity reduced transiently
	Retinal neovascularization	Vitrectomy

Source: Applicant SCS addendum, Table 2.7.4.102, page 259 of 293

These potential diabetic retinopathy complications were rare and none were serious, occurring in 7/623 (1.1%) tirzepatide- and 2/315 (0.6%) placebo-treated subjects (Table 85).

Table 85. Potential Diabetic Retinopathy Complications in Trial GPHK

System Organ Class Preferred Term	n (%)		
	Placebo (N=315)	TZP 10 mg (N=312)	TZP 15 mg (N=311)
Subjects with ≥1 treatment-emergent diabetic retinopathy complication	2 (0.6%)	5 (1.6%)	2 (0.6%)
Diabetic retinopathy	1 (0.3%)	3 (1.0%)	0
Vision blurred	1 (0.3%)	2 (0.6%)	1 (0.3%)
Diabetic retinal edema	0	0	1 (0.3%)
Macular edema	1 (0.3%)	0	0

Abbreviations: n = number of participants with events meeting specified criteria; N = number of participants who were randomly assigned and received ≥1 dose of the study drug; TZP = tirzepatide.

Source: Applicant ISS addendum, Table 2.7.4.9, page 59 of 73

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In trial GPHK, worsening of fundoscopic examination results was observed for 5 (0.8%) tirzepatide- and 2 (0.6%) placebo-treated subjects. Results for these 7 subjects are in Table 86, showing one subject (b) (6) with a post-baseline severe non-proliferative retinopathy resulting in discontinuation of study drug (tirzepatide 10 mg).

Table 86. Subjects with Worsening Dilated Fundoscopic Exam Results in Trial GPHL

Participant ID Treatment Group Age, Sex	Eye	Categories	Baseline Results	Baseline Severity	Days from Baseline to Postbaseline Examination Date	Postbaseline Results	Postbaseline Severity	Action Taken with Study Drug
(b) (6) Placebo 59 years old, Male	Left	PR ME	No	N/A	464	Yes	-	Dose not changed Completed study on study drug
(b) (6) TZP 10 mg 39 years old, Male	Right	PR	No	N/A	368	Yes	-	Dose not changed Completed study on study drug
(b) (6) Placebo 67 years old, Female	Both	NPR	No	N/A	525	Yes	Mild	Discontinued Study Drug on Day 183 due to withdrawal by participant
(b) (6) TZP 10 mg 45 years old, Male	Left	NPR	No	N/A	512	Yes	Mild	Dose not changed Completed study on study drug
(b) (6) TZP 10 mg 66 years old, Male	Right	NPR	Yes	Moderate	77	Yes	Severe	Study drug was discontinued due to NPR on Day 336
(b) (6) TZP 10 mg 66 years old, Female	Left	NPR	No	N/A	510	Yes	Mild	Dose not changed Completed study on study drug
(b) (6) TZP 15 mg 66 years old, Male	Left	ME	No	N/A	486	Yes ^a	-	Dose not changed Completed study on study drug

Abbreviations: - = severity not applicable to this category of medical condition; ID = identifier; ME = macular edema; NA = not applicable; NPR = non-proliferative diabetic retinopathy; PR = proliferative diabetic retinopathy; TEAE = treatment-emergent adverse event; TZP = tirzepatide.

The Applicant conducted similar reviews of diabetic retinopathy safety in the development of tirzepatide for T2D, as detailed in the review of NDA 215866 and the Applicant's Summary of Clinical Safety for CWM. These results in T2D trials are generally in agreement with the results above in CWM trial GPHK in subjects with T2D:

- No imbalances between tirzepatide and comparators were found in potential diabetic retinopathy-related PTs by custom MedDRA queries, with adjusted incidence rates of approximately 0.8%, comparable to trial GPHL.
- Some serious AEs (such as retinal detachment and retinal vein occlusion) occurred in the T2D development, but these were rare and balanced between tirzepatide and comparator groups (0.11% versus 0.10%).
- Across the phase 3 T2D program, worsening of fundoscopic exam results occurred in 0.36% of tirzepatide-treated subjects and 0.25% comparator-treated participants. The higher rates observed in trial GPHL may reflect the longer treatment duration.

The Applicant proposes listing diabetic retinopathy complications in label Section 5, Warnings and Precautions, and I concur. The Applicant is also conducting a dedicated diabetic retinopathy substudy as part of CVOT GPGN, which will better inform the risk of new onset or worsening

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diabetic retinopathy with tirzepatide use.

8.5.9. Psychiatric Disorders

Suicidality and depression are safety issues of concern for all centrally acting obesity drugs.⁴³ Among GLP-1R agonists for CWM, an imbalance in suicidal behavior and ideation was observed for liraglutide but not for semaglutide. Nonetheless “suicidal behavior and ideation” is currently labeled as a class effect for all CWM drugs, including GLP-1R agonists.

Suicidality

There were no completed suicides in tirzepatide phase 3 CWM trials GPHK and GPHL. Across the tirzepatide clinical development program, there has been one completed suicide. Subject (b) (6) randomized to tirzepatide 15 mg in the T2D phase 3 trial GPGH (SURPASS-3, reviewed in NDA 215866) had a history of depression and had the fatal serious adverse event “depression suicidal” on study 320. However, this subject had discontinued study drug on Day 78 due to elevated pancreatic enzymes, so this suicide (occurring 242 days after drug discontinuation) was unlikely related to tirzepatide.

In the tirzepatide phase 3 CWM trials GPHK and GPHL, subjects with severe past or present psychiatric disorders were not eligible for enrollment. Both trials deployed the Patient Health Questionnaire-9 (PHQ-9) and the Columbia Suicide Severity Rating Scale (C-SSRS) questionnaires, which are often used in screening and monitoring of CWM phase 2 and 3 trials. Specific exclusions were:

- History of significant active or unstable Major Depressive Disorder or other severe psychiatric disorder (for example, schizophrenia, bipolar disorder, or other serious mood or anxiety disorder) within the last 2 years. (Patients with depression or generalized anxiety disorder whose disease state is considered stable and expected to remain stable throughout the course of the study, in the opinion of the investigator, may be considered for inclusion if they are not on excluded medications.)
- Any lifetime history of a suicidal attempt
- Baseline PHQ-9 score of ≥ 15
- Any suicidal ideation or behavior on the C-SSRS that occurred in the past month: ideation of type 4 (Active Suicidal Ideation with Some Intent to Act, Without Specific Plan) or type 5 (Active Suicidal Ideation with Specific Plan and Intent), or any suicide related behavior (Actual Attempt, Interrupted Attempt, Aborted Attempt, Preparatory Act or Behavior).

Psychiatric diagnoses are common in patients with obesity or T2D. Per the Applicant, at baseline 18.3% of subjects in trials GPHK and GPHL reported at least 1 event in the SOC of

⁴³ See FDA Clinical Reviews of (b) (4) NDA 22580 (phentermine/topiramate), and NDA 200063 (naltrexone/bupropion).

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Psychiatric disorders. The most commonly reported terms were anxiety (7.7%), depression (6.8%), and insomnia (5.9%). Additionally, based on the PHQ-9 total scores, 24.0% of subjects had mild depression and 8.2% had moderate depression at baseline.

The safety database for trials GPHK and GPH^{(b) (4)} were reviewed for suicidal ideation and behavior. The sponsor used the “suicide/self-injury” SMQ, and I used the “self-harm” FMQ and custom MedDRA queries for all terms including suicide (i.e., Columbia suicide severity rating scale abnormal, Completed suicide, Depression suicidal, Suicidal behavior, Suicidal ideation, Suicide attempt, Suicide threat, Suspected suicide, Suspected suicide attempt). These analyses each identified the same three subjects:

- Subject ^{(b) (6)} randomized to placebo had suicidal ideation.
- Subject ^{(b) (6)} randomized to tirzepatide 10 mg had two suicide attempts. She was a 22-year-old Hispanic female with baseline BMI 38.7 kg/m² with a history of anxiety. At baseline she answered “No” to all C-SSRS questions about suicidal ideation or behavior in her lifetime, and her PHQ-9 total score was 8 at Day -14 (her maximum recorded during the trial, scores of 5-9 indicate mild depression) and 3 at baseline on Day 0. On study Day 341 she had lost -22.1% of her baseline body weight and had no suicidal ideation or behavior by C-SSRS and a PHQ-9 score of 5. On study Day 360, she had a first event reported as a suicide attempt. This event was described as ingesting a large amount of alcohol, becoming anxious and agitated, then taking an unknown number of sertraline and fluoxetine pills before leaving home for 5 hours, then returning home to sleep. No action was taken with study drug since the subject did not report this event at the time, and her C-SSRS was negative for suicidal ideation or behavior 9 days after the incident (study Day 369). On study Day 370, a second suicide attempt was reported, with the subject experiencing agitation and back pain, and wanting to “take her life to end the pain.” She took an unknown number of clonazepam, quetiapine, bromazepam, and venlafaxine pills and went to sleep. She was found “sleepy” by her partner but was not taken to the emergency department and recovered. The subject also had adverse events of “panic syndrome” on Days 363 and 373, before and after the second suicide attempt. She saw her psychiatrist for medication adjustments on study Day 373, and study medication was discontinued by the investigator on Day 376. Three potential life events or triggers were identified in the case narrative: an abortion 5 years ago, two children she cared for recently moving to another city, and dissatisfaction with her body due to weight loss (“breasts falling to the abdomen”). Her only affirmative answers to C-SSRS questions on suicidal ideation and behavior were on Day 411, referring to the event since her last visit on Day 369, and subsequent answers were all negative on Days 431, 445, 519, and 539. Her PHQ-9 total scores ranged from 2-5 during treatment (Days 90-341) and from 1-5 after treatment was discontinued (Days 431-539). An association with weight loss or tirzepatide cannot be ruled out, though the case is confounded by pre-existing psychiatric disease and likely substance abuse.
- Subject ^{(b) (6)} randomized to tirzepatide 15 mg had one suicide attempt. She was a 30-year-old Black female with baseline BMI 42.2 kg/m² and a history of

depression and post-traumatic stress disorder (PTSD). At baseline she answered “No” to all C-SSRS questions about suicidal ideation or behavior in her lifetime, and her PHQ-9 total scores showed no depression at baseline (1 on Day -14 and 0 on Day 0). On study Day 120 she had lost -10.9% of her baseline body weight and had no suicidal ideation or behavior by C-SSRS and a PHQ-9 total score of 2 on Day 88. On study Day 140, she was hospitalized for “an interrupted suicide attempt by scissors with intent to cut her wrists.” She had been taking sertraline but had recently discontinued it because the prescription ran out and she was unable to refill it. She reported a trigger event related to past sexual abuse by her step-brother, whom she had just seen on a family video chat. Sertraline was resumed and the dose was increased, and the study drug was interrupted from Days 139 to 207, when it was resumed after consultation with her psychologist. Her only affirmative answers to C-SSRS questions on suicidal ideation and behavior were on Day 152, referring to the event since her last visit on Day 120, and subsequent answers were all negative on Days 196, 224, 258, 280, 308, 336, 365, 393, 424, 448, 480, 503, and 580. After the suicide attempt, her PHQ-9 total scores indicated moderate depression (defined as scores 10-15) on Days 258, 424, and 503 (14, 10, and 10, respectively) but indicated no depression on Day 336 and 580 (scores of 2). This case was confounded by baseline depression, nonadherence to her antidepressant medication, and exposure to a triggering event for her PTSD.

These three subjects in trials GPHK and GPHL with events of “suicide attempt” or “suicidal ideation” were balanced at 2/2519 (0.08%) and 1/958 (0.10%) in tirzepatide- and placebo-treated subjects. No other subjects with suicide-related AEs were identified by the Applicants “suicide/self-injury” SMQ and by my “self-harm” FMQ.

Based on “yes” answers to C-SSRS questions 1-5 there were additional subjects with lesser degrees of suicidal ideation, also balanced at 14/2519 (0.6%) and 7/958 (0.7%). The only subjects with suicidal behavior by C-SSRS questions 6-10 were the two above with suicide attempt AEs.

Depression and other Psychiatric AEs

In trials GPHK and GPHL, TEAEs in the SOC Psychiatric Disorders were balanced between tirzepatide-treated (6.5%) and placebo-treated (7.1%) subjects (Table 87).

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Table 87. TEAEs in SOC Psychiatric Disorders, PTs Occurring in ≥2 Tirzepatide-Treated Subjects (Trials GPHK and GPHL)

Preferred Term	TZP All N = 2519 n (%)	Placebo N = 958 n (%)
SOC Psychiatric Disorders	164 (6.5)	68 (7.1)
Insomnia	65 (2.6)	21 (2.2)
Depression	32 (1.3)	18 (1.9)
Anxiety	31 (1.2)	25 (2.6)
Libido decreased	11 (0.4)	2 (0.2)
Depressed mood	8 (0.3)	5 (0.5)
Major depression	4 (0.2)	2 (0.2)
Panic disorder	4 (0.2)	0 (0.0)
Anxiety disorder	3 (0.1)	0 (0.0)
Initial insomnia	3 (0.1)	0 (0.0)
Sleep disorder	3 (0.1)	1 (0.1)
Stress	3 (0.1)	0 (0.0)
Irritability	2 (0.1)	0 (0.0)
Mania	2 (0.1)	0 (0.0)
Nightmare	2 (0.1)	0 (0.0)
Suicide attempt	2 (0.1)	0 (0.0)

Besides the two subjects with suicide attempts described above, there were 5 other serious TEAEs in the “Psychiatric disorders” SOC, all in tirzepatide-treated subjects (Table 88). Case narratives for these AEs were reviewed and all cases were confounded by social stressors and/or pre-existing mental health issues, including depression, PTSD, or anxiety.

Table 88. Serious TEAEs in the SOC Psychiatric Disorders (Trials GPHK and GPHL)

Preferred Term	TZP All N = 2519 n (%)	Placebo N = 958 n (%)
SOC: Psychiatric Disorders	6 (0.2)	0 (0.0)
Suicide attempt	2 (0.1)	0 (0.0)
Substance abuse	1 (0.0)	0 (0.0)
Major depression	1 (0.0)	0 (0.0)
Bulimia nervosa	1 (0.0)	0 (0.0)
Anxiety disorder	1 (0.0)	0 (0.0)
Adjustment disorder with mixed anxiety and depressed mood	1 (0.0)	0 (0.0)

Source: Generated by reviewer using OCS Analysis Studio, Safety Explorer.

I also performed an exploratory analysis of psychiatric TEAEs using FMQs for “Depression” and “Anxiety.” Both of these FMQs, either narrow or broad, suggested a reduction in these events

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in tirzepatide- compared to placebo-treated subjects, with negative risk differences of 0.5-1% that were not significant (the 95% CIs cross 0, Table 89).

Table 89. FMQs for Anxiety and Depression TEAEs (Trials GPHK and GPHL)

FMQ	Scope	TZP All N=2519 n (%)	Placebo N=958 n (%)	Risk Difference RD (95% CI)
Depression	Narrow	44 (1.7)	25 (2.6)	-0.86 (-1.99, 0.27)
	Broad	78 (3.1)	38 (4.0)	-0.87 (-2.28, 0.54)
Anxiety	Narrow	44 (1.7)	26 (2.7)	-0.97 (-2.12, 0.18)
	Broad	73 (2.9)	33 (3.4)	-0.55 (-1.87, 0.78)

Source: Generated by reviewer using JMP Clinical

The Applicant analyzed shifts in PHQ-9 score categories (none, mild, moderate, or moderately severe) to identifying changes in depressive symptoms.⁴⁴ In this analysis, shifts to worsened depression were more common in placebo-treated (21.7%) than tirzepatide-treated (17.7%) subjects; conversely shifts to improved depression were more common in tirzepatide-treated (17.9%) than placebo-treated (13.7%) subjects.

Reviewer comment: Both my FMQ analysis for depression/anxiety and the Applicant's shift analysis of PHQ-9 scores suggest that tirzepatide may improve these conditions. These findings may be consistent with the observed improvements in psychosocial patient-reported outcomes (PROs) described above (Figure 20 and Figure 21, though these endpoints were exploratory and the changes were small and of uncertain clinical meaningfulness).

Psychiatric Disorders Conclusion

In the tirzepatide CWM phase 3 program, and consistent with the T2D program reviewed under NDA 215866, there was no evidence to suggest an increased risk of psychiatric adverse events or suicidal behavior or ideation on tirzepatide. However, since suicidal ideation and behavior is listed as warning for other CWM products (including the GLP-1R agonist semaglutide which also has no apparent risk imbalance in clinical trials), for consistency with the class labeling I believe this warning should be included in Section 5 of the tirzepatide label for CWM.

8.5.10. Hypotension

To identify hypotension-related AEs in trials GPHK and GPHL, the Applicant defined a "Hypotension narrow" cluster including the PTs hypotension, orthostatic hypotension, and blood pressure decreased. These are the same 3 relevant terms that I independently identified in these trials using the narrow FMQ "hypotension." By these 3 terms in the narrow FMQ,

⁴⁴ Applicant ISS addendum, Table ISS.4.44, page 1703 of 2079

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hypotension occurred in 1.6% of tirzepatide- and 0.1% of placebo-treated subjects, with a significant risk difference of 1.5% (Table 90).

Table 90. Hypotension AEs in Trials GPHK and GPHL

	TZP 5mg N=630 n (%)	TZP 10mg N=948 n (%)	TZP 15mg N=941 n (%)	TZP All N=2519 n (%)	Placebo N=958 n (%)	Risk Difference RD (95% CI)
Hypotension (FMQ Narrow)	7 (1.1)	13 (1.4)	20 (2.1)	40 (1.6)	1 (0.1)	1.48 (0.95, 2.01)
Hypotension	4 (0.6)	9 (0.9)	15 (1.6)	28 (1.1)	1 (0.1)	1.01 (0.55, 1.46)
Orthostatic hypotension	3 (0.5)	4 (0.4)	4 (0.4)	11 (0.4)	0	0.44 (0.18, 0.69)
Blood pressure decreased	0	2 (0.2)	1 (0.1)	3 (0.1)	0	0.12 (-0.02, 0.25)
Hypotension (FMQ Broad)	7 (1.1)	22 (2.3)	25 (2.7)	54 (2.1)	2 (0.2)	1.93 (1.30, 2.57)

Reviewer comment: The applicant's "Hypotension_broad" cluster and the broad FMQ for hypotension (Table 90) both included symptomatic terms only potentially related to hypotension (syncope, presyncope, dizziness). I agree that these terms should be considered separately in the label, with dizziness as a distinct common adverse reaction in the table in section 6.1, though it is difficult to distinguish the most common adverse reaction of nausea (see Section 8.4.5 above).

(b) (4)

Dose-dependent hypotensive TEAEs occurred in 2.16% of tirzepatide-treated subjects taking baseline antihypertensive medications, compared to 1.23% of tirzepatide-treated subjects not taking such medications (Table 91). The 21 tirzepatide-treated subjects taking one or more concomitant antihypertensives had 23 hypotension events, of which 15/23 (65%) led to at least one antihypertensive medication being discontinued or dose-reduced.

Table 91. Subjects with Hypotension AEs by Baseline Antihypertensive Medication Use (Trials GPHK and GPHL)

	TZP 5mg N=630 n/N1 (%)	TZP 10mg N=948 n/N1 (%)	TZP 15mg N=941 n/N1 (%)	TZP All N=2519 n/N1 (%)	Placebo N=958 n/N1 (%)
Hypotension Narrow FMQ Events					
Baseline Antihypertensive Use					
Yes	1/196 (0.51)	7/390 (1.79)	13/384 (3.39)	21/970 (2.16)	1/387 (0.26)
No	6/434 (1.38)	6/558 (1.08)	7/557 (1.26)	19/1549 (1.23)	0/571

Source: Adapted by reviewer from Applicant ISS addendum, Table ISS.4.78, page 2068 of 2079

Hypotension TEAEs tended not to recur in the same subjects, as 36 of the 40 (90%) of

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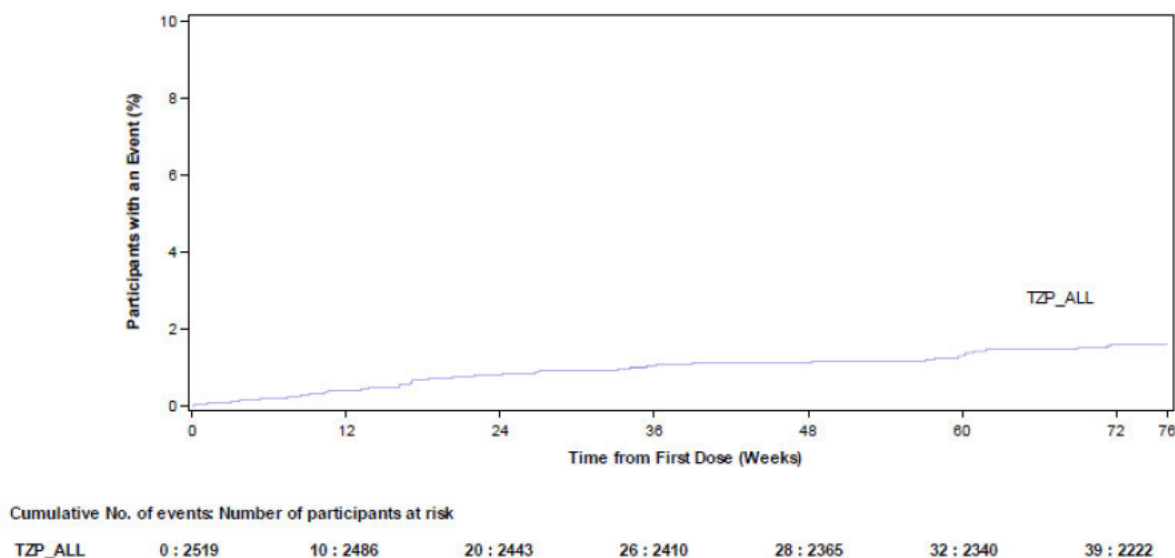
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tirzepatide-treated subjects with hypotensive events had a single event. Four (10%) had two such events, and the second events occurred 244, 201, 306, and 138 days after the initial event.⁴⁵ First occurrences of hypotensive events occurred throughout the treatment period (Figure 40).

Figure 40. Time to First Occurrence of Hypotension Events in Tirzepatide-Treated Subjects (Trials GPHK and GPHL)



Note 1: This cluster "Hypotension narrow" includes 3 preferred terms: Hypotension, Orthostatic hypotension, and Blood pressure decreased.

Note 2: (b) (6) reported a hypotension event after Week 76.

Source: Applicant response to FDA information request

In addition to antihypertensive medications, other TEAEs could be causally associated with hypotension, such as hypovolemia due to GI TEAEs of nausea, vomiting, or diarrhea (as discussed in Section 8.5.3 above for AKI). Four of the 40 (10%) tirzepatide-treated participants with hypotensive event also reported temporally-related hypovolemia and/or AKI TEAEs. The Applicant conducted a manual review to identify potential causes of hypotension events (44 events in 40 tirzepatide-treated subjects). For 33 events (75%), no other relevant (potentially causal AEs) were temporally-associated with hypotension. The other 11 events, all in different subjects, had relevant potentially causal AEs detailed in Table 92. Based on this analysis, six subjects had diarrhea or vomiting as potential contributing causes to hypotension.

⁴⁵ Per the Applicant's response to an FDA information request.

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Table 92. Tirzepatide-Treated Subjects with Hypotension and Relevant Associated AEs (Trials GPHK and GPHL)

Subject ID (b) (6)	Treatment	Preferred Term of AE	Severity/ SAE (Yes/No)	AE Start Day	Outcome	Other Relevant AEs ^a	Action Taken with Study Drug
	TZP 15 mg	Hypotension	Moderate/ Yes	154	Recovered	Reported concurrent TEAEs of dehydration, hypokalemia, renal cyst, and AKI on Study Day 154.	Dose not changed; completed primary study period on study drug
	TZP 10 mg	Hypotension	Severe/ Yes	129	Recovered	Reported TEAE of vomiting on Study Day 116; reported concurrent TEAEs of colitis ulcerative, septic shock, AKI, acute respiratory failure, and hypokalemia on Study Day 129	Dose not changed; completed primary study period on study drug
	TZP 5 mg	Hypotension	Moderate/ No	59	Recovered	Reported concurrent TEAEs of intermittent diarrhea on Study Days 2 to 157, dizziness on Study Day 59.	Dose not changed; completed primary study period on study drug
	TZP 10 mg	Hypotension	Mild/ No	297	Not recovered	Gastrointestinal parasitic infection reported on Study Day 289	Dose not changed; completed primary study period on study drug
	TZP 15 mg	Hypotension	Mild/ No	92	Recovered	Vomiting on Study Day 71-80; AKI on Study Day 92	Dose not changed; completed primary study period on study drug
	TZP 10 mg	Hypotension	Mild/ No	26	Recovered	Renal impairment on Study Day 29	Dose not changed for renal impairment; Discontinued study drug on Study Day 32 due to nausea
	TZP 10 mg	Hypotension	Mild/ No	142	Not recovered	Heat illness reported on Study Day 139	Dose not changed; completed primary study period on study drug
	TZP 5 mg	Orthostatic hypotension	Moderate/ No	52	Recovered	Vomiting reported from Study Days 1 to 86	Dose not changed; completed primary study period on study drug
	TZP 15 mg	Hypotension	Mild/ No	37	Recovered	Reported nausea and vomiting on Study Day 30	Discontinued study drug on Study Day 30 due to nausea
	TZP 10 mg	Hypotension	Moderate/ Yes	499	Recovered	Reported vomiting and diarrhea on Study Day 471 and discontinued study drug due to vomiting on Study Day 474; at time of hypotension, participant was already off TZP for more than 3 weeks	Not applicable
	TZP 10 mg	Hypotension	Moderate/ No	64	Recovered	Reported vomiting on Study Day 64	Dose not changed; completed study on study drug

Abbreviations: AE = adverse event; AKI = acute kidney injury; eCRF = electronic case report form; ID = identification; SAE = severe adverse event;

TEAE = treatment-emergent adverse event; TZP = tirzepatide.

^a As recorded by the investigator on the AE eCRF.

Source: Applicant response to FDA information request

Hypotension Conclusion

Hypotension will be included in Section 6.1 of the label, with a subheading under Common Adverse Reactions, noting the risk factors of concomitant antihypertensive therapy and GI TEAEs leading to dehydration.

8.5.11. Injection Site Reactions

Injection site reactions are common with incretin products administered by SC injection. In the tirzepatide development program, these reactions were identified using predefined MedDRA queries for spontaneous reports with high level terms “injection site reaction,” “administration site reaction,” and “infusion site reaction.” Based on this analysis, more subjects in trials GPHK and GPHL had injection site reactions in tirzepatide (192/2519, 7.62%) than placebo (17/1958, 1.77%) groups, with a dose-effect of tirzepatide (5.71%, 8.33%, and 8.18% for 5, 10, and 15 mg). None of these reactions were serious or graded as severe. Two subjects discontinued tirzepatide due to multiple mild injection site reaction events:

- Subject (b) (6) (TZP 10 mg) had 5 mild events of injection site rash.
- Subject (b) (6) (TZP 15 mg) had 2 mild events of injection site reaction.

The Applicant also solicited qualitative information on injection site reactions using electronic case report forms (eCRFs). Based this analysis,⁴⁶ the Applicant notes that:

- Approximately one-half of tirzepatide-treated participants with injection site reactions experienced at least 2 events.
- Events typically occurred more than 6 hours after drug administration (71.8% of events), with 38.5% of events occurring between 24 hours and 14 days after tirzepatide injection.
- The most common symptoms were erythema and pruritus.
- The overall results as reported on the dedicated injection site reaction eCRF were consistent with the analysis based on the MedDRA search strategy in terms of the nature of events, and were also consistent with the pooled Analysis Set 1 (of placebo-controlled tirzepatide trials) in terms of the timing of reaction and reaction signs and symptoms.

Injection site reactions conclusion

Injection site reactions, including the association with ADA positivity (see Section 8.4.10 on immunogenicity), will be included as a subheading under common reactions in Section 6.1 of the label.

⁴⁶ From ISS addendum Table ISS.4.72-73, page 1891 of 2079

Weight loss by various methods (lifestyle, surgery, medications) is associated with alopecia, or hair loss. Telogen effluvium is thinning or shedding of hair resulting from the early entry of hair in the telogen phase (the resting phase of the hair follicle), which commonly occurs after severe physical, emotional, or metabolic stress, and it has been noted since the 1970s in patients rapidly losing weight by following extreme diets.⁴⁷ There is an extensive literature on hair loss following bariatric surgery,⁴⁸ which may be partially attributed to the stress of surgery and postoperative nutritional deficiencies and rapid weight loss. Hair loss is listed in common adverse reaction tables in the label for the most effective approved CWM drug, semaglutide 2.4 mg weekly (3% of semaglutide- versus 1% of placebo-treated adult subjects, with higher incidence also noted in pediatric subjects [4% versus 0%]).

As detailed in Section 8.4.5 under common adverse reactions, the PT “Alopecia” occurred more often in tirzepatide- (4.7%) than placebo-treated (0.8%) subjects. This PT accounted for 126 of the 128 subjects with hair-loss related TEAEs identified in trials GPHK and GPHL; one subject reported “alopecia areata” (autoimmune hair loss) and another “androgenetic alopecia” (male pattern baldness) and these two PTs are also included in the analyses below. I also reviewed the lower level terms (Table 93) and verbatim-reported terms (Table 94) for these AEs, and “hair loss” and “alopecia” were most common for both, and other events like “hair thinning” or “worsening of alopecia” were rare.

Table 93. Lowest Level Terms for Hair Loss AEs (Trials GPHK and GPHL)

Preferred Term Lowest Level Term	TZP All (N=2519)	Placebo (N=958)
Alopecia		
Alopecia	35 (1.4)	1 (0.1)
Hair loss	79 (3.1)	7 (0.7)
Hair thinning	4 (0.2)	0
Alopecia areata		
Alopecia areata	1 (0.0)	0
Androgenic alopecia		
Androgenic alopecia	1 (0.0)	0

Source: Generated by reviewer.

⁴⁷ Goette DK, Odom RB. Alopecia in Crash Dieters. JAMA. 1976;235(24):2622–2623. doi:10.1001/jama.1976.03260500038026

⁴⁸ Zhang W, Fan M, Wang C, et al. Hair Loss After Metabolic and Bariatric Surgery: A Systematic Review and Meta-analysis. Obes Surg. 2021;31(6):2649-2659. doi:10.1007/s11695-021-05311-2

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Table 94. Reported Terms for Hair Loss AEs (Trials GPHK and GPHL)

Preferred Term Reported Term	TZP All (N=2519)	Placebo (N=958)
Alopecia		
ALOPECIA	34 (1.3)	1 (0.1)
HAIR LOSS	58 (2.3)	3 (0.3)
HAIR LOSS GENERALIZED SCALP	0	1 (0.1)
HAIR LOSS-SCALP	1 (0.0)	0
HAIR LOSS, GENERALIZED	1 (0.0)	0
HAIR THINNING	1 (0.0)	0
HAIRLOSS	2 (0.1)	1 (0.1)
INCREASED HAIR LOSS	2 (0.1)	0
LOSS HAIR	1 (0.0)	0
LOSS OF HAIR	15 (0.6)	1 (0.1)
MILD HAIR LOSS	0	1 (0.1)
THINNING HAIR	3 (0.1)	0
WORSENING OF ALOPECIA	1 (0.0)	0
Alopecia areata		
ALOPECIA AREATA	1 (0.0)	0
Androgenetic alopecia		
ANDROGENIC ALOPECIA	1 (0.0)	0

Source: Generated by reviewer.

Hair loss was more commonly reported in the trial GPHK (SURMOUNT-1, subjects without T2D, with more female subjects) than in trial GPHL (SURMOUNT-2, subjects with T2D, sex-balanced), but the relative risk (tirzepatide vs placebo) of 5-6 fold was consistent across these two trials without any apparent dose-effect of tirzepatide on incidence of hair loss (Table 95).

Table 95. Subjects with Hair Loss by Trial and Sex (Trials GPHK and GPHL)

	TZP 5mg N=630		TZP 10mg N=948		TZP 15mg N=941		TZP All N=2519		Placebo N=958		Relative Risk	
	n/Ns	(%)	n/Ns	(%)	n/Ns	(%)	n/Ns	(%)	n/Ns	(%)	RR	(95% CI)
Any Alopecia, n (%)	33/630	(5.2%)	40/948	(4.2%)	47/941	(5.0%)	120/2519	(4.8%)	8/958	(0.8%)	5.7	(2.8, 11.6)
Trial												
SURMOUNT-1	33/630	(5.2%)	31/636	(4.9%)	36/630	(5.7%)	100/1896	(5.3%)	6/643	(0.9%)	5.7	(2.5, 12.8)
SURMOUNT-2			9/312	(2.9%)	11/311	(3.5%)	20/623	(3.2%)	2/315	(0.6%)	5.1	(1.2, 21.5)
Sex												
Female	31/426	(7.3%)	40/585	(6.8%)	44/584	(7.5%)	115/1595	(7.2%)	8/595	(1.3%)	5.4	(2.6, 10.9)
Male	2/204	(1.0%)	0/363	(0.0%)	3/357	(0.8%)	5/924	(0.5%)	0/363	(0.0%)	3.9	(0.2, 71.8)

Notably, hair loss was reported almost exclusively in female trials subject (123/128 subjects with hair loss events, 96%), and 7.2% of tirzepatide-treated females reported hair loss

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compared to 1.3% of placebo-treated females. Therefore, I analyzed the incidence of hair loss in different demographic subgroups of only female trial subjects (Table 96). The incidence of hair loss (~7%) and relative risk (~5-fold higher with tirzepatide than placebo) in females were consistent across subgroups by trial (i.e., the overall difference between trials GPHK and GPHL was due to different sex ratios), age, race, ethnicity, country, and comorbidity, with two exceptions:

- The incidence of hair loss reports was notably higher in females at trial sites in Brazil (22.8% of tirzepatide- versus 4.8% of placebo-treated subjects), though the relative risk was consistent with other countries at 4.8-fold.
- The relative risk of hair loss appeared higher (at around 10-fold) in female subjects with anxiety/depression or osteoarthritis at baseline.

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Table 96. Female subjects with alopecia by demographic subgroups (Trials GPHK and GPHL)

	TZP All N=1595		Placebo N=595		Relative Risk	
	n/Ns	(%)	n/Ns	(%)	RR	(95% CI)
Any Alopecia, n (%)	115/1595	(7.2%)	8/595	(1.3%)	5.4	(2.6, 10.9)
Trial						
GPHK/SURMOUNT-1	95/1278	(7.4%)	6/436	(1.4%)	5.4	(2.4, 12.2)
GPHL/SURMOUNT-2	20/317	(6.3%)	2/159	(1.3%)	5.0	(1.2, 21.2)
Age Group, years						
18-39	31/452	(6.9%)	2/173	(1.2%)	5.9	(1.4, 24.5)
40-64	74/994	(7.4%)	5/369	(1.4%)	5.5	(2.2, 13.5)
≥65	10/149	(6.7%)	1/53	(1.9%)	3.6	(0.5, 27.1)
Race						
White	88/1193	(7.4%)	6/453	(1.3%)	5.6	(2.5, 12.6)
Asian	9/111	(8.1%)	0/42	(0.0%)	6.9	(0.4, 116.3)
Black / African American	8/146	(5.5%)	1/55	(1.8%)	3.0	(0.4, 23.5)
American Indian / Alaskan Native	4/173	(2.3%)	0/58	(0.0%)	2.7	(0.1, 50.4)
Ethnicity						
Hispanic or Latino	59/822	(7.2%)	5/319	(1.6%)	4.6	(1.9, 11.3)
Not Hispanic or Latino	55/698	(7.9%)	3/249	(1.2%)	6.5	(2.1, 20.7)
Country						
U.S. (incl. Puerto Rico)	46/730	(6.3%)	4/266	(1.5%)	4.2	(1.5, 11.5)
Argentina	12/297	(4.0%)	1/121	(0.8%)	4.9	(0.6, 37.2)
Mexico	9/219	(4.1%)	0/73	(0.0%)	6.0	(0.4, 102.9)
Brazil	39/171	(22.8%)	3/63	(4.8%)	4.8	(1.5, 14.9)
Russia	3/79	(3.8%)	0/35	(0.0%)	2.7	(0.1, 52.4)
China, India, Japan, Taiwan	6/99	(6.1%)	0/37	(0.0%)	4.5	(0.3, 79.4)
Comorbidity						
Hypertension	36/579	(6.2%)	3/219	(1.4%)	4.5	(1.4, 14.6)
Dyslipidemia	41/535	(7.7%)	3/204	(1.5%)	5.2	(1.6, 16.6)
Anxiety/Depression	31/298	(10.4%)	1/97	(1.0%)	10.1	(1.4, 72.9)
Osteoarthritis	26/247	(10.5%)	1/100	(1.0%)	10.5	(1.4, 76.5)
Asthma/COPD	12/171	(7.0%)	3/85	(3.5%)	2.0	(0.6, 6.9)
NAFLD	12/114	(10.5%)	1/47	(2.1%)	4.9	(0.7, 37.0)
Obstructive Sleep Apnea	8/86	(9.3%)	1/36	(2.8%)	3.3	(0.4, 25.8)

Source: Generated by reviewer in OCS analysis studio using adsl.xpt and adae.xpt datasets.

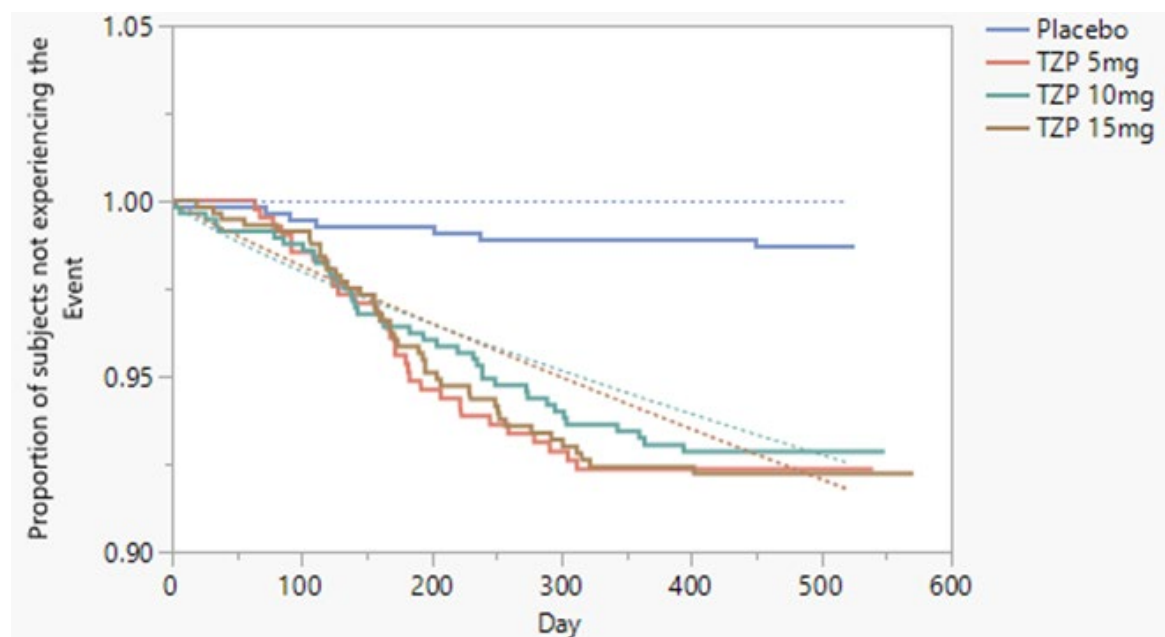
It is also relevant to labeling whether reported hair loss AEs were considered severe, led to changes in study drug, or resolved over time. In the 120 tirzepatide-treated subjects reporting

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hair loss TEAEs:

- 95 (79.2%) were reported as mild, 25 (20.8%) as moderate, and none as severe.
- One subject (0.8%) interrupted treatment, and none discontinued treatment due to hair loss. (One placebo-treated subject discontinued treatment due to hair loss).
- By the end of the trial, 62 (51.7%) were reported as recovered, 19 (15.8%) as recovering, 38 (32.5%) as not recovered, and one (0.8%) as unknown. The Applicant notes that the trial duration may have been too short to fully capture the recovery from telogen effluvium events, and I concur.

I performed a time-to-event analysis of hair loss AEs in female trial subjects (Figure 41), confirming a lack of dose-effect. This analysis also showed a divergence of the tirzepatide and placebo curves at around Day 100, and a plateau around Day 300 (when the planned treatment period of 72 weeks continued for about 200 more days).

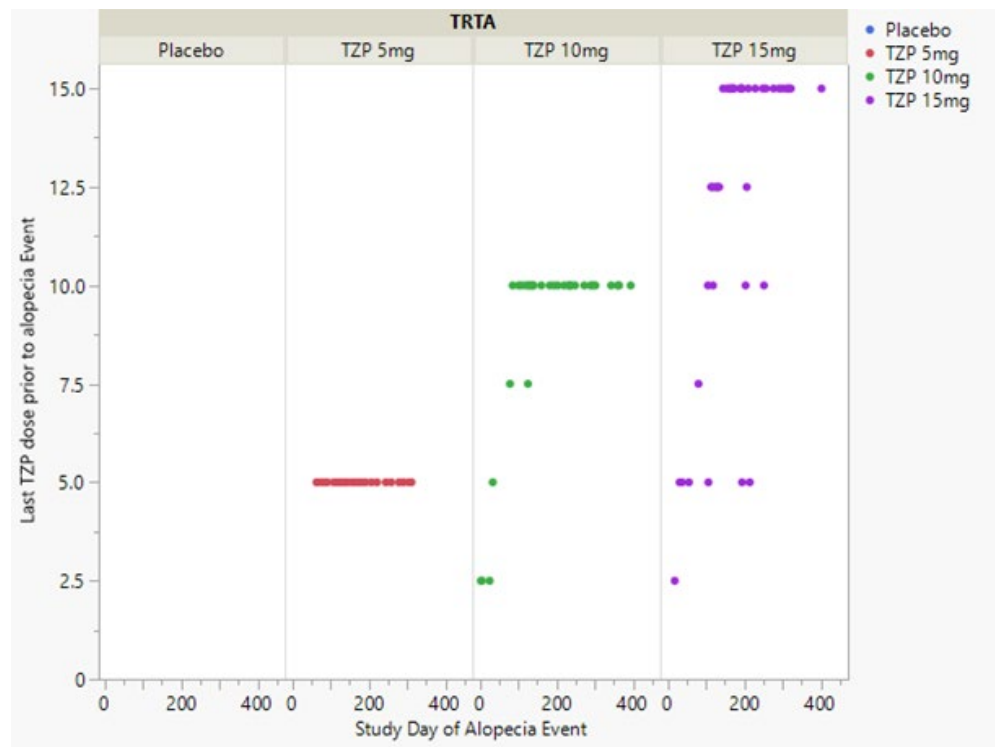
Figure 41. Time to Hair Loss TEAEs in Female Subjects (Trials GPHK and GPHL)



Source: Generated by reviewer in JMP clinical, Adverse Events Time to Event analysis

For all subjects (female or male) with hair loss events, the mean ($\pm$ SD) start for alopecia AEs in tirzepatide-treated subjects was Day 179.3 ($\pm$ 86.4), with 102/120 (85%) first reporting alopecia on Day 100 or later. I analyzed the last tirzepatide doses prior to alopecia events (Figure 42), showing that 94/120 (78%) tirzepatide-treated subjects had reached their trial arm's maintenance dose when hair loss was reported.

Figure 42. Last Tirzepatide Doses Prior to Hair Loss TEAEs (Trials GPHK and GPHL)



Source: Generated by reviewer in JMP using adae.xpt

For each subject (female or male) reporting hair loss, I identified the body weight measurement from the study visit nearest before or after the AE report (Figure 43). Overall, 98/120 (81.6%) subjects with hair loss had lost $\geq 10\%$ of their body weight near the time hair loss was first reported, with a mean weight loss of -15.1%, -16.5%, and -18.3% with tirzepatide 5, 10, and 15 mg (compared to 2.2% with placebo near the time of hair loss).

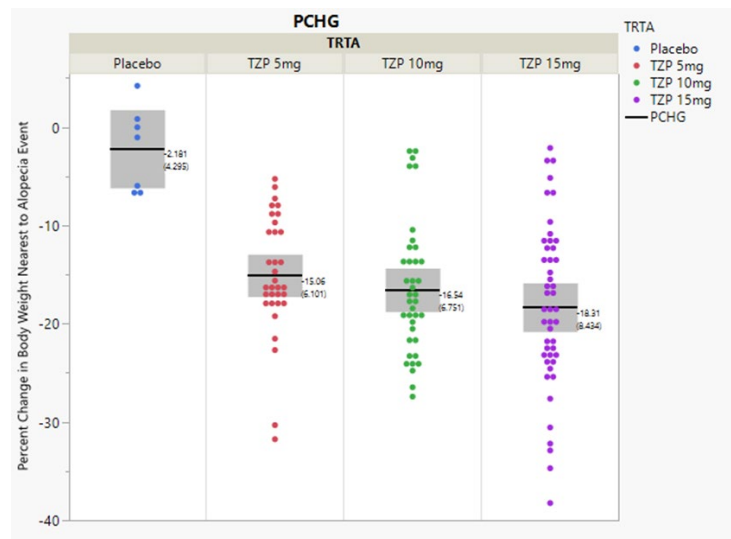
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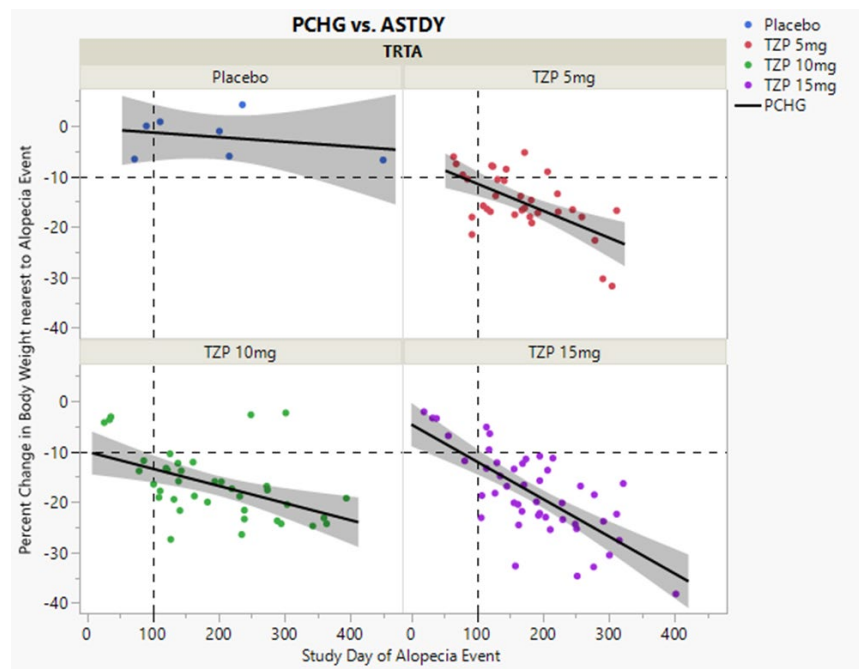
Figure 43. Percent Change in Body Weight Nearest the Time of Hair Loss TEAE reports (Trials GPHK and GPHL)



Source: Generated by reviewer using JMP

In subjects reporting hair loss, percent weight loss was correlated with study Day as expected, and the large majority of tirzepatide-treated subjects first reported alopecia after study Day 100 and with $\geq 10\%$ weight loss (dotted lines in Figure 44).

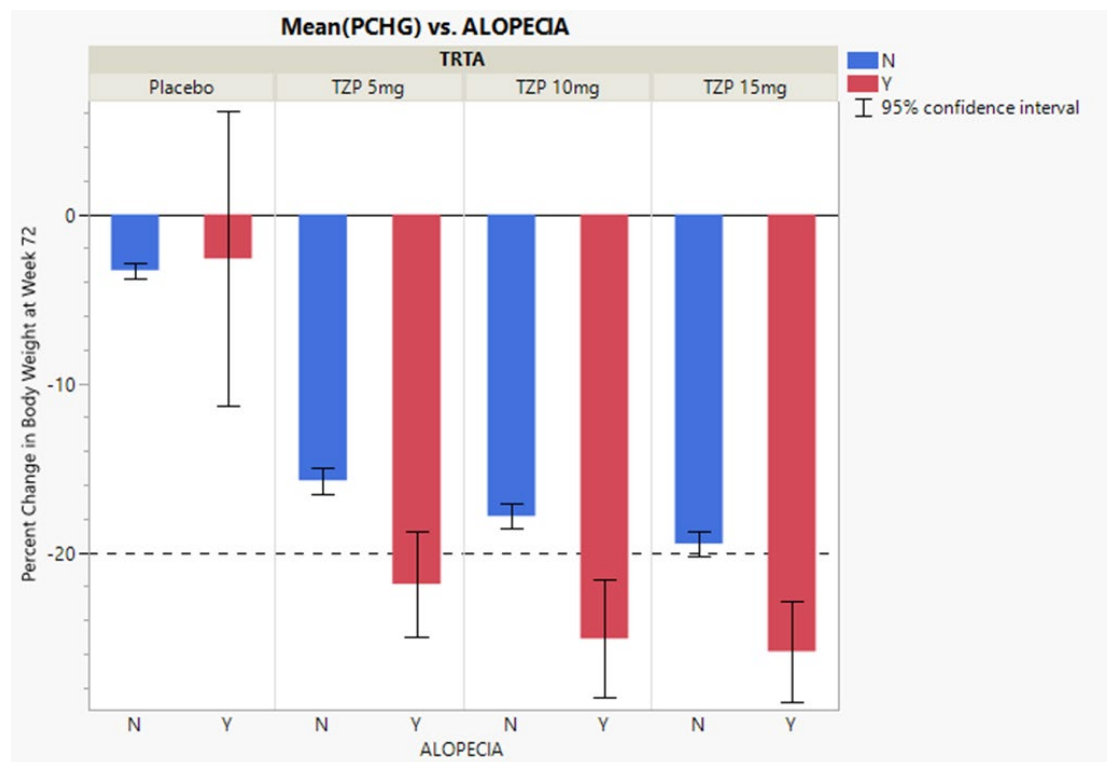
Figure 44. Percent Weight Loss Versus Study Day at First Report of Hair Loss TEAE (Trials GPHK and GPHL)



Source: Generated by reviewer using JMP

Finally, I analyzed weight loss at the end of treatment (Week 72) in subjects reporting hair loss during the trial compared to those not reporting hair loss (Figure 45). At each tirzepatide dose, subjects reporting a hair loss AE had an absolute >6% greater mean weight loss at Week 72 versus those not reporting hair loss: -21.8% vs -15.7% for tirzepatide 5 mg, -25.1% vs -17.9% for tirzepatide 10 mg, and -25.8% vs -19.5% for tirzepatide 15 mg (all significant differences based on non-overlapping 95% CIs). The few placebo-treated subject reporting hair loss had -2.6% mean weight loss compared to -3.3% in those not reporting hair loss.

Figure 45. Percent Change in Body Weight at Week 72 in Subjects Reporting Hair Loss (Trials GPHK and GPHL)



Source: Generated by reviewer using JMP

Reviewer comment: As noted above, substantial or rapid weight loss by various methods can increase the risk of hair loss, and it is unknown whether tirzepatide further increases this risk by weight-independent mechanisms.

Alopecia AEs were rarely observed in the development of tirzepatide for T2D. I queried the Applicant's pooled analysis set 4 (all comparator-controlled trials) eliminating trial GPHK (SURMOUNT-1) for CWM, leaving data from all subjects (regardless of BMI) in phase 2 trials GPHB and GPGF, SURPASS trials 1-5, and SURPASS-J Mono. Hair loss AEs were reported in

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<0.5% of all subjects and <1.0% of females in T2D trials (Table 97, note the results are not corrected for trial duration and exposure).

Table 97. Incidence of Hair Loss in Tirzepatide Comparator-Controlled T2D trials

	TZP All	Placebo	Semaglutide	Dulaglutide	Insulin
Subjects with Alopecia Events	n/N1 (%)	n/N1 (%)	n/N1 (%)	n/N1 (%)	n/N1 (%)
All subjects	19/5659 (0.34)	0/312	3/469 (0.63)	0/223	1/1580 (0.06)
Female subjects	16/2492 (0.64)	0/149	3/244 (1.23)	0/72	1/613 (0.16)

Source: Generated by review from Applicants pooled dataset adsl.xpt and adsl.xpt

Reviewer comment: This is consistent with the review of tirzepatide for T2D under NDA 215866, which did not identify hair loss as a common adverse reaction. Even without correction for trial duration, the much lower incidence of hair loss TEAE reports in tirzepatide T2D trials compared to CWM trials (including trial GPHL in subjects with diabetes) is surprising. Even a T2D trial duration of 40 weeks (280 days) covers the typical period of rapid weight loss and hair loss TEAE reporting noted above.

Hair loss conclusion

The Applicant proposed including “Hair Loss” in the label Section 6.1 table of common adverse reactions, and I concur. My analysis above showed markedly sex-imbalanced reporting of hair loss in CWM trials GPHK and GPHL, and the clear positive correlation of hair loss with degree of weight loss. I believe this information would be useful to prescribers and justifies a dedicated sub-header and paragraph in Section 6.1 addressing these higher risk subgroups.

8.5.13. Cardiovascular Safety

Some cardiovascular effects of tirzepatide are considered elsewhere in this review:

- Effects on blood pressure are considered for efficacy in Section 6.1.2.
- Effects of tirzepatide on pulse, ECG findings, and arrhythmia risk are reviewed in sections 8.4.7 and 8.4.8.
- Hypotension safety is reviewed in Section 8.5.10 above.
- Cardiovascular deaths are described in Section 8.4.1.

This section will focus on MACE, which were CEC-adjudicated in trials GPHK and GPHL. Overall, MACE occurred in 16 (0.64%) tirzepatide- and 9 (0.94%) placebo-treated subjects (Table 98).

Table 98. CEC-adjudicated MACE (Trials GPHK and GPHL)

	Placebo N=958 n (%)	TEP 5mg N=630 n (%)	TEP 10mg N=948 n (%)	TEP 15mg N=941 n (%)	TEP_ALL N=2519 n (%)
Confirmed by Clinical Endpoint Committee					
MACE	9 (0.94)	4 (0.63)	9 (0.95)	3 (0.32)	16 (0.64)
Death Due to CV Cause	3 (0.31)	1 (0.16)	2 (0.21)	0	3 (0.12)
MI	1 (0.10)	1 (0.16)	2 (0.21)	0	3 (0.12)
Hospitalization for Unstable Angina	1 (0.10)	0	1 (0.11)	1 (0.11)	2 (0.08)
Hospitalization for Heart Failure	1 (0.10)	0	0	0	0
Coronary Interventions	3 (0.31)	0	3 (0.32)	2 (0.21)	5 (0.20)
CABG	0	0	0	0	0
PCI	3 (0.31)	0	3 (0.32)	2 (0.21)	5 (0.20)
Cerebrovascular Events	3 (0.31)	2 (0.32)	4 (0.42)	1 (0.11)	7 (0.28)
Stroke	1 (0.10)	2 (0.32)	3 (0.32)	1 (0.11)	6 (0.24)
TIA	2 (0.21)	0	1 (0.11)	0	1 (0.04)

Source: Applicant ISS addendum

MACE events were more common in trial GPHL (SURMOUNT-2, 1.12% with tirzepatide and 1.27% with placebo), which enrolled T2D trial population that was older with more other CV risk factors than in trial GPHK (SURMOUNT-1, 0.47% with tirzepatide and 0.78% with placebo). I reviewed case narratives for MACE, and these did not raise safety concerns for tirzepatide. These CWM trials (as well as T2D trials reviewed under NDA 215866) showed a trend towards numerically fewer MACE events in tirzepatide-treated subjects, and the Applicant is conducting phase 3b CVOTs in the T2D and CWM programs to test the hypothesis that tirzepatide reduces risk of MACE events in high-risk populations.

8.5.14. Liver Safety

Trials GPHK and GPHL excluded subjects with:

- acute or chronic hepatitis
- signs and symptoms of any liver disease other than NAFLD
- ALT >3×ULN
- Alkaline phosphatase (ALP) >1.5×ULN
- Total bilirubin (TBL) >1.2×ULN (except for cases of known Gilbert’s syndrome).

The Applicant identified hepatic TEAEs using a MedDRA SMQ approach. Overall, hepatic TEAEs were balanced between tirzepatide (1.95%) and placebo (2.09%) arms.⁴⁹ This agrees with my FMQ analysis for “Hepatic injury” (Table 99).

⁴⁹ Applicant ISS Addendum, Table 1SS.4.31, page 1456 of 2079

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Table 99. FMQ for Liver Injury TEAEs (Trials GPHK and GPHL)

	TZP 5mg N=630 n (%)	TZP 10mg N=948 n (%)	TZP 15mg N=941 n (%)	TZP All N=2519 n (%)	Placebo N=958 n (%)	Risk Difference RD (95% CI)
Hepatic Injury (FMQ Narrow)	5 (0.8)	9 (0.9)	9 (1.0)	23 (0.9)	9 (0.9)	-0.03 (-0.74, 0.69)
Hepatic Injury (FMQ Broad)	15 (2.4)	21 (2.2)	18 (1.9)	54 (2.1)	22 (2.3)	-0.15 (-1.26, 0.95)

Source: Generated by Applicant using JMP Clinical, FMQ Reports

Review of individual PTs for hepatic injury AEs was not informative, as these were a combination of clinical diagnoses (like “hepatic steatosis”) and laboratory abnormalities (“transaminase increased”) often co-occurring in the same subjects. Therefore, this review focuses on those subjects with severe and serious hepatic events and extreme laboratory abnormalities, in order to identify potential cases of DILI.

Six tirzepatide- (0.24%) and no placebo-treated subjects reported severe and/or serious hepatic adverse events:

- There was one serious event:
 - Subject (b) (6) was the 45-year-old female randomized to tirzepatide 5 mg with the serious fatal AE of hepatic failure. Her death from hepatic and multiorgan failure in the setting of substance abuse and COVID-19 positivity is described in Section 8.4.1.
- One severe event led to study drug discontinuation:
 - Subject (b) (6) was a 42-year-old female randomized to tirzepatide 10 mg who had the severe AE “liver function test increased.” Her baseline ALT and AST were normal but were elevated to 482 (ALT >16x ULN) and 190 U/L, respectively on study Day 85 when she received her last dose of study drug. She underwent a comprehensive liver evaluation which identified positive antinuclear antibodies (1:40 titer in a speckled pattern). While systemic lupus erythematosus (SLE) often manifests as abnormal liver enzymes, no final diagnosis was reported. On study Day 225, last available results showed all liver laboratory tests in the normal range.
- Three severe events were isolated enzyme elevations that returned to normal without study drug discontinuation:
 - (b) (6) was a potential Hy’s Law case described below, with DILI ruled out due to a clear alternate etiology.
 - Subject (b) (6) (tirzepatide 10 mg) who had elevations in ALT (434 IU/L), AST (not reported), and ALP (231 IU/L) on study Day 85. At baseline, ALT and AST were normal and ALP was mildly elevated (138 IU/L, ULN 129), and on Day 92, ALT and ALP were normal, and AST was mildly elevated (52 IU/L, ULN 40). Study drug was interrupted for one week, with dosing on Day 85 and resuming on Day 92. All hepatic labs were normal on study drug on study Days

167, 253, 334, 421, and 505.

- Subject (b) (6) (tirzepatide 10 mg) had an isolated elevation in ALT. On Study Day 421, ALT was 197 U/L (4×ULN), but on retest 8 days later, ALT was within normal limits. The subject had normal hepatic lab values for the remainder of the study and completed the trial on study drug.
- One subject had a severe event transaminase elevation noted during safety follow-up over one year after discontinuing study drug:
 - Subject (b) (6) (tirzepatide 10 mg) had ALT and AST values within normal range at baseline, with only slight fluctuations in AST not exceeding 48 U/L during the treatment period. On Day 541, at the safety follow-up visit and more than one year after last dose of study drug, ALT was 264 U/L (5×ULN) and AST was 437 U/L (10×ULN), in the setting of a serious adverse event of acute kidney injury (see Section 5.5.3).

The Applicant also analyzed trial subjects with elevated maximum post-baseline values in liver blood tests above defined thresholds (Table 100). Such shifts were rare, but some shifts were numerically imbalanced occurring more in tirzepatide- than placebo-treated subjects.

Table 100. Maximum Postbaseline Shifts in Liver Blood Tests (Trials GPHK and GPHL)

	TZP All N1=2476 n (%)	Placebo N1=935 n (%)
ALT		
≥3x ULN	31 (1.3)	14 (1.5)
≥5x ULN	11 (0.4)	4 (0.4)
≥10x ULN	6 (0.2)	1 (0.1)
AST		
≥3x ULN	21 (0.8)	5 (0.5)
≥5x ULN	13 (0.5)	1 (0.1)
≥10x ULN	6 (0.2)	0
Total bilirubin		
≥2x ULN	11 (0.4)	1 (0.1)
Alkaline phosphatase		
≥2x ULN	8 (0.3)	0

Source: Generated by reviewer from Applicant ISS addendum, Tables ISS.4.33-34, page 1464 of 2079

The Applicant provided cases narratives for all subjects with elevations in ALT and/or AST ≥5x ULN. I reviewed these and summarize below the 9 tirzepatide-treated subjects with identified post-baseline ALT and/or AST ≥10x ULN (0.36%, compared to 0.10% in placebo-treated subjects):

- Two subjects had potential Hy's Law cases (DILI ruled out) described further below:

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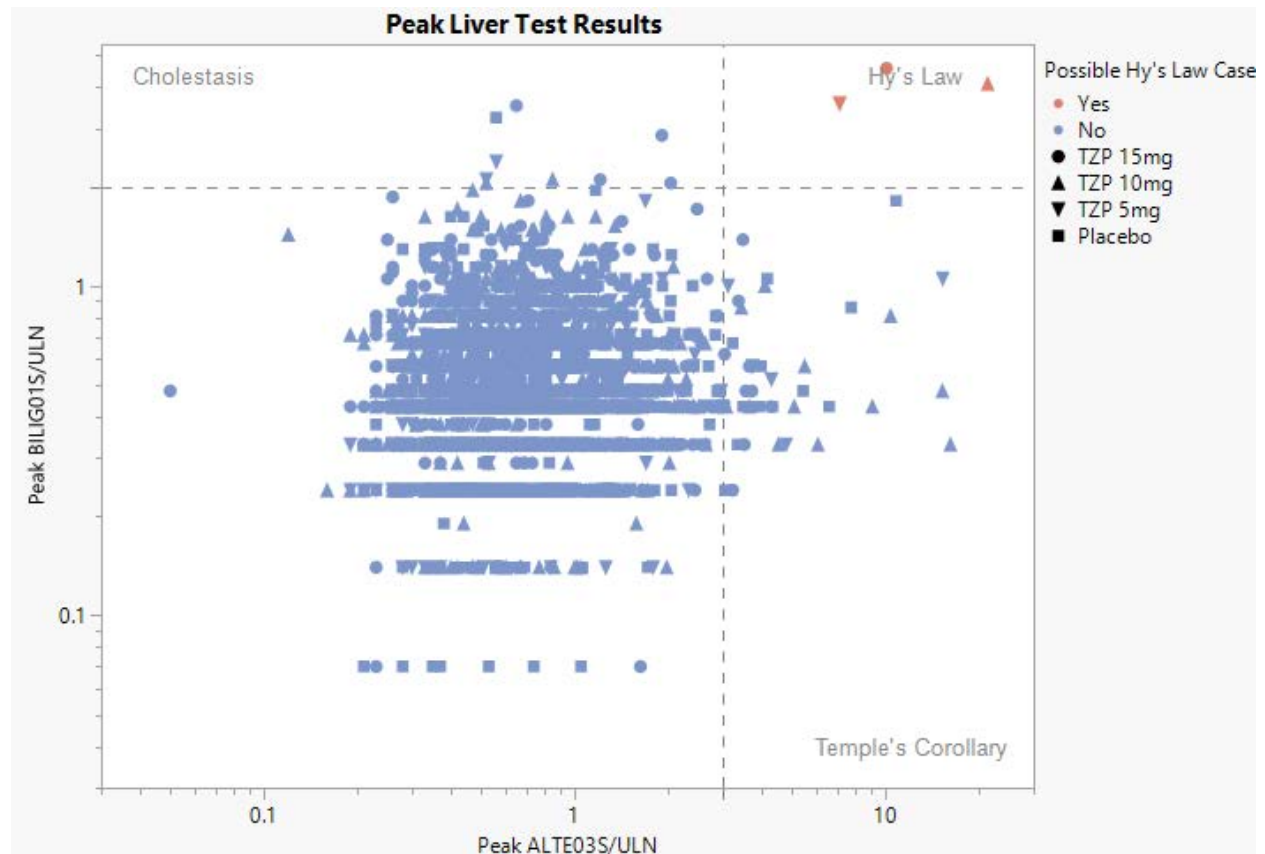
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- (b) (6)
- (b) (6)
- Two subjects had transaminase elevation AEs graded as severe and described above:
 - Subject (b) (6) (tirzepatide 10 mg) discontinued study drug with subsequent liver enzyme normalization.
 - Subject (b) (6) (tirzepatide 10 mg) had elevated transaminases noted more than a year after study drug discontinuation.
- One subject had isolated transaminase elevations that returned to normal without study drug discontinuation:
 - Subject (b) (6) (tirzepatide 10 mg) had isolated Day 84 elevations of ALT and AST to 656 and 606 IU/L, respectively. These were potentially spurious since all other liver chemistries were normal before and after, and there was no interruption of study drug.
- Two subjects had elevated transaminases attributable to gallstone-related events (see Section 5.5.4), making DILI unlikely:
 - Subject (b) (6) (tirzepatide 5 mg) had Day 54 elevations of ALT and AST to 658 and 246 IU/L, respectively, in the setting of a cholelithiasis AE. Study drug was interrupted after Day 78 prior to elective lap cholecystectomy surgery on Day 84, which was complicated by acute pancreatitis on Days 88-95. By study Day 112, liver blood tests returned to normal and study drug was resumed on Day 117.
 - Subject (b) (6) (tirzepatide 10 mg) had Day 337 elevations of ALT and AST to 447 and 288 IU/L, respectively, in the setting of a cholelithiasis AE. Study drug was interrupted on Day 351, on Day 370 the subject had cholecystitis and cholecystectomy. Transaminases declined towards normal and study drug was resumed on Day 395.
- Two subjects had on ALT elevations $\geq 10 \times$ ULN, both with a likely source from muscle rather than liver as events occurred in the setting of extreme exercise and creatine kinase elevations:
 - Subject (b) (6) (tirzepatide 5 mg) on Day 338 had AST $\geq 10 \times$ ULN and marked CK elevation (29,745 U/L) in setting on new vigorous gym exercise, and AST normalized 8 days later.
 - Subject (b) (6) (tirzepatide 15 mg) completed study drug treatment on Day 498, and at safety follow-up of Day 533 was noted to have AST 575 and ALT 175 IU/L with marked CK elevation (34,257 U/L) in setting on new intense exercise with personal trainer since end of treatment to maintain weight loss.

Transaminase elevations are more concerning for DILI if associated with elevations in TBL. For evaluation of drug-induced serious hepatotoxicity (eDISH), the Applicant generated eDISH plots to identify 3 possible Hy's law cases (all in tirzepatide-treated subjects in trial GPHK). I conducted two similar analyses of the Applicant's laboratory data from trials GPHK and GPHL (using JMP clinical in Figure 46 below, and OCS Analysis Studio's Hepatic Explorer [not shown]),

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both confirming the Applicant's results.

Figure 46. Hy's Law eDISH Screening for Drug-Induced Liver Injury (Trials GPHK and GPHL)



Source: Generated by reviewer using JMP clinical, Hy's Law Screening

Note: Possible Hy's Law cases are flagged "Yes" if ALT or AST $\geq 3 \times$ ULN and total bilirubin $\geq 2 \times$ ULN within 0 days of ALT/AST elevation.

The Applicant states that these three potential Hy's Law cases do not meet criteria for DILI due to clear alternate etiologies, and I concur. The three cases all have alternative possible non-DILI etiologies for the abnormal liver chemistry results:

- Subject (b) (6) was a 27-year-old male randomized to tirzepatide 5 mg, whose elevated liver enzymes were confounded by concomitant use of albendazole (an anthelmintic drug known to cause elevations in liver enzymes⁵⁰) and returned to normal

⁵⁰ Albendazole prescribing information includes a Section 5 Warning and Precaution on hepatic effects: "In clinical trials, treatment with albendazole has been associated with mild to moderate elevations of hepatic enzymes in approximately 16% of patients. These elevations have generally returned to normal upon discontinuation of therapy. There have also been case reports of acute liver failure of uncertain causality and hepatitis. Monitor liver

after albendazole was discontinued, such that study drug was resumed. He reported right upper quadrant abdominal pain from Study Days 250 through 252, while taking albendazole from Study Days 250 through 255. On Study Day 253, an isolated elevation of ALT activity was observed, followed by elevation of multiple liver enzymes, including ALT, AST, ALP, gamma glutamyl transferase, and TBL, between Days 278 and 284. On Day 278, ALT was 335 U/L, AST was 433 U/L, and total bilirubin was 0.7 mg/dL. On Day 284, laboratory tests revealed ALT elevated $>3\times$ ULN and TBL increased $>3\times$ ULN. On Day 281, he was diagnosed with cholecystitis, cholelithiasis, and hepatic steatosis, which were all reported to be ongoing upon study completion. Liver enzyme activity, including ALT, AST, ALP, and total bilirubin, returned to normal at the next laboratory testing, on Day 337. No further increase in any liver enzyme and bilirubin was observed from Day 337 through the end of the treatment period (Day 539). Study drug was temporarily interrupted from Day 253 and then reinitiated on Day 344. The subject completed the treatment period on study drug.

- Subject (b) (6) (tirzepatide 15 mg) was 47-year-old female whose liver chemistry abnormalities were attributable to acute gallbladder disease (see Section 8.5.4) and returned to normal after endoscopic and surgical treatment, such that study drug was resumed. Her baseline weight was 100.3 kg, and on Day 169 she had achieved a weight loss of 18.6 kg. On Day 227 she last received study drug prior to interruption, on Day 236 she had the serious AE of choledocholithiasis with biliary duct obstruction (based on CT and MRCP), on Day 238 she was treated by endoscopic retrograde cholangiopancreatography (ERCP), on Day 276 she had a cholecystectomy, on Day 298 study drug was resumed, and on Day 337 liver testing had returned to normal.
- Subject (b) (6) (tirzepatide 10 mg) was a 55-year-old male whose liver chemistry abnormalities were attributable to Hepatitis B, which resulted in study drug discontinuation. On Day 421, his ALT and AST were $\geq 10\times$ ULN and TBL was 2.11 mg/dl in the setting of the AE Hepatitis B, and study drug was discontinued. He last received study drug on Day 422, and on Day 511 his ALT and AST remained mildly elevated (90 and 80 IU/L, respectively) with normal TBL.

Liver laboratory value profiles are shown in Figure 47 for these 3 potential Hy's law cases.

enzymes (transaminases) before the start of each treatment cycle and at least every 2 weeks during treatment. If hepatic enzymes exceed twice the upper limit of normal, consideration should be given to discontinuing albendazole therapy based on individual patient circumstances. Restarting albendazole treatment in patients whose hepatic enzymes have normalized off treatment is an individual decision that should take into account the risk/benefit of further albendazole tablets usage. Perform laboratory tests frequently if albendazole treatment is restarted. Patients with elevated liver enzyme test results are at increased risk for hepatotoxicity and bone marrow suppression. Discontinue therapy if liver enzymes are significantly increased or if clinically significant decreases in blood cell counts occur."

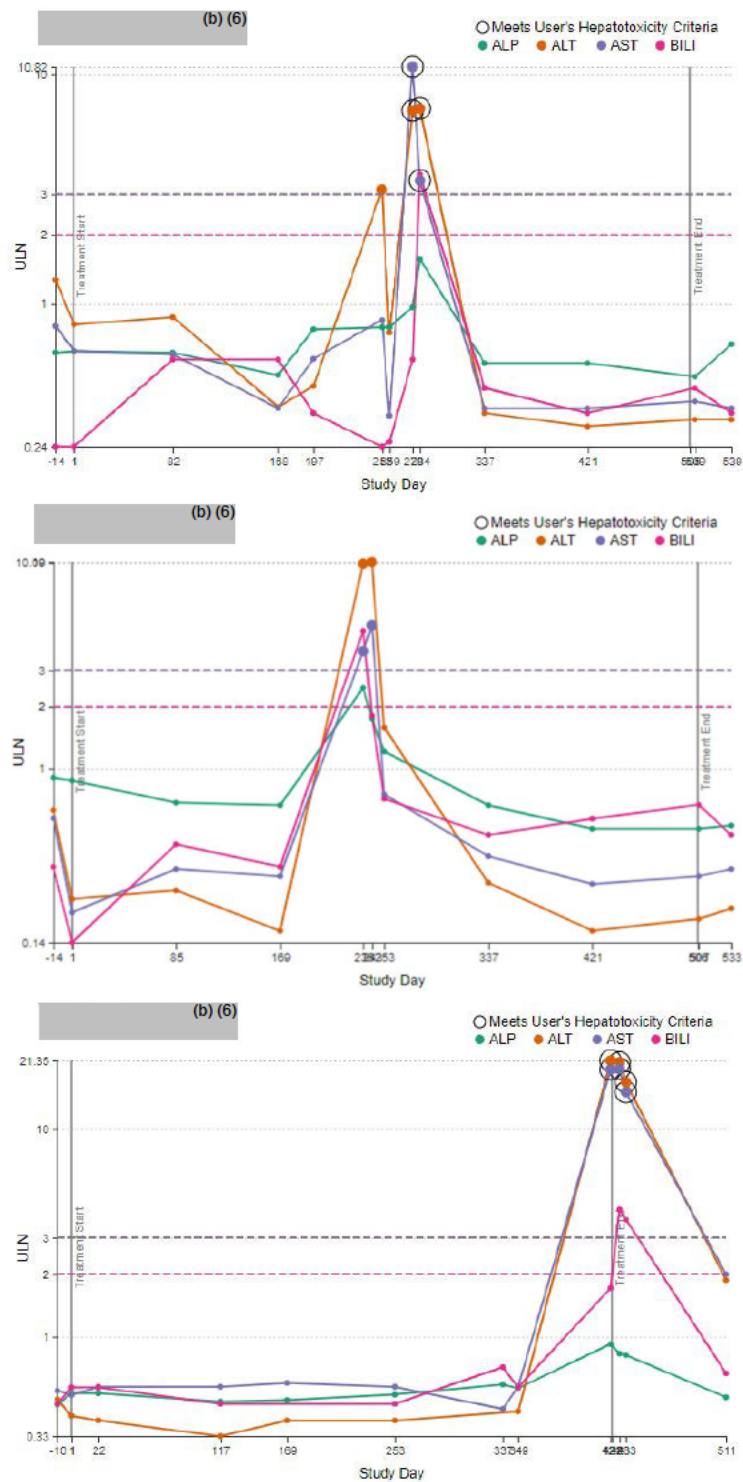
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Figure 47. Liver Blood Test Profiles Over Time in 3 Potential Hy's Law Cases (Trial GPHK)



Source: Generated by reviewer using OCS Analysis Studio, Hepatic Explorer

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No potential Hy's law cases have been identified to date in the development of tirzepatide in subjects with T2D, including CWM trial GPHL, the SURPASS trials reviewed under NDA 215866, and trials completed since then and reviewed in the 120-day safety update.

Shifts and Changes in Transaminases

The Applicant notes that there were statistically-significant decreases in mean transaminase values for tirzepatide groups compared to placebo groups in trials GPHK and GPHL.⁵¹ For instance, Table 101 summarizes these data at end of treatment (Week 72) and safety follow-up (SFU) in trial GPHK. In tirzepatide-treated subjects, there were up to 30.3% declines in mean ALT and 14.2% declines in mean AST in subjects randomized to tirzepatide 15 mg (still significant at 12.3% and 3.9%, respectively, when placebo-corrected).

Table 101. Hepatic Enzyme Profiles at Week 72 and Safety Follow-up Compared to Baseline (Trial GPHK)

Parameter	Placebo (N = 643)		TZP 5 mg (N = 630)		TZP 10 mg (N = 636)		TZP 15 mg (N = 630)	
	72 weeks	SFU	72 weeks	SFU	72 weeks	SFU	72 weeks	SFU
ALT								
Baseline (IU/L)	23.5		23.1		23.5		23.6	
Change from baseline (IU/L)	-3.0	-2.8	-6.0	-2.9	-6.6	-2.5	-7.1	-2.9
Percent change from baseline (%)	-12.8 ^{†††}	-12.1 ^{†††}	-25.7 ^{†††}	-12.5 ^{†††}	-28.1 ^{†††}	-10.7 ^{†††}	-30.3 ^{†††}	-12.3 ^{†††}
Placebo adjusted change difference (%) (95% CI)	N/A	N/A	-14.9 ^{***} (-19.2, -10.3)	-0.5 (-7.3, 6.9)	-17.6 ^{***} (-21.8, -13.1)	1.5 (-5.6, 9.1)	-20.2 ^{***} (-24.2, -15.8)	-0.3 (-7.2, 7.0)
AST								
Baseline (IU/L)	20.6		20.3		20.6		20.8	
Change from baseline (IU/L)	-1.4	-1.2	-2.4	-1.3	-2.5	-0.5	-2.9	-0.8
Percent change from baseline (%)	-6.6 ^{†††}	-5.9 ^{†††}	-11.4 ^{†††}	-6.4 ^{†††}	-12.1 ^{†††}	-2.3	-14.2 ^{†††}	-3.9 [†]
Placebo adjusted change difference (%) (95% CI)	N/A	N/A	-5.2 ^{**} (-8.5, -1.8)	-0.5 (-5.2, 4.6)	-6.0 ^{***} (-9.2, -2.5)	3.8 (-1.2, 9.1)	-8.2 ^{***} (-11.4, -4.8)	2.1 (-2.8, 7.3)

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CI = confidence interval; mITT = modified intent-to-treat; MMRM = mixed model for repeated measures; N = number of participants who were randomly assigned, received at least 1 dose of study drug, and had baseline and postbaseline values at the specified time point; N/A = not applicable; SFU = safety follow-up; TZP = tirzepatide.

Note 1: MMRM analysis with log-transformed data.

Note 2: Estimated means are shown.

*p-Value <0.05, **p-value <0.01, ***p-value <0.001 versus placebo.

†p-Value <0.05, ††p-value <0.001 versus baseline.

Source: Applicant CSR for trial GPHK, Table GPHK.5.54, page 280 of 3021

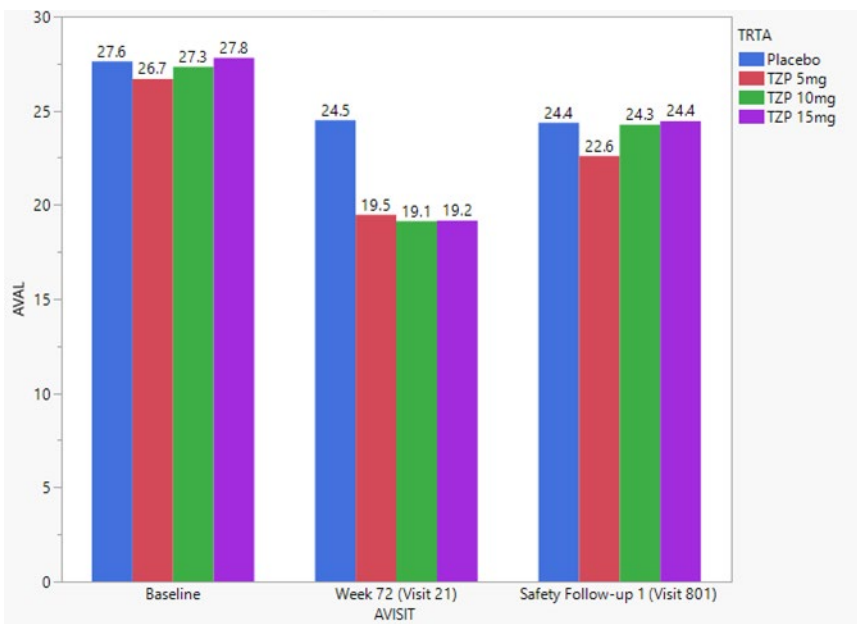
Reviewer comment: These reductions in liver enzymes could represents improvements in NAFLD, since the GPHK trial population had about 7% of subjects with baseline diagnoses of NAFLD, and undiagnosed NAFLD (including NASH) is likely present in even more subjects. Given this hypothesis, I was surprised to see the reduced mean transaminases at Week 72 increasing back towards baseline at Week 72. I reasoned that since weight loss is the likely mechanism of NALFD improvement, and weight loss is mostly maintained at the 4-week SFU, then reduced transaminases should also be maintained at SFU. However, the design of trial GPHK includes the 2-year treatment extension for subjects with prediabetes (who are also most likely to have NAFLD/NASH), and these subjects do not have 4-week SFU data due to the extension, likely contributing to skewed transaminase results at SFU.

⁵¹ These changes over time are detailed in the ISS addendum, Tables ISS.4.35-36, page 1472 of 2079.

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I performed an exploratory analysis of laboratory data from trial GPHK and confirmed the Applicant's result that mean ALT values were reduced from baseline at Week 72 in tirzepatide more than placebo arms, but the difference from placebo is largely lost at SFU (Figure 48).

Figure 48. Mean ALT values (IU/L) at Baseline, Week 72, and Safety Follow-Up for All Subjects in Trial GPHK



Source: Generated by reviewer using adlb.xpt data in JMP

However, when I restricted this analysis to subjects with elevated ALT >40 IU/L at baseline and ALT values at all three timepoints (n=165 subjects), then the reductions in ALT at Week 72 are larger and maintained at SFU (Figure 49).

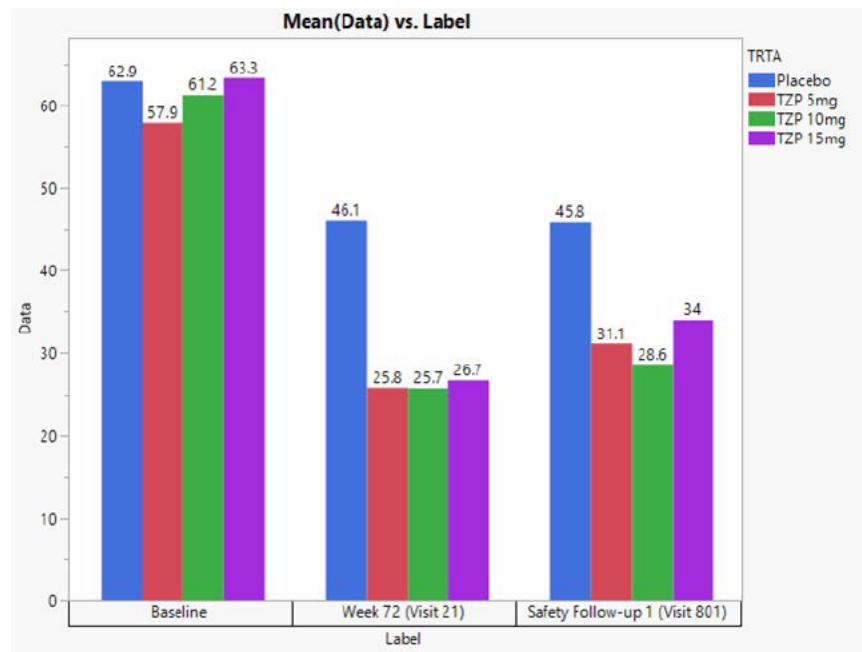
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Figure 49. Mean ALT values (IU/L) at Baseline, Week 72, and Safety Follow-Up for Subjects in Trial GPHK with Baseline ALT>40 IU/L



Reviewer comment: This exploratory analysis of trial GPHK subjects with elevated ALT values at baseline (likely reflecting NAFLD/NASH) shows potentially meaningful reductions in mean ALT values during the trial consistent with weight loss achieved, and largely maintained at SFU.

I also conducted a shift analysis for ALT values in trials GPHK and GPHL. Subjects with abnormal high ALT values at baseline were more likely to have normal values at Week 72 if randomized to tirzepatide versus placebo (89.2% versus 63.5%, Table 102). Conversely, subject with normal ALT values at baseline are less likely to have abnormal high values at Week 72 if randomized to tirzepatide versus placebo (2.9% versus 4.5%, Table 103).

Table 102. Normalization of Baseline High ALT Values at Week 72 (Trials GPHK and GPHL)

	TZP All N=250		Placebo N=96		Risk Difference (%)	
	n	(%)	n	(%)	RD	(95% CI)
Week 72 ALT ≤ ULN	223	(89.2)	61	(63.5)	25.66	(15.29, 36.03)

Source: Generated by reviewer

Note: N reflects the subjects with baseline ALT >ULN and ALT values at week 72

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NDA 217806

Zepbound (tirzepatide)

Table 103. Shifts to Abnormal High ALT Values at Week 72 (Trials GPHK and GPHL)

	TZP All N=1924		Placebo N=646		Risk Difference (%)	
	n	(%)	n	(%)	RD	(95% CI)
Week 72 ALT > ULN	55	(2.9)	29	(4.5)	-1.63	(-3.39, 0.13)

Source: Generated by reviewer

Note: N reflects the subjects with baseline ALT ≤ULN and ALT values at Week 72

Reviewer comment: *The results above for mean ALT values and shifts in ALT values suggest a beneficial effect of tirzepatide in reducing or preventing ALT elevations, perhaps due to improvements in NAFLD/NASH. Consistent with this hypothesis, the treatment-emergent PT of hepatic steatosis was spontaneously reported in fewer tirzepatide-treated subjects (13/2519, 0.52%) than placebo-treated subjects (8/958, 0.84%).* (b) (4)

Liver Safety Conclusion

The review above includes case vignettes for all hepatic events in tirzepatide-treated subject graded as serious (n=1) or severe (n=6), all transaminase elevations ≥10x ULN (n=9), and all potential Hy's Law cases (n=3). Each case has a clear non-DILI etiology, except for subject (b) (6) with the severe TEAE of transaminase elevation leading to study drug discontinuation. This subject underwent a comprehensive liver evaluation identifying antinuclear antibodies, but a diagnosis of SLE was not made which may have provided an alternate etiology. Given these overall results in CWM trials, and results across the development of tirzepatide, there is no evidence of risk for DILI with tirzepatide at this time.

(b) (4)

8.5.15. Neoplasm Safety

For trials GPHK and GPHL, the incidences of pancreatic cancer (one in a placebo-treated subject) and MTC or C-cell hyperplasia (no cases) are discussed under exocrine pancreas and thyroid safety (Sections 8.5.5 and 8.5.1).

Trials GPHK and GPHL excluded subjects with:

- a family or personal history of MTC or MEN2
- a history of an active or untreated malignancy or are in remission from a clinically significant malignancy (other than basal or squamous cell skin cancer, in situ carcinomas of the cervix, or in situ prostate cancer) for less than 5 years

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The Applicant conducted an SMQ analysis of “malignant tumors” and “tumors of unspecified malignancy,” finding such events in 21/2519 (0.83%) tirzepatide- versus 14/958 (1.46%) placebo-treated subjects. These numbers are consistent with my broad FMQ analysis for “malignancy” (22 with tirzepatide versus 13 with placebo), for a risk difference of -0.48% (95% CI -1.3 to 0.33). I reviewed all PTs identified the sponsor’s SMQ and my FMQ, as shown in Table 104, which divides these tumors into categories of my own devising.

Table 104. Potentially Malignant Neoplasm TEAEs Identified in Trials GPHK and GPHL

Neoplasm Category (reviewer-generated)	TZP All N=2519	Placebo N=958
Preferred Term	n (%)	n (%)
Skin or undefined		
Basal cell carcinoma	3(0.12)	1(0.10)
Squamous cell carcinoma	1(0.04)	0
Malignant melanoma	2(0.08)	0
Ear neoplasm	1(0.04)	0
Tumor excision	2(0.08)	0
Neoplasm skin	0	1(0.10)
Female reproductive system ^a		
Endometrial Cancer	2(0.13)	0
Adeonosquamous carcinoma of the cervix	1(0.06)	0
Adenocarcinoma of the cervix	0	1(0.17)
Ovarian cancer	0	1(0.17)
Ovarian germ cell endodermal sinus tumor stage 1	1(0.06)	0
Breast ^a		
Breast cancer	1(0.06)	0
Invasive breast carcinoma	0	1(0.17)
Invasive ductal breast carcinoma	1(0.06)	0
Intraductal proliferative breast lesion	1(0.06)	1(0.17)
Other solid tumors		
Prostate cancer ^b	3(0.32)	1(0.28)
Lung adenocarcinoma	1(0.04)	0
Papillary thyroid cancer	1(0.04)	1(0.10)
Colon neoplasm	1(0.04)	0
Adenocarcinoma of the colon	1(0.04)	1(0.10)
Colon cancer	0	1(0.10)
Renal cancer	0	1(0.10)
Prolactin-producing pituitary tumor	1(0.04)	0
Gastric neoplasm	1(0.04)	0
Pancreatic carcinoma metastatic	0	1(0.10)
Blood cancers		
Leukemia	0	1(0.10)
Mantle cell lymphoma	0	1(0.10)
Plasma cell myeloma	0	1(0.10)

^a Denominator-adjusted female sex-specific events: N= 1595 (TZP), 595 (Placebo)

^b Denominator-adjusted male sex-specific event: N=924 (TZP), 363 (Placebo)

Source: Generated by reviewer, using JMP Clinical FMQ Report and Applicant's ISS addendum Table ISS.4.61 (page 1847 of 2079)

Reviewer comment: These malignancy-related events are rare, and I do not note any potential imbalances that are concerning.

Most malignancy AEs were considered serious, and the malignancy AEs considered non-serious included skin cancers (basal and squamous cell) and papillary thyroid cancer. Serious AEs in the SOC “Neoplasms benign, malignant and unspecified (incl cysts and polyps)” occurred in 15/2519 (0.59%) tirzepatide- versus 13/958 (1.36%) placebo-treated subjects (see Table 43).

Reviewer comment: This analysis of serious neoplasm-related event suggests reduced risk with tirzepatide. The Applicant is conducting a phase 3b trial GPIJ (SURMOUNT-MMO) with an exploratory endpoint testing the hypothesis that tirzepatide reduces the incidence of obesity-associated cancers.

I also searched the GPHK and GPHL safety database for benign neoplasms occurring in in two or more tirzepatide-treated subjects, which I identified as the five PTs identified in these trials in SOC “Neoplasms benign, malignant and unspecified (incl cysts and polyps)” but not in Table 104 above of potentially malignant neoplasms. Colorectal adenoma, lipoma, and meningioma had balanced occurrence in tirzepatide- versus placebo-treated subjects (Table 105). However, the PTs “uterine leiomyoma” and “leiomyoma” occurred in 12 of tirzepatide- versus no placebo-treated subjects, for a significant risk difference.

Table 105. Benign Neoplasm TEAEs in Trials GPHK and GPHL

Preferred Term	TZP All N = 2519	Placebo N = 958	Risk Difference	
	n (%)	n (%)	RD (95% CI)	Forest Plot
Uterine leiomyoma	10 (0.4)	0 (0.0)	0.40 (0.15, 0.64)	
Leiomyoma	2 (0.1)	0 (0.0)	0.08 (-0.03, 0.19)	
Colorectal adenoma	3 (0.1)	2 (0.2)	-0.09 (-0.41, 0.23)	
Lipoma	3 (0.1)	1 (0.1)	0.01 (-0.23, 0.26)	
Meningioma	2 (0.1)	1 (0.1)	-0.02 (-0.26, 0.21)	

Source: Generated by reviewer in OCS Analysis Studio, Safety Explorer.

Since leiomyoma only occurs in females, the denominator should be adjusted: 12/1595 (0.75%) with tirzepatide and 0/599 with placebo, for a significant risk difference of 0.75% (95% CI 0.33-1.18%). No reported TEAEs of leiomyoma were in trial GPHL (SURMOUNT-2, with T2D), and all were in trial GPHK (SURMOUNT-1), which enrolled subjects without T2D and a trial population that was younger with more females.

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I reviewed these 12 tirzepatide-treated subjects with leiomyoma AEs (Table 106):

- Subject (b) (6) had a serious and severe event resulting in drug interruption, with the AE of vaginal hemorrhage occurring on the same day.
- Subject (b) (6) had a serious event graded as mild in severity, resulting in no change to study drug but likely contributing along with an ovarian cyst to a hysterectomy and unilateral salpingo-oophorectomy 400 days later.
- All other events were mild to moderate and did not result in changes to study drug.
 - 4 cases had other diagnoses at the same time (adenomyosis, endometriosis, cholecystitis and cholelithiasis, and hepatic and ovarian cysts)
 - 3 cases were associated with mild intermenstrual or vaginal bleeding
 - 3 cases had no associated AEs.

Table 106. Subjects in Trial GPHK with Leiomyoma AEs

Subject ID	Age / Sex / BMI / Treatment	Serious? / Severity / Action Taken	Day	Related or temporally-associated AEs
(b) (6)	43 / F / 49.94 / TZP 15mg	Y / Severe / Drug interrupted	295	Vaginal hemorrhage reported same Day 295, end Day 383, underwent partial hysterectomy
	48 / F / 33.02 / TZP 15mg	Y / Mild / Dose not changed	17	Ovarian cyst (Day 113), Hysterectomy and unilateral salpingo-oophorectomy (Day 434)
	34 / F / 36.52 / TZP 15mg	N / Moderate / Dose not changed	591	Discontinued study drug Day 196 due to nausea, then discontinued study due to pregnancy; adenomyosis also reported on Day 591
	49 / F / 35.24 / TZP 15mg	N / Mild / Dose not changed	315	Endometriosis reported at same time
	38 / F / 39.82 / TZP 10mg	N / Mild / Dose not changed	428	Reported during serious events of cholelithiasis and chronic cholecystitis
	43 / F / 44.3 / TZP 10mg	N / Mild / Dose not changed	464	Hepatic cyst and ovarian cyst also reported on Day 464
	52 / F / 36.02 / TZP 15mg	N / Mild / Not Applicable	243	Mild intermenstrual bleeding reported on Days 242-354
	38 / F / 38.03 / TZP 5mg	N / Mild / Dose not changed	198	Mild vaginal hemorrhage reported on Days 283-299
	34 / F / 49.12 / TZP 10mg	N / Mild / Dose not changed	87	Mild intermenstrual bleeding reported on Day 411
	44 / F / 43.98 / TZP 5mg	N / Mild / Dose not changed	178	None
	42 / F / 40.96 / TZP 5mg	N / Moderate / Dose not changed	230	None
	39 / F / 36.65 / TZP 10mg	N / Mild / Dose not changed	248	None

Source: OCS Analysis Studio, Listing Table Tool.

An information request was sent to the Applicant regarding the risk of uterine leiomyomas (also called fibroids). The Applicant noted that:

- Two subjects had temporal relationships inconsistent with drug causality: subject (b) (6) discontinued study drug 395 days before leiomyoma was reported, and subject (b) (6) had leiomyoma reported on study Day 17.
- The 10 remaining subjects had marked obesity at baseline: all 10 had BMI ≥ 35.0 kg/m² and 5 had BMI ≥ 40 kg/m².
- Weight loss was generally substantial at the time of leiomyoma reports: 9 of these 10 subjects had lost $\geq 10\%$ at the time of leiomyoma report, and 5 had lost $\geq 15\%$.
- The two subjects with serious leiomyoma AEs had hysterectomies due to apparent mass

effects: subject (b) (6) for a pelvic mass diagnosed as leiomyoma, subject (b) (6) elected for surgery as “she was worried about the feeling of abdominal mass.”

- The prevalence of leiomyomas is high, and 30% to 50% of premenopausal women with no previous diagnosis have ultrasound evidence of fibroid tumors, and obesity is associated with increased risk of fibroids.
- There is no known biological plausibility to explain the apparent treatment difference.

Reviewer comment: I also conducted an exploratory literature search and found no potential connection between uterine leiomyomas and incretins like tirzepatide.

The Applicant proposed detection bias due to weight loss, and the high general prevalence of leiomyomas, as an alternate explanation for the apparent treatment difference, with the following points supported by literature citations:

- The abdominal pannus limits the ability to palpate the uterus and ovaries,⁵² and weight loss may have increased the ability of healthcare practitioners to detect gynecological masses.
- Obesity is associated with PCOS and ovulatory dysfunction. Weight loss restores menstrual cycle,⁵³ and in turn, this may have led to changes in symptoms related to menstrual periods, prompting further investigations, and increasing detection of leiomyomas.
- Weight bias in the health care setting has been associated with decreased routine gynecological screening.⁵⁴ Weight reduction may have increased the occurrence of routine gynecological exams in female participants.

I also queried the Applicant’s pooled analysis set 3 including SURPASS trials of tirzepatide for T2D. In these trials, leiomyoma was reported in 12/6884 (0.17%) tirzepatide-treated subjects, compared to 0/312 placebo-treated, 2/1580 (0.13%) subjects treated with active comparator insulin, and 0/622 subjects treated with other GLP-1R agonist active comparators (dulaglutide or semaglutide). The Applicant conducted a query of leiomyoma events in female subjects in pooled analysis set 4 and noted similar small numbers with imbalance that was not statistically significant (Table 107). The Applicant notes that the lower incidence of leiomyoma in trial subjects with T2D (CWM trial GPHL/SURMOUNT-2 and T2D SURPASS trials) is potentially consistent with underlying populations differences (older age and lower BMI leading to fewer leiomyomas) and treatment effects (less weight loss in subjects with T2D, leading to less of the proposed detection bias).

⁵² Breitkopf, D.M. Lateral decubitus position to facilitate pelvic examination of the patient with severe obesity. BMC Women's Health. 2021;21(1):143. <https://doi.org/10.1186/s12905-021-01289-2>

⁵³ Lee R, Mathew CJ, Jose MT, et al. A review of the impact of bariatric surgery in women with polycystic ovary syndrome. Cureus. 2020;12(10): e10811. <https://doi.org/10.7759/cureus.10811>

⁵⁴ Aldrich T, Hackley B. The impact of obesity on gynecologic cancer screening: an integrative literature review. J Midwifery Womens Health. 2010;55(4):344-356. <https://doi.org/10.1016/j.jmwh.2009.10.001>

Table 107. Uterine Leiomyoma TEAEs in Female Subjects in Phase 2/3 T2D Comparator-Controlled Trials (Analysis Set 4)

	TZP_ALL (N = 2492) n (%)	Pooled Comparator (N = 1078) n (%)	TZP_ALL vs. Pooled Comparators		
			CMH p-value	Odds ratio	Heterogeneity p-value
Female participants with ≥1 TEAE	10 (0.4)	2 (0.1)	0.390	1.89	0.239
Uterine leiomyoma	9 (0.4)	2 (0.1)	0.466	1.72	0.284
Leiomyoma	1 (0.0)	0	0.569	N/A	N/A

Abbreviations: BMI = body mass index; CMH = Cochran-Mantel-Haenszel; N/A = not applicable; N = total number of participants in treatment group; n = total number of participants reporting at least 1 event; T2DM = type 2 diabetes mellitus; TEAE = treatment-emergent adverse event; TZP = tirzepatide; vs. = versus.

Note: Odds ratio is calculated using the pooled comparator group as the denominator.

Studies included: NDA 217806, Seq 0001, Module 2.7.4, Table 2.7.4.2

Source: Applicant response to FDA information request

Reviewer comment: The Applicant's case for leiomyoma detection bias in trial GPHK (SURMOUNT-1) is plausible, and only two subjects had serious events leading to hysterectomy (apparently due to mass effects not bleeding). Given this and the lack of preclinical or mechanistic data supporting causality of tirzepatide, I agree with not describing leiomyoma risk in the current label. Leiomyoma events should be monitored in future trials and post-marketing data.

Neoplasm conclusion

Tirzepatide will include the class labeling for GLP-1R agonists about MTC, though no cases have been reported to date in clinical trials. There was no apparent increase in malignant tumors in tirzepatide-treated subjects. There was an apparent imbalance in the benign tumor leiomyoma with higher incidence in tirzepatide-treated subjects, which may be attributable to detection bias.

8.5.16. Other Diabetes-Related Safety Issues

The Applicant reviewed three additional AESIs relevant to subjects with T2D in trial GPHL (SURMOUNT-2, for CWM in subjects with T2D). For these AESIs, data from trial GPHL were consistent with the known safety profile of tirzepatide in subjects with T2D (reviewed in NDA 215866).

Metabolic Acidosis

The Applicant conducted a customized MedDRA search to identify potential TEAEs of metabolic acidosis in trial GPHK are SURPASS trials for T2D. The PTs queried were:

- diabetic ketoacidosis

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- ketoacidosis
- euglycemic diabetic ketoacidosis
- ketonuria
- diabetic ketosis
- diabetic nonketotic hyperglycemic coma
- ketosis
- lactic acidosis
- urine ketone body present
- blood ketone body
- blood ketone body increased
- urine ketone body
- blood ketone body present

This search strategy identified no potential event of metabolic acidosis in CWM trial GPLH, consistent with no such potential events in either tirzepatide or comparator arms of trials of tirzepatide for T2D.

The Applicant concludes that the trial data do not suggest an association between tirzepatide and occurrence of metabolic acidosis, and I concur. There are rare postmarketing and literature reports of ketoacidosis in subjects taking tirzepatide and other incretins, but these are difficult to interpret.

Hyperglycemia Requiring Rescue Therapy

The protocol for trial GPLH prespecified criteria (Table 108) that investigators were to use when considering the addition of rescue therapy in participants not reaching glycemic targets. Investigators were to first confirm the participant was fully compliant with the assigned therapeutic regimen and there was not an acute condition causing persistent hyperglycemia.

Table 108. Criteria for Persistent Hyperglycemia Requiring Rescue Therapy in Trial GPLH

Criteria	Time period postrandomization
>270 mg/dL (>15.0 mmol/L) ^a	Weeks 0-8
>240 mg/dL (>13.3 mmol/L) ^a	Week 9-16
>200 mg/dL (>11.1 mmol/L) ^a	Beyond Week 16
HbA1c ≥8.5% (≥69 mmol/mol)	On and after Week 24 (only 1 value needed)

^a Two confirmed fasting SMBG values over at least a consecutive 2-week period.

A total of 17 (2.7%) tirzepatide- and 101 (32.1%) placebo-treated participants were prescribed rescue therapy due to persistent hyperglycemia in trial GPLH.⁵⁵ These results are consistent with the percentage of tirzepatide-treated subjects receiving rescue therapy due to hyperglycemic events across studies in the phase 3 T2D clinical program (0%-3.3%).

⁵⁵ CSR for trial GPLH, Table GPLH.8.16

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The percentage of tirzepatide-treated subjects receiving rescue therapy due to persistent hyperglycemia was low and meaningfully reduced compared to placebo-treated subjects. The Applicant concludes that there is no association of tirzepatide use with persistent hyperglycemia, and I concur. Indeed, due to its antihyperglycemic effects, tirzepatide reduced events of hyperglycemia and the need for rescue therapy in trial GPHL as expected.

Amputation or Peripheral Revascularization

The Applicant searched the trial GPHL database for the MedDRA PTs “amputation” and “peripheral revascularization,” and searched the Lilly Safety System case narratives for amputation events.

A total of 4 (0.64%) tirzepatide- and 3 (0.95%) placebo-treated subjects in trial GPHL had an amputation or peripheral revascularization events (Table 109).

Table 109. Amputation and Peripheral Revascularization Cases (Trial GPHL)

Patient ID	Treatment Group	Preferred Term	Description
(b) (6)	Placebo	Gangrene	On Study Day 518, the participant was hospitalized due to an SAE of wet gangrene of the right foot. On Study Day 525, the first and second toes of the right foot were amputated. The participant recovered from the SAE on Study Day 538. The participant did not complete the study on study drug due to personal reasons.
	Placebo	Diabetic foot	On Study Day 37, the participant was hospitalized for partial amputation of the right hallux due to infected diabetic foot. The study drug was interrupted due to the SAE. On Study Day 51, the participant recovered from the SAE, and the study drug was re-initiated. The participant completed the study on study drug.
	Placebo	Osteomyelitis	This participant had a history of osteomyelitis in the right foot and diabetic foot. Previous medical procedures included toe amputation. On Study Day 403, the participant was hospitalized due to an SAE of right foot osteomyelitis. On Study Day 406, the participant underwent right foot transmetatarsal amputation with debridement of the wound on left foot as corrective treatment. The study drug was temporarily interrupted from Study Days 400 to 421 due to the AE. On Study Day 415, the participant recovered from the SAE and completed the study on study drug.
	Tirzepatide 10 mg	Peripheral venous disease	On Study Day 430, the participant was hospitalized due to left venous insufficiency which led to saphenectomy. On Study Day 431, the participant recovered from the SAE and completed the study on study drug.
	Tirzepatide 10 mg	Limb traumatic amputation	On Study Day 315, the participant accidentally cut the distal phalanx of the little finger of the left hand while exercising, resulting in traumatic amputation, and was hospitalized. On the following day (Study Day 316), the participant recovered. The participant completed the study on study drug.
	Tirzepatide 15 mg	Shunt thrombosis	The participant had a history of obliterating atherosclerosis of the lower extremities and occlusion of the right tibial artery. On Study Day 388, the participant was hospitalized due to thrombosis of the femoral-tibial artery shunt, resulting in dry gangrene and subsequent limb amputation above the knee. On Study Day 418, the participant recovered from the SAE of shunt thrombosis and completed the study on study drug.
	Tirzepatide 15 mg	Cellulitis	The participant had a history of diabetic polyneuropathy. On Study Day 499, the participant was diagnosed with right plantar cellulitis and was hospitalized. On Study Day 508, the participant had right foot amputation. The SAE was reported as ongoing at the end of the study. The participant withdrew consent from the study on Study Day 515.

The Applicant notes the following:

- Two of the 7 subjects had preexisting peripheral vascular disease.

- There was a total of 6 amputations (3 in tirzepatide- and 3 in placebo-treated subject, of which 1 (tirzepatide 10 mg) was due to an accident (limb traumatic amputation). The 2 non-accidental events in the tirzepatide groups correspond to an event rate of 0.25 events per 100 patient-years.
- There was one peripheral revascularization event in a tirzepatide-treated subject in trial GPHL, compared to none in placebo-treated subjects, and corresponding to an event rate of 0.12 events per 100 patient-years.
- The event rates of amputation and peripheral revascularization in tirzepatide-treated trial GPHL subjects were consistent with those reported for participants with obesity/overweight in the phase 3 T2D studies (0.14 events per 100 patient-years for both amputation and peripheral revascularization).

The Applicant concludes that rates of amputation and peripheral revascularization in tirzepatide-treated participants in CWM trial GPHL were consistent with the known safety profile of tirzepatide for T2D, and the results do not suggest an association of tirzepatide with amputation or peripheral revascularization. I concur.

Other Diabetes-related Safety Issues Conclusion

These three T2D-related AESIs (metabolic acidosis, hyperglycemia, and amputation) are not included in the tirzepatide label for T2D, and based on the review above I do not think they merit inclusion in the label for CWM.

8.5.17. Rare events

Fall

My review of trials GPHK and GPHL noted the rare AE of “Fall” occurring in more tirzepatide- (0.71%) than placebo-treated (0.21%) subjects, with a statistically significant risk difference (95% CI does not cross zero) and an apparent inverse dose-dependence (highest incidence of fall in subjects randomized to tirzepatide 5 mg, Table 110).

Table 110. Fall TEAEs in Trials GPHK and GPHL

	TZP 5mg	TZP 10mg	TZP 15mg	TZP All	Placebo	Risk
	N=630	N=948	N=941	N=2519	N=958	Difference
	n (%)	n (%)	n (%)	n (%)	n (%)	RD (95% CI)
Fall	7 (1.1)	8 (0.8)	3 (0.3)	18 (0.7)	2 (0.2)	0.51 (0.07, 0.94)

I reviewed profiles for the 18 subjects reporting the PT of Fall, summarized in Table 111 and showing:

- No falls were serious, 2 were graded as severe, and the remainder were graded as mild to moderate. All 18 cases were reported as not causally related to study drug by the

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investigator.

- The average age of the 18 patients reporting a fall was 54 years (range 28 to 69 years).
- Most subjects who reported fall had injury-related AEs occurring concurrently or after the day of the fall, suggesting to me that reporting of fall may have been biased towards falls that resulted in injury.
- The reported terms generally do not provide mechanism (except one “slipped on leaves” and one “mechanical fall”).
- The study Days of the falls occur spread throughout the treatment period without a temporal pattern.

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Table 111. Subjects with Fall TEAEs (Trials GPHK and GPHL)

Subject / Age/Sex/Treatment	Reported Term	Serious? / Severity	Day	AEs potentially due to fall	Comment or Potentially Causal AE
(b) (6) / 56 / F / Placebo	Fall	N / Moderate	440	wrist fracture, Day 440-	
(b) (6) / 57 / M / Placebo	Fall down stairs	N / Moderate	316		
(b) (6) / 68 / F / TZP 5mg	Fall	N / Mild	123	tooth fracture Day 123-169, face injury Day 169-445	Dizziness and fatigue later, starting Day 287
(b) (6) / 46 / F / TZP 5mg	Fall (slipped on leaves)	N / Moderate	78	arthralgia, Day 78-85	Fatigue later, starting Day 106
(b) (6) / 50 / F / TZP 5mg	Fall	N / Moderate	95	back pain, Day 95-	medical history of sciatica and peripheral neuropathy
(b) (6) / 41 / F / TZP 5mg	Fall from own height	N / Mild	438	fractured coccyx, Day 438- 443	
(b) (6) / 57 / M / TZP 5mg	Fall from height- chair	N / Mild	187	arthralgia and spinal pain, Day 187-197	
(b) (6) / 47 / F / TZP 5mg	Fall from height onto coccyx	N/ Severe	163	coccydynia, Day 163-202	
(b) (6) / 69 / F / TZP 5mg	Fall	N / Mild	432	spinal column injury, Day 432-	Medical history on Meniere's syndrome
(b) (6) / 55 / F / TZP 10mg	Fall	N/ Severe	460	joint dislocation, Day 460	*Syncope on same Day 460
(b) (6) / 28 / F / TZP 10mg	Fall	N / Mild	41	back pain, Day 41-57	
(b) (6) / 35 / F / TZP 10mg	Fall	N / Mild	272		Dizziness ended earlier on Days 45-46
(b) (6) / 49 / F / TZP 10mg	Mechanical fall	N / Mild	260	contusion, Day 260-276	*Muscular weakness starting Day 257
(b) (6) / 68 / F / TZP 10mg	Fall from own height	N / Mild	436		Also fell on Day -20 prior to treatment
(b) (6) / 65 / M / TZP 10mg	Fall from own height	N / Mild	330	musculoskeletal pain, Days 331-376	Hypotension earlier on Days 71 and 210
(b) (6) / 62 / F / TZP 10mg	Fall from own height	N / Mild	361	back pain, Days 361-374	
(b) (6) / 61 / F / TZP 10mg	Fall	N / Mild	502	contusion, Days 502-25, arthralgia Day 502-	medical history of bilateral lower extremity nondiabetic neuropathy
(b) (6) / 47 / F / TZP 15mg	Fall	N / Mild	95	foot fracture, Days 95-134	Medical history of vertigo
(b) (6) / 66 / M / TZP 15mg	Multiple falls	N / Mild	124	sciatica Days 62-	Dizziness prior to treatment on Day -6, vertigo on Day 270
(b) (6) / 65 / F / TZP 15mg	Fall from own height	N / Moderate	14	pain in extremity, Days 14- 175	

Source: generated by reviewer from adae.xpt dataset and Applicant's response to IR

*Identifies potentially causal AEs temporally related to fall

Other AEs of concern that could potentially lead to falls include hypotension, dizziness, fatigue, and syncope. Only 5 of the 20 subjects with falls (in red in Figure 50) reported these other AEs

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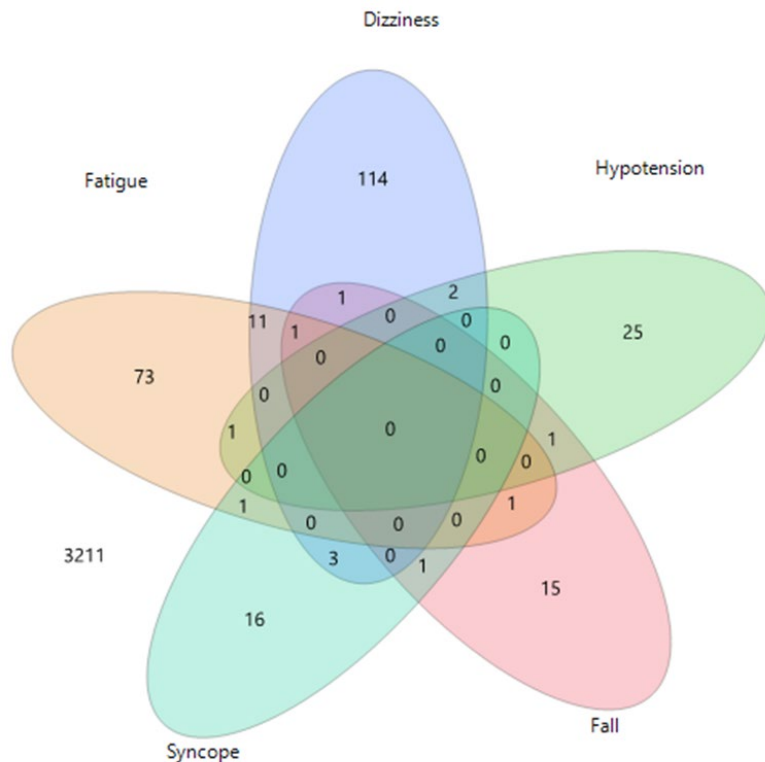
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during the trial, and the events did not appear temporally related (Table 111). Two subjects had temporally related AEs of syncope and weakness (starred in Table 111) that could potentially explain the falls.

Figure 50. Venn Diagram of Subjects with Fall and Potentially Other Causal AEs (Trials GPHK and GPHL)



Source: Generated by reviewer in JMP clinical

The Applicant notes that there was no pattern of potential causes or reasons for falls, and thus did not consider falls to be a safety concern for tirzepatide, and I concur. Based on the analysis above, the imbalance in fall events is unexplained but unlikely due to tirzepatide. Therefore, I do not think the tirzepatide label should include the rare TEAE of falls.

Gastroparesis

There are post-marketing reports of severe gastroparesis events in patients treated with incretin drugs, and some events were reported to persist after drug discontinuation. Delayed gastric emptying is an incretin pharmacodynamic effect that may contribute to the weight loss efficacy and to GI AEs. However, “delayed gastric emptying” is also the PT used for reported terms of “gastroparesis.” Other PTs may also indicate gastroparesis-related events, so I used the following 10 PTs for a custom MedDRA query:

- Impaired gastric emptying

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- Diabetic gastroparesis
- Gastroparesis postoperative
- Gastric atony
- Gastric emptying study
- Gastric hypertonia
- Gastric hypomotility
- Gastric ileus
- Gastric residual assessment
- Gastric residual increased

In trials GPHK and GPHL, two subjects reported the PT “impaired gastric emptying” (both AEs non-serious, mild in severity, and resulting in no change in study drug dose), one subject reported non-serious event “diabetic gastroparesis” (moderate severity resulting in study drug discontinuation, Table 112). All three subjects were tirzepatide-treated, and no gastroparesis events were reported in placebo-treated subjects.

Table 112. Subjects with Gastroparesis TEAEs (Trials GPHK and GPHL)

Subject Age/Sex/HbA1c	Treatment	Preferred Term	Reported Term	Serious / Severity	Outcome	Action Taken
(b) (6) 41 / M / 7.3%	TZP 15mg	Diabetic gastroparesis	Diabetic Gastroparesis	No / Moderate	Recovered	Drug withdrawn
(b) (6) 64 / F / 7.7%	TZP 15mg	Impaired gastric emptying	Gastroparesis	No / Mild	Not Recovered	Dose not changed
(b) (6) 30 / F / 5.2%	TZP 10mg	Impaired gastric emptying	Gastric Retention	No / Mild	Recovering	Dose not changed

In response to an information request, the Applicant provided patient narratives for the three cases:

- Subject (b) (6) was a 41-year-old male with T2D for 5 years taking metformin with a baseline HbA1c of 7.3%, who reported a TEAE of diabetic gastroparesis (moderate, nonserious) on Day 128 while on tirzepatide 12.5 mg. There was no available information regarding whether a gastric emptying study was performed to confirm the diagnosis. Itopride and pantoprazole were prescribed for the treatment of diabetic gastroparesis. Dose of tirzepatide was first reduced to 10 mg on Day 141; then 2 doses of tirzepatide were interrupted (on Days 148 and 162) due to the event. His last dose of tirzepatide (10 mg) was on Day 170, the event resolved on Day 184, study drug was permanently discontinued due to diabetic gastroparesis on Day 197, and the subject permanently discontinued from the study due to diabetic gastroparesis on Day 281. The investigator considered this event to be related to the study drug. During the study, the participant also reported a TEAE of vomiting (mild, nonserious) on Day 123, five days prior to the onset of diabetic gastroparesis.

Ondansetron was prescribed to treat vomiting, and this event resolved on Day 124 while on study drug.

- Subject (b) (6) was a 64-year-old White female with T2D taking metformin and baseline HbA1c 7.7% randomly assigned to tirzepatide 15 mg who reported impaired gastric emptying (mild, nonserious) on Study Day 303 while taking placebo. Prior to the event of impaired gastric emptying, she reported decreased appetite on Study Day 256, and study drug dose was reduced from tirzepatide 7.5 mg (last dose on Day 274) to placebo in a blinded fashion due to decreased appetite on Day 287. She completed the study on placebo, and the impaired gastric emptying event was ongoing at the end of the study (Day 545). There was no available information regarding whether a gastric emptying study was performed to confirm the diagnosis. She also reported multiple other GI-related TEAEs during the tirzepatide treatment period, including nausea, eructation, vomiting, abdominal distension, and abdominal pain. Ondansetron and famotidine were prescribed to treat nausea and vomiting. All these GI-related events were mild or moderate in severity and resolved during the study.
- Subject (b) (6) was a 30-year-old Asian female without T2D and baseline HbA1c of 5.2% who reported impaired gastric emptying (mild, nonserious) on Day 156 while taking tirzepatide 10 mg. There was no available information regarding whether a gastric emptying study was performed to confirm the diagnosis. Concomitant medications included multiple traditional Chinese medicines and unspecified herbal medicines. No action was taken with study drug due to the impaired gastric emptying reported on Day 156, but the subject permanently discontinued study drug on Day 426 due to “withdrawal by subject” (further described as “adopt other ways to lose weight”). Her last dose of tirzepatide (10 mg) was taken on Day 414 and impaired gastric emptying was resolving at the end of the study (Day 540). Throughout the study treatment period, she also reported multiple other GI-related AEs, including nausea, diarrhea, constipation, vomiting, chronic gastritis, GERD, helicobacter infection, and gastritis erosive. Amoxicillin, bismuth, clarithromycin, and esomeprazole were prescribed for the eradication of helicobacter infection. Chronic gastritis, helicobacter infection, and gastritis erosive were moderate in severity and were resolving at the end of the study (Day 540). GERD was mild in severity and was resolving at the end of the study. All remaining GI-related events were mild in severity and resolved during the study treatment period.

Reviewer comment: Based on these narratives, it remains unclear how the diagnosis of gastroparesis was made in these subjects, and all three had other common GI AEs. Many other trials subjects without reported AEs of gastroparesis had similar GI AEs, including many that led to study drug discontinuation. Gastroparesis was nonetheless a rare event reported in tirzepatide treated subjects (3/2519, 0.12%), and the three narratives are consistent with these events not being serious or severe.

Section 5 (Warning and Precautions) of labeling on “Severe Gastrointestinal Diseases” will note

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that tirzepatide “has not been studied in patients with severe gastrointestinal disease, including severe gastroparesis, and is therefore not recommended in these patients.” At this time, further language regarding gastroparesis in labeling is not supported. However, post-marketing reports of gastroparesis for tirzepatide or other incretin drugs will continue to be monitored, and labeling will be updated as needed.

8.6. Safety Analyses by Demographic Subgroups

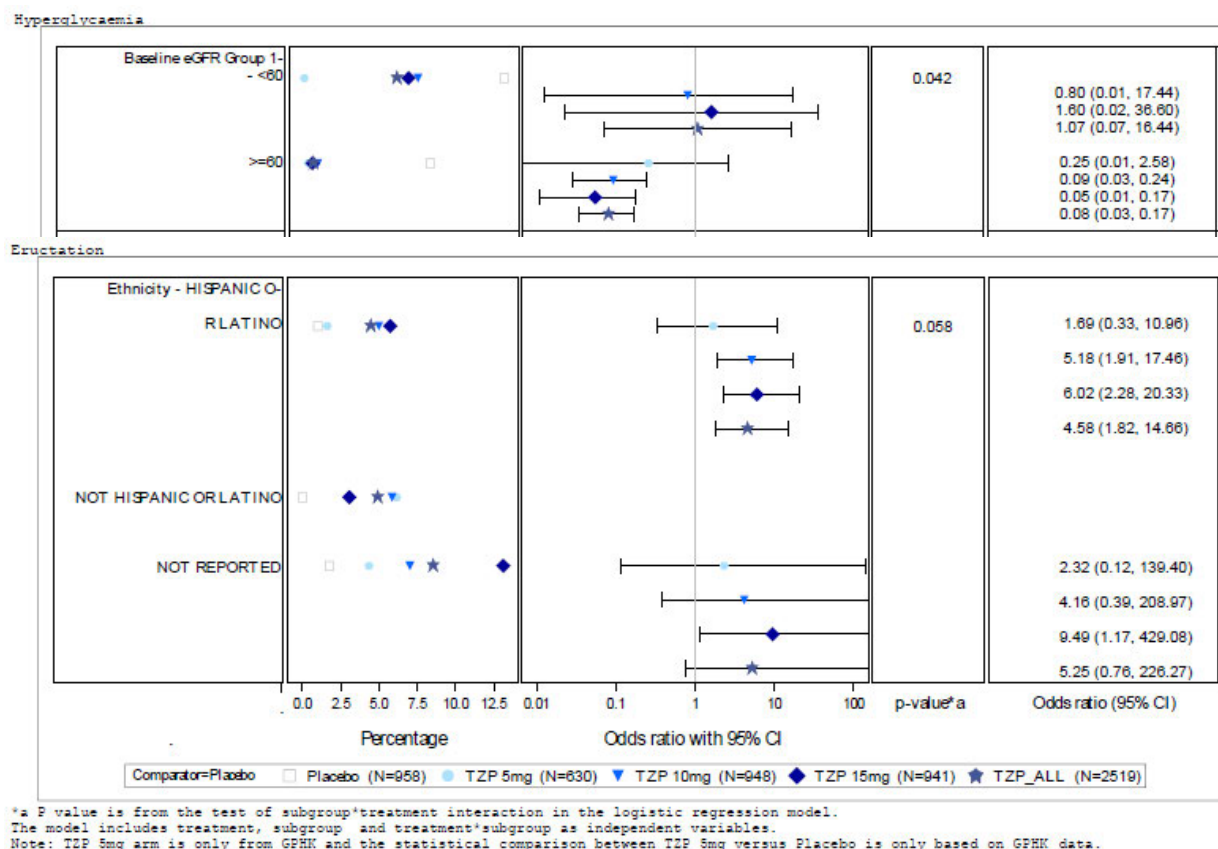
The Applicant assessed frequent TEAEs (>5%: abdominal pain, alopecia, COVID-19, constipation, decreased appetite, diarrhea, dizziness, dyspepsia, eructation, headache, hyperglycemia, nausea, and vomiting) by the following subgroups for trials GPHK and GPHL:

- age <65 and ≥65
- sex
- race (American Indian/Alaska Native, Asian, Black/African American, White, Multiple)
- ethnicity (Hispanic or Latino, not Hispanic or Latino, not reported)
- baseline BMI (<30, ≥30 and <35, ≥35, and ≥40 kg/m²)
- baseline eGFR (<60, ≥60 mL/min/1.73 m²).

In this analysis, Forest plots showed all subgroup-by-treatment interactions p-values were ≥0.1 (non-significant), using a logistic regression model, with two exceptions (Figure 51):

- Hyperglycemia and eGFR: There was no apparent reduction in hyperglycemia by tirzepatide in the small number of subjects in the low eGFR subgroup, but only 4 subjects reported hyperglycemia in this subgroup.
- Eructation and Latino ethnicity: There was an isolated lack of difference between tirzepatide 5 mg and placebo arms.

Figure 51. Subgroup by Treatment Interactions: eGFR and Hyperglycemia, Ethnicity and Eructation (Trials GPHK and GPHL)



Source: ISS Addendum Figure ISS.4.10, page 1930 of 2079

Reviewer comment: These statistically significant subgroup-by-treatment interactions are likely due to chance and are not clinically meaningful, so they should not be included in labeling. All common TEAEs are considered to apply across all subgroups.

Notably for tirzepatide's proposed indication of CWM, the Applicant found no interactions by BMI subgroups, indicating that common AEs occur at similar frequency regardless of baseline BMI. I found the same lack of apparent interaction by T2D status (see Section 8.4.5), indicating that common TEAEs occur at similar frequency in subjects with and without T2D.

The Applicant also analyzed frequent TEAEs occurring in >1% of subjects by geographic region to evaluate potential regional differences in trials GPHK and GPHL:

- North America
- Central/South America and Mexico
- Asia (excluding Japan)

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- Japan
- Rest of World (includes Russian Federation)

In this analysis, the greater frequency of dizziness, abdominal pain, and injection site pruritus in tirzepatide groups, compared to placebo appears to be driven by the North America region (for example, results for dizziness are shown in Table 113). However, the Applicant concludes that potential regional difference in these few TEAEs are not clinically relevant, and I agree that the AEs for tirzepatide should be labeled as applicable across geographies.

Table 113. Dizziness TEAEs by geographic region (Trial GPHK and GPHL)

Region	TSP ALL (N=2519) n/m (%)	Placebo (N=958) n/m (%)
North America	72/1081 (6.66)	6/402 (1.49)
Central/South America and Mexico	28/1065 (2.63)	8/406 (1.97)
Asia (excluding Japan)	9/124 (7.26)	4/47 (8.51)
Japan	3/137 (2.19)	1/54 (1.85)
Rest of the World	0/112	1/49 (2.04)

Source: Applicant ISS addendum

See elsewhere in the safety review for other relevant subgroup analyses:

- Alopecia: Female subgroups described in Section 8.5.12, Table 96.
- Heart rate changes: Japan versus other countries in Section 8.4.7, Table 65.

In conclusion, the Applicant conducted acceptable safety subgroup analyses and identified no meaningful subgroup differences.

8.7. Specific Safety Studies/Clinical Trials

Based on the Division's guidance, the Applicant conducted two substudies in trial GPHK (DXA and ABPM) to support the safety and favorable benefit/risk of tirzepatide.

Trial GPHK Dual-Energy X-ray Absorptiometry (DXA) Addendum

The design of this substudy involved sites performing body composition DXA scans at Baseline (between Visits 2 and 3, Weeks -1 and 0) and at end of treatment (Visit 21, Week 72, or early termination), with the objectives and endpoints in Table 114.

Table 114. Endpoints for Trial GPHK DXA Substudy

Objectives	Endpoints
Primary, at 72 weeks	
To demonstrate that tirzepatide (5, 10, and 15 mg combined) QW is superior to placebo for total body fat mass	Percent change in total body fat mass from baseline
Secondary, at 72 weeks	
To demonstrate that tirzepatide (5, 10, and 15 mg combined) QW is superior to placebo for total body fat mass	• Mean change in total body fat mass (kg) from baseline • Percent change in total body lean mass from baseline
To assess tirzepatide (5, 10, and 15 mg combined) QW for • percent change in total body lean mass and • change in total body lean mass	• Change in total body lean mass (kg) from baseline

Source: Applicant GPHK CSR, page 397 of 3021

The main eligibility criteria included participation at sites with either Hologic™ or Lunar™ DXA scanners with total body composition capabilities and a body size permitted by the DXA manufacturer's specification. Despite the latter exclusion, the full range of BMIs including ≥ 40 kg/m² was represented in the 255 subjects enrolled in the DXA substudy (Table 115). Of note, the placebo group in the DXA substudy had higher body weights, BMI, and waist circumference than the tirzepatide 5 mg group, though the 10 mg and 15 mg groups were more similar to placebo. Given the prespecified pooling of tirzepatide arms for the efficacy analyses, the lower weights in the 5 mg group are unlikely to affect overall results. The DXA substudy trial population was also notable for being 72.2% female, 82.0% white race, and 53.7% enrolled in the U.S.

Table 115. Weight-related Demographics for Trial GPHK DXA Substudy

Attribute	Placebo (N = 56)	TZP 5 mg (N = 68)	TZP 10 mg (N = 63)	TZP 15 mg (N = 68)	Total (N = 255)
Weight (kg), mean $\pm$ SD	107.2 $\pm$ 22.4	97.9 $\pm$ 16.5	104.3 $\pm$ 20.2	102.9 $\pm$ 16.6	102.9 $\pm$ 19.1
Height (cm), mean $\pm$ SD	164.3 $\pm$ 9.9	163.0 $\pm$ 8.6	164.9 $\pm$ 9.2	165.7 $\pm$ 9.2	164.4 $\pm$ 9.2
BMI (kg/m ²), mean $\pm$ SD	39.7 $\pm$ 7.2	36.8 $\pm$ 5.6	38.4 $\pm$ 6.9	37.4 $\pm$ 4.9	38.0 $\pm$ 6.2
BMI Group (kg/m²), n (%)					
<30	1 (1.8)	7 (10.3)	3 (4.8)	4 (5.9)	15 (5.9)
≥ 30 to <35	16 (28.6)	20 (29.4)	22 (34.9)	19 (27.9)	77 (30.2)
≥ 35 to <40	14 (25.0)	25 (36.8)	18 (28.6)	27 (39.7)	84 (32.9)
≥ 40	25 (44.6)	16 (23.5)	20 (31.7)	18 (26.5)	79 (31.0)
Waist Circumference (cm), mean $\pm$ SD	115.76 $\pm$ 14.6	108.87 $\pm$ 11.4	113.94 $\pm$ 12.5	112.67 $\pm$ 11.9	112.65 $\pm$ 12.7

Source: Applicant GPHK CSR, Table GPHK.5.99, page 402 of 3021

The key results of the DXA substudy are in Table 116. Tirzepatide resulted in a placebo-corrected -25.7% decrease in fat mass (primary endpoint) and -8.3% decline in lean mass (a secondary endpoint).

Table 116. Results of Trial GPHK DXA Substudy, Percent Change in Fat and Lean Mass

Fat mass	Placebo (N = 36)	TZP 5/10/15 mg (N = 124)
Baseline (kg)	49.4	46.6
Percent change from baseline at 72 weeks (%)	-8.2 ^{††}	-33.9 ^{†††}
Percent change difference from placebo at 72 weeks (%) (95% CI)	N/A	-25.7*** (-31.4, -20.0)

Lean mass	Placebo (N = 36)	TZP 5/10/15 mg (N = 124)
Baseline (kg)	53.0	50.8
Percent change from baseline at 72 weeks (%)	-2.6 [†]	-10.9 ^{†††}
Percent change difference from placebo at 72 weeks (%) (95% CI)	N/A	-8.3*** (-10.6, -6.1)

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; DXA = dual-energy X-ray absorptiometry; LOCF = last observation carried forward; mITT = modified intent-to-treat; N = number of participants with baseline and postbaseline value; N/A = not applicable; TZP = tirzepatide.

Note 1: ANCOVA, LOCF. Only the nonmissing postbaseline observation on or prior to the last dose date + 14 days was carried forward.

Note 2: Least-squares means are shown.

[†]p-Value <0.05, ^{†††}p-value <0.001 versus baseline.

***p-Value <0.001 versus placebo.

Source: Applicant GPHK CSR, Tables GPHK.5.100 and GPHK.5.102, page 403 of 3021

Reviewer comment: The observed loss in fat mass is supportive for efficacy in CWM, but from the FDA perspective the main reason for analyzing body composition is to demonstrate safety. Per the Division's guidance, DXA sub-studies serve to ensure that weight loss is caused primarily by reduction in fat content rather than lean body mass. The results for tirzepatide (with about 3-fold more loss of fat mass than lean mass) are consistent with other approved medications for CWM and do not raise safety concerns.

Trial GPHK Ambulatory Blood Pressure Monitoring (ABPM) Addendum

The design of this substudy involved sites performing 24-hour ABPM at baseline (between Visits 2 and 3, Weeks -1 and 0) and Week 36 (Visit 12) during the treatment period when all tirzepatide arms had reached maintenance dosages for at least 16 weeks. Each ABPM session was considered technically acceptable if at least 70% of the readings were valid, otherwise a second session could be performed. The two ABPM substudy endpoints are in Table 117.

Table 117. Endpoints for Trial GPHK ABPM Substudy

Objectives	Endpoints
Primary objective, 36 weeks	
To assess tirzepatide (5, 10, and 15 mg) compared with placebo for 24-hour mean HR and 24-hour mean BP (SBP/DBP)	- Mean change in 24-hour mean HR from baseline - Mean change in 24-hour mean BP from baseline

Source: Applicant GPHK CSR, page 406 of 3021

The main eligibility criteria for the ABPM substudy included:

- well-controlled BP that was less than 140/90 mmHg, regardless of antihypertensive treatment
- stable hypertension treatment regimen for at least 3 months prior to screening (if treated for hypertension)
- no history of frequent, intermittent, or chronic tachycardia syndromes
- no shift work (worked during the 22:00 to 07:00 hours period)
- no unavoidable strenuous manual labor during the monitoring period
- nondominant arm circumference ≤ 55 cm and able to obtain a valid baseline ABPM reading.

Despite the latter exclusion, the full range of BMIs including ≥40 kg/m² was represented in the 600 subjects enrolled in the ABPM substudy, and weight parameters were balanced across the arms (Table 118). The ABPM substudy trial population was also notable for being 68.7%% female, 66.8% white race, and 82.3% enrolled in the U.S.

Table 118. Weight-related Demographics for Trial GPHK ABPM Substudy

Attribute	Placebo (N = 155)	TZP 5 mg (N = 145)	TZP 10 mg (N = 152)	TZP 15 mg (N = 148)	Total (N = 600)
Weight (kg), mean ± SD	102.9 ± 23.1	100.6 ± 19.3	105.4 ± 23.0	104.1 ± 19.9	103.3 ± 21.5
Height (cm), mean ± SD	165.8 ± 9.4	165.4 ± 9.1	166.2 ± 8.9	166.7 ± 9.8	166.0 ± 9.3
BMI (kg/m ²), mean ± SD	37.4 ± 7.7	36.8 ± 6.6	38.0 ± 7.0	37.4 ± 5.6	37.4 ± 6.8
BMI Categories (kg/m²), n (%)					
<30	15 (9.7)	14 (9.7)	13 (8.6)	11 (7.4)	53 (8.8)
≥30 to <35	59 (38.1)	58 (40.0)	53 (34.9)	46 (31.1)	216 (36.0)
≥35 to <40	34 (21.9)	36 (24.8)	36 (23.7)	40 (27.0)	146 (24.3)
≥40	47 (30.3)	37 (25.5)	50 (32.9)	51 (34.5)	185 (30.8)
Waist Circumference (cm), mean ± SD	112.4 ± 15.7	111.6 ± 12.9	114.3 ± 15.2	114.4 ± 14.5	113.2 ± 14.7

Source: Applicant GPHK CSR, Tables GPHK.5.107, page 409 of 3021

Similar to the main study, use of anti-hypertensive medications decreased in the tirzepatide 10 mg and 15 mg arms at end of treatment Week 72 (see above, not shown for ABPM substudy),

though the Applicant does not present these medications at Week 36 when the second ABPM measurements were taken. Nonetheless, as before, the reduction in these medications would be expected to reduce (not enhance) the treatment effect of tirzepatide versus placebo on blood pressure.

The key results of the ABPM substudy are in Table 119. Tirzepatide resulted in significant:

- decreases in 24-hour systolic blood pressure and variable decreases in 24-hour diastolic blood pressure, consistent with blood pressure efficacy endpoints above
- increases in mean 24-hour heart rate as described below in safety in Section 8.4.6.

Table 119. Results of Trial GPHK ABPM Substudy, Changes in 24-hour Blood Pressure and Heart Rate

Parameters	Placebo (N = 131)	TZP 5 mg (N = 116)	TZP 10 mg (N = 123)	TZP 15 mg (N = 124)
Mean 24-hour SBP (mmHg)				
Baseline	123.8	125.8	124.5	124.4
Change from baseline at 36 weeks	1.8	-5.6 ^{†††}	-8.8 ^{†††}	-6.2 ^{†††}
Change difference from placebo at 36 weeks (95% CI)	N/A	-7.4*** (-10.0, -4.7)	-10.6*** (-13.2, -8.0)	-8.0*** (-10.6, -5.4)
Mean 24-hour DBP (mmHg)				
Baseline	71.4	72.9	71.6	72.5
Change from baseline at 36 weeks	0.5	-1.5 [†]	-2.4 ^{†††}	0.0
Change difference from placebo at 36 weeks (95% CI)	N/A	-2.0* (-3.6, -0.3)	-2.9*** (-4.5, -1.3)	-0.5 (-2.0, 1.1)
Mean 24-hour Heart Rate (bpm)				
Baseline	76.8	77.8	77.2	78.0
Change from baseline at 36 weeks	-1.8 ^{††}	0.3	0.5	3.6 ^{†††}
Change difference from placebo at 36 weeks (95% CI)	N/A	2.1* (0.3, 3.9)	2.3* (0.6, 4.1)	5.4*** (3.6, 7.1)

Abbreviations: ABPM = ambulatory blood pressure monitoring; CI = confidence interval; DBP = diastolic blood pressure; mITT population = modified intent-to-treat population; N = number of participants with baseline and postbaseline values; N/A = not applicable; SBP = systolic blood pressure; TZP = tirzepatide.

Note: Least squares means are shown.

*p-Value <0.05, ***p-value <0.001 versus placebo.

[†]p-Value <0.05, ^{††}p-value <0.01, ^{†††}p-value <0.001 versus baseline.

Source: Applicant GPHK CSR, Tables GPHK.5.100 and GPHK.5.102, page 403 of 3021

The Applicant also conducted other analyses of the ABPM data:

- Abnormally high daytime, nighttime, and 24-hr blood pressures thresholds were defined, and tirzepatide-treated subjects had significantly fewer abnormally high systolic blood pressure values compared to placebo-treated subjects (not shown).
- Circadian patterns of nighttime systolic blood pressure changes were defined (dipper,

nondipper, and riser) and shift patterns were analyzed, without meaningful effects of tirzepatide versus placebo on shifts to different circadian patterns.

Reviewer comment: The observed reduction in systolic blood pressure in tirzepatide arms measured by ABPM is consistent with the secondary efficacy endpoint measured by routine vitals, but from the FDA perspective the main reason for ABPM is to demonstrate safety.⁵⁶ For drugs intended for chronic use, FDA recommends conducting ABPM in the indicated population to rule out drug-induced sustained elevations in blood pressure (excluding a 3-mmHg increase in 24-hour average systolic blood pressure), as well as daytime or nighttime elevations. Since tirzepatide notably reduces systolic blood pressure, there is no safety concern for a pressor effect, though tirzepatide has the expected GLP-1R agonist class effect of increasing heart rate (see Section 8.4.7, which details that these changes are unlikely to be clinically meaningful). Indeed, a key reason for the ABPM substudy and interim analysis was to generate early data on heart rate effects of tirzepatide.

8.8. Additional Safety Explorations

8.8.1. Human Carcinogenicity or Tumor Development

Refer to Section 8.5.15 on Neoplasm Safety.

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 occurred 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.

The Division of Pediatric and Maternal Health (DPMH) was consulted to assist with the pregnancy and lactation subsections of labeling, and Dr. Wenjie Sun's review is dated September 11, 2023. Briefly, Dr. Sun notes that the prevalence of obesity in U.S. women of reproductive age (20-39 years) is 39.7%, and that maternal obesity increases the risk of spontaneous abortions, recurrent miscarriage, certain fetal malformations, and various complications in the antepartum, intrapartum, and postpartum periods. Additional screening is recommended for pregnant women with obesity, including early screening for gestational

⁵⁶ FDA guidance "Assessment of Pressor Effects of Drugs"

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diabetes by oral glucose tolerance test, additional antenatal fetal surveillance, and anesthesia consultation for those with OSA. The CDC recommends weight gain during pregnancy even for women with overweight or obesity (15-25 pounds if BMI is 25.0-29.9 kg/m² [overweight] and 11-20 pounds if ≥ 30 kg/m² [obese]).⁵⁷

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, study drug was to be stopped and the investigators were to collect data on the outcome for both mother and fetus.

In trials GPHK and GPHL, there were 26 pregnancies with maternal exposure to study drug, with 6 in subjects randomized to placebo. The 20 cases of maternal tirzepatide exposure correspond to a rate of 2.15% in women of child-bearing potential. The pregnancy outcomes for these 20 pregnancies were:

- 7 reported full-term delivery
- 4 reported pre-term delivery
- 4 terminated their pregnancies
- 1 reported spontaneous abortion
- 1 reported ectopic pregnancy
- 3 outcomes unknown/not reported
- There were no reported major or minor fetal malformations in the offspring of subjects exposed to tirzepatide.

Reviewer comment: Dr. Sun's review notes that 4 of 11 reported live births in these trials were classified as pre-term; although this is higher than the expected background rate, the small number of cases are difficult to interpret and labeling is not currently warranted. Two pregnancy-related PMRs, for a registry and a descriptive study, will be issued to collect additional post-marketing data on pregnancy outcomes (see Section 12).

Three tirzepatide-treated subjects reported maternal complications during pregnancy:

- 1 reported pre-eclampsia
- 1 reported hypertension and gestational diabetes
- 1 reported hyperglycemia.

Reviewer comment: Based on the enrolled trial populations, these maternal events are not unexpected.

In trials GPHK and GPHL, there were 5 pregnancies with paternal exposure to study drug, with 2

⁵⁷ <https://www.cdc.gov/reproductivehealth/maternalinfanthealth/pregnancy-weight-gain.htm>

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in subjects randomized to placebo. Of the three pregnant partners of male tirzepatide-treated subjects, one reported no maternal complications, maternal complications are unknown for the other two, and fetal outcomes are unknown for all three.

To date, there have been 7 other pregnancies with maternal exposure to tirzepatide in clinical trials (5 reviewed in T2D NDA 215866⁵⁸ and two others), and an additional 20 exposed pregnancies reported from postmarket experience. Please refer to Dr. Sun's review for details of these exposures.

Dr. Sun's DPHM review reached the following conclusions:

- **Pregnancy:** Although tirzepatide is not recommended to be used during pregnancy due to its weight loss effect, it will likely be used in females of reproductive potential, and there may be unintended exposures during the first trimester before the pregnancy is recognized. Because there are currently insufficient data regarding tirzepatide use in pregnancy, use of tirzepatide in pregnant animals resulted in fetal growth reduction and fetal malformations, and unintended pregnancy exposure has occurred with the already approved tirzepatide product, it is important to evaluate the safety of tirzepatide during pregnancy via Post-Marketing Requirements (PMRs, see Section 12).
- **Lactation:** There are insufficient data currently to characterize the effects of tirzepatide on the breastfed infant, as postmarketing surveillance identified only 2 spontaneously reported cases of tirzepatide exposure during lactation (neither with reported AEs). Other peptide GLP-1R agonists are present in human milk, so tirzepatide is likely to be present in human milk. FDA issued a PMR for a clinical lactation study at the time of T2D NDA 215866 approval, and since this study is underway another PMR for a clinical lactation study is not required for this NDA.
- **Fertility:** Animal reproductive studies did not show any adverse effects of tirzepatide on fertility, and there are no human data on tirzepatide adversely affecting male or female fertility. Four postmarket cases of decreased libido or sexual problems do not raise concerns due to the likely high background occurrence of such issues. Like tirzepatide for T2D (Mounjaro), the label for this NDA should include language on delayed gastric emptying and oral contraceptive use (see Section 4.5).

8.8.3. Pediatrics and Assessment of Effects on Growth

Not applicable; this submission only included studies in adults (i.e., for eligibility subjects had to be ≥18 years of age). Please refer to Section 12 for information related to Postmarketing Requirements and Commitments for pediatric assessments.

⁵⁸ Review of NDA 215866,
https://www.accessdata.fda.gov/drugsatfda_docs/nda/2022/215866Orig1s000OtherR.pdf

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

In clinical development of tirzepatide, overdose was defined as taking more than 15 mg of tirzepatide in less than 72 hours. In CWM trials GPHK and GPHL, a total of 11 subjects met this definition of overdose, each with one event. No tirzepatide overdose events were serious or severe, or resulted in study drug discontinuation. One subject experienced AEs at the time of the overdose event: subject (b) (6) had two pre-existing mild TEAEs of nausea and dyspepsia increase in severity to moderate on the day of the overdose, but there was no subsequent dose adjustment, interruption, or discontinuation.

Reviewer comment: Given the rarity of tirzepatide overdoses, risk evaluation is limited. GI AEs are the likeliest outcome of a tirzepatide overdose, but the risk of more significant effects (e.g., hypoglycemia, acute renal failure due to volume losses) cannot be ruled out.

The Applicant used “Drug abuse and dependence” SMQs to screen for drug abuse events in trials GPHK and GPHL, and only one AE of “substance abuse” was found: subject (b) (6) is described in Section 8.4.1 on deaths, as she died of acute hepatic failure and multiorgan failure after being found unresponsive in the setting of alcohol use, a positive urine drug screen for opiates and cocaine, and COVID-19 infection.

Reviewer comment: I feel that an association of tirzepatide with substance abuse in this subject is unlikely, and this one case with many confounding factors does not change the overall safety profile of tirzepatide.

The Applicant used a “Drug withdrawal” SMQ to screen for potential withdrawal and rebound events in trials GPHK and GPHL, and none were found.

The findings for overdose, drug abuse, withdrawal and rebound in tirzepatide trials for CWM are consistent with trials for T2D as reviewed in NDA 215866, and with other incretin products. In conclusion, the concern for overdose, drug abuse, withdrawal, or rebound is low with the use of tirzepatide.

8.9. Safety in the Postmarket Setting

8.9.1. Safety Concerns Identified Through Postmarket Experience

Tirzepatide was FDA-approved for treatment of T2D in the U.S. on May 13, 2022, and it has since been authorized for T2D in 42 other countries. It is estimated that (b) (4) patients have received tirzepatide worldwide.

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To identify post-marketing safety issues, the Office of Pharmacovigilance and Epidemiology, Division of Pharmacovigilance-I (DPV-I), has documented their Postmarket Drug Safety Surveillance Summary for Mounjaro. Please refer to Dr. Christine Chamberlian's report on October 13, 2023, for details. Briefly, DPV-1 conducted:

- a search of the FAERS database covering May 13, 2022, to August 3, 2023
- a search of the medical literature
- a review of the Periodic Safety Update Reports (PSURs) and Periodic Adverse Drug Experience Reports (PAEERs) submitted for tirzepatide.

DPV-I summarized the following New Identified Safety Signals (NISS) for tirzepatide, for evaluation in post-marketing data:

- Hypoglycemia (in patients without concomitant use of insulin or insulin secretagogues) was identified as a NISS in the most recent surveillance summary and is in pre-evaluation
- Impaired gastric emptying is in pre-evaluation
- Alopecia, Aspiration, and Suicidal Ideation are under evaluation
- Intestinal obstruction (ileus) and Dysgeusia had action taken
- Eosinophilia, Hypersensitivity, and Cutaneous Amyloidosis are closed.

I also reviewed the Applicant's 120-day safety update submitted on August 8, 2023 (Table 120), which included postmarketing safety data through May 13, 2023. The Applicant concludes these data are consistent with the initial tirzepatide CWM NDA, and I concur.

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Table 120. Applicant Tirzepatide Trials Contributing Safety Data to the 120-Day Safety Update Report

Phase Disease/State Study	Completed ^a	Ongoing	Blinded	Unblinded	Presented Individually	Pooled
Phase 2, 3, and 4 studies						
CWM						
GPHK ^b						
GPHM						
GPHN ^c		X	X			X
GPHZ						
GPIA						
T2DM						
GPHD	X			X	X	
GPHE		X		X	X	
GPIH		X		X	X	
GPII		X		X	X	
GPII		X	X		X	
GPGV		X	X		X	
CVOT						
GPGN		X	X		X	
HFpEF						
GPID		X	X		X	
OSA						
GPIF master protocol		X	X			X
GPI1						
GPI2						
MMO						
GPIJ		X	X		X	
NASH						
GPHR		X	X		X	
CKD						
GPIG		X	X		X	
Phase 1 studies						
GPGU	X			X	X	
GPHH		X	X		X	
GPHV ^d		X		X	X	
GPIP		X		X	X	

Abbreviations: CKD = chronic kidney disease; CWM = chronic weight management; CVOT = cardiovascular outcome trial; HFpEF = heart failure with preserved ejection fraction; MMO = morbidity and mortality in obesity; NASH = nonalcoholic steatohepatitis; OSA = obstructive sleep apnea; T2DM = type 2 diabetes mellitus.

^a Completed studies are defined as having an approved clinical study report.

^b The data include only the ongoing additional 2-year treatment period (including the 17-week safety follow-up) for participants with prediabetes at randomization.

^c The data include only the 52-week double-blind treatment period and 4-week safety follow-up.

^d Study GPHV is investigator- and participant-blinded, but not sponsor-blinded. Therefore, it is treated as unblinded for purposes of the safety update report.

Note: Phase 3 CWM Study GPHJ is considered ongoing, but contributed no safety data because no participants had been randomized to treatment as of 28 April 2023.

Source: Applicant Safety Update dated August 8, 2023.

8.9.2. Expectations on Safety in the Postmarket Setting

The tirzepatide clinical development program provides a substantial amount of safety information to characterize the safety profile of tirzepatide in adult populations for CWM and/or T2D. Older patients (age ≥ 75 years), patients with renal insufficiency, and patients with high cardiovascular risk were not highly represented in phase 3a trials for approval, but these populations are being studied in ongoing trials including CVOTs.

While the Division does not endorse off-label use, I anticipate that tirzepatide may be used off-label for weight loss in people with BMI $< 27 \text{ kg/m}^2$ and without T2D, a population in which safety has not been established. Although tirzepatide could be reasonably expected to produce weight loss in these patients, there is no expected clinical benefit of weight loss in patients with normal/healthy baseline BMI, and it is unknown whether weight loss in patients who are overweight but without weight-related comorbidities would translate to improved clinical outcomes (such as cardiovascular benefit). Therefore, given the uncertain benefit/risk, the Division does not currently indicate weight management drugs for use individuals with normal weight (BMI $< 25 \text{ kg/m}^2$) or mild overweight (BMI 25.0 to $< 27 \text{ kg/m}^2$), or in those with overweight (BMI 27.0 to $< 30 \text{ kg/m}^2$) without comorbidities. The pharmacokinetics of tirzepatide (see Section 4.5) indicate higher exposures at lower body weight or BMI, though no weight-based dose adjustment is recommended due to the dose titration approach and routine clinical monitoring. Therefore, it is unknown whether those with lower BMIs using tirzepatide off-label may be at increased risk for some dose-related adverse events.

The observed safety concerns identified in these submissions can be adequately addressed with proposed product labeling and routine pharmacovigilance for the indicated population. In conclusion, no additional risk evaluation and mitigation strategy (REMS) is recommended for this product.

8.9.3. Additional Safety Issues from Other Disciplines

Safety issues from other disciplines are discussed elsewhere in this review (see Section 4).

8.10. Integrated Assessment of Safety

The safety of tirzepatide for CWM was primarily evaluated in two phase 3 trials (GPHK and GPHL), in which 2519 subjects were exposed to at least one dose. The safety profile of tirzepatide in the CWM program is generally consistent with the safety profile characterized in the tirzepatide T2D program (at the same dosages) as well as other GLP-1R agonists, including liraglutide and semaglutide for CWM.

In trials GPHK and GPHL, deaths and serious TEAEs were balanced between tirzepatide and

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placebo groups and did not raise safety concerns. More TEAEs graded as severe and/or leading to study drug discontinuation were reported in tirzepatide groups, driven by GI events. Overall subjects with any TEAEs were relatively balanced between tirzepatide and placebo (with slight imbalances tirzepatide > placebo in trial GPHK and placebo > tirzepatide in trial GPHL).

Section 8.5 on Analysis of Submission-Specific Safety Issues has 17 subsections reviewing categories of AESI or special safety concerns.

Nine of these safety issues (Sections 8.5.1-9) detail known safety concerns for tirzepatide and other incretin drugs. These issues will be labeled in Section 5 (Warnings and Precautions) of the USPI and elsewhere in the tirzepatide label for CWM:

- **Thyroid safety (8.5.1)**: Though no cases of MTC or C-cell hyperplasia were observed in trials, there was the expected small increase in blood calcitonin that was not clinically meaningful. Label Section 5 will include “Risk of Thyroid C Cell Tumors” describing nonclinical data, and Section 4 will include the contraindication for personal or family history of MTC of MEN2. Since MTC is rare, tirzepatide will also have a postmarketing MTC registry as required for other incretin drugs.
- **Gastrointestinal disorders (8.5.2)**: GI TEAEs including serious and severe events occurred as expected for tirzepatide. Label Section 5 will include “Severe Gastrointestinal Disease” and Section 6.1 “Gastrointestinal Adverse Reactions.”
- **Acute kidney injury (8.5.3)**: This risk is labeled in Section 5 for other incretin drugs for T2D or CWM, noting the association with hypovolemia caused by GI TEAEs. Rare but slightly imbalanced events of AKI and dehydration occurred in tirzepatide CWM trials, so this labeling in Section 5 is appropriate.
- **Acute gallbladder disease (8.5.4)**: This risk is labeled in Section 5 for other incretin drugs and will be for tirzepatide for CWM. Rare but imbalanced gallbladder events (correlated with degree of weight loss) occurred in tirzepatide CWM trials, so this labeling in Section 5 is appropriate.
- **Pancreas safety (8.5.5)**: Risk of acute pancreatitis is labeled in Section 5 for other incretin drugs, noting any numerical imbalances in exposure-controlled incidences (events per 100 patient years of exposure). Such an imbalance (0.23 with tirzepatide versus 0.11 with comparators) is noted in the label of tirzepatide for T2D, but imbalance was not observed in the CWM trials (0.14 with tirzepatide versus 0.15 with placebo). Therefore, labeling of “acute pancreatitis” in Section 5 will include all four of these exposure-controlled incidences. Tirzepatide was also associated with the expected small increases in blood amylase and lipase that was not apparently clinically meaningful, and this will be noted in Section 6.1 under laboratory abnormalities.
- **Hypersensitivity reactions (8.5.6)**: These are in label Section 5 for tirzepatide for T2D, noting postmarketing reports of serious events in tirzepatide-treated patients. In the CWM trials, serious hypersensitivity reactions were very rarely (0.1%) reported in tirzepatide-treated subjects and not in placebo-treated subjects, and this will be noted in Section 5 of the CWM label. Mild and moderate hypersensitivity reactions were

common and will be listed in the Section 6.1 table of common adverse reactions, with a subsection noting the distinction between immediate and non-immediate hypersensitivity reactions, and the association with ADA-positivity.

- **Hypoglycemia (8.5.7)**: Hypoglycemia in patients with T2D is in label Section 5 for tirzepatide for T2D, with similar findings in CWM trial GPHL justifying the similar language in Section 5 of the label for CWM. In trial GPHK of subjects without T2D, there was also Imbalanced occurrence of blood glucose <54 mg/dl, so potential risk of hypoglycemia in patients without T2D will be addressed in label Section 5, with the incidence numbers in Section 6.1.
- **Diabetic retinopathy complications in T2D (8.5.8)**: These are in label Section 5 for tirzepatide for T2D, with similar findings in CWM trial GPHL justifying the similar language in Section 5 of the label for CWM.
- **Psychiatric Disorders (8.5.9)**: All CWM products currently include a Section 5 warning and precaution about “Suicidal behavior and ideation,” even when no imbalances are found in the respective in clinical trials, as was the case for tirzepatide as detailed above.

Three safety issues (Sections 8.5.10-12) detail common TEAEs for tirzepatide and some other incretin drugs that merit subheadings in label Section 6.1:

- **Hypotension (8.5.10)**: These events were imbalanced, and the review above found associations with antihypertensive medication use, and with GI AEs leading to dehydration, so these will be noted in label Section 6.1.
- **Injection site reactions (8.5.11)**: These events were imbalanced, and the review above found associations with ADA-positivity, and this will be noted in label Section 6.1.
- **Hair loss (8.5.12)**: No other incretin products to date have a Section 6.1 subheading on hair loss (it is noted in the table of common of adverse reactions for semaglutide for CWM without a subheading), but this is justified for tirzepatide for CWM. The detailed review of hair loss above demonstrates higher occurrence in female subjects correlated with the degree of weight loss, and these will be noted in the label.

The remaining five safety issues (Sections 8.5.13-17) were reviewed in detail and did not raise any safety concerns that would be included in labeling:

- **Cardiovascular safety (8.5.13)**: MACE events were rare and CEC-adjudicated in tirzepatide CWM trials, with a higher incidence in the placebo than tirzepatide arms. A CVOT is ongoing.
- **Liver safety (8.5.14)**: There were 3 potential Hy’s Law case and other cases of transaminase elevations in the development of tirzepatide for CWM, but a review of these cases revealed no concern for DILI that would merit inclusion in labeling.
- **Neoplasm safety (8.5.15)**: Malignant neoplasm TEAEs were rare in tirzepatide CWM trials, with a higher incidence in the placebo than tirzepatide arms. Reports of the benign neoplasm of uterine leiomyoma showed a higher incidence in tirzepatide than placebo arms, but these events were rare and potentially attributable to detection bias.
- **Other diabetes-related safety issues (8.5.16)**: The Applicant analyzed CWM trial GPHL

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in subjects with T2D for occurrence of metabolic acidosis, hyperglycemia, and amputation or peripheral revascularization. The same analyses were conducted in the development of tirzepatide for T2D, and there were no concerning findings in either development program that would lead to inclusion in labeling.

- **Rare events (8.5.17):** Falls were identified as a rare but imbalanced AE, but a case-level review revealed no safety concern for tirzepatide. Regarding risk of gastroparesis, Section 5 of the tirzepatide label for T2D and proposed label for CWM notes that tirzepatide “has not been studied in patients with severe gastrointestinal disease, including severe gastroparesis, and is therefore not recommended in these patients.” Review of 3 potential gastroparesis TEAEs in the two CWM trials also did not raise a safety concern that would merit further mention in labeling.

In addition, incretin drugs increase heart rate as a class effect, and this was the case for tirzepatide. As detailed in Section 8.4.7 on vital signs, these pulse increases are small and unlikely to be clinically meaningful, so inclusion as a subheading in label Section 6.1 is appropriate and consistent with the labeling of tirzepatide for T2D and most other incretin drugs.

The most significant uncertainty regarding the safety of tirzepatide and other incretin drugs regards long-term use. The indications of CWM and T2D require chronic use, and of course the clinical trials are limited in duration. Given the widespread use of incretin drugs like tirzepatide, post-marketing and real-world data will inform the long-term safety profile of this class and the individual drugs. Despite this inevitable uncertainty, tirzepatide merits approval since it meets the Division’s expectations for CWM products, with one-year data in a large development program with two adequate and well-controlled trials and a sufficiently-sized safety database.

The safety of tirzepatide in pregnancy is another area of uncertainty. Weight loss is not recommended in pregnant patients, but patients may become pregnant while taking tirzepatide for CWM, prior to discontinuing it as recommended when pregnancy is discovered. Limited available clinical data do not raise concerns for fetal or maternal harm on tirzepatide, but two PMRs for pregnancy surveillance are recommended to collect more data (see Section 12).

In summary, taking into consideration tirzepatide’s safety profile as expected for an incretin and its substantial efficacy for CWM in adults, I conclude that the safety data submitted to this NDA is acceptable for approval of this product.

9. Advisory Committee Meeting and Other External Consultations

Not applicable.

10. Labeling Recommendations

10.1. Prescription Drug Labeling

The Applicant submitted proposed prescribing information (PI) for ZEPBOUND, which was reviewed for accuracy, consistency with labeling of tirzepatide for T2D (MOUNJARO), consistency with labeling of other products (including other CWM drugs and GLP-1R agonists, particularly semaglutide/WEGOVY), and to remove any language that might minimize safety findings or imply efficacy claims. Edits to the PI were made directly in that document as part of labeling negotiations with the Applicant. Those label sections with relevant issues identified in this review are discussed below.

Section 1. Indications and Usage

- (b) (4) was removed as a weight-related comorbid condition, (b) (4)

Section 2. Dosage and Administration

- A section 2.1 on “Patient Selection” including a Table 1 “BMI conversion chart” was added based on FDA feedback. Although I do not believe such a chart is necessary as most patients and providers use online BMI calculators, it will be included for consistency with other CWM product labels.
- A section 2.3 on “Recommendations Regarding Missed Dose” was added, moving information on missed doses and administration day changes to here.
- Section 2.2 on “Recommended Dosage”:
 - The final label will include language to “consider treatment response and tolerability when selecting the maintenance dosage.” This language allows providers and patient flexibility in dose selection without unnecessarily pushing for higher doses that may be poorly tolerated.
 - The FDA review team reached consensus that, based on the trial designs, three “recommended maintenance dosages” of 5, 10, and 15 mg will be labeled. Only the 2.5 mg dosage will be specifically excluded (“for treatment initiation and not intended for weight management”), allowing prescribers the flexibility to use intermediate dosages of 7.5 mg and 12.5 mg in selected patients.
 - The 5 mg maintenance dosage was not studied for CWM in subject with T2D (Trial GPLH), but as detailed in Section 7.1.1 and Section 8.4.5, there is evidence supporting 5 mg as an effective and safe recommended maintenance dosage in patients with or without T2D.
 - The label will include information on dose reduction due to intolerability, recommending reduction to a lower maintenance dosage..

Section 5. Warnings and Precautions

- To provide better context on the absolute and relative risks of these events, incidence data in CWM trials was added to each subsection where relevant.
- In Section 5.3 on “Acute Kidney Injury,” the Applicant proposed monitoring renal function [REDACTED] (b) (4) [REDACTED] the final label states to “monitor renal function in patients reporting adverse reactions to ZEPBOUND that could lead to volume depletion.”
- For Section 5.5 on “Acute Pancreatitis,” the Applicant had included exposure-controlled incidence only in the tirzepatide CWM trials, in which there was no apparent imbalance. However, the label for MONJARO includes this data for tirzepatide T2D trials, in which there was an approximately 2-fold imbalance noted. Therefore, both data will be included to avoid minimizing the potential risk.
- The title and content of Section 5.7 were changed from [REDACTED] (b) (4) [REDACTED] to the more general “Hypoglycemia” including patients with and without T2D. This is consistent with labeling of WEGOVY and supported by the hypoglycemia incidence in patients without T2D, which will be included in Section 6.1.
- A Section 5.9 on “Suicidal Behavior and Ideation” was added for consistency with other CWM products, including the GLP-1R agonists WEGOVY and SAXENDA.

Section 6. Adverse Reactions

- I agree with the Applicant’s proposed combinations of adverse event PTs as described in the Table 2 footnotes.
- In Section 6.1 under “Common Adverse Reactions” and subheading “Hypotension,” we added incidences and noted that GI events and dehydration could cause hypotension even in the absence of concomitant antihypertensive medications (see Section 8.5.10).
- In Section 6.1 under “Common Adverse Reactions” and subheading “Hypersensitivity Reactions,” we added the relevant distinction between immediate and non-immediate reactions since the incidences of these differed (see Section 8.5.6).
- In Section 6.1 under “Common Adverse Reactions,” we added a subheading and section on “Hair Loss.” While the WEGOVY label lists hair loss is listed in the section 6.1 table of common reactions, for tirzepatide it was necessary to provide additional context that the AE was sex-dependent and correlated with weight loss (see Section 8.5.12).
- In Section 6.1 under “Other Adverse Reactions,” we added data about AKI, acute gallbladder disease, acute pancreatitis, and hypoglycemia, repeating information from Section 5. 21 CFR 201.57(c)(7) states that Section 6 “must describe the overall adverse reaction profile of the drug based on the entire safety database,” which FDA currently interprets as even if discussed in another section of labeling (e.g., Warnings and Precautions).
- “Heart Rate Increase” is Section 6.1 under “Other Adverse Reactions,” consistent with the labeling of MOUNJARO. “Heart Rate Increase” is in Section 5 for WEGOVY, but I

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believe that labeling in Section 6.1 is appropriate for tirzepatide (see Section 8.4.7).

- In Section 6.2 “Postmarketing Experience,” we added ileus for consistency with the current MOUNJARO label.

Section 8. Use in Specific Populations

- In Section 6.1 on “Pregnancy,” we added and revised language including “Weight loss offers no benefit to a pregnant patient and may cause fetal harm. Advise pregnant patients that weight loss is not recommended during pregnancy and to discontinue ZEPBOUND when a pregnancy is recognized.” This language reinforces the guideline that some weight gain is recommended during pregnancy even in patients with overweight or obesity (see Section 8.8.2).

Section 12. Clinical Pharmacology

- In Section 12.1 on “Mechanism of Action,” edits were made as detailed in the nonclinical review (see Section 4.4).
- In Section 12.2 on “Pharmacodynamics,” we qualified the statement on insulin sensitivity noting the clamp study was performed in subjects with T2D as detailed in the clinical pharmacology review (see Section 4.5).

Section 14. Clinical Studies

- [REDACTED] (b) (4)
- In Section [REDACTED] (b) (4) revisions were made to the data tables, including replacing [REDACTED] (b) (4) with percent differences from placebo and revising some statistical footnotes.
- In Section [REDACTED] (b) (4) we advised removal of [REDACTED] (b) (4)
- In Section [REDACTED] (b) (4) we also advised removal of [REDACTED] (b) (4)

Labeling for this NDA was also reviewed collaboratively by Dr. Kelly Jackson from the Division of Medical Policy Programs (DMPP) and Dr. Ankur Kalola from the Office of Prescription Drug Promotion (OPDP). Their consult (dated October 17, 2023) reviews that the Applicant’s proposed PI, Medication Guide (MG), and Instructions for Use (IFU). Their review:

- simplified wording and clarified concepts where possible in all labeling including the PI
- ensured that the MG and IFU are consistent with the PI
- removed unnecessary or redundant information
- ensured that the MG and IFU is free of promotional language or suggested
- revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20

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- ensured that the MG and IFU meets the criteria as specified in FDA’s Guidance for Useful Written Consumer Medication Information (published July 2006).

DMEPA also reviewed this NDA for safety, with a review from Drs. Ariane Conrad and Idalia Rychlik filed on August 17, 2023. They performed a risk assessment of the proposed PI, IFU, container labels, and carton labeling for Zepbound to identify areas of vulnerability that may lead to medication errors and other areas of improvement. They found the PI and IFU were acceptable from a medication error perspective, while they identified some areas of concern for the proposed carton and container labels, recommending changes to improve clarity. These changes included capitalization and font colors, formatting of the expiration date, separation of the two barcodes on each container, and inclusion of product identifier on each carton, as detailed in Dr. Conrad’s DMEPA review. The Applicant submitted revised container and carton labeling, and Drs. Conrad and Rychlik filed a memo on October 31, 2021, confirming that the Applicant had implemented their recommendations. The DMEPA-1 human factors team also recommended labeling of the needle end of the auto-injector to avoid user error, and the Applicant agreed to this (see Section 4.7).

Comments from DMPP, OPDP, and DMEPA, in addition to other review disciplines, were sent to the Applicant during labeling negotiations, and the final labeling is pending at the time of this review.

10.2. Nonprescription Drug Labeling

Not applicable for this submission.

11. Risk Evaluation and Mitigation Strategies (REMS)

A REMS is not necessary for this NDA, as the safety issues can be addressed through labeling, postmarketing requirements, and routine pharmacovigilance.

12. Postmarketing Requirements and Commitments

Below in bold are the 6 postmarketing requirements (PMRs) that will be issued for tirzepatide; no postmarketing commitments (PMCs) are recommended for this application. The text provides rationale from a clinical perspective. Note that a milk-only lactation study is a PMR for

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tirzepatide under T2D NDA 215866 (see Section 8.8.2), so this study is not a PMR for the current CWM NDA.

Under the Pediatric Research Equity Act (PREA), all applications for new active ingredients, 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. As part of the agreed initial Pediatric Study Plan (iPSP) for tirzepatide for CWM under IND 139721, the Division agreed to waiving the pediatric study requirement for ages 0 through 5 years (inclusive), and to deferring the studies in ages 6-11 and 12-17 (inclusive). The Applicant's deferred pediatric studies are required as postmarketing studies.

As detailed in the iPSP, the phase 3 CWM trial in adolescent subjects should be initiated once preliminary safety and efficacy are established in adults aged ≥ 18 years, by trials GPHK and GPHL in the current NDA. The final protocol I8F-MC-GPHP (SURMOUNT-ADOLESCENTS) was submitted, so there is no protocol submission milestone for this PMR.

- 1) Conduct a 72-week, randomized, double-blind, placebo-controlled, multicenter, parallel-arm study to evaluate the safety and efficacy of Zepbound (tirzepatide) as an adjunct to lifestyle intervention for chronic weight management in pediatric patients aged 12 to 17 years (inclusive) with obesity.**

Study Completion: February 2027

Final Report Submission: August 2027

For younger pediatric subjects aged 6-10 years, the Applicant is conducting a PK study for dose selection prior to the phase 3 safety and efficacy study. The final PK protocol I8F-MC-GPHV was submitted, so there is no protocol submission milestone for this PMR.

- 2) Conduct a safety, tolerability, pharmacokinetic, and pharmacodynamic study of Zepbound (tirzepatide) administered subcutaneously in pediatric patients aged 6 to 11 years (inclusive) with obesity. Data from this study should be considered when choosing dose(s) for the safety and efficacy trial in this pediatric population.**

Study Completion: May 2025

Final Report Submission: October 2025

(b) (4)

- 3) Conduct a 72-week, randomized, double-blind, placebo-controlled, multicenter, parallel-arm study to evaluate the safety and efficacy of Zepbound (tirzepatide) as an**

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adjunct to lifestyle intervention for chronic weight management in pediatric patients aged 6 to 11 years (inclusive) with obesity.

Draft Protocol Submission: October 2025

Final Protocol Submission: April 2026

Study Completion: December 2029

Final Report Submission: June 2030

Two complementary pregnancy PMRs are recommended, a registry and an additional study, as detailed in the DPMH consult from Dr. Wenjie Sun dated September 11, 2023.

- 4) Collect global data from a prospective pregnancy exposure registry, preferably a disease-based multi-product pregnancy registry, using a registry-based cohort study to compare the maternal, fetal, and infant outcomes of women exposed to Zepbound (tirzepatide) for chronic weight management during pregnancy with unexposed comparator population(s). Align the study protocol with protocol(s) outside the United States to reach the target sample size. The registry will identify and record pregnancy complications, major and minor congenital malformations, spontaneous abortions, stillbirths, elective terminations, preterm births, small-for-gestational-age births, and any other adverse outcomes, including postnatal growth and development. These outcomes will be assessed throughout pregnancy. Infant outcomes, including effects on postnatal growth and development, will be assessed through at least the first year of life.**

Draft Protocol Submission: June 2024

Final Protocol Submission: June 2025

Interim Report Submission: June 2026

June 2028

June 2030

June 2032

June 2034

Study Completion: June 2035

Final Report Submission: June 2036

- 5) Conduct an additional pregnancy study that uses a different design from the pregnancy exposure registry (for example a cohort study using claims or electronic medical record data) to compare the risks and prevalence of pregnancy and infant outcomes (including but not limited to major congenital malformations, spontaneous abortions, stillbirths, small-for-gestational-age births, preterm births, and postnatal growth and development) between women exposed to Zepbound (tirzepatide) for chronic weight management during pregnancy and unexposed comparator population(s).**

Draft Protocol Submission: September 2024

Final Protocol Submission: September 2025

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Interim Report Submission: September 2026
September 2028
September 2030
Study Completion: September 2031
Final Report Submission: September 2032

Since approval of the first long-acting GLP-1R agonist in 2010, sponsors of long-acting GLP-1R agonists have been required to participate in a MTC surveillance study (registry-based case series of at least 15 years in duration) as a PMR to systematically monitor the annual incidence of MTC in the U.S., and to identify any increase in incidence related to the introduction of long-acting incretin drugs into the U.S. marketplace.

- 6) Conduct a medullary thyroid carcinoma registry-based case series 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 Zepbound (tirzepatide) for the treatment of overweight and obesity into the marketplace. This study will also establish a registry of incident cases of medullary thyroid carcinoma and characterize their medical histories related to the use of Zepbound (tirzepatide) for the treatment of obesity/overweight.**

Draft Protocol Submission: May 2024
Final Protocol Submission: May 2025
Interim Report Submission: May 2026
May 2027
May 2028
May 2029
May 2030
May 2031
May 2032
May 2033
May 2034
May 2035
May 2036
May 2037
May 2038
May 2039
May 2040
Study Completion: August 2040
Final Report Submission: August 2041

PMR communications from FDA were sent to the Applicant during NDA review, and the final PMR language was agreed upon by the Applicant on November 1, 2023.

13. Appendices

13.1. References

References appear throughout this review document in footnotes.

13.2. Financial Disclosure

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The Applicant has adequately disclosed financial interests/arrangements with clinical investigators. As detailed above for the individual trials in Section 6 of this review, these financial interests/arrangements do not raise concerns about integrity of the data.

Covered Clinical Study (Name and/or Number): SURMOUNT-1 (18F-MC-GPHK)

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: <u>700</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>7</u>		
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: <u>0</u> Significant payments of other sorts: <u>7</u> Proprietary interest in the product tested held by investigator: <u>0</u> Significant equity interest held by investigator in Sponsor of covered study: <u>0</u>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>0</u>		
Is an attachment provided with the reason: not applicable	Yes ☐	No ☐ (Request explanation from Applicant)

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Covered Clinical Study (Name and/or Number): SURMOUNT-2 (18F-MC-GPHL)

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: <u>410</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>3</u>		
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: <u>0</u> Significant payments of other sorts: <u>2</u> Proprietary interest in the product tested held by investigator: <u>0</u> Significant equity interest held by investigator in Sponsor of covered study: <u>1</u>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>0</u>		
Is an attachment provided with the reason: not applicable	Yes ☐	No ☐ (Request explanation from Applicant)

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

RAYMOND E SOCCIO
11/07/2023 04:58:05 PM

LAURA B HIGGINBOTHAM
11/07/2023 05:04:00 PM