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APPLICATION NUMBER:

217806Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader Summary Review for Regulatory Action

Date	(electronic stamp)
From	Laura Higginbotham, MD, MPH
Subject	Cross-Discipline Team Leader Summary Review
NDA/BLA # and Supplement #	NDA 217806
Applicant	Eli Lilly and Company
Date of Submission	November 17, 2022; May 8, 2023 (rolling review)
PDUFA Goal Date	November 8, 2023
Proprietary Name	Zepbound
Established or Proper Name	Tirzepatide
Dosage Form(s)	Injection, for subcutaneous use
Applicant Proposed Indication(s)/Population(s)	<p><i>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:</i></p> <ul style="list-style-type: none"> ○ <i>30 kg/m² or greater (obesity) or</i> ○ <i>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)</i>
Action or Recommended Action:	Approval
Approved/Recommended Indication(s)/Population(s) (if applicable)	<p><i>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:</i></p> <ul style="list-style-type: none"> ○ <i>30 kg/m² or greater (obesity) or</i> ○ <i>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)</i>

Material Reviewed/Consulted	Names of Discipline Reviewers
OND Action Package, including:	
Clinical Review	Raymond Soccio, MD, PhD
Statistical Review	Kyunghee K. Song, PhD; Feng Li, PhD
Pharmacology Toxicology Review	Elena Braithwaite, PhD; Patricia Brundage, PhD
OPQ Review – Lead	Theodore Carver, PhD
Process/Facility	Naresh Pavurala, PhD; Nallaperumal Chidambaram, PhD
Microbiology Review	Aditi Das, PhD; Yuansha Chen, PhD
OBP Review	Faruk Sheikh, PhD; Harold Dickensheets, PhD
DBVI Consult Review	Tengfei Li, PhD; Meiyu Shen, PhD
Clinical Pharmacology Review	Mohamad Kronfol, PhD; Edwin Chow, PhD
Pharmacometrics Review	Jiajun Liu, PharmD, MSc; Justin Earp, PhD
DCOA Consult Review	Qing Xie, PhD; Selena Daniels, PharmD, PhD
PFSS Consult Review	Xin Yuan, PhD; Lili Garrard, PhD
DPMH	Wenjje Sun, MD; Miriam Dinatale, DO
Human Factors	Neha Kumar, PharmD; Murewa Oguntimein, PhD, MHS; Jason Flint, MBA
OSI	Ling Yang, MD, PhD; Min Lu, MD, MPH
OPDP	Ankur Kalola, PharmD
DMPP	Kelly Jackson, PharmD; Marcia Williams, PhD
DMEPA	Ariane Conrad, PharmD; Idalia Rychlik, PharmD
DEPI	Po-Yin Chang, PhD; Yandong Qiang, MD
DPV	Christine Chamberlain, PhD; Daniel Woronow, MD
RPM	Arati Kamath, PhD

OND=Office of New Drugs
 OPQ=Office of Pharmaceutical Quality
 OBP=Office of Biotechnology Products
 DBVI=Division of Biometrics VI
 DCOA=Division of Clinical Outcome Assessment
 PFSS=Patient-Focused Statistical Support
 DPMH=Division of Pediatrics and Maternal Health
 OSI=Office of Scientific Investigations
 OPDP=Office of Prescription Drug Promotion
 DMPP=Division of Medical Policy Programs
 DMEPA=Division of Medication Error Prevention and Analysis
 DEPI=Division of Epidemiology
 DPV=Division of Pharmacovigilance
 RPM=Regulatory Project Manager

APPEARS THIS WAY ON ORIGINAL

1. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

Obesity and overweight are conditions that increase the risk of chronic health disorders, including hypertension, dyslipidemia, type 2 diabetes, cardiovascular disease, and certain cancers. Weight loss of 5-10% in patients through diet and exercise is generally accepted as beneficial on cardiometabolic risk factors. Lifestyle intervention with a reduced-calorie diet and increased physical activity (at least 150 minutes of moderate activity/week) is the standard of care but is usually not successful in achieving sustained weight loss. Use of pharmacologic or surgical therapies is limited by factors including adverse effects, cost, and insurance coverage, and there remains an unmet medical need.

This application provides substantial evidence of effectiveness that tirzepatide injection, administered subcutaneously once weekly, results in clinically meaningful weight loss and improvement in anthropometric and cardiometabolic parameters in patients with obesity or overweight. The benefit of tirzepatide (body weight loss) was demonstrated in two adequate and well-controlled clinical trials. The observed placebo-adjusted weight loss was greater than the goal of 5-10% weight loss from baseline and can reasonably be expected to result in improvement in health outcomes.

The efficacy of tirzepatide was evaluated in two 72-week, randomized, double-blind, placebo-controlled trials. The first randomized, placebo-controlled trial (SURMOUNT-1) evaluated tirzepatide 5 mg, 10 mg, and 15 mg subcutaneously once weekly as adjunctive therapy to a reduced-calorie diet and increased physical activity in patients without diabetes; and the second (SURMOUNT-2) evaluated tirzepatide 10 mg and 15 mg subcutaneously once weekly as adjunctive therapy to reduced-calorie diet and increased physical activity in patients with type 2 diabetes.

In patients without type 2 diabetes, the estimated treatment effect of tirzepatide (5 mg, 10 mg, or 15 mg) as an adjunct to diet and exercise is an approximately 12 to 18% reduction in body weight from baseline compared to placebo. At the highest dose (tirzepatide 15 mg), 91% of patients assigned to tirzepatide achieved at least 5% weight loss and approximately 84% achieved 10% weight loss compared to baseline. In patients with type 2 diabetes, the estimated treatment effect of tirzepatide (10 mg or 15 mg) as an adjunct to diet and exercise is an approximately 10 to 12% reduction in body weight from baseline compared to placebo. At the highest dose (tirzepatide 15 mg), approximately 83% of patients assigned to tirzepatide lost at least 5% of baseline body weight, and 65% lost at least 10% compared to baseline.

Tirzepatide was effective among patients who tolerated target doses of 5 mg, 10 mg, or 15 mg. Effectiveness was not assessed at other dose levels.

The trial results were clinically meaningful and statistically robust. Overall trial quality, including high trial retention, low proportions of treatment discontinuation, and appropriate handling of missing data, support the validity of trial results.

The safety profile of tirzepatide for chronic weight management is similar to that of GLP-1 receptor agonists and the tirzepatide product approved for a type 2 diabetes indication. There were no new safety issues identified in the weight management development program. The most frequent adverse events observed with tirzepatide were gastrointestinal disorders. Other frequent adverse events included injection site reactions, fatigue, hypersensitivity reactions, and hair loss. Acute kidney injury, hypotension and syncope, serious hypersensitivity reactions, and acute gallbladder disease occurred infrequently.

In summary, the weight loss benefit of tirzepatide 5 mg, 10 mg, or 15 mg once weekly outweighs the potential risks in the indicated population. The treatment effect on weight loss is clinically meaningful and expected to improve health outcomes in patients with obesity or overweight. The most common adverse reactions primarily impact tolerability. Other risks, including less common but serious safety issues, are adequately mitigated with labeling, such as a contraindication in patients with history of hypersensitivity to tirzepatide and warnings for severe gastrointestinal disease and acute pancreatitis.

Tirzepatide is safe for use in the indicated population under the proposed conditions of use, as an adjunct to reduced-calorie diet and increased physical activity, for chronic weight management.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
<u>Analysis of Condition</u>	<ul style="list-style-type: none"> • Obesity is a chronic, relapsing disease that impacts millions of patients in the US. The CDC estimates that the prevalence of obesity among adults was 41.9% in 2017. • Obesity increases the risk of comorbid conditions including hypertension, dyslipidemia, type 2 diabetes (T2D), cardiovascular disease, osteoarthritis, obstructive sleep apnea, and certain cancers. • Weight loss of 5-10% in patients with obesity and overweight through lifestyle intervention (diet and exercise) is generally accepted as beneficial on cardiometabolic risk factors. • The cardiovascular benefit of pharmacologic-induced weight loss has not yet been demonstrated in clinical trials to date, though cardiovascular outcomes trials in obese/overweight populations are underway or recently completed (under FDA review). 	<p>Obesity is a chronic disease which increases the risk of cardiovascular disease and other conditions. Any weight loss is considered beneficial, but weight loss of 5-10% is associated with improved cardiovascular biomarkers. Current FDA guidance recommends evaluating drugs intended for chronic weight management in patients with obesity and those with overweight and at least one comorbid condition. Effects on weight should be evaluated after at least one year.</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
<p><u>Current Treatment Options</u></p>	<ul style="list-style-type: none"> • Lifestyle intervention, typically consisting of reduced-calorie diet and moderate-intensity physical activity, is the current standard of care treatment. • Bariatric surgery is effective but is generally reserved for patients with severe obesity. • Currently approved drugs for obesity include orlistat, phentermine/topiramate, naltrexone/bupropion, liraglutide, and semaglutide. • Use of approved medications for chronic weight management is limited by issues such as modest treatment effects, early treatment discontinuation, cost, and lack of insurance coverage, although public acceptance and utilization is increasing. • GLP-1 RAs (liraglutide and semaglutide) have demonstrated cardiovascular benefit in patients with T2D. A cardiovascular outcomes trial (CVOT) of semaglutide 2.4 mg in patients with obesity/overweight recently completed and is under FDA review. 	<p>Lifestyle intervention is not effective in most patients. GLP-1 RAs are increasingly prescribed for chronic weight management based on improved treatment effect and evidence of cardiovascular benefit in a related population. The cardiovascular benefit of pharmacologic-induced weight loss has not yet been demonstrated in clinical trials to date.</p>
<p><u>Benefit</u></p>	<ul style="list-style-type: none"> • Change in mean percent weight reduction from baseline to Week 72, placebo-adjusted treatment difference <ul style="list-style-type: none"> ○ Patients without diabetes <ul style="list-style-type: none"> ▪ Tirzepatide 5 mg: -11.9% (-13.4%, -10.4%) ▪ Tirzepatide 10 mg: -16.4% (-17.9%, -14.8%) ▪ Tirzepatide 15 mg: -17.8% (-19.3%, -16.3%) ○ Patients with diabetes <ul style="list-style-type: none"> ▪ Tirzepatide 10 mg: -9.6% (-11.1%, -8.1%) ▪ Tirzepatide 15 mg: -11.6% (-13.0%, -10.1%) • Proportion of subjects achieving a clinically meaningful threshold of weight reduction (at least 5%) from baseline to Week 72 	<p>The two randomized, placebo-controlled phase 3 clinical trial results represent substantial evidence of effectiveness that tirzepatide 5 mg, 10 mg, and 15 mg injections result in clinically meaningful weight loss and improvement in cardiometabolic parameters in patients with obesity and overweight, with and without type 2 diabetes.</p> <p>The benefit of tirzepatide was demonstrated in a population of patients that is adequately representative of the intended U.S. population, including demographic groups and patients with</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<ul style="list-style-type: none"> ○ Patients without diabetes <ul style="list-style-type: none"> ▪ Tirzepatide 5 mg: 85.1% ▪ Tirzepatide 10 mg: 88.9% ▪ Tirzepatide 15 mg: 90.9% ▪ Placebo: 34.5% ○ Patients with diabetes <ul style="list-style-type: none"> ▪ Tirzepatide 10 mg: 79.2% ▪ Tirzepatide 15 mg: 82.8% ▪ Placebo: 32.5% <ul style="list-style-type: none"> • Associated cardiometabolic endpoints (waist circumference, blood pressure, glycemic parameters, lipids) were nominally statistically significant or trended in favor of tirzepatide. 	<p>common comorbid conditions.</p>
<p><u>Risk and Risk Management</u></p>	<ul style="list-style-type: none"> • There were no new issues identified in the tirzepatide weight management program that were not previously seen with GLP-1 receptor agonists. • Serious potential risks, such as acute pancreatitis, diabetic retinopathy complications, and suicidal behavior, are unconfirmed, occurred only rarely in patients exposed to tirzepatide, and generally at similar incidence to placebo. • Gallbladder disease, hypoglycemia, acute kidney injury, increased heart rate, and hypotension occurred in clinical trials. • Risks may be addressed in labeling, including a boxed warning for the potential risk of medullary thyroid cancer (MTC). Some risks are the subject of postmarketing requirements. • Common adverse reactions including gastrointestinal disorders resolved without discontinuation in most patients. 	<p>The safety database was adequate to support the proposed indication. Serious risks are rare and can be adequately addressed through labeling and PMRs. Common adverse reactions can be adequately addressed in labeling.</p>

2. Background

Obesity and overweight are chronic, relapsing conditions characterized by excess body fat. Excess body fat increases the risk of cardiovascular and all-cause mortality and the incidence of major comorbid conditions such as type 2 diabetes, hypertension, dyslipidemia, and cardiovascular disease. Obesity affects over 40% of American adults and is difficult to treat. The purpose of medical weight loss is long-term reduction in fat mass with a goal of reduction in morbidity and mortality.

In some observational studies of individuals with obesity and overweight, weight loss of 5% to 10% through diet and exercise has been associated with improvement in cardiovascular risk factors and a reduced risk of cardiovascular disease. FDA's draft guidance for industry, *Developing Products for Weight Management* recommends that weight management medications may be approved on the basis of their effect on body weight and cardiovascular risk factors; nevertheless, medication-induced weight loss has not yet been shown to reduce the risk of cardiovascular events in a randomized controlled trial, although such trials are currently underway or recently completed.

Currently, five drugs are approved in the U.S. as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in patients with obesity, or overweight with at least one weight-related comorbidity: orlistat, phentermine/topiramate, naltrexone/bupropion, liraglutide, and semaglutide. Use of these medications is limited by cost and lack of insurance coverage, although public acceptance and utilization of drugs for weight management, particularly GLP-1 receptor agonists, is increasing.

Tirzepatide is a GLP-1 and GIP receptor agonist. Mounjaro (tirzepatide) injection, at doses of 5 mg to 15 mg once weekly subcutaneously (SC), is approved in the U.S. for glycemic control in adults with type 2 diabetes.

A joint pre-IND / End-of-Phase 2 meeting (later converted to Type C meeting) was held on June 26, 2019. Major topics included phase 3 trial design, dose selection, eligibility criteria, and cardiovascular safety. The NDA Applicant and IND sponsor (Eli Lilly and Company) submitted IND 139721 on October 30, 2019, to evaluate tirzepatide for weight management. The initial clinical protocol was a phase 3, double-blind, placebo-controlled trial (SURMOUNT-1).

A pre-NDA teleconference was held on August 11, 2022. The Applicant submitted the NDA in two sequences (rolling review) on November 17, 2022, and May 8, 2023.

This review serves as the Cross-Discipline Team Leader (CDTL) review and the Decisional Memo. It summarizes the major issues related to approvability and labeling of the NDA. All review disciplines recommend approval. For additional details regarding the trial design, methods, and results, refer to the individual discipline reviews and consult reviews referenced in this document.

3. Product Quality

The Office of Pharmaceutical Quality (OPQ) recommends approval, including approval for all facilities listed in the application. NDA 217806 cross-references all chemistry, manufacturing, and controls (CMC) information to NDA 215866; no new CMC information was submitted in the original NDA 217806. The OPQ team reviewed manufacturing to confirm adequacy of process and facilities, microbiology to address a specific requirement for validation of analytical procedures, quality aspects of the drug product labeling, and the claim for categorical exclusion from environmental assessment. Refer to the OPQ *Integrated Quality Assessment*, authored by the Application Technical Lead Dr. Theodore Carver, for details. I concur with the conclusions and recommendations of the OPQ reviewers.

No new drug substance or drug product data were submitted. Data pertinent to labeling are summarized here. Tirzepatide is a synthetic 39-amino acid modified peptide based on the GIP sequence and contains 2 non-coded amino acids (aminoisobutyric acid, Aib) in positions 2 and 13, a C-terminal amide, and Lys residue at position 20 that is attached to 1,20-eicosanedioic acid via a linker. The molecular weight is 4813.53 Da, and the empirical formula is $C_{225}H_{348}N_{48}O_{68}$. The proposed drug product, Zepbound (tirzepatide) injection, is a clear, colorless to slightly yellow, preservative free, sterile solution provided as a single-dose prefilled pen injector in six strengths (2.5 mg/0.5 mL, 5 mg/0.5 mL, 7.5 mg/0.5 mL, 10 mg/0.5 mL, 12.5 mg/0.5 mL, and 15 mg/0.5 mL) with the following excipients: 4.1 mg of sodium chloride, 0.7 mg of sodium phosphate dibasic heptahydrate, and water for injection, adjusted to pH 6.5 to 7.5 with hydrochloric acid or sodium hydroxide.

Dr. Carver reviewed and recommends approval of the final carton and container labeling, agreed upon with the Applicant.

The Applicant sought exemption from environmental impact analysis, and Dr. Carver granted categorical exclusion from this requirement.

The microbiology reviewer, Dr. Aditi Das, concluded that the proposed microbiological controls are adequate to support approval. Refer to her review for details.

No new manufacturing information was submitted. The process reviewer, Dr. Naresh Pavurala, concluded that the process and facilities information provided and cross-referenced to in NDA 215866 were adequate to support approval.

Dr. Carver recommends that the Zepbound drug product should be stored at 2°C to 8°C (36°F to 46°F) for up to 24 months protected from light.

In summary, Dr. Carver and the individual discipline reviewers all support approval of the application, and I concur with their recommendations.

Device Review

The proposed U.S. commercial presentation is the same as approved under Mounjaro (tirzepatide) NDA 215866. The delivery device consists of a single-use, needle-based injection system that, when activated, automatically inserts the needle into the subcutaneous tissue and delivers 0.5 mL of tirzepatide drug product. Under NDA 215866, Dr. Sreya Tarafdar, the CDRH reviewer evaluated the device component of the combination product and

recommended approval. I concur with her prior recommendation.

Human Factors

The Division of Medication Error Prevention and Analysis (DMEPA) reviewer, Dr. Neha Kumar, concluded that the use-related risk analysis (URRA) provided by the Applicant and the human factors validation data submitted under NDA 215866 did not identify any new, differing, or unique risks for the proposed product compared to representative users for a type 2 diabetes indication. Identified use-related risks for Zepbound can be adequately mitigated by labeling. The DMEPA review provided recommendations for the carton and container labeling and the *Instructions for Use*. I concur with the recommendations.

Immunogenicity Review

The Office of Biotechnology Products (OBP) reviewer, Dr. Faruk Sheikh, concluded that the screening and confirmatory assays used in monitoring the anti-drug antibody (ADA) response were validated and suitable for their intended purpose.

Dr. Sheikh concluded that immunogenicity assessment data suggest that Zepbound (tirzepatide) is highly immunogenic. Using a tiered system of appropriately validated immunogenicity assays, 64.5% of patients treated with tirzepatide in SURMOUNT-1 and SURMOUNT-2 developed treatment emergent ADAs. Of these ADA+ patients, 40% and 16.5% demonstrated ADAs cross-reactive to native GIP and native GLP-1, respectively. Approximately 2.8% and 2.7% of ADA+ patients developed neutralizing antibodies (NAb) against tirzepatide activity on the GIP and GLP-1 receptors, respectively. In addition, 0.8% and 0.1% of the overall ADA+ population were cross-reactive NAb+ against native GIP and GLP-1, respectively. Clinical implications of the high ADA titer are discussed in Section 8 below; however, no significant safety or efficacy concerns were identified in patients who develop ADA. Dr. Sheikh supports approval of the application from an immunogenicity perspective and concluded that a PMC is not required for this application. I concur with these recommendations.

4. Nonclinical Pharmacology/Toxicology

The FDA nonclinical reviewer, Dr. Elena Braithwaite, supports approval of the application. No new nonclinical studies were conducted to support the chronic weight management indication. The Applicant previously conducted a nonclinical program under IND 128801. These studies were submitted and reviewed under NDA 215866 in support of the diabetes indication for tirzepatide. Refer to Dr. Braithwaite's review for details. Major findings relevant to labeling are summarized here.

Tirzepatide is a 39-amino acid peptide agonist of the GLP-1 and GIP receptors, which demonstrated binding to both receptors in humans and nonclinical species. In vivo and in vitro studies, previously reviewed under NDA 215866, indicate that tirzepatide plays a role in lowering body weight and decreasing food consumption. In normal, fasted mice, subcutaneous administration of tirzepatide decreased the rate of gastric emptying. When evaluated in rats fed a high fat/high sucrose diet and in diet-induced obese (DIO) mice,

tirzepatide caused decreases in food intake and body weight. Subcutaneously administered tirzepatide also reduced fat mass, fat-free mass, and plasma cholesterol and increased metabolic rates in DIO mice. In vitro, tirzepatide stimulated cAMP production and lipolysis in mature adipocytes that express the GIPR.

The potential of tirzepatide to induce tumors during long-term clinical use was assessed in a 2-year rat carcinogenicity study and a 6-month transgenic RasH2 mouse study. Consistent with the results of carcinogenicity studies with the GLP-1 receptor agonist class, tirzepatide caused C-cell tumors in the rat carcinogenicity study at clinical exposures. Due to species-specific differences in GLP-1 receptor (GLP-1R) expression and activation, the relevance of these findings to humans is unclear. While no association with GLP-1R agonism and clinical incidence of C-cell tumors has been established to date, a boxed warning has been included in labeling, consistent with long-acting GLP-1R agonist class labeling. No tirzepatide-related neoplastic findings occurred in the 6-month mouse study.

Tirzepatide was tested in a comprehensive battery of assessments in rats and rabbits to evaluate all stages of reproduction and development. To evaluate the safety of treatment from mating to implantation, a combined fertility and embryonic development study was conducted in rats. No tirzepatide effects on male fertility were observed. At clinically relevant exposures, an increased number of female rats experienced prolonged estrous cycles or persistent diestrus and decreases in the number of corpora lutea, implantation sites, and viable embryos. Dr. Braithwaite concluded, under NDA 215866, these observations were likely secondary to the pharmacodynamic effects on food consumption and decreased weight gain related to tirzepatide. Embryofetal development studies showed findings related to reduced food consumption and body weight gain in both pregnant rats and rabbits at clinically relevant exposures. According to Dr. Braithwaite, several of the findings that occurred at clinically relevant exposures, including increased incidences of external, visceral, and skeletal malformations, could not be directly attributed to reduced maternal body weight. Uncertainty regarding the clinical relevance of these findings will be communicated in labeling.

5. Clinical Pharmacology

The FDA clinical pharmacology review team recommends approval, and I concur with the recommendation. Refer to the Office of Clinical Pharmacology review, authored by Dr. Mohamad Kronfol and Dr. Jiajun Liu for details. Major findings are summarized here.

The recommended maintenance dosages of tirzepatide injection for weight management are 5 mg, 10 mg, and 15 mg administered subcutaneously once weekly. Dose escalation is used to mitigate gastrointestinal adverse events. The starting dose is 2.5 mg once weekly followed by a dose-escalation regimen consisting of 2.5 mg increments (2.5 mg, 5 mg, 7.5 mg, 10 mg, 12.5 mg, 15 mg) every 4 weeks until a recommended maintenance dosage is reached. Tirzepatide should be injected subcutaneously in the abdomen, thigh, or upper arm. No dose adjustment is necessary for intrinsic or extrinsic factors or drug-drug interaction. Tirzepatide delays gastric emptying and thereby has the potential to impact the absorption of concomitantly administered oral medications.

The to-be-marketed drug product was used in the two adequate and well-controlled phase 3 chronic weight management (CWM) trials that form the basis of this NDA submission. Additionally, there is no difference between the currently approved formulation under NDA 215866 and the to-be-marketed product for CWM.

Absorption, Distribution, and Elimination

PK is dose proportional between 5 mg and 15 mg. The maximum plasma concentration (C_{max}) was reached at 8 to 72 hours (t_{max}). Absolute bioavailability is approximately 80%, and plasma protein binding is 99%. The apparent volume of distribution at steady state is 9.7 L. Steady-state is reached at approximately 4 weeks following once weekly administration.

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

The terminal half-life is approximately 5 days. Clearance was 0.056 L/h. Renal excretion is the primary route of elimination.

Dose

Exposure-response data from phase 2 dose-finding and dose-escalation trials support the dosing regimen. Results of GPGF, a phase 2 dose-escalation trial, demonstrated that starting treatment on lower doses and escalating dose levels in smaller increments reduced discontinuations due to GI events. This study, together with GPGB (a phase 2 study that examined efficacy in the dose range of 5 mg to 15 mg), provide data to support the final dose selection and dose-escalation regimen.

QT Evaluation

The Applicant did not conduct a dedicated thorough QT study due to challenges with the long half-life of tirzepatide and the titration schedule required to achieve steady-state concentrations at the highest dose of 15 mg. Nonclinical and clinical data (concentration-QT analysis using ECG readings from phase 1/2 trials GPGA, GPGB, and GPGF and from phase 3 trials) do not indicate any unexpected or important effect of tirzepatide at clinically relevant exposures. See the QT-IRT review dated February 16, 2022, under NDA 215866, for details.

6. Clinical Microbiology

The FDA microbiology reviewer, Dr. Das, concluded that the proposed microbiological controls are adequate to support approval. Refer to Section 3 – *Product Quality* of this review and Dr. Das’s review for details.

7. Clinical/Statistical-Efficacy

This section discusses the major design features of the phase 3 clinical trials, the analysis of the primary endpoint, and analyses of secondary endpoints pertinent to labeling. For in-depth discussion of the trials and endpoints not immediately relevant to approval or labeling, refer to the FDA clinical review by Dr. Raymond Soccio. For details of the statistical methods, refer to the FDA statistical review by Dr. Kyunghhee Song.

The efficacy of tirzepatide as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adults with obesity or overweight in the presence of at least one weight-related comorbid condition was evaluated in two 72-week, randomized, double-blind, placebo-controlled trials.

Both Dr. Soccio and Dr. Song recommend approval of tirzepatide as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in the proposed population. I agree with their conclusions.

The data from these trials represent substantial evidence of effectiveness consisting of two adequate and well-controlled trials. The randomized, double-blind, placebo-controlled design allowed the reviewers to distinguish the treatment effect of tirzepatide on body weight from other influences and provided a quantitative estimate of the treatment effect of the drug as an adjunct to a reduced-calorie diet and increased physical activity in patients without and with type 2 diabetes.

Trial Design – Overview

Studies I8F-MC-GPHK (SURMOUNT-1) and I8F-MC-GPHL (SURMOUNT-2) consisted of a 4- to 20-week dose-escalation period, during which tirzepatide or placebo was escalated to 5 mg, 10 mg, or 15 mg subcutaneous weekly (blinded), followed by an at least 52-week maintenance-dose treatment period.

In SURMOUNT-1 and SURMOUNT-2, patients received instruction for a reduced-calorie diet (approximately 500 kcal/day deficit) and increased physical activity counseling (recommended minimum of 150 min/week) beginning with the first dose of study medication or placebo. In both trials, patients who developed persistent intolerable gastrointestinal (GI) symptoms during the treatment period (not responsive to symptomatic control or temporary drug interruption) could be de-escalated to a lower maintenance dose in a blinded fashion:

- Subjects at 5 mg or 2.5 mg could decrease to placebo
- Subjects at 7.5 mg or 10 mg could decrease to 5 mg
- Subjects at 12.5 mg or 15 mg could decrease to 10 mg.

Refer to the FDA clinical review authored by Dr. Soccio for details.

Statistical methods were similar across trials. Refer to the FDA statistical review by Dr. Song for details. Major principles are described here.

In both trials, the primary endpoints were the percent change from baseline to Week 72 in body weight and the proportion of subjects who achieved at least 5% body weight reduction from baseline to Week 72, assessed for tirzepatide 10 mg and 15 mg arms versus placebo. The

primary estimand quantified the treatment effect in all randomized subjects regardless of adherence to treatment or initiation of other anti-obesity therapies (i.e., treatment-regimen estimand). The full analysis set (FAS) included all randomized subjects according to the intention-to-treat principle. The analysis model for continuous variables was an analysis of covariance model (ANCOVA) with treatment and stratification groups as factors and baseline body weight as a covariate. The analysis model for categorical endpoints was a logistic regression model with treatment and stratification groups as factors and baseline body weight as a covariate. Type I error was controlled at 0.05 across all primary and key secondary endpoints using a sequential testing approach.

Missing values were handled using missing at random and retrieved-dropout multiple imputation approaches based on an Applicant-defined hybrid estimand framework. Missing events were categorized into Category 1 and Category 2, where Category 1 was for missing data due to exceptional circumstances (pandemic or natural disaster) and Category 2 was for missing data due to all other intercurrent events. Category 1 data were considered missing at random and were imputed using all non-missing data of the primary outcome measurements from the same treatment arm. Category 2 data were imputed based on retrieved dropouts from the same treatment arm. For additional details, refer to Dr. Song's statistical review.

Dr. Song concluded that there were no major statistical issues with the submission.

Individual Trials

SURMOUNT-1

SURMOUNT-1 was a phase 3, multicenter, multinational, randomized, double-blind, 4-arm, placebo-controlled, 72-week trial to evaluate the effect of tirzepatide 5 mg, 10 mg, and 15 mg on body weight as an adjunct to a reduced-calorie diet and increased physical activity in adult patients with obesity or overweight. The trial consisted of a 72-week treatment period (which included a 4- to 20-week blinded dose-escalation period and a 52- to 68-week blinded dose-maintenance period), a 4-week safety follow-up period, and a 2-year extension period for patients with prediabetes (not reported with this submission). Refer to Dr. Soccio's review for details of the trial. The results are summarized here.

The trial enrolled 2539 patients at least 18 years of age with obesity (BMI greater than or equal to 30 kg/m²) or with overweight (BMI 27-29.9 kg/m²) and at least one weight-related comorbid condition (hypertension, dyslipidemia, obstructive sleep apnea, or cardiovascular disease). Patients with diabetes mellitus and patients with body weight change >5 kg within 90 days before screening were excluded. Patients were randomized 1:1:1:1 to tirzepatide 5 mg, 10 mg, 15 mg, or placebo; randomization was stratified by country, sex, and prediabetes status. A subpopulation of 255 patients with BMI ≤40 kg/m² at screening were enrolled in a body composition study using dual x-ray absorptiometry (DXA) scanning, and a subpopulation of 600 patients with well-controlled blood pressure and no history of tachycardia syndromes were enrolled in an ambulatory blood pressure monitoring (ABPM) study.

The two co-primary endpoints in SURMOUNT-1 were:

- Mean percent change in body weight from baseline to Week 72 (tirzepatide 10 mg, 15 mg)
- Proportion of patients achieving weight loss ≥5% from baseline to Week 68 (tirzepatide 10 mg, 15 mg)

Secondary endpoints included proportion of patients achieving $\geq 10\%$ weight loss, proportion of patients achieving $\geq 15\%$ weight loss, proportion of patients achieving $\geq 20\%$ weight loss, change in waist circumference, change in systolic blood pressure, change in triglycerides, change in non-HDL-C, change in HDL-C, and change in SF-36v2 acute form Physical Functioning score. All endpoints were assessed from baseline (Week 0) to Week 72.

All randomized patients (1896 tirzepatide and 643 placebo) were exposed to treatment and included in the full analysis set. Approximately 89% of patients in tirzepatide arms (5 mg, 10 mg, and 15 mg) and 77% of patients in the placebo arm completed the trial. Approximately 85% of patients in tirzepatide arms and 74% of patients in the placebo arm remained on treatment. The most frequently reported reason for permanent treatment discontinuation in tirzepatide arms was an adverse event.

Demographic characteristics were similar among arms. At baseline, the mean age was 45 years (range 18-84 years; 94% were < 65 years), 68% of patients were female, and 45% were from the U.S. Approximately 71% identified as White race, 11% as Asian, 9% as American Indian or Alaskan Native, and 8% as Black; 48% were Hispanic or Latino ethnicity.

Baseline characteristics were similar among arms. Mean baseline body weight was 104.8 kg, mean BMI was 38.0 kg/m², and mean waist circumference was 114.1 cm; 94% of patients were obese and 6% were overweight with a weight-related comorbidity.

Treatment with tirzepatide resulted in statistically significant and clinically meaningful weight loss compared to placebo. Table 1 summarizes the co-primary endpoints, mean percent change in weight from baseline and proportion of patients achieving at least 5% body weight loss, for tirzepatide 10 mg and 15 mg.

Table 1. Primary Endpoint Results, Tirzepatide 10 mg and 15 mg, SURMOUNT-1

	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)

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, adccovid.xpt, adds.xpt]

The FDA statistical reviewer, Dr. Song, confirmed the results of the co-primary endpoints and concluded that the multiple prespecified sensitivity analyses were consistent with the primary analysis. Additionally, she concluded that tipping point analyses supported the robustness of the conclusion derived from the primary analysis. Refer to the FDA statistical review for additional details.

Table 2 summarizes the percent change in body weight and proportion of patients losing at least 5% body weight loss for tirzepatide 5 mg; both endpoints were key secondary endpoints controlled for Type 1 error. Results were statistically significant and clinically meaningful.

Table 2. Weight-Related Endpoints, Tirzepatide 5 mg, SURMOUNT-1

SURMOUNT-1	Tirzepatide 5 mg N=630	Placebo N=643
%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]

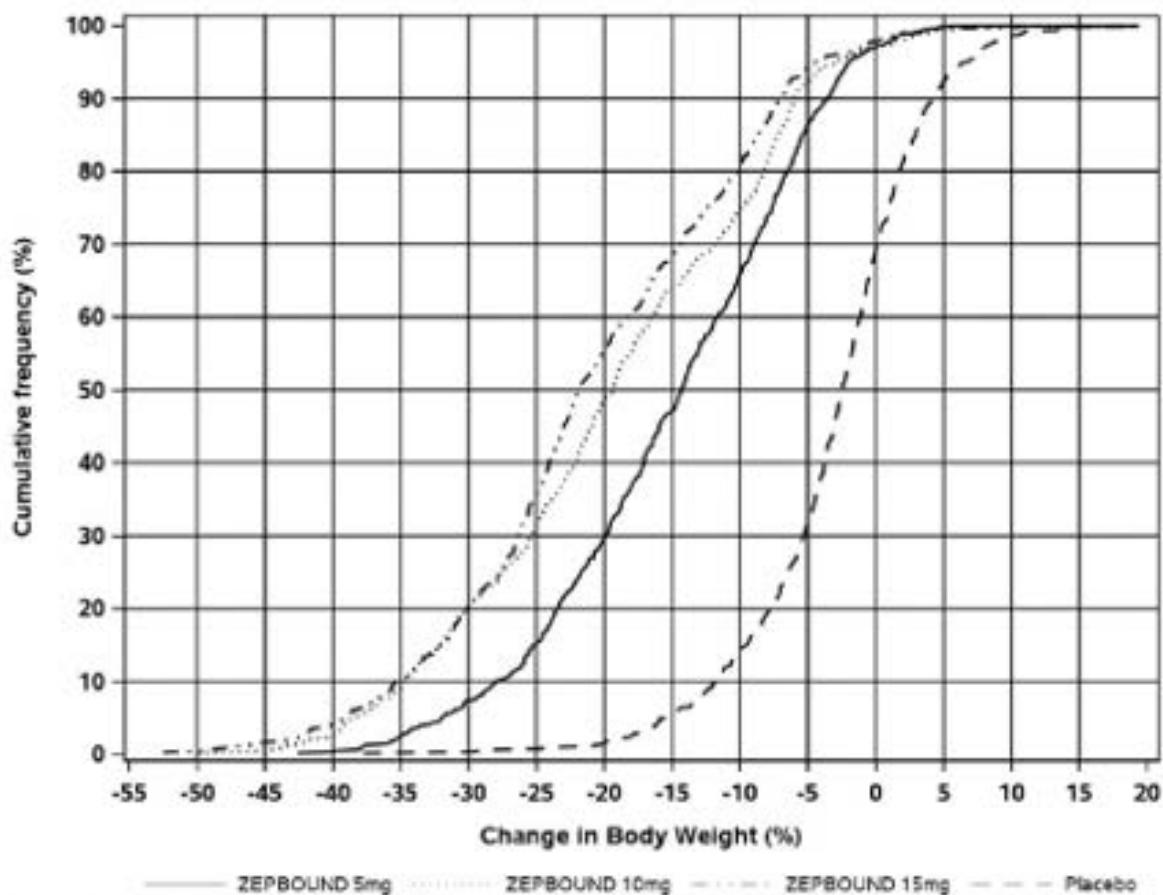
Table 3 summarizes the first four secondary endpoints in the testing hierarchy, the proportions of patients achieving $\geq 10\%$, $\geq 15\%$, and $\geq 20\%$ body weight loss from baseline and change in waist circumference for tirzepatide 10 mg and 15 mg doses. Figure 1 presents the cumulative distribution for percent change in body weight by treatment arm.

Table 3. Key Secondary Endpoints, Tirzepatide 10 mg and 15 mg, SURMOUNT-1

SURMOUNT-1	Tirzepatide 10 mg N=636	Tirzepatide 15 mg N=630	Placebo N=643
10% Body weight loss			
Proportion estimate ¹	79.0	84.3	18.1
Difference from placebo (95% CI)	61.0 (55.7, 66.3)	66.3 (61.2, 71.4)	
P-value	<0.001	<0.001	
Missing, n(%)	67 (10.5)	59 (9.4)	139 (21.6)
15% Body weight loss			
Proportion estimate ¹	67.5	71.4	8.3
Difference from placebo (95% CI)	59.2 (54.3, 64.1)	63.1 (58.3, 68.0)	
P-value	<0.001	<0.001	
Missing, n(%)	67 (10.5)	59 (9.4)	139 (21.6)
20% Body weight loss			
Proportion estimate ¹	50.2	57.0	2.8
Difference from placebo (95% CI)	47.5 (42.8, 52.1)	54.2 (49.6, 58.8)	
P-value	<0.001	<0.001	
Missing, n(%)	67 (10.5)	59 (9.4)	139 (21.6)
Change in Waist Circumference			
Baseline (cm), mean (SD)	114.8 (15.8)	114.4 (15.6)	114.0 (14.9)
Estimate, LSMean (SE) ²	-17.7 (0.5)	-18.5 (0.4)	-4.0 (0.6)
Difference from placebo (95% CI)	-13.8 (-15.2, -12.3)	-14.5 (-15.9, -13.0)	
P-value	<0.001	<0.001	
Missing, n(%)	68 (10.7)	59 (9.4)	139 (21.6)

Abbreviations: N = number of subjects randomized; SD=standard deviation; LSMean=least squares mean; SE=standard error; CI=confidence interval; ¹Estimates based on a logistic regression using treatment and stratification group as factors and baseline value as a covariate; ²Model based estimates and standard error, the ANCOVA model included 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]

Figure 1. Cumulative Frequency Distribution of Body Weight Changes (SURMOUNT-1)



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

All secondary endpoints (in addition to the categorical endpoints, addressed above) were evaluated from baseline to Week 72 and were statistically significant per the prespecified testing procedure to control the type I error rate. Refer to Dr. Soccio's review for details of the clinical relevance of these analyses and to Dr. Song's review for details of the statistical methods and confirmation of the analyses.

Cardiometabolic parameters and patient-reported outcomes are discussed later in this review.

Body composition assessments by DXA in a subset of patients suggested a decrease in fat mass (-26%) along with a smaller decrease in lean body mass (-8%) from baseline, placebo-adjusted. Refer to the FDA clinical review for details and relevance of these endpoints.

SURMOUNT-2

SURMOUNT-2 was a phase 3, multicenter, multinational, randomized, double-blind, 3-arm, placebo-controlled, 72-week trial to evaluate the effect of tirzepatide 10 mg or 15 mg once weekly on body weight as an adjunct to a reduced-calorie diet and increased physical activity in adult patients with obesity or overweight with concomitant type 2 diabetes. The trial consisted of a 72-week treatment period (which included a 12- to 20-week blinded dose-escalation period and a 52- to 60-week blinded dose-maintenance period) and a 4-week safety

follow-up period. Refer to the FDA clinical review for additional details. Trial results are summarized here.

The trial enrolled 938 patients at least 18 years of age with type 2 diabetes and BMI greater than or equal to 27 kg/m². Patients included in the trial had HbA1c 7% to 10% and were treated with either diet and exercise alone or any oral antihyperglycemic drug (excluding DPP-4 inhibitors, insulin, and oral or injectable GLP-1RAs). Patients with a body weight change >5 kg within 90 days before screening or uncontrolled and potentially unstable diabetic retinopathy or maculopathy were excluded. Patients were randomized 1:1:1 to tirzepatide 10 mg, tirzepatide 15 mg, or placebo; randomization was stratified by country, sex, and type of antihyperglycemic medication (categorized by impact on weight: weight neutral, associated with weight gain, associated with weight loss).

The co-primary endpoints in SURMOUNT-2 were:

- Mean percent change in body weight from baseline to Week 72 (tirzepatide 10 mg, 15 mg)
- Proportion of patients achieving weight loss of $\geq 5\%$ from baseline to Week 72 (tirzepatide 10 mg, 15 mg)

Secondary endpoints included proportion of patients achieving $\geq 10\%$ weight loss, proportion of patients achieving $\geq 15\%$ weight loss, proportion of patients achieving $\geq 20\%$ weight loss, change in waist circumference, change in HbA1c, change in fasting glucose, change in non-HDL-C, change in triglycerides, change in HDL-C, and change in systolic blood pressure. All endpoints were assessed from baseline (Week 0) to Week 72.

All randomized patients (623 tirzepatide and 315 placebo) were exposed to treatment and included in the full analysis set. Approximately 93% of patients in tirzepatide arms (tirzepatide 10 mg and tirzepatide 15 mg) and 89% of patients in the placebo arm completed the trial. Approximately 88% of patients in tirzepatide arms and 85% of patients in the placebo arm remained on treatment. The most frequently reported reason for permanent treatment discontinuation in tirzepatide arms was an adverse event.

Demographic characteristics were similar among arms. At baseline, the mean age was 54 years (range 18-85 years), 51% of patients were female, and 37% were from the U.S. Approximately 76% identified as White race, 13% as Asian, and 8% as Black or African American; 60% were Hispanic or Latino ethnicity.

Baseline characteristics were similar among arms. Mean baseline body weight was 100.7 kg, mean BMI was 36.1 kg/m², and mean waist circumference was 114.9 cm; 83% of patients were obese and 17% were overweight. Mean HbA1c was 8.0%, and mean duration of diabetes was 8.5 years.

Treatment with tirzepatide in patients with type 2 diabetes resulted in statistically significant and clinically meaningful weight loss compared to placebo. Table 4 summarizes the primary endpoints, mean percent change in body weight from baseline and the proportion of patients achieving at least 5% body weight loss from baseline, for tirzepatide 10 mg and tirzepatide 15 mg compared to placebo. The estimated treatment effect versus placebo in this trial was numerically smaller than that observed in SURMOUNT-1, suggesting that the expected clinical effect in patients with type 2 diabetes is smaller (a finding consistent across approved GLP-1 RAs). Nevertheless, this cross-trial comparison should be interpreted cautiously.

Differences in patient population, including allowed concomitant medications, could impact the results.

Table 4. Primary Endpoint Results, Tirzepatide 10 mg and 15 mg, SURMOUNT-2

SURMOUNT-2	Tirzepatide 10 mg N=312	Tirzepatide 15 mg N=311	Placebo 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]

Dr. Song confirmed the results of the primary endpoint and concluded that the data were statistically robust. Refer to the FDA statistical review for additional details.

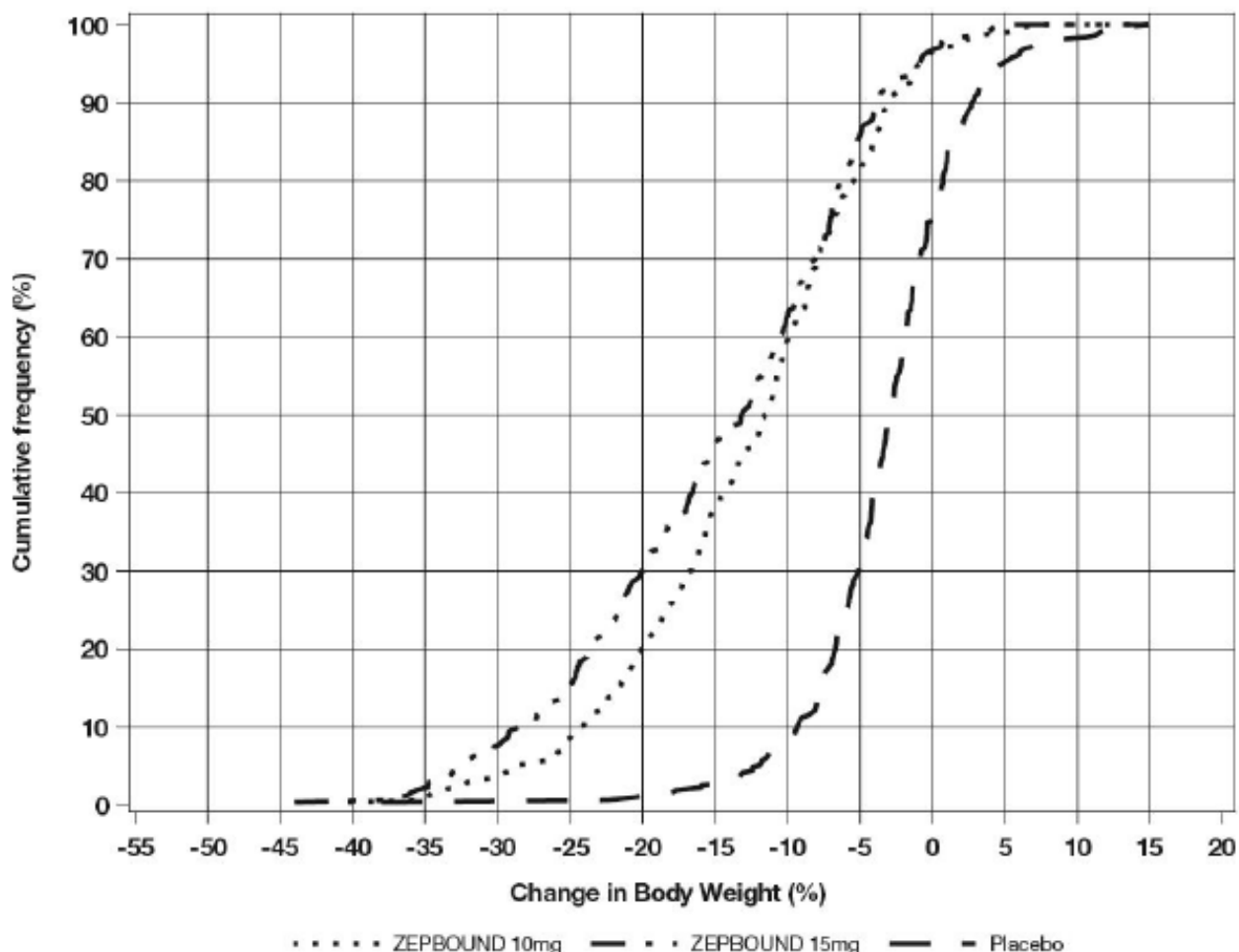
Table 5 summarizes the first two key secondary endpoints, the proportions of patients achieving $\geq 10\%$ and $\geq 15\%$ body weight loss from baseline. Figure 2 presents the cumulative distribution for percent change in body weight by treatment arm.

Table 5. Key Secondary Endpoints, SURMOUNT-2

SURMOUNT-2	Tirzepatide 10 mg N=312	Tirzepatide 15 mg N=311	Placebo N=315
10% Body weight loss			
Proportion estimate ¹	61.0	65.4	8.9
Difference from placebo (95% CI)	52.1 (45.4, 58.8)	56.5 (49.8, 63.1)	
P-value	<0.001	<0.001	
Missing, n(%)	15 (4.8)	26 (8.4)	35 (11.1)
15% Body weight loss			
Proportion estimate ¹	39.0	47.8	2.5
Difference from placebo (95% CI)	36.6 (30.5, 42.6)	45.4 (39.1, 51.6)	
P-value	<0.001	<0.001	
Missing, n(%)	15 (4.8)	26 (8.4)	35 (11.1)

Source: FDA statistical review

Figure 2. Changes in Body Weight (%) from Baseline to Week 72 (SURMOUNT-2)



Source: adapted from draft USPI

The remaining key secondary endpoints were evaluated from baseline to Week 68 and were statistically significant per the prespecified testing procedure. Refer to the clinical and statistical reviews for details. Supportive cardiometabolic parameters are discussed below.

Anthropometry and Cardiometabolic Parameters

Supportive secondary endpoints in SURMOUNT-1 and SURMOUNT-2 included assessment of cardiometabolic risk factors including changes in waist circumference, systolic blood pressure (SBP), diastolic blood pressure (DBP), HbA1c, and lipid parameters. Change in waist circumference for tirzepatide 10 mg and 15 mg doses was a key secondary endpoint, controlled for type 1 error, in both trials and achieved statistical significance. Other cardiometabolic endpoints, including lipids, SBP, and HbA1c, were prespecified as key secondary endpoints for pooled tirzepatide doses (tirzepatide 5 mg, 10 mg, and 15 mg) and also achieved statistical significance.

Treatment with tirzepatide was associated with nominally significant improvement in all parameters. Notable changes include placebo-adjusted SBP reduction from -4 to -7 mmHg

from baseline and TG reduction from -17% to -25% from baseline with tirzepatide use. See Table 6 for details.

Table 6. Changes in Anthropometry and Cardiometabolic Parameters at Week 72 (SURMOUNT-1 and SURMOUNT-2)

Intention-to-Treat (ITT) Population ^a	Study 1				Study 2		
	Placebo N = 643	ZEPBOUND 5 mg N = 630	ZEPBOUND 10 mg N = 636	ZEPBOUND 15 mg N = 630	Placebo N = 315	ZEPBOUND 10 mg N = 312	ZEPBOUND 15 mg N = 311
Waist Circumference (cm)							
Baseline mean	114.0	113.2	114.8	114.4	116.0	114.2	114.6
Change from baseline ^b	-4.0	-14.0	-17.7	-18.5	-3.3	-10.8	-13.1
Difference from placebo ^b (95% CI)		-10.1 (-11.6, -8.6) [*]	-13.8 (-15.2, -12.3) [†]	-14.5 (-15.9, -13.0) [‡]		-7.4 (-9.0, -5.9) [‡]	-9.8 (-11.2, -8.3) [‡]
Systolic Blood Pressure (mmHg)							
Baseline mean	122.9	123.6	123.8	123.0	131.0	130.6	130.0
Change from baseline ^b	-1.0	-6.6	-7.7	-7.4	-1.2	-5.6	-7.1
Difference from placebo ^b (95% CI)		-5.6 (-7.2, -3.9) [*]	-6.7 (-8.4, -5.0) [*]	-6.4 (-8.0, -4.8) [*]		-4.4 (-6.7, -2.1) [*]	-5.9 (-8.3, -3.6) [*]

Diastolic Blood Pressure (mmHg)							
Baseline mean	79.6	79.3	79.9	79.3	79.4	80.2	79.7
Change from baseline ^b	-0.8	-4.9	-5.0	-4.5	-0.3	-2.1	-2.9
Difference from placebo ^b (95% CI)		-4.1 (-5.2, -3.0)*	-4.2 (-5.3, -3.0)*	-3.7 (-4.8, -2.7)*		-1.8 (-3.3, -0.4)*	-2.7 (-4.2, -1.2)*
Pulse Rate (beats per minute)							
Baseline mean	72.9	72.4	71.8	72.4	74.8	75.9	75.6
Change from baseline ^c	0.1	0.6	2.3	2.6	-0.5	0.6	1.0
Difference from placebo ^c (95% CI)		0.5 (-0.5, 1.5)*	2.2 (1.2, 3.2)*	2.5 (1.5, 3.4)*		1.2 (-0.1, 2.5)*	1.5 (0.2, 2.8)*
Total Cholesterol (mg/dL)							
Baseline mean ^a	187.5	187.1	190.6	187.5	174.9	173.9	167.0
% change from baseline ^b	-1.8	-3.8	-4.4	-6.3	2.8	-2.8	-1.0
Relative difference from placebo ^b (95% CI)		-2.1 (-4.5, 0.4) ^{c*}	-2.7 (-5.1, -0.2) ^{c*}	-4.6 (-6.8, -2.2) ^{c*}		-5.5 (-8.7, -2.2) ^{c*}	-3.8 (-7.1, -0.3) ^{c*}
LDL Cholesterol (mg/dL)							
Baseline mean ^a	109.4	108.7	112.3	109.3	92.4	90.5	85.7
% change from baseline ^b	-1.7	-4.6	-5.6	-7.1	7.4	1.8	4.1
Relative difference from placebo ^b (95% CI)		-2.9 (-6.6, 0.9) ^{c*}	-4.0 (-7.5, -0.5) ^{c*}	-5.5 (-8.9, -2.0) ^{c*}		-5.2 (-10.1, 0.1) ^{c*}	-3.0 (-8.4, 2.6) ^{c*}
HDL (mg/dL)							
Baseline mean ^a	46.6	47.6	47.6	47.6	42.7	43.8	42.2
% change from baseline ^b	-0.7	6.9	9.2	8.0	0.2	8.2	9.7
Relative difference from placebo ^b (95% CI)		7.7 (4.6, 10.8) ^{c*}	9.9 (6.7, 13.2) ^{c*}	8.7 (5.7, 11.8) ^{c*}		8.0 (4.2, 11.8) ^{c*}	9.5 (5.6, 13.5) ^{c*}
Non-HDL (mg/dL)							
Baseline mean ^a	138.3	137.0	140.4	137.5	129.6	127.2	121.9
% change from baseline ^b	-2.3	-8.0	-9.4	-11.7	3.7	-6.6	-5.2
Relative difference from placebo ^b (95% CI)		-5.8 (-8.9, -2.6) ^{c*}	-7.2 (-10.3, -4.1) ^{c*}	-9.6 (-12.4, -6.6) ^{c*}		-9.9 (-14.1, -5.6) ^{c*}	-8.5 (-12.9, -4.0) ^{c*}
Triglycerides (mg/dL)							
Baseline mean ^a	130.8	128.7	125.7	128.1	165.0	158.8	158.5
% change from baseline ^b	-5.6	-21.2	-23.8	-29.1	-3.3	-27.1	-27.3
Relative difference from placebo ^b (95% CI)		-16.5 (-21.2, -11.4) ^{c*}	-19.3 (-23.9, -14.4) ^{c*}	-24.9 (-29.1, -20.4) ^{c*}		-24.6 (-30.0, -18.7) ^{c*}	-24.8 (-30.3, -18.9) ^{c*}
HbA1c (%)							
Baseline mean	5.6	5.6	5.5	5.6	8.0	8.0	8.1
Change from baseline ^b	-0.1	-0.4	-0.4	-0.4	-0.5	-2.1	-2.1
Difference from placebo ^b (95% CI)		-0.3 (-0.3, -0.2)*	-0.4 (-0.4, -0.3)*	-0.4 (-0.4, -0.3)*		-1.6 (-1.7, -1.4) ^d	-1.6 (-1.8, -1.4) ^d

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; N = number of patients randomly assigned to study drug.

^a The intention-to-treat population includes all randomly assigned patients. 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 Analyzed using log-transformed data.

^d p-value<0.001 (unadjusted 2-sided) for superiority, controlled for type I error rate.

- Not controlled for type I error rate.
- † Least-squares mean from mixed model for repeated measures adjusted for baseline value and other stratification factors.
- Baseline value is the geometric mean.

Source: adapted from draft USPI

Clinical Outcomes Assessment

The FDA clinical outcomes assessment reviewer, Dr. Qing Xie, and patient-focused statistical scientist (PFSS) reviewer, Dr. Xin Yuan, evaluated the use of the SF-36v2 Acute Form Physical Functioning domain in the phase 3 program. Refer to the COA review for details of these analyses. The major conclusions are summarized here.

The data from SURMOUNT-1 demonstrated a statistically significant improvement in the SF-36 Physical Functioning domain with tirzepatide compared to placebo. The Applicant proposed that the observed differences in mean changes of transformed, normalized data should be considered to represent meaningful within-patient score changes. Drs. Xie and Yuan observed, however, that there were minimal observed score changes, if any, when looking at the item- and domain-level data on the raw score scale (i.e., non-normalized and non-transformed data) – e.g., all item scores reflect less than one category mean change on the raw score scale. Additionally, they noted that the changes in normalized scores were also minimal as evidenced by minimal separation between treatment arms on cumulative distribution function plots.

There was no formal statistical testing of COA endpoints in SURMOUNT-2.

The COA team concluded that although the SF-36v2 Physical Functioning domain measures some important aspects of physical functioning, insufficient impairment of physical function at baseline and lack of a clinically meaningful observed change (b) (4)

I concur with the recommendation.

Efficacy Summary

The data from the phase 3 trials represent substantial evidence of effectiveness consisting of two adequate and well-controlled trials to support approval of tirzepatide as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adults with overweight and at least one weight-related comorbid condition or obesity (with or without comorbidities). The FDA clinical reviewer, Dr. Soccio, supports approval on the basis of these trials, and I agree with his conclusions.

The two randomized, double-blind, placebo-controlled trials clearly distinguished the treatment effect of tirzepatide on body weight from other influences, such as placebo effect, biased observation, or other factors. These trials provide a quantitative estimate of the treatment effect of the drug as an adjunct to a reduced-calorie diet and exercise in patients without diabetes (SURMOUNT-1) and in patients with type 2 diabetes (SURMOUNT-2). The FDA statistical reviewer, Dr. Song, concluded that the trials provided evidence of a robust treatment effect for the study population. Furthermore, she observed that efficacy was supported by the secondary endpoints in each trial. I agree with her conclusions.

The effects of tirzepatide versus placebo represent a 12% to 18% reduction in body weight

compared to placebo in patients without type 2 diabetes at baseline. At the highest dose (tirzepatide 15 mg), 91% of patients achieved at least 5% weight loss and approximately 84% achieved 10% weight loss compared to baseline. At the lowest dose (tirzepatide 5 mg), 85% of patients achieved at least 5% weight loss and approximately 69% achieved 10% weight loss compared to baseline. The results were clinically meaningful and statistically robust.

The estimated treatment effect observed in these trials is substantially greater than that observed in any comparable weight loss trial conducted to support approval for other approved CWM products, although such cross-study comparisons should be interpreted cautiously. Nevertheless, the overall trial quality (relatively low proportion of treatment discontinuation, high participant retention, appropriate handling of missing data) strongly support the validity of these findings.

In patients with type 2 diabetes, the estimated treatment effect of tirzepatide as an adjunct to a reduced-calorie diet and increased physical activity represents a 10% to 12% reduction in body weight compared to placebo. At the highest dose (tirzepatide 15 mg), approximately 83% of patients assigned to tirzepatide lost at least 5% of baseline body weight, and 65% lost at least 10% compared to baseline. The effects were clinically meaningful and statistically robust.

In summary, the trials support the primary indication:

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).*

The data support inclusion of descriptions of the two phase 3 trials in Section 14 of labeling. SURMOUNT-1 and SURMOUNT-2 represent the estimated treatment effect of tirzepatide as an adjunct to a reduced-calorie diet and exercise in patients without and with type 2 diabetes, respectively. I agree with including trial descriptions and weight loss results in Section 14, including tabular descriptions of the primary and secondary weight loss endpoints, cumulative distribution plots, and figures depicting change from baseline over time, similar to labeling for other approved weight management products. Additionally, it is appropriate to include changes in anthropometric and cardiometabolic parameters, such as waist circumference, blood pressure, heart rate, HbA1c, and lipid parameters, which are supportive of the favorable effects of weight loss. Trial data indicate similar results across important subgroups, including age, sex, race, ethnicity, and baseline body weight.

(b) (4) The FDA COA team concluded that the relevance of the items used was unclear in patients with mild limitations in physical functioning at baseline and that the minimal changes observed, both in raw data and in transformed, normalized data, limited their interpretability.

8. Safety

In the FDA clinical review, Dr. Soccio concluded that the most common risks with tirzepatide are monitorable and may be mitigated with labeling. Tirzepatide is safe for use under the recommended conditions of use. I agree with his assessment. This discussion focuses on those issues that affect approvability and labeling. For details of the safety evaluation, refer to the clinical review.

Safety Database

The safety profile of tirzepatide 5 mg, 10 mg, and 15 mg for weight management was primarily characterized in two randomized, placebo-controlled, phase 3 trials (SURMOUNT-1 and SURMOUNT-2). This included 2519 patients randomized to tirzepatide for 72 weeks compared to 958 randomized to placebo. Adverse events were classified using the Medical Dictionary for Regulatory Activities (MedDRA) version 25.1. Safety data in this review describes events occurring in the Safety Population (defined as all randomized patients exposed to at least one dose of trial product) during the in-trial period. For patients completing the trial, the date of last contact corresponds to the final safety visit at Week 76 (4 weeks after the final dose of trial product). Unless otherwise specified, pooled results for both trials (SURMOUNT-1 and SURMOUNT-2) and all tirzepatide doses (5 mg, 10 mg, and 15 mg) are presented. Differences between trial populations or evidence of dose-response are discussed when pertinent. See the clinical review for details of safety analyses by individual trial and dose. Supportive safety data from phase 2 CWM trials, ongoing phase 3 CWM trials, or phase 2/3 glycemic control trials do not impact approvability or labeling and are thus not presented in this review. Refer to the clinical review for additional discussion of supportive safety data.

In the two randomized, controlled trials, the mean age was 47 years and 63% of patients were women; 72% identified as White race, 12% as Asian, 8% as Black or African American, and 7% as American Indian or Alaskan Native; 51% identified as Hispanic or Latino ethnicity. Common comorbid conditions included hypertension (41%), dyslipidemia (37%), type 2 diabetes (25%), obstructive sleep apnea (7%), and cardiovascular disease (4%).

General Safety Issues

Refer to Dr. Soccio's review for detailed analyses. This section presents a summary and focuses on issues related to approvability and labeling.

Adverse Events

There was no meaningful trend in deaths. Thirteen (13) deaths occurred in the phase 3 trials but were balanced between arms (tirzepatide 0.4% and placebo 0.4%) and were consistent with the expected morbidity and mortality of the trial population. Refer to the clinical review for details.

Serious adverse events (SAEs) occurred more frequently with placebo (7%) than with tirzepatide (6%). The most frequent SAEs in tirzepatide arms were consistent with the overall safety profile and trial population and included AEs in the MedDRA System Organ Classes

(SOCs) *Infections and infestations, Hepatobiliary disorders, and Gastrointestinal disorders.*

A higher proportion of patients assigned to tirzepatide experienced AEs leading to permanent treatment discontinuation (6.0% vs. 3.4%). The most frequently reported AEs leading to discontinuation in the tirzepatide arm were gastrointestinal disorders.

A higher proportion of patients assigned to tirzepatide (79%) experienced one or more treatment-emergent AEs during the in-trial period compared to patients assigned to placebo (73%). The most frequently reported AEs in the tirzepatide arm were gastrointestinal disorders (nausea, diarrhea, vomiting, constipation, abdominal pain, dyspepsia), injection site reactions, and fatigue. Table 7 summarizes the proportion of patients with one or more AEs with incidence of 2% or greater and more frequently than placebo.

Table 7. Adverse Reactions ($\geq 2\%$ and Greater than Placebo) in Tirzepatide-Treated Adults with Obesity or Overweight for Chronic Weight Management

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
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

^a Includes diarrhea, frequent bowel movements.

^b Includes constipation, feces hard.

^c Includes abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, abdominal tenderness.

^d 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.

^e Includes asthenia, fatigue, lethargy, malaise.

^f Includes blood pressure decreased, hypotension, orthostatic hypotension.

Source: adapted from draft Prescribing Information

Laboratory, Vital Signs, and ECG

Relevant findings affecting approval and labeling are discussed among safety issues of special interest. For details of these evaluations, refer to the FDA clinical review by Dr. Soccio.

Safety Issues of Special Interest

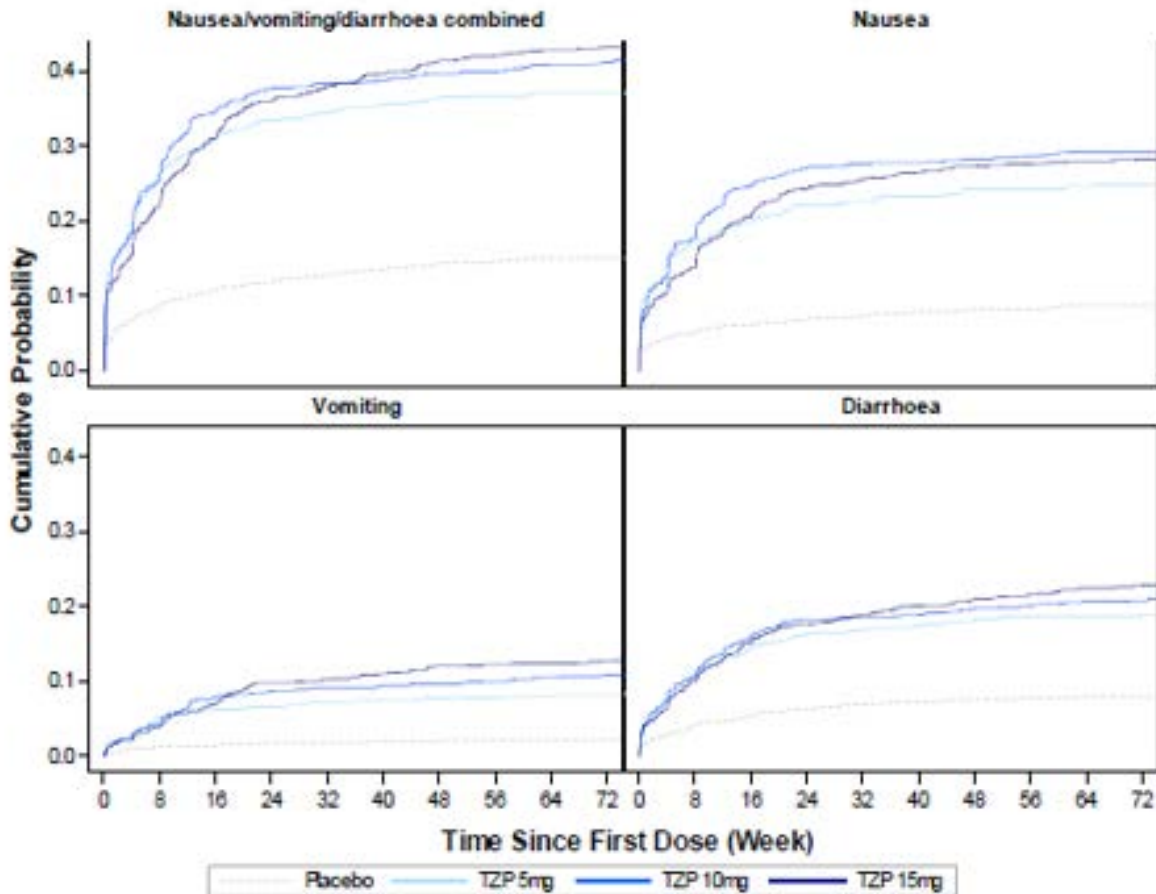
This section summarizes important safety issues relevant to approval, labeling, and postmarketing studies and is not intended to be comprehensive. Where applicable, findings in the tirzepatide weight management program are discussed in the context of previously identified safety issues for GLP-1 receptor agonists. For details of the overall tirzepatide safety evaluation, refer to Dr. Soccio's review.

Gastrointestinal Disorders

Gastrointestinal adverse events (nausea, diarrhea, vomiting, constipation) were the most commonly reported AEs in tirzepatide arms of phase 3 clinical trials and the most frequently reported AEs leading to treatment discontinuation among patients assigned to tirzepatide. Most events were categorized as mild or moderate severity. In some cases, gastrointestinal adverse events led to volume depletion, orthostatic hypotension or syncope, dehydration, electrolyte disturbances, and acute kidney injury (discussed later in this section of the review).

In phase 3 trials, gastrointestinal adverse events were most frequently reported during dose escalation. Figure 3 presents time-to-event analyses demonstrating this phenomenon.

Figure 3. Time to Onset of Nausea, Vomiting, or Diarrhea (SURMOUNT-1 and SURMOUNT-2)



Source: Applicant ISS

CDER Cross-Discipline Team Leader Summary Review
NDA 217806, Zepbound (tirzepatide) injection

Refer to Dr. Soccio's review for additional details.

Acute Kidney Injury

Acute kidney injury (AKI) was an infrequent AE reported at a higher incidence in patients randomized to tirzepatide compared to placebo. Serious events of AKI were reported in 0.36% of patients randomized to tirzepatide and 0.21% of patients randomized to placebo. In some cases, AKI was associated with gastrointestinal AEs or dehydration. Mean eGFR change over the course of the trial was similar in both the tirzepatide and placebo arms.

Acute Gallbladder Disease

Obesity and rapid weight loss are associated with increased risk for gallstone formation. GLP-1 receptor agonists are also associated with gallstone formation, independent of weight change. Gallbladder events in the tirzepatide weight management program were generally consistent with previous data. In the two randomized, controlled, phase 3 trials, cholelithiasis was reported with similar incidence between tirzepatide- and placebo-treated patients; however, cholecystitis was reported in a greater proportion of patients in the tirzepatide arm compared to placebo (0.7% versus 0.2%), and cholecystectomy was reported in 0.2% of tirzepatide-treated patients versus 0% placebo-treated patients. Refer to Dr. Soccio's review for additional analyses and discussion.

Acute Pancreatitis

Acute pancreatitis has been reported in patients taking GLP-1 receptor agonists. In the tirzepatide chronic weight management program, the overall incidence of pancreatitis events was low and occurred with similar incidence between tirzepatide- and placebo-treated patients; however, an imbalance was observed in the glycemic control program under NDA 215866.

In tirzepatide arms of the phase 3 trials, mean concentrations of amylase and lipase increased 20-25% and 28-35%, respectively, compared to minimal change in the placebo arm. The clinical significance of these mild elevations is unclear.

Hypoglycemia

GLP-1 receptor agonists stimulate insulin secretion in a glucose-dependent manner and may increase the risk of hypoglycemia, particularly in patients with type 2 diabetes taking insulin or insulin secretagogues. Hypoglycemia in this section uses the American Diabetes Association (ADA) 2018 definitions.

In SURMOUNT-2 (patients with type 2 diabetes), 4.8% of patients in the tirzepatide 15 mg arm and 3.5% of patients in the tirzepatide 10 mg arm experienced at least one episode of clinically significant (Level 2) hypoglycemia (defined as a plasma glucose less than 54 mg/dL) compared to 1.3% of patients in the placebo arm. No patients experienced severe (Level 3) hypoglycemia (defined as severe cognitive impairment requiring external assistance for recovery). The risk of hypoglycemia was increased among patients taking sulfonylureas.

Hypoglycemia was not systematically evaluated (e.g., through glucometers, glucose diaries, or dedicated case report forms) in patients without type 2 diabetes in the phase 3 clinical program. AE reporting in SURMOUNT-1 did not demonstrate any consistent imbalances in the proportion of patients reporting hypoglycemia. A small imbalance of plasma glucose <54

mg/dL, 0.3% tirzepatide vs. 0% placebo, was detected by routine laboratory testing. Refer to Dr. Soccio's review for details of hypoglycemia data in patients without diabetes.

Diabetic Retinopathy

In patients with type 2 diabetes, rapid improvement in glucose control is associated with transient worsening of diabetic retinopathy. Increases in diabetic retinopathy complications were observed in a CVOT of the GLP-1R agonist semaglutide. A randomized, placebo-controlled trial to evaluate the effect of semaglutide on diabetic retinopathy over 5 years is ongoing.

In SURMOUNT-2 (patients with type 2 diabetes), 9 AEs of retinal disorders were identified using a pre-defined MedDRA search. A greater proportion of patients randomized to tirzepatide (1.1%) experienced events compared to patients randomized to placebo (0.6%). The reported events amongst tirzepatide-treated patients were the MedDRA preferred terms *Diabetic retinopathy*, *vision blurred*, and *diabetic retinal edema*. No SAEs of retinal disorders were reported. Refer to Dr. Soccio's review for details.

Psychiatric Disorders

Suicidal ideation and behaviors have been reported in clinical trials of centrally acting weight management products. There was no apparent increase in suicidal behaviors, suicidal ideation, or AEs of psychiatric disorders with tirzepatide compared to placebo.

There were no completed suicides in the tirzepatide weight management clinical program. One completed suicide in the glycemic control development program (reviewed under NDA 215866) is unlikely related to study drug as it occurred approximately 8 months (242 days) after study drug discontinuation.

Three events of suicidal behavior or ideation (2 tirzepatide [0.08%], 1 placebo [0.1%]) occurred in the CWM clinical trials. These events are confounded by pre-existing psychiatric disease. There were no signals for worsening of suicidality or depression by C-SSRS or PHQ-9 monitoring in the clinical trials. According to Dr. Soccio's clinical review, shift to improved depression was more common in tirzepatide-treated patients (17.9%) than placebo-treated patients (13.7%).

Heart Rate Increases

Heart rate (HR) increases are associated with GLP-1 receptor agonists. A mean increase in HR of approximately 1 to 3 beats per minute (bpm) compared to no increase in placebo-treated patients was observed in the phase 3 trials. HR generally increased during the 20-week dose-escalation period with subsequent reduction during the remaining treatment period. Sinus tachycardia (HR >100 bpm) occurred more frequently in patients treated with tirzepatide than placebo (5.1% vs. 3.2%) and appeared to be dose-related (1.9%, 6.3%, and 6.0% for tirzepatide 5 mg, 10 mg, and 15 mg, respectively). Maximum HR change from baseline ≥ 20 bpm occurred in 10% of patients randomized to tirzepatide versus 3.4% of patients randomized to placebo. However, tachycardia events were generally isolated with spontaneous resolution; persistent tachycardia was rare and not meaningfully different between treatment arms.

Immunogenicity

Results of validated ADA assays demonstrated that tirzepatide is highly immunogenic. In SURMOUNT-1 and SURMOUNT-2, 1591 (64.5%) tirzepatide-treated patients developed anti-tirzepatide ADAs. ADAs occurred similarly across tirzepatide doses. Cross-reactive binding of tirzepatide ADAs to endogenous GIP and GLP-1 occurred in 40.3% and 16.5% of patients.

Of tirzepatide-treated patients, 2.8% and 2.7% developed neutralizing antibodies (NAb) against tirzepatide activity on the GIP and GLP-1 receptors, respectively, and 0.8% and 0.1% developed NAb against native GIP or GLP-1, respectively. There was no apparent effect of ADA or NAb on the PK or efficacy of tirzepatide. Patterns of weight loss were similar among patients with confirmed positive ADA compared to ADA-negative patients. A greater proportion of ADA-positive patients than ADA-negative patients experienced hypersensitivity events (6.2% vs. 3.0%) or injection site reactions (11.3% vs. 1.0%).

Refer to the FDA clinical review by Dr. Soccio for details of efficacy and safety analyses and ADA. Refer to the FDA clinical pharmacology review by Dr. Kronfol for details of PK analyses and ADA. Refer to the Immunogenicity review by Dr. Sheikh for details of the ADA assays.

Other Safety Issues

Pregnancy

In the tirzepatide phase 3 weight management program, there were 32 pregnancies (26 tirzepatide and 6 placebo). Pregnancy outcomes in patients exposed to tirzepatide and patients randomized to placebo were generally consistent with the relatively higher risk patient population (including healthy outcome, ongoing pregnancy, spontaneous abortion, and elective abortion). There were no reported major or minor fetal malformations amongst patients exposed to tirzepatide.

Major Adverse Cardiovascular Events (MACE)

In the tirzepatide weight management program, adjudicated MACE (composed of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, hospitalization for unstable angina, hospitalization for heart failure, coronary revascularization) was analyzed in the randomized phase 3 pool (SURMOUNT-1 and SURMOUNT-2). The number of events observed was too few to infer the risk of MACE in this population but was numerically lower in tirzepatide-treated patients compared to placebo (0.6% vs 0.9%). A cardiovascular outcomes trial of tirzepatide in patients with obesity/overweight is ongoing. Refer to Dr. Soccio's review for additional analyses and discussion.

Liver Safety

There was no signal of hepatic toxicity in the tirzepatide weight management program. The proportions of patients reporting hepatic AEs was similar between tirzepatide and placebo. Rare serious AEs and transaminitis elevations were associated with confounders. Three potential Hy's law cases (ALT/AST >3× ULN concurrent with total bilirubin >2× ULN) were detected in the weight management program through central laboratory routine monitoring. In all 3 cases, alternative etiologies were present (acute gallbladder disease, n=2; Hepatitis B,

n=1). Dr. Soccio concluded there was no evidence to support drug-induced liver injury (DILI) in these cases. I concur with his assessment. Refer to Dr. Soccio's review for additional discussion.

Safety Summary

The safety profile of tirzepatide for chronic weight management is similar to that of other approved GLP-1 receptor agonists and to tirzepatide product approved for a diabetes indication. There were no new safety issues identified in the weight management development program.

The most frequent AEs associated with tirzepatide were gastrointestinal disorders. Other frequent adverse events included injection site reactions, fatigue, hypersensitivity reactions, and hair loss. Acute kidney injury, hypotension and syncope, and serious hypersensitivity reactions occurred infrequently. These reactions are monitorable and may be mitigated with appropriate labeling.

Gallbladder disorders are a previously identified risk with GLP-1 receptor agonists. In the tirzepatide program, the risk of gallbladder events appeared higher in association with greater weight loss. The risk may be addressed in labeling.

Hypoglycemia is a risk with GLP-1 receptor agonists, especially following initiation and dose escalation. The risk is greater in patients with type 2 diabetes on insulin or insulin secretagogues. Prescribers may consider decreasing the doses of insulin or insulin secretagogues when initiating or escalating the dose of tirzepatide to reduce the risk.

Diabetic retinopathy complications occurred in association with rapid improvement in glucose control in a cardiovascular outcomes trial of another GLP-1R agonist in patients with type 2 diabetes. The relevance of this signal to the conditions of use for weight management is unclear. Labeling is adequate to mitigate the risk.

Other safety issues associated with GLP-1 receptor agonists, such as acute pancreatitis, neoplasms, and suicidal behavior, are infrequent or unconfirmed. These risks are addressed in current labeling of approved GLP-1 receptor agonists. Labeling includes a boxed warning for the potential risk of medullary thyroid cancer. Tirzepatide will be contraindicated in patients with a personal or family history of medullary thyroid cancer or MEN 2. FDA will issue a PMR for a medullary thyroid cancer registry study.

In nonclinical studies, tirzepatide was associated with a risk of pregnancy loss and fetal malformations at clinical exposures associated with maternal weight loss, and these findings should be labeled. FDA will issue postmarketing requirements to evaluate the risks of exposure to tirzepatide during pregnancy.

9. Advisory Committee Meeting

An Advisory Committee Meeting was not convened for this application. The Division and the Applicant agreed on the components of the development program and the key design features of the clinical trials during development, and the development program was consistent with FDA's draft guidance for industry, *Developing Products for Weight Management*. No new efficacy or safety issue arose during review of this application.

10. Pediatrics

Safety and efficacy in pediatric patients have not been established. The application is subject to Pediatric Research Equity Act (PREA) requirements because weight management is a new indication for the active ingredient. The Applicant requested a partial waiver for pediatric studies in patient aged <6 years because the product fails to represent a meaningful therapeutic benefit over existing therapies for this age group. The Applicant requested a deferral of pediatric studies in patients aged 6 to <18 years. The Pediatric Review Committee (PeRC) agreed with the partial waiver and deferral. FDA will issue postmarketing requirements for pediatric studies with the approval of this application.

11. Other Relevant Regulatory Issues

Clinical Inspections

The Office of Scientific Investigations (OSI) reviewer, Dr. Ling Yang, concluded that the inspectional findings support validity of the data reported in this application and support approval. I concur with the recommendation.

OSI conducted good clinical practice (GCP) inspections of six sites covering trials SURMOUNT-1 and SURMOUNT-2. The selected sites accounted for 8.4% of subjects enrolled in the trials.

No significant deficiencies were identified. OSI concluded that based on the overall inspection results, the data generated by these sites are verifiable. SURMOUNT-1 and SURMOUNT-2 appear to have been conducted adequately, and the clinical data submitted by the Applicant appear acceptable in support of the proposed indication.

Financial Disclosure

The applicant reported disclosable financial interests for the two phase 3 trials. In SURMOUNT-1, 7 of 700 investigators (1%) had disclosable interests, while 3 of 410 (0.7%) investigators in SURMOUNT-2 had a disclosable financial interest.

The investigators with disclosable interests in each trial are not mutually exclusive (i.e., one investigator may be counted in two or more trials). Overall, the proportions of investigators

with disclosable financial interests, sites with one or more investigators with disclosable financial interests, and patients enrolled at sites with one or more investigators with disclosable financial interests were small. The clinical reviewer, Dr. Soccio, concluded that the disclosures were unlikely to affect the outcome of the trials, and I agree.

Proprietary Name

The DMEPA reviewer, Dr. Sherly Abraham, concluded that the proposed proprietary name, Zepbound, is acceptable. In the proprietary name review, Dr. Abraham concluded that the name would not misbrand the product, and that there were no safety concerns, such as orthographic, spelling, or phonetic similarities with other approved products. I concur with the recommendation.

12. Labeling

Prescribing Information

This section summarizes major changes to proposed labeling agreed upon during labeling negotiations.

- INDICATIONS AND USAGE section:
 - Removed (b) (4) as a weight-related comorbidity
- DOSAGE AND ADMINISTRATION section:
 - Identified tirzepatide 5 mg, 10 mg, and 15 mg as the recommended maintenance doses
- WARNINGS AND PRECAUTIONS section:
 - Added incidence data and additional description of risk or mitigation strategies to relevant subsections
 - Added a warning for suicidal behavior and ideation for consistency with other chronic weight management drugs
- ADVERSE REACTIONS section:
 - Added a subheading for hair loss
 - Added additional data and details to several subheadings
- USE IN SPECIFIC POPULATIONS section:
 - Revised language to note that weight loss offers no benefit to a pregnant patient, that weight loss is not recommended during pregnancy, and that tirzepatide should be discontinued when pregnancy is recognized
- CLINICAL PHARMACOLOGY section:
 - Removed (b) (4)
 - Provided additional details regarding immunogenicity
- CLINICAL STUDIES section:
 - Updated tables and figures for consistency with other chronic weight management drugs
 - Removed (b) (4)

Other Labeling

The review team, with guidance from the Division of Medical Policy Programs and the Office of Prescription Drug Promotions, made changes to the Patient Information, consistent with the

Prescribing Information, guidance, and current practices.

13. Postmarketing

The Division of Epidemiology (DEPI) I reviewer, Dr. Po-Ying Chang, concluded that the Sentinel Active Risk Identification and Analysis (ARIA) system is not sufficient to address the postmarketing requirement to evaluate the medullary thyroid cancer (MTC) signal in humans because of insufficiency in exposure and study outcome, and that the ARIA system is also insufficient to address the postmarketing requirement to evaluate maternal, neonatal, and infant outcomes in patients exposed to tirzepatide during pregnancy because necessary covariates are not reliably available and because of the multiple outcomes targeted. Refer to the respective ARIA Sufficiency Assessments by Dr. Chang for details.

The following list includes postmarketing requirements required under PREA and the Food and Drug Amendments Act of 2007 (FDAAA):

- 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

- 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

- 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 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

- 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
Interim Report Submission:	September 2026
	September 2028
	September 2030
Study Completion:	September 2031
Final Report Submission:	September 2032

- 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

Study Completion:	May 2040
	August 2040
Final Report Submission:	August 2041

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/

LAURA B HIGGINBOTHAM
11/08/2023 10:24:28 AM

JOHN M SHARRETT
11/08/2023 10:48:27 AM
I concur.