CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

217806Orig1s000

OTHER REVIEW(S)

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research | Office of Surveillance and Epidemiology (OSE)
Epidemiology: ARIA Sufficiency

Date:	November 8, 2023
Reviewer(s):	Po-Yin Chang, PhD Division of Epidemiology I
Team Leader:	Yandong Qiang, MD, PhD, MHS, MPH Division of Epidemiology I
Division Director:	Wei Hua, MD, PhD, MS, MHS Division of Epidemiology I
Subject:	Active Risk Identification and Analysis (ARIA) Sufficiency Assessment for Medullary Thyroid Carcinoma (MTC) Following Tirzepatide Use for Chronic Weight Management
Drug Name(s):	Zepbound (Tirzepatide) injection for subcutaneous use
Application Type/Number:	NDA 217806
Submission Number:	9
Applicant:	Eli Lilly and Company
TTT:	2022-2846

EXECUTIVE SUMMARY *(place "X" in appropriate boxes)*

Memo type	
-Initial	
-Interim	
-Final	X
Source of safety concern	
-Peri-approval	X
-Post-approval	
Is ARIA sufficient to help characterize the safety concern?	
-Yes	
-No	X
If "No", please identify the area(s) of concern.	
-Surveillance or Study Population	
-Exposure	
-Outcome(s) of Interest	X
-Covariate(s) of Interest	X
-Surveillance Design/Analytic Tools	

1. BACKGROUND INFORMATION

1.1. Medical Product

Zepbound (Tirzepatide, New Drug Application [NDA] 217806, Eli Lilly and Company) is a glucose-dependent insulinotropic polypeptide (GIP) and glucagonlike peptide-1 (GLP-1) receptor agonist. Food and Drug Administration (FDA) granted Zepbound fast track designation on October 2, 2022 and rolling review on November 4 2022.[1,2] The Applicant initiated the rolling submission on November 17, 2022 with NDA 217806 sequence 1 (S-0001) and completed this NDA submission on May 8, 2023. The Applicant is seeking FDA's approval of Zepbound as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management (CWM) in adults with an initial body mass index (BMI) of

- 30 kg/m^2 or greater (obesity) or
- 27 kg/m^2 or greater (overweight) in the presence of at least one weight-related comorbid condition (e.g., hypertension, dyslipidemia, (b) (4), type 2 diabetes mellitus, obstructive sleep apnea or cardiovascular disease).

Zepbound is a once-weekly subcutaneous injection. The recommended starting dosage is 2.5 mg, with a 2.5 mg dosage increment after at least four weeks on the current dose. The recommended maintenance dosages are 5 mg, 10 mg, or 15 mg.

On May 13, 2022, FDA approved Mounjaro (NDA 215866, tirzepatide) as an adjunct to diet and exercise to improve glycemic control in adults with Type 2 Diabetes Mellitus (T2DM).[3] The formulation, route of administration, and dosage regimen of tirzepatide for T2DM and CWM treatment are identical.[4]

1.2. Describe the Safety Concern

Medullary thyroid carcinoma (MTC) is a rare neuroendocrine malignancy of the thyroid C cells, characterized by calcitonin production.[5] MTC may be sporadic (75% of cases) or hereditary, as part of the multiple endocrine neoplasia type 2 (MEN2) syndrome.[6] Compared to other types of thyroid cancer, MTC does not respond to manipulation of thyroid stimulating hormone and is more likely to present with an advanced and aggressive disease.[6] Of all thyroid cancers, MTC accounts for roughly 2% of the female patients and <4% of the male patients.[5,7] The incidence rate of MTC increases with older age.[5,7] The U.S. Surveillance, Epidemiology, and End Results (SEER) registry data in 2010 to 2013 showed that the age-adjusted incidence rate of MTC was 0.18 per 100,000 person-years.[8] It may take longer than 10 years for MTC to be visible on imaging evaluation given the slow progress of MTC.[5]

Safety Signal of MTC related to Tirzepatide or GLP-1 Receptor Agonists in Animals
In both male and female rats, tirzepatide causes dose-related and treatment-duration-dependent thyroid C-cell adenomas and carcinomas in a 2-year study at clinically relevant exposures based on area under the curve (AUC) .[9] A hypothesized carcinogenic mechanism of GLP-1 receptor agonists in rodents includes GLP-1 receptor activation-related calcitonin release, upregulation of calcitonin gene expression, and subsequently thyroid C-cell activation and hyperplasia.[10]

Safety Signal of MTC related to Tirzepatide or GLP-1 Receptor Agonists in Human

Human relevance of tirzepatide-induced C-cell tumors in rodents has not been established.[9] While C-cells are abundant in the rodent thyroid, C-cells are sparsely distributed in normal human thyroids and often difficult to identify on routine sections.[11] Studies have reported inconsistent findings of GLP-1 receptor expression in human thyroid glands and inconclusive effect of GLP-1 receptor agonists on C-cell proliferation.[11,12] In one study, GLP-1 receptor expression was low on C-cells in human thyroids and GLP-1 receptor agonist liraglutide did not seem to cause calcitonin release.[12] In contrast, another study has shown frequent GLP-1 receptor expression in thyroid tissues of 12 MTC cases and nine C-cell hyperplasia cases, and "not infrequently present" on normal C-cells of 15 control subjects.[11]

Cases of MTC have been reported in patients treated with liraglutide in the postmarketing setting.[13] A nested case-control study in patients with T2DM using the French healthcare insurance database between January 1, 2006, and December 31, 2018, reported that,[14] compared to the age-, sex-, and duration of diabetes-matched controls (n=6,993), MTC cases (n=398) appeared 1.76 times likely (95% Confidence Interval [CI], 1.16-2.69) to be a current user of GLP-1 receptor agonists and 1.45 times likely (95% CI, 0.84-2.50) to have used GLP1 receptor agonists in the past; MTC cases were 1.78 times likely (95% CI, 1.04-3.05) to have used GLP-1 receptor agonists[a] for one to three years. However, these data are insufficient to establish a causal relationship between GLP-1 receptor agonists and MTC in humans because of uncertainties in case assessment, lack of controlling for major confounders (e.g., family history, radiation exposure), and serious biases from misclassification, detection, and selective reporting.[13,15] Additionally, in the tirzepatide clinical development program, no treatment-emergent adverse events of thyroid malignancies, including MTC or thyroid C-cell hyperplasia, were reported. Calcitonin levels did not change in tirzepatide-treated groups.

Postmarketing Requirement of MTC Registry

For all FDA approved long-acting GLP-1 receptor agonists,[9,13,16-23] FDA has issued postmarketing requirements (PMRs) of MTC case series registry study to systematically monitor the annual incidence of MTC in the United States, to identify any increase of MTC related to the introduction of long-acting GLP1 receptor agonist, and to characterize the medical histories of MTC cases following long-acting GLP1 receptor agonist use. Table 1 lists the FDA approved long-acting GLP-1 receptor agonists as of October 19, 2023.[9,13,16-23]

To address these PMRs, Applicants have established the MTC case series registry (termed "MTC registry" hereafter) in collaboration with the American Thyroid Association in 2012, using the North American Association of Central Cancer Registries (NAACCR). The MTC registry also collects data from participating State Cancer Registries (SCRs) to characterize medical histories and possible risk factors for MTC.

Previously, FDA also required a class-wide Risk Evaluation and Mitigation Strategy (REMS) for approved long-acting GLP-1 receptor agonists to ensure the benefits outweigh the potential risk of MTC and the risk of acute pancreatitis. FDA determined a REMS is no longer required for long-acting GLP-1 receptor agonists after reviewing available REMS assessment findings.[24]

[a] Bezin et al 2023 study included all both short acting and long acting GLP1 receptor agonists[14]

Table 1. List of FDA-approved single long-acting GLP-1 receptor agonists with a PMR for MTC risk, as of October 19, 2023*

Brand name[i]	Active ingredient	Applicant	Application number	FDA Approval Date	FDA Approved Indication[ii]			Marketing Status
					Glycemic Control	Reduce the risk of MACE	CWM	
Victoza	Liraglutide	Novo Nordisk	NDA-022341	January 25, 2010	Yes	Yes	No	Prescription
Bydureon	Exenatide	AstraZeneca	NDA-022200	January 27, 2012	Yes	No	No	Discontinued
Tanzeum[iii]	Albiglutide	GlaxoSmithKline	BLA-125431	April 15, 2014	Yes	No	No	Discontinued
Trulicity	Dulaglutide	Eli Lilly	BLA-125469	September 18, 2014	Yes	Yes	No	Prescription
Saxenda	Liraglutide	Novo Nordisk	NDA-206321	December 23, 2014	No	No	Yes	Prescription
Bydureon BCise	Exenatide	AstraZeneca	NDA 209210	October 20, 2017	Yes	No	No	Prescription
Ozempic	Semaglutide	Novo Nordisk	NDA-209637	December 5, 2017	Yes	Yes	No	Prescription
Rybelsus	Semaglutide	Novo Nordisk	NDA-213051[iv]	September 20, 2019	Yes	No	No	Prescription
Wegovy	Semaglutide	Novo Nordisk	NDA-215256	June 4, 2021	No	No	Yes	Prescription
Mounjaro	Tirzepatide	Eli Lilly	NDA-215866	May 13, 2022	Yes	No	No	Prescription

* Modified from Table 1 "List of FDA-approved single long acting GLP-1 receptor agonists with a PMR for MTC risk, as of January 4, 2022," in the April 29, 2022 ARIA Sufficiency Memo for NDA 215866 MOUNJARO (tirzepatide) by Dr. Youjin Wang. [25]

i All FDA approved long acting GLP-1 receptor agonist contained products have a class wide Boxed Warning of thyroid C-cell tumor including MTC. Xultophy (BLA 208583) is a combination product of insulin degludec and liraglutide. FDA did not issue a MTC PMR for Xultophy because there have been MTC PMRs for single liraglutide products and most Xultophy users would use less than 1.8 mg of liraglutide (See Dr. Wang ARIA Sufficiency Memo for NDA 215866 MOUNJARO[25])

ii Detailed indications may be found in product labeling.[9,13,16-23]

iii GlaxoSmithKline (GSK), the Applicant of Tanzeum, voluntarily revoked the license of Tanzeum on October 20, 2021, based on a business decision. FDA released the product from all PMRs. However, GSK agrees to continuously update FDA annually regarding Tanzeum exposed MTC case until 2029, 15 years after the drug' approval in 2014 (See Dr. Wang ARIA Sufficiency Memo for NDA 215866 MOUNJARO[25]).

iv The Applicant submitted NDA 213182 for the addition of efficacy and safety information to the Rybelsus Prescribing Information based on the data from the PIONEER 6 cardiovascular outcomes trial. FDA administratively closed NDA 213182 on January 16, 2020 and required the Applicant to make submissions to the original NDA 213051.

MACE, major adverse cardiovascular events. *CWM* chronic weight management

1.3. Labeling

All FDA approved long-acting GLP-1 receptor agonists have a Boxed Warning of the risk of thyroid C-cell tumors.[9,13,16-23] The drafted Boxed Warning for Zepbound is listed below (as of Nov 7, 2023). Relevant information of MTC in the Zepbound labeling is included in Appendix I.

WARNING: RISK OF THYROID C-CELL TUMORS

See full prescribing information for complete boxed warning.

- **In rats, tirzepatide causes thyroid C-cell tumors. It is unknown whether ZEPBOUND causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans as the human relevance of tirzepatide-induced rodent thyroid C-cell tumors has not been determined (5.1, 13.1).**
- **ZEPBOUND is contraindicated in patients with a personal or family history of MTC or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Counsel patients regarding the potential risk of MTC and symptoms of thyroid tumors (4, 5.1).**

1.4. FDAAA Purpose (per Section 505(o)(3)(B))

Purpose (place an "X" in the appropriate boxes; more than one may be chosen)	
Assess a known serious risk	
Assess signals of serious risk	X
Identify unexpected serious risk when available data indicate potential for serious risk	

1.5. Statement of Purpose

The purpose of the MTC registry is to monitor, assess, and characterize MTC, an extremely rare disease, following tirzepatide use for CWM. This MTC registry will collect descriptive data for at least 15 years.

1.6. Effect Size of Interest or Estimated Sample Size Desired

Not applicable. Because this study is for descriptive purposes only, effect size or sample size calculation is not required.

2. SURVEILLANCE OR DESIRED STUDY POPULATION

2.1 Population

The desired population would consist of patients who are obese or who are overweight with weight-related comorbid condition.

2.2 Is ARIA sufficient to assess the intended population?

ARIA is sufficient to assess the intended population using codes-based algorithms for obese/overweight population, excluding subjects with type 2 diabetes, and indexing study population on exposure of interest.

3 EXPOSURES

3.1 Treatment Exposure(s)

If approved, exposure to Zepbound will likely be adequately captured via NDC codes.

3.2 Comparator Exposure(s)

Not applicable.

3.3 Is ARIA sufficient to identify the exposure of interest?

ARIA is sufficient to identify exposure of interest.

4 OUTCOME(S)

4.1 Outcomes of Interest

The outcome of interests is MTC.

4.2 Is ARIA sufficient to assess the outcome of interest?

No, ARIA is insufficient to assess MTC because

- MTC is a rare disease with a long latency
    - Only about 1,000 people are diagnosed with MTC each year in the United States. Additionally, it may take longer than 10 years for MTC to be visible on imaging evaluation given the slow progress of MTC.[5] The Sentinel system typically has only 2-3 years of follow-up. In the Sentinel database, 19.9% of the patients (92.2 million patients) have cumulative enrollment for over 5 years by Feb 2023.[26]
- There is a lack of specific codes or validated algorithms to identify MTC
    - Available ICD-10 code for thyroid cancer (C73 "Malignant neoplasm of thyroid gland") and procedure codes for surgical thyroid removal (Appendix Table 1) are not specific to MTC.

- The Sentinel system currently does not provide results of diagnostic tests for MTC, such as fine-needle aspiration biopsy, calcitonin blood test, carcinoembryonic antigen blood test, and genetic testing for germline RET mutations. Claims-based information is insufficient to accurately capture and describe the onset time of MTC.

5 COVARIATES

5.1 Covariates of Interest

Covariates of interest may include demographics (such as age and gender), family history of MTC, radiation exposure prior to and during the follow-up.

5.2 Is ARIA sufficient to assess the covariates of interest?

ARIA is insufficient to assess major covariates of interest (e.g., family history of MTC, radiation exposure at baseline and during the follow-up).

6 SURVEILLANCE DESIGN / ANALYTIC TOOLS

6.1 Surveillance or Study Design

The study of interest is a prospective observational study.

6.2 Is ARIA sufficient with respect to the design/analytic tools available to assess the question of interest?

ARIA is sufficient with respect to the design or analytic tools available to assess the question of interest.

7 NEXT STEPS

We have determined that ARIA is insufficient to evaluate the safety concern of MTC related to Zepbound due to the inabilities to identify and ascertain the outcome of interest and covariates of interest.

The PMR language:

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

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Appendix I. Relevant information of MTC in U.S. Product Information for ZEPBOUND

4 CONTRAINDICATIONS

ZEPBOUND is contraindicated in patients with:

- A personal or family history of MTC or in patients with MEN 2 [see Warnings and Precautions (5.1)].

5 WARNINGS AND PRECAUTIONS

5.1 Risk of Thyroid C Cell Tumors

In rats, tirzepatide caused a dose-dependent and treatment-duration-dependent increase in the incidence of thyroid C cell tumors (adenomas and carcinomas) in a 2-year study at clinically relevant plasma exposures [see Nonclinical Toxicology (13.1)]. It is unknown whether ZEPBOUND causes thyroid C cell tumors, including MTC, in humans as human relevance of tirzepatide-induced rodent thyroid C cell tumors has not been determined.

ZEPBOUND is contraindicated in patients with a personal or family history of MTC or in patients with MEN 2. Counsel patients regarding the potential risk for MTC with the use of ZEPBOUND and inform them of symptoms of thyroid tumors (e.g., a mass in the neck, dysphagia, dyspnea, persistent hoarseness).

Routine monitoring of serum calcitonin or using thyroid ultrasound is of uncertain value for early detection of MTC in patients treated with ZEPBOUND. Such monitoring may increase the risk of unnecessary procedures, due to the low test specificity for serum calcitonin and a high background incidence of thyroid disease. Significantly elevated serum calcitonin values may indicate MTC and patients with MTC usually have calcitonin values >50 ng/L. If serum calcitonin is measured and found to be elevated, the patient should be further evaluated. Patients with thyroid nodules noted on physical examination or neck imaging should also be further evaluated.

Appendix Table 1. Current Procedural Terminology (CPT) Codes for thyroid surgical procedures

CPT Code	CPT Code Description
60210	Partial thyroid lobectomy: unilateral; with or without isthmusectomy
60212	Partial thyroid lobectomy with contralateral subtotal lobectomy, including isthmusectomy
60220	Total thyroid lobectomy, unilateral with or without isthmusectomy
60240	Total thyroidectomy
60260	Completion thyroidectomy
60271	Thyroidectomy – cervical approach
60225	Thyroid lobectomy with contralateral subtotal lobectomy, including isthmusectomy
60252	Thyroidectomy with limited neck dissection
60254	Thyroidectomy with radical neck dissection
60270	Thyroidectomy – sternal split or transthoracic approach

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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/

PO YIN CHANG
11/07/2023 12:30:15 PM

YANDONG QIANG
11/07/2023 12:35:10 PM

WEI HUA
11/07/2023 01:18:19 PM

DAVID G MOENY on behalf of JUDITH W ZANDER
11/07/2023 05:05:21 PM

SARAH K DUTCHER
11/07/2023 09:53:07 PM

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research | Office of Surveillance and Epidemiology (OSE)
Epidemiology: ARIA Sufficiency

Date:	November 8, 2023
Reviewer(s):	Po-Yin Chang, PhD Division of Epidemiology I
Team Leader:	Yandong Qiang, MD, PhD, MHS, MPH Division of Epidemiology I
Division Deputy Director:	Wei Hua, MD, PhD, MS, MHS Division of Epidemiology I
Subject:	Active Risk Identification and Analysis (ARIA) Sufficiency Assessment for Pregnancy Exposure of Tirzepatide Treatment for Chronic Weight Management
Drug Name(s):	Zepbound (tirzepatide) injection for subcutaneous use
Application Type/Number:	NDA 217806
Submission Number:	9
Applicant/sponsor:	Eli Lilly and Company
OSE RCM #:	2022-2846

1. BACKGROUND INFORMATION

1.1. Medical Product

Zepbound (tirzepatide, New Drug Application [NDA] 217806, Eli Lilly and Company) is a glucose-dependent insulinotropic polypeptide (GIP) and glucagonlike peptide-1 (GLP-1) receptor agonist. Food and Drug Administration (FDA) granted Zepbound fast track designation on October 2, 2022 and rolling review on November 4 2022.[1,2] The Applicant initiated the rolling submission on November 17, 2022 with NDA 217806 sequence 1 (S-001) and completed this NDA submission on May 8, 2023, seeking FDA's approval of Zepbound as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management (CWM) in adults with an initial body mass index (BMI) of

- 30 kg/m^2 or greater (obesity) or
- 27 kg/m^2 or greater (overweight) in the presence of at least one weight-related comorbid condition (e.g., hypertension, dyslipidemia, (b) (4), type 2 diabetes mellitus, obstructive sleep apnea or cardiovascular disease).

Zepbound is a once-weekly subcutaneous injection. The recommended starting dosage is 2.5 mg, with a dosage increment of 2.5 mg after at least four weeks on the current dose. The recommended maintenance dosages are 5 mg, 10 mg, or 15 mg.

On May 13, 2022, Food and Drug Administration (FDA) approved Mounjaro (NDA 215866, tirzepatide) as an adjunct to diet and exercise to improve glycemic control in adults with Type 2 Diabetes Mellitus (T2DM).[3] The formulation, route of administration, and dosage regimen of tirzepatide for T2DM and CWM treatment are identical.[4]

1.2. Describe the Safety Concern

According to American College of Obstetricians and Gynecologists (ACOG),[5] weight loss during pregnancy offers no benefit to a pregnant patient and may cause harm. Weight loss is not recommended during pregnancy.

Reproduction and development evaluation were based on the complete tirzepatide nonclinical program to support the diabetic indication, and there were no new toxicology studies to support the weight management indication.[6,7] In animal reproduction studies, tirzepatide exposure during pregnancy has shown an adverse effect on fetal growth and development.[8]

- Decreased fetal weights and fetal abnormalities[a] occurred in pregnant rats exposed to clinically relevant dose of tirzepatide during organogenesis at twice weekly subcutaneous doses of 0.02, 0.1, and 0.5 mg/kg (0.03-, 0.07-, and 0.5-fold the maximum recommended human dose [MRHD] of 15 mg once weekly based on area under the curve [AUC])
- Maternal mortality or abortion occurred in rabbits administered tirzepatide doses of 0.01, 0.03, or 0.1 mg/kg (0.01-, 0.06-, and 0.2-fold the MRHD) during organogenesis[b].

[a] Fetal abnormalities included increased incidences of external, visceral, and skeletal malformations and increased incidences of visceral and skeletal developmental variations

In Division of Pediatrics and Maternal Health (DPMH) review of the Applicant's Pregnancy, Lactation, and Reproductive Potential (PLRP) data, submitted on May 8, 2023, for NDA 217806, the DPMH reviewer assessed 45 maternally tirzepatide-exposed pregnancies from clinical trials and postmarketing data sources, as of February 28, 2023:[9]

Table 1. Data source and study population of 45 pregnancies maternally exposed to tirzepatide reviewed by the DPMH reviewer

Number of Pregnancy	Data Source*	Study Population
16	SURMONT-1	Obesity/Overweight subjects without T2DM
2	SURMONT-2	Obesity/Overweight subjects with T2DM
1	SURMONT-4	Obesity/Overweight subjects without T2DM
1	SURPASS-1	T2DM
2	SURPASS-2	T2DM
1	SURPASS-3	T2DM
1	SURPASS-AP-Combo	T2DM
20	Postmarketing safety studies, published literature, and spontaneous reported adverse events from postmarketing experience from May 13, 2022**	

* All clinical studies were Phase 3 randomized controlled trials, based on information in Applicant's June 5, 2023 responses to May 30, 2023 information request, as well as information in Pregnancy, Lactation, and Reproductive Potential (PLRP) data, submitted on May 8, 2023, for NDA 217806

** Applicant did not provide specific number of pregnancies from each individual postmarketing data source

Outcomes of these pregnancies included:[9]

- 12 livebirths (four of them were preterm births – all in clinical trials)
- Two ectopic pregnancies (both in clinical trials)
- Four spontaneous abortions (three in clinical trials, one in postmarketing data sources)
- Five elective pregnancy terminations (all in clinical trials)
- 11 lost to follow-up (three in clinical trials, eight in postmarketing data sources)
- Two "not reported" outcomes (both in postmarketing data sources)
- Nine pending outcomes as ongoing pregnancy (all in postmarketing data sources)

There were no reported major or minor fetal malformations among these 45 exposed pregnancies. The DPMH reviewer noted the following maternal complications among 18 exposed pregnancies in SURMONT-1 and SURMONT-2:[9,c]

- Pre-eclampsia in one pregnancy
- Hypertension and gestational diabetes in one pregnancy
- Hyperglycemia in one pregnancy

Although thirty percent (n=4) of the 12 livebirths reported were classified as preterm birth, which is higher than the background rate of preterm births, the DPMH reviewer considers the relationship between tirzepatide and preterm birth is inconclusive due to small number of preterm births.[9] Additionally, the results interpretation is also limited by including patients with T2DM, which is a known risk factor for adverse pregnancy and infant outcomes.

[c] The DPMH review did not provide maternal complications for tirzepatide-exposed pregnancies observed in other data sources.

As of Nov 7, 2023, the proposed labeling of Zepbound states

- *Pregnancy: May cause fetal harm. When pregnancy is recognized, discontinue ZEPBOUND. (8.1)*

- *Females of Reproductive Potential: Advise females using oral contraceptives to switch to a non-oral contraceptive method or add a barrier method of contraception for 4 weeks after initiation and for 4 weeks after each dose escalation. (8.3)*

Appendix I provides relevant labeling information for tirzepatide use in special populations, including pregnancy, as of Nov 7, 2023.

Currently, there are insufficient safety data for tirzepatide use in pregnancy. Although weight loss is not recommended during pregnancy, females of reproductive potential may experience unintended exposures to tirzetide during the first trimester before they recognize pregnancy. Given that the half-live of tirzepatide is approximately five days, the chance of unintended exposure could be high. Indeed, unintended pregnancy exposure to tirzepatide has occurred among Mounjaro users in the postmarketing setting even though the Mounjaro labeling states that: advise females of reproductive potential *using oral contraceptives to switch to a non-oral contraceptive method, or add a barrier method of contraception for 4 weeks after initiation and for 4 weeks after each dose escalation.*[8]

Given the abovementioned concerns and knowledge gaps, the Agency plans to issue a dual postmarketing requirement (PMR) to build up the pregnancy safety of Zepbound.

1.3. FDAAA Purpose (per Section 505(o)(3)(B))

- Please ensure that the selected purpose is consistent with the other PMR documents in DARRTS

Purpose (place an "X" in the appropriate boxes; more than one may be chosen)	
Assess a known serious risk	
Assess signals of serious risk	
Identify unexpected serious risk when available data indicate potential for serious risk	x

2. REVIEW QUESTIONS

2.1. Why is pregnancy safety a safety concern for this product? Check all that apply.

☐ Specific FDA-approved indication in pregnant women exists and exposure is expected

☐ No approved indication, but practitioners may use product off-label in pregnant women

☒ No approved indication, but there is the potential for inadvertent exposure before a pregnancy is recognized

☒ No approved indication, but use in women of child-bearing age is a general concern

2.2. Regulatory Goal

☒ *Signal detection* – Nonspecific safety concern with no prerequisite level of statistical precision and certainty
☒ *Signal refinement of specific outcome(s)* – Important safety concern needing moderate level of statistical precision and certainty. †
☒ *Signal evaluation of specific outcome(s)* – Important safety concern needing highest level of statistical precision and certainty (e.g., chart review). †

† ***If checked, please complete General ARIA Sufficiency Template.***

2.3. What type of analysis or study design is being considered or requested along with ARIA? Check all that apply.

☒ Pregnancy registry with internal comparison group
☐ Pregnancy registry with external comparison group
☐ Enhanced pharmacovigilance (i.e., passive surveillance enhanced by with additional actions)
☒ Electronic database study with chart review
☐ Electronic database study without chart review
☐ Other, please specify: *Click here to enter text.*

2.4. Which are the major areas where ARIA not sufficient, and what would be needed to make ARIA sufficient?

☐ Study Population
☐ Exposures
☒ Outcomes
☒ Covariates
☒ Analytical Tools

For any checked boxes above, please describe briefly:

Outcomes
These PMRs target a broad spectrum of pregnancy and infant outcomes, including pregnancy complications, major and minor congenital malformations, spontaneous abortions, stillbirths, elective terminations, preterm births, small-for-gestational-age births, and any other adverse outcomes, including postnatal growth and development.

Several of the desired outcomes cannot be reliably assessed in the Sentinel Distributed Database, including infant outcomes (i.e., postnatal growth and development) that require clinical assessments not reflected in healthcare claims data, but would be collected in a registry. Additionally, spontaneous and elective abortions may not always be ascertainable in healthcare claims databases.

ARIA also lacks access to medical records. The pregnancy registry being considered requires that expert clinical geneticists or dysmorphologists review and classify medical records of all major congenital malformations. Also, although in a first stage, the study using claims or

electronic medical data may be algorithm-based, if it shows an imbalance in any of the outcomes being investigated, FDA will require outcome validation in the selected database(s) or a chart-confirmed analysis.

Covariates
The Sentinel system has incomplete information on important covariates for pregnancy and infant outcomes, such as maternal smoking, alcohol and drug use, nonprescription drug use.

Analytical Tools
The PMRs target on a broad spectrum of pregnancy and infant outcomes. ARIA might address the complexity presented by multiple discrete outcomes using appropriate data mining approach. However, a suitable data mining approach (e.g., TreeScan) has not been fully tested and implemented for signal detection, specifically for non-prespecified outcomes.

2.5. Please include the proposed PMR language in the approval letter.

The proposed PMR language in the approval letter

1. *Collect global data from a prospective pregnancy exposure registry, preferably a disease-based multi-product pregnancy registry, using a registry-based cohort study to compare the maternal, fetal, and infant outcomes of women exposed to Zepbound (tirzepatide) for chronic weight management during pregnancy with unexposed comparator population(s). Align the study protocol with protocol(s) outside the United States to reach the target sample size. The registry will identify and record pregnancy complications, major and minor congenital malformations, spontaneous abortions, stillbirths, elective terminations, preterm births, small-for-gestational-age births, and any other adverse outcomes, including postnatal growth and development. These outcomes will be assessed throughout pregnancy. Infant outcomes, including effects on postnatal growth and development, will be assessed through at least the first year of life.*

2. Conduct an additional pregnancy study that uses a different design from the pregnancy exposure registry (for example a cohort study using claims or electronic medical record data) to compare the risks and prevalence of pregnancy and infant outcomes (including but not limited to major congenital malformations, spontaneous abortions, stillbirths, small-for-gestational-age births, preterm births, and postnatal growth and development) between women exposed to Zepbound (tirzepatide) for chronic weight management during pregnancy and unexposed comparator population(s).

REFERENCE

1. IND 139721. Tirzepatide for injection. Correspondence: Rolling Review. DARRTS Reference ID: 5072631 (November 4, 2022).

2. IND 139721. Tirzepatide for injectin. Correspondence: Fast Track/Rolling Review. DARRTS Reference ID: 5054793 (October 3, 2022).

3. U.S. Food and Drug Administration. NDA 215866 Approval Letter. MOUNJARO (tirzepatide) injection. DARRTS Reference ID: 4983783. Accessed Oct 20, 2023. https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2022/215866Orig1s000ltr.pdf

4. Kronfol M, Chow EC, Liu J, Earp J. *Office of Clinical Pharmacology Review. NDA 217806 ZEPBOUND* October 11, 2023.

5. American College of Obstetricians and Gynecologists. ACOG Committee opinion number 548. January 2013 (Reaffirmed 2023): weight gain during pregnancy. Accessed October 25, 2023. https://www.acog.org/clinical/clinical-guidance/committee-opinion/articles/2013/01/weight-gain-during-pregnancy

6. Braithwaite E. *NDA 217806 ZEPBOUND (tirzepatide). Pharmacology/Toxicology ND/BLA Review and Evaluation. DARRTS Reference ID: 5260489*. November 17, 2022.

7. Braithwaite E. *NDA 215866 MOUNJARO (tirzepatide/LY3298176). Pharmacology/Toxicology NDA/BLA Review and Evaluation. DARRTS Reference ID: 4953686*. September 15, 2021.

8. U.S. Food and Drug Administration. Product Labeling. MOUNRAJO (tirzepatide) injection, for subcutaneous use. NDA 215866. Accessed October 19, 2023. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/215866Orig1s002s006lbl.pdf

9. Sun W. *NDA 217806. ZEPBOUND (tirzepatide). Division of Pediatrics and Maternal Health Memo: Pregnancy and Lactation Labeling. DARRTS Reference ID: 5238752*. September 6, 2023.

Appendix I.

Proscribing Information for ZEPBOUND

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There will be a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to ZEPBOUND (tirzepatide) during pregnancy. Pregnant patients exposed to ZEPBOUND and healthcare providers are encouraged to contact Eli Lilly and Company at 1 800 LillyRx (1 800 545 5979).

Risk Summary

Weight loss offers no benefit to a pregnant patient and may cause fetal harm. Advise pregnant patients that weight loss is not recommended during pregnancy and to discontinue ZEPBOUND when a pregnancy is recognized (see Clinical Considerations). Available data with tirzepatide in pregnant patients are insufficient to evaluate for a drug-related risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes. Based on animal reproduction studies, there may be risks to the fetus from exposure to tirzepatide during pregnancy.

In pregnant rats administered tirzepatide during organogenesis, fetal growth reductions and fetal abnormalities occurred at clinical exposure in maternal rats based on AUC. In rabbits administered tirzepatide during organogenesis, fetal growth reductions were observed at clinically relevant exposures based on AUC. These adverse embryo/fetal effects in animals coincided with pharmacological effects on maternal weight and food consumption (see Data).

The estimated background risk of major birth defects and miscarriage for the indicated population is increased when compared to the general population. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk

Appropriate weight gain based on pre-pregnancy weight is currently recommended for all pregnant patients, including those with obesity or overweight, due to the obligatory weight gain that occurs in maternal tissues during pregnancy.

Data

Animal Data

In pregnant rats given twice weekly subcutaneous doses of 0.02, 0.1, and 0.5 mg/kg tirzepatide (0.03 , 0.07 , and 0.5-fold the maximum recommended human dose (MRHD) of 15 mg once weekly based on AUC) during organogenesis, increased incidences of external, visceral, and skeletal malformations, increased incidences of visceral and skeletal developmental variations, and

decreased fetal weights coincided with pharmacologically-mediated reductions in maternal body weights and food consumption at 0.5 mg/kg. In pregnant rabbits given once weekly subcutaneous doses of 0.01, 0.03, or 0.1 mg/kg tirzepatide (0.01 , 0.06 , and 0.2-fold the MRHD) during organogenesis, pharmacologically- mediated effects on the gastrointestinal system resulting in maternal mortality or abortion in a few rabbits occurred at all dose levels. Reduced fetal weights associated with decreased maternal food consumption and body weights were observed at 0.1 mg/kg. In a pre- and post-natal study in rats administered subcutaneous doses of 0.02, 0.10, or 0.25 mg/kg tirzepatide twice weekly from implantation through lactation, F1 pups from F0 maternal rats given 0.25 mg/kg tirzepatide had statistically significant lower mean body weight when compared to controls from post-natal day 7 through post-natal day 126 for males and post-natal day 56 for females.

8.2 Lactation

Risk Summary

There are no data on the presence of tirzepatide or its metabolites in animal or human milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ZEPBOUND and any potential adverse effects on the breastfed infant from ZEPBOUND or from the underlying maternal condition.

8.3 Females and Males of Reproductive Potential

Contraception

Use of ZEPBOUND may reduce the efficacy of oral hormonal contraceptives due to delayed gastric emptying. This delay is largest after the first dose and diminishes over time. Advise patients using oral hormonal contraceptives to switch to a non-oral contraceptive method, or add a barrier method of contraception, for 4 weeks after initiation with ZEPBOUND and for 4 weeks after each dose escalation [see Drug Interactions (7.2) and Clinical Pharmacology (12.2, 12.3)].

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/s/

PO YIN CHANG
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WEI HUA
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DAVID G MOENY on behalf of JUDITH W ZANDER
11/07/2023 05:00:11 PM

SARAH K DUTCHER
11/07/2023 09:52:45 PM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

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

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	October 31, 2023
Requesting Office or Division:	Division of Diabetes, Lipid Disorders, and Obesity (DDLO)
Application Type and Number:	NDA 217806
Product Name, Dosage Form, and Strength:	Zepbound (tirzepatide) injection, 2.5 mg/0.5 mL, 5mg/0.5 mL, 7.5 mg/0.5 mL, 10 mg/0.5 mL, 12.5mg/0.5 mL, 15 mg/0.5 mL
Applicant/Sponsor Name:	Eli Lilly and Company (Lilly)
TTT ID #:	2022-2848-1
DMEPA 1 Safety Evaluator:	Ariane O. Conrad, PharmD, BCACP, CDCES
DMEPA 1 Team Leader:	Idalia E. Rychlik, PharmD

1 PURPOSE OF MEMORANDUM

Lilly submitted revised Zepbound container labels and carton labeling on October 30, 2023. The Division of Diabetes, Lipid Disorders, and Obesity (DDLO) requested that we review the revised container labels and carton labeling for Zepbound (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a] In addition, we note that the DMEPA 1 human factors team provided advice to Lilly to add a "needle end" statement to the pen label based on prior recommendations they have provided to Lilly for another product using the same device platform.[b]

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

[a] Conrad, A. Label and Labeling Review for Zepbound (NDA 217806). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2023 Aug 17. TTT ID No.: 2022-2848.

[b] Kamath, A. FDA Communication: NDA 217806/tirzepatide/FDA labeling comments 10-13-2023. Silver Spring (MD): FDA, CDER, OND, DDLO (US); 2023 Oct 13. NDA 217806. Available from: https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af806fe789.

2 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

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/s/

ARIANE O CONRAD
10/31/2023 09:52:41 AM

IDALIA E RYCHLIK
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CLINICAL OUTCOME ASSESSMENT (COA) CONSULT REVIEW

COA Tracking ID:	C2023017
NDA#/Referenced IND for NDA:	NDA 217806/IND 139721
Applicant:	Eli Lilly and Co.
Established Name/Trade Name:	Tirzepatide (ZEPBOUND)
Indication:	Weight management in conjunction with a reduced-calorie diet and increased physical activity ☐Rare Disease/Orphan Designation ☐Pediatrics
PDUFA Goal Date:	November 8, 2023
Review Division:	Division of Diabetes, Lipid Disorders, and Obesity
Clinical Reviewer:	Raymond Soccio
Clinical Team Leader (TL)	Laura Higginbotham
Regulatory Project Manager:	Arati Kamath
Patient-Focused Statistical Scientists (PFSS) reviewer	Xin Yuan
PFSS secondary reviewer	Lili Garrard
COA Reviewer:	Qing Xie
COA TL/Deputy Division Director:	Selena Daniels
COA Director:	David Reasner
Instruments reviewed:	1. 36-item Short Form Health Survey Version 2 (SF-36v2) Physical Functioning domain ☒ Patient-reported outcome (PRO)

Table of Contents

1. EXECUTIVE SUMMARY

In this submission, the applicant is seeking approval of tirzepatide as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adults with an initial body mass index (BMI) of ≥30 kg/m^2 (obese) or BMI ≥27 kg/m2 (overweight) in the presence of at least one weight-related comorbid condition (e.g., hypertension, dyslipidemia, type 2 diabetes mellitus, obstructive sleep apnea or cardiovascular disease). The specific clinical outcome assessment (COA) (b) (4) is related to improvement in physical functioning, which is derived from two multicenter, randomized, placebo-controlled, double-blinded phase 3 clinical trials (Studies I8F-MC-GPHK and I8F-MC-GPHL, also referred to as SURMOUNT-1 and SURMOUNT-2, respectively). The primary objective of this review is to evaluate from a COA perspective if the submitted information supports the COA (b) (4) related to these concept(s) of interest.

(b) (4)

The data from the SURMOUNT-1 study demonstrated that tirzepatide had statistically significant improvement in physical functioning measured by the SF-36 v2 Acute Form Physical Functioning domain (hereon referred to as SF-36v2 Physical Functioning domain). Despite achievement of statistical significance, there were minimal observed score changes, if any, when looking at the item- and domain-level data at the raw score scale (e.g., all item scores reflect less than one category mean change on the raw score scale [non-normalized and -transformed scores]). The changes observed in the normalized scores were also minimal as evidenced by minimal separation between the treatment arms in the empirical cumulative distribution function (eCDF) curves (see Section 5.4).

For the SURMOUNT-2 study, there was no formal hypothesis testing for the COA-based endpoints.

From a COA perspective, the SF-36v2 Physical Functioning domain measures some important aspects of physical functioning. (b) (4) Specifically, for a subgroup of participants with physical function impairment at baseline (i.e., Patient Global Impression of Status for Physical Activity (PGIS) response of at least "Moderately limited"), if also supported by the clinical trial study design, statistical analysis, and consistent findings with the other administered weight-specific physical function assessment.

2 REVIEW CONCLUSIONS

The applicant submitted an evidence dossier for the SF-36v2. The SF-36v2 Physical Functioning domain was reviewed for content validity, other measurement properties, and score interpretability (i.e., meaningful within-patient score change).

Review Summary

- The SF-36v2 Physical Functioning domain measures some important aspects of physical functioning, and appears content relevant for the target patient population.
- The applicant has established the other measurement properties of the SF-36v2.
- It is difficult to estimate the range of change on the SF-36v2 Physical Functioning domain that represents clinically meaningful within-patient score changes due to the minimal magnitude of changes was observed at the item- and domain-level of the measure at Week 72.

Key Issues Identified

Issue 1: Content validity

- The relevance of some of the items is questionable in participants who may have mild limitations in physical functioning based on the qualitative and quantitative data. For both SURMOUNT-1 and SURMOUNT-2 studies, the baseline SF-36v2 Physical Functioning domain scores showed large ceiling effects at item and domain levels (i.e., participants endorsed the least severe response category). For example, in SURMOUNT-1, more than half of the participants ($\geq$50%) reported "No, not limited at all." These findings indicate that participants may not be sufficiently limited in physical functioning at baseline. As such, there was no to very little room for improvement to occur in the trials.

Issue 2: Other measurement properties

- While the applicant established the other measurement properties of the instrument, the dimensionality of SF-36v2 Physical Functioning domain may need to be further explored as there may be some potential measurement redundancy.

Issue 3: Data interpretability

- Although the efficacy analysis based on all participants showed statistically significant results, the differences between the treatment and placebo means were small and minimal magnitude of changes was observed at the item- and domain-level of the SF-36v2 Physical Functioning domain score, using both norm-based and raw scores. Because there is minimal change demonstrated, it is difficult to assess whether the change constitutes a clinically meaningful change. Further, the eCDF curves show minimal separation between the treatment arms. As such, there is concern with the inclusion of the data using the overall population (i.e., participants with and without physical function impairment).

- The applicant conducted a subgroup analysis specified in their statistical analysis plans but not adjusted for multiplicity to evaluate the treatment effect in participants who have impaired physical function at baseline, which is defined as PGIS response at baseline of "Moderately limited," "Very much limited," or "Extremely limited." The analysis results for this subgroup of participants are nominally statistically significant and likely to be clinically meaningful to subjects (refer to Section 5.6.6). (b) (4) Specifically, for a subgroup of participants with physical function impairment at baseline, if also supported by the clinical trial study design, statistical analysis, and consistent findings with the other administered weight-specific physical function assessment.

3 RECOMMENDATIONS FOR FUTURE STUDIES

For future clinical trials in this indication, we recommend that sponsors specify and define functional impacts that are relevant and important to patients who are obese or have excess weight and that are likely to demonstrate meaningful and interpretable changes in the planned clinical trial(s). Sponsors seeking to demonstrate clinical benefit of a therapeutic on a particular set of functional impacts should select a sufficiently impaired population for their studies or otherwise plan for stratification or appropriate statistical analyses. Additionally, sponsors should carefully consider the frequency and timing of assessments. Collecting frequent data points to assess treatment effect and durability is helpful for data interpretability. Further, it will be important for the Agency to review and comment on applicants' plans for qualitative research (e.g., concept elicitation interviews, cognitive interviews, exit interviews) early in the development program to the extent possible.

4 BACKGROUND AND CORRESPONDENCE ON CLINICAL OUTCOME ASSESSMENT(S)

Regulatory Background:
In May 2022, tirzepatide was approved in the United States (US) for the treatment of adults with type 2 diabetes mellitus (T2DM).

There have been multiple communications regarding the applicant's COA measurement strategy related to the SF-36v2 Physical Functioning Domain for their weight management development program during the IND stage (IND 139721):

- Advice/Information Request Letter dated June 23, 2023
  - Commented that the additional secondary and tertiary endpoints are viewed as exploratory endpoints as they are not adjusted for multiplicity.

  Reviewer's comment(s): *DCOA also provided the following comments based on review of Protocol I8F-MC-GPIJ1 (SURMOUNT-MMO) on October 12, 2022:*
  - *Reiterated previous comments regarding the adequacy of the SF-36v2 Physical Functioning domain for use as a key secondary endpoint.*
  - *Commented that the additional secondary and tertiary endpoints are viewed as exploratory endpoints as they are not adjusted for multiplicity.*

- Advice/Information Request Letter dated August 27, 2021
  - Requested user and scoring manual for the SF-36v2 and justification for deviation (if any) from the scoring algorithm including handling of missing data.
  - Recommended conducting subgroup analyses (participants with sufficient physical function impairment) for ongoing study SURMOUNT-1 and proposed studies SURMOUNT-2 and SURMOUNT-4.
  - Commented on the revised psychometric analysis plan including additional item- and domain-level analyses, test-retest reliability, and meaningful within-patient change analyses including consideration of exit interviews or surveys to supplement anchor-based analyses.

  Reviewer's comment(s): *The comments given in the Advice/Information Request Letter dated August 27, 2021 were from the Statistical Reviewer and PFSS Reviewer.*

- Advice/Information Request Letter dated June 14, 2021
  - Expressed concerns regarding limitations of the proposed anchor scale (i.e., PGIS).

  Reviewer's comment(s): *DCOA has requested the Division to consult the PFSS group for additional input on the appropriate sample size for subset of participants to establish a meaningful change threshold in phase 3 trials.*

- Final Written Response dated September 21, 2020
  - Concluded that the SF-36v2 Physical Functioning domain appears content relevant for the target population and the completed qualitative and quantitative data will be further reviewed at the time of NDA submission.
  - Requested a full and detailed psychometric analysis plan for review.

- Type C Meeting Minutes dated July 25, 2019
  - Concluded there is a lack of evidence regarding content validity of SF-36v2 for the target population.

[1] I8F-MC-GPIJ1 is an international, randomized, double-blind, parallel group, event-driven phase 3 study, which is designed to investigate the reduction of morbidity and mortality with once weekly tirzepatide treatment compared to placebo in adults (≥40 years of age) with body mass index >27 kg/m2 who have established cardiovascular disease (CVD) OR who do not have established CVD but have the presence of CV risk factors.

- Expressed openness to confirmation of the other measurement properties of SF-36v2 in the target population using one trial (blinded data).

Previous COA reviews[2]:

- C2019167 IND139721 Ju dated September 3, 2020 (DARRTS Reference ID: 4666123)
- C2020301 IND139721 Ju dated September 17, 2020 (DARRTS Reference ID: 4671527)
- C2021140 IND139721 Ju dated May 26, 2021 (DARRTS Reference ID: 4802140)
- C2022108 IND139721 Chung dated March 24, 2022 (DARRTS Reference ID: 4954395)
- C2022291 IND139721 Xie dated October 12, 2022 (DARRTS Reference ID: 5059370)
- C2023106 IND139721 Xie dated June 16, 2022 (DARRTS Reference ID: 5192828)

Disease Background:
Obesity is a complex, chronic disease involving an excessive amount of body fat. Obese and overweight individuals may present with health risks associated with obesity, such as atherosclerosis, ischemic heart disease, heart failure, stroke, diabetes mellitus, chronic kidney disease, and cancer (e.g., breast, colorectal, kidney, endometrial, and pancreatic).

Investigational Product:
Tirzepatide is a glucose-dependent insulinotropic polypeptide (GIP) and glucagonlike peptide-1 (GLP-1) receptor agonist. It is administered once weekly (QW) by subcutaneous (SC) injection.

5 CLINICAL OUTCOME ASSESSMENT REVIEW

5.1 Clinical Trial Population

5.1.1 SURMOUNT-1 Study

The target population for Study SURMOUNT-1 were adults without T2DM who are either obese (BMI ≥30 kg/m^2) or overweight (≥27 kg/m^2) with at least one weight-related comorbid condition (e.g., hypertension, dyslipidemia, or cardiovascular disease).

A complete list of the inclusion and exclusion criteria is summarized in Section 5 of the clinical study protocol for the SURMOUNT-1 study.

5.1.2 SURMOUNT-2 Study

The target population for Study SURMOUNT-2 were adults with T2DM who are either obese (BMI ≥30 kg/m^2) or overweight (≥27 kg/m^2).

A complete list of the inclusion and exclusion criteria is summarized in Section 5 of the clinical study protocol for the SURMOUNT-2 study.

[2] COA Reviews for IND 139721 related to weight management as an adjunct to diet and exercise in subjects with overweight or obesity indication.

5.2 Clinical Trial Design

5.2.1 SURMOUNT-1 Study

Study SURMOUNT-1[3] was a multicenter, randomized, placebo-controlled, double-blinded phase 3 study of the safety and efficacy of 5 mg, 10 mg, and 15 mg tirzepatide QW, compared with placebo, when used in conjunction with a reduced-calorie diet and increased physical activity for weight management, in participants who do not have T2DM, and have obesity (BMI ≥30 kg/m^2) or are overweight (BMI ≥27 kg/m^2) with at least 1 weight-related comorbid condition (for example, hypertension, dyslipidemia, or cardiovascular disease). A total of 2539 participants were recruited for SURMOUNT-1 and randomized 1:1:1:1, all of whom had available PRO data.

The study included three periods:
- A screening period (up to 2 weeks)
- A treatment period (72 weeks) including a 20-week dose escalation
- A safety follow-up period of 4 weeks.

Refer to the clinical study protocol for the SURMOUNT-1 study for more details on the clinical trial design.

5.2.2 SURMOUNT-2 Study

Study SURMOUNT-2[4] was a multicenter, randomized, parallel-arm, placebo-controlled, double-blinded, 72-week Phase 3 study that investigated the safety and efficacy of treatment with tirzepatide 10 and 15 mg QW SC compared with placebo QW, in conjunction with a reduced-calorie diet and increased physical activity, on weight management in participants with T2DM who have obesity (BMI ≥30 kg/m2) or are overweight (BMI ≥27 kg/m2). 938 participants screened were randomly assigned to treatment received ≥1 dose of study drug.

The study included three periods:
- A screening period (up to 2 weeks)
- A treatment period including a 20-week dose escalation
- A safety follow-up period of 4 weeks.

Refer to the clinical study protocols for the, SURMOUNT-2 study for more details on the clinical trial design.

Reviewer's comment(s): *The applicant has an ongoing multicenter, randomized, parallel-arm, double-blind, placebo-controlled, 88-week study (known as SURMOUNT-4) that investigated the impact of maximum tolerated dose (MTD) of tirzepatide (10 mg or 15 mg), compared with placebo, on the maintenance of weight reduction after an initial 36-week open-label tirzepatide*

[3] Study I8F-MC-GPHK was conducted at 118 centers that screened 3238 participants and randomized 2539 participants in Argentina, Brazil, China, India, Japan, Mexico, Russian Federation, Taiwan, and the US, including Puerto Rico.
[4] Study I8F-MC-GPHL was conducted at 77 centers that screened 1514 participants and randomly assigned 938 participants in Argentina, Brazil, India, Japan, Russian Federation, Taiwan, and the US, including Puerto Rico.

lead-in treatment period, in study participants without T2DM who have obesity or overweight with at least 1 weight-related comorbid condition (for example, hypertension, dyslipidemia, obstructive sleep apnea or cardiovascular disease). A total of 783 participants were recruited for SURMOUNT-4 in the open-label phase, with 670 continuing to the blinded phase. Following a 36-week open-label tirzepatide treatment period, study participants were randomized in a double-blind 1:1 ratio (tirzepatide MTD once weekly or placebo).

5.3 Endpoint Position, Definition, and Assessment Schedule

5.3.1 SURMOUNT-1 Study

Table 1 summarizes the primary and secondary efficacy COA endpoints including the endpoint definition and assessment schedule for Study SURMOUNT-1.

Table 1. Endpoint Position, Definition, and Assessment Schedule for Study SURMOUNT-1.

Endpoint Position	Assessment	Endpoint Definition	Assessment Frequency
Primary	Body weight measured by a calibrated electronic scale	• Mean percent change in body weight from Randomization • Percentage of study participants who achieve ≥5% body weight reduction from randomization	Baseline, Weeks 4, 8, 12, 16, 20, 24, 36, 48, 60, and 72
Secondary ☒ Multiplicity adjusted	SF-36v2 Physical Functioning domain (PRO)	Mean change in SF-36v2 Physical Functioning domain score from randomization at 72 weeks (doses 10 mg and 15 mg pooled)	Baseline, Week 72, or ED (early discontinuation of treatment)

PRO= Patient-reported outcome
Source: Reviewer's table.

Reviewer's comment(s): *This reviewer has concerns that the two collected timepoints (i.e., baseline and Week 72) may not be sufficient and may have missed important information on the benefits of the product throughout the trial.*

5.3.2 SURMOUNT-2 Study

The primary and secondary efficacy COA endpoints are the same as in the SURMOUNT-1 study; the exception is that the secondary efficacy COA endpoint was not adjusted for multiplicity and the doses were not pooled.

Reviewer's comment(s): *According to the submission, the SF-36v2 Physical Functioning is a key secondary endpoint (alpha-controlled for Type 1 error) in the SURMOUNT-1 study, and is an additional, non-alpha controlled, secondary endpoint in the SURMOUNT-2 study. The SF-36v2 Physical Functioning domain is a generic PRO instrument designed to assess general health status and includes several specific domains including the Physical Functioning domain. There*

are a lot of external factors that could impact participants' health status (e.g., co-morbidities), which might limit the interpretability of the results.

The applicant also administered other COAs for use as exploratory endpoints, which included the Impact of Weight on Quality of Life-Lite Clinical Trials (IWQOL-Lite-CT) Physical Function domain and the EuroQoL Five Dimension-Five Level (EQ-5D-5L) instrument.

- *The IWQOL-Lite-CT Physical Function domain is a 5-item domain within the 20-item IWQOL-Lite-CT PRO instrument. The IWQOL-Lite-CT Physical Function domain is designed to assess physical functioning, Each item is rated on a 5-point verbal rating scale (VRS), ranging from 1 ("never" or "not at all true") to 5 ("always" or "completely true"). The recall period is momentary (i.e., "currently").*

- *The EQ-5D-3L is a 6-item generic patient-reported preference-based instrument designed to assess health status across five dimensions (i.e., mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). Each item in the dimension is rated on a 3-point VRS ranging from 1 ("No problems") to 3 ("Extreme problems or inability to perform specified activity"). The second section of the instrument measures self-rated (global) health status utilizing a vertically oriented visual analogue scale (VAS) where 100 represents the "best possible health state" and 0 represents the "worst possible health state." Participants are asked to rate their current health by placing a mark along this continuum. The recall period is "today" for the entire instrument.*

  This reviewer notes that the EQ-5D-5L is a generic preference-based measure intended to provide a single health utility index value for use in economic analyses and lacks evidence of content validity for use in estimating clinical benefit (b) (4) *However, it is acknowledged that the EQ-5D-5L may be necessary for other regulatory authorities and/or payers.*

5.4 Assessment of Efficacy

Table 2 below summarizes the efficacy results of change from baseline at Week 72 in the SF-36v2 Physical Functioning domain score (norm-based) for Studies SURMOUNT-1 and SURMOUNT-2, respectively. Although a statistically significant result was reported for SURMOUNT-1 and a nominally statistically significant result was reported for SURMOUNT-2, the differences between the treatment and placebo means were small in both studies.

The baseline means of the SF-36v2 Physical Functioning domain score (norm-based) for each arm in Studies SURMOUNT-1 and SURMOUNT-2 are similar to the general population (mean of 50) (Table 2; shown on next page). Specifically, the means are between 49.5 to 49.6 across arms in SURMOUNT-1, and between 47.9 to 48.5 across arms in SURMOUNT-2. Participants were not sufficiently limited in physical functioning at baseline for an adequate assessment of improvement. As such, there was no to very little room for change to occur, which impedes further evaluation of meaningful change. This also is evidenced by the minimal magnitude of changes observed at the item- and domain-level of the SF-36v2 Physical Functioning domain score using raw scores (Table 7 and Table 8).

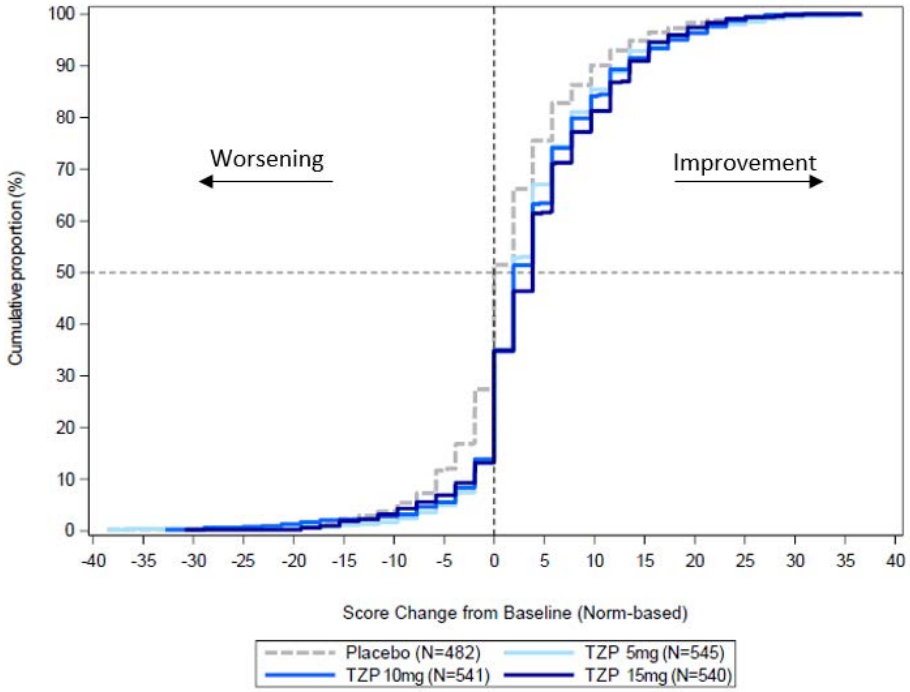
Table 2. Mean Change from Baseline in SF-36v2 Physical Functioning Domain Score (Norm-Based) at Week 72; mITT Population – Full Analysis Set

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

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; mITT = modified intent-to-treat; N = number of participants who were randomly assigned and received at least 1 dose of study drug; n = number of participants in the mITT analysis set with baseline and at least 1 postbaseline value; N/A = not applicable; SF-36v2 = Short-Form-36 Health Survey, Version 2; TZP = tirzepatide.
Note: ANCOVA with hybrid imputation for missing values at 72 weeks.
Shown are least-squares means.
***p-Value <0.001 versus placebo for superiority.
Source: Tables GPHK.5.9 of the SURMOUNT-1 Clinical Study Report and Table GPHL.5.25 of the SURMOUNT-2 Clinical Study Report.

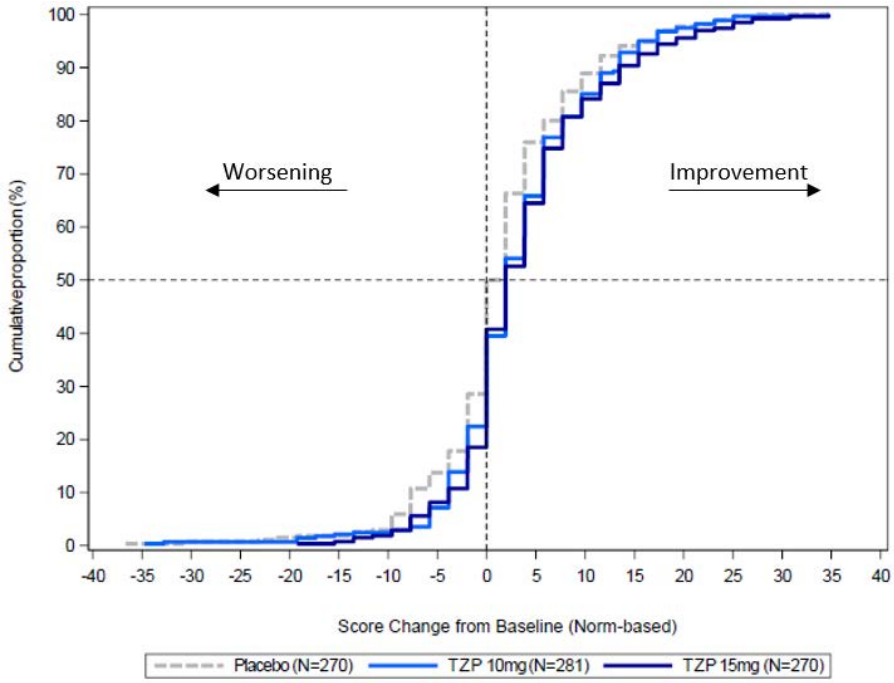
Figure 1 and Figure 2 (shown on next page) depict the distributions of the change from baseline in the SF-36v2 Physical Functioning domain scores by treatment arm through eCDF curves. From the figures, a clear and consistent separation between the treatment and placebo arms cannot be observed for either of the two studies.

Figure 1. eCDF Curve for Change from Baseline to Week 72 in SF-36v2 Physical Functioning Domain Score (Norm-based): mITT Population – SURMOUNT-1 Efficacy Analysis Set



Abbreviations: N = number of subjects in specified treatment group; mITT = modified intent-to-treat; SF-36v2 = short form survey-36 version 2; TZP = tirzepatide.
Note: Post-baseline values are derived from raw data.
50th percentile is marked with a dashed line on the y-axis and a reference value for no change is marked with a dashed line on the x-axis.
Source: Figure modified from Figure 5.1 of the applicant response to FDA IR dated August 11, 2023.

Figure 2. eCDF Curve for Change from Baseline to Week 72 in SF-36v2 Physical Functioning Domain Score (Norm-based): mITT Population – SURMOUNT-2 Efficacy Analysis Set



Abbreviations: N = number of subjects in specified treatment group; mITT = modified intent-to-treat; SF-36v2 = short form-36 health survey version 2; TZP = tirzepatide.
Note: Post-baseline values are derived from raw data.
50th percentile is marked with a dashed line on the y-axis and a reference value for no change is marked with a dashed line on the x-axis.
Source: Figure modified from Figure 5.2 of the applicant response to FDA IR dated August 11, 2023.

Reviewer's comment(s): *In the information request (IR) dated August 27, 2021, FDA recommended conducting subgroup analyses for participants with sufficient physical function impairment for the endpoint based on the SF-36v2 Physical Functioning domain score. The applicant then included the analyses in their statistical analysis plans for both Studies SURMOUNT-1and SURMOUNT-2. In the clinical study reports, the applicant provided the efficacy analysis results using data of participants with impaired physical function at baseline, defined as a PGIS response at baseline of:*

- *Moderately limited,*
- *Very much limited, or*
- *Extremely limited*

During the midcycle review, DCOA/PFSS expressed concerns that the participants enrolled into the two studies were not sufficiently limited in physical function at baseline for an adequate assessment of improvement. Subsequently, the Clinical team expressed interest in evaluating the treatment effect in the subgroup of participants with impaired physical function at baseline (b) (4)

Table 3 and Table 4 depict the distribution of the SF-36v2 Physical Functioning domain score across the PGIS categories at baseline for Studies SURMOUNT-1 and SURMOUNT-2, respectively. The mean SF-36 v2 Physical Functioning domain scores for the PGIS response categories of "Moderately limited", "Very much limited", and "Extremely limited" are lower/worse than the general population[5] (mean score of 50), as opposed to the response category of "A little limited", whose corresponding SF-36 v2 Physical Functioning domain mean scores are similar to the general population.

Reviewer's comment(s): *This reviewer considers it appropriate to define the subgroup of participants with impaired physical function as a PGIS response at baseline of at least "Moderately limited."*

Table 3. Description of the SF-36v2 Physical Functioning Domain Score (Norm-based) at Baseline Across PGIS Categories at Baseline; SURMOUNT-1 Full Analysis Set

	PGIS				
SF-36v2 Physical Functioning Domain Score (Norm-Based)	Not at All Limited (N = 1264)	A Little Limited (N = 749)	Moderately Limited (N = 360)	Very Much Limited (N = 150)	Extremely Limited (N = 16)
n (missing)	1263 (1)	748 (1)	358 (2)	150 (0)	16 (0)
Mean (SD)	53.1 (5.7)	48.2 (6.8)	**44.3 (7.9)**	**39.3 (9.0)**	**38.6 (10.5)**
Skewness	-2.4	-1.0	-0.5	-0.2	-0.1
Median	55.7	49.9	46.0	40.2	40.2
Q1, Q3	51.8, 57.6	44.1, 53.7	38.3, 49.9	32.5, 46.0	29.6, 45.1
P10, P90	46.0, 57.6	38.3, 55.7	32.5, 53.7	26.7, 49.9	24.8, 53.7
Min, Max	19.0, 57.6	19.0, 57.6	21.0, 57.6	21.0, 57.6	19.2, 57.6

Abbreviations: Max = maximum; Min = minimum; N = number of participants with baseline value; n = number of participants with both baseline and Week 72 value; P10 = 10th percentile; P90 = 90th percentile; PGIS = Patient Global Impression of status for physical activity; Q1 = 25th percentile; Q3 = 75th percentile; SD = standard deviation; SF-36v2 = 36-Item Short-Form Health Survey.
Source: Table APP.3 of the applicant response to FDA IR dated September 25, 2023.

Table 4. Description of the SF-36v2 Physical Functioning Domain Score (Norm-based) at Baseline Across PGIS Categories at Baseline; SURMOUNT-2 Full Analysis Set

	PGIS				
SF-36v2 Physical Functioning Domain Score (Norm-Based)	Not at All Limited (N=448)	A Little Limited (N = 274)	Moderately Limited (N = 141)	Very Much Limited (N = 60)	Extremely Limited (N = 15)
n (missing)	448 (0)	274 (0)	141 (0)	60 (0)	15 (0)
Mean (SD)	52.9 (5.4)	46.4 (7.9)	**42.3 (7.4)**	**37.2 (9.1)**	**36.4 (11.5)**
Skewness	-1.9	-0.8	-0.2	0.6	0.7
Median	53.7	48.0	42.2	36.4	36.4
Q1, Q3	49.9, 57.6	42.2, 51.8	36.4, 48.0	30.6, 42.2	26.7, 46.0
P10, P90	46.0, 57.6	34.5, 55.7	32.5, 51.8	26.7, 50.9	22.0, 57.6
Min, Max	21.0, 57.6	22.9, 57.6	22.9, 57.6	21.0, 57.6	22.9, 57.6

Abbreviations: Max = maximum; Min = minimum; N = number of participants with baseline value; n = number of participants with both baseline and Week 72 value; P10 = 10th percentile; P90 = 90th percentile; PGIS = Patient

5 The norm of the SF-36v2 was developed from the QualityMetric 2009 Norming Study based on a large, representative sample of the U.S. general population.

Global Impression of status for physical activity; Q1 = 25th percentile; Q3 = 75th percentile; SD = standard deviation; SF-36v2 = 36-Item Short-Form Health Survey.
Source: Table APP.3 of the applicant response to FDA IR dated September 25, 2023.

Table 5 shows the efficacy analysis results for participants with impaired physical function at baseline. From the results presented in the tables, lower baseline means of the SF-36v2 Physical Functioning domain score are observed in this subgroup of patients (43.0 to 43.1 for SURMOUNT-1 and 39.2 to 40.4 for SURMOUNT-2) than the overall population (i.e., participants with and without physical function impairment). The analysis results are nominally statistically significant, with larger treatment differences between the treatment and placebo arms observed than the overall population in both studies.

Table 5. Mean Change from Baseline in SF-36v2 Physical Functioning Domain Score (Norm-Based) at 72 Weeks in Participants Who Had Impaired Physical Function at Baseline; mITT Population – Full Analysis Set

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

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; mITT = modified intent-to-treat; N = number of participants who were randomly assigned and received at least 1 dose of study drug; n = number of participants in the mITT analysis set with baseline and at least 1 postbaseline value; N/A = not applicable; SF-36v2 = Short-Form-36 Health Survey, Version 2; TZP = tirzepatide.
Note: ANCOVA with hybrid imputation for missing values at 72 weeks.
Shown are least-squares means.
Source: Table GPHK.5.10 of the SURMOUNT-1 Clinical Study Report and Table 4.1 of the applicant response to FDA IR dated September 25, 2023.

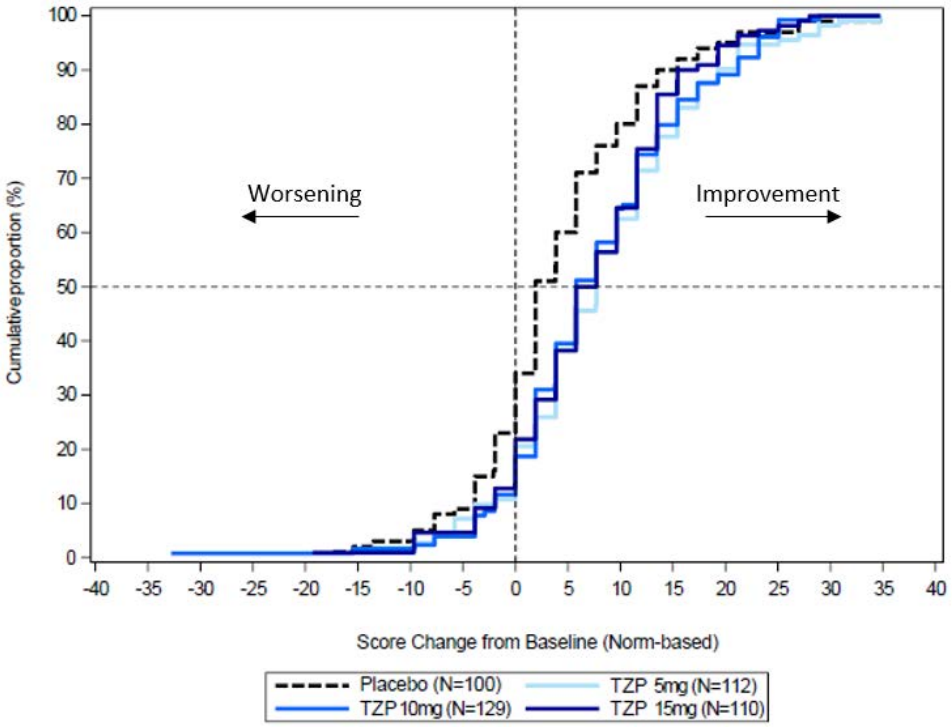
5.4.1 Interpretation of the Subgroup Efficacy Analysis Results

A definitive range of meaningful change in SF-36v2 Physical Functioning domain scores in the subgroup cannot be identified, given that no other appropriate anchor scales are available in the studies (refer to Section 5.6.6). As such, interpretation of the subgroup efficacy analysis results did not rely on the anchor-based analysis that uses the PGIS as an anchor. Instead, this section focuses on the eCDF plots for distributions of the change from baseline SF-36v2 Physical Functioning domain scores by treatment arms. Data from the IWQOL-Lite-CT Physical Function domain score were also examined to provide additional support to the interpretation of the SF-36v2 Physical Functioning domain score endpoint results.

Figure 3 and Figure 4 depict the distributions of the change from baseline in the SF-36v2 Physical Functioning domain score at Week 72 by treatment arm in Studies SURMOUNT-1 and SURMOUNT-2, respectively. Of note, the applicant's eCDF plots are slightly different presentations of a typical eCDF plot that represents the observed values and the corresponding cumulative percentages. The proportion of participants who experienced a meaningful change at a particular threshold should be interpreted as 100% minus the corresponding cumulative percentage on the curves. Specifically, when interpreting the cumulative proportion of participants reaching a specific threshold, the plot should be viewed from the top down.

From Figure 3 below, separations between treatment arms (TZP 10 mg and TZP 15 mg) and placebo arms in SURMOUNT-1 can be observed. Consistent patterns also are shown for the IWQOL-Lite-CT Physical Function domain score in participants who had impaired physical function at baseline, which further supports the treatment benefit on physical functioning (Figure 5).

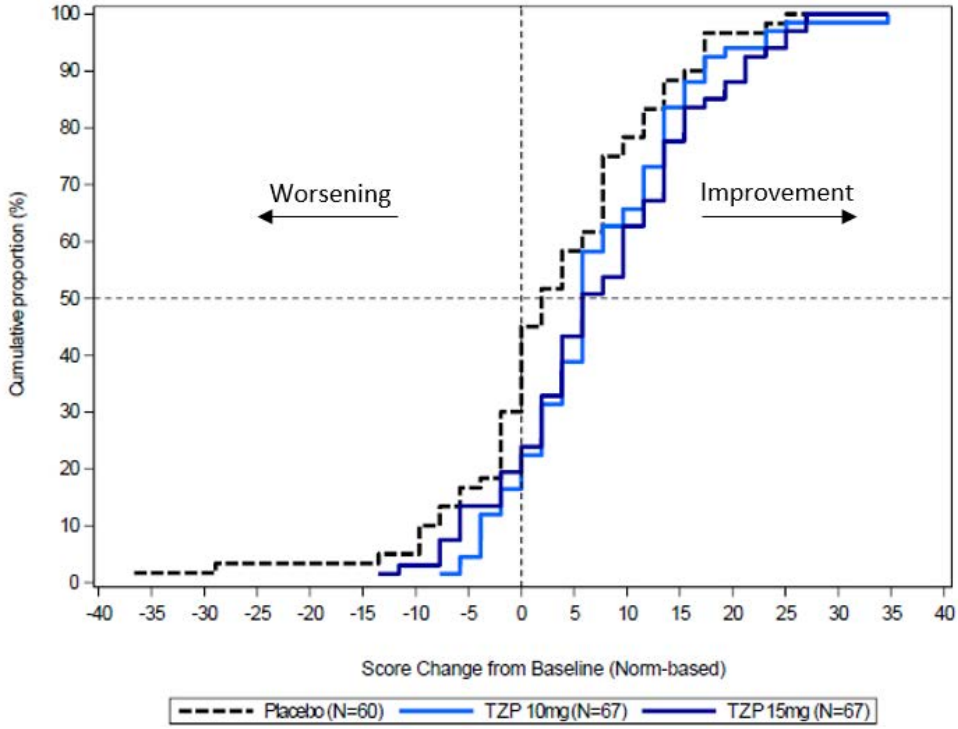
Figure 3. eCDF Curve for the Change from Baseline to Week 72 in SF-36v2 Physical Functioning Domain Score (Norm-based) in Participants Who Have Impaired Physical Function at Baseline; mITT Population – SURMOUNT-1 Full Analysis Set



Abbreviations: N = number of subjects in specified treatment group; mITT = modified intent-to-treat; SF-36v2 = short form survey-36 version 2; TZP = tirzepatide.
Note: Post-baseline values are derived from raw data.
50th percentile is marked with a dashed line on the y-axis and a reference value for no change is marked with a dashed line on the x-axis.
Source: Figure modified from Figure APP.1 of the applicant response to FDA IR dated September 25, 2023.

In SURMOUNT-2, separations between the TZP 15 mg and the placebo arms are also observed. However, the separation is not clear between the TZP 10 mg and placebo arms.

Figure 4. eCDF Curve for the Change from Baseline to Week 72 in SF-36v2 Physical Functioning Domain Score (Norm-based) in Participants Who Have Impaired Physical Function at Baseline; mITT Population – SURMOUNT-2 Full Analysis Set



Abbreviations: N = number of subjects in specified treatment group; mITT = modified intent-to-treat; SF-36v2 = short form survey-36 version 2; TZP = tirzepatide.
Note: Post-baseline values are derived from raw data.
50th percentile is marked with a dashed line on the y-axis and a reference value for no change is marked with a dashed line on the x-axis.
Source: Figure modified from Figure APP.3 of the applicant response to FDA IR dated September 25, 2023.

Reviewer's comment(s): *While a definitive range cannot be identified for the SF-36v2 Physical Functioning domain score, results from both the SF-36v2 Physical Functioning domain score and IWQOL-Lite-CT Physical Function domain score provide confidence that the observed treatment effect on physical functioning is likely to be clinically meaningful to participants in SURMOUNT-1.*

(b) (4)

(b) (4)

5.6 Clinical Outcome Assessment(s)

5.6.1 Clinical Outcome Assessment Description(s)

5.6.1.1 36-item Short Form Health Survey Version 2 (SF-36v2) Physical Functioning domain

The SF-36v2 Physical Functioning domain (Appendix A) is a 10-item domain within the SF-36 v2 Acute form, a 36-item generic PRO instrument designed to assess general health status. The Physical Functioning domain is designed to assess physical functioning. Each item in the domain is rated on a 3-point VRS ranging from 1 ("Yes, limited a lot") to 3 ("No, not limited at all"). The recall period is momentary (i.e., "now"). The SF-36v2 Physical Functioning domain was administered at Baseline and Week 72, or ED (early discontinuation of treatment).

Reviewer's comment(s): *The SF-36 v2.0 Physical Functioning domain measures the limitation of physical function as it pertains to a participant's health status rather than the specific disease of interest (i.e., obesity), which may make it difficult to interpret its data, as well as describe clinical benefit.*

5.6.2 Conceptual Framework(s)

The conceptual framework for the SF-36v2 Physical Functioning domain is shown in Table 6 (shown on next page).

Table 6. Conceptual Framework of the SF-36v2 Physical Functioning Domain

Items	Domain	General Concept
The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?	Physical Functioning	Physical functioning limitation severity
Item 3a: *Vigorous activities such as running, lifting heavy objects, participating in strenuous sports*		
Item 3b: *Moderate activities such as moving a table, pushing a vacuum, bowling, or playing golf*		
Item 3c: *Lifting or carrying groceries*		
Item 3d: *Climbing several flights of stairs*		
Item 3e: *Claiming 1 flight of stairs*		
Item 3f: *Bending, kneeling, or stooping*		
Item 3g: *Walking more than a mile*		
Item 3h: *Walking several hundred yards*		
Item 3i: *Walking one hundred yards*		
Item 3j: *Bathing or dressing yourself*		

Source: Reviewer's table.

5.6.3 Scoring Algorithm

5.6.3.1 SF-36v2 Physical Functioning domain

The raw scores for the SF-36v2 Physical Functioning domain ranges from 10 to 30 as possible responses values, with higher scores indicating better physical functioning. The SF-36v2 Physical Functioning domain is converted to a T-score metric (also referred to as norm-based scores (NBS)) based on data from the 2009 US general population, resulting in a scale with discrete numbers with increments of 1.93 as possible values, thus, an increment of 1.93 corresponds to an increment of 1 for the raw scores. Specifically, the domain is scored using the same mean (50) and the same standard deviation (10 points) found in the 2009 US general population. The NBS for SF-36v2 Physical Functioning domain score ranges from 19.03 to 57.60. Higher scores (within this range) indicate better physical functioning and lower scores indicate significant limitations in performing physical activities.

The norm-based score is calculated through the following steps:
1) Raw sum score is transformed to 0-100 scaled score through a linear transformation:
Transformed 0-100 scaled score = (Actual raw sum score – Lowest possible raw sum score) / Possible raw sum score range

2) The 0-100 scaled score is then transformed to a z-score by subtracting the mean of the 2009 US general population, and then dividing the standard deviation of the general population:
z-score = (0-100 scaled score – 80.29542) / 26.12419

3) The z-score is then converted to a norm-based T-score. To do so, the z-score is multiplied by 10, and then 50 is added to the resulting product:
Norm-based score = (z-score *10) + 50

In the presence of missing data at item level, item response theory (IRT) scores were calculated, with a minimum of two items with non-missing values required.

Reviewer's comment(s): *The applicant indicated that they used the QualityMetric Health Outcomes™ Scoring Software (PRO_CoRe V2.0) to derive the SF-36v2 Physical Functioning norm-based domain score. DCOA and PFSS had a teleconference with the applicant regarding details of the scoring algorithm and handling of missing data for SF-36v2 Physical Functioning domain on August 30, 2023. Refer to the teleconference memo dated September 19, 2023 for further details [DARRTS Reference ID: 5247198].*

5.6.4 Content Validity

The applicant completed the following instrument development activities to evaluate the content validity of the SF-36v2 Physical Functioning domain:

- Literature review
- Patient input (hybrid concept elicitation and cognitive interviews)

A summary of the results for each activity and instrument is described below. Refer to the PRO evidence dossier for full details regarding the methodology and results of each activity.

5.6.4.1 Literature review

The applicant conducted two literature reviews to inform the development of their PRO measurement strategy for the phase 3 clinical program. The objectives of the literature reviews were to:

- Identify all PRO measures used in previous studies of chronic weight management, and
- Conduct a gap analysis to evaluate the available evidence describing the measurement properties of the SF-36v2 and IWQOL-Lite-CT (results not included here) in chronic weight management.

The SF-36 (either the original version or v2) was identified in seven published research articles in chronic weight management and included in 10 phase 2, 3 or 4 clinical trials in chronic weight management.

The measurement properties of the SF-36v2 in chronic weight management were identified and described in four research articles. Refer to Table 1 in the PRO evidence dossier for a summary of the measurement properties.

After reviewing the available evidence from the literature, the applicant concluded that:

- A qualitative study was necessary to obtain insights into the experience of living with obesity or overweight (concept elicitation) and to cognitively debrief the SF-36v2 and to confirm the content validity of the SF-36v2 PF for use in individuals living with obesity or overweight without T2DM.
- Psychometric properties should be confirmed within a population of adults living with obesity or overweight, without T2DM, ideally either using quantitative data from phase 2 or a standalone quantitative study.

5.6.4.2 Hybrid concept elicitation and cognitive interviews

The applicant conducted concept elicitation and cognitive interviews to:

- Explore the impacts of obesity and investigate unmet treatment needs with a particular focus on physical functioning
- Develop a conceptual model to present the concepts of importance and relevance to the experience of obesity
- Evaluate the content validity of the SF-36v2 PF, and
- Determine qualitatively the amount of change on the SF-36v2 PF, at the item level, that is perceived as minimally important for individuals living with obesity or overweight.

Thirty-three adult participants were interviewed across three clinical sites in the US. All participants weighed over 163 lbs (mean: 241 lbs, range: 163-375 lbs). Participants were categorized into 1 of 3 subgroups based on their BMI and the presence of comorbidities.

- 12 individuals who were obese (BMI ≥30kg/m^2) without T2DM, and with ≥1 weight-related comorbidity
- 9 individuals who were obese (BMI ≥30kg/m^2) without T2DM, and without weight-related comorbidities
- 12 individuals who were obese or overweight (BMI ≥27 kg/m^2) with T2DM

The majority of the participants were male (n=17/33, 52%) with a mean age of 45, ranging from 19 to 81 years. Approximately a third of the participants were White (n= 12/33, 36%) and Black (n= 9/33, 27%) with at least a high school diploma (n= 14/33, 42%) or higher education (n= 16/33, 48%). Additionally, approximately a third of the participants had T2DM (n=12/33, 36%) and hypertension (n=11/33, 33%).

Reviewer's comment(s): *The qualitative sample was skewed towards educated participants, which may introduce bias.*

For the concept elicitation portion:

- All participants (n=33, 100%) reported that living with obesity or overweight had resulted in weight-related impacts on their physical functioning, including movements/mobility and activities of daily living.

- Movement and mobility concepts reported as difficult by >50% of participants included: running, bending, walking, standing for prolonged periods, lifting/carrying, and standing from a seated position. Subsequently impacts on activities of daily living included: climbing stairs, completing household chores and shopping.

- There were no notable differences in reporting of movement and mobility and activity of daily living impacts between participants who had a diagnosis of T2DM and those who did not. One concept ('Sports/Hobbies') was reported by participants (n=15/33, 45%) as being impacted more often by those with T2DM than those without T2DM (with diabetes: 67%; without diabetes: 33%).

- Regarding movement and mobility:

  - Thirty-one participants (94%) reported that running was difficult because of their weight.
  - Twenty-seven participants (82%) reported bending had become more difficult because of their weight.
  - Twenty-six participants (79%) reported that walking had become more difficult due to their weight.
  - Twenty-two participants (66%) described how their weight affected their ability to stand for prolonged periods of time, defined by interviewers as 20-30 minutes.
  - Nineteen participants (57%) reported that their weight had affected their ability to lift.
  - Seventeen participants (51%) reported that their ability to stand from a seated position had become more difficult because of their weight.

- Regarding activities of daily living:
  - Thirty participants (91%) reported experiencing difficulty climbing stairs due to their weight.
  - Twenty-one participants (64%) reported that their ability to complete household chores had been impacted by their weight.
  - Eighteen participants (55%) reported difficulty with shopping due to their weight.
  - Fifteen participants (45%) spontaneously described how sports and hobbies had been impacted by their weight.

- Being physically active was ranked in the top 3 by over half (n=16/21, 76%) of the participants as one of the most important activities/aspects that they would most like to improve with treatment. Further, it was ranked as the most important factor for 10 of these participants. Other highly ranked factors included: bending, kneeling, or stooping (n=9/21, 43%), walking for long distances (n=8/21, 38%), pain (n=6/21, 29%), climbing stairs (n=5/21, 24%) and being comfortable in small seats (n=5/21, 24%).

Reviewer's comment(s): *In general, the results of the concept elicitation portion supported and confirmed the relevance of impact of obesity or overweight on physical functioning in the target population. The applicant conducted a concept mapping exercise, and concluded that almost all of the physical functioning concepts reported during concept elicitation are assessed as part of the SF-36v2 Physical Functioning domain with the exception of four movement and mobility concepts: difficulty standing (reported by 67% of the sample), standing from a seated position (52%), unable to move quickly (27%), and getting up (24%). The SF-36v2 Physical Functioning domain appears to cover most of the important physical functioning concepts reported by participants, including concepts that reflect "being physically active."*

For the cognitive testing portion:

- The majority of the participants (n≥25/33, 75.8%) understood each item. Each item of the SF-36v2 Physical Functioning domain was understood by at least 75% of the sample (refer to Table 4 of the PRO evidence dossier).

- Few participants had difficulty impetrating the terms including “several hundred yards” (n=8/33, 24%), “vigorous” (n=4/33, 12%) and “one hundred yards” (n=4/33, 12%).

- The majority of the participants (n≥17/33, 51.5%) reported that they had currently or previously experienced difficulties with most activities (7 out of 10 items in the SF-36v2 Physical Functioning domain) and were impacted by their weight. Among the participants asked, few participants reported that climbing one flight of stairs (n=6/20, 30.0%), walking one hundred yards (n=7/19, 36.8%), and bathing or dressing (n=8/20, 40.0%) were impacted by their weight.

  Reviewer’s comment(s): *It is unclear whether the participants were currently experiencing difficulty with any physical activities at the time of the interview, as the results are summarized as participants that “had currently” or “previously experienced” difficulties with physical activities.*

  Refer to Figure 5 in the PRO evidence dossier regarding summary of the SF-36v2 Physical Functioning domain relevance across the three subgroups based on their BMI and the presence of comorbidities in the qualitative sample. The applicant stated that there were no substantial differences in item-relevance across individuals with and without T2DM, and therefore the results were presented for the total sample.

- Most of the participants (n=27/29, 93.1%) found the response scale appropriate. The majority of the participants (n=26/33, 78.8%) considered the recall period (momentary “now”) easy to interpret.

  Reviewer’s comment(s): *In the cognitive testing portion, the participants were also asked questions regarding meaningful weight reduction and perceptions of meaningful within-patient change on the SF-36v2 Physical Functioning domain. Refer to Section 5.6.6.2 of this review for a summary of those findings.*

5.6.5 Other Measurement Properties

The applicant evaluated the psychometric properties of the SF-36v2 Physical Functioning domain using data from the following studies:

- SURMOUNT-1 (n=2539)
- SURMOUNT-4 (n=782)

The analysis population for the SURMOUNT-1 study used to evaluate the measurement properties of the SF-36v2 Physical Functioning domain were predominantly White (70.6%) and female (67.5%) with a mean age of 44.9 years (range: 18.0-84.0 years), and from the US (44.9%). The mean weight and BMI at baseline was 104.78kg and 37.99kg/m² (range: 26.90 to 69.90 kg/m²)

The analysis population for SURMOUNT-4 study were predominantly White (80.3%) and female (69.8%) with a mean age of 47.6 years (range: 18.0 to 80.0 years) and from the US (65.1%). The mean weight and BMI was 106.97kg and 38.31 kg/m² (range: 27.00 to 85.80 kg/m²).

Reviewer's comment(s): *According to the submission, the analyses were conducted on the full analysis set (FAS) following SURMOUNT-1 primary database lock (14 April 2022). The FAS for SURMOUNT-1 study is defined in SURMOUNT-1 study protocol as all randomly assigned participants who are exposed to at least 1 dose of the study drug, regardless of adherence to the study drug. Data from SURMOUNT-4 (open-label phase interim data, Week 0 to Week 36) were used to evaluate the test-retest reliability only.*

This reviewer notes that the quantitative samples may not be sufficiently representative of individuals who are obese and/or overweight in the US.

A summary of the psychometric findings is provided below. For more details on the methodology and results of these analyses, refer to the Section 11 of the PRO evidence dossier.

5.6.5.1 Item-level descriptive statistics:

- The majority of the participants (n=2481/2539, 97.7%) completed all items at baseline and (n=2061/2212, 93.2%) at Week 72.

- The mean and standard deviation (SD) SF-36v2 Physical Functioning domain score was 49.51 (7.87) at baseline, and 52.98 (6.80) at Week 72. A quarter of the participants had the maximum possible score at Week 72 (third quartile [Q3]=57.59).

- More than half of the participants (≥50%) reported the response option "No, not limited at all" to 8 of the 10 items at baseline and all 10 items at Week 72.

  Reviewer's comment(s): *The distributions were skewed towards higher physical function at baseline and Week 72, and majority of the items showed a strong ceiling effect (i.e., participants endorsing the least severe response category). Both qualitative and quantitative data suggests that these items may not be experienced frequently, resulting in participants not sufficiently limited in physical functioning at baseline for an adequate assessment of improvement. Similar results were seen with the IWQOL-Lite-CT Physical Functioning domain.*

- The median change scores from baseline to Week 72 in the SF-36v2 Physical Functioning domain are shown in Table 7 and Table 8 (shown on the next page) for the SURMOUNT-1 and SURMOUNT-2 studies, respectively.

Table 7. Summary of Median SF-36v2 Physical Functioning Domain Score (Raw) at Item-level at Baseline, Week 72, and Change from Baseline in the Study SURMOUNT-1

	Placebo (n=643)			TZP 5mg (n=630)			TZP 10mg (n=636)			TZP 15mg (n=629)		
Items	Baseline	Week 72	Change from baseline	Baseline	Week 72	Change from baseline	Baseline	Week 72	Change from baseline	Baseline	Week 72	Change from baseline
Vigorous activities	2	2	0	2	3	0	2	3	0	2	3	0
Moderate activities	3	3	0	3	3	0	3	3	0	3	3	0
Lifting or carrying groceries	3	3	0	3	3	0	3	3	0	3	3	0
Climbing several flights of stairs	2	3	0	2	3	0	2	3	0	2	3	0
Claiming 1 flight of stairs	3	3	0	3	3	0	3	3	0	3	3	0
Bending, kneeling, or stooping	2	3	0	3	3	0	2	3	0	3	3	0
Walking more than a mile	3	3	0	3	3	0	3	3	0	3	3	0
Walking several hundred yards	3	3	0	3	3	0	3	3	0	3	3	0
Walking one hundred yards	3	3	0	3	3	0	3	3	0	3	3	0
Bathing or dressing yourself	3	3	0	3	3	0	3	3	0	3	3	0

Source: Reviewer's table.

Table 8. Summary of Median SF-36v2 Physical Functioning Domain Score (Raw) at Item-level at Baseline, Week 72, and Change from Baseline in the Study SURMOUNT-2

	Placebo (n=315)			TZP 10mg (n=312)			TZP 15mg (n=311)		
Items	Baseline	Week 72	Change from baseline	Baseline	Week 72	Change from baseline	Baseline	Week 72	Change from baseline
Vigorous activities	2	2	0	2	2	0	2	2	0
Moderate activities	3	3	0	3	3	0	3	3	0
Lifting or carrying groceries	3	3	0	3	3	0	3	3	0
Climbing several flights of stairs	2	3	0	2	3	0	2	3	0
Claiming 1 flight of stairs	3	3	0	3	3	0	3	3	0
Bending, kneeling, or stooping	2	3	0	2	3	0	3	3	0
Walking more than a mile	3	3	0	3	3	0	3	3	0
Walking several hundred yards	3	3	0	3	3	0	3	3	0
Walking one hundred yards	3	3	0	3	3	0	3	3	0
Bathing or dressing yourself	3	3	0	3	3	0	3	3	0

Source: Reviewer's table.

Reviewer's comment(s): *There is nearly no change from baseline by treatment and placebo at item level for the SF-36v2 Physical Functioning domain, as the majority of the participants reported a score of 3 ("No, not limited at all") or 2("No, limited a little"). Refer to the IR response received on September 1, 2023 for further details regarding the summary of descriptive statistics by treatments and visits from baseline to Week 72. The applicant did not provide item-level data by visits for the IWQOL-lite-CT Physical Functioning domain in the submission. As such, it is unknow whether similar results were seen with the IWQOL-Lite-CT Physical Functioning domain.*

- Item-to-item correlation coefficients between each pair of items of the SF-36v2 Physical Functioning domain ranged from 0.36 to 0.91. The Spearman's rank-order correlation coefficients between the items and item-corrected score (summing all other items) ranged from 0.35 to 0.71.

  Reviewer's comment(s): *Some of the item-to-item correlations appear high and show potential measurement redundancy. For example,*

Pair of items	***Item-to-item correlations***
3b. Moderate activities and 3c. Lifting or carrying groceries	*0.82*
3d. Climbing several flights of stairs and 3e. Climbing one flight of stairs	*0.86*
3g. Walking more than a mile and 3h. walking several hundred yards	*0.81*
3h. Walking several hundred yards and 3i. Walking one hundred yards	*0.91*

Source: Reviewer's table

The applicant did not conduct factor analysis to support the unidimensionality of the SF-36v2 Physical Functioning domain. On face, the items included in the total domain score are of similar concepts (i.e., physical functioning).

5.6.5.2 Reliability

- For assessment of internal consistency reliability, Cronbach's alpha was 0.89 (n=2517) at baseline.

- For assessment of test-retest reliability[6] using data from the SURMOUNT-4 study, the intra-class correlation coefficient (ICC) estimate for the analysis population (n=773) defined by weight between screening and baseline was 0.72. The ICC estimate for the analysis population (n= 418) defined by the PGIS response at screening and baseline was 0.76.

Reviewer's comment(s): *In general, the Cronbach's alpha and ICCs were within an acceptable and reasonable range for the analysis.*

5.6.5.3 Validity

- For assessment of construct validity, correlation analyses were conducted with clinical outcomes (BMI, weight) and patient-reported assessments (IWQOL-Lite-CT Physical Functioning domain).
    - Low correlation was observed between the SF-36v2 Physical Functioning domain and BMI at baseline (r= -0.31).
    - A negligible correlation ($\leq$0.3) was observed between the change in SF-36v2 Physical Functioning domain and the change in BMI (r= -0.26) and the change in weight from baseline (r= -0.27).
    - A moderate correlation (> 0.40 to 0.7) was observed between the SF-36v2 Physical Functioning domain score and the IWQOL-Lite CT Physical Function domain score (r= 0.67).
    - Moderate correlations were observed between the SF-36v2 Physical Functioning domain and other SF-36v2 domains and IWQOL-Lite-CT scores (e.g., SF-36v2

[6] Stable participants were defined according to weight reduction and the PGIS as two separate subsamples: (1) Participants with weight reduction ≤5% between screening and baseline and (2) Participants with the same PGIS item response at screening and baseline.

Vitality domain: r= 0.45; SF-36v2 Role-Physical domain: r= 0.59; IWQOL-Lite-CT Pain/Discomfort domain: r= 0.53) as hypothesized.

Reviewer's comment(s): *The following hypotheses were tested:*

- *SF-36v2 Physical Functioning domain scores were expected to show moderate to high correlations with BMI at baseline*
- *The change in SF-36v2 Physical Functioning domain scores were expected to show moderate to high correlations with weight reduction at Visit 21 (Week 72)*
- *The correlation between PRO scores assessing level of physical functioning (for example, the SF-36v2 Physical Functioning domain and the IWQOL-Lite-CT Physical Function domain score) were expected to show moderate to high correlations*
- *SF-36v2 Physical Functioning domain was expected to show moderate correlations with the SF-36v2 Vitality domain and Role-Physical domain scores*
- *SF-36v2 Physical Functioning domain was expected to show moderate correlations with the IWQOL-Lite-CT Pain/Discomfort score, and*
- *SF-36v2 Physical Functioning domain was expected to show low to moderate correlations with the IWQOL-Lite-CT Psychosocial score*

The relationship between physical functioning and BMI may need to be further explored. This reviewer notes that the applicant's submitted data does not show a strong relationship between physical functioning and BMI (or weight) across the studied range, and given the observed range restriction.

In general, the SF-36v2 Physical Functioning domain appears to have the expected relationship to assessments with similar and/or dissimilar concepts.

- For assessment of known groups validity,
  - The mean SF-36v2 Physical Functioning domain score observed across the baseline response categories of the PGIS (Much better, Better, A little better, The same, A little worse, Worse, Much worse) decreased with increasing severity (mean scores ranged from 53.1 to 38.6). The differences were statistically significant ($p < 0.0001$).
  - The mean SF-36v2 Physical Functioning domain score observed across BMI categories decreased with higher BMI categories (mean scores ranged from 52.6 to 46.6). The differences were statistically significant ($p < 0.0001$).

Reviewer's comment(s): *In general, the SF-36v2 Physical Functioning domain appears to be able to differentiate between clinically distinct groups.*

5.6.5.4 Responsiveness (ability to detect change)

- Medium-to-large improvement in the SF-36v2 Physical Functioning domain scores was observed for participants who reported improved ability to perform physical activities as measured by PGIS, with effect sizes (ES) in participants with 1- to 4-category improvement in PGIS ranging from 0.77 to 1.23.

- Small improvement in SF-36v2 Physical Functioning domain scores was observed for participants who did not report any change in PGIS (ES of 0.31 for the SF-36v2 Physical Functioning domain score).
- Small-to-medium worsening in SF-36v2 Physical Functioning domain scores was observed for participants with any worsening in the PGIS (ES ranging from -0.40 to -0.77).

Reviewer's comment(s): *The results for the 2-category worsening and 3 or 4-category worsening may be cautiously interpreted due to the small sample sizes associated with these categories (n = 39 and 20, respectively). Refer to Table 5.3.1 for summary of results in Appendix 6 in the PRO evidence dossier.*

In general, the SF-36v2 Physical Functioning domain appears to identify differences in scores over time in individuals or groups who have changed with respect to the concept.

5.6.6 Clinically Meaningful Within-Patient Score Changes

The applicant performed the following analyses to support the proposed threshold(s) for meaningful within-patient change in the SF-36v2 Physical Functioning domain score:

- Anchor-based analyses
- Qualitative methods (Cognitive interviews)

5.6.6.1 Anchor-based analyses

The applicant proposed to use the PGIS as an external anchor. The PGIS is a single item PRO instrument designed to assess the limitation of health on the ability to perform physical activity. It is rated on a 5-point VRS ranging from "Not at All Limited" to "Extremely Limited." The recall period is the previous 7 days ("past week"). The PGIS was administered at baseline and Week 72. See Appendix B for a copy of the PGIS.

Table 9 and Table 10 (shown on next page) describe the distributions of the PGIS at baseline and Week 72 for the SURMOUNT-1 and SURMOUNT-2 studies, separately. Overall, around half of the participants reported being "Not at all limited" to perform physical activities at baseline (i.e., 1100 out of 2181 participants in SURMOUNT-1 and 413 out of 855 participants in SURMOUNT-2), with no room for improvement during the studies. For participants who endorsed other PGIS response categories at baseline, most of them achieved "Not at all limited" at Week 72. Specifically, for participants who reported being "A little limited" to perform physical activities at baseline, most of the participants improved by one category at Week 72 (67.3% in SURMOUNT-1 and 54.4% in SURMOUNT-2). For participants who reported being "Moderately limited" to perform physical activities at baseline, more participants improved by two categories (53.5% in SURMOUNT-1 and 41.4% in SURMOUNT-2). For participants who reported being "Very much limited" to perform physical activities at baseline, more participants improved by three categories at Week 72 (52.6% in SURMOUNT-1 and 28.8% in SURMOUNT-2). Participants who reported being "Extremely limited" to perform physical activities are not discussed here due to small sample size.

Table 9. Cross-tabulation of PGIS at Baseline and Week 72; mITT Population – SURMOUNT-1 Full Analysis Set

PGIS at Baseline	PGIS at Week 72					
	Not at all limited	A little limited	Moderately limited	Very much limited	Extremely limited	Total
Not at all limited	936 (85.1)	120 (10.9)	27 (2.5)	15 (1.4)	2 (0.2)	1100
A little limited	424 (67.3)	150 (23.8)	45 (7.1)	8 (1.3)	3 (0.5)	630
Moderately limited	162 (53.5)	87 (28.7)	41 (13.5)	9 (3.0)	4 (1.3)	303
Very much limited	70 (52.6)	30 (22.6)	18 (13.5)	13 (9.8)	2 (1.5)	133
Extremely limited	5 (33.3)	5 (33.3)	2 (13.3)	2 (13.3)	1 (6.7)	15
Total	1597	392	133	47	12	2181

Source: Table modified from Table APP.11 of the applicant response to FDA IR dated August 11, 2023.
Abbreviation: PGIS = Patient Global Impression of Status for Physical Activity.

Table 10. Cross-tabulation of PGIS at Baseline and Week 72; mITT Population – SURMOUNT-2 Full Analysis Set

PGIS at Baseline	PGIS at Week 72					
	Not at all limited	A little limited	Moderately limited	Very much limited	Extremely limited	Total
Not at all limited	342 (82.8)	58 (14.0)	5 (1.2)	6 (1.5)	2 (0.5)	413
A little limited	135 (54.4)	83 (33.5)	22 (8.9)	6 (2.4)	2 (0.8)	248
Moderately limited	53 (41.4)	47 (36.7)	22 (17.2)	4 (3.1)	2 (1.6)	128
Very much limited	15 (28.8)	14 (26.9)	11 (21.2)	11 (21.2)	1 (1.9)	52
Extremely limited	5 (35.7)	3 (21.4)	2 (14.3)	3 (21.4)	1 (7.1)	14
Total	550	205	62	30	8	855

Source: Table modified from Table APP.12 of the applicant response to FDA IR dated August 11, 2023.
Abbreviation: PGIS = Patient Global Impression of Status for Physical Activity.

Reviewer's comment(s): *The distributions of the PGIS score at baseline and Week 72 indicate that around half of the enrolled participants in Studies SURMOUNT-1 and SURMOUNT-2 had no limitations in performing physical activities (i.e., physical functioning) at baseline. This reviewer is concerned that treatment effects on physical function cannot be detected as*

participants were not sufficiently limited in physical functioning at baseline. During the mid-cycle meeting dated August 3, 2023, the reviewers communicated this concern to Clinical and stated that a sufficiently impaired population should be used to demonstrate clinical benefit on a functional impact (e.g., physical functioning). Clinical showed interests in the treatment effect on the subgroup of participants with impaired physical function at baseline for both Studies SURMOUNT-1 and SURMOUNT-2. These subgroup analyses were included in the clinical study reports, but not adjusted for multiplicity. The reviewers then filed an IR on September 25, 2023 requesting additional analyses to aid in the interpretation of the subgroup analyses.

Of note, given that the PGIS scale was used to define the subgroup of participants who had impaired physical function at baseline, interpretation of the subgroup analysis results should ideally be based on a different anchor scale. However, no other anchor scales were available in the studies. As such, a definitive range of meaningful change in SF-36v2 Physical Functioning domain scores cannot be identified. See Section 5.4.1 of this review for more discussion.

5.6.6.2 Qualitative methods

The applicant conducted cognitive interviews (n=33) to obtain patient input to help inform the meaningful change of weight reduction and the SF-36v2 Physical Functioning domain score. The sample characteristics are summarized in Section 5.6.4 of this review.

To explore the concept of clinically meaningful weight reduction, participants in the qualitative interview study were introduced to thinking about percentages of their total body weight and the smallest percentage of weight that they would need to lose to notice an improvement in performing physical activities. The majority of participants (70%) reported that a 5% total body weight reduction would be noticeable; however, all participants (100%) noted that a 10% and 15% weight reduction would be noticeable.

Thirty-one participants were presented with SF-36v2 Physical Functioning item 3f (bending, kneeling, or stooping) and asked a series of questions to explore what was considered a meaningful change. A hypothetical approach was used in which participants were asked to imagine that they had selected “Yes, limited a lot” when answering the item and to consider this as their starting point. The results from this task are summarized as follows:

- Twenty-eight participants were asked what the smallest meaningful improvement would be to them. The majority of participants (n=26, 93%) considered a 1-point change to “A little limited” to be the smallest change to indicate a meaningful improvement when considering how their health limits their ability to perform physical activities. Two participants (7%) considered a 2-point change to ‘Not at all limited’ to be the smallest meaningful improvement to them.
- Twenty-eight participants were also asked about the smallest meaningful worsening changes. The most frequently reported worsening was a 1-point change to “Very much limited” (n=22, 79%). Six participants (21%) reported that a 2-point change to “Extremely limited” would be considered a meaningful worsening to them.

Refer to the Section 10.2.6.4 of the PRO evidence dossier for full details regarding the methodology and results of the cognitive interviews.

Reviewer's comment(s): *There are limitations to how the meaningful change was conducted. This reviewer has the following concerns:*

- *The applicant queried on the smallest meaningful improvement. From a regulatory standpoint, we are more interested in what constitutes a clinically meaningful within-patient change in scores versus the "smallest" meaningful within-patient change.*
- *The applicant did not query participants on every item of the SF-36v2 Physical Functioning domain. It is unknown whether a meaningful change in one item is applicable to other items. Further, the Item 3f is not generalizable to the other items.*
- *The applicant used a hypothetical approach. Using actual responses from COAs in the meaningful change exercises is a more ideal approach. However, the use of hypothetical responses is an acceptable option if actual responses are not available. This reviewer acknowledges that this was a standalone qualitative study and clinical trial responses were not feasible to use.*

On August 11, 2023, the Agency sent an IR requesting a rationale as to why the meaningful change exercises in the qualitative interviews focused only on Item 3f (bending, kneeling or stooping) of the SF-36v2 Physical Functioning domain. In the IR response received on August 25, 2023, the applicant stated that

> *"The Physical Functioning domain of the SF-36v2 includes a total of 10 items. Conducting the meaningful change exercise on all 10 items would have been overly burdensome to participants. Item 3f was selected because it is the most general item of the activities assessed by the Physical Functioning domain, as bending, kneeling, or stooping are actions involved in all other activities assessed by the domain."*

This reviewer does not find the results of the meaningful change task to be helpful to inform the meaningful change for the SF-36v2 Physical Functioning domain score.

6. APPENDICES

Appendix A: 36-item Short Form Health Survey Version 2 (SF-36v2) Physical Functioning domain

Appendix B: Anchor Scale Patient Global Impression of Status for Physical Activity (PGIS)

Appendix C: eCDF Plots for Change from Baseline to Week 72 in IWQOL-Lite-CT Physical Functioning domain score in participants who have impaired physical function at baseline (SURMOUNT-1 and SURMOUNT-2)

Appendix A: 36-item Short Form Health Survey Version 2 (SF-36v2) Physical Functioning domain

3. The following questions are about activities you might do during a typical day. Does <u>your health now limit you</u> in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	☐ 1	☐ 2	☐ 3
b Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐ 1	☐ 2	☐ 3
c Lifting or carrying groceries	☐ 1	☐ 2	☐ 3
d Climbing several flights of stairs	☐ 1	☐ 2	☐ 3
e Climbing one flight of stairs	☐ 1	☐ 2	☐ 3
f Bending, kneeling, or stooping	☐ 1	☐ 2	☐ 3
g Walking more than a mile	☐ 1	☐ 2	☐ 3
h Walking several hundred yards	☐ 1	☐ 2	☐ 3
i Walking one hundred yards	☐ 1	☐ 2	☐ 3
j Bathing or dressing yourself	☐ 1	☐ 2	☐ 3

Source: Appendix B within Appendix 5 from the PRO Evidence Dossier received on November 17, 2022 (SDN1).

Appendix B: Patient Global Impression of Status for Physical Activity (PGIS)

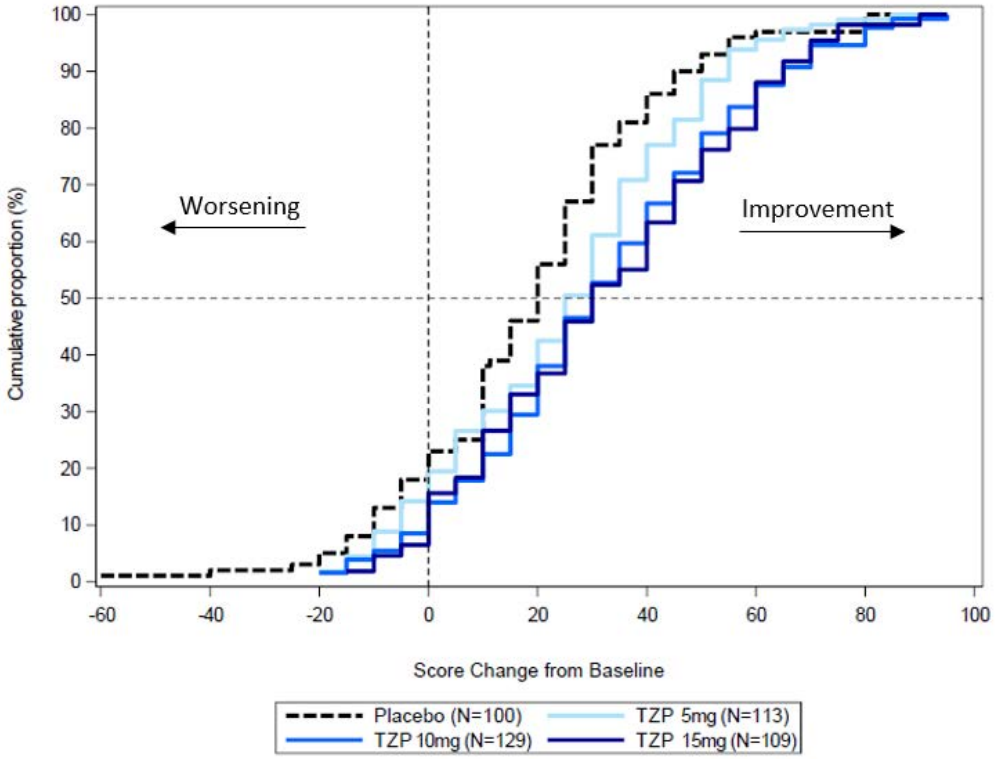
Please choose the response below that best describes overall how your health limited your ability to perform physical activities during the past week:

Not at all limited	A little limited	Moderately limited	Very much limited	Extremely limited

Source: Figure 13 within Appendix 5 from the PRO Evidence Dossier received on November 17, 2022 (SDN1).

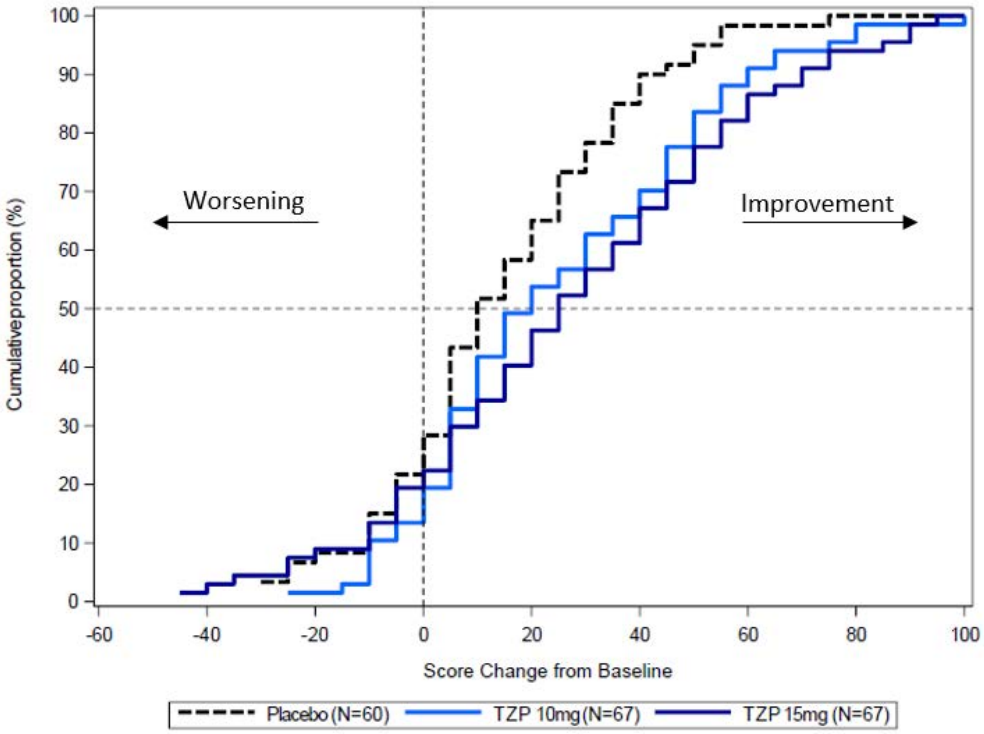
Appendix C: eCDF Plots for Change from Baseline to Week 72 in IWQOL-Lite-CT Physical Functioning domain score in participants who have impaired physical function at baseline (SURMOUNT-1 and SURMOUNT-2)

Figure 5. eCDF Curve for Change from Baseline to Week 72 in IWQOL-Lite-CT Physical Function Domain Score in Participants Who Have Impaired Physical Function at Baseline; mITT Population – SURMOUNT-1 Full Analysis Set



Abbreviations: N = number of subjects in specified treatment group; mITT = modified intent-to-treat; TZP = tirzepatide.
Note: Post-baseline values are derived from raw data.
50th percentile is marked with a dashed line on the y-axis and a reference value for no change is marked with a dashed line on the x-axis.
Source: Figure modified from Figure APP.2 of the applicant response to FDA IR dated September 25, 2023.

Figure 6. eCDF Curve for Change from Baseline to Week 72 in IWQOL-Lite-CT Physical Function Domain Score in Participants Who Have Impaired Physical Function at Baseline; mITT Population – SURMOUNT-2 Full Analysis Set



Abbreviations: N = number of subjects in specified treatment group; mITT = modified intent-to-treat; TZP = tirzepatide.
Note: Post-baseline values are derived from raw data.
50th percentile is marked with a dashed line on the y-axis and a reference value for no change is marked with a dashed line on the x-axis.
Source: Figure modified from Figure APP.4 of the applicant response to FDA IR dated September 25, 2023.

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/

QING XIE
10/17/2023 07:39:10 PM

XIN YUAN
10/18/2023 09:14:08 AM

SELENA R DANIELS
10/18/2023 10:05:42 AM

LILI GARRARD
10/18/2023 10:07:59 AM

DAVID S REASNER
10/18/2023 10:50:32 AM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	October 17, 2023
To:	Arati Kamath, PhD Regulatory Project Manager **Division of Diabetes, Lipid Disorders, and Obesity (DDLO)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Marcia Williams, PhD Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Kelly Jackson, PharmD Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Ankur Kalola, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG) and Instructions for Use (IFU)
Drug Name (established name):	ZEPBOUND (tirzepatide)
Dosage Form and Route:	injection, for subcutaneous use
Application Type/Number:	NDA 217806
Applicant:	Eli Lilly and Company

1 INTRODUCTION

2 On November 17, 2022, Eli Lilly and Company submitted for the Agency's review a New Drug Application (NDA) 217806 under Section 505(b) for ZEPBOUND (tirzepatide). The proposed indication is an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adult patients with an initial body mass index (BMI) of 30 kg/m2 or greater (obesity), or 27 kg/m2 or greater (overweight) in the presence of at least one weight-related comorbid condition (e.g., hypertension, dyslipidemia, obstructive sleep apnea, cardiovascular disease, or type 2 diabetes). ZEPBOUND (tirzepatide) for chronic weight management has been granted a Fast Track Designation. Tirzepatide was previously approved under the tradename MOUNJARO as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (13 May 2022, NDA 215866).

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Diabetes, Lipid Disorders and Obesity (DDLO) on March 12, 2023, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) and Instructions for Use (IFU) for ZEPBOUND (tirzepatide) injection, for subcutaneous use.

3 MATERIAL REVIEWED

- Draft ZEPBOUND (tirzepatide) MG and IFU received on November 17, 2022, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on October 4, 2023.
- Draft ZEPBOUND (tirzepatide) Prescribing Information (PI) received on November 17, 2022, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on October 4, 2023.

4 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the MG and IFU the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the MG and IFU document using the Arial font, size 10.

In our collaborative review of the MG and IFU we:

- simplified wording and clarified concepts where possible
- ensured that the MG and IFU is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG and IFU is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG and IFU meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

5 CONCLUSIONS

The MG and IFU are acceptable with our recommended changes.

6 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG and IFU is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG and IFU.

Please let us know if you have any questions.

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/s/

KELLY D JACKSON
10/17/2023 09:36:03 AM

ANKUR S KALOLA
10/17/2023 09:40:27 AM

MARCIA B WILLIAMS
10/17/2023 09:48:30 AM

LASHAWN M GRIFFITHS
10/17/2023 09:51:06 AM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: October 16, 2023

To: Arati Kamath, Regulatory Project Manager, Division of Diabetes, Lipid Disorders, and Obesity (DDLO)

Melinda Wilson, Associate Director for Labeling, DDLO

From: Ankur Kalola, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Sapna Shah, Team Leader, OPDP

Subject: OPDP Labeling Comments for ZEPBOUND™ (tirzepatide) Injection, for subcutaneous use

NDA: 217806

Background:
In response to DDLO's consult request dated March 12, 2023, OPDP has reviewed the proposed Prescribing Information (PI), Medication Guide, Instructions for Use, and carton and container labeling for the original NDA submission for Zepbound.

PI/Medication Guide/IFU:
OPDP's review of the proposed PI is based on the draft labeling accessed from SharePoint on October 16, 2023, and our comments are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed for the proposed Medication Guide and IFU, and comments will be sent under separate cover.

Carton and Container Labeling:
OPDP's review of the proposed carton and container labeling is based on the draft labeling accessed from SharePoint on October 5, 2023, and we do not have any comments at this time.

Thank you for your consult. If you have any questions, please contact Ankur Kalola at 301-796-4530 or Ankur.Kalola@fda.hhs.gov.

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/s/

ANKUR S KALOLA
10/16/2023 01:45:44 PM

Immunogenicity Review Memo
Office of Biotechnology Products

NDA Number:	217806
Sequence/SDN number:	0001/1, 11/17/2022
Product Name	TIRZEPATIDE (LY3298176)
Proposed Proprietary Name	ZEPBOUND™
Pharmacologic Class	TIRZEPATIDE is a dual glucose-dependent insulinotropic polypeptide (GIP) receptor and glucagon-like peptide-1 (GLP-1) receptor agonist.
Proposed Indication(s)	Chronic Weight Management in patients with obesity, or with overweight and comorbidities.
Route of Administration	Subcutaneous injection
Sponsor	Eli Lilly and Co.
Requested Division/Office	OND/ORO/DRO-CHEN/Division of Diabetes, Lipid Disorders, and Obesity (DDLO)
Fast track designation	10/03/2022
Regulatory Project Manager	Arati B. Kamath, Ph.D., DDLO
Received Date	05/09/2023
Desired Completion Date	10/06/2023 Primary, 10/10/2023 Secondary
Primary Assessor(s)	Faruk Sheikh, Ph.D., Chemist, OBP, DBRR-II, CDER
Secondary Assessor (s)	Harold Dickensheets, Ph.D., Lab Chief, OBP, DBRR-II, CDER
PDUFA Date	11/08/2023
Mid-Cycle meeting	08/03/2023
Recommended Regulatory Action	The immunogenicity assessment data submitted in support of the immunogenicity of NDA 217806 suggest that ZEPBOUND (tirzapatide) is highly immunogenic. Using a tiered system of appropriately validated immunogenicity assays, it was determined that approximately 64.5% of Chronic Weight Management (CWM) trial subjects treated with tirzepatide during the 72-week treatment period in two clinical studies (SURMOUNT-1 and SURMOUNT-2) developed treatment emergent ADAs. Of these ADA-positive (ADA+) patients, 40% and 16.5% demonstrated ADAs cross-reactive to native GIP and native GLP-1, respectively. About 2.8% and 2.7% ADA+ patients were tested positive for neutralizing antibody (NAb) against tirzepatide activity on the GIP and GLP-1 receptors, respectively. In addition, 0.8% and 0.1% of the overall ADA+ population were classified as cross-reactive NAb-positive against native GIP and GLP 1, respectively. The ADA titers in ADA+ patients ranged from 1:20 to 1:20480 (median: 1:320). and 5.0% ADA+ participants had ADA titers ≥1:5120. The clinical significance of the high ADA titer is unclear, and no safety or efficacy concern(s) were correlated with ADA development in patients from current clinical studies under this NDA. I recommend approval of this product from immunogenicity perspective.

TABLE OF CONTENTS

1. Executive Summary:

Eli Lilly submitted this New Drug Application (NDA) on November 17, 2022, for Tirzepatide (manufacturer code LY3298176) as NDA 217806 for chronic weight management (CWM) in adult patients with an initial body mass index (BMI) of 30 kg/m2 or greater (obesity), or 27 kg/m2 or greater (overweight) in the presence of at least one weight-related comorbid condition (e.g., hypertension, dyslipidemia, obstructive sleep apnea, cardiovascular disease, or type 2 diabetes). On October 03, 2022, FDA granted a Fast-Track Designation for investigation of Tirzepatide (TZP) as a CWM treatment in adults with obesity, or overweight with weight-related comorbidities.

TZP development for CWM has been conducted under IND 139721. This application relies on the trial results from two Phase 3 studies SURMOUNT-1 and SURMOUNT-2 including eight SURPASS studies (see Table 1 below) conducted under IND 139721 that provide support of effectiveness for TZP as a CWM treatment in adults with obesity, or overweight with weight-related comorbidities with type 2 diabetes mellitus (T2DM).

The applicant performed an analysis of risk factors that may contribute to TZP immunogenicity. It is important to note that the submission states that the proposed commercial US presentation TZP single-dose pen as used in Phase 3 CWM clinical development program (except for SURPASS-4 study) is the same as approved for the T2DM indication (Section 2.5.2 – Overview of Biopharmaceutics). Applicant's risk assessment discussed in the Integrated Summary of Immunogenicity (ISI) in Section 5.3.5.3 included evaluation of various factors that may be contributory to TZP's potential immunogenicity. These factors included TZP's intrinsic immunogenic potential as a peptide, various Quality parameters (purity of starting materials, stability/impurities, formulation and packaging, and changes in manufacturing, as evaluated by the Quality team), and the Clinical parameter Conditions of Use (TZP is administered once weekly in the abdomen, thigh, or upper arm by subcutaneous (SC) route). This SC administration route is known to be associated with an enhanced immune response, therefore, samples for monitoring the anti-drug antibody (ADA) status were scheduled during the respective Phase 3 trials supporting this application.

To support the understanding of TZP immunogenicity of this application, the applicant used a multi-tiered immunogenicity assessment strategy to assess and characterize the ADA to TZP in patients from ten Phase 3 CWM studies (see Table 1). These immunogenicity assays were validated previously under NDA 215866 for patients with T2DM who received the same drug product, TZP (DARRTS Reference ID: 4451422, 06/24/2019; 4858440, 9/16/2021).

The Sponsor determined new assay cut points (CP) for all immunogenicity assays using pre-dose serum samples from CWM subjects and same validated methods. The applicability of using previously validated cut points in T2DM subjects was then evaluated against the newly determined CPs for CWM subjects. This analysis supports the appropriateness of the use of T2DM CPs in analyzing clinical immunogenicity samples from CWM studies under NDA 217806.

The ADA incidence determined using the T2DM ADA assay CP, during the planned treatment period in SURMOUNT-1 (I8F-MC-GPHK) study that showed that out of a total of 1858 TZP-treated patients who had evaluable sample, 1226 participants (66.0%) were treatment emergent (TE) ADA+, while in SURMOUNT-2 (I8F-MC-GPHL) studies, out of a total of 609 TZP-treated patients who had evaluable sample, 365 participants (59.9%) patients were TE ADA+. The clinical significance of this difference in ADA incidence between SURMOUNT-1 (obese without T2DM subjects) and SURMOUNT-2 (Obese with T2DM subjects) is unclear and discussed internally with clinical team during product labeling meeting. The team did not find any difference clinically. Therefore, together, during the 72-week treatment period with ADA sampling in the CWM studies from two Phase 3 clinical Studies SURMOUNT-1 and SURMOUNT-2, 64.5% (1591/2467) of TZP-treated patients developed anti-TZP antibodies during the planned treatment period.

A total of 6206 TZP-treated participants were tested from eight Phase 3 SURPASS studies for TE ADA in the planned treatment period. Of 6206 participants, 3320 (56.4%) were TE ADA+ (source: ISI Table ISI.8.4). The rate of incidence of ADA development is lower than that from SURMOUNT studies (64.5% versus 56.4%) presumably due to difference in length of treatment period. The treatment period for SURMOUNT studies are 72-weeks while most SURPASS studies are 40-weeks or 52-weeks long. Nevertheless, the incidence of ADA development to TZP treatment is very high in all studies and the ADA development was dose dependent.

In SURMOUNT-1 and SURMOUNT-2 trials, 985 of 2444 (40.3%) and 404 of 2444 participants (16.5%) who developed antibodies to TZP of ZEPBOUND-treated patients showed cross-reactivity to native glucose-dependent insulinotropic polypeptide (GIP) or native glucagon-like peptide-1 (GLP-1), respectively. About 35.9% (2115 of 5888), and 14.5% (851 of 5888) who developed antibodies to TZP of ZEPBOUND-treated patients in SURPASS studies showed cross-reactivity to native GIP (nGIP) or native GLP-1 (nGLP-1), respectively.

Among the TE ADA evaluable population, 2.8% (68 of 2444) and 2.7% (65 of 2444) of the ZEPBOUND-treated patients in SURMOUNT-1 and SURMOUNT-2 clinical Studies, had NAb against TZP activity on the GIP receptor (GIPR) and GLP-1 receptor (GLP-1R), respectively, and 0.8% (20 of 2444) and 0.1% (2 of 2444) had cross-reactive NAb against nGIP and nGLP-1, respectively. While 2.2% (128 of 5888) SURPASS participants were NAb+ against TZP activity on GIPR, while 2.4% (144 of 5888) participants were NAb+ against TZP activity on GLP-1R suggesting the neutralizing ability of the antibodies developed against TZP at corresponding receptors for GIP and GLP-1 is low and similar. In comparison to SURMOUNT studies, SURPASS studies had similar levels of cross-reactive NAb against nGIP and nGLP-1. About 0.8% (49 of 5888) participants were positive for cross-reactive NAb against nGIP in SURPASS studies, while 0.3% (17 of 5888) participants were positive for cross-reactive NAb against nGLP-1.

The ADA titers in TZP-treated TE ADA+ participants from the SURMOUNT-1 and SURMOUNT-2 study ranged from 1:20 to 1:20480 during the planned treatment period (median: 1:160). The ADA titers in TZP-treated TE ADA+ participants from the SURPASS studies, on the other hand ranged from 1:20 to 1:81920 (median 1:160) during the planned treatment period.

Of 1591, 79 (4.9%) TE ADA+ participants from SURMOUNT studies showed maximum ADA titers ≥1:5120, whereas 137 of 3484 (3.9%) TE ADA+ participants from SURPASS studies showed maximum ADA titers ≥1:5120, suggesting that the profiles of developing the ADA titers ≥1:5120, is somewhat higher in SURMOUNT studies (4.9% to 3.9% for SURMOUNT and SURPLUSS studies respectively). However, the median ADA titer is 1:160 across all Phase 3 studies. The clinical significance of the high ADA titer is unclear but high titer ADAs may potentially impact on the pharmacokinetics or effectiveness of ZEPBOUND, although as stated above, no discernible impact of ADA on clinical effectiveness or pharmacokinetics was noted by the relevant discipline assessors.

Table 1: Phase 3 Clinical Studies (recreated by the assessor from the ISI submission)

Immunogenicity Assays	Cut Points Implemented	Phase 3 Clinical Studies
Tier 1 (ADA Screening Assay) Tier 2a (ADA Confirmatory Assay) Tier 2b (Cross-reactivity for $nGIP_{1-42}$) Tier 2c (Cross-reactivity for $nGLP\text{-}1_{7-36}$) Tier 3 (ADA Titering Assay) Tier 4a (NAb Assay at GIPR) Tier 4b (NAb Assay at GLP-1R) nGIPR = native GIP Receptor	DSCP	18F-MC-GPHK (GPHK; SURMOUNT-1) in participants without diabetes who had obesity (BMI ≥ 30 kg/m^2), or overweight (BMI ≥ 27 kg/m^2) with at least 1 weight-related comorbidity (N=1896 on TZP)
		I8F-MC-GPHL (GPHL; SURMOUNT-2) in participants with diabetes who had obesity

nGLP-1R = native GLP-1 Receptor NAb = Neutralizing Antibody	DSCP=Disease Specific Cut Point	or overweight and T2DM (N = 623 on TZP).
		Following 8 SURPASS studies in participants with T2DM (N=4430 on TZP with baseline BMI ≥ 27 kg/m^2). 18F-MC-GPGK (GPGK; SURPASS-1) 18F-MC-GPGL (GPGL; SURPASS-2) 18F-MC-GPGH (GPGH; SURPASS-3) 18F-MC-GPGM (GPGM; SURPASS-4) 18F-MC-GPGI (GPGI; SURPASS-5) 18F-JE-GPGP (GPGP; SURPASS-J combo) 18F-JE-GPGO (GPGO; SURPASS-J mono) 18F-MC-GPHO (GPHO; SURPASS-AP-Combo)

With this information about the development and characterization of antibodies to TZP in CWM studies, I recommend approval of this product from immunogenicity perspective.

2. Introduction and Background

Tirzepatide is a 39-amino acid synthetic peptide (alternative name LY3298176) derived from glucose-dependent insulinotropic polypeptide (GIP) peptide sequence. TZP includes a C20 fatty diacid moiety via a linker connected to the lysine residue at position 20 (Figure S.1.2-1) for prolonged duration of action, allowing for once-weekly subcutaneous administration. Residues 2 and 13 consist of a non-human amino acid, aminoisobutyric acid.

This peptide has agonist activities of both the GIP and glucagon-like peptide-1 (GLP-1) native endogenous peptides. Both peptides are gut hormones that act to potentiate insulin secretion from the pancreas in a glucose-dependent manner. Native GIP (nGIP) acts through binding to its cognate receptor, GIP receptor (GIPR), whereas native GLP-1 (nGLP-1) acts through binding to the GLP-1 receptor (GLP-1R) on pancreatic beta cells, resulting in an increased insulin secretion in a glucose-dependent manner. The TZP peptide was engineered from the nGIP sequence as an agonist for both receptors, to aid in maintenance of post-prandial blood glucose levels.

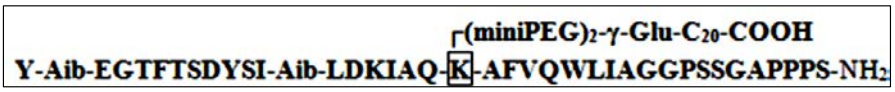

Figure S.1.2-1 Amino acid sequence of TZP with the Standard Single Letter Amino Acid Code and its structure. Aib =Aminoisobutyric Acid (Source: LY3298176 – S.1.2 Structure - v001)

3. Tiered system of Immunogenicity Assays

To characterize the potential immune response of TZP in humans, Lilly used a multi-tiered immunogenicity testing strategy (summarized in Figure ISI.6.1, Section 5.3.5.3). A ligand-binding method was used for several assays, including those to screen (Tier 1), confirm (Tier 2a), and titer (Tier 3) ADA, and to assess cross-reactive binding of ADA against nGIP (Tier 2b)

or nGLP-1 (Tier 2c) peptides. Two separate cell-based assays have been developed to test confirmed positive ADA for TZP-neutralizing antibody (NAb) activity (GIP receptor NAb assays for TZP, and GLP-1 receptor NAb assays for TZP), and in-silico classification methods are used to define cross-reactive NAb against nGIP and nGLP-1.

To screen for ADAs to TZP in serum samples from clinical studies, the sponsor used an ACE-ELISA (Affinity Capture and Elution - enzyme-linked immunosorbent assay) ligand-binding method. In this method, serum samples potentially containing ADAs and TZP were incubated on an ELISA plate coated with a mixture of N- and C-terminal biotin-labeled TZP analogs to capture anti- TZP antibodies (front-end). Free TZP drug peptides were washed away, ADAs were eluted off the plate by acid treatment (back-end), and then samples were pH-neutralized on a second ELISA plate, where ADAs were allowed to bind. The bound ADAs were detected by MSD method using a mixture of labeled TZP.

The ADAs were further characterized in cell-based assays detecting NAb against TZP activity on the GIPR and GLP-1R using same assay principle in reporter cells expressing GIPR and GLP-1R, respectively.

4. Binding Antibody Assays (BAA)

4.1 BAA- Global Study Participants Outside of China

The ADA assays used to analyze clinical immunogenicity samples in this study were fully validated using serum samples from healthy individual as well as from subjects with T2DM under Phase 3 studies for the approved NDA 215866 for TZP. The cut-points to be used in analyzing the clinical samples under the current NDA 217806, were verified using serum samples from a Phase 3 study 18F-MC-GPHK (GPHK; SURMOUNT-1) under this NDA. These subjects were obese but without diabetes. The results are discussed below in Table ISI.6.3 (from submission).

Table ISI.6.3. Immunogenicity Assay Validation Parameters (Tiers 1, 2a, 2b, 2c, and 3) – BAA

Source of Documents: (b) (4)-15-061-360, Amendment 1, 2, 3; Addendum 1, 2, 3 and 4, and (b) (4)-21-061-1206 and DARRTS Reference ID: 4938651 DARRTS Reference ID: 4858440		
Assay Parameter	Results	Comments
Assay Principle	Affinity Capture and Elution (ACE) Bridge ECL immunoassay.	*This assay was developed and validated previously under IND 1228801 for TZP, reviewed by OBP reviewer and accepted to use in analyzing clinical immunogenicity samples in support of NDA 215866 (DARRTS: 4938651 and 4858440).*
Positive Control Material	affinity purified (AP) Anti-LY3298176 Antibody generated from	*In house*

	hyperimmune monkey, AP-HIMS	
Positive control samples	LPC = 1:102400; MPC = 1:6400 and HPC = 1:1200, prepared in NHS Pool.	*PC samples were selected appropriately (DARRTS Reference IDs: 4938651 and 4858440).*
MRD	1:10	*During assay development and validation, the Sponsor evaluated 1:2, 1:5, 1:10, 1:20, 1:40, and 1:80 MRD, and selected an MRD of 1:10 that provides minimal serum interference relative to buffer.*
Screening Cut Point Factor (Tier 1)	Floating cut point T2DM/Obesity: 1.22/1.35 Note: The assay was run by 5 analysts, 1-3 runs/analyst, 4 plates/run, and 2 technical replicates per plate. CP was determined based on pre-dose serum samples from 177 of 200 patients analyzed from Phase 3 study 18F-MC-GPHK with an additional 2,496 baseline patient samples, after removal of outliers using non-parametric approach.	*The obese CP was estimated to be 1.30 by the Sponsor using a non-parametric approach at 5% false positive rate (FPR) with 90% confidence (histogram provided in Figure 6). Division of Biometrics, OB was consulted for verification of the CP determined in samples from CWM studies (DARRTS Ref: 5183722). The CMC statistical reviewers evaluated the DSCP (DARRTS Ref: 5257062; 10/10/2023), using tolerance interval-based method considering random effects on samples and analysts and determined the screening CP to be 1.35. The method applied by the CMC statistical reviewer and the Sponsor is different. How this difference impact on CP determination is not understood. The Sponsor chose to use T2DM CP 1.22 to analyze clinical samples from CWM studies. Since among the screening cut points generated by the Sponsor using T2DM (CP=1.22), obesity (CP=1.30) and the CMC statistical reviewer (CP=1.35), T2DM CP is more conservative approach, the use of T2DM CP is acceptable.*
Confirmation Cut Point (Tier 2a)	T2DM/Obesity: 30.4%/28.8% Note: CP was determined based on pre-dose serum samples from 177 of 200 patients analyzed from Phase 3 study 18F-MC-GPHK, after removal of outliers using parametric approach.	*For obesity subjects, Tier 2a CP was determined to be 28.8%, after removal of outliers (Appendix C, (b) (4) 21-061-1206; Page 63). The CP could not be verified from the submission since the Sponsor did not identify the samples that were excluded from CP analysis. An information request (IR) was sent on 04 April 2023 for these data for each of the Tier 1, 2a, 2b, 2c, 4a and 4b immunogenicity assay to verify the CPs determined by the Sponsor.* *The Sponsor submitted these data on 21 April 2023. Using these data, the assessor calculated the CCP for the CWM subjects based on 1% FPR, using mean+2.326SD (2.326 for 99th percentile), where mean was 9.3 and SD= 8.3632. The CCP was calculated to be 28.7097, equivalent to 28.8,*

		thereby confirming the CCP determined by the Sponsor to be acceptable. *The Sponsor compared the CWM CCP 28.8% and T2DM CCP 30.4%, and determined that the cut-points were not statistically different by bootstrap test of equivalence (p>0.05, Appendix C, Figures 1-4, Figures 1-5, Pages 54-56, (b) (4) -21-061-1206). Therefore, the Sponsor chose to use T2DM CCP 30.4% to analyze samples from CWM studies. Additionally, manual inspection of the nominal data suggests the false-positive rate was 0.5% when 30.4% CP was used, supporting the suitability of the assay. Since no difference was found between T2DM and CWM CP, for consistency, use of the T2DM CP is acceptable.*
Cross-Reactivity Cut Point (nGIP (1-42)) -Tier 2b	T2DM/Obesity: 14.5%/24% Note: CP was determined based on pre-dose serum samples from 181 of 200 patients analyzed from Phase 3 study 18F-MC-GPHK, after removal of outliers using parametric approach.	*The obesity cut point for Tier 2b nGIP inhibition assay was calculated to 24%, which was determined to be statistically different from previously validated T2DM DSCP 14.5% (p<0.05, Figures 1-5, Pages 64- 67, (b) (4) 21-061-1206).* *The Obesity CP of 24% was verified by the Office of Biostatistics' consult assessor using the individual data submitted in response to an IR on 02 June 2023 (DARRTS Ref: 5183722) and determined to be 21.6% using a two-way REM method. The Sponsor used a different conception for the data analysis for CP determination. Nevertheless, the Sponsor chose to use previously validated T2DM DSCP 14.5% as Tier2b CP to analyze clinical samples from CWM studies, which is more conservative approach, therefore, acceptable.*
Cross-reactivity Cut Point (nGLP-1 (7-36) -Tier 2c)	T2DM/Obesity: 18.1%/19.7% (CP was determined based pre-dose serum samples from 184 of 200 patients analyzed from Phase 3 study 18F-MC-GPHK, after removal of outliers using parametric approach.)	*The obesity cut point for Tier 2c nGLP-1 inhibition assay was calculated to be 19.7%, which was not found to be statistically significantly different from the T2DM DSCP of 18.1% (p>0.05, Figures 1-5, Pages 74-75, (b) (4) 21-061-1206). Therefore, the Sponsor chose to use T2DM CP to analyze CWM samples.* *The CMC statistician (Office of Biostatistics) evaluated the data in response to OBP consult (DARRTS Ref: 5183722) and determined the CP for Tier 2c to be 19.2% by using by two-way REM method (DARRTS Ref: 5257062; 10/10/2023), which is similar*

		to CWM CP of 19.7%. Given that the Sponsor used a different statistical method [independent and identically distributed (IID)], and use of T2DM DSCP 18.1% is being more conservative approach, the use of T2DM DSCP is acceptable for this study.
Titration Cut Point (TCP) (Tier 3)	T2DM/Obesity: 1.42	*The screening TCP for the samples from T2DM and obesity subjects from CWM studies are determined appropriately to be same. Acceptable.*
Assay Sensitivity	2.8 ng/mL	*The Sponsor showed that the T2DM DSCP that was established previously is applicable for analyzing samples from CWM studies. Therefore, the associated assay sensitivity and drug tolerance reestablishments are not needed (DARRTS Reference IDs: 4938651 and 4858440).*
Drug Tolerance	≥250 µg/mL TZP at 100 ng/mL of ADA	
Serum Factor Interference	No interference (±30% from reference) seen up to 10 mg/mL lipid 80 µg/mL bilirubin 2 mg/mL hemoglobin	*The Sponsor demonstrated the serum factor interference previously during the validation of immunogenicity assays under IND128881 for TZP. Since no significant difference was observed between T2DM and CWM CPs and sponsor proposes use of T2DM CP in analyzing clinical samples from CWM subjects, the reestablishments of the serum sample interference are not needed.*
Assessor Conclusion: The applicant determined ADA assay cut-points (Tiers 1, 2a, 2b and 2c) using baseline serum samples from obese subjects from Phase 3 CWM Study 18F-MC-GPHK and compared with the corresponding validated cut points previously determined using pre-dose clinical samples from T2DM subjects. Based on the statistical comparison data, the Sponsor plans to use T2DM cut points for Tiers 1, 2a, 2b and 2c including titering assay (Tier 3). The use of the validated cut-points from T2DM appears adequately justified and acceptable to analyze clinical samples from Phase3 CWM studies.		

4.2 BAA- China Study Participants

In support of clinical trials with sites located within China, the same ACE assay was transferred from Lilly to (b) (4) to enable analysis of clinical trial samples from patients in China. Only Tiers 1, 2a, 2b, 2c, and 3 were validated at (b) (4) no NAb assessment (Tier 4) was performed in samples from sites within China.

The sponsor used same assay format and method for Tier 1-3 sample testing scheme from that used at (b) (4) so, they did not include certain validation studies in validation package at (b) (4) including stability and negative specificity. These are characteristics of overall assay and are not expected to change, therefore are acceptable. The assay validation parameters at (b) (4) are provided in table below.

Table ISI.6.6. TZP Immunogenicity Assay Validation Parameters (Tiers 1, 2a, 2b, 2c, and 3) – (b) (4)

Source Documents: Validation Report 19BASM188V1, Amendment 1 and Amendment 2 Testing laboratory: (b) (4) Signed on 10 Dec 2020		
Assay Format: The same validated affinity capture elution (ACE) assay method was used on the Meso Scale Discovery (MSD) platform.		
Assay Parameter	Results	Comments
Positive Control Material	Affinity purified anti-LY3298176 antibody generated from hyperimmune monkey, AP-HIMS	*In-house (same positive control used)*
Negative Control (NC)		*NC was prepared from forty-nine NHS individual donor samples for use as an NC. The NHS donor samples were screened appropriately to generate NC.*
MRD	1:10	*The MRD was re-evaluated using previously validated method at this site and confirmed to be 1:10.*
Screening Cut Point Factor, (Tier 1)	Floating cut point determined NHS: 1.14 T2DM: 1.33	*NHS samples (N = 56) and T2DM pre-dose samples (N =138 + 661 from Study 18F-MCGPHO) were analyzed to determine CP.* *The Sponsor chose to use T2DM CP for T2DM sample analysis. It is disease-specific, therefore more appropriate to use. Acceptable.*
Confirmation Cut Point (Tier 2a)	NHS: 17.5% T2DM: 25.5%	*CCP determined from NHS samples (N = 56) and baseline samples from 138 participants of CWM Study I8F-MC-GPHO were analyzed. The cut points between NHS and T2DM participants different; the Sponsor determined to use the T2DM CP.* *The T2DM DSCP determined previously from T2DM subjects was 28.8%, which is closer to 25.5%. Nevertheless, the assay validation was appropriate in this location, and the T2DM CP is more disease-specific than NHS CP, and therefore is acceptable.*
Cross-Reactivity Cut Point (native $GIP_{(1-42)}$; Tier 2b)	NHS: 14.5% T2DM: 17.5%	*Tier 2b CP determined from NHS samples (N = 56) and baseline samples from 138 participants of*

		CWM Study I8F-MC-GPHO were analyzed using approved method. The cut points between NHS and T2DM participants were different; the Sponsor determined to use the T2DM CP, which is acceptable since it is disease-specific CP.
Cross-Reactivity Cut Point (native GLP-$1_{(7-36)}$; Tier 2c)	NHS: 14.5% T2DM: 16.9%	*Tier 2c CP determined from NHS samples (N = 56) and baseline samples from 138 participants of CWM Study I8F-MC-GPHO were analyzed. The cut points between NHS and T2DM participants were different; the Sponsor chose to use the T2DM CP, which is acceptable since it is disease-specific CP and more appropriate for the study subjects.*
Titration Cut Point (Tier 3)	NHS: 1.25 T2DM: 1.71	*NHS samples (N = 56) and T2DM baseline samples (N =138 + 661) from Study I8F-MCGPHO were analyzed. The Sponsor chose to use the T2DM TCP, which is acceptable since it is disease-specific CP and more appropriate for the study subjects.*
Assay sensitivity	6.6ng/mL Method outline: A pooled NHS sample was spiked with 4000 ng/mL of anti-LY3298176 AP-HIMS serially diluted with NHS pool to the following concentrations: 2000, 1000, 500, 250, 125, 62.5, 31.3, 15.6, 7.8, 3.9, 2.0, and 0 ng/mL.	*This assay sensitivity was determined appropriately to 6.6ng/mL from a dose response curve and is less than 100 ng/mL as expected according to 'FDA guidance for immunogenicity methods (2019)', to detect clinically relevant ADA using the T2DM cut points. The assay sensitivity is also comparable to 2.81 ng/mL that was determined at* (b) (4) *for this method at Tier 1, and is therefore, acceptable.*
Drug Tolerance (DT)	≥250 µg/mL of TZP in the presence of 100 ng/mL AP-HIMS. Method outline: Final concentrations of LY3298176 was 250, 125, 62.5, 31.3, 15.6, 7.8, 3.9, 1.95, 0.98, 0.49, 0.24, and 0 µg/mL and anti-LY3298176 AP-HIMS	*The DT was assessed appropriately, and the assay demonstrated DT well above the maximum expected drug concentration. Further, the DT is determined to be same as determined at* (b) (4) *for this method (see above). Therefore, the determined DT is acceptable.*

	concentrations were 100, 25, and 12.5 ng/mL, prepared in NHS pool.	
Intra-Assay Precision	Negative = 11.7% LPC = 6.1% MPC = 7.6% HPC = 8.1%	*Intra-assay precision met the acceptance criteria of having a %CV ≤ 25% for each PC in the absence of LY3298176, demonstrating intra-assay precision of the assay.*
Inter-Assay Precision, CV% (Screening)	Negative = 17.1% LPC = 12.6% MPC = 15.3% HPC = 17.1%	*Inter-assay precision met the acceptance criteria of %CV ≤ 25% in the absence of LY3298176, demonstrating precision of this assay.*
Inter-Assay Precision, CV% (confirmatory)	LPC = 5.2% MPC = 0.6% HPC = 0.2%	*Inter-assay precision met the acceptance criteria of %CV ≤ 25% in the presence of 50 µg/mL of LY3298176, demonstrating the precision of this assay.*
Robustness	Assessed after changing experimental method in incubation time at ±10% at several steps.	*The assay was demonstrated to be robust with regard to sample plate position, incubation time, MSD and streptavidin plate lots, and MSD plate reader models.*
Conclusion: The sponsor used same assay format and method for Tier 1, Tier2a, Tier2b, Tier2c and Tier-3 sample testing scheme that was also used at (b) (4) The inter-assay precision was determined at (b) (4) supports that these assays could be performed at (b) (4) suitable with high precision for the screening as well as confirmatory assay. Therefore, acceptable to analyze clinical samples from participants in China at this testing site. NAb assays are not validated at this lab, therefore, the Nab assay results provided in ISI did not include results on samples from participants in China.		

5. Neutralizing Antibody Assays (NAb)

Lilly developed 2 cell-based NAb assays to detect ADA capable of neutralizing the ability of TZP to activate the GIPR (Tier 4a) and to activate the GLP-1R (Tier 4b). These assays were fully validated previously and applied in clinical samples from studies in T2DM subjects under NDA 215866 (DARRTS Reference IDs: 4938651 and 4858440). Briefly, in the NAb assay methods, anti-TZP antibodies in ADA-positive samples are first captured on a streptavidin plate coated with a mixture of two differently biotinylated TZP molecules (GIP740 and GIP735). In next step, the anti-TZP antibodies are eluted, and pH neutralized in the presence of TZP to allow ADA binding to the study drug. The resulting mixtures are finally added to reporter cell lines to assess the ability of ADAs to inhibit TZP signaling via GIP or GLP-1 receptors (GIPR and GLP-1R, respectively) expressed by the reporter cells. Human embryonic kidney 293 (HEK293) cells stably transfected with either GIPR or with GLP-1R are used in these assays. Binding of TZP to corresponding cell surface receptors leads to cAMP production, which is reduced or abolished in presence of neutralizing antibodies present in the sample.

To determine the applicability of these, NAb assays in analyzing clinical immunogenicity samples from CWM study subjects, the sponsor verified the assay parameters using pre-dose clinical samples from 200 subjects with obesity from CWM Phase 3 Study I8F-MC-GPHK. The

applicability of the validation parameters for these NAb assays are discussed in the following tables.

5.1 Neutralization of TZP Activity on GIPR (Tier 4a)

Table ISI.6.9. NAb Assay - Tier 4a

This is GIP-R cell-based NAb assay that measures anti-LY3298176 neutralizing antibodies in human serum samples that inhibits TZP GIP activity at GIP-R. Two hundred single-donor I8F-MC-GPHK baseline samples were analyzed in Tier 4a using the current version of method (b) (4)-18-061-MTH-056 and each run contained 2 sets of PCs for each level, 4 sets of NC, and 4 sets of ACs for each condition, and all samples were run in duplicate. This assay was run over 9 days by 4 analysts and generated 2 reportable results per sample (Ref: (b) (4)-21-061-1228).		
Source of Documents: (b) (4)-17-061-585, Addendum 1, Addendum 2, and Addendum 3. Study (b) (4)-21-061-1228 and DARRTS Reference ID: 4938651 DARRTS Reference ID: 4858440		
Assay Parameter	Results	Comments
Contract Research Org	(b) (4)	None
Positive control (PC) neutralizing antibody (NAb)	Mouse monoclonal Anti-GIP707 antibody, 5H12 - targets N-terminus of TZP	*In-house*
Cell Line	Passage 5 through passage 15.	*HEK293 cell line stably transfected with the GIP receptor (ELHEK293-GIPR-CRE-Luc) was used in this assay. Supplier –* (b) (4)
MRD	1:5	*MRD 1:5 was validated previously, as the assay performs adequately with maximal sensitivity and minimal assay variability (Addendum 1 and DARRTS Ref ID: 4858440).*
Positive control samples	LPC = 2 µg/mL MPC = 5 µg/mL and HPC = 10 µg/mL of mAb 5H12 in NC NHS pool.	*Positive control samples were established previously during the validation of the GIP-R cell-based NAb assay using serum samples from T2DM subjects for NDA 215866. The Sponsor used same concentrations for LPC, MPC and HPC and recalculated the assay performance controls for using in-study serum samples CWM study. Acceptable.*
Cut Point (Tier 4a)	NHS: 11.2% T2DM/Obesity: 10.8%/10.5%	*The Tier 4a CP for CWM population was determined to be 10.5% using serum samples from 199 of 200 patients from CWM Study I8F-MC-GPHK excluding one outlier. The data were not initially provided but in response to IR comment 04 April*

		2023, the Sponsor submitted revised data for Tier 4a study. Division of Biometrics was consulted to verify this CP (DARRTS Ref: 5183722), who evaluated the data and determined the CP for Tier 4a to be 9.5% by using two-way REM method (DARRTS Ref: 5257062; 10/10/2023). The Sponsor used a different statistical method, that could account for this small difference in CP determination. Nevertheless, the use of the T2DM CP 10.8% is relatively more stringent approach to minimize false positives. In addition, manual inspection of 'delta %neutralization' data of 199 data-point yields a false-positive rate of 0.5%, which supports 1% FPR of the CP analysis, therefore, acceptable for this study. *The Sponsor chose to use the CP determined using T2DM studies, based on their bootstrap analysis of the CPs between T2DM and obesity DSCPs, which were not statistically significant different (p>0.05, Figures 3-4). Acceptable.*
Sensitivity	866 ng/mL	
Drug tolerance	DT was determined by interpolation of the concentrations of the drug using cut-points that demonstrated to be 159ng/mL for at T2DM CP in the presence of up to 5µg/mL NAb antibodies (MPC), whereas it was 314ng/mL in the presence of up to 10µg/mL NAb.	*The sensitivity and drug tolerance reestablishments were not necessary, as the previously established T2DM DSCP were found appropriate for use in analyzing clinicals samples from CWM studies (DARRTS Ref ID: 4858440) at the same laboratory.*
Potency	0.61 ng/mL	*Potency was determined during assay development by the Sponsor, for Tier 4a which is above EC_{50} and within the linear portion of the potency curve. This concentration was used to determine the final concentration of the drug on cells that was used as stimulant in this assay and it was reviewed previously (DARRTS Ref ID: 4858440 and (b) (4) 17-061-585.02).*

GIP-R cell-based NAb assay	Suitable for intended purpose	Acceptable.

5.2 Neutralization of TZP Activity on GLP-1R (Tier 4b)

Table ISI.6.10. NAb Assay – Tier 4b

This is GLP-1R cell-based NAb assay that measures anti-LY3298176 neutralizing antibodies in human serum samples. Baseline samples from 200 single-donor from Phase 3 CWM study I8F-MC-GPHK were analyzed in Tier 4b and each run contained 2 sets of PCs for each level (LPC, MPC and HPC), 2 sets of NC, and 2 sets of ACs (assay control, Max and Min) for each condition, and all samples were run in duplicate. This assay was run 5 analysts over 9 days, 1-2 runs/analyst, 1-2 plates/run, and 2 technical replicates per plate. (Ref: Page 120, (b) (4)-21-061-1228).		
Source of Documents: (b) (4)-17-061-728, Addendum 1, Addendum 2 and (b) (4)-21-061-1228 DARRTS Reference ID: 4938651 DARRTS Reference ID: 4858440		
Assay Parameter	Results	Comments
Contract Research Org	(b) (4)	None
Cells Line	Passage 5 through passage 15.	*HEK293 cell line stably transfected with the GLP1 receptor (ELHEK293-GLP1R) was used in this assay.*
MRD	1:5	*The assay performs adequately at MRD 1:5 with maximal sensitivity and minimal assay variability, therefore, the applicant MRD 1:5 was chosen (reviewed in DARRTS Reference ID: 4858440).*
Positive control antibody	Mouse monoclonal IgG1 antibody, IBA391 - targets C-terminus of TZP.	*In-house*
Positive control samples	LPC = 2 µg/mL MPC = 4 µg/mL and HPC = 10 µg/mL of mAb in NC NHS pool.	*Performance control PCs were established previously during the validation of the GLP-1R cell-based NAb assay using serum samples from T2DM subjects for NDA 215866. The Percent Neutralization was recalculated for LPC, MPC and HPC to be used for the NAb assay performances during analyzing clinical samples from CWM study. Acceptable.*
Cut Point (Tier 4b)	T2DM/Obesity: 6.6%/4.7%	*The CP from CWM study samples from 186 patients after excluding outlier (N = 200, Study I8F-MC-GPHK) to be 4.7%, which is different than*

		T2DM DSCP of 6.6% approved previously. *Based on bootstrap test of equivalence, the T2DM DSCP (6.6%) and CWM CP (4.7%) were found to be significantly different (p<0.05, Figures 3-4, Page 123 – 124, (b) (4) 21-061-1228). The Sponsor chose to use T2DM DSCP for analyzing samples from each Phase 3 clinical study population, for consistency.* *Between 4.7% and 6.6% DSCP, the latter will minimize the risk of reporting false-positive results, therefore may be acceptable, but to further understand if the 6.6% CP can be used in analyzing samples from CWM studies, we consulted 'Office of Biostatics' (DARRTS Ref: 5183722), who analyzed the same set of data and determined the CP to be 6.0% using two-way REM method (DARRTS Ref: 5257062; 10/10/2023).* *Two CPs are closer (6% vs 6.6%), and both are stringent, but the latter is more appropriate to minimize the risk of false-positive results. Additionally, the Sponsor used a different statistical method [independent and identically distributed] to CP determination that may have resulted to 6.6% implicating more inclusive results, therefore, this CP is acceptable for this study.*
Sensitivity	680 ng/mL	*The sensitivity and drug tolerance reestablishments were not necessary, as the previously established T2DM DSCP at the same laboratory were found appropriate for use in analyzing clinicals samples from CWM*
Drug Tolerance	Drug tolerance ≥ 0.54 µg/mL TZP in presence of 5000 ng/mL NAb IBA391.	

		studies (DARRTS Ref ID: 4858440).
Potency	1.04 ng/mL	*The concentration of 5.6 ng/mL LY3298176 (or 1.04ng/mL final concentration on cells) was determined to fall within the lower linear portion of the final averaged curve generated during the potency assessment and used as potency in final assay validation method (DARRTS Ref ID: 4858440 and (b) (4) 8-061-728.01).*
GLP-1R cell-based NAb assay	Suitable for intended purpose	Acceptable.

In addition, Lilly developed two in silico classifications using Tier 2b and 4a results to detect ADA capable of neutralizing the ability of nGIP to activate the GIPR (Tier 4c) and using Tier 2c and 4b results to detect ADA capable of neutralizing the ability of nGLP-1 to activate the GLP-1R (Tier 4d). This system was previously used for in silico classification of patient samples in Tier 4c and Tier 4d for cross-reactive ADA capable of neutralizing nGIP and nGLP-1 in the approved tirzepatide T2DM indication application.

Verification of Cut points for immunogenicity assays:

Cut Points	Tier 1	Tier 2a (%)	Tier 2b (%)	Tier 2c (%)	Tier 4a (%)	Tier 4b (%)
Sponsor - CWM	1.22	28.80	24.00	19.7	10.5	4.70
Assessor - CWM	-	28.71	23.89	21.5	9.7	4.49
Office of Biostatics	1.35	22.70	21.60	19.2	9.5	6.00
Validated – T2DM	1.30	30.40	14.50	18.1	10.8	6.60
CP proposed to use	1.22	30.40	14.50	18.1	10.8	6.60

Assessor comment: The CPs were verified by the assessor using the assay data provided in spreadsheet by the sponsor and appropriate formula for each assay that is commonly practiced by the industries, found that the CPs are similar to the Sponsor's determination. These data were further verified by the Office of Biostatics. Based on all analysis, it is agreed that T2DM DSCP can be used for analyzing clinical samples from CWM studies.

6. Evaluation Plan for Immunogenicity Samples

The Sponsor evaluated the appropriateness of using the validated T2DM disease specific cut-points (for Tiers 1, 2a, 2b, 2c, 4a, and 4b) in analyzing samples from obesity disease-state Studies. Each CP was evaluated by analyzing 200 randomly selected baseline serum samples from Study GPHK (SURMOUNT-1, obese participants without T2DM) against the CP derived previously in serum samples from T2DM subjects. Following table shows the cut-points implemented for immunogenicity assays across Phase 3 clinical trials.

Table. ADA and NAb Assay Cut Points for Each Phase 3 Study

Phase 3 study	ADA Assay Cut Points (%)				NAb Assay Cut Points (%)	
	Screening (Tier 1)	Confirmatory (Tier 2a)	Cross- reactivity to		for GIPR (Tier 4a)	for GLP-1R (Tier 4b)
			nGIP (Tier 2b)	nGLP-1 (Tier2c)		
SURMOUNT-1 (without diabetes who had obesity (BMI ≥ 30 kg/m^2), or overweight (BMI ≥ 27 kg/m^2)						
GPHK	1.22	30.4	14.5	18.1	10.8	6.6
SURPASS studies (with T2DM with baseline BMI ≥ 27 kg/m^2)						
GPGK	1.22	30.4	14.5	18.1	10.8	6.6
GPGL	1.22	30.4	14.5	18.1	10.8	6.6
GPGH	1.22	30.4	14.5	18.1	10.8	6.6
GPGM	1.22	30.4	14.5	18.1	10.8	6.6
GPGI	1.22	30.4	14.5	18.1	10.8	6.6
GPGP	1.22	30.4	14.5	18.1	10.8	6.6
GPGO	1.22	30.4	14.5	18.1	10.8	6.6
GPHO	1.22	30.4	14.5	18.1	10.8	6.6

* Created by the Assessor based on available information in Table ISI.7.1 and Table ISI.7.2 in ISI.

7. In Silico Classification for Cross-Reactive NAbs

The ADA capable to neutralize the ability of nGIP to activate the GIPR (Tier 4c) and the ADA capable of neutralizing the ability of nGLP-1 to activate the GLP-1R (Tier 4d) were determined in an in-silico approach rather than in vitro cell-based assay. This method uses Tier 2b and Tier 4a results to identify anti-nGIP cross-reactive NAb (Tier 4c) and Tier 2c and Tier 4b results to identify anti-nGLP-1 cross-reactive NAb (Tier 4d). This method was also previously found acceptable and was applied for Tier 4c & 4d assessment of immunogenicity in samples from the tirzepatide NDA 215866 for the T2DM indication.

8. Immunogenicity Sampling Schedule (Phase 3 studies CWM):

The ADA sampling times for the nine Phase 3 clinical trials were designed with follow up periods for at least 3-4 weeks after dosing to adequately assess immunogenicity. The sponsor collected all samples on dosing days before dosing. An overview of the antibody collection time points is presented in the following Table (Source: ISI – Table ISI.7.3).

Table ISI.7.3. Overview of Immunogenicity Sampling Schedule for TZP Phase 3 Studies in Participants Who Have Overweight/Obesity with and without T2DM

Study	Sampling Time Points (Weeks)														
	0	4	12	24	40	42	44	48	52	56	72	76	78	104	108
GPHK	X	X	X	X				X			X	X (SFU)			
GPHL	X	X	X	X				X			X	X (SFU)			
GPGK	X	X	X	X	X		X (SFU)								
GPGL	X	X	X	X	X		X (SFU)								
GPGH	X	X	X	X	X				X	X (SFU)					
GPGM	X	X	X	X		X			X				X[a]	X[a]	X (SFU)
GPGI	X	X	X	X	X		X (SFU)								
GPGP	X	X	X	X	X				X	X (SFU)					
GPGO	X	X	X	X	X				X	X (SFU)					
GPHO	X	X	X	X	X		X (SFU)								

Abbreviations: SFU = safety follow-up; T2DM = type 2 diabetes mellitus.
[a] For participants that continued past the primary endpoint at 52 weeks in GPGM, SFU (scheduled follow up) visits occurred 4 weeks after the last treatment visit that could have occurred between 52 and 104 weeks.

All Phase 3 studies included a 4-week SFU visit, to be conducted after the last scheduled treatment visit or early discontinuation visit. For Study GPHK, SFU was performed 4 weeks after the last visit during the 72-week treatment period only for participants without prediabetes at randomization and for participants with prediabetes at randomization who discontinued the study within the 72-week treatment period.

Study GPHK is a 193-week study with a completed 72-week primary study period and an ongoing 104-week additional treatment period for participants with prediabetes at the time of randomization.

Assessor comment: The immunogenicity evaluation data were generated from 8 SURPASS studies, one SURMOUNT-1 and one SURMOUNT-2 studies. The sampling time for testing the development of anti-drug antibodies is adequately designed.

9. Immunogenicity Results from Phase 3 studies:

The analysis of immunogenicity incidence is discussed in following table for A) SURMOUNT-1 (I8F-MC-GPHK), B) SURMOUNT-2 (I8F-MC-GPHL) and C) SURPASS Phase 3 studies as shown in Table below (created by the assessor).

Incidence of ADA to TZP – analysis sets				
Study sets	Duration	Description	Patients	TZP Treatment
SURMOUNT Phase 3 Studies				
A. 18F-MC-GPHK	72-week	SURMOUNT-1	Overweight/Obesity Without T2DM	Placebo, TZP 5mg, 10mg and 15 mg
B. I8F-MC-GPHL	72-week	SURMOUNT-2	Overweight/Obesity With T2DM	Placebo, TZP 10mg and 15 mg
SURPASS Phase 3 studies				
a. 18F-MC-GPGK	40-week	SURPASS-1	T2DM, and baseline BMI ≥ 27 kg/m2	TZP 5mg TZP 10mg TZP 15 mg
b. 18F-MC-GPGL	40-week	SURPASS-2		
c. 18F-MC-GPGH	52-week	SURPASS-3		
d. 18F-MC-GPGM	104-week	SURPASS-4		
e. 18F-MC-GPGI	40-week	SURPASS-5		

f. 18F-MC-GPGP	52-week	SURPASS-J mono		
g. 18F-JE-GPGO	52-week	SURPASS-J combo		
g. 18F-JE-GPHO	40-week	SURPASS-AP combo		

TZP or placebo was administered SC once weekly via single-dose pen. For participants randomly assigned to TZP, the starting dose 2.5 mg, injected QW for 4 weeks and then increased by 2.5 mg every 4 weeks until the maintenance dose was reached.

A. SURMOUNT 1 (18F-MC-GPHK) - 72-week, placebo-controlled study

Participants: Obesity (BMI ≥ 30 kg/m2) or overweight (BMI ≥ 27 kg/m2) without diabetes. A total of 1858 participants received TZP (5mg, 10mg or 15mg) and 631 patients received placebo.

ADA Results – Planned treatment period (Source Tables: ISI.8.1 and ISI.8.2)

Category	Placebo (N=643), n (%)	TZP 5mg (N=630) n (%)	TZP 10mg (N=636) n (%)	TZP 15mg (N=630) n (%)	TZP All (N=1896) n (%)
ADA evaluable patients	631 [98.1]	619 [98.3]	624 [98.1]	615 [97.6]	1858 [98.0]
Baseline ADA+	47 (7.4)	46 (7.4)	36 (5.8)	50 (8.1)	132 (7.1%)
Total postbaseline ADA+	22 (3.5)	396 (64.0)	407 (65.2)	423 (68.8)	1226 (66.0%)
Treatment-Induced ADA+	20 (3.2)	372 (60.1)	381 (61.1	392 (63.7)	1145 (61.6%)
Treatment-Boosted ADA+	2 (0.3)	24 (3.9)	26 (4.2)	31 (5.0)	81 (4.4%)

*TE induced: baseline status is ADA negative and at least 1 postbaseline status of ADA+ with titer ≥2× MRD of the ADA assay
*TE boosted: baseline and postbaseline status is ADA+ with the postbaseline titer being 2 dilutions (4-fold) greater than the baseline titer.

Cross-reactive and NAb Results – Planned treatment period (Source Table: ISI.8.2)

Category (postbaseline samples)	Placebo (N=636) n (%)	TZP 5mg (N=621) n (%)	TZP 10mg (N=629) n (%)	TZP 15mg (N=623) n (%)	TZP All (N=1873) n (%)
Patients Evaluable for TE ADA*	624	610	617	608	1835
GIP Cross-Reactive	9 (1.4)	238 (39.0)	239 (38.7)	255 (41.9)	732 (39.9)
GLP-1 Cross-Reactive	2 (0.3)	88 (14.4)	93 (15.1)	89 (14.6)	270 (14.7)
TZP NAb for GIPR	0 (0.0)	14 (2.3)	15 (2.4)	26 (4.3)	55 (3.0)
TZP NAb for GLP-1R	0 (0.0)	18 (3.0)	24 (3.9)	19 (3.1)	61 (3.3)
Cross-Reactive NAb to nGIP (In Silico)	0 (0.0)	6 (1.0)	5 (0.8)	5 (0.8)	16 (0.9)
Cross-Reactive NAb to nGLP-1 (In Silico)	0 (0.0)	0 (0.0)	2 (0.3)	0 (0.0)	2 (0.1)

*All numbers are calculated against the ADA evaluable patients for 5mg, 10mg, 15mg and all. Patients from sites in China are excluded in this evaluation.

Assessor Comment:

- *ADA incidence during the planned treatment period shows that out of a total of 1858 TZP-treated patients who had evaluable sample in this study, 1226 participants (66.0%) were TE ADA+. Of these ADA+ participants, 1145 participants (61.6%) were classified as treatment-induced, while 81 participants (4.4%) were classified as treatment-boosted suggesting that majority of the participants (62%) developed ADAs as treatment-induced pathway.*

- *The ADA development was dose-dependent. Percent of ADA+ patients increased from a cohort treated with 5mg (64%) to 10mg (65.2%) to 15 mg (68.8%) TZP suggesting a dose-dependent ADA-positivity.*

- *732 of 1858 (39.9%) participants were positive for cross-reactive binding ADA to nGIP, while 270 (14.7%) participants were positive for cross-reactive binding ADA to nGLP-1, suggesting majority of ADAs cross-reacts to native GIP, compared to ADAs cross-reacting with native GLP-1.*

- *55 (3.0%) participants were NAb+ against TZP activity on GIPR, while 61 (3.3%) participants were NAb+ against TZP activity on GLP-1R suggesting that the NAB development against TZP activity on the corresponding receptors were similar.*

- *However, 16 (0.9%) participants were positive for cross-reactive NAb against nGIP, and only 2 (0.1%) participants were positive for cross-reactive NAb against nGLP-1.*

B. SURMOUNT 2 (I8F-MC-GPHL), 72- week placebo-controlled study

Participants: Obesity (BMI ≥ 30 kg/m2) or overweight (BMI ≥ 27 kg/m2) with type 2 diabetes mellitus. A total of 938 participants received TZP (10mg or 15mg) and placebo.

ADA Results – GPHL study (Sourced from Table: ISI.8.1, ISI Addendum, received May 08, 2023):

Category	Placebo (N=315), n (%)	TZP 10mg (N=312), n (%)	TZP 15mg (N=311), n (%)	TZP 10+15 (N=623), n (%)
ADA evaluable patients	310 [98.4]	307 [98.4]	302 [97.1]	609 [97.8]
Baseline ADA+	28 (9.0)	35 (11.4)	32 (10.6)	67 (11.0%)
Total postbaseline ADA+	4 (1.3)	179 (58.3)	186 (61.6)	365 (59.9%)
Treatment-Induced ADA+	4 (1.3)	160 (52.1)	172 (57.0)	332 (54.5%)
Treatment-Boosted ADA+	0 (0.0)	19 (6.2)	14 (4.6)	33 (5.4%)

Cross-reactive and NAb antibody Results (GPHL study) – treatment period (Sourced from Table ISI.8.2, ISI Addendum)

Category (postbaseline samples)	Placebo (N=315) n (%)	TZP 10mg (N=312), n (%)	TZP 15mg (N=311), n (%)	TZP 10+15 (N=623), n (%)
Patients Evaluable for TE ADA *	310 [98.4]	307 [98.4]	302 [97.1]	609 [97.8]
GIP Cross-Reactive	4 (1.3)	130 (42.3)	123 (40.7)	253 (41.5)
GLP-1 Cross-Reactive	0 (0.0)	70 (22.8)	64 (21.2)	134 (22.0)
TZP NAb for GIPR	0 (0.0)	9 (2.9)	4 (1.3)	13 (2.1)
TZP NAb for GLP-1R	0 (0.0)	4 (1.3)	0 (0.0)	4 (0.7)
Cross-Reactive NAb to nGIP*	0 (0.0)	3 (1.0)	1 (0.3)	4 (0.7)
Cross-Reactive NAb to nGLP-1*	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

*All numbers are calculated against the ADA evaluable patients, for 5mg, 10mg, 15mg and all. Patients from sites in China are excluded in this evaluation.

Assessor Comment:

- *59.9 % (365 of 609) patients developed ADAs; 54.5% ADA+ patients were categorized as treatment-induced ADA+, whereas 5.4% patients had treatment boosted ADA indicating that majority of TE ADA+ is treatment induced rather than treatment boosted.*
- *The incidence of ADA development was dose dependent.*
- *Of 609, 253 (41.5%) patients were positive for cross-reactive binding ADA to nGIP, while 134 (22.0%) patients were positive for cross-reactive binding ADA to nGLP-1 majority of ADAs cross-reacts to native GIP.*
- *13 (2.1%) patients were NAb+ against TZP activity on GIPR, majority of ADAs had neutralizing activity against GIPR, whereas 4 (0.7%) patients were NAb+ against TZP activity on GLP-1R suggesting*
- *4 (0.7%) patients were positive for cross-reactive NAb against nGIP, and none were positive for cross-reactive NAb against nGLP-1.*

The impact of these cross-reactive and neutralizing antibodies is unknown.

C. SURPASS Studies - in patients with baseline BMI **≥27** (AS2C)

The immunogenicity data for the eight SURPASS studies (GPGK, GPGL, GPGH, GPGM, GPGI, GPGP, GPGO and GPHO) are submitted altogether in one table. A total of 6206 patients, treated with 5mg (N=2109), 10mg (N=2095) and 15mg (N=2122) were identified as TE ADA evaluable participants who had a baseline BMI ≥ 27 kg/m2. The results are shown in tables (Source Tables: ISI.8.3 and Table ISI.8.4) below for the participants during the planned treatment period.

ADA Results - SURPASS studies

Category	TZP 5 mg (N=2109), n (%)	TZP 10mg (N=2095), n (%)	TZP 15mg (N=2122), n (%)	TZP All (N=6326), n (%)
ADA evaluable patients	2070 [98.2]	2057 [98.2]	2079 [98.0]	6206 [98.1]
Baseline ADA+	144 (7.0)	136 (6.6)	147 (7.1)	427 (6.9)
Total postbaseline ADA+	1126 (54.4)	1159 (56.3)	1199 (57.7)	3484 (56.1)
Treatment-Induced ADA+	1053 (50.9)	1093 (53.1)	1119 (53.8)	3265 (52.6)
Treatment-Boosted ADA+	73 (3.5)	66 (3.2)	80 (3.8)	219 (3.5)

Cross-reactive and NAb antibody Results - SURPASS studies

Category (postbaseline samples)	TZP 5 mg (N=2001) n (%)	TZP 10mg (N=1998) n (%)	TZP 15mg (N=2008) n (%)	TZP All (N=6007) n (%)
Patients Evaluable for TE ADA*	1962 [98.1]	1960 [98.1]	1966 [97.9]	5888 [98.0]
GIP Cross-Reactive	688 (35.1)	694 (35.4)	733 (37.3)	2115 (35.9)
GLP-1 Cross-Reactive	271 (13.8)	302 (15.4)	278 (14.1)	851 (14.5)
TZP NAb for GIPR	40 (2.0)	37 (1.9)	51 (2.6)	128 (2.2)
TZP NAb for GLP-1R	43 (2.2)	52 (2.7)	49 (2.5)	144 (2.4)
Cross-Reactive NAb to nGIP*	18 (0.9)	9 (0.5)	22 (1.1)	49 (0.8)
Cross-Reactive NAb to nGLP-1*	7 (0.4)	7 (0.4)	3 (0.2)	17 (0.3)

*All numbers are calculated against the ADA evaluable patients, for 5mg, 10mg, 15mg and all. Patients from sites in China are excluded in this evaluation.

Assessor Comment:

- *A total of 6206 TZP-treated participants were tested from SURPASS studies for TE ADA in the planned treatment period. Of 6206 participants, 3320 (56.4%) were TE ADA+ of which 3265 (52.6%) were classified as treatment-induced, and 219 (3.5%) were classified as treatment-boosted (source: ISI Table ISI.8.4) suggesting that the incidence of immunogenicity to TZP treatment is very high in these subjects with baseline BMI ≥27.*

- *The incidence of ADA development increased in a dose dependent manner from 5mg, 10mg and 15mg in all studies.*

- *Of 5888, 2115 (35.9%) participants were positive for cross-reactive ADA to nGIP, while 851 (14.5%) participants were positive for cross-reactive ADA to nGLP-1 indicating more ADA developed against TZP are cross-reactive to native GIP than native GLP-1*

- *128 (128/5888 = 2.2%) participants were NAb+ against TZP activity on GIPR, while 144 (144/5888 = 2.4%) participants were NAb+ against TZP activity on GLP-1R suggesting*

the neutralizing ability of the antibodies developed against TZP at corresponding receptors for GIP and GLP-1 is low and similar.

- *49 (49/5888 = 0.8%) participants were positive for cross-reactive NAb against nGIP, while 17 (17/5888 = 0.3%) participants were positive for cross-reactive NAb against nGLP-1.*

D. Summary of ADAs to TZP - SURMOUNT-1 and SURMOUNT-2 studies

The results are shown in tables included below, adapted from the submission (Source, ISI Addendum, Tables: ISI.8.3 and Table ISI.8.4) for the participants during the planned treatment period and baseline ADA results.

Incidence of ADA development (SURMOUNT-1 and SURMOUNT-2 studies)

Category	TZP 5mg (N=630), n (%)	TZP 10mg (N=948), n (%)	TZP 15mg (N=941), n (%)	TZP all (N=2519), n (%)
ADA evaluable patients	619 [98.3]	931 [98.2]	917 [97.4]	2467 [97.9]
Total Baseline ADA+	46 (7.4)	71 (7.6)	82 (8.9)	199 (8.1)
Total Postbaseline TE ADA+	396 (64.0)	586 (62.9)	609 (66.4)	1591 (64.5)
Treatment-Induced TE ADA+	372 (60.1)	541 (58.1)	564 (61.5)	1477 (59.9)
Treatment-Boosted TE ADA+	24 (3.9)	45 (4.8)	45 (4.9)	114 (4.6)

Cross-Reactive and Neutralizing Antibodies – summary (treatment period)

Category (postbaseline samples)	TZP 5mg (N=621), n (%)	TZP 10mg (N=941), n (%)	TZP 15mg (N=934), n (%)	TZP all (N=2496), n (%)
Patients Evaluable for TE ADA+ *	610 [98.2]	924 [98.2]	910 [97.4]	2444 [97.9]
GIP Cross-Reactive	238 (39.0)	369 (39.9)	378 (41.5)	985 (40.3)
GLP-1 Cross-Reactive	88 (14.4)	163 (17.6)	153 (16.8)	404 (16.5)
TZP NAb for GIPR	14 (2.3)	24 (2.6)	30 (3.3)	68 (2.8)
TZP NAb for GLP-1R	18 (3.0)	28 (3.0)	19 (2.1)	65 (2.7)
Cross-Reactive NAb to nGIP**	6 (1.0)	8 (0.9)	6 (0.7)	20 (0.8)
Cross-Reactive NAb to nGLP-1**	0 (0.0)	2 (0.2)	0 (0.0)	2 (0.2)

*All numbers are calculated against the ADA evaluable patients, for 5mg, 10mg, 15mg and all. Patients from sites in China are excluded in this evaluation.
**In Silico

Cross-Reactive and Neutralizing Antibodies – summary (baseline)

Category (baseline samples)	TZP 5mg (N=621), n (%)	TZP 10mg (N=941), n (%)	TZP 15mg (N=934), n (%)	TZP all (N=2496), n (%)
Patients with baseline ADA+	46 (7.5)	71 (7.7)	82 (9.0)	199 (8.1)
GIP Cross-Reactive	12 (2.0)	19 (2.1)	30 (3.3)	61 (2.5)
GLP-1 Cross-Reactive	8 (1.3)	9 (1.0)	9 (1.0)	26 (1.1)
TZP NAb for GIPR	1 (0.2)	0 (0.0)	0 (0.0)	1(0.0)
TZP NAb for GLP-1R	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Assessor Comment:

- *Together in SURMOUNT-1 and SURMOUNT-2 studies, 64.5% participants developed ADAs against tirzepatide. Of these, 59.9% (1477 of 2467) participants developed antibodies in a treatment-induced manner, while only 4.6% (114 of 2467) participants had treatment boosted ADA development in SURMOUNT-1 and SURMOUNT-2 studies. The incidence of ADA development is also dose dependent.*

- *Together in SURMOUNT-1 and SURMOUNT-2 studies, 40.3% (985 of 2444) participants who developed ADAs against TZP, cross-reacted with native GIP, while 16.5% (404 of 2444) participants who developed antibodies to TZP, cross-reacted to native GLP-1. TZP is developed by modifying GIP peptide sequence which might be the reason of more antibodies developed to TZP are cross-reactive to native GIP.*

- *Similarly, cross-reactive neutralizing antibodies (NAb) to native GIP were more (0.8%, 20 of 2444 participants) compared to cross-reactive NAb to native GLP-1 (only 2 of 2467 participants). The neutralizing antibodies (NAb) to GIPR and GLP-1R, were similar. About 2.7% (68 of 2444) participants had TZP NAb against GIPR, while 2.6% (65 of 2444) participants had TZP NAb against GLP-1R.*

- *The baseline samples from about 8% participants were ADA+ and the samples from 2.5% participants at baseline showed cross-reactivity with native GIP, while 1.1% of the participants showed cross-reactivity with native GLP-1. None detected positive for cross-reactive NAb to nGIP or nGLP-1 at baseline by in silico method.*

E. Comparative analysis of ADAs to TZP between SURMOUNT-1, SURMOUNT-2 and SURPASS studies (Source: Tables: ISI.8.1, ISI.8.2, ISI.8.3 and ISI.8.4 (original ISI submission), ISI Addendum Tables: ISI.8.3 and Table ISI.8.4)

ADA Results during treatment period

Category (postbaseline samples)	SURMOUNT-1 (N = 1858)	SURMOUNT-2 (N = 609)	SURPASS (N = 6206)
Total Baseline ADA+	132 (7.1%)	67 (11.0%)	427 (6.9)
Total postbaseline ADA+	1226 (66.0%)	365 (59.9%)	3484 (56.1)
Treatment-Induced ADA+	1145 (61.6%)	332 (54.5%)	3265 (52.6)
Treatment-Boosted ADA+	81 (4.4%)	33 (5.4%)	219 (3.5)

Cross-reactive & NAb Assay Results during treatment period

Category (postbaseline samples)	SURMOUNT-1	SURMOUNT-2	SURPASS
Patients Evaluable for TE ADA+ *	1835	609	5888
GIP Cross-Reactive	732 (39.9)	253 (41.5)	2115 (35.9)
GLP-1 Cross-Reactive	270 (14.7)	134 (22.0)	851 (14.5)
TZP NAb for GIPR	55 (3.0)	13 (2.1)	128 (2.2)
TZP NAb for GLP-1R	61 (3.3)	4 (0.7)	144 (2.4)
Cross-Reactive NAb to nGIP (In Silico)	16 (0.9)	4 (0.7)	49 (0.8)
Cross-Reactive NAb to nGLP-1 (In Silico)	2 (0.1)	0 (0.0)	17 (0.3)

Assessor Comment:

The incidence of ADA development was dose dependent. More patients participating in SURMOUNT-1 study developed ADAs (66%) compared to patients who participated in SURMOUNT-2 (59.9%) and SURPASS studies (56.1%). The significance of this difference is unclear.

Cross-reactive antibodies to GIP is similar in SURMOUNT studies (39.9 vs 41.5%) but less in SURPASS studies (35.9%). NAb for GIPR appears to be similar in all studies (2.1% -3%).

Cross-reactive antibodies to GLP-1 is similar (14.5%) between SURMOUNT-1 and SURPASS studies, but higher in SURMOUNT-2 studies. On the other hand, NAb for GLP-1R is less in SURMOUNT-2 study (0.7%) compared to SURMOUNT-1 (3.3%) and SURPASS studies (2.4%). SURMOUNT studies are 72 weeks long and most SURPASS studies are 40 weeks or 52 weeks long, that may have the reason of the observed difference.

10.Antidrug Antibody Dynamics

11.1 Time to first ADA titer development in TZP-treated participants

The cumulative frequency of the development of TE ADA titer by specific time points from each Phase 3 study is reported in Table below, during the planned treatment period (Adapted from Table ISI.8.5 in ISI).

Times to First TE ADA+ Titer, Cumulative categories										
Study	N	≤4Wks n (%)	≤12Wks n (%)	≤24Wks n (%)	≤40Wks n (%)	≤52Wks n (%)	≤72Wks n (%)	≤78Wks n (%)	≤104Wks n (%)	>104Wks n (%)
SURMOUNT Studies										
GPHK (SURMOUNT-1)	1858	7 (0.4)	153 (8.2)	676 (36.4)	1086 (58.4)	1210 (65.1)	1212 (65.2)	1226 (66.0)		
GPHL (SURMOUNT-2)	609	3 (0.5)	38 (6.2)	186 (30.5)	307 (50.4)	355 (58.3)	360 (59.1)	365 (59.9)		
SURPASS Studies										
GPGH	925	9 (1.0)	69 (7.5)	233 (25.2)	405 (43.8)	453 (49.0)	469 (50.7)			
GPGI	298	3 (1.0)	24 (8.1)	79 (26.5)	140 (47.0)	154 (51.7)				
GPGK	275	0	12 (4.4)	72 (26.2)	126 (45.8)	145 (52.7)				
GPGL	1234	6 (0.5)	85 (6.9)	327 (26.5)	585 (47.4)	645 (52.3)				
GPGM	815	7 (0.9)	52 (6.4)	168 (20.6)	263 (32.3)	322 (39.5)	334 (41.0)	339 (41.6)	346 (42.5)	0
GPGO	240	1 (0.4)	30 (12.5)	102 (42.5)	149 (62.1)	165 (68.8)	170 (70.8)			
GPGP	200	1 (0.5)	20 (10.0)	60 (30.0)	114 (57.0)	128 (64.0)	132 (66.0)			
GPHO	361	2 (0.6)	33 (9.1)	114 (31.6)	183 (50.7)	197 (54.6)				

*Wks represents the first TE ADA+ titer time since the first doses.

Assessor comment:

- *The cumulative frequency of the development of ADA titer at various timepoints suggests that the development of ADA increases over the length of the study and continue to increase in the follow-up period.*
- *The percent of participants with a positive ADA titer peaked at week 24 for all studies and the cumulative frequency of ADA development had similar profiles across all Phase 3 studies.*
- *The kinetics of the development of ADA titer appears slightly greater at all time-points tested in samples from SURMOUNT-1 studies when compared with results from SURMOUNT-2 and SURPASS studies. The implication of this small difference is not understandable. Nevertheless, the development of ADA+ titer followed similar profiles across all Phase 3 studies, with majority of TE ADA+ participants developing an ADA titer within 24 weeks (the ADA titer peaked at week 24, see below) and the number of participants developing an ADA titer almost doubled within 52 weeks.*

11.2 Antidrug Antibody Titers

The following table containing the number of participants with ADA titer is recreated from ISI figures (Figures ISI.8.1 from ISI and ISI addendum) and presented in table below.

Distribution of ADA titer in ADA+ participants in SURMOUNT-1, SURMOUNT-2 and SURPASS studies													
Titer	20	40	80	160	320	640	1280	2560	5120	10240	20240	40960	81920
SURMOUNT-1 study													

n	103	121	171	185	167	169	154	96	38	19	3	0	0
SURMOUNT-2 study													
n	44	46	43	57	43	56	41	16	14	2	3	0	0
SURPASS studies													
n	358	426	498	534	486	417	402	229	88	40	7	1	1

n = number of ADA+ participants with corresponding ADA titer.

Assessor Comment:

- *The ADA titers in TZP-treated TE ADA+ participants from the SURMOUNT-1 and SURMOUNT-2 study ranged from 1:20 to 1:20480 during the planned treatment period.*
- *The development of ADA titer in participants from all Phase 3 studies follows similar profiles with a median ADA titer is 1:160 for all studies.*
- *For SURMOUNT-1 and SURMOUNT-2 studies, the ADA titers peaked at Week 24 (median of 1:160), plateaued up to Week 48, and then declined to lower levels. For SURPASS studies, the titers peaked similarly at Week 24 (median of 1:160), plateaued up to Week 52, and then declined to lower levels.*
- *Sixty (3.2%) out of 1858 TE ADA+ participants showed an ADA titer ≥1:5120 in SURMOUNT-1 study, while 19 out of 609 (3.1%) TE ADA+ participants showed ADA titers ≥1:5120. Therefore, number of TE ADA+ participants with ADA titers ≥1:5120, were similar between SURMOUNT-1 and SURMOUNT-2 studies.*

The ADA titers in TZP-treated TE ADA+ participants from the eight Phase 3 studies ranged from 1:20 to 1:81920 (median 1:160) during the planned treatment period. One hundred thirty-seven of 3484 TE ADA+ participants (3.9%) showed maximum ADA titers ≥1:5120 suggesting that the profiles of developing the ADA titers ≥1:5120, is somewhat higher in SURPASS studies (3.9% to 3.2% for SURMOUNT-1 and 3.1% of SURMOUNT-2 studies) Phase 3 studies, however the median ADA titer is 1:160 across Phase 3 studies

11.3 Relationship of ADA+ status with hypersensitivity or injection site reactions

Hypersensitivity:
Per discussion summary in Section 2.7.4 – Summary of Clinical Safety, in general a higher percentage of TE ADA+ patients (4.9%) than TE ADA- patients (3.0%) reported hypersensitivity reactions in SURPASS studies. For SURMOUNT studies (I8F-MC-GPHK and I8F-MC-GPHL), during planned treatment period, 6.2% TE ADA+ participants experienced hypersensitivity reactions, compared to 3.0% TE ADA-participants. However, the events reported in TE ADA+ participants were mild or moderate, and no pattern of a temporal relationship was found between treatment-emergent (TE) ADA status, or ADA titer, with the emergence of or resolution of individual hypersensitivity reactions.

Injection site reactions:
Per discussion summary in Section 2.7.4 – Summary of Clinical Safety, a higher percentage of TZP-treated TE ADA+ patients (7.3%) did have some level of injection site reactions, compared to those TE ADA-patients (0.8%), and this difference appeared greater at higher TZP doses. However, about 11.3% TE ADA+ participants experienced injection-site reactions in SURMOUNT studies, compared to 1.0% TE ADA- participants. More participants in SURMOUNT studies are reported to have ISR compared to participants from SURPASS studies. The reason is unknown

but SURMOUNT studies had longer treatment period compared to SURPASS studies, may be one of the reasons of this observed difference. Nevertheless, the majority of these events were non-serious and non-severe, with no indication of a pattern in temporal relationship between ADA status or titer and emergence or resolution of individual injection site reactions.

11.Conclusions

During the 72-week treatment period with ADA sampling in the chronic weight management studiesfrom two Phase 3 clinical Studies GPHK and GPHL, 64.5% (1591/2467) of ZEPBOUND-treated patients developed anti-tirzepatide antibodies during the planned treatment period. In these trials, anti-tirzepatide antibody formation in 40.0% and 16.5% of ZEPBOUND-treated patients showed cross-reactivity to native GIP or native GLP 1, respectively.

Among the TE ADA evaluable population, 2.8% and 2.7% Of the ZEPBOUND-treated patients in clinical Studies GPHK and GPHL, had NAb against tirzepatide activity on the GIPR and GLP-1R, and 0.8% and 0.1% had cross-reactive NAb against nGIP and nGLP-1, respectively.

The ADA titers in TE ADA-positive participants ranged from 1:20 to 1:20480 (median: 1:320). and seventy-nine (5.0%) out of 1591 TE ADA-positive participants showed maximum ADA titers ≥1:5120. The clinical significance of the high ADA titer is unclear but high titer ADAs may potentially impact on the pharmacokinetics or effectiveness of ZEPBOUND.

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Clinical Inspection Summary

Date	September 12, 2023
From	Ling Yang, M.D., Ph.D., FAAFP Min Lu, M.D., M.P.H., Team Leader Jenn Sellers, M.D., Ph.D., Branch Chief Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	Raymond Soccio, M.D., Clinical Reviewer Laura Higginbotham, M.D., Clinical Team Leader Arati Kamath, Senior Regulatory Project Manager Division of Diabetes, Lipid Disorders and Obesity
NDA #	217806
Applicant	Eli Lilly and Company
Drug	Zepbound (Tirzepatide; LY3298176)
NME (Yes/No)	No
Review Priority	Priority
Proposed Indication(s)	As an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adult patients with an initial body mass index (BMI) of 30 kg/m^2 or greater (obesity), or 27 kg/m^2 or greater (overweight) in the presence of at least one weight-related comorbid condition (e.g., hypertension, dyslipidemia, obstructive sleep apnea, cardiovascular disease, or Type 2 Diabetes)
Submission Date	May 08, 2023
Consultation Request Date	May 30, 2023
Summary Goal Date	September 15, 2023
Action Goal Date	November 08, 2023
PDUFA Date	November 08, 2023

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Clinical data from Studies **I8F-MC-GPHK** entitled "Efficacy and Safety of Tirzepatide Once Weekly in Participants without Type 2 Diabetes Who Have Obesity or Are Overweight with Weight-Related Comorbidities: A Randomized, Double-Blind, Placebo-Controlled Trial (SURMOUNT-1)" and **I8F-MC-GPHL** entitled "Efficacy and Safety of Tirzepatide Once Weekly in Participants with Type 2 Diabetes Who Have Obesity or Are Overweight: A Randomized, Double-Blind, Placebo-Controlled Trial (SURMOUNT-2)" were submitted in this original New Drug Application (NDA) for Tirzepatide (LY3298176) for the proposed indication as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adult patients with an initial body mass index (BMI) of 30 kg/m^2 or greater (obesity), or 27 kg/m^2 or greater (overweight) in the presence of at least one weight-related comorbid condition [e.g., hypertension, dyslipidemia, obstructive sleep apnea, cardiovascular disease, or type 2 Diabetes Meletus (T2DM)].

Two clinical investigators (CIs) in Argentina: Drs. Federico Manghi (Site #503 for Study I8F-MC-GPHK and Site #54333 for Study I8F-MC-GPHL) and Diego Aizenberg (Site #85301 for Study I8F-MC-GPHL); and 4 domestic CIs: Drs. Seth Forman (transferred from Dr. Tanya Bogle; Site #111 for Study I8F-MC-GPHK), Timothy Smith (Site #114 for Study I8F-MC-GPHK), Joanna Van (Site #83971 for Study I8F-MC-GPHL) and Gregorio Cortes-Maisonet (Site #92464 for Study I8F-MC-GPHL) were inspected for the submitted two studies.

Based on the overall inspection results of these CIs and the regulatory assessments, the data generated by these CI sites are verifiable. Studies I8F-MC-GPHK and I8F-MC-GPHL appear to have been conducted adequately and the clinical data submitted by the sponsor appear acceptable in support of the respective indication.

The inspections identified the following discrepancies that the review division may consider including in the efficacy evaluation, although these were isolated events and would not significantly affect the overall study results of these large trials:

- Subject (b) (6) (TZP 10 mg group) weight at Visit 21 (Week 72; end of the study) was 101.1 kg in the source records but was 81.1 kg in the submission.
- Subjects (b) (6) (TZP 10 mg group) and (b) (6) (TZP 10 mg group) were incorrectly stratified as “not pre-diabetes”, despite both subjects met the definition of “pre-diabetes”.

The following adverse events (AEs) were not reported to the FDA and not included in the proposed draft label. The review division may consider these AEs in the safety analysis of this drug:

- Subject (b) (6) (TZP 10 mg group) AE of insomnia
- Subject (TZP 15 mg group) AE of skin rash

II. BACKGROUND

Mounjaro™ (tirzepatide) subcutaneous (SC) injection was approved on 05/13/2022 under NDA 215866 as an adjunct to diet and exercise to improve glycemic control in adults with T2DM. Fast track designation was granted to tirzepatide on 10/03/2022.

Eli Lilly and Company (Lilly) submitted NDA 217806 for Zepbound (tirzepatide) SC injection on 11/17/2022 to extend the indication to as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adult patients with an initial BMI of ≥ 30 kg/m^2 (obesity), or ≥ 27 kg/m^2 (overweight) in the presence of at least one weight-related comorbid condition (e.g., hypertension, dyslipidemia, obstructive sleep apnea, cardiovascular disease, or T2DM).

The submission was a rolling two parts submission. The first sequence was submitted on 11/17/2022 with data from a Phase 3 study **I8F-MC-GPHK** entitled “Efficacy and Safety of Tirzepatide Once Weekly in Participants without Type 2 Diabetes Who Have Obesity or Are Overweight with Weight-Related Comorbidities: A Randomized, Double-Blind, Placebo-

Controlled Trial". The second and final sequence was submitted on 05/08/2023 with data from a Phase 3 study **I8F-MC-GPHL** entitled "Efficacy and Safety of Tirzepatide Once Weekly in Participants with Type 2 Diabetes Who Have Obesity or Are Overweight: A Randomized, Double-Blind, Placebo-Controlled Trial".

Study I8F-MC-GPHK

Study I8F-MC-GPHK was a Phase 3, multicenter, randomized, placebo controlled, double-blinded study of safety and efficacy of 5, 10, and 15 mg tirzepatide (TZP) once weekly (QW) compared with placebo for weight management when used in conjunction with a reduced-calorie diet and increased physical activity, in participants with obesity (BMI ≥ 30 kg/m^2) or overweight (BMI ≥ 27 kg/m^2) with weight-related comorbidities (excluding T2DM).

The primary study objectives were to demonstrate superiority of QW TZP 10 mg and/or 15 mg to placebo for percent change in body weight; and for the percentage of participants achieving at least 5% body weight reduction.

The primary efficacy endpoints were the mean percent change in body weight from baseline to Week 72 and the percentage of participants achieving at least 5% body weight reduction from baseline to 72 weeks.

Study Procedures

The study included 4 periods:

- **Period I**: screening: 3 weeks
- **Period II**: treatment: 72 weeks
  - Eligible subjects were randomized at a 1:1:1:1 ratio to receive QW SC injection of tirzepatide 5 mg, 10 mg, 15 mg, or placebo via a single-dose pen.
  - 20-week dose-escalation period: The starting dose of tirzepatide was 2.5 mg QW for 4 weeks and the dose was increased by 2.5 mg every 4 weeks until the maintenance dose was reached. The study product's escalation period lasted up to 24 weeks.
  - 52-week dose-maintenance period
- **Period III**: safety follow-up: 4 weeks.
- **Period IV:** 2-year treatment extension: all subjects, except those with prediabetes at randomization.

The study screened 3238 subjects and randomized 2539 subjects (630 subjects in the TZP 5 mg group, 636 subjects in the 10 mg group, 630 subjects in the 15 mg group, and 643 subjects in the placebo group) at 118 study sites in Argentina, Brazil, China, India, Japan, Mexico, Russian Federation, Taiwan, and the United States (US), including Puerto Rico. The first subject's first visit was on 12/04/2019 and the last subject's last visit was on 04/01/2022. A total of 2080 (540 in the TZP 5 mg group, 532 in the 10 mg group, 535 in the 15 mg group, and 473 in the placebo group) subjects completed Period III of the study. The data cutoff date was 04/14/2022, except immunogenicity and PK data, which were locked on 06/10/2022.

Study I8F-MC-GPHL

Study I8F-MC-GPHL was a Phase 3, multicenter, randomized, parallel-arm, placebo-controlled, double-blinded, 72-week study that studied the safety and efficacy of TZP 10 mg and 15 mg QW SC treatments compared with placebo, in conjunction with a reduced-calorie diet and increased physical activity, on weight management in participants with T2DM who had obesity (BMI ≥ 30 kg/m^2) or overweight (BMI ≥ 27 kg/m^2).

The primary study objectives were to demonstrate that TZP 10 mg and/or 15 mg QW is superior to placebo at 72 weeks for percent change in body weight; and for the proportion of participants with ≥ 5% body weight reduction.

The primary efficacy endpoints were the mean percent change in body weight from randomization and percentage of participants who achieve ≥ 5% body weight reduction from randomization to 72 weeks.

Study Procedures

The study consisted of 3 periods:

- **Period I**: screening: 3 weeks
- **Period II**: treatment: 72 weeks
  - Eligible subjects were randomized at a 1:1:1 ratio to receive QW SC injection of TZP 10 mg, 15 mg, or placebo via a single-dose pen.
  - 20-week dose-escalation period: The starting dose of TZP was 2.5 mg QW for 4 weeks and the dose was increased by 2.5 mg every 4 weeks until the maintenance dose was reached. The study product's escalation period lasted up to 24 weeks.
  - 52-week dose-maintenance period
- **Period III**: safety follow-up: 4 weeks.

The study screened 1514 subjects and randomized 938 subjects (312 subjects in the TZP 10 mg group, 311 subjects in the 15 mg group, and 315 subjects in the placebo group) at 77 study sites in Argentina, Brazil, India, Japan, Russian Federation, Taiwan, and the US, including Puerto Rico. The first subject's first visit was on 03/29/2021 and the last subject's last visit was on 04/10/2023. A total of 819 subjects completed Period III of the study (296 subjects in the TZP 10 mg group, 282 subjects in the 15 mg group, and 281 subjects in the placebo group). The primary database was locked on 04/13/2023, except immunogenicity and PK data, which was locked on 04/19/2023.

III. RESULTS

1. Seth B. Forman, M.D. (transferred from Tanya Bogle, M.D., Site #111 for Study I8F-MC-GPHK)
15416 N. Florida Avenue
Tampa, FL 33613

This CI was inspected on 07/10-13/2023 as a data audit for Study I8F-MC-GPHK. This was the second inspection of Dr. Forman. The CI for this site was initially Dr. Tanya Bogle, who signed

Form FDA 1572 on 10/03/2019, but left the site on 01/16/2023. The study was suspended by the Institutional Review Board (IRB) on 02/07/2023 and the suspension was lifted on 02/28/2023, when Dr. Forman, a previous Sub-CI, was approved by the IRB to be the CI for the site. The inspection confirmed that there were no activities during the CI transition time, as all subjects had completed the 72-week treatment period, with 4 active subjects in the long-term safety evaluation period.

For the inspected study, the site screened 35 subjects and enrolled 27 subjects, with 18 subjects completed the 72-week treatment period of the study. The first subject consented on 12/17/2019 and the last subject was enrolled on 03/19/2020. Informed Consent Forms (ICFs) for all 27 enrolled subjects and all source records of 14/27 enrolled subjects were reviewed.

The inspection reviewed the study protocol and amendments, ICFs and versions, documentation of eligibility criteria and enrollment logs, medical records [including visit data, laboratory tests, physical exam results, AEs and serious AEs (SAEs) reports], investigational product (IP) accountability records, electronic Case Report Forms (eCRFs) and electronic data capture (EDC) system audit trails, protocol deviations and related regulatory documents (e.g., IRB approvals and communications, staff trainings, monitoring log, records retention, financial disclosures and delegation of authority).

The submitted data were verifiable with source records at the study site. The primary efficacy endpoint data of the mean percent change in body weight from baseline and the percentage of participants achieving at least 5% body weight reduction from baseline to 72 weeks were verified with body weight measurements and waist circumference measurements parameters; and no discrepancies were noted. The inspection confirmed that subjects' body weight and waist measurements were conducted at the site by the staff and the weight measurement scales were routinely calibrated per manufacture recommendations.

One AE was not reported: Subject (b) (6) (TZP 10 mg group) AE of insomnia started on (b) (6) that was documented in the source record was not reported in the submission. There was no underreporting of SAEs.

Reviewer's Comment:
"Insomnia" is not a labeled AE for this product under NDA 215866. Subject (b) (6) AE of "insomnia" should have been reported and submitted, although it was considered as mild and not related event by investigator.

In general, the inspection verified adequate source data for the inspected study subjects, with no significant deficiencies reported.

2. Timothy R. Smith, M.D. (Site #114 for Stud I8F-MC-GPHK)
3862 Mexico Road
Saint Peters, MO 63303-3041

This CI was inspected on 07/25-28/2023 as a data audit for Study I8F-MC-GPHK. This was the second FDA inspection of Dr. Smith. Previous inspection was conducted in 08/2019.

The study site screened 34 subjects and enrolled 29 subjects, with 14 subjects completed the 72-week treatment period of the study. The first subject consented on 12/05/2019 and the study was ongoing at the time of the inspection with the 2-year treatment extension period. The inspection reviewed the ICFs for all screened subjects; and source records of 22/29 enrolled subjects.

The inspection reviewed the study protocol and amendments, ICFs and versions, documentation of eligibility criteria and enrollment logs, medical records (including visit data, laboratory tests, AEs and SAEs reports), IP accountability records, paper CRFs with eCRFs entries and the audit trails, protocol deviations and related regulatory documents (e.g., IRB approvals and communications, staff trainings, monitoring procedure and logs, ClinicalTrials.gov registration, records retention, financial disclosures and delegation of authority).

The submitted data were verifiable with source records at the study site. Body weight measurements and the waist circumference measurements parameters were reviewed to verify the primary efficacy endpoint data of the mean percent change in body weight from baseline; and the percentage of participants achieving at least 5% body weight reduction from baseline to 72 weeks, with no discrepancies noted. The inspection confirmed that subjects' body weight and waist measurements were conducted at the site by the staff and the weight measurement scales were routinely calibrated per manufacture recommendations. There were no underreporting of AEs or SAEs.

In general, the inspection verified adequate source data for the inspected study subjects, with no deficiencies reported.

3. Federico Perez Manghi, M.D. (Site #503 for Study I8F-MC-GPHK; Site #54333 for Study I8F-MC-GPHL)
Calle Viamonte 2278
Centro de Investigaciones Metabólicas SA
Ciudad Autónoma Buenos Aires
Capital Federal, C1056ABJ
Argentina

This CI was inspected on 08/14-25/2023 as a data audit for Studies I8F-MC-GPHK and I8F-MC-GPHL. This was the third FDA inspection of Dr. Manghi. Previous inspections were in 02/2014 and 02/2019.

For Study I8F-MC-GPHK, the study site screened 72 subjects and enrolled 62 subjects, with 52 subjects completed the 72-week treatment period of the study. Of the 10 subjects discontinued the study, 3 subjects were due to pregnancy; 4 subjects were lost to follow up; and 3 subjects withdrew ICFs. Source records for 25/62 enrolled subjects were reviewed.

For Study I8F-MC-GPHL, the study site screened 85 subjects and enrolled 63 subjects, with 60 subjects completed the study. Of the 3 subjects discontinued the study, one subject was due to pregnancy, one lost to follow up; and one withdrew the ICF. Source records for 25/63 enrolled subjects were reviewed.

The inspection reviewed the study protocol and amendments, ICFs and versions, documentation of eligibility criteria and enrollment logs, medical records (including visit data, laboratory tests, AEs and SAEs reports), IP accountability records, paper CRFs with eCRFs entries with the audit trails, the EDC system, protocol deviations and related regulatory documents [e.g., Ethic Committee (EC) approvals and communications, staff trainings, monitoring procedure and logs, records retention, financial disclosures and delegation of authority].

The submitted data were verifiable with source records at the study site. Body weight measurements and the waist circumference measurements parameters were reviewed to verify the primary efficacy endpoint data of the mean percent change in body weight from baseline; and the percentage of participants achieving at least 5% body weight reduction from baseline to 72 weeks, with no discrepancies noted. The inspection confirmed that subjects' body weight and waist measurements were conducted at the site by the staff and the weight measurement scales were routinely calibrated per manufacture recommendations. There were no underreporting of SAEs.

The following were discovered during the inspection:

- Subject (b) (6) (TZP 15 mg group) AE of "dyspepsia" and "skin rash" on (b) (6) treated with methylprednisolone 10 mg and ibuprofen 600 mg on (b) (6) documented in the source record were not reported in the submission.
- Subject (b) (6) (TZP 15 mg group) moderate AE of "acid reflux syndrome" on (b) (6) documented in the source record was not reported in the submission.
- Both Subject (b) (6) (TZP 10 mg group) and Subject (b) (6) (TZP 10 mg group) were stratified as "not pre-diabetes" despite both subjects met the definition of "pre-diabetes".

Reviewer's Comments:

- *"Rash" is not a labeled AE. Therefore, the review division may consider this AE in the safety review of the drug.*
- *Acid reflux and dyspepsia are labeled AEs for tirzepatide. Thus, the underreporting of these AEs should not affect the safety profile of the product.*
- *Subjects (b) (6) and (b) (6) incorrect stratification as "not pre-diabetes", despite both subjects met the definition of "pre-diabetes", should have been reported, although they were isolated findings that may not affect the efficacy evaluation of the study.*

In general, the inspection verified adequate source data for the inspected study subjects, with no significant deficiencies reported.

4. Joanna T. Van, M.D. (Site #83971 for Stud I8F-MC-GPHL)
2492 Walnut Avenue, Suite #130
Tustin, CA 92780-6953

This CI was inspected on 08/03-11/2023 as a data audit for Study I8F-MC-GPHL. This was the second FDA inspection of Dr. Van. Previous inspection was in 12/2016.

The study site screened 33 subjects and enrolled 16 subjects, with 14 subjects completed the study. The first subject consented on 03/31/2022 and the last subject's last visit was on 04/10/2023. ICFs for all 33 screened subjects and source records for all 16 enrolled subjects were reviewed.

The inspection reviewed the study protocol and amendments, ICFs and versions, documentation of eligibility criteria and enrollment logs, medical records (including visit data, laboratory tests, EKG readings, AEs and SAEs reports), IP accountability records, patients' diary, paper CRFs with eCRFs entries with the audit trails, the EDC system, protocol deviations and related regulatory documents (e.g., IRB approvals and communications, staff trainings, monitoring procedure and logs, ClinicalTrials.gov registration, records retention, financial disclosures and delegation of authority).

The submitted data were verifiable with source records at the study site. The primary efficacy endpoint data of the mean percent change in body weight from baseline and the percentage of participants achieving at least 5% body weight reduction from baseline to 72 weeks were verified by reviewing body weight measurements and the waist circumference measurements parameters with no discrepancies noted. The inspection verified that subjects' body weights were measured on sight by trained staff; and the scales were calibrated per recommendation. There were no underreporting of AEs or SAEs.

There was one discussion item: Subject (b) (6) (TZP 10 mg group) AE of "decreased appetite" on (b) (6) documented in the source record was not in the submission.

Reviewer's Comment:
Subject (b) (6) AE of "decreased appetite" on (b) (6) should have been reported and submitted, although it may not affect the safety profile of the product.

In general, the inspection verified adequate source data for the inspected study subjects, with no significant deficiencies reported.

The final inspection report is pending at the present time and an addendum will be filed if there are significant changes in the inspection findings.

5. Diego Aizenberg, M.D. (Site #85301 for Stud I8F-MC-GPHL)
Centro Médico Viamonte
Córdoba Av. 2019
Buenos Aires, C1120AAC

Argentina

This CI was inspected on 07/17-25/2023 as a data audit for Study I8F-MC-GPHL. This was the second FDA inspection of Dr. Aizenberg. Previous inspection was in 06/2014. The inspection was conducted with the help of an independent interpreter.

The study site screened 94 subjects and enrolled 81 subjects, with all 81 subjects completed the study. The first subject consented on 03/30/2021 and the last subject's last visit was on 04/03/2023. AEs and primary endpoint records for all enrolled 81 subjects and full source records for 38/81 enrolled subjects were reviewed.

The inspection reviewed the study protocol, ICFs and versions, documentation of eligibility criteria and enrollment logs, medical records (including visit data, laboratory tests, AEs and SAEs reports), IP accountability records, paper CRFs with eCRFs entries and the audit trails, the EDC system, protocol deviations and related regulatory documents (e.g., EC approvals and communications, staff trainings, monitoring procedure and logs, ClinicalTrials.gov registration, records retention, financial disclosures and delegation of authority).

The submitted data were verifiable with source records at the study site. The primary efficacy endpoint data of the mean percent change in body weight from baseline and the percentage of participants achieving at least 5% body weight reduction from baseline to 72 weeks were verified by reviewing body weight measurements and the waist circumference measurements parameters. The inspection also verified that subjects' body weights were measured on site by trained staff; and the scales used were calibrated per recommendation. Secondary endpoint HbA1c levels were verified with no discrepancies. There was no underreporting of SAEs.

The inspection identified the following discrepancy which was relevant to the primary efficacy endpoint analysis:

- Subject (b) (6) (TZP 10 mg group) weight at Visit 21 (Week 72; end of the study) was 101.1 kg in the source records but was 81.1 kg in the submission.

Reviewer's Comments:

- *Subjects (b) (6) weight discrepancy for Visit 21 (Week 72; end of the study) should be corrected for efficacy analysis. However, this isolated discrepancy may not significantly affect the efficacy evaluation of this large trial.*

The following AEs and related concomitant medication use were not reported:

- Subject (b) (6) (TZP 15 mg group)'s AE of mild "nausea" (possibly IP related) treated with Metoclopramide 15 mg on (b) (6) documented on (b) (6) at Visit 7 was not in the submission; and the concomitant medication use was not reported.
- Subject (b) (6) (TZP 15 mg group)'s AE of mild "nausea and diarrhea" (probably IP related) started on (b) (6) that was treated with Metoclopramide 10 mg and loperamide 2 mg on (b) (6) at Visit 7 was not in the submission and the concomitant medications use were not reported.

- Subject [redacted] (TZP 15 mg group)'s AE of mild "dyspepsia" (possibly IP related) started on [redacted] that was treated with Metoclopramide 15 mg on [redacted] at Visit 8 was not in the submission and the concomitant medication use was not reported.
- Subject [redacted] (placebo group)'s AE of "hyperlipidemia" (possibly not IP related) started on [redacted] that was treated with fenofibrate 20 mg on [redacted] at Visit 1 was not in the submission and the concomitant medication use was not reported.
- Subject [redacted] (placebo group)'s AE of mild "microalbuminuria" (not IP related) that was treated with Enalapril 10 mg on [redacted] at Visit 9 was not in the submission and the concomitant medication use was not reported.
- Subject [redacted] (placebo group)'s use of Empagliflozin (an SGL-2 inhibitor) 25 mg/day for hyperglycemia (the AE was reported as starting on [redacted]) starting on [redacted] was not in the submission.
- Subject [redacted] (TZP 15 mg group) use of Loperamide 20 mg for mild "diarrhea" (possibly IP related) on [redacted] documented on [redacted] at Visit 6 was not in the submission.
- Subject [redacted] (TZP 15 mg group) use of Metoclopramide 10 mg/day and Omeprazole 20 mg/day for "nausea" (the AE was reported in the submission) as documented on [redacted] at Visit 12 were not in the submission.

Reviewer's Comments:
Most of underreported AEs identified are gastrointestinal symptoms that are labeled AEs, although they should have been reported and submitted. In addition, none of the concomitant medications used were prohibited by the protocol. Thus, these findings may not significantly affect the efficacy or safety evaluation of the study.

In general, the inspection verified adequate source data for the inspected study subjects, with no significant deficiencies reported.

6. Gregorio Cortes-Maisonet, M.D. (Site #92464 for Stud I8F-MC-GPHL)
62 Calle Jose Marti, GCM Medical Group
San Juan, Puerto Rico 00917-3104

This CI was inspected on 07/31-08/04/2023 as a data audit for Study I8F-MC-GPHL. This was the first FDA inspection of Dr. Cortes-Maisonet.

The study site screened 25 subjects and enrolled 18 subjects, with 15 subjects completed the study. The first subject consented on 04/22/2021 and the last subject's last visit was on 03/10/2023. Source records for all 18 enrolled subjects were reviewed.

The inspection reviewed the study protocol and amendments, ICFs and versions, documentation of eligibility criteria and enrollment logs, medical records (including visit data, laboratory tests, AEs and SAEs reports), IP accountability records, paper CRFs with eCRFs entries with the audit trails, the EDC system, protocol deviations and related regulatory documents (e.g., IRB

approvals and communications, staff trainings, monitoring procedure and logs, ClinicalTrials.gov registration, records retention, financial disclosures and delegation of authority).

The submitted data were verifiable with source records at the study site. The primary efficacy endpoint data of the mean percent change in body weight from baseline and the percentage of participants achieving at least 5% body weight reduction from baseline to 72 weeks were verified by reviewing body weight measurements and the waist circumference measurements parameters with no discrepancies noted. The inspection also verified that subjects' body weights were measured on site by trained staff; and the scales used were calibrated per recommendation. There were no underreporting of AEs or SAEs.

The inspection found that Subject [redacted] (b) (6) (TZP 10 mg group) concomitant medication, empagliflozin (a SGLT-2 inhibitor) 5 mg, twice a day, during [redacted] (b) (6) as documented in the source record was not reported in the submission.

Reviewer's Comment:
Per the protocol, the use of SGL-2 inhibitor was not prohibited during the study. The subject's concomitant use of empagliflozin (an SGL-2 inhibitor) should have been submitted, although it may not affect the efficacy or safety evaluation of the study.

In general, the inspection verified adequate source data for the inspected study subjects, with no significant deficiencies reported.

{See appended electronic signature page}

Ling Yang, M.D., Ph.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Min Lu, M.D., M.P.H.
Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE: {See appended electronic signature page}

Jenn Sellers, M.D., Ph.D.
Branch Chief
Good Clinical Practice Assessment Branch
Director, Division of Clinical Compliance Evaluation

Office of Scientific Investigations

CC:
Central Doc. Rm.\NDA 217806
DDLO\CDTL\Laura Higginbotham
DDLO\Reviewer\Raymond Soccio
DDLO\Project Manager\Arati Kamath
OSI\Director\David Burrow
OSI\Deputy Director\Laurie Muldowney
OSI\DCCE\Division Director\Kassa Ayalew
OSI\DCCE\GCPAB\Branch Chief\Jenn Sellers
OSI\DCCE\GCPAB\Team Leader\Min Lu
OSI\DCCE\GCPAB\Reviewer\Ling Yang
OSI\DCCE\Program Analysts\Yolanda Patague

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/

LING YANG
09/12/2023 11:44:15 AM

MIN LU
09/12/2023 12:08:52 PM

JENN W SELLERS
09/12/2023 01:56:02 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatrics and Maternal Health
Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

Division of Pediatrics and Maternal Health Memo

Date: 9/6/2023 **Date consulted:** 5/19/2023

From: Wenjie Sun, MD, Medical Officer, Maternal Health
Division of Pediatrics and Maternal Health (DPMH)

Through: Miriam Dinatale, DO, Team Leader, Maternal Health, DPMH

Lynne P. Yao, MD, OND, Division Director, DPMH

To: Division of Diabetes, Lipid Disorders, and Obesity (DDLDO)

Drug: Zepbound (tirzepatide) Injection, for subcutaneous use

NDA: 217806

Applicant: Eli Lilly and Company

Subject: Pregnancy and Lactation Labeling

Proposed Indication: is a glucose-dependent insulinotropic polypeptide (GIP) receptor and glucagon-like peptide-1 (GLP-1) receptor agonist indicated as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adults with an initial body mass index (BMI) of:

- 30 kg/m2 or greater (obesity) or
- 27 kg/m2 or greater (overweight) in the presence of at least one weight-related comorbid condition (e.g., hypertension, dyslipidemia, (b) (4), type 2 diabetes mellitus, obstructive sleep apnea or cardiovascular disease).

Limitations of Use:

- ZEPBOUND should not be used in combination with other tirzepatide-containing products or any GLP-1 receptor agonist.

- The safety and efficacy of coadministration with other products for weight management have not been established.
- ZEPBOUND has not been studied in patients with a history of pancreatitis.

Materials Reviewed:

- Applicant's submitted background package and proposed labeling for NDA 215866
- DDLDO consult form for DPMH, DARRTS Reference ID 5176878
- DPMH review of Mounjaro on January 19, 2022, by Wenjie Sun, MD, NDA 215866, DARRTS Reference ID 4922584 and Addendum Memo on March 18, 2022, DARRTS Reference ID 4955128.[1]

Consult Question:

The review team requests DPMH's input on the labeling to be consistent with the Pregnancy and Lactation Labeling Rule.

INTRODUCTION AND BACKGROUND

On May 8, 2021, the applicant (Eli Lilly and Company) submitted a 505(b)(1) New Drug Application for Zepbound (tirzepatide) Injection under NDA 217806, for subcutaneous use indicated as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adults with obesity, or overweight in the presence of at least one weight-related comorbid condition. The Division of Diabetes, Lipid Disorders, and Obesity (DDLDO) consulted the Division of Pediatric and Maternal Health (DPMH) on May 19, 2023, to assist with the Pregnancy and Lactation subsections of labeling.

Regulatory History

- Tirzepatide was approved by FDA on May 13, 2022, in accordance with Section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act, under the brand name Mounjaro injection, NDA 215866, as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.
- Tirzepatide was approved in the European Union on September 15, 2022, and subsequently in Canada and in Australia as an adjunct to diet and exercise to treat adults whose type 2 diabetes is not satisfactorily controlled.
- On November 17, 2022, and May 19, 2023, Eli Lilly submitted an New Drug Application for tirzepatide as an adjunct to a reduced calorie diet and increased physical activity for chronic weight management in adults with obesity, or overweight in the presence of at least one weight-related comorbid condition.
- NDA 217806 was granted Fast Track designation on October 3, 2022 and rolling review under IND 139721 on November 4, 2022. The NDA will be reviewed on a six-month PDUFA clock.
- On May 19, 2023, DDLDO consulted DPMH to assist with development of subsections 8.1 and 8.2 of the product's labeling.

[1] The Mounjaro review was part of the materials reviewed but was not a source relied upon for the labeling recommendations below.

- On May 30, 2023, FDA sent an Information Request (IR) to the applicant to obtain clarification on the pregnancies reported in the submission.
- On June 5, 2023, the applicant replied to the IR.

Drug Characteristics

Tirzepatide Characteristics[2]

Drug Class	Glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide 1 (GLP 1) receptor agonist
Mechanism of action	(b) (4)
Dosing	Started at 2.5 mg once weekly. After 4 weeks, the dose is increased to 5 mg weekly. (b) (4) the dose is increased in 2.5 mg increments after at least 4 weeks on the current dose. The maximum dosage is 15 mg subcutaneously once weekly.
Molecular weight	4813.53 Dalton
Half-life	5 days
Protein Binding	99% plasma albumin
Bioavailability	80%

Serious adverse reactions[3]

- Severe gastrointestinal disease
- Acute kidney injury
- Acute gallbladder disease
- Acute Pancreatitis
- Hypoglycemia in patients with type 2 diabetes mellitus
- Hypersensitivity
- Diabetic retinopathy

Tirzepatide caused thyroid C-cell tumor in rats, including medullary thyroid carcinoma (MTC). It is contraindicated in patients with personal or family history of MTC or patients with multiple endocrine neoplasia syndrome type 2 (MEN2).

Approved labeling for Mounjaro (tirzepatide) injection, NDA 215866[4]

- The approved labeling is in Pregnancy and Lactation Labeling Rule (PLLR) format and reviewed by DPMH in 2022.
- There is a boxed warning for a contraindication in patients with a personal or family history of medullary thyroid carcinoma (MTC) or in patients with Multiple Endocrine

[2] Approved Labeling for Mounjaro, NDA 215855, Drugs@FDA, Last updated 5/13/2022. Access 5/24/23.
[3] Approved Labeling for Mounjaro, NDA 215855, Drugs@FDA, Last updated 5/13/2022. Access 5/24/23.
[4] Approved Labeling for Mounjaro, NDA 215855, Drugs@FDA, Last updated 5/13/2022. Access 5/24/23.

Neoplasia syndrome type 2 (MEN 2) due to nonclinical finding of thyroid C-cell tumor in rats.

- Tirzepatide is contraindicated for persons with a personal or family history of MTC or MEN2. It is also contraindicated in those with serious hypersensitivity to tirzepatide or any of the excipients.
- Tirzepatide delays gastric empty and, therefore, interacts with oral medications including oral contraceptives.

7.2 Oral medications

MOUNJARO delays gastric emptying, and thereby has the potential to impact the absorption of concomitantly administered oral medications. (b) (4) . Monitor patients on oral medications dependent on threshold concentrations for efficacy and those with a narrow therapeutic index (e.g., warfarin) when concomitantly administered with MOUNJARO.

Advise patients using oral hormonal contraceptives to use a non-oral contraceptive method or add a barrier method of contraception (b) (4) hormonal contraceptives that are not administered orally (b) (4)

8.1 Pregnancy

Risk Summary

Available data with MOUNJARO use in pregnant women are insufficient to evaluate for a drug-related risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes. There are risks to the mother and fetus associated with poorly controlled diabetes in pregnancy *(see Clinical Considerations).* Based on animal reproduction studies, there may be risks to the fetus from exposure to tirzepatide during pregnancy. MOUNJARO should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

In pregnant rats administered tirzepatide during organogenesis, fetal growth reductions and fetal abnormalities occurred at clinical exposure in maternal rats based on AUC. In rabbits administered tirzepatide during organogenesis, fetal growth reductions were observed at clinically relevant exposures based on AUC. These adverse embryo/fetal effects in animals coincided with pharmacological effects on maternal weight and food consumption *(see Data).*

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk

Poorly controlled diabetes in pregnancy increases the maternal risk for diabetic ketoacidosis, pre-eclampsia, spontaneous abortions, preterm delivery and delivery complications. Poorly controlled diabetes increases the fetal risk for major birth defects, stillbirth, and macrosomia-related morbidity.

8.2 Lactation

Risk Summary

There are no data on the presence of tirzepatide in animal or human milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for MOUNJARO and any potential adverse effects on the breastfed infant from MOUNJARO or from the underlying maternal condition.

8.3 Females and Males of Reproductive Potential

Contraception

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

PREGNANCY

Pregnancy and Obesity[5]

Based on the 2017-2018 National Health and Nutrition Examination Survey, the prevalence of obesity in women of reproductive age (20-39 years) in United States is 39.7%. [6]

Obesity is associated with increased risk of spontaneous abortions (SAB) (OR 1.2; 95% CI, 1.01-1.46) and recurrent miscarriage (OR 3.5; 95% CI, 1/03-12.01) compared with age-matched controls.[7] Obesity also increased the risk of neural tube defects, hydrocephaly, and cardiovascular, orofacial, and limb reduction anomalies.[8] The risk of gastroschisis in the neonates among obese gravidas, however, was significantly reduced (OR, 0.17; 95% CI, 0.10-0.30).[5]

Antepartum complications related to obesity include increased risk of cardiac disfunction, proteinuria, sleep apnea, nonalcoholic fatty liver disease,[9] gestational diabetes (GDM),[10]preeclampsia, and stillbirth.[11] Intrapartum complications include preterm birth (PTB), increased risk of cesarean delivery, failed trial of labor, endometritis, wound rupture or

[5] ACOG Practice Bulletin: Number 230 Obesity in Pregnancy. July 2021.
[6] Hales CM , Carroll MD , Fryar CD , Ogden CL . Prevalence of obesity and severe obesity among adults: United States, 2017-2018 . NCHS Data Brief 2020 ; 360 : 1 – 8 . (Level II-2)
[7] Lashen H, Fear K, Sturdee DW. Obesity is associated with increased risk of first trimester and recurrent miscarriage: matched case-control study. Hum Reprod 2004; 19: 1644 – 6. (Level II-3)
[8] Stothard KJ, Tennant PW, Bell R, Rankin J. Maternal overweight and obesity and the risk of congenital anomalies: a systematic review and meta-analysis. JAMA 2009; 301: 636 – 50. (Meta-analysis)
[9] Catalano PM. Management of obesity in pregnancy. Obstet Gynecol 2007; 109: 419 – 33. (Level III)
[10] Weiss JL, Malone FD, Emig D, Ball RH, Nyberg DA, Comstock CH, et al. Obesity, obstetric complications and cesarean delivery rate--a population-based screening study. FASTER Research Consortium. Am J Obstet Gynecol 2004; 190: 1091 – 7. (Level II-2)
[11] Salihu HM, Dunlop AL, Hedayatzadeh M, Alio AP, Kirby RS, Alexander GR. Extreme obesity and risk of stillbirth among black and white gravidas. Obstet Gynecol 2007; 110: 552 – 7. (Level II-3)

dehiscence, and venous thrombosis.[12,13] Postpartum complication include future metabolic dysfunctions in the mother. Fetuses of obese pregnant females are at increased risk of macrosomia and impaired growth.[14,15]

The Institute of Medicine recommends weight loss prior to pregnancy and weight gain during pregnancy are list below:

Body Mass Index (BMI) 25-29, weight gain of 15-25 lb
BMI 30 or more, weight gain of 11-20 lb.

During pregnancy, the American College of Obstetricians and Gynecologists (ACOG) recommends counseling obese women about the limitations of ultrasound in identifying structural anomalies. Additionally, pregnant women with a BMI of 30 or more should have early screening for glucose intolerance. For patients with a pre-pregnancy BMI of 35.0–39.9, weekly antenatal fetal surveillance may be considered beginning by 37 0/7 weeks of gestation. For patients with pre-pregnancy BMI 40 or greater, weekly antenatal fetal surveillance may be considered beginning at 34 0/7 weeks of gestation. Consultation with anesthesia service should be considered for obese pregnant women with obstructive sleep apnea because they are at an increased risk of hypoxemia, hypercapnia, and sudden death. Preoperative skin cleansing before cesarean delivery with an alcohol-based solution should be performed unless contraindicated. Vaginal cleansing before cesarean delivery in laboring patients and those with ruptured membranes using either povidone–iodine or chlorhexidine gluconate may be considered.[16]

Data Review

DPMH has previously completed a reviewed of tirzepatide for another indication, for glycemic control, in 2022[17] and concluded the following:

Pregnancy

The available human data are insufficient to assess a drug-related risk of congenital malformations, miscarriage, or adverse maternal or fetal outcomes.

Based on animal studies, tirzepatide may cause fetal harm. Increased incidences of external, visceral, and skeletal malformations and increased incidences of visceral and skeletal developmental variations were observed in rat pups with maternal exposures to tirzepatide at doses that were less than the human clinical dose based on AUC. However, the DDLO Pharmacology/Toxicology Team noted that the fetal toxicities appear to be

[12] Hibbard JU, Gilbert S, Landon MB, Hauth JC, Leveno KJ, Spong CY, et al. Trial of labor or repeat cesarean delivery in women with morbid obesity and previous cesarean delivery. National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. Obstet Gynecol 2006; 108: 125 – 33. (Level II-2)
[13] Chu SY, Kim SY, Schmid CH, Dietz PM, Callaghan WM, Lau J, et al. Maternal obesity and risk of cesarean delivery: a meta-analysis. Obes Rev 2007; 8: 385 – 94. (Meta-analysis)
[14] Sewell MF, Huston-Presley L, Super DM, Catalano P. Increased neonatal fat mass, not lean body mass, is associated with maternal obesity. Am J Obstet Gynecol 2006; 195: 1100 – 3. (Level II-2)
[15] Hull HR, Dinger MK, Knehans AW, Thompson DM , Fields DA . Impact of maternal body mass index on neonate birthweight and body composition. Am J Obstet Gynecol 2008; 198: 416.e1 – e6. (Level II-2)
[16] Use of prophylactic antibiotics in labor and delivery. ACOG Practice Bulletin No. 199. American College of Obstetricians and Gynecologists [published erratum appears in Obstet Gynecol 2019; 134:883-4]. Obstet Gynecol 2018; 132: e103 – 19. (Level III)
[17] DPMH review of Mounjaro on January 19, 2022 by Wenjie Sun, MD, NDA 215866, DARRTS Reference ID 4922584 and Addendum Memo on March 18, 2022, DARRTS Reference ID 4955128

secondary to maternal toxicity caused by the pharmacological activity of tirzepatide (decreased body weight and body weight gain observed in pregnant dams).

Lactation
There are no data on the presence of tirzepatide in human or animal milk, the effects of tirzepatide on the breastfed infant and the effects on milk production.
Tirzepatide is likely to be present in human milk because it is a GLP-1 agonist and other GLP agonists are present in animal milk. When a drug is present in animal milk, it is likely to be present in human milk. Additionally, GLP-1 is naturally present in human milk.

Fertility
There are no human data on tirzepatide adversely affecting male or female fertility. Animal reproductive studies do not show any adverse effects of tirzepatide on fertility. Like other GLP-1 receptor agonists, tirzepatide also delays gastric emptying. Because the efficacy of the oral hormonal contraceptive is affected by administration of tirzepatide secondary to delayed gastric emptying, DPMH recommends insertion of language regarding oral hormonal contraceptive use under subsection 8.3 and section 17 of the labeling.

Since the last DPMH review, there are some new data presented by the applicant. Please see new data under each of the respected sections below.

Pregnancy
Although pregnant women were excluded from the clinical trials, the applicant reported 18 maternal exposures to tirzepatide[18] in the SURMOUNT-1 (n= 16) and SURMOUNT-2 (n=2) studies.

Of the 18 pregnancies exposed to tirzepatide, the outcomes are as follows (Appendix B)[19]:

- 10 livebirths
  - 3 preterm births (PTB) (1 complicated by preeclampsia, 1 unknown reason, 1 premature preterm rupture of membrane (PPROM))
  - 7 term births
- 1 ectopic pregnancy
- 1 spontaneous abortion (SAB)
- 4 elective terminations (TAB) (1 due to medical reason, reasons not given for others)
- 2 lost to follow-ups

The following maternal complications during pregnancy were reported:

- 1 reported pre-eclampsia,
- 1 reported hypertension and gestational diabetes, and
- 1 reported hyperglycemia

[18] Based on the submission and the response to FDA IR submitted on June 5, 2023.
[19] Based on Reviewer's table under Appendix B. This count is discrepant from the Sponsor's report under "Summary of Clinical Safety," as well of IR response under June 5, 2023.

There were no reported major or minor fetal malformations among participants exposed to tirzepatide.

For more details of the cases, the reader is referred to Appendix A for a reviewer's table of pharmacovigilance cases extracted from the submitted narratives (pregnancy outcomes were updated from Applicants' response to FDA IR submitted on June 5, 2023).

The applicant also completed a cumulative search of their global safety database since approval. and identified 50 unique (45 maternal and 5 paternal) tirzepatide exposed cases.[20]

Of the 45 maternally exposed pregnancies, there were 25 cases from the clinical trials and 20 from the postmarket reports.[21] In addition to the 18 clinical trial cases listed above, there were 5 clinical trial exposed pregnancies[22] (two livebirths (one preterm), one pregnancy termination, one spontaneous abortion, and one lost to follow up) reviewed previously for NDA 215866 and two new pregnancies in clinical trials not reviewed above or previously (two maternal exposed cases resulted in one ectopic pregnancy and one spontaneous abortion).[23]

Additionally, there were 20 exposed pregnancies reported from the postmarket experience. There are no pregnancy outcomes reported for these cases except one pregnancy that ended in a spontaneous abortion.

There were no cases of congenital birth defect reported within the pharmacovigilance database to date.

The reader is referred to Appendix B for the applicant's table of cumulative pharmacovigilance cases. The outcomes are summarized below:

- 12 livebirths (4 were preterm from the clinical trials, one was unexposed)
    - Patient (b) (6) was delivered at 34 weeks due to preeclampsia and decreased fetal heart rate secondary due to umbilical cord compression. Exposure occurred first trimester, drug stopped at gestational week 5, 245 days prior due date.
    - Patient (b) (6) was delivered preterm at 34 weeks gestational age. Infant was admitted to NICU for 24 days due to prematurity. Exposure occurred during first trimester (and maybe longer, there were two reported stop dates).
    - Patient (b) (6) was delivered preterm at 25 weeks due to premature preterm rupture of membrane. Patient was exposed during first trimester near conception.

[20] Based on applicant's report titled "Pregnancy, lactation, and Reproductive Potential Data," there were 49 unique (44 maternal and 5 paternal) tirzepatide exposed cases reported. However, this reviewer identified one more exposed case from the clinical trials that was reported previous under NDA 215866, Phase I Study I8F-MC-GPGR (a termination), which was not included in the applicant's count. The applicant only included Phase 2 and 3 studies (see Question 4 of the applicant's June 5, 2023 IR response). This makes the total of 50 unique cases. There were 45 maternal exposed cases.
[21] Table 4.3 and 4.4 of applicant's June 5, 2023 IR response.
[22] Study GPGH, GPGK, GPGL, GPGR.
[23] Applicant's June 5, 2023 IR response.

    - Patient [redacted] (b) (6) was a premature delivery via c-section at unknown gestational age with exposure during first trimester. Infant had respiratory distress and hypoglycaemia after birth.
- 2 ectopic pregnancies
- 4 SAB (3 clinical trial, 1 postmarket)
- 5 TAB
- 11 lost to follow up (3 clinical trial, 8 postmarket)
- 2 "not reported" outcomes (postmarket cases)
- 9 "in utero" (postmarket cases)

Reviewer comment: Although thirty percent of the live births reported were classified as preterm, which is higher than the background rate of preterm births, the total number of cases is small. Therefore, DPMH does not recommend labeling this adverse outcome at this time.

The applicant conducted a search of the published literature including OVID Embase, PubMed, and Google Scholar using search "tirzepatide" or "GLP-1 RA" or "incretin" and "pregnant" or "pregnancy". The applicant identified one case report[24] of an uncomplicated unplanned pregnancy of a patient with Type 2 Diabetes Mellitus (T2DM) exposed to dulaglutide (1.5mg/week) and metformin (100mg twice per day) during the first 15 weeks of gestation which resulted in a term birth via emergency c-section. The infant weighted 2860g and had jaundice after birth but resolved spontaneously. No other adverse events were reported.

DPMH performed a search of published literature using PubMed, Embase, and reference sites (Micromedex,[25] ReproTox,[26] Shepard's)[27] and found no additional published data on the use of tirzepatide in pregnancy.

Lactation

There was no exposure to tirzepatide during lactation within the clinical trials.

The applicant completed a cumulative search of their pharmacovigilance database since approval and found 2 spontaneous cases of exposure of tirzepatide during lactation. There were no adverse events reported.

The applicant conducted a search of the published literature including OVID Embase, PubMed, and Google Scholar using search "tirzepatide" or "GLP-1 RA" or "incretin" and "pregnant" or "breastfeeding" or "lactating". No literature articles or abstracts citing tirzepatide or GLP-1 RA have been reported during the period of this review.

DPMH also conducted an updated search of published literature using PubMed, Embase, and

[24] Burlina S, Dalfra MG, Caprino R, Lapolla A. A case report on use of dulaglutide during the first weeks of pregnancy in woman affected by type 2 diabetes mellitus. Acta Diabetol. 2023;60(1):137-138.
[25] Truven Health Analytics information, http://www.micromedexsolutions.com/. Accessed 5/23/2023.
[26] ReproTox Website: www.Reprotox.org. REPROTOX was developed as an adjunct information source for clinicians, scientists, and government agencies. Accessed 5/23/23.
[27] 2020 Shepard's: A Catalog of Teratogenic Agent. Accessed 5/23/23.

reference sites (Micromedex,[28] LactMed,[29] Brigg's,[30] or Hales[31]) regarding tirzepatide use in lactation, no new study was identified.

Fertility

Tirzepatide was used in male and females of reproductive potential during the clinical trial. There are no cases of infertility related to tirzepatide use identified.

The applicant conducted a search of their global safety database for fertility analysis, fertility and fertilization interventions female, and sexual function and fertility disorder NEC, and found four postmarket cases.

- (b) (6) – Female patient of unknown age using tirzepatide for weight loss. The patient experienced libido-decrease and sensory loss. Time to onset was approximately 2 weeks. Action taken was not provided and outcome is not resolved.
- (b) (6) – Male patient of 45 years of age using tirzepatide for an unknown indication. The patient experienced the event of libido decrease on an unknown date. Information related to action taken and outcome were not provided.
- (b) (6) – Male patient of 56 years of age using tirzepatide for weight loss. Treatment started on (b) (6) using 2.5 mg. Drug dosage was increased to 5 mg in (b) (6) and to 7.5 mg on (b) (6). The patient described libido decrease on both 5- and 7.5-mg doses. Information related to action taken and outcome were not provided.
- (b) (6) – Male patient of 68 years of age using tirzepatide for insulin resistance and weight loss. Treatment started in (b) (6) with 7.5 mg. After the first injections (as reported), the patient started to have sexual problems and would be unable to ejaculate. He also lost 6 to 7 pounds. Information related to action taken and outcome were not provided.

The applicant conducted a review of literature in OVID Embase, PubMed, and Google Scholar using search criteria "tirzepatide" or "GLP-1 RA" or "incretin" and "pregnancy" or "fertility" cumulatively through March 2023. There are no articles regarding use of tirzepatide adversely effecting fertility. The applicant notes there are several studies that describe the benefit of GLP-1 RA treatment to address fertility among women with polycystic ovarian syndrome.

Reviewer comment:
Tirzepatide is used in females and males of reproductive potential. Approximately 2463/4740 females of reproductive potential (defined as age 15-50) were enrolled in the clinical trials.[32] Although there are four cases of sexual problem reported in the safety database, there were

[28] Truven Health Analytics information, http://www.micromedexsolutions.com/. Accessed 5/23/2023.
[29] http;//toxnet.nlm.nih.gov/newtoxnet/lactmed.htm. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The lactMed data base provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfeeding infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility. Access 5/24/23.
[30] Briggs GG, Freeman RK. Drugs in pregnancy and lactation: a reference guide to fetal and neonatal risk. 10th Ed. 2015.
[31] Hale, Thomas. Hale's Medications and Mother's Milk 2019. Springer Publishing Company, New York, NY.
[32] Applicant's June 5, 2023 IR response.

(b) (4) *sales made in female and males of 18-64 years of age; therefore, DPMH concludes that this finding does not represent a signal at this time.*[33] *There are no new signals identified regarding the effect of tirzepatide on human fertility.*

DISCUSSION AND CONCLUSIONS

Pregnancy

No new substantive safety signals were identified in this updated review since the last DPMH review in 2022. There were a few cases of pre-term birth and "sexual problem" identified during this review, but the cases were too limited to draw any clear conclusions. There are no new data with respect to drug-related risk of congenital malformations, miscarriage, or adverse maternal outcomes.

Additionally, weight loss is not recommended during pregnancy and therefore tirzepatide is not recommended to be used during pregnancy. DPMH recommends including this recommendation under subsection 8.1 "Risk Summary." DPMH also recommends inserting a "Clinical Consideration" heading to describe the effect of obesity on pregnancy to be consist with other drugs indicated or weight loss. Currently approved Mounjaro labeling includes the statement: "should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus." DPMH recommends that this statement is not included in labeling for the current NDA.

Obesity is an epidemic in United States with a prevalence of 39.7% in females of reproductive potential (20-39 years in United States).[34] Although tirzepatide is not recommended to be used during pregnancy due to its weight loss effect, it will likely be used in females of reproductive potential (FRP), and there may be unintended exposures during the first trimester before the pregnancy is recognized. Because there are currently insufficient data regarding tirzepatide use in pregnancy, use of tirzepatide in pregnant animals resulted in fetal growth reduction and fetal malformations, and unintended pregnancy exposure has occurred with the already approved tirzepatide product, it is important to evaluate the safety of tirzepatide during pregnancy. With a proposed indication of weight loss, there is likely to be an increase in unintended exposure to tirzepatide during pregnancy. Therefore, DPMH recommends a postmarket requirement (PMR) for a pregnancy registry study and a complementary study of a different design to collect these data to better inform the safety of this drug in pregnancy.

Lactation

DPMH did not identify an additional safety signal regarding use of tirzepatide during lactation. There are no data on the presence of tirzepatide in human or animal milk and the effects on milk production. There are insufficient data currently to characterize the effects of tirzepatide on the breastfed infant.

FDA issued a PMR for a clinical lactation study at the time of NDA 215866 approval for T2DM. The current applicant is already in the process of completing a clinical lactation study for Mounjaro. Therefore, another PMR for a clinical lactation study is not required for this NDA.

[33] Applicant's June 5, 2023 IR response.

[34] Hales CM, Carroll MD , Fryar CD , Ogden CL . Prevalence of obesity and severe obesity among adults: United States, 2017-2018. NCHS Data Brief 2020; 360 : 1 – 8 . (Level II-2)

Females and Males of Reproductive Potential

DPMH did not identify a new safety signal regarding use of tirzepatide and effect on fertility. Therefore, this labeling should be consistent with the approved labeling for tirzepatide.

LABELING RECOMMENDATIONS

DPMH revised subsections 8.1, 8.2, and 17 of labeling for compliance with the PLLR (see below). DPMH refers to the final NDA action for final labeling.

(b) (4)

2 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

APPENDIX A

Reviewer's Table[35] of Pregnant Subjects with T2DM in study SURMOUNT 1 (Protocol I8F-MC-GPHK)

#	ID	Age/Race	BMI	Dose (mg/week)	Timing (trimester)	Pregnancy Outcome
1	(b) (6)	35 B	48.7	5	1st	Ectopic pregnancy (treated with methotrexate and followed until zero) - Updated as elective termination*
2		28 W/H	45.8	5	1st	Spontaneous abortion (SAB)
3		26 W/H	35.2	Placebo	1st	Unknown (patient discontinued study)
4		28 B	41.1	10	1st	Termination for unknown reason
5		38 B	42.4	15	1st	Unknown (patient discontinued study) - Updated as lost to follow up*
6		22 A	36	10	1st	Induced abortion (termination for unknown reason)
7		34 A	36.5	15	Unexposed, stopped >1 year prior to pregnancy	Spontaneous abortion
8		20 W H	33.9	10	1st	ongoing last reported- no outcome reported - Updated as lost to follow up*
9		24 W H	47.3	10	1st	Term birth via vaginal delivery*
10		25 W H	41.8	15	1st	Preterm delivery via C-section* at 34 weeks due to preeclampsia and decreased fetal heart rate; NICU admission and later discharged; female infant, weight 1800g.
11		22 W H	37.1	10	1st (last dose on day 428, positive pregnancy test on 443, edc 681)	Preterm live birth at 7 month gestation, weight 3.5 lb. admitted to NICU due to prematurity.
12		21 W	38	10	1st	Livebirth at 38 weeks, weight 9 lb 1 oz. No birth defect reported by the mother.
13		37 A	39.3	placebo	1st	Livebirth at term by C-section, girl, weight 3950 g, Apgar 10/10/10

[35] Based on narrative from SURMONT 1 from Applicant's submission

#	ID	Age/Race	BMI	Dose (mg/week)	Timing (trimester)	Pregnancy Outcome
14	(b) (6)	23 W H	54.5	10	1st	Term C-section*
15		39 B	35.3	15	1st	Livebirth delivery via c-section* at 37 weeks, male, weight 3.482 kg. No birth defect reported. Infant was admitted to NICU for 8 days for premature delivery (per report). COVID-19 infection maternal 37 weeks; maternal hyperglycemia at term.
16		30 W H	53.5	15	1st	Livebirth at term via C-section, weight 2.7 kg. Gestational diabetes and hypertension, low AFI at term
17		37 W H	35.2	5	1st	PPROM. Preterm delivery via C-section* at 25 weeks, female, weight 1.4 kg.
18		26 W H	44.9	5	1st	Termination due to medical reason (history of HELLP) by misoprostol
19		27 W H	44.2	15	1st	Term C-section*
20		25 American Indian/AN, H	42.1	Placebo	Unexposed (stopped drug prior to pregnancy)	Ongoing, no outcome reported. Vaginal infection (yeast? Was treated with nystatin)
21		31 W H	40.9	Placebo	1st	GDM. Livebirth term, male, weight 8.3 lb.
22		30 A	34.6	5	unexposed	Preterm delivery*

*Outcome updated by applicant's response to FDA IR on June 5, 2023.

Reviewer comment:

There are a total of 22 pregnancies reported from study participants under SURMOUNT I, four of which were exposed to placebo and 18 were on the tirzepatide arm of the study. Participants ID (b) (6) *and* (b) (6) *were on the tirzepatide arm but not exposed to tirzepatide during pregnancy. This was confirmed via applicant's response to FDA IR (Question 1). Therefore, there were a total of 16 pregnancies exposed to tirzepatide during pregnancy.*

Patient ID (b) (6) *was categorized by the applicant as an elective termination. This reviewer disagrees. From the narratives, this was a case of ectopic pregnancy treated with methotrexate.*

<u>Paternal exposures from SURMOUNT I</u>

(b) (6) (5 mg), ongoing pregnancy, no outcome reported

(b) (6) (10mg), ongoing, no outcome reported

(b) (6) (placebo), ongoing, no outcome reported. Partner did experience GDM.

Reviewer's Table[36] of Pregnant Subjects with Obesity and T2DM in SURMOUNT 2 I8F-MC-GPHL

ID	Age/Race	BMI	Dose (mg/week)	Timing (trimester)	Pregnancy Outcome
(b) (6)	25 W H	36.9	Placebo	1st	Ongoing, no outcome reported
	39 W H	32.5	Placebo	1st	Ongoing, no outcome reported
	37 A H	37.4	15	1st	Livebirth at 37.5 weeks by C-section, Apgar 9 and 10, weight 3465g.
	38 W H	39.3	15	1st	Pregnancy stopped by misoprostol, reason unknown. - Updated as elective termination*

* Outcome updated by applicant's response to FDA IR on June 5, 2023.

Paternal exposure from SURMOUNT II

(b) (6) (15mg), no outcome reported, updated as lost to follow-up*

(b) (6) (placebo), live birth

Seven pregnancies were reported under submission for NDA 215866.

[36] Based on narrative from SURMONT 2 from Applicant's submission

Table 2.7.4.121. List of Pregnancies Reported in Completed Tirzepatide Clinical Studies

Study Patient ID	Age of Mother (years)	Study Drug	Estimated Period of Exposure (weeks)	Pertinent Clinical Information	Maternal Complications	Fetal Outcome
(b) (6)	28	TZP 5 mg	7.9	• Contraception: cyproterone/ ethinylestradiol • Preexisting condition of polycystic ovaries	None reported	Good condition
	28	Sema 1 mg	9.1	• Contraception: drospirenone and ethinylestradiol	No report	No report
	35	TZP 15 mg	5.6	• Contraception: ethinylestradiol/ norelgestromin	No report	No report
	27	TZP 5 mg	8.9	• Contraception: drospirenone and ethinylestradiol • Medical history of Cesarean section	No report	No report
	39	TZP 10 mg	16.3	• Contraception: birth control pills (unspecified)	None reported	No report
	41	TZP 10 mg	5.1	• Contraception: Male or female condom with spermicide • Medical history of miscarriages, infertility due to excision of fallopian tube, postoperative adhesions, pregnancy (b) (6) gestational diabetes.	Spontaneous abortion	--
	26	TZP 5 mg	1.7	• Negative medical history specific to pregnancy • Previously used drospirenone and ethinylestradiol and during screening for study	Elective termination	--
				• Study OC was her contraception during active dosing phase • Did not resume previous OC contraception after end of study dosing phase • Used only condom without an additional effective method as required per protocol, during final follow-up period when no longer on any OC.		

Abbreviations: ID = identification; OC = oral contraception; Sema = semaglutide; TZP = tirzepatide.

[a] Male patient reported pregnancy of partner.

Source: GPGK, GPGL, GPGH, GPGR narratives

Reviewer comment:

Updated report from applicant reply to FDA IR submitted on June 5, 2023, states that

- *Subject ID* (b) (6) *ended preterm birth, which was previous reported as unknown.*
- *Subject ID is now reported as in utero.*
- *Subject ID is reported as SAB.*
- *Subject ID (paternal exposure) is reported as in utero.*

APPENDIX B. Pregnancies Reported from the Pharmacovigilance Database[37]

LSS Case Number	Trimester Exposed Initial Report [Further Evaluation]	Study Code	Site ID	Patient ID	Report Type	Neonatal Birth Type Initial Report [Further Evaluation]	Neonate Delivery Type	Neonate Fetal Outcome	Exposure Type	Other Comments
(b) (6)	1st	GPHK	0203	(b) (6)	PRO	Elective termination	NA	NA	Maternal	
	1st, 2nd	GPHK	0208		PRO	Full-term	Cesarean	Normal	Paternal	
	1st [before pregnancy]	GPHK	0203		PRO	Spontaneous abortion	NA	NA	Maternal	
	Before pregnancy	GPHK	0703		PRO	Premature	NR	Normal	Maternal	
	UNK	GPHK	0703		PRO	Premature	NR	Normal	Infant	
	1st	GPHK	0131		RETRO	Spontaneous abortion	NA	NA	Maternal	
	1st	GPHK	0147		PRO	In utero [LTF]	NA	NA	Maternal	
	1st	GPHK	0139		PRO	Full-term	Cesarean	Normal	Maternal	
	1st	GPHK	0128		PRO	Premature	Cesarean	Normal	Maternal	Pre-eclampsia
	1st	GPHK	0128		PRO	Premature	Cesarean	Normal	Infant	
	1st	GPHK	0105		PRO	In utero [LTF]	NA	NA	Maternal	
	UNK	GPHK	0144		PRO	Elective termination	NA	NA	Maternal	
	1st	GPHK	0119		PRO	In utero [elective termination]	NA	NA	Maternal	Ectopic pregnancy
	1st	GPHK	0129		PRO	Premature	NR	Normal	Maternal	
	1st	GPHK	0129		PRO	Premature	NR	Normal	Infant	
	1st	GPHK	0126		PRO	Full-term	Vaginal	Normal	Maternal	
	1st	GPHL	054333		PRO	Elective termination	NA	NA	Maternal	

[37] Appendix 1 from applicant's response to FDA IR submitted on June 6, 2023.

Table APP 1. Listing of Pregnancies from Clinical Trials and Postmarketing Reports, Including Updates Based on Further Evaluation of Initial Cases

LSS Case Number	Trimester Exposed Initial Report [Further Evaluation]	Study Code	Site ID	Patient ID	Report Type	Neonatal Birth Type Initial Report [Further Evaluation]	Neonate Delivery Type	Neonate Fetal Outcome	Exposure Type	Other Comments
Reports from Clinical Trials										
(b) (6)	1st	GPGH	0508	(b) (6)	PRO	In utero [spontaneous abortion]	NA	NA	Maternal	
	1st	GPGL	0663		PRO	In utero [LTF]	NA	NA	Maternal	
	1st	GPGL	0654		PRO	Premature	Cesarean	Normal	Maternal	
	1st	GPGL	0654		PRO	Premature	Cesarean	Normal	Infant	Neonatal respiratory distress, hypoglycemia neonatal
	1st, 2nd, 3rd	GPGL	0758		PRO	In utero [LTF]	NA	NA	Paternal	
	1st	GPGK	0701		PRO	NR	NR	Normal	Maternal	
	1st	GPHK	0505		PRO	Elective termination	NA	NA	Maternal	
	1st	GPHK	0503		PRO	Full-term	Cesarean	Normal	Maternal	
	1st	GPHK	0510		PRO	Full-term	Cesarean	Normal	Maternal	
	1st	GPHK	0503		PRO	Premature	Cesarean	Normal	Maternal	
	1st	GPHK	0503		RETRO	Premature	Cesarean	Normal	Infant	
	1st	GPHK	0406		PRO	Full-term	Cesarean	Perinatal complication	Maternal	
	1st, 2nd, 3rd	GPHK	0405		PRO	Full-term	Cesarean	Normal	Paternal	
	1st	GPHK	0401		PRO	Full-term	Cesarean	Normal	Maternal	

LSS Case Number	Trimester Exposed Initial Report [Further Evaluation]	Study Code	Site ID	Patient ID	Report Type	Neonatal Birth Type Initial Report [Further Evaluation]	Neonate Delivery Type	Neonate Fetal Outcome	Exposure Type	Other Comments
(b) (6)	1st	GPHL	040941	(b) (6)	PRO	Full-term	Cesarean	Normal	Maternal	
	UNK	GPHL	033649		PRO	In utero [LTF]	NA	NA	Paternal	
	1st	GPHN	097450		PRO	Spontaneous abortion	NA	NA	Maternal	
	1st	GPHO	0120		RETRO	Elective termination	NA	NA	Maternal	Ectopic pregnancy
	1st	GPHO	0102		RETRO	Elective termination	NA	NA	Paternal	
Postmarketing/Spontaneous Reports										
(b) (6)	UNK	-	-	-	PRO	NR	NA	NA	Maternal	
	1st	-	-	-	PRO	In utero	NA	NA	Maternal	
	UNK	-	-	-	PRO	NR	NA	NA	Maternal	
	1st	-	-	-	PRO	In utero	NA	NA	Maternal	
	UNK	-	-	-	PRO	In utero [LTF]	NA	NA	Maternal	
	UNK	-	-	-	RETRO	Full-term	NA	NA	Maternal	Exposure was during breastfeeding only
	UNK	-	-	-	PRO	In utero	NA	NA	Maternal	
	UNK	-	-	-	PRO	In utero [LTF]	NA	NA	Maternal	
	UNK	-	-	-	PRO	In utero [LTF]	NA	NA	Maternal	
	UNK	-	-	-	PRO	In utero [LTF]	NA	NA	Maternal	
	1st	-	-	-	PRO	In utero	NA	NA	Maternal	

LSS Case Number	Trimester Exposed Initial Report [Further Evaluation]	Study Code	Site ID	Patient ID	Report Type	Neonatal Birth Type Initial Report [Further Evaluation]	Neonate Delivery Type	Neonate Fetal Outcome	Exposure Type	Other Comments
(b) (6)	UNK	-	-	-	PRO	In utero [LTF]	NA	NA	Maternal	
	UNK	Tirzepatide patient support program	-	(b) (6)	PRO	In utero [LTF]	NA	NA	Maternal	
	UNK	-	-	-	PRO	In utero	NA	NA	Maternal	
	UNK	-	-	-	PRO	In utero [LTF]	NA	NA	Maternal	
	UNK	-	-	-	PRO	In utero [LTF]	NA	NA	Maternal	
	1st	-	-	-	PRO	In utero	NA	NA	Maternal	
	1st	-	-	-	RETRO	Spontaneous abortion	NA	NA	Maternal	
	UNK	-	-	-	PRO	In utero	NA	NA	Maternal	
	UNK	-	-	-	PRO	In utero	NA	NA	Maternal	
	UNK	-	-	-	PRO	In utero	NA	NA	Maternal	

Abbreviations: GPGH = Study I8F-MC-GPGH; GPGK = Study I8F-MC-GPGK; GPGL = Study I8F-MC-GPGL; GPHK = Study I8F-MC-GPHK; GPHL = Study I8F-MC-GPHL; GPHN = Study I8F-MC-GPHN; GPHO = Study I8F-MC-GPHO; ID = identifier; LSS = Lilly Safety System; LTF = lost to follow-up; NA = not applicable; NR = not reported; PRO = prospective; RETRO = retrospective; UNK = unknown.

[a] Reported as part of postmarketing study.

Notes: Rows with heavy border lines indicate corresponding maternal and infant cases.

Gray shading indicates cases that were confirmed as unexposed to tirzepatide during pregnancy upon further review.

Lost to follow-up includes no response from investigator following 2 attempts, no contact information, or reporter did not consent to be contacted.

Reviewer comment:

This reviewer notes that case (b) (6) *from the previous submission is missing from this table. This clinical trial subject received tirzepatide 5 mg and the pregnancy ended in a TAB.*

Additionally, this reviewer saw there were three more clinical trial pregnancies listed in this table that were not previously reviewed or presented in SURMOUNT 1 and 2.

- *Two were maternal exposures (ID* [redacted] *) that resulted in one ectopic pregnancy and one SAB.*
- *One* [redacted] *was a paternal exposure which resulted in a TAB.*

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/s/

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LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	August 17, 2023
Requesting Office or Division:	Division of Diabetes, Lipid Disorders, and Obesity (DDLO)
Application Type and Number:	NDA 217806
Product Name, Dosage Form, and Strength:	Zepbound (tirzepatide) injection, 2.5 mg/0.5 mL, 5mg/0.5 mL, 7.5 mg/0.5 mL, 10 mg/0.5 mL, 12.5mg/0.5 mL, 15 mg/0.5 mL
Product Type:	Combination Product (Drug-Device)
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Eli Lilly and Company (Lilly)
FDA Received Date:	November 17, 2022 and May 8, 2023
TTT ID #:	2022-2848
DMEPA 1 Safety Evaluator:	Ariane O. Conrad, PharmD, BCACP, CDCES
DMEPA 1 Team Leader:	Idalia E. Rychlik, PharmD

1 REASON FOR REVIEW

As part of the approval process for Zepbound (tirzepatide) injection, the Division of Diabetes, Lipid Disorders, and Obesity (DDLO) requested that we review the proposed Zepbound prescribing information, Instructions for Use, container labels, and carton labeling for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
ISMP Newsletters*	N/A
FDA Adverse Event Reporting System (FAERS)*	N/A
Other	N/A
Labels and Labeling	C

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We performed a risk assessment of the proposed prescribing information (PI), Instructions for Use (IFU), container labels, and carton labeling for Zepbound to identify areas of vulnerability that may lead to medication errors and other areas of improvement. The PI and IFU are acceptable from a medication error perspective. We identified some areas of concern for the proposed carton and container labels, and we provide our recommendations below in Section 4.1 for Lilly.

4 CONCLUSION & RECOMMENDATIONS

The proposed prescribing information and Instructions for Use for Zepbound are acceptable from a medication error perspective; however, we note that the proposed carton and container labels are not acceptable, and we have provided recommendations to improve clarity below in Section 4.1.

We note that DMEPA 1's evaluation of the Use-Related Risk Analysis has been completed and that there were no additional label and labeling comments from those reviews.[a]

4.1 RECOMMENDATIONS FOR ELI LILLY AND COMPANY

We recommend the following be implemented prior to approval of this BLA:

A. General Comments (Container labels & Carton Labeling)

1. We note that the first letter of the proprietary name, Zepbound, is not capitalized and that you choose to utilize two colors for the proprietary name, splitting the name in half as "zep" and "bound" which could impact the readability of the name. This may lead to misinterpretation of the proprietary name; thus, we recommend that you capitalize the first letter of the proprietary name and consider the use of a single color to improve prominence. Additionally, we note (b) (4) and the intended meaning is unclear so we recommend that you delete these (b) (4)
2. As currently presented, the format for the expiration date is not defined. To minimize confusion and reduce the risk for deteriorated drug medication errors, identify the format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.

B. Container Labels

1. As currently presented, there are two barcodes (i.e., linear barcode and Quick Response Code) on the pen container label. Since the drug barcode is often used as an additional verification before drug administration in the inpatient setting, the presence of multiple barcodes is confusing to the healthcare providers. Therefore, we recommend you move the barcode that does not contain the NDC number away from the barcode containing the NDC number and present it in a

[a] Kumar, N. Use-Related Risk Analysis Review for Zepbound (IND 139721 and NDA 217806). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2023 May 9. TTT ID No.: 2022-2717 and 2022-2849.

size that does not compete with or distract from the presentation of other required or recommended information on the label.

C. Carton Labeling

1. In June 2021, FDA finalized the Guidance for Industry on product identifiers required under the Drug Supply Chain Security Act (DSCSA). The Act requires manufacturers and re-packagers to affix or imprint a product identifier to each package and homogenous case of a product intended to be introduced in a transaction in(to) commerce. The product identifier includes the NDC, serial number, lot number, and expiration date in both a human-readable form and machine-readable (2D data matrix barcode) format. We note that the proposed cartons do not appear to contain the machine-readable product identifier; thus, we recommend that you review the draft guidance to determine if the product identifier requirements apply to your product's labeling. See *Guidance for Industry: Product Identifiers under the Drug Supply Chain Security Act - Questions and Answers (June 2021)*. If you determine that the product identifier requirements apply to your product's labeling, we request you add a place holder to the carton labeling.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Zepbound received on May 8, 2023 from Eli Lilly and Company.

Table 2. Relevant Product Information for Zepbound	
Initial Approval Date	N/A
Active Ingredient	tirzepatide
Indication	an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adults with an initial body mass index (BMI) of: • 30 kg/m^2 or greater (obesity) or • 27 kg/m^2 or greater (overweight) in the presence of at least one weight-related comorbid condition (e.g., hypertension, dyslipidemia, (b) (4), type 2 diabetes mellitus, obstructive sleep apnea or cardiovascular disease)
Route of Administration	subcutaneous
Dosage Form	injection
Strength	2.5 mg/0.5 mL, 5mg/0.5 mL, 7.5 mg/0.5 mL, 10 mg/0.5 mL, 12.5mg/0.5 mL, 15 mg/0.5 mL
Dose and Frequency	start 2.5 mg once weekly then increase the dose to 5 mg once weekly after 4 weeks. If needed, can increase dose in 2.5 mg increments after a minimum of 4 weeks on the current dose. The maximum maintenance dose is 15 mg administered once a week.
How Supplied	4 Single dose prefilled pens for each strength (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) per carton
Storage	refrigerate at 2°C to 8°C (36°F to 46°F); store in the original carton to protect from light
Container Closure	single-dose prefilled pen (autoinjector) 

APPENDIX B. PREVIOUS DMEPA REVIEWS

On August 14, 2023, we searched for previous DMEPA reviews relevant to this current review using the terms, NDA 217806. Our search identified 1 previous review[b], and we considered our previous recommendations to see if they are applicable for this current review.

[b] Kumar, N. Use-Related Risk Analysis Review for Zepbound (IND 139721 and NDA 217806). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2023 May 9. TTT ID No.: 2022-2717 and 2022-2849.

APPENDIX C. LABELS AND LABELING

C.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[c] along with postmarket medication error data, we reviewed the following Zepbound labels and labeling submitted by Eli Lilly and Company.

- Container labels received on November 17, 2022
- Carton labeling received on November 17, 2022
- Instructions for Use received on November 17, 2022, available from \\CDSESUB1\EVSPROD\nda217806\0001\m1\us\proposed-ifu-pen.docx
- Prescribing Information received on May 8, 2023, available from \\CDSESUB1\EVSPROD\nda217806\0009\m1\us\proposed-uspi.docx
- Medication Guide received on May 8, 2023, available from \\CDSESUB1\EVSPROD\nda217806\0009\m1\us\proposed-medguide.docx

C.2 Label and Labeling Images

[c] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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USE-RELATED RISK ANALYSIS REVIEW

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	May 9, 2023
Requesting Office or Division:	Division of Diabetes, Lipid Disorders, and Obesity (DDLO)
Application Type and Number:	IND 139721, NDA 217806
Product Name, Dosage Form and Strength	Zepbound[1] (tirzepatide) 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
Product Type:	Combination Product (Drug-Device)
Device Constituent:	Prefilled pen
Rx or OTC:	Rx
Applicant Name:	Eli Lilly and Company
FDA Received Date:	November 3, 2022, November 17, 2022
OSE TTT #:	2022-2717, 2022-2849
DMEPA 1 Human Factors Evaluator:	Neha Kumar, PharmD
DMEPA 1 Team Leader:	Murewa Oguntimein, PhD, MHS, CPH, MCHES
DMEPA 1 Associate Director for Human Factors:	Jason Flint, MBA, PMP

[1] The proprietary name, Zepbound, was found conditionally acceptable on March 6, 2023.

1. REASON FOR REVIEW

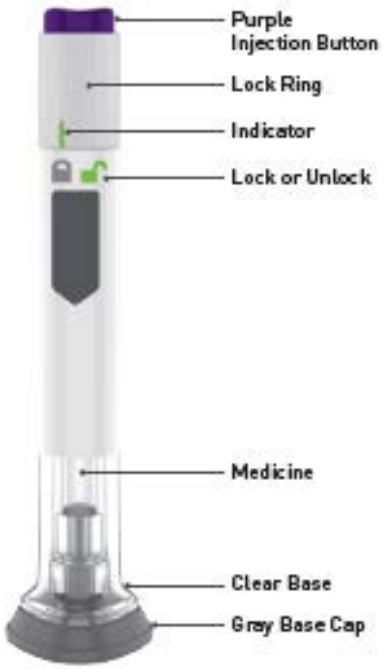
The review evaluates the use-related risk analyses (URRA) and justification to not submit results of a human factors (HF) validation study as part of the marketing application, submitted under IND 139721 and NDA 217806, for Zepbound (tirzepatide) prefilled pen (PFP).

For their proposed product, Zepbound, the Applicant proposes to leverage HF validation data from their currently approved product, US-licensed Mounjaro (tirzepatide), hereafter called Mounjaro, and indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

1.1 PRODUCT DESCRIPTION

Table 1 presents relevant tirzepatide product information that Eli Lilly and Company submitted on November 3, 2022.

Table 1. Relevant Product Information	
Product Name	Zepbound (tirzepatide)
Initial Approval Date	N/A
Active Ingredient	Tirzepatide
Indication	Adjunct to a reduced-calorie diet and increased physical activity for chronic weight management (CWM) in adults with an initial body mass index (BMI) of 30 kg/m^2 or greater (obesity), or 27 kg/m^2 or greater (overweight) in the presence of at least one weight-related comorbid condition (e.g., hypertension, dyslipidemia, obstructive sleep apnea, cardiovascular disease, or type 2 diabetes mellitus)
Route of Administration	Subcutaneous
Dosage Form	Injection
Strength	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
Dose and Frequency	One pen once per week
How Supplied	Clear, colorless to slightly yellow solution available in prefilled single-dose pens. Each carton will contain four prefilled pens of one strength.
Storage	• Store in a refrigerator at 2°C to 8°C (36°F to 46°F). • If needed, each single-dose pen can be stored unrefrigerated at temperatures not to exceed 30°C (86°F) for up to 21 days. • Do not freeze. Do not use if frozen. • Store in the original carton to protect from light.

Container Closure/Device Constituent(s)	
Intended User Group(s)	Patients, caregivers, healthcare professionals
Intended Use Environment(s)	Home, clinic

1.2 REGULATORY HISTORY RELATED TO THE PROPOSED PRODUCT'S HUMAN FACTORS DEVELOPMENT PROGRAM

- On May 16, 2022, the Applicant requested a Type B Pre-New Drug Application (NDA) meeting under IND 139721 to gain Agency agreement on the proposed NDA to support filing and review of tirzepatide as an adjunct to a reduced calorie diet and increased physical activity for chronic weight management (CWM) in adults with obesity, or overweight with weight-related comorbidities. The Applicant asked, "*Is FDA supportive of the strategy of the additional prominent labeling elements, in conjunction with the unique tirzepatide CWM proprietary name to distinguish the CWM product line from MOUNJARO (tirzepatide T2DM product) such that confirmation of differentiation of carton and container labeling between the two product lines through a human factors study is neither warranted nor required?*" In the meeting minutes dated September 12, 2022, we responded, "*We note your intention to cross-reference all device information to NDA 215866. You indicate that the device constituent part is functionally identical to the device constituent part of already approved products Trulicity (BLA 125469) and Mounjaro (NDA 215866). You also indicate that the user characteristics are same or similar as that of NDA 215866 Mounjaro (T2DM), and therefore, the use-related risks are identical. However, you have not submitted a comprehensive risk analysis for our review*

and concurrence for your proposed product for the indication of CWM. We also note your plans to conduct a human factors (HF) differentiation study to compare the tirzepatide for CWM and T2DM indication products and that the study results will not be submitted to the NDA but maintained in the usability/device history file. We agree that you do not need to submit the results of your differentiation study in your marketing application and that this information can be added to your design history file. We recommend you conduct a comprehensive use-related risk analysis if you have not already completed one. The comprehensive use-related risk analysis should include a comprehensive and systematic evaluation of all the steps involved in using your product (e.g., based on a task analysis), the errors that users might commit or the tasks they might fail to perform, and the potential negative clinical consequences of use errors and task failures.

Your risk analysis should also discuss risk-mitigation strategies you employed to reduce risks you have identified and the methods you intend to use for validating the risk-mitigation strategies. This information is needed to ensure that all potential risks involved in using your product have been considered and adequately mitigated and the residual risks are acceptable.

Based on the aforementioned information and data, you should determine whether you need to submit the results of a HF validation study conducted under simulated use conditions with representative users performing necessary tasks to demonstrate safe and effective use of the product. If you determine that an HF validation study does not need to be submitted for your product, submit your risk analysis, comparative analyses, and justification for not submitting the HF validation study to the Agency for review under the IND. We will notify you if we concur with your determination. You may choose to refer to our draft guidance for industry and FDA staff titled, Contents of a Complete Submission for Threshold Analyses and Human Factors Submissions to Drug and Biologic Applications for the content of a HF validation study protocol submission."[2]

- On November 3, 2022 and November 17, 2022, the Applicant submitted their URRA and justification to not submit results a HF validation study as part of the marketing application, under IND 139721 and NDA 217806, respectively, for Zepbound

[2] White, M. Type B Pre-NDA meeting minutes for tirzepatide. Silver Spring (MD): FDA, CDER, OND, DDLO (US); 2022 SEP 12. IND 139721.

(tirzepatide) prefilled pen (PFP). The aforementioned HF documents are the subject of this review.

2. MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review.

Table 2. Materials Considered for this Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	Section 1.1
Background Information Previous HF Reviews	B
Use-related risk analysis and justification to not submit HF study results	C
Label and Labeling	D

3. OVERALL ASESSMENT OF THE MATERIALS REVIEWED

The sections below provide our evaluation of the use-related risk analysis (URRA) and justification to not submit the results of a HF validation study.

3.1 USE-RELATED RISK ANALYSIS

The Applicant submitted a use-related risk analysis (URRA) for their proposed product, Zepbound. Based on the information we have at this time, our review of the URRA determined that the tasks evaluated appear to be comprehensive and appropriate based on what the Applicant proposes for the design and intended use of Zepbound. Furthermore, for the tasks evaluated in the URRA, we did not identify any additional use-related issues that were not analyzed. Based on the identified use-related risks for Zepbound, we determined the risks are mitigated by the proposed labels and labeling.

3.2 JUSTIFICATION TO NOT SUBMIT THE HUMAN FACTORS VALIDATION STUDY RESULTS

Regarding Zepbound physical characteristics and tasks, the Applicant stated that Zepbound has the same PFP device constituent, drug product, strengths, and use steps as Mounjaro. The Applicant also stated that the proposed Zepbound container labels and carton labeling will differ from Mounjaro's in branding elements. All other container labels and carton labeling content is the same as Mounjaro. Additionally, the Applicant stated the Zepbound instructions for use (IFU) differs from Mounjaro only where the brand name text replaces "Mounjaro". The Applicant states that all other IFU content and layouts are the same as Mounjaro.
Based on the information we have at this time, we note the following in terms of:

- Physical characteristics - Zepbound uses the same PFP device constituent with the same drug product and strengths as Mounjaro.
- Tasks - we did not identify any new, differing, or unique tasks for Zepbound as compared to Mounjaro.

- Labeling - apart from the difference in branding elements and the proposed name, Zepbound, replacing Mounjaro, we have not identified labeling differences between Zepbound and Mounjaro. The final acceptability of the labels and labeling will be a review issue when the marketing application is submitted.

Additionally, regarding the intended users, the Applicant stated that Zepbound users are healthcare professionals (HCPs), lay caregivers, and patients. Both HCPs and caregivers were included in the HF validation study for Mounjaro. The Applicant compared and evaluated patient user characteristics of vision, hearing, physical strength, tactile sensitivity, cognitive abilities, mental and emotional state, handedness, and dexterity characteristics and co-morbidities for Mounjaro patient users and the intended patient population for Zepbound. We find that the user characteristics evaluated by the Applicant are appropriate and note that there are no differences identified between the user groups that would impact the proposed intended users' interactions with the user interface. Additionally, the Applicant stated that some of the participants included in the HF validation study for Mounjaro included type 2 diabetes patients with obesity (see table 3 below), which aligns with the proposed indication for Zepbound. We reviewed the HF validation study for Mounjaro on February 15, 2022, and found the results acceptable.[3] Therefore, in this instance we agree with the Applicant's justification to leverage data from the Mounjaro HF validation study.

Table 3. Mounjaro (tirzepatide) HF validation study patient participants

Obesity class	BMI	Number of participants with type 2 diabetes in HF validation testing		
		Validation study	Supplemental study	Totals
Overweight	< 30	8	14	22
Class 1	≥ 30 to < 35	9	8	17
Class 2	≥ 35 to < 40	8	7	15
Class 2	≥ 40 or higher	5	1	6
Totals		30	30	60

4. CONCLUSION AND RECOMMENDATIONS

Our review of the URRA did not identify any new, differing, or unique risks for the proposed product. As such, we agree with the Applicant's justification for not submitting the results from a human factors (HF) validation study with their marketing application for the proposed Zepbound (tirzepatide) 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 PFP. We have no HF recommendations for this marketing application.

[3] Kumar N. Mounjaro (tirzepatide) human factors study results review NDA 215866. Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2022 FEB 15. RCM No.: 2021-1827.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX B. BACKGROUND INFORMATION

B.1 PREVIOUS HF REVIEWS

B.1.1 Methods

On January 17, 2023, we searched the L:drive and AIMS using the terms "139721", "217806", and "tirzepatide" to identify human factors reviews previously performed by DMEPA.

B.1.2 Results

Our search did not identify reviews related to human factors.

APPENDIX C. USE-RELATED RISK ANALYSIS

The use-related risk analysis can be accessed in EDR via: \\CDSESUB1\EVSPROD\ind139721\0126\m5\53-clin-stud-rep\535-rep-effic-safety-stud\obesity\5354-other-stud-rep\hfe\rpt-924743-att-2.pdf

Justification to not submit HF study results as part of the marketing application can be accessed in EDR via: \\CDSESUB1\EVSPROD\nda217806\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\chronic-weight-management\5354-other-stud-rep\hfe\rpt-924743-att-2.pdf

APPENDIX D. LABELS AND LABELING

List of Labels and Labeling Images received on November 17, 2022

- Container labels
- Carton labeling
- Quick Reference Guide
- Instructions for use (image not shown), available in EDR via: \\CDSESUB1\EVSPROD\nda217806\0001\m1\us\proposed-ifu-pen.docx

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