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APPLICATION NUMBER:

215866Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader Review

Date	Refer to electronic signature
From	Michael Nguyen, MD Clinical Team Lead Division of Diabetes, Lipid Disorders and Obesity
Subject	Cross-Discipline Team Leader Review
NDA #	215866
Applicant	Eli Lilly
Date of Submission	9/16/2021
PDUFA Goal Date	5/15/2022
Proprietary Name	Mounjaro
Established or Proper Name	tirzepatide
Dosage Form(s)	Once weekly injection (5mg, 10mg or 15mg)
Applicant Proposed Indication(s)/Population(s)	An adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
Applicant Proposed Dosing Regimen(s)	Start at 2.5 mg subcutaneously once weekly. After 4 weeks, increase the dose to 5 mg once weekly. If needed, dose increases can be made in 2.5 mg increments after a minimum of 4 weeks on the current dose, up to 15 mg.
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus

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1. Benefit-Risk Assessment and Discussion of Demonstration of Substantial Evidence of Effectiveness

Type 2 diabetes mellitus (T2D) is a chronic condition characterized by hyperglycemia, insulin resistance and relative impairment in insulin secretion that affects over 30 million Americans. Complications of hyperglycemia include increased risk of microvascular (neuropathy, nephropathy, retinopathy) and macrovascular (myocardial infarction, stroke) complications, and premature mortality. The overall goal of T2D care is to achieve and maintain glycemic control to prevent these complications. Although there are 12 drug product classes of FDA approved anti-diabetic therapies, many adults with T2D do not achieve glycemic goals. The Diabetes Control and Complications Trial determined that intensive glycemic control effectively delays the onset and slowed the progression of diabetic retinopathy (including vision threatening lesions), nephropathy and neuropathy of patients with diabetes mellitus by a range of 35% to more than 70%.[1] Based on the DCCT, HbA1c is a validated surrogate endpoint for microvascular risk reduction in clinical trials in diabetes for anti-hyperglycemic drugs.

Tirzepatide is the first dual glucose-dependent insulinotropic polypeptide (GIP) receptor and glucagon-like peptide-1 (GLP-1) receptor agonist. The Applicant submitted 19 clinical studies, including two Phase 2 clinical trials (GPGB, GPGF), five Phase 3 randomized, double-blind, placebo-controlled or active-comparator controlled trials (SURPASS-1 (GPGK), SURPASS-2 (GPGL), SURPASS-3 (GPGH), SURPASS-4 (GPGM), and SURPASS-5 (GPGI)), two studies conducted in Japan (GPGO, GPGP), and ten other biopharmaceutic and clinical pharmacology studies. Five Phase 3 trials met the criteria for adequate and well-controlled studies (21 CFR 314.126) and support approval of tirzepatide, demonstrating substantial evidence of effectiveness. Tirzepatide was evaluated at three different doses (5, 10, and 15 mg) and administered either as a monotherapy; in combination with metformin, sulfonylureas, and sodium-glucose cotransporter-2 (SGLT-2) inhibitors; or in combination with basal insulin, with or without metformin. Compared to placebo, semaglutide 1 mg, insulin degludec and insulin glargine, at every dose level, tirzepatide demonstrated a statistically superior effect on the primary efficacy endpoint of change from baseline in hemoglobin A1c (HbA1c) at Week 40 or Week 52. Across the Phase 3 studies, each comparator-subtracted reduction in HbA1c was considered to be clinically meaningful (-0.41% to -1.64%), except for the tirzepatide 5 mg arm compared to semaglutide 1 mg arm (comparator-subtracted reduction of 0.16%, 95% CI: -0.29, -0.04). Sensitivity analyses were consistent with the results from the primary analyses. Subgroup analyses suggested that efficacy was not impacted by age category, sex, race, or region. Results from the key secondary endpoints (including weight change from baseline, fasting serum glucose change from baseline, and incidence of HbA1c < 7% at Week 40 or 52) also showed favorable results, and provided supportive evidence of efficacy. Indeed, trial results showed statistically superior weight loss at Week 40 with tirzepatide compared to a GLP-1 receptor agonist, semaglutide 1 mg, at each dose level (1.9, 3.6, and 5.5 kg with tirzepatide 5, 10 and 15 mg, respectively).

The safety profile characterized by the premarket safety database, containing 5,415 patients in Phase 2 and 3 exposed to tirzepatide and 4,821 patients with at least 24 weeks of exposure, is consistent with other products with activity at the GLP-1 receptor. In SURPASS-2 (GPGL) comparing tirzepatide to another GLP-1 receptor

[1] Diabetes Control and Complications Trial Research Group. The Effect of Intensive Treatment of Diabetes on the Development and Progression of Long-Term Complications in Insulin-Dependent Diabetes Mellitus. N Engl J Med 1993; 329:977-986. Available at: https://www.nejm.org/doi/full/10.1056/NEJM199309303291401

agonist (RA) (semaglutide 1 mg), tirzepatide-treated subjects experienced more treatment discontinuations due to adverse events (7.7% tirzepatide group versus 4.1% semaglutide group), primarily due to gastrointestinal (GI) related events (nausea, vomiting, diarrhea) with the greatest difference at the higher doses of tirzepatide. In clinical studies, an imbalance was noted in pancreatitis with 14 events of acute pancreatitis in 13 tirzepatide-treated patients (0.23 patients per 100 years of exposure) versus 3 events in 3 GLP-1 RA comparator-treated patients (0.11 patients per 100 years of exposure). Six of these events in tirzepatide-treated patients were serious adverse events, compared to 3 non-serious events in comparator-treated subjects. Tirzepatide was associated with gastrointestinal adverse events including nausea, diarrhea, decreased appetite, dyspepsia, vomiting, constipation, and abdominal pain in a dose-related manner. Tirzepatide was also associated with hypoglycemia when used concomitantly with insulin secretagogues or insulin and associated with injection site reactions and hypersensitivity reactions. However, in the clinical trials comparing tirzepatide to placebo, semaglutide, insulin degludec, or insulin glargine, patients randomized to treatment with tirzepatide did not experience increased risk of hypoglycemia compared to patients randomized to treatment with the comparators. Tirzepatide will also carry the boxed warning for thyroid C-cell tumors due to safety signals observed in non-clinical carcinogenicity studies.

Except for adverse reactions shared by GLP-1 receptor agonists (pancreatitis, gastrointestinal disorders, hypersensitivity reactions, and injection site reactions), numeric imbalances that were both interpretable and clinically meaningful were not observed for other adverse events of special interest evaluated in the premarket safety database. In addition, there were no safety signals that prompted concern requiring postmarketing follow up. Product labeling for tirzepatide will list the following risks in the in Warnings and Precautions section: pancreatitis, hypoglycemia with concomitant insulin or insulin secretagogue, hypersensitivity reactions, acute kidney injury (AKI), severe gastrointestinal disease, diabetic retinopathy complications in patients with a history of diabetic retinopathy, and acute gallbladder disease. The risk of AKI is included tirzepatide labeling based on postmarketing reports of acute kidney injury related to severe GI adverse reactions with the use of GLP-1 RA products. Thus, labeling for most GLP-1 RAs encourage prescribers to monitor renal function in patients with or without renal impairment if they experience severe adverse GI reactions. Also, the short-term risk of diabetic retinopathy complications, hypothesized to be related to the large rapid reduction in HbA1c, is included in tirzepatide labeling based on clinical trial findings in other GLP-1 RAs. Improving glycemic control, however, is expected to reduce the risk of retinopathy over the long-term. Lastly, the risk of acute gallbladder events is included in tirzepatide labeling in conjunction with recent FDA-required class-wide labeling for GLP-1 RAs that was based on evidence from spontaneous adverse event reports and published case reports. This decision was supported by the finding of higher numbers of tirzepatide-treated subjects experiencing acute gallbladder events in Phase 3 clinical trials.

In summary, tirzepatide effectively reduces HbA1c and is expected to result in long term microvascular disease risk reduction, preventing blindness, kidney failure with need for dialysis, and amputation due to neuropathy. Tirzepatide in addition appears to provide superior glycemic control to some other available therapies, including insulin semaglutide 1 mg, insulin degludec and insulin glargine. Another notable benefit of this drug is the favorable body weight change (weight loss) given that overweight and obesity contribute to the pathophysiology of T2D. The adverse reaction profile is similar to that of the marketed GLP-1 RAs and given the prevalent use of this drug class, is expected to be well-accepted by patients with diabetes. The most common adverse reactions are related to gastrointestinal tolerability and decreased appetite. At the highest dose of 15 mg, 6.6% of patients discontinued tirzepatide due to gastrointestinal adverse events. These adverse reactions are easily identifiable by patients who may choose to discontinue therapy with no residual harms and the dose is expected to be

titrated clinically according to tolerability and glycemic control needs. Potential serious harms include acute pancreatitis and acute cholecystitis, but these were rare and do not outweigh the anticipated benefit(s). The identified safety concerns can be addressed through labeling and routine pharmacovigilance. In addition, two safety postmarket required studies (PMRs) to monitor the potential risk of thyroid cancers and assess whether tirzepatide is present in human breastmilk (FDAAA authority) will be issued.

The benefit risk profile is favorable and supports FDA approval of tirzepatide for the proposed indication "as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus".

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Over 30 million Americans have T2D. • Patients with T2D are at increased risk for serious microvascular and macrovascular complications. • Approximately one-third to one-half of patients with T2D in the US fail to achieve glycemic targets.	• Type 2 diabetes mellitus is a serious and life-threatening condition that if left untreated leads to an increased risk of morbidity and mortality.
Current Treatment Options	• Despite the 12 available drug classes of anti-diabetic drugs, diabetes is a progressive disease and patients often require multiple therapies to achieve their treatment targets. • Each drug class has different routes of administration, and efficacy and safety profiles.	• Additional therapies to improve glycemic control are needed, particularly those with new mechanisms of action. As a "first-in-class" medication, tirzepatide would provide a distinct treatment option.
Benefit	• Tirzepatide demonstrated a statistically superior effect compared to placebo on change from baseline in HbA1c as monotherapy (-1.6%) or as add-on to insulin glargine (-1.3 to -1.5%), and to semaglutide (-0.2 to -0.5%), insulin degludec (-0.5 to -0.9%), and insulin glargine (-0.8 to -1%). • Secondary efficacy endpoints showed statistically significant improvements in the proportions of subjects with HbA1c <7% and <5.7%, change in fasting serum glucose, and change in body weight for the tirzepatide 10 mg and 15 mg doses for all comparisons across all trials, as well as for the tirzepatide 5 mg dose for all comparisons - except semaglutide 1 mg for the proportions of subjects achieving an HbA1c <7% in trial SURPASS-2 (GPGL). Uncertainties of Benefit: • The trial populations predominantly White (88%), underrepresented some racial subgroups (e.g., <4% of subjects were Black)	• The submitted clinical trial data provides substantial evidence of efficacy for the proposed indication. • Tirzepatide is expected to provide benefits to patients including microvascular risk reduction and body weight loss that appears greater than several available therapies including basal insulins and a GLP-1 RA (semaglutide).

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Limited data on persons 75 years of age or older (<5% trial subjects)	
Risk and Risk Management	• The safety findings were consistent with those of GLP-1 receptor agonist drugs. • Tirzepatide was associated with higher incidences of nausea, diarrhea, decreased appetite, dyspepsia, vomiting, constipation, and abdominal pain compared to placebo. • Acute pancreatitis and acute cholecystitis were more frequent in tirzepatide treated subjects. • A risk of MTC cannot be excluded. Nonclinical data showed that tirzepatide causes thyroid c-cell tumors in rats. It is unknown whether this risk translates to humans. • Like other GLP-1 RAs, tirzepatide is associated with the following risks: hypoglycemia with concomitant insulin or insulin secretagogue, hypersensitivity reactions, AKI with severe gastrointestinal disease, and diabetic retinopathy complications in patients with a history of diabetic retinopathy. Uncertainties for Risks: • No data on pregnant women or breastfeeding. • No data on subjects with severe gastrointestinal disease, including severe gastroparesis. • No data on subjects with a history of non-proliferative diabetic retinopathy requiring acute therapy, proliferative diabetic retinopathy, or diabetic macular edema. • Limited safety data in subjects with an eGFR <30 mL/min/1.73 m^2. • The duration of treatment exposure and follow-up in the clinical trials was not adequate to evaluate long latency events, including cancer. • The clinical relevance of increases in heart rate observed in Japanese subjects is uncertain. • Unknown long term rate of development and clinical impact of neutralizing anti-drug antibodies and antibodies against native GIP or GLP-1.	• The most common risks to patients are related to gastrointestinal tolerability and may be self-limiting. Patients may choose to discontinue therapy if not tolerated and symptoms are expected to resolve. There are no long-term harms from these GI tolerability symptoms. Potential serious harms include acute pancreatitis, and cholecystitis, although these were uncommon. These were expected based on the GLP-1 RA class and do not require further assessment in the postmarket setting. • Although there is a short term risk of progression of diabetic retinopathy, longer term risk should be lower due to improved glycemic control. Retinopathy will be further assessed in the ongoing cardiovascular outcomes trial. • The potential risk of MTC will be included in a boxed warning consistent with the long-acting GLP-1 RAs, and an MTC registry will be a postmarket requirement.

Dimension	Evidence and Uncertainties	Conclusions and Reasons

2. Background

Eli Lilly and Company seeks FDA approval for MOUNJARO (tirzepatide) under Section 505(b)(1) of the Federal Food, Drug, and Cosmetics Act as an adjunct to diet and exercise to improve glycemic control in adults with T2D. In this NDA, the Applicant submitted 19 completed clinical trials in healthy subjects or patients with T2D:

- 3 biopharmaceutic studies (GPHI, GPGS, GPGE)
- 7 clinical pharmacology studies, including 1 mechanism of action study (GPGR, GPGA, GPGG, GPGQ, GPHX, GPGT, GPGC)
- 2 Phase 2 clinical trials (GPGB, GPGF)
- 5 global Phase 3 trials (GPGK, GPGL, GPGH, GPGM, GPGI)
- 2 regional Phase 3 studies conducted in Japan (GPGO, GPGP)

The 10 biopharmaceutic and clinical pharmacology studies were designed to assess the pharmacokinetics (PK), pharmacodynamics (PD), the effects of extrinsic and intrinsic factors on tirzepatide PK, the impact of tirzepatide on PK of orally administered drugs, and safety and tolerability of tirzepatide. The Phase 1 pharmacodynamic mechanism of action study (GPGT) evaluated the effect of tirzepatide on insulin and glucagon secretion and insulin sensitivity in patients with T2D. The two Phase 2 studies were multicenter, double-blind studies that provided assessments of the efficacy, safety, and tolerability of tirzepatide between 1 mg and 15 mg to support dose selection and optimization of the dose-escalation scheme for Phase 3 studies. Because these two Phase 2 studies used different dose-escalation schemes than the scheme used in the Phase 3 studies, their data contributed only to the safety assessment and not the efficacy assessment. The five Phase 3 trials were designed to assess the efficacy and safety (40- or 52-week treatment duration at the primary endpoint) versus placebo or active comparators in adults with T2D. Treatment exposure in Study GPGM lasted up to 104 weeks. The 2 regional Phase 3 studies were 52-week, multicenter studies conducted in Japan to meet registration requirements of the Pharmaceuticals and Medical Devices Agency (PMDA). Study GPGO was a double-blind, active controlled study designed to assess the safety and efficacy of tirzepatide compared with dulaglutide 0.75 mg (the dose registered in Japan). Study GPGP was an open-label study without comparator assessing tirzepatide as an add-on to another oral anti-diabetic medication. The data from these regional studies were not included in the efficacy assessments but contributed to the safety assessment as they used the same dosage regimen and escalation scheme.

2.1 Product Information

Tirzepatide (LY3298176) is a single synthetic 39-amino acid modified peptide that selectively binds to and activates both the GIP and GLP-1 receptors. The structure was engineered from the GIP sequence and includes a C20 fatty diacid moiety that binds albumin and prolongs the half-life. Based on findings from clinical pharmacology studies, including study GPGT entitled “The Effect of Tirzepatide on α and β Cell Function and Insulin Sensitivity in Patients with Type 2 Diabetes Mellitus” the following information was added to tirzepatide labeling:

- Tirzepatide enhances first- and second-phase insulin secretion, and reduces glucagon levels, both in a glucose-dependent manner.
- Tirzepatide lowers fasting and postprandial glucose concentration, decreases food intake, and reduces body weight in patients T2D.

- Tirzepatide increases insulin sensitivity and delays gastric emptying, as demonstrated in a hyperinsulinemic euglycemic clamp study after 28 weeks of treatment.

The drug is administered subcutaneously using a single-dose pen autoinjector. Tirzepatide has a mean half-life of approximately 5 days enabling once-weekly dosing. Tirzepatide is available in six different strengths (2.5 mg, 5 mg, 7.5 mg, 10 mg, 12.5 mg, and 15 mg), each in a single-dose 0.5 mL pen.

2.2 Therapeutic Context

There are no FDA approved drugs that activate both GIP and GLP-1 receptors.

GLP-1 receptor agonists are known to improve glycemic control, reduce body weight and inhibit inappropriate postprandial glucagon release. These benefits are mediated by activation of GLP-1 receptors expressed on pancreatic beta cells, gastrointestinal tract, and the central and peripheral nervous systems, leading to glucose-dependent insulin secretion, delayed gastric emptying and reduction in body weight. Shown below are the FDA approved GLP-1 receptor agonist drugs (some in combination with long-acting insulin).

Table 1: FDA Approved GLP-1 Receptor Agonist Therapies

	Trade Name	Proper Name	Application No.	FDA Approval
1	BYETTA	Exenatide	NDA 021773	2005
2	VICTOZA	Liraglutide	NDA 022341	2010
3	BYDUREON	Exenatide extended-release	NDA 022200	2012 (discontinued)
4	TANZEUM	Albiglutide	BLA 125431	2014 (discontinued)
5	TRULICITY	Dulaglutide	BLA 125469	2014
6	SAXENDA	Liraglutide	NDA 206321	2014
7	ADLYXIN	Lixisenatide	BLA 208471	2016
8	XULTOPHY	Liraglutide plus insulin degludec	BLA 208583	2016
9	SOLIQUA 100/33	Lixisenatide plus insulin glargine	BLA 208673	2016
10	BYDUREON BCISE	Exenatide extended-release	NDA 209210	2017
11	OZEMPIC	Semaglutide	NDA 209637	2017
12	RYBELSUS	Semaglutide	NDA 213051	2019
13	WEGOVY	Semaglutide	NDA 215256	2021

GIP is an incretin secreted from intestinal K cells. GIP exhibits differential effects during hypoglycemic and hyperglycemic conditions. GIP enhances glucagon activity during periods of hypoglycemia, while enhancing insulin secretion during hyperglycemic conditions. In response to food, GIP and GLP-1 are co-secreted, acting in an additive fashion. Although both GIP receptors and GLP-1 receptors are present in beta-cells, GIP receptor expression is abundant in adipose tissue and non-overlapping areas of the CNS.

Table 2: Summary of Known Physiological Functions of GIP and GLP-1 in Glucose and Energy Metabolism

Location of Action	GLP-1 (glucagon-like peptide-1)	GIP (glucose-dependent insulinotropic polypeptide)
Pancreas (glucose-dependent actions)		
-Beta-cells	Increased insulin synthesis, increased insulin secretion, increased beta-cell proliferation, increased glucose sensing under hyperglycemic states	
-Alpha-cells	Decreased glucagon secretion under hyperglycemic states	Increased glucagon secretion under euglycemic or hypoglycemic states
Gastrointestinal (GI) System	Decreased GI motility, delayed gastric emptying	---

Adipose Tissues	---	Increased intravascular lipolysis and increased fatty acid uptake
Brain	Decreased appetite, increased satiety	---

Source: Reproduced from the Applicant's Clinical Overview, page 12 of 118. Adapted from Min and Bain 2021.

2.3 Regulatory Background and Marketing History

Tirzepatide is not currently marketed in any country. The IND for this product (IND 128801) was opened in 2016, the End of Phase 2 meeting held in 2018 and the Pre-NDA meeting held in June 2021. The NDA (215866) was submitted September 15, 2021. The applicant used a priority review voucher and the application was designated a priority review. (b) (4) Please see Dr. Pucino's review for further details on the regulatory history.

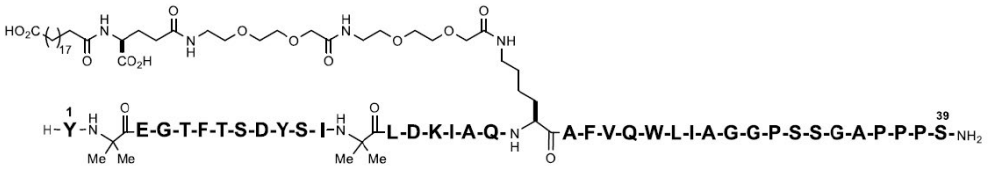
3. Product Quality

The Office of Pharmaceutical Quality (OPQ) recommended approval of this NDA for the proposed indication, and I concur with their review. Dr. Theodore Carver was the Application Technical Lead, Dr. Joseph Leginus was the Drug Substance reviewer, Dr. Rao Kambhampati was the reviewer for the Drug Product, Labeling, and Environmental Assessment, Dr. Carl Lee was the Process and Facility reviewer, and Dr. Aditi Das was the Microbiology reviewer. In the Integrated Quality Assessment Review, Dr. Carver stated that there were no outstanding deficiencies related to drug substance, drug product, microbiology, manufacturing, and environmental assessment. With respect to the Chemistry, Manufacturing, and Controls (CMC), OPQ determined that this Application met all applicable standards to support the identity, strength, quality, and purity that it purports to have, and therefore recommended approval from a quality perspective. Brief summaries of their reviews are discussed below. Please refer to the Integrated Quality Assessment Review (dated February 15, 2022) for more detailed information.

3.1 Drug Substance

Tirzepatide is a synthetic 39-amino acid modified peptide engineered from the GIP sequence containing 2 non-proteingenic amino acids (aminoisobutyric acid, Aib) in positions 2 and 13, a C-terminal amide, and Lys residue at position 20 that is attached to a 1,20-eicosanedioic acid via a linker consisting of a γ-Glu and two 8-amino-3,6-dioxaoctanoic acids, as shown in the chemical structure figure below. Dr. Leginus reviewed the drug substance information and found it to be adequate, and I concur.

Figure 1: Chemical Structure of Tirzepatide with the Standard Single Letter Amino Acid Code with Exception of the Residues Aminoisobutyric Acid 2, Aminoisobutyric 13 and Lysine 20

Molecular Formula:	$C_{225}H_{348}N_{48}O_{68}$
Molecular Weight:	4810.52 Da (monoisotopic mass) 4813.45 Da (average mass IUPAC 2007)
Chirality/Stereochemistry:	L-form for natural amino acids except no chiral center for Gly and 2-aminoisobutyric acid (Aib) in positions 2 and 13
Structural Formula:	

Source: Reproduced from the Applicant's Drug Substance Structure Information Section 3.2.S.1.2, page 1 of 1.

The tirzepatide manufacturing process uses [redacted] (b) (4) [redacted]. Tirzepatide was structurally characterized using a variety of methods including liquid chromatography with mass spectrometry (LC-MS), tandem mass spectrometry (LC-MS/MS) and LC-MS peptide mapping analysis, and circular dichroism (CD) spectroscopy.

Four related substance impurities are identified in the specifications [redacted] (b) (4) [redacted] The FDA nonclinical review team determined these impurities to be adequately qualified at their respective proposed limits. Drug substance testing confirmed that the levels of all evaluated elemental impurities are significantly lower than the ICH Q3D permissible daily exposure levels for these at the maximum daily dose of the drug product. Additionally, genotoxic impurities [redacted] (b) (4) [redacted] were extremely low, and there was negligible risk of [redacted] (b) (4) [redacted] for the drug substance in the manufacturing process.

3.2 Drug Product

The applicant proposed a drug-device combination product, which is a single dose pen containing a semi-finished syringe (SFS) and an autoinjector. The drug product solution (tirzepatide injection) is manufactured 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). In addition to the tirzepatide drug substance, the formulation contains the following compendial excipients: dibasic sodium phosphate heptahydrate [redacted] (b) (4) [redacted] sodium chloride [redacted] (b) (4) [redacted] and hydrochloric acid and sodium hydroxide for pH adjustment as needed. All the excipients are compendial grade and their amounts are the same in all the drug product strengths. No novel or animal or human derived excipients were proposed.

The primary container closure system for tirzepatide injection is a [redacted] (b) (4) [redacted] glass syringe barrel with [redacted] (b) (4) [redacted] Dr. Kambhampati felt that adequate information was provided for the container closure components and

adequate formulation development and product design studies were conducted. Results of extractable and leachable studies confirmed the safety and compatibility of the syringe container closure systems for use in the tirzepatide injection products. The drug product solution was found to be photosensitive on ICH photostability testing but the secondary packaging (carton) provides adequate protection from light. Real-time stability data demonstrated that the drug product is stable for 18 months when stored at 5°C (long-term conditions), while statistical analyses suggested that the drug product would be stable for 23.5 months under long-term conditions. Dr. Kambhampati's review of the semi-finished syringe containing tirzepatide injection solution concluded that there were no remaining drug product quality deficiencies, and I concur.

Table 3. Composition of Tirzepatide Injection

Ingredient	Quantity (mg) per Syringe						Function	Reference to Standards
	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	15 mg/0.5 mL		
Active Ingredient								
Tirzepatide	2.5	5	7.5	10	12.5	15	Active ingredient	See Section 3.2.S.4.1, Specification
Other Ingredients[a]								
Dibasic Sodium Phosphate Heptahydrate	(b) (4)							USP-NF
Sodium Chloride								USP-NF, Ph.Eur.
Hydrochloric Acid Solution, (b) (4)								USP-NF, Ph.Eur.
Sodium Hydroxide Solution, (b) (4)								USP-NF, Ph.Eur.
Water for Injection								USP-NF, Ph.Eur.

Abbreviations: Ph.Eur. = European Pharmacopoeia; q.s. = quantity sufficient; USP-NF = United States Pharmacopoeia National Formulary

(b) (4)

***Source**: Reproduced from the Applicant's Drug Product Information Section 3.2.P.1, page 2 of 3.*

Figure 2: Tirzepatide Injection Primary Container Closure System

***Source**: Reproduced from the Applicant's Drug Product Container Closure Information Section 3.2.P.7, page 1 of 6.*

3.3 Manufacturing

(b) (4)

Dr. Lee concluded that the overall commercial manufacturing process and controls were adequate.

3.4 Manufacturing Facilities

Dr. Lee conducted assessments of the manufacturing facilities, examining manufacturing risk, in-process controls, and GMP compliance history and noted no deficiencies for any facility. Dr. Lee determined that the drug substance, drug product and contract testing facilities are adequate and recommended approval based on the previous history for each manufacturing facility.

3.5 Microbiology

Dr. Das reviewed the manufacturing process and in-process controls to ensure microbiological quality, including bioburden reduction, and found them to be adequate. Validation studies for the proposed (b) (4) were determined to

be adequate. Analytical procedures and acceptance criteria for endotoxins and sterility in the drug product were deemed acceptable. Dr. Das concluded that the information to support microbiological quality is adequate.

3.6 Device

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. The device portion of the tirzepatide autoinjector is functionally the same as the approved Trulicity autoinjector. Dr. Sreya Tarafdar from the Center for Devices and Radiologic Health (CDRH) evaluated the device constituent and recommended approval based on a review of device performance, labeling, design verification/validation, and facilities information for sites involved in device manufacture/assembly. Dose accuracy, injection time, and visual/functional testing were performed following storage under multiple conditions including routine storage (2°C - 8°C for up to 24 months), room temperature storage (30°C for up to 2 weeks), and accelerated aging conditions (25°C or 30°C for up to 6-months). All specifications were met with no major changes observed during the study duration. CDRH's clinical validation review of the 19 completed studies and (b) (4) did not identify any specific adverse events directly linked to the auto-injector.

4. Nonclinical Pharmacology/Toxicology

Dr. Elena Braithwaite completed the nonclinical review for this application and concluded that the overall nonclinical data support market approval of tirzepatide in patients with type 2 diabetes mellitus. I concur with her assessment. Her comments are briefly summarized here, please see her review for further details.

4.1 Pharmacology and Toxicology

In human and nonclinical species, tirzepatide binds to the intended targets (GIP and GLP-1 receptors), while showing minimal to no agonist activity at the glucagon receptor or the glucagon-like peptide 2 (GLP-2) receptor. Activity at both GIP and GLP-1 receptors in regulating glucose tolerance was demonstrated in GIP receptor null mice and GLP-1 receptor null mice. Tirzepatide resulted in decreased food intake, lower body weight and improved glucose tolerance in rats fed a high fat/high sucrose diet and diet induced obese (DIO) mice. Compared to a GLP-1 receptor agonist, tirzepatide had greater effects on reduced fat mass, fat-free mass, plasma cholesterol, and increased metabolic rates in DIO mice. Tirzepatide stimulated cAMP production and lipolysis in mature adipocytes that express the GIP receptors and not the GLP-1 receptor. Chronic dosing in rats resulted in decreased food consumption, decreased body weight, statistically significant increase in glucose infusion rate (index of whole body insulin sensitivity), decreased endogenous glucose production. Tirzepatide is highly protein bound in nonclinical species and preferentially distributed to the plasma compartment of whole blood. Small amounts were found to cross the blood brain barrier in quantitative whole body autoradiography studies in male rats.

The toxicity profile was evaluated after repeated dosing in rats and monkeys. Most findings were consistent with those observed in the GLP-1 receptor agonist class and have been observed previously with peptide-based GIP receptor agonists in DIO mice (decreased food consumption and reduced body weight/body weight gain).

4.2 Metabolism

The primary metabolic pathway in nonclinical species consists of proteolytic cleavage of the peptide backbone, β-oxidation of the C20-fatty diacid moiety and amide hydrolysis. Tirzepatide was cleared by metabolism and no parent drug was found in the urine or feces in any species.

4.3 Cardiovascular Effects

Consistent with other GLP-1 receptor agonists, increased heart rates and blood pressure were observed in monkeys administered tirzepatide at clinically relevant exposures in repeat dose studies up to 6 months. There was no effect on QTc intervals with single or repeat dosing in monkeys. Tirzepatide did not inhibit hERG current.

4.4 Carcinogenicity and Genotoxicity

In rats, minimal to slight thyroid C-cell hyperplasia occurred at clinical exposures and are findings that have been previously observed with the GLP-1 receptor agonist class. C-cell hyperplasia observed in the 6-month study progressed to thyroid neoplasms in the 2-year rat carcinogenicity study.

Consistent with other GLP-1 receptor agonists, 2-year preclinical studies of tirzepatide in rodents identified C-cell tumors at clinical exposures. A statistically significant increase in thyroid C-cell adenomas was observed in males and females, and a statistically significant increase in thyroid C-cell adenomas and carcinomas combined was observed in males and females at all doses examined. In a 6-month carcinogenicity study in rasH2 transgenic mice, tirzepatide at doses of 1, 3, and 10 mg/kg administered by subcutaneous injection twice weekly did not produce increased incidences of thyroid C cell hyperplasia or neoplasia at any dose. Tirzepatide was also not genotoxic in a rat bone marrow micronucleus assay.

Reviewer Comment: Dr. Braithwaite noted that, "Due to species-specific differences in GLP-1R expression and activation, the relevance of these findings to humans is unclear." While no conclusive association with GLP-1 receptor agonism and incident C-cell tumors in humans has been established to date, a boxed warning should be included in labeling regarding the potential risk for thyroid C-cell tumors, consistent with long-acting GLP-1 receptor agonist class labeling.

4.5 Reproductive Toxicology

Tirzepatide was evaluated with 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. In fertility and early embryonic development studies, male and female rats were administered twice weekly subcutaneous doses of 0.5, 1.5, or 3 mg/kg (0.30-, 1.03-, and 1.72-fold and 0.29-, 0.90-, and 1.88-fold, respectively, the MRHD of 15 mg once weekly based on AUC).

- ***Fertility***: No tirzepatide effects were observed on male fertility (sperm morphology, mating, fertility, or conception). At clinically relevant exposures, an increased number of female rats experienced prolonged estrous cycles or persistent/prolonged diestrus at all doses examined, and decreases in the numbers of corpora lutea, implantation sites, and viable embryos, which was likely secondary to the pharmacodynamic-related effects on food consumption and decreased body weight gain related to tirzepatide.
- ***Embryonic Fetal Development***: Fetal development studies showed findings related to reduced food consumption and body weight gain in both pregnant rats and rabbits at clinically relevant exposures. Reductions in food consumption and body weight gain are known to be associated with reduced/delayed ossification and/or reduced fetal weight in rats and fetal loss/abortion in rabbits. However, Dr. Braithwaite noted that several findings in rats occurring at clinically relevant exposures could not be directly attributed to reduced maternal body weight, including increases in the incidences of external, visceral, and skeletal malformations and variations in rat fetuses that exceeded concurrent

and historical control incidences (litter %) and generally occurred across different litters. Dr. Braithwaite concluded, and I concur, that the uncertainty regarding the clinical relevance of these findings can be adequately communicated in product labeling. Notably, potentially drug-related imbalances in malformations have been seen in other GLP-1 receptor agonist nonclinical reproduction studies, which suggests that inclusion of these findings in the risk summary section of pregnancy labeling is warranted.

- *Prenatal and Postnatal Development*: In a pre- and postnatal development study in rats to evaluate effects in the period from implantation through weaning, lower mean body weights in F1 pups from dams treated with tirzepatide were likely due to the pharmacodynamic reductions in food consumption and body weight in the maternal animals at clinically relevant exposures that persisted throughout lactation. The reduction in pup weight was considered adverse at the highest dose and weight reductions were observed from birth or soon thereafter through postnatal day 91.

5. Clinical Pharmacology

Dr. Mohamad Kronfol completed the review of the clinical pharmacology data consisting of one disposition and metabolism study (GPHX); two single or multiple ascending dose studies (GPGA, GPGC); a study evaluating the effect of the injection delivery device on PK (GPGS); three studies evaluating the effect of intrinsic factors (BMI, renal impairment, hepatic impairment); one study examining the effect of tirzepatide on combined hormonal contraceptives (GPGR); a mechanistic pharmacodynamic study evaluating the effect on pancreatic alpha and beta cell function and insulin sensitivity (GPGT); and nine Phase 2 and Phase 3 studies that contributed a Population PK/PD model (GPGB, GPGF, GPGH, GPGI, GPGK, GPGL, GPGM, GPGO, GPGP). The intended commercial drug product including to-be-marketed device was used in all Phase 3 trials except for GPGM, which used the same drug formulation but in a pre-filled syringe. The Applicant conducted a relative bioavailability (BA) study (GPGS) to show comparable BA, thereby bridging the pre-filled syringe to the single-dose pen. He concluded, and I concur, that the clinical pharmacology data submitted is acceptable and supports approval. Please see his memo for further details.

6.1 General Pharmacology and Pharmacokinetics

In Dr. Kronfol's review, he stated that tirzepatide enhanced the first- and second-phase insulin secretion rate, reduced fasting and postprandial glucagon secretion, fasting glucose, and food intake in the pharmacodynamic study GPGT. Tirzepatide also increased insulin sensitivity, as demonstrated in a hyperinsulinemic euglycemic clamp study after 28 weeks of treatment. The impact of tirzepatide on gastric emptying delay was studied using acetaminophen as a gastric emptying marker in Study GPGA. In healthy participants and patients with T2D in Study GPGA, tirzepatide delayed gastric emptying by about 1 hour, an effect that was greatest after the first dose and diminished following once-weekly doses. The general clinical pharmacokinetics are summarized below.

Table 4: General Clinical Pharmacokinetics of Tirzepatide

Absorption	• PK is dose proportional in the dose ranging from 0.25-15 mg based on population PK (popPK) analysis • The time to reach maximum plasma concentration (t_{max}) ranges from 8 to 72 hours • Absolute bioavailability is approximately 80%
Distribution	• Plasma Protein Binding is 99% • Apparent Volume of Distribution at steady state (Vd_{ss}) is 10.3 L • Steady State is reached at 4 weeks after once-weekly administration

Metabolism	• Proteolytic cleavage of the peptide backbone, beta-oxidation of the C20 fatty diacid moiety and amide hydrolysis • The 4 minor metabolites in plasma resulting from proteolytic cleavage of the peptide backbone each individually accounted for less than 5.7% of total circulating radioactivity.
Elimination	• Plasma Clearance (CL) is 0.061 L/h • Terminal half-life ($t_{1/2}$) is approximately 5 days • Renal excretion is the primary route of elimination. Intact parent is not detected in urine or feces. Approximately 70% of radiolabeled dose recovered as metabolites in urine (50%) and feces (20%)

Source: Reproduced and modified from Clinical Pharmacology Review Memo, page 6.

6.2 Dosage Regimen

Dr. Kronfol concluded that the proposed dosing regimen is appropriate for the proposed indication. General dosing instructions start at 2.5 mg once weekly given subcutaneously in the upper arm, abdomen, or thigh. Injections can be administered with or without food. If needed, the dose can be escalated stepwise in 2.5 mg increments after a minimum of 4 weeks on the current dose, up to 15 mg per week. Tirzepatide can be administered within 4 days of a missed dose based on results showing <20% increase in C_{max} associated with the subsequent scheduled dose. If more than 4 days have passed, patients should skip the missed dose and resume with the next regularly scheduled dose.

6.3 Therapeutic Individualization

Impact of Intrinsic Factors on PK

Dr. Kronfol concluded no dose adjustments are necessary for therapeutic individualization for intrinsic factors like age, gender, race, ethnicity, renal impairment, or hepatic impairment as none of these factors had clinically relevant effects on the PK of tirzepatide. For example, no clinically relevant effects on the PK were observed based on AUC, C_{max}, and $t_{1/2}$ of a single SC dose of 5 mg tirzepatide for participants with mild, moderate, or severe renal impairment or end stage renal disease (ESRD) when compared to participants with normal renal function. Similarly, no clinically relevant effects were observed for participants with mild-moderate or severe hepatic impairment compared to subjects with normal hepatic function. The pharmacokinetics are similar in both healthy individuals and patients with T2D.

Effect of Body Mass Index (BMI) and Injection site on PK

The effect of BMI and injection site on the PK of tirzepatide was assessed in a dedicated Study GPHI. PK in participants with a high BMI (27.1 to 45.0 kg/m^2; N = 27) were compared to participants with a low BMI (18.5 to 27.0 kg/m^2; N=27). Participants in each BMI group were randomized to 1 of 3 injection site sequences and received 3 single 5 mg subcutaneous injections of tirzepatide into the upper arm (test 1), the thigh (test 2), and the abdomen (reference). No clinically relevant effects on the PK were observed based on AUC and Cmax.

The overall systemic exposure to tirzepatide as measured by $AUC_{0-\infty}$ across all 3 injection sites was 19% to 25% higher in participants with low BMI compared with participants with high BMI. The overall C_{max}, irrespective of injection site, was comparable between the low and high BMI groups, with a geometric LS means ratio of 1.11 and the 90% CI falling within the 0.80 to 1.25 range. Dr. Kronfol also noted that BMI had no apparent effect on the rates of tirzepatide absorption and elimination, with median t_{max} and mean $t_{1/2}$ observed at similar times across all administration sites for both BMI groups. He concluded that no dose adjustments are warranted based on differences in BMI and no specific recommendations are needed based on different injection sites.

Population PK Analysis: Body Weight and Heart Rate

Dr. Kronfol noted that in population PK analyses, the body weight covariate affected tirzepatide exposure. Relative to a 90 kg subject, tirzepatide exposure (C_{max} and AUC) are expected to be 23% higher and 21% lower in a 70 kg and 120 kg subject, respectively. However, because these differences in exposures are not expected to be clinically impactful, Dr. Kronfol concluded that no dose adjustment is required based on body weight.

Dr. Kronfol also noted that in the Phase 3 studies, Japanese patients had 17% higher tirzepatide exposure and $C_{max,ss}$ compared to non-Japanese patients at least in part due to lower body weight (median weight 90 kg non-Japanese compared to 76 kg Japanese patients). Although the heart rate increases were higher in Japanese patients compared to non-Japanese patients, the proposed gradual titration of tirzepatide would allow for assessment and control of adverse events, leading the Clinical Pharmacology team to conclude that no dose adjustment was needed based on body weight and in the Japanese population.

6.4 Drug-Drug Interactions and Food Effects

Dr. Kronfol determined that in vitro data indicated a low clinical risk of potential DDI involving inhibition or induction or CYP enzymes by tirzepatide. Additionally, in vitro data indicated that the potential for tirzepatide to inhibit renal and hepatic transporters (P-gp, BCRP, OATP1B1, OATP1B3, OCT1, OCT2, OAT1, OAT2, MATE1, and MATE2-K) was also low.

Tirzepatide delays gastric emptying and thereby has the potential to impact the absorption of concomitantly administered oral medications. This effect is consistent with the known effect of GLP-1 receptor agonists. Although study GPGA observed a delay in acetaminophen t_{max} of approximately 1 hour and maximum decrease of C_{max} of about 50% with no clinically relevant change in AUC, the delay in gastric emptying showed evidence of tachyphylaxis (an effect greatest after the first dose of tirzepatide but dissipating after repeated doses of tirzepatide within the 4 week period).

To further evaluate the potential impact on delayed gastric emptying, Dr. Yuching Yang evaluated the Applicant's physiologically based pharmacokinetic (PBPK) model to predict the effect of tirzepatide mediated delayed gastric emptying on the pharmacokinetics of acetaminophen, atorvastatin, digoxin, ethinyl estradiol, lisinopril, metformin, metoprolol, norgestimate, sitagliptin, and S-warfarin. The PBPK reviewer considered the analysis adequate to provide a qualitative assessment of PK changes for the test drugs and concluded that the totality of evidence suggested that no clinically meaningful effect was expected and that no dose modification would be needed with these drugs when administered concomitantly with tirzepatide.

In Study GPGR, the Applicant assessed the effect of a single dose 5 mg tirzepatide on the PK of oral contraceptives (OC) (0.035 mg ethinyl estradiol and 0.25 mg norgestimate) in healthy female subjects. In this study the plasma concentrations of norgestimate (parent), norelgestromin (active metabolite) and ethinyl estradiol were measured to evaluate the PK of the combination OC. The Applicant found that tirzepatide led to a 28.8% lower $AUC_{0\text{-}tau}$ for norelgestromin and 27% lower AUC for ethinyl estradiol (the lower bound of the 90% CI), and that the C_{max} of norelgestromin and ethinyl estradiol was reduced by 55% to 59% compared to taking oral contraceptives alone. Delays in t_{max} of 2.5 to 4.5 hours were also observed when the OC was administered in the presence of 5mg of tirzepatide. The Applicant concluded that reduction in C_{max} is of limited clinical relevance because the AUC drives contraceptive efficacy. Moreover, the Applicant felt that the impact of delayed gastric emptying would be mitigated by the diminishing effect with repeated dosing. However, the Clinical Pharmacology team determined that the reduction in AUC and C_{max} of the progestin and estrogen components could pose a clinically significant risk of loss of efficacy of contraception and unintended pregnancy. The Clinical

Pharmacology team also determined that the risk with higher tirzepatide doses was unknown. Although dose separation of OC and tirzepatide administration was considered, it was determined not to be adequate due to the once weekly dosing interval for tirzepatide.

Table 5: Statistical Analysis of the Pharmacokinetic Parameters of Oral Contraceptive

		Ethinyl Estradiol			Norelgestromin		
Parameter	**Treatment**	**Geometric Mean (N)**	**Ratio of Geometric Means (OC+TZP: OC)**	**90% CI for Ratio (Lower, Upper)**	**Geometric Mean (N)**	**Ratio of Geometric Means (OC+TZP: OC)**	**90% CI for Ratio (Lower, Upper)**
AUC(0-τ) (pg.h/mL)	OC + TZP	811 (21)	0.788	(0.730, 0.850)	16008 (25)	0.775	(0.712, 0.843)
	OC	1029 (21)			20659 (25)		
AUC(0-t_{last}) (pg.h/mL)	OC + TZP	912 (23)	0.800	(0.722, 0.888)	25994 (25)	0.838	(0.771, 0.912)
	OC	1139 (23)			31005 (25)		
Cmax (pg/mL)	OC + TZP	49.6 (24)	0.410	(0.355, 0.473)	983 (25)	0.451	(0.402, 0.505)
	OC	121 (24)			2181 (25)		
		Ethinyl Estradiol			**Norelgestromin**		
Parameter	**Treatment**	**Median (N)**	**Median of differences (OC + TZP – OC)**	**Approximate 90% CI for differences (Lower, Upper)**	**Median (N)**	**Median of differences (OC + TZP – OC)**	**Approximate 90% CI for differences (Lower, Upper)**
tmax (hour)	OC + TZP	5.99 (24)	4.23	(1.50, 6.50)	6.00 (25)	4.50	(1.50, 5.00)
	OC	1.00 (24)			1.50 (25)		

Abbreviations: AUC = area under the concentration versus time curve; AUC(0-t_{last}) = AUC from time zero to time t, where t is the last time point with a measurable concentration; AUC(0-τ) = AUC during 1 dosing interval; CI = confidence interval; Cmax = maximum observed drug concentration; N = number of subjects; OC = oral contraceptive (21 days of active tablets [0.035 mg ethinyl estradiol and 0.25 mg norgestimate] and 7 days of nonactive tablets); tmax = time of maximum observed drug concentration; TZP = tirzepatide 5 mg administered subcutaneously.

Source: From the Applicant's Summary of Clinical Pharmacology Studies, Table 2.7.2.13, page 59.

REVIEWER COMMENT: In accordance with the Draft Guidance for Industry: Clinical Drug Interactions Studies with Combined Oral Contraceptives (November 2020), if the 90% CI for the geometric mean systemic exposure ratios fall outside the no-effect boundaries of 80% to 125% for the combined oral contraceptive (COC), the totality of evidence should be considered when determining the clinical impact of the DDI on the COC. Tirzepatide will have labeling advising patients using oral hormonal contraceptives to switch to a non-oral contraceptive method or add a barrier method of contraception for 4 weeks after initial of tirzepatide and for 4 weeks after each dose escalation.

6.5 QT studies

Due to the long half-life and titration scheme needed to achieve steady state concentrations at the highest doses for tirzepatide, the FDA interdisciplinary review team (IRT) recommended an integrated assessment using non-clinical data and ECGs from Phase 3 studies in lieu of a thorough QT study. A PopPK model was developed based on data from three Phase 3 clinical studies (GPGA, GPGB & GPGF) that collected triplicate ECG information at pre-dose and multiple post-dose intervals to investigate the relationship between drug concentration and corrected QT interval (QTc) and PR intervals. Dr. Christine Garnett concluded, "The QTcF interval values in the Phase 3 studies were generally within clinically acceptable limits."

Additionally, a non-clinical hERG assay using terfenadine as a positive control was conducted to assess the potential for tirzepatide to inhibit hERG potassium current. Single and repeat dose in vivo studies in monkeys were also conducted, revealing no QTc prolongation at exposures up to 2.6x of clinical exposure and suggested that tirzepatide had a low risk for prolonging QTc but did observe increased in heart rate and mean arterial pressure.

REVIEWER COMMENT. The Interdisciplinary Review Team for Cardiac Safety Studies concluded that the nonclinical and clinical data do no indicate any unexpected or important effects of tirzepatide on the QTc interval at clinically relevant exposures up to 15 mg once weekly. I concur with their assessment. The applicant did not propose QT labeling language in Section 12.2 and the IRT agreed with the Applicant's proposal because it is consistent with labeling practices for peptides and large targeted proteins when a dedicated QT study has not been conducted. Recent IRT assessments of peptides comprised of naturally occurring amino acids have shown that they have a low likelihood of direct ion channel interactions and that thorough QT studies are not necessary unless there are mechanistic reasons that they drug would be associated with proarrhythmic risk.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical Efficacy

The efficacy of tirzepatide was reviewed by Drs. Wenda Tu and Frank Pucino. For additional detail, please see Dr. Tu's and Dr. Pucino's review memos. Drs. Tu and Pucino identified no major statistical issues and recommended approval based on the cumulative evidence from the five Phase 3 trials that demonstrated robust evidence of efficacy with compelling effect sizes. I concur with their conclusion.

7.1 Overview of Pivotal Efficacy Trials

Five Phase 3 trials were submitted in support of this application. Three doses were studied (5, 10, 15mg) and the product was evaluated as monotherapy; in combination with metformin, sulfonylureas and SGLT2 inhibitors; or in combination with basal insulin with or without metformin. Key features of these studies are summarized below.

Table 6: Overview of Pivotal Efficacy Trials

Trial ID	GPGK SURPASS-1	GPGL SURPASS-2	GPGH SURPASS-3	GPGM SURPASS-4	GPGI SURPASS-5
Design	Double blind	Open label	Open Label	Open Label	Double Blind

Tirzepatide weekly dose	5, 10, 15mg	5, 10, 15mg	5, 10, 15mg	5, 10, 15mg	5, 10, 15mg
Comparator	Placebo	Semaglutide 1mg	Insulin degludec	Insulin glargine	Placebo
Randomization	1:1:1:1	1:1:1:1	1:1:1:1	1:1:1:3	1:1:1:1
No. Subjects Randomized	475	1876	1435	1989	471
Background Medications	None (lifestyle changes only)	Metformin	Metformin +/- SGLT2i	1 to 3 OAMs +/- metformin +/- SU +/- SGLT2i	Insulin glargine +/- metformin
Treatment Duration	40 weeks	40 weeks	52 weeks	52 weeks, plus 52 weeks long term safety	40 weeks
Endpoints	*Primary*: change from baseline in HbA1c *Key Secondary*: • Incidence of A1c<7% • Change from baseline body weight • Incidence of A1c<5.7% • Change from baseline FSG	*Primary*: change from baseline in HbA1c *Key Secondary*: • Incidence of A1c<7% • Change from baseline in body weight • Incidence of A1c<5.7%	*Primary*: change from baseline in HbA1c *Key Secondary*: • Incidence of A1c<7% • Change from baseline in body weight	*Primary*: change from baseline in HbA1c *Key Secondary*: • Incidence of A1c<7% • Change from baseline in body weight	*Primary*: change from baseline in HbA1c *Key Secondary*: • Incidence of A1c<7% • Change from baseline in body weight • Incidence of A1c<5.7% • Change from baseline FSG
HbA1c Inclusion Criteria	≥7.0 to ***≤9.5%***	≥7.0 to ≤10.5%	≥7.0 to ≤10.5%	***≥7.5*** to ≤10.5%	≥7.0 to ≤10.5%

Abbreviations: OAM: oral antihyperglycemic medication; SU: sulfonylurea; SGLT2i: sodium glucose cotransporter-2 inhibitor; FSG: fasting serum glucose

7.1.1 Dose Escalation and Titration

All Phase 3 trials used the following stepwise tirzepatide dosing algorithm starting at 2.5 mg with escalation every 4 weeks to minimize GI tolerability concerns. The maximum dose 15 mg was selected to maintain an exposure multiple of 1.6 to 2.4 to the no-observed-adverse-effect level (NOAEL) doses in 6-month monkey and rat toxicology studies, respectively. Doses of the comparator products were titrated to a FBG <100 md/dl (insulin glargine), FBG < 90 mg/dl (insulin degludec) or per approved labeling at the time of trial initiation (semaglutide 1 mg).

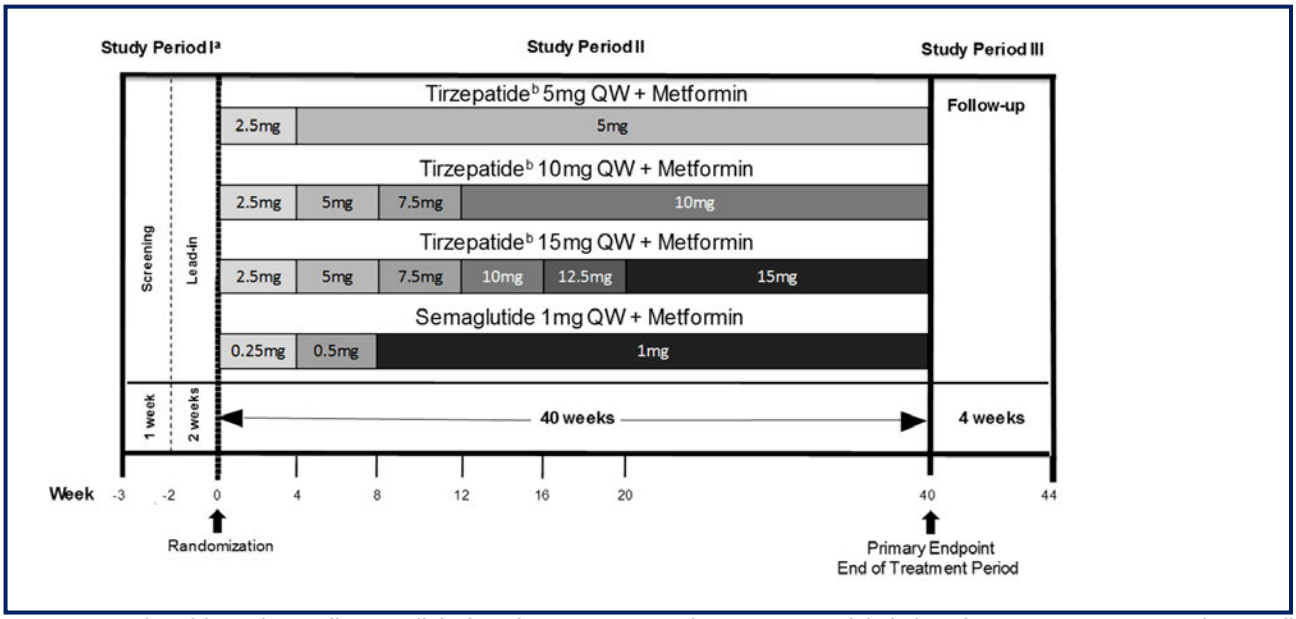
Table 7: Dose Escalation Scheme Used in the 5 Phase 3 Clinical Trials

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

7.1.2 Study Designs

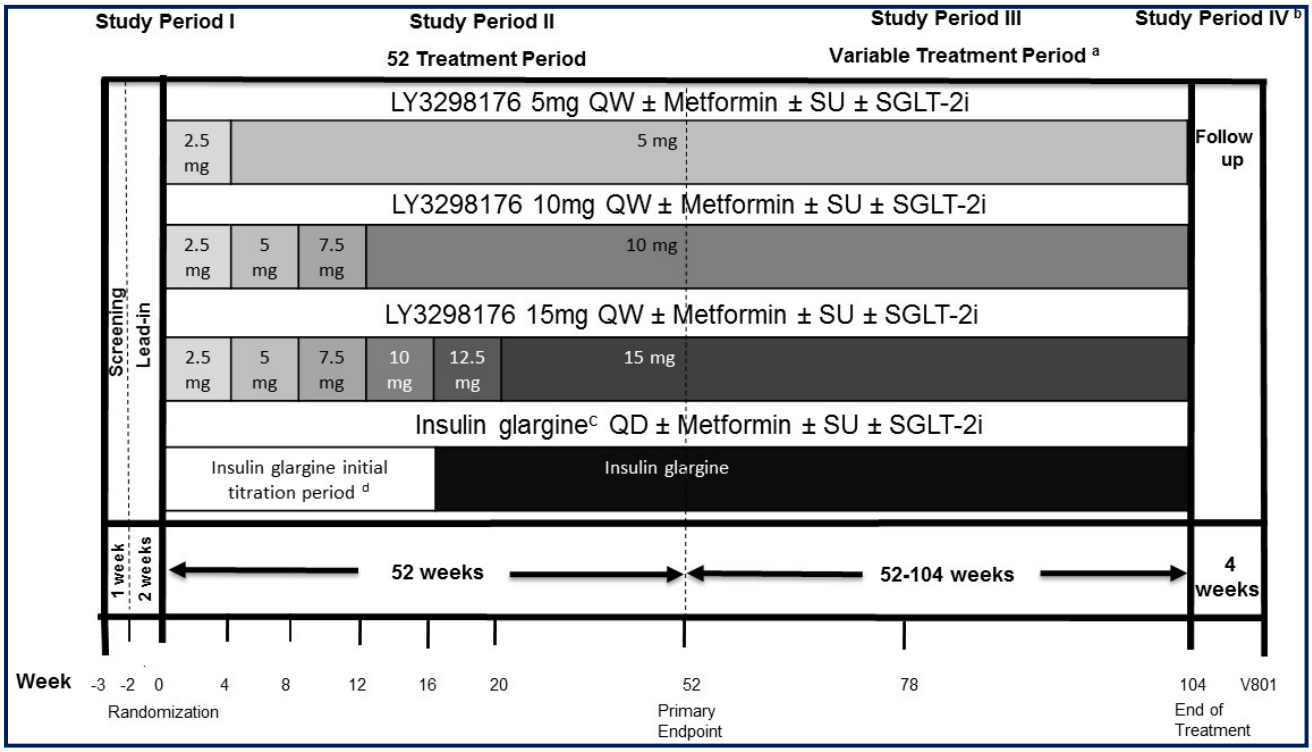
All Phase 3 tirzepatide trials shared similar study designs. Each study enrolled patients with inadequately controlled T2D into a multicenter, randomized trial with 3 study periods: a 3-week screening/lead-in period, followed by a 40- or 52-week treatment period, and a 4-week safety follow-up period. Shown below are the study designs for SURPASS-2 (GPGL) and SURPASS-4 (GPGM), the two largest trials, both excerpted from Dr. Pucino's clinical review. Please see his review for further details.

Figure 3. Study Design of Trial GPGL



Source: Reproduced from the Applicant's Clinical Study Report, Protocol 18F-MC-GPGL, labeled as Figure GPGK.1, page 27 of 98, available at: \\CDSESUB1\evsprod\nda215866\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\type-2-diabetes-mellitus\5351-stud-rep-contr\i8f-mc-gpgl\gpgl-05-protocol--b-.pdf
Abbreviations: QW, once weekly.
[a] *Stable doses of metformin (≥1500 mg/day) for ≥3 months*
[b] *All tirzepatide doses were double-blinded.*

Figure 4. Study Design of Trial GPGM



Source: Reproduced from the Applicant's Clinical Study Report, Protocol 18F-MC-GPGM, labeled as Figure, page 28 of 93, available at: \\CDSESUB1\evsprod\nda215866\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\type-2-diabetes-mellitus\5351-stud-rep-contr\i8f-mc-gpgm\gpgm-05-protocol--b-.pdf
Abbreviations: QD, daily; and QW, once weekly; SGLT-2i, sodium-glucose cotransporter-2 inhibitor;' and SU, sulfonylurea.
[a] Patients will be on IP for at ≥12 months.
[b] All subjects will perform a Visit 801 4 weeks after their last treatment visit
[c] The starting dose of insulin glargine was 10 IU/day at bedtime, titrated to a fasting blood glucose (FBG) <100 mg/dL, following a TTT algorithm.
[d] Subjects will titrate insulin glargine dose in a weekly manner and will make the dose decision with the investigator for the first 8 weeks (phone or clinic visit). From Week 8 to Week 16, subjects will continue the titration by a phone consultation or clinic visit every other week, with 3 weeks between Visits 13 and 14.

7.1.3 Statistical Methods

Dr. Tu reviewed the efficacy data. The modified intention-to-treat (mITT) population, defined as all randomized subjects who took at least one dose of the study drug, excluding those who failed to meet inclusion/exclusion criteria, was used for both the primary and key secondary analyses. The full analysis set (FAS) was used, defined as all available data obtained during the Treatment Period (or Treatment Period I for SURPASS-4), regardless of adherence to study drug or initiation of rescue medication.

Missing data was handled using multiple imputation based on retrieved dropouts in SURPASS-2, -3 and -4. For each arm in the study, a regression model adjusted for baseline HbA1c measurement was constructed based on observed data from subjects in the same arm who discontinued treatments but still had their endpoints measured. Missing data were imputed as random draws from a normal distribution centered at the value predicted by the regression model, and with variance set to the variance of the predicted value. SURPASS-1 and

-5 used the placebo-based multiple imputation due to insufficient retrieved dropout data. For each study, a regression model adjusted for baseline HbA1c was built based on completers (*i.e.,* subjects with non-missing primary endpoint measures) from the placebo arm.

For each study, an ANCOVA model adjusted for treatment, baseline HbA1c (%), country/pooled country, and past/baseline use of antidiabetic medication was used for the primary efficacy analysis. Sensitivity analyses with missing data imputed based on the return-to-baseline method were performed to assess the robustness of the primary analysis results.

For each study, subgroup analyses on HbA1c (%) change from baseline were conducted with respect to baseline characteristics: sex (Male or Female), region (the US or outside the US), race (Asian, Black, and White, etc.), and age (< 65 years or >= 65 years). Each analysis applied the same statistical method as the corresponding primary efficacy analysis (i.e., ANCOVA models with missing primary endpoints imputed based on retrieved dropout for SURPASS-2, -3 and -4, or placebo washout for SURPASS-1 or -5). For each baseline characteristic, interactions between subgroups and treatment arms were tested. Additionally, the Bayesian shrinkage analyses based on the sample estimates derived from the traditional subgroup analyses were performed. For each study, while estimating the treatment effect within a subgroup of a given baseline characteristic (e.g., the male subgroup), the shrinkage method borrowed information from other subgroup(s) (the female subgroup), and thus was considered a "weighted" average of the sample estimate and the overall estimate.

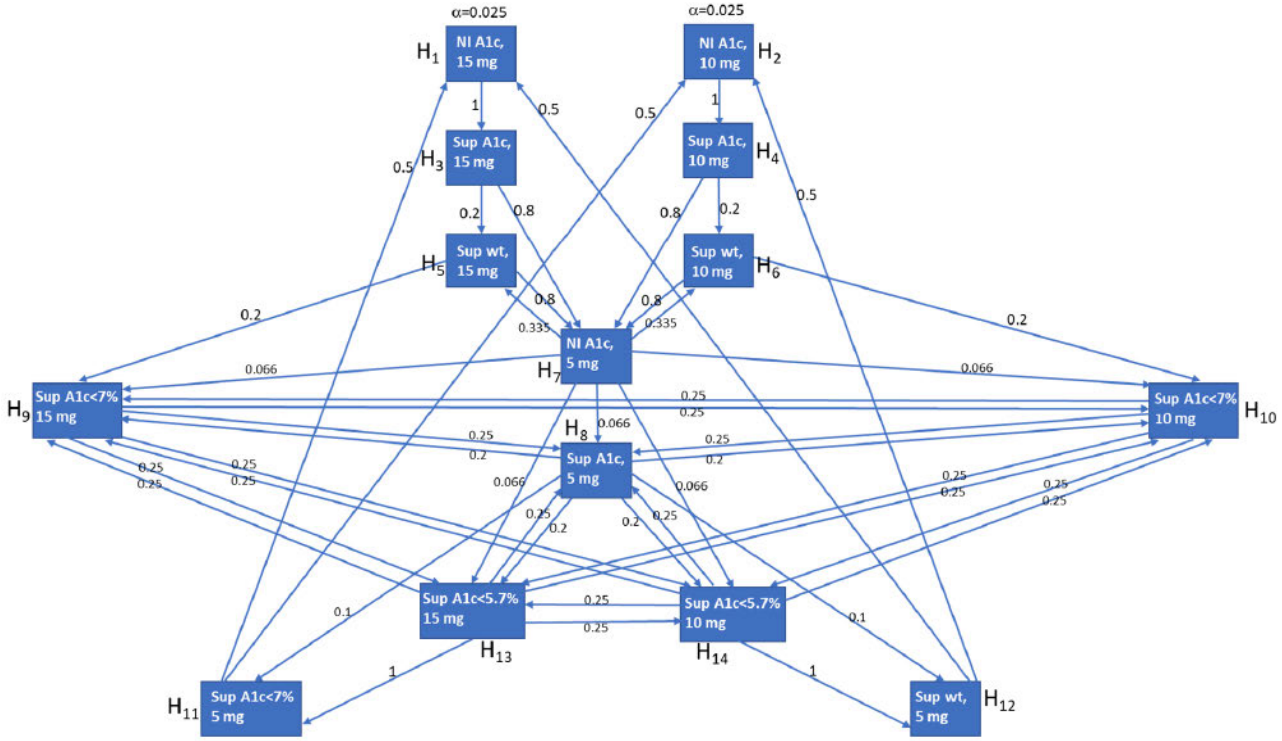
7.1.4 Hypothesis Testing Strategy

All Phase 3 tirzepatide trials used a graphical testing hierarchy to adjust for multiple testing. Shown below is the graphic testing hierarchy for SURPASS-2. Please refer to the statistical review memo for further detail on the remainder of the statistical designs for the other trials.

For SURPASS-2, the primary and key secondary hypotheses were represented in this manner:

- H1 and H2: Noninferiority test of tirzepatide 10 mg and 15 mg versus semaglutide in HbA1c change from baseline at 40 weeks.
- H3 and H4: Superiority test of tirzepatide 10 mg, and 15 mg versus semaglutide in HbA1c change from baseline at 40 weeks.
- H5 and H6: Superiority test of tirzepatide 10 mg, and 15 mg versus semaglutide in bodyweight change from baseline at 40 weeks.
- H7: Noninferiority test of tirzepatide 5 mg versus semaglutide in HbA1c change from baseline at 40 weeks.
- H8: Superiority test of tirzepatide 5 mg versus semaglutide in HbA1c change from baseline at 40 weeks.
- H9, H10, and H11: Superiority test of tirzepatide 10 mg, 15 mg, and 5 mg versus semaglutide in proportion of patients achieving HbA1c <7% at 40 weeks.
- H12: Superiority test of tirzepatide 5 mg versus semaglutide in body weight change from baseline at 40 weeks.
- H13 and H14: Superiority test of tirzepatide 10 mg, and 15 mg versus semaglutide in proportion of patients achieving HbA1c < 5.7% at 40 weeks.

Figure 5. Graphical Testing Hierarchy for SURPASS-2 (GPGL)



Source: Reproduced/Adapted from the Applicant's 18F-MC-GPGL Statistical Analysis Plan (Version 2), pages 21-22 of 44, available at: \\CDSESUB1\evsprod\NDA215866\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\type-2-diabetes-mellitus\5351-stud-rep-contr\i8f-mc-gpgl\gpgl-stat-analysis-plan-v2.pdf

Abbreviations: A1c, hemoglobin A1c; NI, noninferiority; Sup, superiority; and wt, body weight.

Reviewer Comment: Dr. Pucino concluded, and I concur, that the trial designs were adequate and consistent with other antihyperglycemic Phase 3 clinical development programs. The Applicant's use of enrichment strategies (high CV-risk in GPGM), inclusion of subjects with renal impairment, allowance of concomitant antihyperglycemic mediations (e.g., basal insulin or up to three antihyperglycemic medications) and comparisons with active comparators (e.g., semaglutide, basal insulins) is reflective of the intended patient populations and consistent with its anticipated use as part of a comprehensive glycemic control regimen.

7.2 Patient Disposition

Shown below is the patient disposition summary for the five global Phase 3 trials. Overall, there was a high study completion rate across the Phase 3 trials (86.1% - 97.5%) and no consistent unfavorable imbalances noted in the proportions of *study discontinuation*, deaths, or lost to follow-up. Across the Phase 3 studies, there were higher proportions of subjects who discontinued *tirzepatide treatment* due to adverse events, compared to subjects receiving either active control or placebo. See Section 8 (Safety) for further assessments.

The overall missing data rate of primary endpoints ranged from 4.2% to 9.6% across the five studies (with missing rate ranging from 4% to 8.8% for TZP 5mg, from 2.5% to 10% for TZP 10mg, 4.4% to 14% for TZP 15mg, and 1.7% to 11.3% for the comparator). See statistical memo for further details.

Table 8. Patient Disposition for the Phase 3 Safety and Efficacy Trials

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

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

Abbreviation: Dula, dulaglutide; Ins Deg, insulin degludec; Ins Glar, insulin glargine; no., number; PBO, placebo; Sema, semaglutide; and TZP, tirzepatide.

7.3 Summary of Primary and Secondary Efficacy Results

7.2.1 Primary Efficacy Endpoints

Table 9. HbA1c (%) Change from Baseline at Week 40 (SUPRASS-1, -2, and -5) or Week 52 (SURPASS-3 and -4)

	SURPASS-1	SURPASS-2	SURPASS-3	SURPASS-4	SURPASS-5
	Placebo	Semaglutide 1 mg	Insulin degludec	Insulin glargine	Placebo
Lsmean change from baseline *HbA1c* (SE)					
Comparator	-0.09 (0.11)	-1.84 (0.05)	-1.23 (0.06)	-1.38 (0.04)	-0.88 (0.08)

TZP 5mg	-1.75 (0.10)	-2.01 (0.05)	-1.83 (0.06)	-2.09 (0.06)	-2.21 (0.08)
TZP 10mg	-1.71 (0.11)	-2.24 (0.05)	-2.02 (0.05)	-2.31 (0.06)	-2.44 (0.08)
TZP 15mg	-1.69 (0.11)	-2.30 (0.05)	-2.13 (0.05)	-2.42 (0.05)	-2.44 (0.08)
Comparator-adjusted change from baseline *HbA1c* (95% CI)					
TZP 5mg	-1.64*** (-1.94, -1.34)	-0.16* (-0.29, -0.04)	-0.54*** (-0.78, -0.30)	-0.76*** (-0.89, -0.64)	-1.25*** (-1.49, -1.01)
TZP 10 mg	-1.60*** (-1.90, -1.30)	-0.41*** (-0.53, -0.28)	-0.73*** (-0.98, -0.48)	-0.92*** (-1.04, -0.79)	-1.53*** (-1.77, -1.30)
TZP 15mg	-1.59*** (-1.90, -1.28)	-0.48*** (-0.60, -0.36)	-0.85*** (-1.10, -0.60)	-1.02*** (-1.14, -0.89)	-1.48*** (-1.72, -1.24)

Source: statistical review memo, page 29 of 45
*P-values (two-sided) for superiority: *p-value < 0.05, *** p-value < 0.001 vs placebo or active comparator.*

7.2.2 Secondary Efficacy Endpoints

Table 10. Change from Baseline in Body Weight (kg), Fasting Serum Glucose (mg/dL), Incidence of HbA1c <7%

	SURPASS-1	SURPASS-2	SURPASS-3	SURPASS-4	SURPASS-5
	Placebo	Semaglutide 1 mg	Insulin degludec	Insulin glargine	Placebo
Lsmean change from baseline body *weight (kg)* (SE)					
Comparator	-1.0 (0.5)	-5.7 (0.3)	1.9 (0.4)	1.7 (0.2)	1.6 (0.6)
TZP 5mg	-6.3 (0.5)	-7.6 (0.3)	-7.0 (0.4)	-6.4 (0.4)	-5.4 (0.6)
TZP 10mg	-7.0 (0.5)	-9.3 (0.3)	-9.6 (0.4)	-8.9 (0.4)	-7.5 (0.6)
TZP 15mg	-7.8 (0.5)	-11.2 (0.3)	-11.3 (0.4)	-10.6 (0.3)	-8.8 (0.6)
Comparator-adjusted change from baseline body *weight (kg)* (95% CI)					
TZP 5mg	-5.3 *** (-6.8, -3.9)	-1.9*** (-2.8, -1.0)	-8.9*** (-10.0, -7.8)	-8.1*** (-8.9, -7.3)	-7.1*** (-8.7, -5.4)
TZP 10 mg	-6.0 *** (-7.4, -4.6)	-3.6*** (-4.5, -2.7)	-11.5*** (-12.6, -10.4)	-10.6*** (-11.4, -9.8)	-9.1*** (-10.7, -7.5)
TZP 15mg	-6.9 *** (-8.3, -5.4)	-5.5*** (-6.4, -4.6)	-13.2*** (-14.3, -12.1)	-12.2*** (-13.0, -11.5)	-10.5*** (-12.1, -8.8)
Lsmean change from baseline *fasting serum glucose (mg/dL)* (SE)					
Comparator	3.7 (4.4)	-49.4 (1.6)	-50.5 (2.5)	-48.8 (1.7)	-39.2 (2.7)
TZP 5mg	-39.6 (4.0)	-54.8 (1.5)	-47.0 (2.0)	-44.3 (2.6)	-58.2 (2.8)
TZP 10mg	-39.8 (4.1)	-59.1 (1.6)	-50.1 (21)	-50.3 (2.4)	-64.0 (2.7)
TZP 15mg	-38.6 (4.4)	-60.2 (1.5)	-54.2 (1.9)	-54.5 (2.3)	-62.6 (2.8)
Comparator-adjusted change from baseline *fasting serum glucose (mg/dL)* (95% CI)					
TZP 5mg	-43.2*** (-54.8, -31.6)	-5.4‡ (-9.7, -1.1)	3.5 (-2.8, 9.7)	4.5 (-1.7, 10.8)	-19.0*** (-26.6, -11.4)
TZP 10 mg	-43.4*** (-55.1, -31.7)	-9.7‡‡‡ (-14.1, -5.2)	0.3 (-6.0, 6.6)	-1.5 (-7.3, 4.3)	-24.9*** (-32.3, -17.4)
TZP 15mg	-42.3*** (-54.4, -30.3)	-10.8‡‡‡ (-15.1, -6.5)	-3.8 (-9.9, 2.4)	-5.7‡ (-11.3, -0.1)	-23.4*** (-31.0, -15.8)
Percentage of subjects achieving *HbA1c < 7%* (SE)					
Comparator	23.0 (4.2)	79.0 (2.0)	58.0 (2.7)	48.8 (1.8)	34.5 (4.4)
TZP 5mg	81.8 (3.7)	82.0 (1.8)	79.2 (2.3)	75.1 (2.7)	87.3 (3.3)
TZP 10mg	84.5 (3.5)	85.6 (1.7)	81.5 (2.4)	82.9 (2.3)	89.6 (2.9)
TZP 15mg	78.3 (4.1)	86.2 (1.7)	83.5 (2.0)	84.9 (2.0)	84.7 (3.6)
Odds ratio (treatment/comparator), incidence of *HbA1c < 7%* (95% CI)					
TZP 5mg	17.4*** (8.5, 35.7)	1.3 (0.9, 1.8)	3.1*** (2.1, 4.4)	3.5*** (2.5, 4.8)	14.7*** (7.0, 30.6)

TZP 10 mg	21.2*** (10.1, 44.4)	1.7** (1.2, 2.5)	3.6*** (2.4, 5.4)	6.0*** (4.2, 8.7)	19.5*** (9.2, 41.3)
TZP 15mg	13.4*** (6.7, 26.8)	1.7** (1.2, 2.5)	4.2*** (2.9, 6.2)	6.8*** (4.8, 9.7)	11.5*** (5.6, 23.3)

Source: excerpted from statistical review memo Tables 14-16.
FSG was a key secondary endpoint only for the two placebo-controlled trials: SURPASS-1 and SURPASS-5.
TZP 5mg failed to demonstrate superiority to semaglutide, because more subjects treated with semaglutide achieved HbA1c <7% than subjects on placebo/insulin control, while the proportion of subjects achieved HbA1c <7% in TZP 5mg was similar across all studies.
P-values for superiority: *p-value < 0.05, **p-value < 0.01, *** p-value < 0.001 vs placebo or active comparator.
P-values not controlled for type 1 error: ǂ P-value < 0.05, ǂǂǂ p-value < 0.001 vs placebo or active comparator.

Dr. Tu concluded, and I concur, that the subgroup analyses of the primary efficacy endpoints indicated that the treatment effect was homogeneous across subgroups by age (< 65 years or ≥ 65 years), sex (Male or Female), race (Asian, Black, or White, etc.) and region (the US or outside the US). Shown below are the results from SURPASS-1, which were obtained from the placebo-controlled trial with a study population comprised of T2D patients treated with lifestyle modification alone. SURPASS-1 contains the least clinically complex population upon which to evaluate demographic subgroup effects.

Table 11. Sample and Shrinkage Estimates of Difference in HbA1c % Change from Baseline within Subgroups, mITT Population, SURPASS-1

	TZP 5mg			TZP 10mg			TZP 15mg		
Overall (95% CI)	-1.64 (-1.94, -1.34)			-1.60 (-1.90, -1.30)			-1.59 (-1.90, -1.28)		
	Sample (95% CI)	Shrinkage (95% CI)	n	Sample (95% CI)	Shrinkage (95% CI)	n	Sample (95% CI)	Shrinkage (95% CI)	n
SEX									
Male	-1.77 (-2.18, -1.36)	-1.70 (-2.07, -1.36)	56	-1.66 (-2.06, -1.27)	-1.63 (-1.98, -1.28)	72	-1.72 (-2.13, -1.31)	-1.64 (-2.01, -1.29)	63
Female	-1.50 (-1.92, -1.07)	-1.58 (-1.94, -1.18)	65	-1.53 (-1.99, -1.06)	-1.57 (-1.96, -1.17)	49	-1.39 (-1.85, -0.94)	-1.48 (-1.85, -1.07)	57
REGION									
The US	-1.62 (-2.18, -1.06)	-1.63 (-2.06, -1.19)	38	-1.62 (-2.17, -1.07)	-1.60 (-2.03, -1.17)	39	-1.33 (-1.91, -0.75)	-1.47 (-1.92, -0.93)	37
Outside the US	-1.65 (-2.02, -1.28)	-1.64 (-1.99, -1.29)	83	-1.57 (-1.95, -1.20)	-1.58 (-1.92, -1.23)	82	-1.70 (-2.08, -1.33)	-1.63 (-2.01, -1.27)	83
RACE*									
American Indian/ Alaskan Native	-1.53 (-2.05, -1.01)	-1.59 (-1.96, -1.21)	31	-1.46 (-2.00, -0.92)	-1.52 (-1.90, -1.12)	31	-1.73 (-2.26, -1.19)	-1.67 (-2.07, -1.30)	30
Asian	-1.68 (-2.21, -1.16)	-1.63 (-2.01, -1.27)	45	-1.70 (-2.22, -1.17)	-1.58 (-1.99, -1.22)	43	-1.82 (-2.36, -1.29)	-1.70 (-2.12, -1.33)	41
White	-1.65 (-2.13, -1.18)	-1.63 (-1.98, -1.27)	38	-1.48 (-1.95, -1.02)	-1.52 (-1.87, -1.15)	43	-1.44 (-1.91, -0.96)	-1.58 (-1.94, -1.17)	43
AGE									
≥ 65	-1.63 (-2.16, -1.11)	-1.64 (-2.04, -1.24)	27	-1.22 (-1.73, -0.70)	-1.38 (-1.82, -0.84)	30	-0.87 (-1.47, -0.28)	-1.03 (-1.66, -0.39)	21
< 65	-1.67 (-2.02, -1.32)	-1.66 (-1.97, -1.35)	94	-1.74 (-2.09, -1.38)	-1.67 (-2.01, -1.34)	91	-1.80 (-2.15, -1.45)	-1.74 (-2.10, -1.40)	99

Source: statistical review memo, Table 21
** Black or African American was excluded from the analyses due to insufficient sample size.*

Reviewer Comment: I conclude that the Applicant has provided the substantial evidence of effectiveness required by law [see 21 CFR 314.126(a)(b)] to support approval. Results from the primary efficacy analyses demonstrated statistically significant superiority of tirzepatide to placebo, semaglutide 1 mg, insulin degludec and insulin glargine with clinically meaningful reductions in HbA1c concentrations compared to the placebo (-1.2 to -1.6% placebo-subtracted) or active comparator (-0.2 to -1% comparator-subtracted) in all five trials for all three tirzepatide doses. Results from secondary analyses (change from baseline in body weight, fasting serum glucose, and incidence of HbA1c < 7%) provided supportive evidence. Comparator-subtracted reductions in body weight ranged from -1.9 to -8.9 kg in the tirzepatide 5 mg arms, -3.6 to -11.5 kg in the tirzepatide 10 mg arms, and -5.5 to -13.2 kg in the tirzepatide 15 mg arms. Similarly, placebo-subtracted change from baseline fasting serum glucose was consistent and clinically meaningful across doses and were superior to active controls at higher dosages.

8. Safety

Dr. Frank Pucino conducted the clinical safety review. Additional safety assessments on specific safety issues were completed by Division of Biometrics 7 (DB7) and DB2. See each respective review memo for further details.

The safety analysis was conducted on all subjects who were randomized and treated (i.e., all subjects who received ≥1 dose of IP). The safety assessments performed by the Applicant were based on all available data through the treatment period and four-week safety follow-up visit and included all events occurring after discontinuation of IP and among subjects who received glycemic rescue therapy with another antihyperglycemic medication. The treatment duration was considered the last dose of study medication plus seven days. Since tirzepatide has approximately a five day half-life, assessment of safety through the safety follow-up visit was reasonable.

8.1 Overall Exposure & Description of Safety Pools

The overall safety database consisted of nine completed Phase 2/3 trials consisting of 7769 randomized subjects, of which 5415 subjects received tirzepatide. Exposure duration ranged from 12-26 weeks for the two Phase 2 trials and 40-104 weeks for the seven Phase 3 trials. In the Phase 3 trials, 5119 subjects were randomized to tirzepatide (5, 10, or 15 mg), of which 2375 subjects were exposed for ≥52 weeks, and 535 were exposed for ≥78 weeks.

FDA assessed the adequacy of the safety database in a Type C meeting on April 24, 2020, and the Division confirmed that provided no new safety issues arise during Phase 3 development, the size of the proposed safety and patient characteristics were reasonable for submitting an NDA.

Table 12. Comparison of Tirzepatide's Development Program to FDA's Guidance for Industry for Evaluating the Safety of New Drugs for Improving Glycemic Control

FDA Draft Guidance for Industry *Type 2 Diabetes Mellitus: Evaluating the Safety of New Drugs for Improving Glycemic Control, March 2020*	Tirzepatide Development Program
≥4,000 patient-years exposure in Phase 3 clinical trials	4,833 patient-years
≥1,500 patients exposed for at least 1 year	2,375 patients
≥500 patients exposure to the new drug for at least 2 years	535 patients exposed for 78 weeks

	17 patients exposed for 104 weeks
≥500 patients with stage 3/4 chronic kidney disease exposed to the new drug	405 patients
≥600 patients with established CV disease (e.g., previous myocardial infarction, documented coronary artery disease, previous stroke, peripheral vascular disease) exposed to the new drug.	1,213 patients
≥600 patients older than 65 years of age exposed to the new drug	1,600 patients

Reviewer Comment: In addition to FDA's determination in the pre-NDA period, Dr. Pucino concluded that the size and characteristics of the safety database for the tirzepatide clinical development program were adequate to support review of the NDA and that the exposure durations were sufficient to evaluate the prespecified AESI. I concur with his conclusion.

Table 13. Applicant's Analysis Sets for Integrated Phase 2/3 Clinical Trial Data

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

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

In the pool of seven Phase 3 trial (AS2), that included two regional trials conducted in Japan (GPGO, GPGP), tirzepatide was evaluated as monotherapy and add-on therapy to oral antihyperglycemic medications or insulin.

8.2 Baseline Demographics

Table 14. Baseline Demographics and Clinical Characteristics of the Phase 2/3 Trials (AS3)

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

	N (%)								
	GPGK	GPGI	GPGF	GPGM	GPGH	GPGO	GPGB	GPGL	GPGP
N	478	475	111	1995	1437	636	316	1878	443
								(100.0)	
2 OAMs	0	0	0	1052 (52.7)	458 (31.9)	0	0	0	0
3 OAMs	0	0	0	217 (10.9)	0	0	0	0	0
Insulin	0	81 (17.1)	0	0	0	0	0	0	0
Insulin + metformin	0	394 (82.9)	0	0	0	0	0	0	0
HbA1c (%)									
Mean ± SD	7.9 ± 0.87	8.3 ± 0.85	8.4 ± 1.09	8.5 ± 0.88	8.2 ± 0.91	8.2 ± 0.87	8.14 ± 0.97	8.3 ± 1.03	8.6 ± 1.09
eGFR CKD-EPI (mL/min/1.73 m^2)									
Mean ± SD	94.1 ± 19.70	85.5 ± 17.78	95.1 ± 15.89	81.3 ± 21.11	94.1 ± 17.04	78.1 ± 12.0	93.1 (17.25)*	96.0 ± 17.07	78.7 ± 12.58
<60 mL/min/1.73 m^2	28 (5.9)	47 (9.9)	4 (3.6)	342 (17.1)	56 (3.9)	44 (6.9)	15 (4.8)*	64 (3.4)	40 (9)
≥60 mL/min/1.73 m^2	450 (94.1)	428 (90.1)	107 (96.4)	1653 (82.9)	1381 (96.1)	592 (93.1)	299 (95.22)*	1814 (96.6)	403 (91)

Source: Adapted from the Applicant's Summary of Clinical Efficacy, pages 141-145 of 190, and from the individual CSRs, available at: \\CDSESUB1\evsprod\nda215866\0001\m2\27-clin-sum\2-7-3-clin-efficacy-sum.pdf

\\CDSESUB1\evsprod\NDA215866\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\type-2-diabetes-mellitus\5351-stud-rep-contr

Abbreviations: AS3, Analysis Set 3 (pool of Phase 2/3 trials); BMI, body mass index; CSR, Clinical Study Report; eGFR, estimated glomerular filtration rate; EU, European Union; FSG, fasting serum glucose; HbA1c, hemoglobin A1c; Min, minimum; Max, maximum; N, subjects randomized; n, number; OAM, oral antihyperglycemic medication; and SD, standard deviation.

**Note: N=314; two subjects missing baseline values; data derived from the adlb.xpt dataset.*

8.3 Discontinuations Due to Adverse Events

Across the pivotal Phase 3 trials, more tirzepatide-treated subjects discontinued due to adverse events at all dose levels, compared to placebo and all studied active comparator groups. This imbalance was driven largely by the 'Gastrointestinal disorders' for tirzepatide-treated subjects with the most common PTs coded as 'Nausea', 'Diarrhoea', and 'Vomiting'.

Table 15. Discontinuations Due to Adverse Events by System Organ Class

	GPGK		GPGI		GPGM		GPGH		GPGL	
System Organ Class	PBO (N=115)	TZP ALL (N=363)	PBO (N=120)	TZP ALL (N=355)	Ins Glar (N=1000)	TZP ALL (N=995)	Ins Deg (N=360)	TZP ALL (N=1077)	Sema 1 mg (N=469)	TZP ALL (N=1409)
Subjects Discontinuing IP due to AEs, no. (%)	3 (2.6)	18 (5.0)	3 (2.5)	30 (8.5)	54 (5.4)	101 (10.2)	5 (1.4)	101 (9.4)	19 (4.1)	108 (7.7)
Gastrointestinal disorders	1 (0.9)	17 (4.7)	---	19 (5.4)	---	45 (4.5)	1 (0.3)	51 (4.7)	15 (3.2)	53 (3.8)
Cardiac disorders	1 (0.9)	---	---	---	12 (1.2)	11 (1.1)	---	1 (<0.1)	---	5 (0.4)
Infections and infestations	---	---	1 (0.8)	2 (0.6)	13 (1.3)	10 (1.0)	1 (0.3)	5 (0.5)	1 (0.2)	7 (0.5)
Investigations	---	1 (0.3)	1 (0.8)	1 (0.3)	1 (0.1)	10 (1.0)	---	16 (1.5)	1 (0.2)	8 (0.6)
Metabolism and nutrition disorders	---	---	---	3 (0.8)	---	8 (0.8)	1 (0.3)	8 (0.7)	---	6 (0.4)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	---	---	1 (0.8)	2 (0.6)	11 (1.1)	6 (0.6)	---	6 (0.6)	---	5 (0.4)

	GPGK		GPGI		GPGM		GPGH		GPGL	
System Organ Class	PBO (N=115)	TZP ALL (N=363)	PBO (N=120)	TZP ALL (N=355)	Ins Glar (N=1000)	TZP ALL (N=995)	Ins Deg (N=360)	TZP ALL (N=1077)	Sema 1 mg (N=469)	TZP ALL (N=1409)
General disorders and administration site conditions	---	---	---	2 (0.6)	4 (0.4)	4 (0.4)	1 (0.3)	6 (0.6)	1 (0.2)	15 (1.1)
Nervous system disorders	---	---	---	---	2 (0.2)	2 (0.2)	---	2 (0.2)	1 (0.2)	3 (0.2)
Hepatobiliary disorders	---	---	---	---	---	1 (0.1)	---	1 (<0.1)	---	---
Injury, poisoning and procedural complications	---	---	---	---	1 (0.1)	1 (0.1)	---	2 (0.2)	---	1 (<0.1)
Musculoskeletal and connective tissue disorders	---	---	---	1 (0.3)	1 (0.1)	1 (0.1)	---	---	---	---
Renal and urinary disorders	---	---	---	---	1 (0.1)	1 (0.1)	---	---	---	2 (0.1)
Respiratory, thoracic and mediastinal disorders	---	---	---	---	7 (0.7)	1 (0.1)	---	---	---	---
Blood and lymphatic system disorders	---	---	---	---	1 (0.1)	---	---	---	---	---
Ear and labyrinth disorders	---	---	---	---	---	---	---	1 (<0.1)	---	---
Endocrine disorders	---	---	---	---	---	---	---	---	---	1 (<0.1)
Eye disorders	1 (0.9)	---	---	---	---	---	---	---	---	---
Immune system disorders	---	---	---	---	---	---	---	---	---	1 (<0.1)
Skin and subcutaneous tissue disorders	---	---	---	---	---	---	1 (0.3)	1 (<0.1)	---	1 (<0.1)
Surgical and medical procedures	---	---	---	---	---	---	---	1 (<0.1)	---	---

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

8.4 Safety Results

8.4.1 Deaths

Across the nine Phase 2/3 trials (AS3 pool), there were 80 deaths, of which 41 deaths (0.76%) occurred after tirzepatide and 39 deaths (1.66%) in the pooled comparator arm. Most deaths (60 subjects) occurred in trial GPGM, which was enriched with patients with high CV risk and included a longer treatment duration. Only one trial had an unfavorable imbalance in deaths for tirzepatide (GPGL). In GPGL, more deaths were reported in the tirzepatide arms (12 (0.9%) tirzepatide vs. 1 (0.2%) semaglutide arm). Six deaths were related to COVID-19 infection (1 subject in the semaglutide arm, 5 subjects randomized to tirzepatide), five deaths were CV-related deaths, and two were "undetermined" by the external Clinical Endpoint Committee.

Table 16. Fatal Adverse Events by System Organ Class and Trial (AS3)*

	GPGK		GPGM		GPGH		GPGB			GPGL	
System Organ Class MedDRA PT	PBO (N=115)	TZP ALL (N=363)	Ins Glar (N=1000)	TZP ALL (N=995)	Ins Deg (N=360)	TZP ALL (N=1077)	PBO (N=51)	Dula 1.5 mg (N=54)	TZP ALL (N=211)	Sema 1 mg (N=469)	TZP ALL (N=1409)
ALL DEATHS											
Total Deaths — no. (%)	1 (0.9)	---	35 (3.5)	25 (2.5)	1 (0.3)	4 (0.4)	1 (2.0)	---	---	1 (0.2)	12 (0.9)
Infections and infestations	---	---	10 (1.0)	10 (1.0)	---	1 (<0.1)	---	---	---	1 (0.2)	5 (0.4)
Cardiac disorders	1 (0.9)	---	9 (0.9)	8 (0.8)	---	2 (0.2)	---	---	---	---	3 (0.2)
General disorders and administration site conditions	---	---	4 (0.4)	3 (0.3)	1 (0.3)	---	---	---	---	---	2 (0.1)
Neoplasms benign, malignant, and unspecified	---	---	2 (0.2)	2 (0.2)	---	---	1 (2.0)	---	---	---	---
Nervous system disorders	---	---	---	1 (0.1)	---	---	---	---	---	---	1 (<0.1)
Respiratory, thoracic, and mediastinal disorders	---	---	7 (0.7)	1 (0.1)	---	---	---	---	---	---	---
Injury, poisoning and procedural complications	---	---	1 (0.1)	---	---	---	---	---	---	---	---
Musculoskeletal and connective tissue disorders	---	---	1 (0.1)	---	---	---	---	---	---	---	---
Psychiatric disorders	---	---	---	---	---	1 (<0.1)	---	---	---	---	---
Renal and urinary disorders	---	---	1 (0.1)	---	---	---	---	---	---	---	1 (<0.1)

Source: adapted from clinical review memo Table 24.
** No deaths were observed in trials GPGI, GPGF, GPGO and GPGP; thus, are not represented above.*

8.4.2 Serious Adverse Events (SAE)

In the placebo-controlled pool (AS1), there was no imbalance in the overall rate of SAEs (5.5% placebo vs. 5.4% pooled tirzepatide arms. Several SOCs had numerically higher SAEs in the tirzepatide arms, but events were few in number.

In the AS2 pool consisting of seven Phase 3 trials, no dose related trend in SAEs was observed in the tirzepatide arms (7.9% (134/1701), 7.9% (135/1702), and 7.1% (122/1716)) in the tirzepatide 5, 10, and 15 mg arms, respectively. Dr. Pucino noted that when SAEs were analyzed by individual trial, rates of SAEs were similar between comparator and pooled tirzepatide arms except for trial GPGL. In this trial, SAEs were higher in the pooled tirzepatide arm compared to the semaglutide arm (6% of vs. 2.8%), with higher proportions for most SOCs, however event counts by individual PTs were too limited to draw meaningful conclusions. Notably, there were four events of 'Acute myocardial infarction' and five events of 'Cholecystitis acute' in the tirzepatide arms, and no cases of these AEs were reported in the semaglutide arm.

Table 17. Serious Adverse Events – Side by Side Comparisons of Phase 3 Trials (AS2)

	GPGK		GPGI		GPGM		GPGH		GPGO		GPGL	
System Organ Class	PBO (N=115)	TZP ALL (N=363)	PBO (N=120)	TZP ALL (N=355)	Ins Glar (N=1000)	TZP ALL (N=995)	Ins Deg (N=360)	TZP ALL (N=1077)	Dula 0.75 mg (N=159)	TZP ALL (N=477)	Sema 1 mg (N=469)	TZP ALL (N=1409)
Subjects with **≥1** SAE—no. (%)	3 (2.6)	8 (2.2)	10 (8.3)	31 (8.7)	193 (19.3)	143 (14.4)	22 (6.1)	75 (7.0)	14 (8.8)	25 (5.2)	13 (2.8)	85 (6.0)
Cardiac disorders	2 (1.7)	1 (0.3)	2 (1.7)	8 (2.3)	64 (6.4)	50 (5.0)	5 (1.4)	12 (1.1)	2 (1.3)	4 (0.8)	1 (0.2)	10 (0.7)
Infections and infestations	---	2 (0.6)	1 (0.8)	6 (1.7)	52 (5.2)	36 (3.6)	8 (2.2)	16 (1.5)	4 (2.5)	5 (1.0)	6 (1.3)	25 (1.8)
Nervous system disorders	---	1 (0.3)	1 (0.8)	3 (0.8)	26 (2.6)	19 (1.9)	3 (0.8)	6 (0.6)	---	1 (0.2)	1 (0.2)	5 (0.4)
Neoplasms benign, malignant and unspecified	1 (0.9)	1 (0.3)	1 (0.8)	3 (0.8)	17 (1.7)	12 (1.2)	1 (0.3)	11 (1.0)	3 (1.9)	6 (1.3)	1 (0.2)	9 (0.6)
General disorders and administration site conditions	---	---	---	2 (0.6)	6 (0.6)	10 (1.0)	1 (0.3)	3 (0.3)	---	---	---	4 (0.3)
Renal and urinary disorders	---	1 (0.3)	1 (0.8)	1 (0.3)	12 (1.2)	10 (1.0)	2 (0.6)	3 (0.3)	---	---	---	5 (0.4)
Gastrointestinal disorders	---	1 (0.3)	2 (1.7)	1 (0.3)	6 (0.6)	9 (0.9)	---	11 (1.0)	1 (0.6)	5 (1.0)	---	11 (0.8)
Injury, poisoning and procedural complications	---	---	1 (0.8)	3 (0.8)	9 (0.9)	9 (0.9)	2 (0.6)	8 (0.7)	2 (1.3)	3 (0.6)	1 (0.2)	8 (0.6)
Vascular disorders	---	1 (0.3)	1 (0.8)	2 (0.6)	10 (1.0)	9 (0.9)	---	2 (0.2)	---	---	2 (0.4)	2 (0.1)
Metabolism and nutrition disorders	---	---	---	2 (0.6)	17 (1.7)	8 (0.8)	---	---	---	---	---	4 (0.3)
Respiratory, thoracic and mediastinal disorders	---	1 (0.3)	1 (0.8)	4 (1.1)	22 (2.2)	7 (0.7)	1 (0.3)	3 (0.3)	---	1 (0.2)	1 (0.2)	6 (0.4)
Hepatobiliary disorders	---	---	---	---	6 (0.6)	5 (0.5)	---	5 (0.5)	---	2 (0.4)	---	5 (0.4)
Musculoskeletal and connective tissue disorders	---	1 (0.3)	---	2 (0.6)	5 (0.5)	3 (0.3)	1 (0.3)	2 (0.2)	1 (0.6)	1 (0.2)	1 (0.2)	1 (<0.1)
Skin and subcutaneous tissue disorders	---	---	---	---	4 (0.4)	2 (0.2)	1 (0.3)	1 (<0.1)	1 (0.6)	---	---	1 (<0.1)

Source: Adapted from clinical review memo Table 26. Derived from the adsl.xpt and adae.xpt datasets, available at: \\CDSESUB1\evsprod\NDA215866\0001\m5\datasets

Abbreviation: AS1, Analysis Set 2 (pool of 7 Phase 3 trials); Dula, dulaglutide; Ins Deg, insulin degludec; Ins Glar, insulin glargine; MedDRA, Medical Dictionary for Regulatory Activities; no., number; PBO, placebo; PT, preferred term; Sema, semaglutide; SOC, system organ class; TEAE, treatment-emergent adverse event; and TZP, tirzepatide.

8.4.3 Treatment Emergent Adverse Events (TEAEs)

Treatment-emergent adverse events were defined as AEs that first occurred or worsened in severity after baseline. The AE information obtained and documented in the electronic case report form (eCRF) included: the onset and duration, the seriousness and severity, relatedness to IP, and the actions taken with respect to study treatment will be recorded. Dr. Pucino noted that across the pivotal Phase 3 trials, higher proportions of tirzepatide-treated subjects experienced gastrointestinal adverse events compared to each control arm and the AE rates were dose-related. Other common adverse events reported for tirzepatide-treated subjects included 'Nasopharyngitis', 'Decreased appetite', and 'Lipase increased'. No new safety concerns were identified upon

review of TEAEs.

Table 18. Summary of Common TEAEs **(≥5%)** by Study – Pivotal Phase 3 Trials

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

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

8.4.4 Laboratory Findings and Vital Signs

Products with GLP-RA activity are known to be associated with increases in heart rate, reductions in blood pressure and decreases in body weight. This section covers only notable findings in the clinical review. Please see Dr. Pucino's review memo for more complete information.

Hemoglobin

Dr. Pucino noted an imbalance in shifts in hemoglobin concentrations from normal/high to postbaseline low concentration in the Phase 3 placebo-controlled trial pool (AS1): 16.3% (107/656) in tirzepatide-treated subjects, compared to 9.2% (20/218) in placebo recipients. The mean change from baseline was -1.7 g/dL and -1.5 g/dL

for tirzepatide and placebo, respectively. Additionally, anemia was reported in 1.1% (8/718) of tirzepatide-treated subjects compared to 0% (0/235) in placebo recipients. However, in the AS2 pool of seven Phase 3 trials, there was no imbalance in the overall rate of anemia-related TEAE was 2.2% pooled tirzepatide, compared to 2.5% pool comparators. Dr. Pucino felt the that observed shifts in hemoglobin did not warrant inclusion in labeling at this time and that the Applicant's ongoing cardiovascular outcomes trial (GPGN) which has enrolled 12,861 subjects may provide additional data to inform the clinical relevance of this finding.

Pulse Rate

Using a mixed model repeated measures (MMRM) model, the Applicant reported mean increases from baseline in pulse rate at Week 40 of 0.1±0.57, 1.1±0.56, 2.8±0.56, and 3.4±0.57 beats per minute (bpm), respectively for the placebo, tirzepatide 5, 10 and 15 mg arms. Differences between the tirzepatide and placebo arms were observed throughout the treatment period but returned towards baseline at the 4-week safety follow-up. Dr. Pucino noted that, compared to placebo, the occurrence of sinus tachycardia (pulse rate >100 bpm) was more frequent in tirzepatide-treated subjects (11.1%) and appeared to be dose-related, with reported events in 6.8%, 7.2%, 9.7%, and 16.3% of subjects in the placebo, and tirzepatide 5, 10, and 15 mg arms, respectively. No subjects in any treatment arm had reported heart rates >130 bpm (i.e., the Applicant's threshold for abnormal pulse rate).

Moreover, in the placebo-controlled pool (AS1), post-randomization pulse rates of >100 bpm with changes from baseline of ≥15 bpm were reported in 7% (3/43), 7.1% (3/42), 9.3% (4/43) and 23.3% (10/43) of subjects from Japan randomized to the placebo, and tirzepatide 5, 10, and 15 mg treatment arms, respectively. At the non-Japan study sites, 3.6% (7/192), 4.1% (8/195), 5.1% (10/197), and 7.1% (14/198) of placebo-, and tirzepatide 5 mg-, 10 mg-, and 15 mg-treated subjects met this abnormal pulse rate criteria, respectively.

Table 19. Abnormal Pulse Rate Changes Postbaseline (AS1)

Abnormal Pulse Rate Changes	Placebo (N=235)	TZP 5mg (N=237)	TZP 10mg (N=240)	TZP 15mg (N=241)	TZP ALL (N=718)
Subjects at timepoint	235	237	237	240	714
Pulse rate criteria — no. (%)					
>100 bpm at any visit	16 (6.8)	17 (7.2)	23 (9.7)	39 (16.3)	79 (11.1)
>100 bpm at ≥2 consecutive visits	5 (2.1)	5 (2.1)	9 (3.8)	12 (5.0)	26 (3.6)
>100 bpm at ≥3 consecutive visits	4 (1.7)	5 (2.1)	6 (2.5)	13 (5.4)	24 (3.4)
>130 bpm at any visit	0	0	0	0	0
CFB>20 bpm at any visit	15 (6.4)	23 (9.7)	29 (12.2)	36 (15.0)	88 (12.3)
CFB>20 bpm at ≥2 consecutive visits	5 (2.1)	5 (2.1)	9 (3.8)	7 (2.9)	21 (2.9)
CFB>20 bpm at ≥3 consecutive visits	1 (0.4)	4 (1.7)	6 (2.5)	7 (2.9)	17 (2.4)
>100 bpm and CFB>15 bpm	10 (4.3)	11 (4.6)	14 (5.9)	24 (10.0)	49 (6.9)

Source: Clinical review memo, Table 33. Adapted from the Applicant's ISS, page 3448 of 7807, available at:

\\CDSESUB1\evsprod\nda215866\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\type-2-diabetes-mellitus\5353-rep-analys-data-more-one-stud\iss\iss-46-integrated-sum-of-safety--t2dm-.pdf.

Abbreviation: AS1, Analysis Set 1 (pool of 2 placebo-controlled Phase 3 trials); bpm, beats per minute;' CFB, change from baseline; and TZP, tirzepatide.

To further investigate these findings, Dr. Elyes Dahmane conducted a combined linear and Emax (maximum drug effect) mixed effects model to evaluate differences in the changes in heart rate (ΔHR) between studies, populations, or demographic characteristics, based on PK and PD time-matched observations from the seven Phase 3 trials (AS2). These analyses showed that the Japanese subjects had a 17% higher tirzepatide exposure and steady-state C_{max} ($C_{max,ss}$) compared to non-Japanese subjects due to a lower median body weight (i.e., 76 kg vs. 90 kg). The Japanese subjects appear to be more sensitive to HR increases than non-Japanese subjects under similar tirzepatide exposures. Although he felt that Japanese patients may need closer monitoring of their pulse rate and the potential for associated cardiovascular events, he did not feel that a specific dose adjustment would be necessary, given that proposed tirzepatide labeling recommends a gradual dose titration to an effective, tolerable dose.

Dr. Gomatam also conducted a hypothesis generating analysis to explore possible explanations for the observed higher numerical change in heart rate from baseline to Week 24 among subjects randomized in Japan. These analyses were conducted for the Phase 3 CV meta-analysis population (GPGH, GPGI, GPGK, GPGL, GPGM, GPGO), excluding the Phase 2 trial GPGB. The change in pulse rate at Week 24 was modeled as a function of dose (linear and quadratic terms), baseline BMI, baseline pulse, and interactions between dose and baseline BMI and between dose and baseline pulse rate. A term for the Japan subset was also fit. Separate models were fit for the overall population, and Japan and non-Japan subsets, to see how the models differed. Dr. Gomatam concluded that only baseline pulse was significant for the Japan subgroup. BMI or interactions of BMI with dose were not significant predictors in these models for any of these groups. The effect of dose was not consistent in the full meta-analysis population and the Japan subset.

Blood Pressure and Lipids

Blood pressure and lipid endpoints were not included in the testing hierarchy and are not included in labeling. However, tirzepatide decreased mean systolic and diastolic blood pressure of approximately 6-9 mmHg and 3-4 mmHg, compared to a mean decrease of approximately 2 mmHg and 2 mmHg in placebo recipients. Additionally, tirzepatide reduced triglycerides, total cholesterol, and very low-density lipoprotein cholesterol (VLDL-C) and increased high-density cholesterol (HDL-C) at Week 40 compared to placebo in trial GPGK.

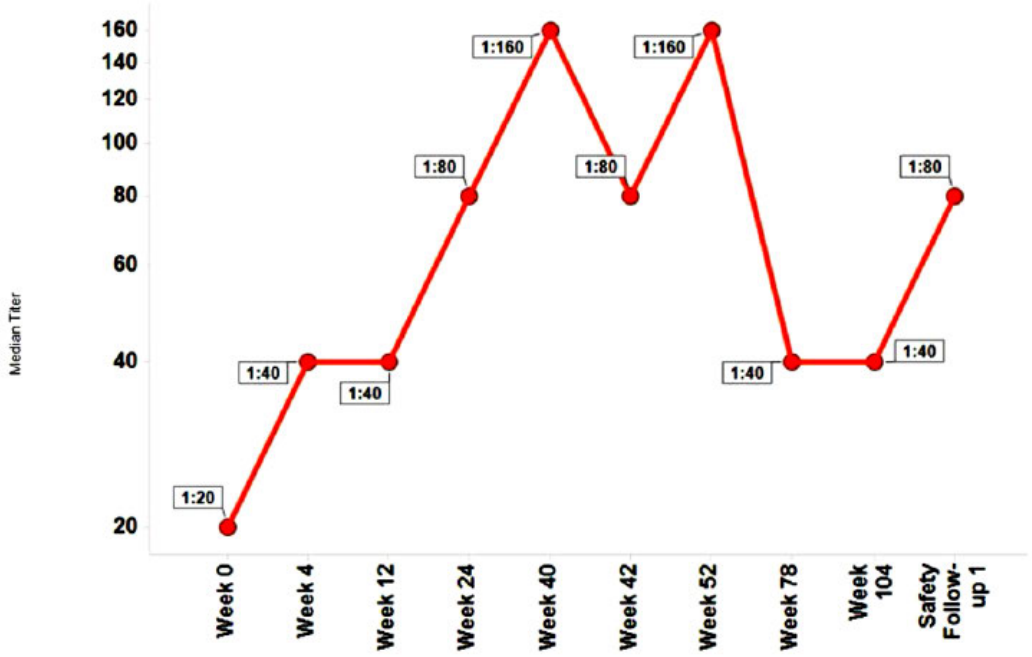
Review Comment: Considering the observed reductions in HbA1c, body weight, and blood pressure in the tirzepatide Phase 3 development program, the limited number of supraventricular tachyarrhythmias, as well as the results from the Applicant's CVMA Dr. Pucino felt that the heart rate changes do not warrant inclusion in Section 5. I concur with his assessment. The tirzepatide labeling, in Section 6, however, should inform of the possibility of increased heart rate and should reflect the potential for abnormal pharmacodynamic responses in the Japanese patient population for which the mechanisms behind these hemodynamic changes remain unknown.

8.4.5 Immunogenicity

In the Phase 3 pool (AS2), 2,570 (51.1%) of 5,025 tirzepatide-treated subjects developed antidrug antibodies (ADAs), with ADA positivity (ADA+) reported in 48.8%, 51.4%, and 53.2% of subjects randomized to the tirzepatide 5, 10, and 15 mg arms, respectively. ADA positivity appeared to increase by dose and duration of exposure. The maximum antibody titers ranged from 1:20 to 1:327,860 (median 1:160). Additionally, 1,705 (33.9% of 5025) and 716 (14.2% of 5025) ADA+ subjects showed cross-reactivity to native GIP and native GLP-1, respectively. Ninety-four (1.9% of 5025) subjects developed neutralizing antibodies (NAb) against tirzepatide on the GIP receptor, and 107 (2.1% of 5025) against tirzepatide on the GLP-1 receptor. Cross-reactive NAb against

native GIP (nGIP) and native GLP-1 (nGLP-1) were observed in 0.9% (43/5025) and 0.4% (18/5025) of tirzepatide-treated subjects, respectively. The plot of the median ADA titer versus the visit weeks during the treatment period indicates that the median titer (1:160) from the Phase 3 studies peaked at week 40, plateaued between median 1:90 at Week 42 and Week 52 (median of 1:160) and then generally declined to lower levels. Across the seven phase trials development of ADAs did not appear to impact the pharmacokinetics (clearance) or efficacy (reductions in HbA1c or body weight) of tirzepatide. Across the seven phase trials development of ADAs did not appear to impact the pharmacokinetics (clearance) or efficacy (reductions in HbA1c or body weight) of tirzepatide.

Figure 6. Median ADA Titer Profile of TE ADA+ Patients at Scheduled Visits During the Planned Treatment Period



Abbreviations: ADA = antidrug antibody; TE = treatment emergent.

Source: Immunogenicity Review Memo, page 34 of 61.

Table 20. Change from Baseline in HbA1c for Tirzepatide-Treated Patients with or without NAb+ Against Tirzepatide Activity to GIPR and/or GLP-1R

Statistic	GPGH			GPGI			GPGK			GPGL			GPGM			GPGO			GPGP		
	TE ADA-	TE ADA+		TE ADA-	TE ADA+		TE ADA-	TE ADA+		TE ADA-	TE ADA+		TE ADA-	TE ADA+		TE ADA-	TE ADA+		TE ADA-	TE ADA+	
		NAb + TZP GIPR	NAb + TZP GLP-1R		NAb + TZP GIPR	NAb + TZP GLP-1R		NAb + TZP GIPR	NAb + TZP GLP-1R		NAb + TZP GIPR	NAb + TZP GLP-1R		NAb + TZP GIPR	NAb + TZP GLP-1R		NAb + TZP GIPR	NAb + TZP GLP-1R		NAb + TZP GIPR	NAb + TZP GLP-1R
N	398	12	11	129	2	5	134	4	1	551	21	20	461	16	26	106	23	25	151	9	11
Mean	-2.1	-2.3	-2.4	-2.5	-2.2	-3.2	-2.0	-1.4	-1.9	-2.3	-2.5	-2.1	-2.4	-2.4	-2.2	-2.6	-2.7	-2.6	-2.8	-3.8	-2.9
SD	1.08	0.58	0.67	1.10	0.28	1.17	1.24	0.98	-	1.28	1.48	0.89	1.16	0.74	0.87	0.97	0.90	0.82	1.05	0.62	1.42
Min	-6.40	-3.30	-3.50	-5.70	-2.40	-4.50	-6.10	-2.70	-1.90	-6.10	-4.60	-3.60	-6.40	-4.00	-4.70	-4.50	-4.70	-4.70	-5.80	-5.00	-5.70
Median	-2.0	-2.3	-2.2	-2.4	-2.2	-3.6	-1.8	-1.3	-1.9	-2.2	-2.9	-2.2	-2.4	-2.3	-2.1	-2.6	-2.5	-2.4	-2.7	-3.5	-2.2
Max	1.4	-1.2	-1.5	0.6	-2.0	-1.4	0.9	-0.4	-1.9	4.3	1.9	-0.4	2.8	-1.1	-0.6	0.1	-1.5	-1.5	-0.1	-3.1	-1.0

Abbreviations: GIPR = glucose-dependent insulinotropic polypeptide receptor; GLP-1R = glucagon-like peptide-1 receptor; HbA1c = glycated hemoglobin; Max = maximum; Mean = arithmetic mean; Min = minimum; N = number of patients; NAb = neutralizing antibody; SD = standard deviation; TE ADA = treatment-emergent antidrug antibody; TZP = tirzepatide.

Source: Immunogenicity Review Memo, page 39 of 61.

In the table above, data are shown from the Applicant's evaluation of whether the HbA1c change from baseline induced by tirzepatide was impacted by NAb against tirzepatide activity on GIPR and GLP-1R status for each Phase 3 studies. Dr. Sheikh concluded that there was, "no significant difference in mean %HbA1c change for patients with NAb+ at GIP1R or at GLP-1R for any studies." He also noted that for study GPGK, the mean %HbA1c was changed from -2.0% for ADA-negative to -1.4% for ADA+ NAb+ patients at GIPR, suggesting that NAb may have influenced the efficacy of tirzepatide in 4 NAb+ patients, but the change did not appear to be significant.

Table 21. Summary of Hypersensitivity Reactions by TE ADA Status During the Planned Treatment Period (Phase 3 Dose Effect Analysis Set (AS2)

	n (%)			
TE ADA status	TZP 5 mg (N=1701)	TZP 10 mg (N=1702)	TZP 15 mg (N=1716)	TZP_ALL (N=5119)
TE ADA+	32 (1.88)	31 (1.82)	43 (2.51)	106 (2.07)
TE ADA-	26 (1.53)	26 (1.53)	21 (1.22)	73 (1.43)

Abbreviations: ADA = anti-drug antibodies; N = total number of patients in specified treatment group; n = number of patients in specified category; TE = treatment-emergent; TZP = tirzepatide.

Source: Table ISS.4.268

Source: Immunogenicity Review Memo, page 40 of 61.

Dr. Sheikh noted that a total of 179 of 5,119 tirzepatide-treated patients experienced hypersensitivity reactions during the planned treatment period: 106 (2.1%) of them were TE ADA positive and 73 (1.4%) were ADA negative, indicating a higher proportion of TE ADA+ patients reported to have hypersensitivity than ADA-negative patients, but these events were noted to be mild to moderate in severity. The majority of hypersensitivity reactions occurred at first onset within 16 weeks of receiving tirzepatide and resolved

independent of the TE ADA status or titer. No anaphylactic reason in tirzepatide treated subjects was observed in the Phase 3 trials.

Moreover, although the incidence of injection site reactions was numerically higher among TE ADA+ patients, Dr. Sheikh noted that "there was no pattern detected between the time of the event reporting and antidrug antibody status or titer level in the individual patient-level data."

Reviewer Comment: Dr. Faruk Sheikh, from OBP, reviewed the immunogenicity assessment data submitted to the Application. Although highly immunogenic, he felt that no safety or efficacy concerns were correlated with ADA development and recommended approval of tirzepatide. I concur with his assessment. Please refer to Dr. Sheikh's review and Dr. Pucino's review for detailed details.

8.5 Adverse Events of Special Interest (AESI)

The Applicant evaluated 17 AESI related to the GLP-1 receptor agonist class: immunogenicity, thyroid safety, exocrine pancreas safety, hypoglycemia, hypersensitivity reactions, injection site reactions, renal safety, gastrointestinal AEs, acute gallbladder disorders, dehydration-related AEs, diabetic retinopathy complications, cardiovascular safety, amputation or peripheral revascularization, hepatobiliary disorders, malignancy, major depressive disorders/suicidal ideation or behavior metabolic acidosis, severe, and persistent hyperglycemia. I will summarize a subset of the AESI below; please refer to Dr. Pucino's review for further details.

- Thyroid Safety and Calcitonin. All long-acting GLP-1 receptor agonists carry a boxed warning for risk of thyroid C-cell tumors, including medullary thyroid cancer (MTC), based on findings from nonclinical studies. The nonclinical signal was also observed in the 2-year carcinogenicity study of tirzepatide in male and female rats. The incidences of thyroid C-cell adenomas and carcinomas were increased in the tirzepatide 0.15, 0.5, and 1.5 mg/kg dose groups, with the 1.5 mg/kg dose in rats approximating the 15 mg dose in humans. However, there were no thyroid malignancies or thyroid C-cell hyperplasia observed in tirzepatide clinical studies. Additionally, there was no persistent elevation in calcitonin concentrations after tirzepatide exposure in human studies. Given the rare background rate of MTC, it is not surprising that the tirzepatide clinical development program did not observe an MTC signal. However, due to the findings in nonclinical studies, tirzepatide will carry the same boxed warning as the long acting GLP-1 RAs. Monitoring of calcitonin, or routine thyroid sonography has not been recommended because it may lead to more unnecessary thyroid biopsies/thyroidectomies with no meaningful impact on MTC risk management.
- Acute Pancreatitis. All products acting on the GLP-1 receptor list pancreatitis in the Warnings and Precautions section, as does the proposed tirzepatide labeling. An imbalance in acute pancreatitis was noted in the pool of Phase 2/3 trials (AS3) (13/5415 (0.24%) tirzepatide vs. 4/2354 (0.13%) in the pooled comparator arm) without evidence of a dose-related trend. There were 7 SAE of acute pancreatitis in 6 of 13 tirzepatide-treated subjects, and no SAEs of pancreatitis in the three subjects with acute pancreatitis in the comparator arms. All six tirzepatide-treated patients with acute pancreatitis recovered and there were no deaths. Proposed labeling will also describe the observed mean increases from baseline in amylase (33%-38%) and lipase (31-42%) in placebo controlled studies and note that their clinical significance is unknown, as serial measurements have limited value in predicting pancreatitis in asymptomatic subjects.
- Hypoglycemia. The risk of hypoglycemia with concomitant insulin secretagogue or insulin is listed in the Warnings and Precautions section of the proposed tirzepatide label. Although rates of Level 2 or Level 3

hypoglycemia were comparable between the tirzepatide and the placebo-treated subjects in the placebo-controlled monotherapy trial (SURPASS-1 / GPGK), they were higher in tirzepatide recipients when used in combination with insulin glargine (SURPASS-5 / GPGI) or sulfonylureas (SURPASS-4 / GPGM).

However, Dr. Tu noted that rates of hypoglycemia were comparable between tirzepatide-treated subjects and semaglutide-treated subjects (SURPASS-2 / GPGL) and significantly lower rate than patients treated with insulin degludec or glargine (SURPASS-3 and SURPASS-4).

Table 22. Hypoglycemic Adverse Events (AS1)

	Placebo %	MOUNJARO 5 mg %	MOUNJARO 10 mg %	MOUNJARO 15 mg %
Monotherapy				
(40 weeks)*	N=115	N=121	N=119	N=120
Blood glucose <54 mg/dL	1	0	0	0
Severe hypoglycemia**	0	0	0	0
Add-on to Basal Insulin with or without Metformin				
(40 weeks)*	N=120	N=116	N=119	N=120
Blood glucose <54 mg/dL	13	16	19	14
Severe hypoglycemia**	0	0	2	1

* *Reflects the study treatment period. Data include events occurring during 4 weeks of treatment-free safety follow up. Events after introduction of a new glucose-lowering treatment are excluded.*

** *Episodes requiring the assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions.*

Source: Proposed Label

- Hypersensitivity Reactions and Injection Site Reactions. All products acting on the GLP-1 receptor list hypersensitivity in the Warnings and Precautions and Contraindications section, as does the proposed tirzepatide labeling. Across all Phase 2/3 trials, the rate of hypersensitivity reactions was 3.5% after tirzepatide compared to 2.6% all comparators pooled. The most common reactions were rash and urticaria; no anaphylactic reactions were reported. There were also higher rates of injection site reactions after tirzepatide compared to placebo (3.2% vs. 0.4% respectively) but no association with ADA positivity.
- Renal Safety. There have been postmarketing reports of acute kidney injury and worsening of chronic renal failure, sometimes requiring hemodialysis, associated with nausea, vomiting, diarrhea, or dehydration with the use of GLP-1 receptor agonist products. Thus, labeling for most GLP-1 receptor agonists include a Warnings and Precautions of renal impairment or acute kidney injury and prescribers are cautioned to monitor renal function in patients with severe adverse GI reactions with and without renal impairment. The proposed tirzepatide labeling does so as well. In the placebo-controlled pool (AS1), mean reductions in eGFR from baseline at Week 40 were higher in the tirzepatide arms compared to the placebo arm (change from placebo: -0.3 to -1.7 mL/min/1.73 m^2), but these differences were not clinically meaningful. A dose-response relationship in eGFR was not observed. Overall rates of renal adverse events were comparable across all Phase 2/3 studies. Serious renal AEs were reported in 7 tirzepatide-treated subjects (0.16%) and 9 subjects (0.26%) in the comparator arms.
- Gastrointestinal Adverse Events. Gastrointestinal AEs are common and labeled events in products with GLP-1 receptor agonist activity. Among all tirzepatide-treated patients, 43.6% experienced GI AEs, 2.1% experienced serious GI AEs, 4.2% discontinued treatment due to a GI-related AE. Proposed product

labeling will include a Warnings and Precaution for the use of tirzepatide in patients with severe GI disease, and to describe the association with serious GI-related adverse events.

- Dehydration-Related Events. Across the pool of Phase 2/3 trials, the rates of dehydration-related events were comparable 6/2354 [adj 0.21%] in the pooled comparator arms and 18/5415 [adj 0.35%] in tirzepatide-treated subjects.
- Hepatobiliary Events. No imbalance was noted in hepatobiliary disorders in the pool of Phase 2/3 trials: 156/5415 tirzepatide-treated subjects [adj 3%] and 63/2354 subjects [adj 2.21%] in the pooled comparator arms.
- Acute Gallbladder. Tirzepatide treated patients experienced greater rates of gallbladder adverse events in both the placebo-controlled pool (4/718 (0.6%) versus 0/235 (0%)) and in the pool of all Phase 2/3 trials (55/5415 [adj 1.1%] vs. 18/2354 [adj 0.6%]). Acute gallbladder disease is listed in the Warnings and Precautions section of the proposed label in conjunction with the class-wide labeling for this event for products with GLP-1 receptor agonist activity.
- Diabetic Retinopathy. Proposed labeling for tirzepatide describe the risk of progression of diabetic retinopathy in the Warnings and Precaution section, stemming largely from results from cardiovascular outcomes trials (CVOT) among products in GLP-1 receptor agonist class. Across all Phase 2/3 trials for tirzepatide, there was no imbalance in rates of diabetic retinopathy complications, although a small imbalance was noted when only Phase 3 trials were examined (18 tirzepatide subjects (0.35%) versus 5 subjects in the comparator arms (0.22%)). A dedicated diabetic retinopathy sub-study is being conducted as part of the tirzepatide CVOT (GPGN) to better characterize the risk of new onset or worsening diabetic retinopathy.
- Amputations. There was no imbalance in amputations in the pool of Phase 2/3 trials: tirzepatide 9/5215 (0.17% [adj 0.2%]) vs. 8/2354 (0.34% [adj 0.26%]) pooled comparator arms.
- Malignancy. There was no imbalance in malignancies in the pool of Phase 2/3 trials: 55/5415 tirzepatide-treated subjects [adj 1.1%] versus 30/2354 subjects [adj 1%] in the comparator arms.

8.6 Cardiovascular Meta-Analysis (CVMA)

Dr. Shanti Gomatam reviewed the prespecified CVMA that the Applicant conducted in accordance with the 2008 FDA Guidance for Industry (since replaced by the 2020 FDA draft Guidance for Industry). The CVMA consisted of 7 trials that randomized a total of 7,215 patients to tirzepatide (1 mg, 5mg, 10mg, 15 mg), placebo or active comparator. The primary objective was to demonstrate that tirzepatide is not associated with an unacceptably high risk for the 4-component major adverse cardiovascular event (MACE-4) defined as a composite of cardiovascular death, myocardial infarction, stroke, and hospitalization for unstable angina. The estimated hazard ratio for the pooled tirzepatide arms versus pooled comparator arms was 0.81, 97.85% CI (0.52, 1.26) based on a total of 116 MACE-4 events at the interim analysis. The upper bound of this confidence interval is less than 1.8 and meets the non-inferiority risk margin pre-specified in the Statistical Analysis Plan. The end-of-meta-analysis (EOMA) results were consistent with the interim analysis: HR = 0.80, 95% CI (0.57, 1.11) based on a total of 142 MACE events.

Table 23. Analysis of Pre-Specified Primary MACE-4 Endpoint in CV Meta-Analysis by Tirzepatide Dose (mITT; EOMA)*

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

* **mITT**: All randomized subjects who took at least one dose of study drug; **EOMA**: End-of-meta-analysis
‡ Hazard ratios for pooled tirzepatide doses computed using a Cox proportional hazards model with fixed effects for treatment and stratified by CV risk (GPGM versus others)

Source: Created by FDA statistical reviewer.

Table 24. Analyses of the MACE-4 Component Endpoints (mITT, EOMA)*

	Tirzepatide N=4887 PY=5099.66§ NumEvents (IR/100PY)	Pooled Comparator N=2328 PY=2756.39§ NumEvents (IR/100PY)	Hazard Ratio‡ (95% CI)
MACE-4 (mITT, EOS)	72 (1.42)	70 (2.58)	0.80 (0.57, 1.11)
Components†:			
CV death	25 (0.49)	22 (0.80)	0.90 (0.45, 1.79)
Non-fatal MI	30 (0.59)	30 (1.10)	0.76 (0.41, 1.40)
Non-fatal ischemic stroke	15 (0.29)	15 (0.55)	0.81 (0.34, 1.90)
Hospitalization for Unstable Angina	5 (0.10)	9 (0.33)	0.46 (0.13, 1.71)

* **mITT**: All randomized subjects who took at least one dose of study drug; **IOMA**: Interim look of the meta-analysis
§: These patient years are for the primary MACE-4 events; patient years for components differed from these.
†Analyses capture all components of MACE-4. Some subjects experienced multiple events, hence totals of component events exceeds number of secondary MACE-4 events which only considers first event for each subject.
‡ All Cox proportional hazards analyses used here to compute hazard ratio are stratified by CV risk.

Source: Created by FDA statistical reviewer.

In a pre-specified analysis for all-cause mortality that was not part of the multiple testing plan, the hazard ratio was 0.80, 95% CI (0.51, 1.25), which includes the null value and does not suggest an excess risk of mortality after tirzepatide.

Table 25. Pre-Specified Analysis of All-Cause Mortality Endpoint (mITT, EOMA)*

	Tirzepatide					Pooled Comparator
	15 mg N=1621	10 mg N=1606	5 mg N= 1608	1 mg N=52	All N= 4887	N=2328
ACM patient years of follow-up	1708.29	1685.82	1676.61	28.67	5099.16	2756.29
ACM events (IR per 100 PY)	13 (0.76)	8 (0.47)	20 (1.19)	0 (0.00)	41 (0.80)	39 (1.41)
HR (95% CI)	0.75 (0.40, 1.41)	0.47 (0.22, 1.01)	1.20 (0.69, 2.08)	0 (0, Inf)	0.80 (0.51, 1.25)	-

* **mITT**: All randomized subjects who took at least one dose of study drug; **EOMA**: end-of-meta-analysis.
‡ Hazard ratios for pooled tirzepatide doses computed using a Cox proportional hazards model with fixed effects for treatment and stratified by study-level CV risk (GPGM versus others)

Source: Created by FDA statistical reviewer.

The table below shows the number of MACE-4 events observed by trial and treatment arm. The majority of events (109/142) observed were from Trial GPGM that enrolled high-risk CV patients and was an open-label trial with active comparator insulin glargine. Notably, the rates of MACE-4 events were lower in the tirzepatide-treated arm compared to subjects in the insulin glargine arm, providing additional reassuring evidence in the most clinically complex group of patients that tirzepatide does not increase the risk of MACE. Interestingly, in trial GPGL, the incidence rate of MACE-4 was higher after tirzepatide treated subjects, compared to subjects treated with semaglutide 1 mg [13/1409 (1.1%) vs. 1/469 (0.25%)].

Table 26. Patients with MACE-4 Events by Trial (mITT, EOMA)*

Trial	Tirzepatide	Pooled Comparator	Total
	Num. Events/Num. Pts. (IR per 100 PY)		
GPGM[a]	47/995 (3.01)	62/1000 (4.05)	**109/1995 (3.52)**
GPGO[b]	2/477 (0.40)	1/159 (0.60)	**3/636 (0.45)**
GPGB[c]	1/211 (0.85)	1/105 (1.71)	**2/316 (1.13)**
GPGH[d]	7/1077 (0.62)	3/360 (0.80)	**10/1437 (0.67)**
GPGI	2/355 (0.69)	1/120 (1.00)	**3/475 (0.77)**
GPGK	0/363 (0.00)	1/115 (1.08)	**1/478 (0.26)**
GPGL[e]	13/1409 (1.10)	1/469 (0.25)	**14/1878 (0.89)**
Total	**72/4887 (1.42)**	**70/2328 (2.57)**	**142/7215 (1.82)**

* **mITT**: All randomized subjects who took at least one dose of study drug; **EOMA**: End-of-meta-analysis
a: Insulin glargine was the active comparator for Trial GPGM.
b: Dulaglutide 0.75 mg was the active comparator for Trial GPGO
c: Dulaglutide 1.5 mg was the active comparator for this trial.
d: Insulin degludec was the active comparator for Trial GPGH.
e: Semaglutide 1 mg was the active comparator for this trial.

Source: Created by FDA statistical reviewer.

In her review, Dr. Gomatam expressed caution when interpreting the results of the CVMA given the following issues:

- 3 of the 7 randomized trials in the meta-analysis were open-label trials (GPGH, GPGL, GPGM) and knowledge of the treatment assignment could cause bias due to differences in patient management and other factors,
- Different comparators, both active and placebo were used in the different studies. Study GPGM which contributed most of the MACE-4 events had insulin glargine as the active comparator and showed a numerically beneficial effect for MACE-4 in the tirzepatide arm, while Study GPGL which had semaglutide as the active comparator, showed a numerically beneficial effect in the semaglutide arm.

Review Comment: Based on the results and confirmatory analyses conducted by Dr. Gomatam, I concur that these data do not suggest an increased risk of major adverse CV events with the use of tirzepatide. Analyses of the all-cause mortality endpoint did not raise any concerns. The Applicant is also conducting trial GPGN (SURPASS-CVOT) to compare tirzepatide to dulaglutide (1.5 mg SC QW) and is expected to enroll more than 12,500 patients with high CV risk. The primary objective of the trial is to demonstrate that tirzepatide is noninferior to dulaglutide (which is indicated to reduce MACE risk in patients with T2D and elevated CV risk) on the composite 3-component MACE endpoint consisting of: CV death, MI, and stroke. This trial is ongoing with an anticipated completion date by 2025.

9. Advisory Committee Meeting

Tirzepatide was not referred to an FDA advisory committee because outside expertise was not necessary as there were no controversial issues that would benefit from advisory committee discussion.

10. Pediatrics

The clinical trials included in this Application did not enroll pediatric subjects. After discussion at the Pediatric Review Committee, FDA waived the pediatric study requirement for ages 0 through 9 years (inclusive) because the necessary studies are impossible or highly impracticable to conduct as there are too few children in this age range with T2D to study. FDA deferred the submission of pediatric study results for ages 10 to 17 years (inclusive) because the product is ready for approval for use in adults and the pediatric study has not been completed; see Postmarketing Recommendations section below for more details.

11. Other Relevant Regulatory Issues

Not applicable.

12. Labeling

I agree with the review team that the submitted data support the proposed indication for tirzepatide “as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus”. I also agree with the proposed dosage and administration recommended in proposed labeling that start with an initial dose of 2.5 mg injected subcutaneously once weekly and increases in 2.5 mg increments after at least 4 weeks on the current dose, if additional glycemic control is needed, to a maximum of 15 mg once weekly.

I agree with the review team's recommendation to include a boxed warning, consistent with other long acting GLP-1 RAs, to describe the potential risk of thyroid c-cell tumors. Additionally, due to a boxed warning of nonclinical findings of thyroid C-cell tumors in rodents and an unknown risk of thyroid tumors in humans, the Division previously recommended that labeling of long-acting GLP-1 RA products which have not demonstrated cardiovascular benefit include the following limitation of use, "Not recommended as first-line therapy for patients inadequately controlled on diet and exercise." However, based on reassuring results for the Applicant's CVMA, statistically superior and clinically meaningful reductions in HbA1c and body weight across the five global phase 3 trials, which included semaglutide and basal insulins as active comparators and at-risk patient populations (e.g., subjects with established CVD, or inadequate glycemic control on up to three antihyperglycemic products or basal insulin), and lack of postmarket evidence for a thyroid cancer risk in humans, this limitation of use was considered not necessary for tirzepatide labeling.

I agree with the review team's recommendations for including the following risks in the Warnings and Precautions section: pancreatitis, hypoglycemia with concomitant use of insulin secretagogues or insulin, hypersensitivity reactions, acute kidney injury, severe gastrointestinal disease, and diabetic retinopathy complications in patients with a history of diabetic retinopathy.

During labeling discussions with the Applicant, FDA argued in favor of several important modifications to the Applicant's proposed labeling. I agree with all these modifications:

- I agree the review team's concerns related to the potential reduction in efficacy when tirzepatide is used concomitantly with oral hormonal contraceptives due to the drug effect of delayed gastric emptying. I support the labeling recommendations to advise females using oral contraceptives to switch to a non-oral contraceptive method or to add a barrier method of contraception for 4 weeks after initiation and for 4 weeks after each dose escalation.
- I agree with the review team's concerns about increases in heart rates that were observed to be higher among patients from Japan than the overall population in clinical studies and supported the inclusion of this information in labeling despite the uncertainty regarding its clinical relevance.
- I agree with the recommendations to include a Warning and Precaution for acute gallbladder disease, consistent with new and recent class-wide labeling for all products with GLP-1 receptor activity.
- I agree with the addition of a new immunogenicity section (in accordance with new FDA Guidance to Industry issued February 2022) to describe the incidence of anti-drug antibodies observed in 51% of tirzepatide-treated subjects. In these trials, 34% and 14% of patients showed cross-reactivity to native GIP or native GLP-1 respectively, and 0.9% and 0.4% developed neutralizing antibodies against native GIP or GLP-1, respectively. There was no identified clinically significant effect of anti-tirzepatide antibodies on pharmacokinetics or effectiveness.

13. Postmarketing Recommendations

The Applicant will be required to conduct three PMRs. No REMS is recommended.

Table 27. Postmarketing Requirements for Tirzepatide

Postmarket Required Study	Regulatory Authority	Timelines

Conduct a 30-week, randomized, double-blind, placebo-controlled, multicenter, parallel- arm study of the safety and efficacy of Mounjaro (tirzepatide) for the treatment of type 2 diabetes mellitus in pediatric patients ages 10 to 17 years (inclusive), followed by a 22- week open-label extension. (b) (4)	Section 505B(a) of the FDCA	Study Completion: 12/2027 Final Report Submission: 09/2028
Conduct a milk-only lactation study in lactating women who have received a dose of tirzepatide to assess concentrations of tirzepatide in breast milk using a validated assay.	Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA)	Draft Protocol Submission: January 2023 Final Protocol Submission: July 2023 Study Completion: July 2024 Final Report Submission: July 2025
Conduct a medullary thyroid carcinoma registry-based case series study of at least 15 years duration to systematically monitor the annual incidence of medullary thyroid carcinoma in the United States and to identify any increase related to the introduction of tirzepatide into the marketplace. This study will also establish a registry of incident cases of medullary thyroid carcinoma and characterize their medical histories related to diabetes and use of tirzepatide.	Section 505(o)(3) of the FDCA	Draft Protocol Submission: November 2022 Final Protocol Submission: May 2023 Study Completion: June 2039 Final Report Submission: June 2040

14. Recommended Comments to the Applicant

All comments have already been conveyed to the 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/

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