CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

217806Orig1s013

Trade Name:	ZEPBOUND® Injection
Generic or Proper Name:	tirzepatide
Sponsor:	Eli Lilly and Company
Approval Date:	December 20, 2024
Indication:	in combination with a reduced-calorie diet and increased physical activity: to treat moderate to severe obstructive sleep apnea (OSA) in adults with obesity.

CENTER FOR DRUG EVALUATION AND RESEARCH

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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APPROVAL LETTER

NDA 217806 S-013

SUPPLEMENT APPROVAL

Eli Lilly and Company
Attention: Ayana Rowley Henderson, PharmD
Director, Global Regulatory Affairs – North America
Lily Corporate Center
Drop Code 2543
Indianapolis, IN 46285

Dear Dr. Henderson:

Please refer to your supplemental new drug application (sNDA) dated and received June 21, 2024, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Zepbound (tirzepatide) solution for subcutaneous injection.

This Prior Approval supplemental new drug application provides for the addition of a new indication for Zepbound: to treat moderate to severe obstructive sleep apnea (OSA) in adults with obesity.

APPROVAL & LABELING

We have completed our review of this application. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information, Instructions for Use, and Medication Guide), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.[2]

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm
[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in Microsoft Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

REQUIRED PEDIATRIC ASSESSMENTS

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

We are waiving the pediatric study requirement for ages 0 to ≤ 5 years because necessary studies are impossible or highly impracticable given the low disease prevalence of OSA, particularly OSA caused by obesity, in pediatric patients ≤ 5 years of age. In addition, the product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this age group and is not likely to be used in a substantial number of pediatric patients in this group.

We are deferring submission of your pediatric studies for ages 6 to < 18 years for this application because pediatric studies should be delayed until additional safety or effectiveness data have been collected. Assessment in pediatric patients aged 6 to <18 years with obesity-related OSA should follow the pediatric studies to assess safety and effectiveness of tirzepatide in children and adolescents with obesity.

Your deferred pediatric studies required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act (FDCA) are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 314.81 and section 505B(a)(4)(C) of the FDCA. These required studies are listed below.

4759-1 Conduct a 72-week randomized, double-blind, placebo-controlled, parallel-group clinical study in adolescents 12 to 17 years of age (inclusive) with obesity-related obstructive sleep apnea (OSA) to assess the safety, efficacy, and pharmacokinetics of tirzepatide.

Draft Protocol Submission: 06/2031

Final Protocol Submission:	12/2031
Study Completion:	04/2036
Final Report Submission:	10/2036

4759-2 Conduct a 72-week randomized, double-blind, placebo controlled, parallel group clinical study in children 6 to 11 years of age (inclusive) with obesity-related obstructive sleep apnea to assess the safety, efficacy, and pharmacokinetics of tirzepatide.

Draft Protocol Submission:	06/2031
Final Protocol Submission:	12/2031
Study Completion:	11/2039
Final Report Submission:	05/2040

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.[3]

Submit the protocol(s) to your IND 139721, with a cross-reference letter to this NDA. Reports of these required pediatric postmarketing studies must be submitted as an NDA or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[4]

You must submit final promotional materials and Prescribing Information, accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at FDA.gov.[5] Information and Instructions for completing the form can be found at FDA.gov.[6]

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[3] See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October 2019).* https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

[4] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.

[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf

[6] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

PATENT LISTING REQUIREMENTS

Pursuant to 21 CFR 314.53(d)(2) and 314.70(f), certain changes to an approved NDA submitted in a supplement require you to submit patent information for listing in the Orange Book upon approval of the supplement. You must submit the patent information required by 21 CFR 314.53(d)(2)(i)(A) through (C) and 314.53(d)(2)(ii)(A) and (C), as applicable, to FDA on Form FDA 3542 within 30 days after the date of approval of the supplement for the patent information to be timely filed (see 21 CFR 314.53(c)(2)(ii)). You also must ensure that any changes to your approved NDA that require the submission of a request to remove patent information from the Orange Book are submitted to FDA at the time of approval of the supplement pursuant to 21 CFR 314.53(d)(2)(ii)(B) and 314.53(f)(2)(iv).

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

Your product is a Part 3 combination product (21 CFR 3.2(e)); therefore, you must also comply with postmarketing safety reporting requirements for an approved combination product (21 CFR 4, Subpart B). Additional information on combination product postmarketing safety reporting is available at FDA.gov.[7]

If you have any questions, contact Linda Ebonine, Senior Regulatory Health Project Manager, at Linda.Ebonine@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Banu Karimi-Shah, MD
Deputy Director
Division of Pulmonology, Allergy, and Critical Care
Office of Immunology and Inflammation
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
  - Prescribing Information
  - Medication Guide
  - Instructions for Use

[7] https://www.fda.gov/combination-products/guidance-regulatory-information/postmarketing-safety-reporting-combination-products

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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/

LINDA EBONINE
12/20/2024 03:24:33 PM

BANU A KARIMI SHAH
12/20/2024 03:48:22 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

217806Orig1s013

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ZEPBOUND safely and effectively. See full prescribing information for ZEPBOUND.

ZEPBOUND® (tirzepatide) Injection, for subcutaneous use
Initial U.S. Approval: 2022

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).**

---------- RECENT MAJOR CHANGES ----------

Indications and Usage (1)	12/2024
Dosage and Administration (2.2)	12/2024
Warnings and Precautions	
Pulmonary Aspiration During General Anesthesia or Deep Sedation (5.10)	10/2024

---------- INDICATIONS AND USAGE ----------

ZEPBOUND® is a glucose-dependent insulinotropic polypeptide (GIP) receptor and glucagon-like peptide-1 (GLP-1) receptor agonist indicated in combination with a reduced-calorie diet and increased physical activity:

- to reduce excess body weight and maintain weight reduction long term in adults with obesity or adults with overweight in the presence of at least one weight-related comorbid condition. (1)
- to treat moderate to severe obstructive sleep apnea (OSA) in adults with obesity. (1)

Limitations of Use:

Coadministration with other tirzepatide-containing products or with any GLP-1 receptor agonist is not recommended. (1)

----------DOSAGE AND ADMINISTRATION----------

Recommended Dose Escalation Schedule

- The recommended starting dosage is 2.5 mg injected subcutaneously once weekly for 4 weeks. Increase the dosage in 2.5 mg increments after at least 4 weeks until recommended maintenance dosage is achieved. (2.1)
- Consider treatment response and tolerability when selecting the maintenance dosage. (2.1)

Recommended Maintenance and Maximum Dosage

- *Weight Reduction and Long-Term Maintenance:* 5 mg, 10 mg, or 15 mg injected subcutaneously once weekly. (2.2)
- *Obstructive Sleep Apnea:* 10 mg or 15 mg injected subcutaneously once weekly. (2.2)

Maximum Recommended Dosage: 15 mg injected subcutaneously once weekly. (2.2)

Administration Instructions

See full prescribing information for administration instructions. (2.4)

----------DOSAGE FORMS AND STRENGTHS----------

Injection: 2.5 mg, 5 mg, 7.5 mg, 10 mg, 12.5 mg, or 15 mg per 0.5 mL in single-dose pen or single-dose vial (3)

---------- CONTRAINDICATIONS ----------

- Personal or family history of medullary thyroid carcinoma or in patients with Multiple Endocrine Neoplasia syndrome type 2 (4)
- Known serious hypersensitivity to tirzepatide or any of the excipients in ZEPBOUND (4)

----------WARNINGS AND PRECAUTIONS----------

- *Severe Gastrointestinal Adverse Reactions:* Use has been associated with gastrointestinal adverse reactions, sometimes severe. Has not been studied in patients with severe gastrointestinal disease and is not recommended in these patients. (5.2)
- *Acute Kidney Injury:* Monitor renal function in patients reporting adverse reactions that could lead to volume depletion. (5.3)
- *Acute Gallbladder Disease:* Has been reported in clinical trials. If cholecystitis is suspected, gallbladder studies and clinical follow-up are indicated. (5.4)
- *Acute Pancreatitis:* Has been reported in clinical trials. Discontinue promptly if pancreatitis is suspected. (5.5)
- *Hypersensitivity Reactions:* Serious hypersensitivity reactions (e.g., anaphylaxis, angioedema) have been reported postmarketing with tirzepatide. If suspected, advise patients to promptly seek medical attention and discontinue ZEPBOUND. (5.6)
- *Hypoglycemia:* Concomitant use with insulin or an insulin secretagogue may increase the risk of hypoglycemia, including severe hypoglycemia. Reducing dose of insulin or insulin secretagogue may be necessary. Inform all patients of the risk of hypoglycemia and educate them on the signs and symptoms of hypoglycemia. (5.7)
- *Diabetic Retinopathy Complications in Patients with Type 2 Diabetes Mellitus:* Has not been studied in patients with non-proliferative diabetic retinopathy requiring acute therapy, proliferative diabetic retinopathy, or diabetic macular edema. Monitor patients with a history of diabetic retinopathy for progression. (5.8)
- *Suicidal Behavior and Ideation:* Monitor for depression or suicidal thoughts. Discontinue ZEPBOUND if symptoms develop. (5.9)
- *Pulmonary Aspiration During General Anesthesia or Deep Sedation:* Has been reported in patients receiving GLP-1 receptor agonists undergoing elective surgeries or procedures. Instruct patients to inform healthcare providers of any planned surgeries or procedures. (5.10)

----------ADVERSE REACTIONS----------

The most common adverse reactions, reported in ≥5% of patients treated with ZEPBOUND are: nausea, diarrhea, vomiting, constipation, abdominal pain, dyspepsia, injection site reactions, fatigue, hypersensitivity reactions, eructation, hair loss, gastroesophageal reflux disease. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Eli Lilly and Company at 1-800-LillyRx (1-800-545-5979) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

---------- DRUG INTERACTIONS ----------

ZEPBOUND delays gastric emptying and has the potential to impact the absorption of concomitantly administered oral medications. (7.2)

----------USE IN SPECIFIC POPULATIONS----------

- *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)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved Medication Guide.

Revised: 12/2024

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: RISK OF THYROID C-CELL TUMORS

- **In rats, tirzepatide causes dose-dependent and treatment-duration-dependent thyroid C-cell tumors at clinically relevant exposures. It is unknown whether ZEPBOUND causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans as human relevance of tirzepatide-induced rodent thyroid C-cell tumors has not been determined *[see Warnings and Precautions (5.1) and Nonclinical Toxicology (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) *[see Contraindications (4)]*. 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 *[see Contraindications (4) and Warnings and Precautions (5.1)]*.**

1 INDICATIONS AND USAGE

ZEPBOUND® is indicated in combination with a reduced-calorie diet and increased physical activity:

- to reduce excess body weight and maintain weight reduction long term in adults with obesity or adults with overweight in the presence of at least one weight-related comorbid condition.
- to treat moderate to severe obstructive sleep apnea (OSA) in adults with obesity.

Limitations of Use

ZEPBOUND contains tirzepatide. Coadministration with other tirzepatide-containing products or with any glucagon-like peptide-1 (GLP-1) receptor agonist is not recommended.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dose Escalation Schedule

- The recommended starting dosage of ZEPBOUND for all indications is 2.5 mg injected subcutaneously once weekly for 4 weeks.
- The 2.5 mg dosage is for treatment initiation and is not approved as a maintenance dosage.
- Follow the dosage escalation below for all indications to reduce the risk of gastrointestinal adverse reactions *[see Warnings and Precautions (5.2) and Adverse Reactions (6.1)]*.
- After 4 weeks, increase the dosage to 5 mg injected subcutaneously once weekly. The dosage may be increased in 2.5 mg increments, after at least 4 weeks on the current dose *[see Dosage and Administration (2.2)]*.
- Consider treatment response and tolerability when selecting the maintenance dosage. If patients do not tolerate a maintenance dosage, consider a lower maintenance dosage.

2.2 Recommended Maintenance and Maximum Dosage

Recommended Maintenance Dosage

Weight Reduction and Long-Term Maintenance

The recommended maintenance dosage is 5 mg, 10 mg, or 15 mg, injected subcutaneously once weekly.

OSA

The recommended maintenance dosage is 10 mg or 15 mg injected subcutaneously once weekly.

Maximum Recommended Dosage

The maximum dosage of ZEPBOUND for all indications is 15 mg injected subcutaneously once weekly.

2.3 Recommendations Regarding Missed Dose

- If a dose is missed, instruct patients to administer ZEPBOUND as soon as possible within 4 days (96 hours) after the missed dose. If more than 4 days have passed, skip the missed dose and administer the next dose on the regularly scheduled day. In each case, patients can then resume their regular once weekly dosing schedule.

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

2.4 Important Administration Instructions

- Prior to initiation of ZEPBOUND, train patients and caregivers on proper injection technique. Refer to the accompanying Instructions for Use for complete administration instructions with illustrations.
- Instruct patients using the single-dose vial to use a syringe appropriate for dose administration (e.g., a 1 mL syringe capable of measuring a 0.5 mL dose).
- Inspect ZEPBOUND visually before use. It should appear clear and colorless to slightly yellow. Do not use ZEPBOUND if particulate matter or discoloration is seen.
- Administer ZEPBOUND in combination with a reduced-calorie diet and increased physical activity.
- Administer ZEPBOUND once weekly at any time of day, with or without meals.
- Inject ZEPBOUND subcutaneously in the abdomen, thigh, or upper arm.
- Rotate injection sites with each dose.

3 DOSAGE FORMS AND STRENGTHS

Injection: Clear, colorless to slightly yellow solution in pre-filled single-dose pens or single-dose vials, each available in the following strengths:

- 2.5 mg/0.5 mL
- 5 mg/0.5 mL
- 7.5 mg/0.5 mL
- 10 mg/0.5 mL
- 12.5 mg/0.5 mL
- 15 mg/0.5 mL

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)]*.
- Known serious hypersensitivity to tirzepatide or any of the excipients in ZEPBOUND. Serious hypersensitivity reactions, including anaphylaxis and angioedema, have been reported with tirzepatide *[see Warnings and Precautions (5.6) and Adverse Reactions (6.2)]*.

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.

5.2 Severe Gastrointestinal Adverse Reactions

Use of ZEPBOUND has been associated with gastrointestinal adverse reactions, sometimes severe *[see Adverse Reactions (6.1)]*. In a pool of two ZEPBOUND clinical trials for weight reduction (Studies 1 and 2), severe gastrointestinal

adverse reactions were reported more frequently among patients receiving ZEPBOUND (5 mg 1.7%, 10 mg 2.5%, 15 mg 3.1%) than placebo (1%). Similar rates of severe gastrointestinal adverse reactions were observed in ZEPBOUND clinical trials for weight reduction and in ZEPBOUND clinical trials for OSA.

ZEPBOUND has not been studied in patients with severe gastrointestinal disease, including severe gastroparesis, and is therefore not recommended in these patients.

5.3 Acute Kidney Injury

Use of ZEPBOUND has been associated with acute kidney injury, which can result from dehydration due to gastrointestinal adverse reactions to ZEPBOUND, including nausea, vomiting, and diarrhea *[see Adverse Reactions (6.1)]*.

In patients treated with GLP-1 receptor agonists, there have been postmarketing reports of acute kidney injury and worsening of chronic renal failure, which may sometimes require hemodialysis. Some of these events have been reported in patients without known underlying renal disease. A majority of the reported events occurred in patients who had experienced nausea, vomiting, diarrhea, or dehydration. Monitor renal function in patients reporting adverse reactions to ZEPBOUND that could lead to volume depletion.

5.4 Acute Gallbladder Disease

Treatment with ZEPBOUND and GLP-1 receptor agonists is associated with an increased occurrence of acute gallbladder disease.

In a pool of two ZEPBOUND clinical trials for weight reduction (Studies 1 and 2), cholelithiasis was reported in 1.1% of ZEPBOUND-treated patients and 1% of placebo-treated patients, cholecystitis was reported in 0.7% of ZEPBOUND-treated patients and 0.2% of placebo-treated patients, and cholecystectomy was reported in 0.2% of ZEPBOUND-treated patients and no placebo-treated patients. Acute gallbladder events were associated with weight reduction. Similar rates of cholelithiasis were reported in ZEPBOUND clinical trials for weight reduction and in ZEPBOUND trials for OSA. If cholecystitis is suspected, gallbladder diagnostic studies and appropriate clinical follow-up are indicated.

5.5 Acute Pancreatitis

Acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis, has been observed in patients treated with GLP-1 receptor agonists or tirzepatide.

In clinical trials of tirzepatide for a different indication, 14 events of acute pancreatitis were confirmed by adjudication in 13 tirzepatide-treated patients (0.23 patients per 100 years of exposure) versus 3 events in 3 comparator-treated patients (0.11 patients per 100 years of exposure). In a pool of two ZEPBOUND clinical trials for weight reduction (Studies 1 and 2), 0.2% of ZEPBOUND-treated patients had acute pancreatitis confirmed by adjudication (0.14 patients per 100 years of exposure) versus 0.2% of placebo-treated patients (0.15 patients per 100 years of exposure). The exposure-adjusted incidence rate for treatment-emergent adjudication-confirmed pancreatitis in the pooled clinical studies for OSA (Studies 5 and 6) was 0.84 patients per 100 years for ZEPBOUND and 0 for placebo-treated patients.

After initiation of ZEPBOUND, observe patients carefully for signs and symptoms of pancreatitis (including persistent severe abdominal pain, sometimes radiating to the back, which may or may not be accompanied by vomiting). If pancreatitis is suspected, discontinue ZEPBOUND and initiate appropriate management. Continuation of ZEPBOUND after a confirmed diagnosis of pancreatitis should be individually determined in the clinical judgment of a patient's health care provider.

5.6 Hypersensitivity Reactions

There have been postmarketing reports of serious hypersensitivity reactions (e.g., anaphylaxis, angioedema) in patients treated with tirzepatide. In a pool of two ZEPBOUND clinical studies for weight reduction (Studies 1 and 2), 0.1% of ZEPBOUND-treated patients had severe hypersensitivity reactions compared to no placebo-treated patients. Similar rates of severe hypersensitivity reactions were observed in ZEPBOUND clinical trials for weight reduction and in ZEPBOUND trials for OSA. If hypersensitivity reactions occur, advise patients to promptly seek medical attention and discontinue use of ZEPBOUND. Do not use in patients with a previous serious hypersensitivity reaction to tirzepatide or any of the excipients in ZEPBOUND *[see Contraindications (4) and Adverse Reactions (6.2)]*.

Serious hypersensitivity reactions, including anaphylaxis and angioedema, have been reported with GLP-1 receptor agonists. Use caution in patients with a history of angioedema or anaphylaxis with a GLP-1 receptor agonist because it is unknown whether such patients will be predisposed to these reactions with ZEPBOUND.

5.7 Hypoglycemia

ZEPBOUND lowers blood glucose and can cause hypoglycemia.

In a trial of patients with type 2 diabetes mellitus and BMI ≥27 kg/m^2 (Study 2), hypoglycemia (plasma glucose <54 mg/dL) was reported in 4.2% of ZEPBOUND-treated patients versus 1.3% of placebo-treated patients. In this trial, patients taking ZEPBOUND in combination with an insulin secretagogue (e.g., sulfonylurea) had increased risk of hypoglycemia (10.3%) compared to ZEPBOUND-treated patients not taking a sulfonylurea (2.1%). There is also increased risk of hypoglycemia in patients treated with tirzepatide in combination with insulin *[see Drug Interactions (7.1)]*.

Hypoglycemia has also been associated with ZEPBOUND and GLP-1 receptor agonists in adults without type 2 diabetes mellitus *[see Adverse Reactions (6.1)]*.

Inform patients of the risk of hypoglycemia and educate them on the signs and symptoms of hypoglycemia. In patients with diabetes mellitus, monitor blood glucose prior to starting ZEPBOUND and during ZEPBOUND treatment. The risk of hypoglycemia may be lowered by a reduction in the dose of insulin or sulfonylurea (or other concomitantly administered insulin secretagogue).

5.8 Diabetic Retinopathy Complications in Patients with Type 2 Diabetes Mellitus

Rapid improvement in glucose control has been associated with a temporary worsening of diabetic retinopathy. Tirzepatide has not been studied in patients with non-proliferative diabetic retinopathy requiring acute therapy, proliferative diabetic retinopathy, or diabetic macular edema. Patients with a history of diabetic retinopathy should be monitored for progression of diabetic retinopathy.

5.9 Suicidal Behavior and Ideation

Suicidal behavior and ideation have been reported in clinical trials with other weight management products. Monitor patients treated with ZEPBOUND for the emergence or worsening of depression, suicidal thoughts or behaviors, and/or any unusual changes in mood or behavior. Discontinue ZEPBOUND in patients who experience suicidal thoughts or behaviors. Avoid ZEPBOUND in patients with a history of suicidal attempts or active suicidal ideation.

5.10 Pulmonary Aspiration During General Anesthesia or Deep Sedation

ZEPBOUND delays gastric emptying *[see Clinical Pharmacology (12.2)]*. There have been rare postmarketing reports of pulmonary aspiration in patients receiving GLP-1 receptor agonists undergoing elective surgeries or procedures requiring general anesthesia or deep sedation who had residual gastric contents despite reported adherence to preoperative fasting recommendations.

Available data are insufficient to inform recommendations to mitigate the risk of pulmonary aspiration during general anesthesia or deep sedation in patients taking ZEPBOUND, including whether modifying preoperative fasting recommendations or temporarily discontinuing ZEPBOUND could reduce the incidence of retained gastric contents. Instruct patients to inform healthcare providers prior to any planned surgeries or procedures if they are taking ZEPBOUND.

6 ADVERSE REACTIONS

The following serious adverse reactions are described below or elsewhere in the prescribing information:

- Risk of Thyroid C-cell Tumors *[see Warnings and Precautions (5.1)]*
- Severe Gastrointestinal Adverse Reactions *[see Warnings and Precautions (5.2)]*
- Acute Kidney Injury *[see Warnings and Precautions (5.3)]*
- Acute Gallbladder Disease *[see Warnings and Precautions (5.4)]*
- Acute Pancreatitis *[see Warnings and Precautions (5.5)]*
- Hypersensitivity Reactions *[see Warnings and Precautions (5.6)]*
- Hypoglycemia *[see Warnings and Precautions (5.7)]*
- Diabetic Retinopathy Complications in Patients with Type 2 Diabetes Mellitus *[see Warnings and Precautions (5.8)]*
- Suicidal Behavior and Ideation *[see Warnings and Precautions (5.9)]*
- Pulmonary Aspiration During General Anesthesia or Deep Sedation *[see Warnings and Precautions (5.10)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Adverse Reactions in Patients for Weight Reduction and Long-Term Maintenance

Pool of Placebo-Controlled Weight Reduction Trials in Adults with Obesity or Overweight, with or without Type 2 Diabetes (Study 1 and Study 2)

ZEPBOUND was evaluated for safety in a pool of two randomized, double-blind, placebo-controlled trials that included 2,519 adult patients with obesity or overweight treated with ZEPBOUND for up to 72 weeks and a 4-week off drug follow-up period (Study 1 and Study 2) *[see Clinical Studies (14.1)]*. The mean age of patients was 47 years and 37% were male. The population was 72% White, 12% Asian, 8% Black or African American, and 7% American Indian or Alaska Native; 51% identified as Hispanic or Latino ethnicity. Baseline characteristics included an average BMI of 37.4 kg/m^2, 29% with a BMI ≥40 kg/m^2, 41% with hypertension, 37% with dyslipidemia, 25% with type 2 diabetes mellitus, 7% with obstructive sleep apnea, and 4% with cardiovascular disease.

Across both trials, 4.8%, 6.3%, and 6.7% of patients treated with 5 mg, 10 mg, and 15 mg of ZEPBOUND, respectively, permanently discontinued treatment as a result of adverse reactions compared to 3.4% of patients treated with placebo. The majority of patients who discontinued ZEPBOUND due to adverse reactions did so during the first few months of treatment due to gastrointestinal adverse reactions.

Common Adverse Reactions

Table 1 shows common adverse reactions associated with the use of ZEPBOUND in the pool of two placebo-controlled trials for weight reduction (Study 1 and Study 2). These adverse reactions occurred more commonly with ZEPBOUND than with placebo and occurred in at least 2% of patients treated with ZEPBOUND.

Table 1: Adverse Reactions (≥2% and Greater than Placebo) in ZEPBOUND-Treated Adults with Obesity or Overweight in Weight Reduction and Long-term Maintenance Trials (Study 1 and Study 2)

Adverse Reaction	Placebo (N=958) %	ZEPBOUND 5 mg (N=630) %	ZEPBOUND 10 mg (N=948) %	ZEPBOUND 15 mg (N=941) %
Nausea	8	25	29	28
Diarrhea[a]	8	19	21	23
Vomiting	2	8	11	13
Constipation[b]	5	17	14	11
Abdominal Pain[c]	5	9	9	10
Dyspepsia	4	9	9	10
Injection Site Reactions[d]	2	6	8	8
Fatigue[e]	3	5	6	7
Hypersensitivity Reactions	3	5	5	5
Eructation	1	4	5	5
Hair Loss	1	5	4	5
Gastroesophageal Reflux Disease	2	4	4	5
Flatulence	2	3	3	4
Abdominal Distension	2	3	3	4
Dizziness	2	4	5	4
Hypotension[f]	0	1	1	2

[a] Includes diarrhea, frequent bowel movements.

[b] Includes constipation, feces hard.

[c] Includes abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, abdominal tenderness.

[d] Includes multiple related adverse event terms, such as injection site bruising, injection site erythema, injection site pruritus, injection site pain, injection site rash, injection site reaction.

[e] Includes asthenia, fatigue, lethargy, malaise.

[f] Includes blood pressure decreased, hypotension, orthostatic hypotension.

In a clinical trial for weight reduction that included an intensive lifestyle intervention lead-in period (Study 3), 287 patients were treated with ZEPBOUND for up to 72 weeks. In a randomized withdrawal trial (Study 4), 783 patients were treated with ZEPBOUND for up to 36 weeks, and 335 of these patients were treated for up to 88 weeks *[see Clinical Studies (14.1)]*. In Study 3, 10% of ZEPBOUND-treated patients and 2% of placebo-treated patients discontinued drug due to adverse reactions. In Study 4, 7% of patients discontinued ZEPBOUND treatment before randomized withdrawal at Week 36 due to adverse reactions. In Study 3 and Study 4, adverse reactions were similar to those reported in the two pooled ZEPBOUND clinical trials (Study 1 and Study 2).

Gastrointestinal Adverse Reactions

In a pool of Study 1 and 2, gastrointestinal adverse reactions occurred more frequently among patients receiving ZEPBOUND (5 mg 56%, 10 mg 56%, 15 mg 56%) than placebo (30%). More patients receiving ZEPBOUND 5 mg (1.9%), ZEPBOUND 10 mg (3.3%), and ZEPBOUND 15 mg (4.3%) discontinued treatment due to gastrointestinal adverse reactions than patients receiving placebo (0.5%). The majority of nausea, vomiting, and/or diarrhea events occurred during dose escalation and decreased over time.

Hypotension

In a pool of Study 1 and 2, hypotension occurred more frequently among patients taking ZEPBOUND (1.6%) than patients taking placebo (0.1%). Hypotension was more frequently seen in ZEPBOUND-treated patients on concomitant antihypertensive therapy (2.2%) compared to ZEPBOUND-treated patients not on antihypertensive therapy (1.2%). Hypotension also occurred in association with gastrointestinal adverse events and dehydration.

Hypersensitivity Reactions

In a pool of Study 1 and 2, immediate hypersensitivity reactions (within one day after drug administration) occurred in 2.1% of ZEPBOUND-treated patients compared to 0.4% of placebo-treated patients, while non-immediate hypersensitivity reactions occurred in 3.5% of ZEPBOUND-treated patients compared to 2.7% of placebo-treated patients. Among ZEPBOUND-treated patients, hypersensitivity reactions were more frequent in those with anti-tirzepatide antibodies (6.2%) compared to those who did not develop anti-tirzepatide antibodies (3%) *[see Clinical Pharmacology (12.6)]*. The majority of the hypersensitivity reactions in trials were skin reactions (e.g., rash, itching).

Injection Site Reactions

In ZEPBOUND-treated patients in a pool of Study 1 and 2, injection site reactions were more frequent in those with anti-tirzepatide antibodies (11.3%) compared to those who did not develop anti-tirzepatide antibodies (1%) *[see Clinical Pharmacology (12.6)]*.

Hair Loss

Hair loss adverse reactions in ZEPBOUND-treated patients were associated with weight reduction. In a pool of Study 1 and 2, hair loss was reported more frequently in female than male patients in the ZEPBOUND (7.1% female versus 0.5% male) and placebo (1.3% female versus 0% male) treatment groups. No ZEPBOUND-treated patients and one placebo-treated patient discontinued study treatment due to hair loss.

Other Adverse Reactions

Acute Kidney Injury

In a pool of Study 1 and 2, acute kidney injury was reported in 0.5% of ZEPBOUND-treated patients compared to 0.2% of placebo-treated patients.

Acute Gallbladder Disease

In a pool of Study 1 and 2, cholelithiasis was reported in 1.1% of ZEPBOUND-treated patients and 1% of placebo-treated patients, cholecystitis was reported in 0.7% of ZEPBOUND-treated patients and 0.2% of placebo-treated patients, and cholecystectomy was reported in 0.2% of ZEPBOUND-treated patients and no placebo-treated patients.

Hypoglycemia

In Study 2, a trial of patients with type 2 diabetes mellitus and BMI ≥27 kg/m^2, hypoglycemia (plasma glucose <54 mg/dL) was reported in 4.2% of ZEPBOUND-treated patients versus 1.3% of placebo-treated patients.

In Study 1, a trial of ZEPBOUND in adults with obesity/overweight without type 2 diabetes mellitus, there was no systematic capturing of hypoglycemia, but plasma glucose <54 mg/dL was reported in 0.3% of ZEPBOUND-treated patients versus no placebo-treated patients.

Heart Rate Increase

In a pool of Study 1 and 2, treatment with ZEPBOUND resulted in a mean increase in heart rate of 1 to 3 beats per minute compared to no increase in placebo-treated patients.

Dysesthesia

In a pool of Study 1 and 2, dysesthesia occurred more frequently among patients receiving ZEPBOUND (5 mg 0.2%, 10 mg 0.2%, 15 mg 0.4%) than placebo (0.1%).

Dysgeusia

In a pool of Study 1 and 2, dysgeusia was reported by 0.4% of ZEPBOUND-treated patients and no placebo-treated patients.

Dry Mouth

In a pool of Study 1 and 2, dry mouth or dry throat was reported by 1% of ZEPBOUND-treated patients and 0.1% of placebo-treated patients.

Laboratory Abnormalities

Amylase and Lipase Increase

In a pool of Study 1 and 2, treatment with ZEPBOUND resulted in mean increases from baseline in serum pancreatic amylase concentrations of 20% to 25% and serum lipase concentrations of 28% to 35%, compared to mean increases from baseline in pancreatic amylase of 2.1% and serum lipase of 5.8% in placebo-treated patients. The clinical significance of elevations in amylase or lipase with ZEPBOUND is unknown in the absence of other signs and symptoms of pancreatitis.

Adverse Reactions in Patients with Obstructive Sleep Apnea

ZEPBOUND was evaluated in 2 randomized, double-blind, placebo-controlled trials (Study 5 and Study 6) that included a total of 467 adult patients with moderate to severe OSA and obesity *[see Clinical Studies (14.2)]*. Study 5 enrolled 234 patients who were unable or unwilling to use Positive Airway Pressure (PAP) therapy and Study 6 enrolled 235 patients who were on PAP therapy. The adverse reactions observed with ZEPBOUND 10 mg or 15 mg administered subcutaneously once weekly were similar to those reported in the two pooled placebo controlled clinical trials for weight reduction (Study 1 and Study 2).

6.2 Postmarketing Experience

The following adverse reactions have been reported during post-approval use of tirzepatide, the active ingredient in ZEPBOUND. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or to establish a causal relationship to drug exposure.

Hypersensitivity: anaphylaxis, angioedema

Gastrointestinal: ileus

Pulmonary: Pulmonary aspiration has occurred in patients receiving GLP-1 receptor agonists undergoing elective surgeries or procedures requiring general anesthesia or deep sedation.

7 DRUG INTERACTIONS

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

ZEPBOUND lowers blood glucose. When initiating ZEPBOUND, consider reducing the dose of concomitantly administered insulin or insulin secretagogues (e.g., sulfonylureas) to reduce the risk of hypoglycemia *[see Warnings and Precautions (5.7)]*.

7.2 Oral Medications

ZEPBOUND delays gastric emptying and thereby has the potential to impact the absorption of concomitantly administered oral medications. Caution should be exercised when oral medications are concomitantly administered with ZEPBOUND.

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 ZEPBOUND.

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. Hormonal

contraceptives that are not administered orally should not be affected *[see Use in Specific Populations (8.3) and Clinical Pharmacology (12.2, 12.3)]*.

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, F_1 pups from F_0 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)]*.

8.4 Pediatric Use

The safety and effectiveness of ZEPBOUND have not been established in pediatric patients.

8.5 Geriatric Use

In a pool of two fixed dose ZEPBOUND clinical studies for weight reduction (Study 1 and Study 2), 226 (9%) ZEPBOUND-treated patients were 65 years of age or older, and 13 (0.5%) ZEPBOUND-treated patients were 75 years of age or older at baseline.

No overall differences in safety or effectiveness of ZEPBOUND have been observed between patients 65 years of age and older and younger adult patients.

ZEPBOUND clinical studies in OSA (Study 5 and Study 6) did not include sufficient numbers of patients age 65 years or older to determine whether they respond differently from younger adult patients. Other reported clinical experience with tirzepatide has not identified differences in responses between the elderly and younger patients.

8.6 Renal Impairment

No dosage adjustment of ZEPBOUND is recommended for patients with renal impairment. In subjects with renal impairment including end-stage renal disease (ESRD), no change in tirzepatide pharmacokinetics (PK) was observed *[see Clinical Pharmacology (12.3)]*. Monitor renal function in patients reporting adverse reactions to ZEPBOUND that could lead to volume depletion *[see Warnings and Precautions (5.3)]*.

8.7 Hepatic Impairment

No dosage adjustment of ZEPBOUND is recommended for patients with hepatic impairment. In a clinical pharmacology study in subjects with varying degrees of hepatic impairment, no change in tirzepatide PK was observed *[see Clinical Pharmacology (12.3)]*.

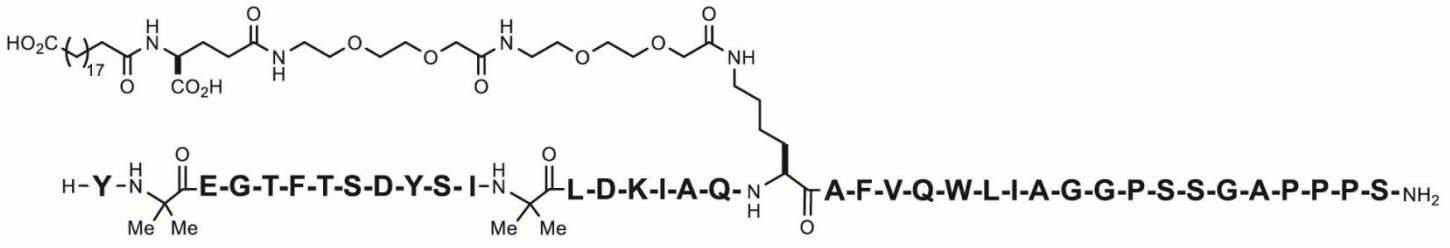
10 OVERDOSAGE

In the event of an overdosage, contact the Poison Help Line (1-800-222-1222) or a medical toxicologist for additional overdosage management recommendations. Appropriate supportive treatment should be initiated according to the patient's clinical signs and symptoms. A period of observation and treatment for these symptoms may be necessary, taking into account the half-life of tirzepatide of approximately 5 days.

11 DESCRIPTION

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

Structural formula:



ZEPBOUND is a clear, colorless to slightly yellow, sterile solution for subcutaneous use. Each single-dose pen or single-dose vial contains preservative-free 0.5 mL solution of 2.5 mg, 5 mg, 7.5 mg, 10 mg, 12.5 mg, or 15 mg of tirzepatide and the following excipients: sodium chloride (4.1 mg), sodium phosphate dibasic heptahydrate (0.7 mg), and water for injection. Hydrochloric acid solution and/or sodium hydroxide solution may have been added to adjust the pH. ZEPBOUND has a pH of 6.5 – 7.5.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Tirzepatide is a GIP receptor and GLP-1 receptor agonist. It contains a C20 fatty diacid that enables albumin binding and prolongs the half-life. Tirzepatide selectively binds to and activates both the GIP and GLP-1 receptors, the targets for native GIP and GLP-1.

GLP-1 is a physiological regulator of appetite and caloric intake. Nonclinical studies suggest the addition of GIP may further contribute to the regulation of food intake.

Both GIP receptors and GLP-1 receptors are found in areas of the brain involved in appetite regulation. Animal studies show that tirzepatide distributes to and activates neurons in brain regions involved in regulation of appetite and food intake.

12.2 Pharmacodynamics

Tirzepatide lowers body weight with greater fat mass loss than lean mass loss.

Tirzepatide decreases calorie intake. The effects are likely mediated by affecting appetite.

Tirzepatide stimulates insulin secretion in a glucose-dependent manner and reduces glucagon secretion. Tirzepatide increases insulin sensitivity, as demonstrated in a hyperinsulinemic euglycemic clamp study in patients with type 2 diabetes mellitus after 28 weeks of treatment. These effects can lead to a reduction of blood glucose.

Tirzepatide delays gastric emptying. The delay is largest after the first dose and this effect diminishes over time.

12.3 Pharmacokinetics

The pharmacokinetics of tirzepatide is similar between healthy subjects, patients with overweight or obesity, and patients with OSA and obesity. Steady-state plasma tirzepatide concentrations were achieved following 4 weeks of once weekly administration. Tirzepatide exposure increases in a dose-proportional manner.

Absorption

Following subcutaneous administration, the median time (range) to maximum plasma concentration of tirzepatide is 24 hours (8 to 72 hours). The mean absolute bioavailability of tirzepatide following subcutaneous administration is 80%. Similar exposure was achieved with subcutaneous administration of tirzepatide in the abdomen, thigh, or upper arm.

Distribution

The mean [coefficient of variation (CV)%] apparent steady-state volumes of distribution of tirzepatide following subcutaneous administration in patients with overweight or obesity and patients with OSA and obesity are approximately 9.7 L (29%) and 11.8 L (37%), respectively. Tirzepatide is highly bound to plasma albumin (99%).

Elimination

The apparent population mean clearance of tirzepatide in patients with overweight or obesity and patients with OSA and obesity is approximately 0.06 L/h (CV% ~ 20%). The elimination half-life is approximately 5-6 days in patients with overweight or obesity, and in patients with OSA and obesity.

Metabolism

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

Excretion

The primary excretion routes of tirzepatide metabolites are via urine and feces. Intact tirzepatide is not observed in urine or feces.

Specific Populations

The intrinsic factors of age (18 to 84 years), sex, race (71% White, 11% Asian, 9% American Indian or Alaska Native, and 8% Black or African American), ethnicity, or body weight do not have a clinically relevant effect on the PK of tirzepatide.

Patients with Renal Impairment

Renal impairment does not impact the pharmacokinetics of tirzepatide. The pharmacokinetics of tirzepatide after a single 5 mg dose were evaluated in patients with different degrees of renal impairment (mild, moderate, severe, ESRD) compared with subjects with normal renal function. Data from clinical studies have also shown that renal impairment in patients with overweight or obesity does not impact the pharmacokinetics of tirzepatide *[see Use in Specific Populations (8.6)]*.

Patients with Hepatic Impairment

Hepatic impairment does not impact the pharmacokinetics of tirzepatide. The pharmacokinetics of tirzepatide after a single 5 mg dose were evaluated in patients with different degrees of hepatic impairment (mild, moderate, severe) compared with subjects with normal hepatic function *[see Use in Specific Populations (8.7)]*.

Drug Interaction Studies

Potential for Tirzepatide to Influence the Pharmacokinetics of Other Drugs

In vitro studies have shown low potential for tirzepatide to inhibit or induce CYP enzymes, and to inhibit drug transporters.

ZEPBOUND delays gastric emptying and thereby has the potential to impact the absorption of concomitantly administered oral medications *[see Drug Interactions (7.2)]*.

The impact of tirzepatide on gastric emptying was greatest after a single dose of 5 mg and diminished after subsequent doses.

Following a first dose of tirzepatide 5 mg, acetaminophen maximum concentration (C_{max}) was reduced by 55%, and the median peak plasma concentration (t_{max}) occurred 1 hour later. After coadministration at Week 6 with tirzepatide 15 mg, there was no meaningful impact on acetaminophen C_{max} and t_{max}. Overall acetaminophen exposure ($AUC_{0\text{-}24hr}$) was not influenced.

Following administration of a combined oral contraceptive (0.035 mg ethinyl estradiol and 0.25 mg norgestimate) in the presence of a single dose of tirzepatide 5 mg, mean C_{max} of ethinyl estradiol, norgestimate, and norelgestromin was reduced by 59%, 66%, and 55%, while mean AUC was reduced by 20%, 21%, and 23%, respectively. A delay in t_{max} of 2.5 to 4.5 hours was observed.

12.6 Immunogenicity

The observed incidence of anti-drug antibodies is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of anti-drug antibodies in the studies described below with the incidence of anti-drug antibodies in other studies.

The incidence of anti-drug antibodies (ADA) to ZEPBOUND was evaluated in adult patients with overweight or obesity or with OSA and obesity in clinical studies lasting 52 weeks or longer. Anti-tirzepatide antibodies were detected in 64.5% (1591/2467) of ZEPBOUND-treated patients in weight reduction clinical studies 1 and 2, and 60.6% (137/226) of ZEPBOUND-treated patients in OSA clinical studies *[see Clinical Studies (14)]*.

Of the ZEPBOUND-treated patients in weight reduction clinical studies 40% and 16.5% of patients developed antibodies that were cross-reactive to native GIP or native GLP-1, respectively.

Of the ZEPBOUND-treated patients in OSA clinical studies, 37.2% and 19.5% of patients developed antibodies that were cross reactive to native GIP and native GLP-1, respectively.

Neutralizing antibodies against tirzepatide activity on the GIP or GLP-1 receptors and against native GIP or GLP-1 were detected in 2.8% and 2.7% and 0.8% and 0.1% respectively, of ZEPBOUND-treated patients in weight reduction clinical studies.

No ZEPBOUND-treated patients in OSA studies developed neutralizing antibodies against tirzepatide activity on the GIP or GLP-1 receptors or against native GIP or native GLP-1.

No clinically significant effect of anti-tirzepatide antibodies on pharmacokinetics or effectiveness of ZEPBOUND has been identified. More ZEPBOUND-treated patients who developed anti-tirzepatide antibodies experienced hypersensitivity reactions or injection site reactions than those who did not develop these antibodies *[see Adverse Reactions (6.1)]*.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

A 2-year carcinogenicity study was conducted with tirzepatide in male and female rats at doses of 0.15, 0.50, and 1.5 mg/kg (0.1-, 0.4-, and 1-fold the MRHD of 15 mg once weekly based on AUC) administered by subcutaneous injection twice weekly. A statistically significant increase in thyroid C-cell adenomas was observed in male rats (≥0.5 mg/kg) and female rats (≥0.15 mg/kg), and a statistically significant increase in thyroid C-cell adenomas and carcinomas combined was observed in male and female rats at all doses examined. In a 6-month carcinogenicity study in rasH2 transgenic mice, tirzepatide at doses of 1, 3, and 10 mg/kg administered by subcutaneous injection twice weekly was not tumorigenic.

Tirzepatide was not genotoxic in a rat bone marrow micronucleus assay.

In fertility and early embryonic development studies, male and female rats were administered twice weekly subcutaneous doses of 0.5, 1.5, or 3 mg/kg (0.3-, 1-, and 2-fold and 0.3-, 0.9-, and 2-fold, respectively, the MRHD of 15 mg once weekly based on AUC). No effects of tirzepatide were observed on sperm morphology, mating, fertility, and conception. In female rats, an increase in the number of females with prolonged diestrus and a decrease in the mean number of corpora lutea resulting in a decrease in the mean number of implantation sites and viable embryos was observed at all dose levels. These effects were considered secondary to the pharmacological effects of tirzepatide on food consumption and body weight.

14 CLINICAL STUDIES

14.1 Weight Reduction and Long-Term Maintenance Studies in Adults with Obesity or Overweight

Weight Reduction in Adults with Obesity or Overweight, with or without Type 2 Diabetes Mellitus (Study 1 and Study 2)

Overview of Study 1 and Study 2

The efficacy of ZEPBOUND for weight reduction in conjunction with a reduced-calorie diet and increased physical activity was studied in two randomized, double-blind, placebo-controlled fixed-dosage trials (Study 1 and Study 2) in adults aged 18 years and older. In Studies 1 and 2, all patients received a standard lifestyle intervention which included instruction on a reduced-calorie diet (approximately 500 kcal/day deficit) and increased physical activity counseling (recommended minimum of 150 min/week) that began with the first dose of study medication or placebo and continued throughout the trial. Patients also received counseling on behavior modification strategies to adhere to diet and exercise recommendations. In both trials, weight reduction was assessed after 72 weeks of treatment (at least 52 weeks at maintenance dose).

Study 1 (NCT04184622) was a 72-week trial that enrolled 2,539 adult patients with obesity (BMI ≥30 kg/m^2), or with overweight (BMI 27 to <30 kg/m^2) and at least one weight-related comorbid condition, such as dyslipidemia, hypertension, obstructive sleep apnea, or cardiovascular disease; patients with type 2 diabetes mellitus were excluded. Patients were randomized in a 1:1:1:1 ratio to once weekly fixed dosage of ZEPBOUND 5 mg, ZEPBOUND 10 mg, ZEPBOUND 15 mg, or placebo, with an escalation period of up to 20 weeks followed by the maintenance period. At baseline, mean age was 45 years (range 18-84 years), 68% were female, 71% were White, 11% were Asian, 9% were American Indian/Alaska Native, and 8% were Black or African American. A total of 48% were Hispanic or Latino ethnicity. Mean baseline body weight was 104.8 kg and mean BMI was 38 kg/m^2. Baseline characteristics included 32% with hypertension, 30% with dyslipidemia, 8% with obstructive sleep apnea, and 3% with cardiovascular disease.

Study 2 (NCT04657003) was a 72-week trial that enrolled 938 adult patients with BMI ≥27 kg/m^2 and type 2 diabetes mellitus. Patients included in the trial had HbA1c 7-10% and were treated with either diet and exercise alone, or any oral anti-hyperglycemic agent except dipeptidyl peptidase-4 (DPP-4) inhibitors or GLP-1 receptor agonists. Patients who were taking insulin or injectable GLP-1 receptor agonists for type 2 diabetes mellitus were excluded. Patients were randomized in a 1:1:1 ratio to once weekly fixed dosage of ZEPBOUND 10 mg, ZEPBOUND 15 mg, or placebo with an escalation period of up to 20 weeks followed by the maintenance period. At baseline, mean age was 54 years (range 18-85 years), 51% were female, 76% were White, 13% were Asian, and 8% were Black or African American. A total of 60% were Hispanic or Latino ethnicity. Mean baseline body weight was 100.7 kg and mean BMI was 36.1 kg/m^2. Baseline characteristics included 66% with hypertension, 61% with dyslipidemia, 8% with obstructive sleep apnea, and 10% with cardiovascular disease.

Results for Study 1 and Study 2

The proportions of patients who discontinued study drug in Study 1 were 14.3%, 16.4%, and 15.1% for the 5 mg, 10 mg, and 15 mg ZEPBOUND-treated groups, respectively, and 26.4% for the placebo-treated group. The proportions of patients who discontinued study drug in Study 2 were 9.3% and 13.8% for the 10 mg and 15 mg ZEPBOUND-treated groups, respectively, and 14.9% for the placebo-treated group.

For Studies 1 and 2, weight reduction was assessed after 72 weeks of treatment (at least 52 weeks at maintenance dose). In both studies, the primary efficacy parameters were mean percent change in body weight and the percentage of patients achieving ≥5% weight reduction from baseline to Week 72 (see Table 2).

After 72 weeks of treatment, ZEPBOUND resulted in a statistically significant reduction in body weight compared with placebo, and greater proportions of patients treated with ZEPBOUND 5 mg, 10 mg, and 15 mg achieved at least 5% weight reduction compared to placebo. Among patients treated with ZEPBOUND 10 mg and 15 mg, greater proportions of patients achieved at least 10%, 15%, and 20% weight reduction compared to placebo (see Table 2). A reduction in body weight was observed with ZEPBOUND irrespective of age, sex, race, ethnicity, baseline BMI, and glycemic status.

Table 2: Changes in Body Weight at Week 72 in Studies 1 and 2 in Patients with Obesity or Overweight

Intention-to-Treat (ITT) Population[a]	Study 1				Study 2		
	Placebo N = 643	**ZEPBOUND 5 mg N = 630**	**ZEPBOUND 10 mg N = 636**	**ZEPBOUND 15 mg N = 630**	**Placebo N = 315**	**ZEPBOUND 10 mg N = 312**	**ZEPBOUND 15 mg N = 311**
Body Weight							
Baseline mean (kg)	104.8	102.9	105.8	105.6	101.7	100.9	99.6
% Change from baseline[b]	-3.1	-15.0	-19.5	-20.9	-3.2	-12.8	-14.7
% Difference from placebo[b] (95% CI)		-11.9 (-13.4, -10.4)[d]	-16.4 (-17.9, -14.8)[d]	-17.8 (-19.3, -16.3)[d]		-9.6 (-11.1, -8.1)[d]	-11.6 (-13.0, -10.1)[d]
% of Patients losing ≥5% body weight	34.5	85.1	88.9	90.9	32.5	79.2	82.8
% Difference from placebo (95% CI)		50.3 (44.3, 56.2)[c,d]	54.6 (49.1, 60.0)[c,d]	56.4 (50.9, 62.0)[c,d]		46.8 (39.5, 54.1)[c,d]	50.4 (43.1, 57.8)[c,d]
% of Patients losing ≥10% body weight	18.8	68.5	78.1	83.5	9.5	60.5	64.8
% Difference from placebo (95% CI)		49.3 (43.6, 54.9)[c,e]	59.5 (54.2, 64.9)[c,d]	64.8 (59.6, 70.1)[c,d]		51.0 (44.4, 57.7)[c,d]	55.3 (48.6, 62.0)[c,d]
% of Patients losing ≥15% body weight	8.8	48.0	66.6	70.6	2.7	39.7	48.0
% Difference from placebo (95% CI)		38.7 (33.6, 43.7)[c,e]	58.1 (53.2, 63.0)[c,d]	62.0 (57.2, 66.8)[c,d]		37.0 (31.1, 42.9)[c,d]	45.4 (39.4, 51.4)[c,d]
% of Patients losing ≥20% body weight	3.1	30.0	50.1	56.7	1.0	21.5	30.8
% Difference from placebo (95% CI)		26.6 (22.4, 30.7)[c,e]	47.3 (42.7, 51.9)[c,d]	53.8 (49.3, 58.3)[c,d]		20.5 (15.7, 25.4)[c,d]	29.7 (24.3, 35.0)[c,d]

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

[a] The intention-to-treat population includes all randomly assigned patients. For Study 1 at Week 72, body weight was missing for 21.6%, 10.2%, 10.5%, and 9.4% of patients randomly assigned to placebo, ZEPBOUND 5 mg, 10 mg, and 15 mg, respectively. For Study 2 at Week 72, body weight was missing for 11.1%, 4.8%, and 8.4% of patients randomly assigned to placebo, ZEPBOUND 10 mg, and 15 mg, respectively. The missing values were imputed by a hybrid approach using retrieved dropouts from the same treatment group (if missing not due to COVID-19) or using all non-missing data assuming missing at random (for missing solely due to COVID-19).

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

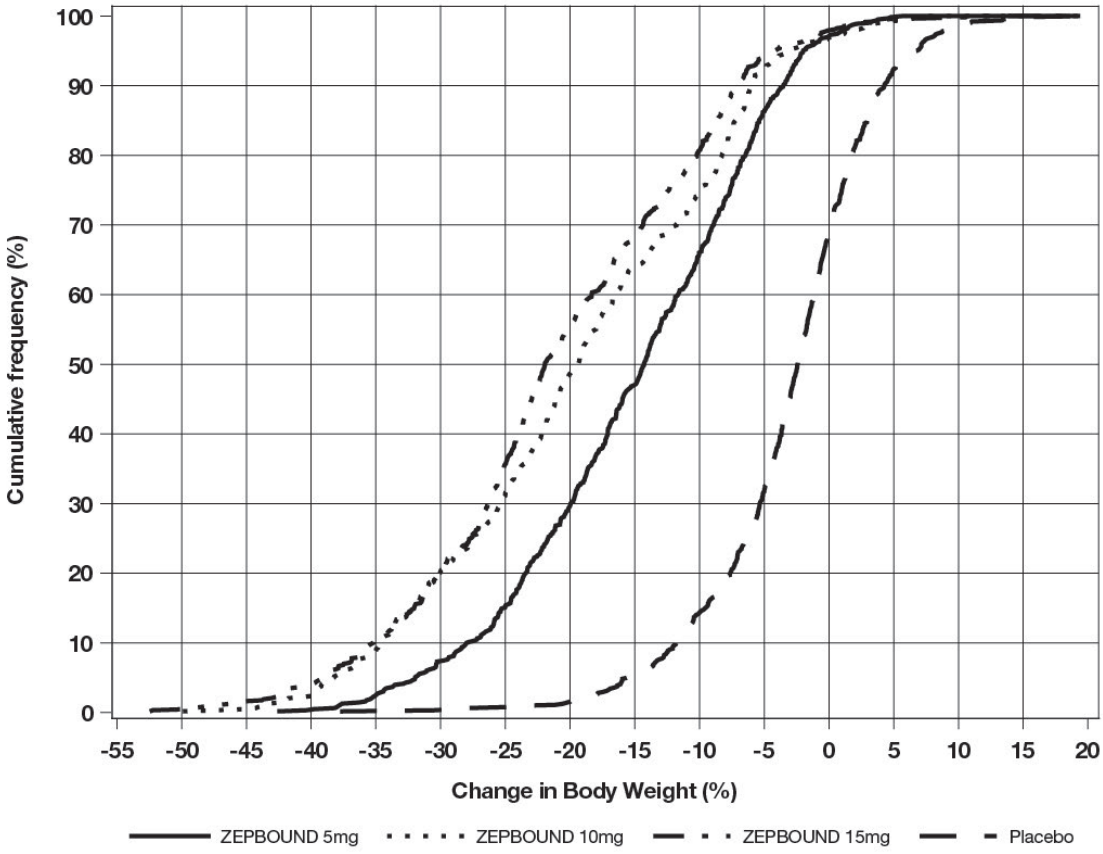
[c] Analyzed using logistic regression adjusted for baseline value.

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

[e] Not controlled for type I error rate.

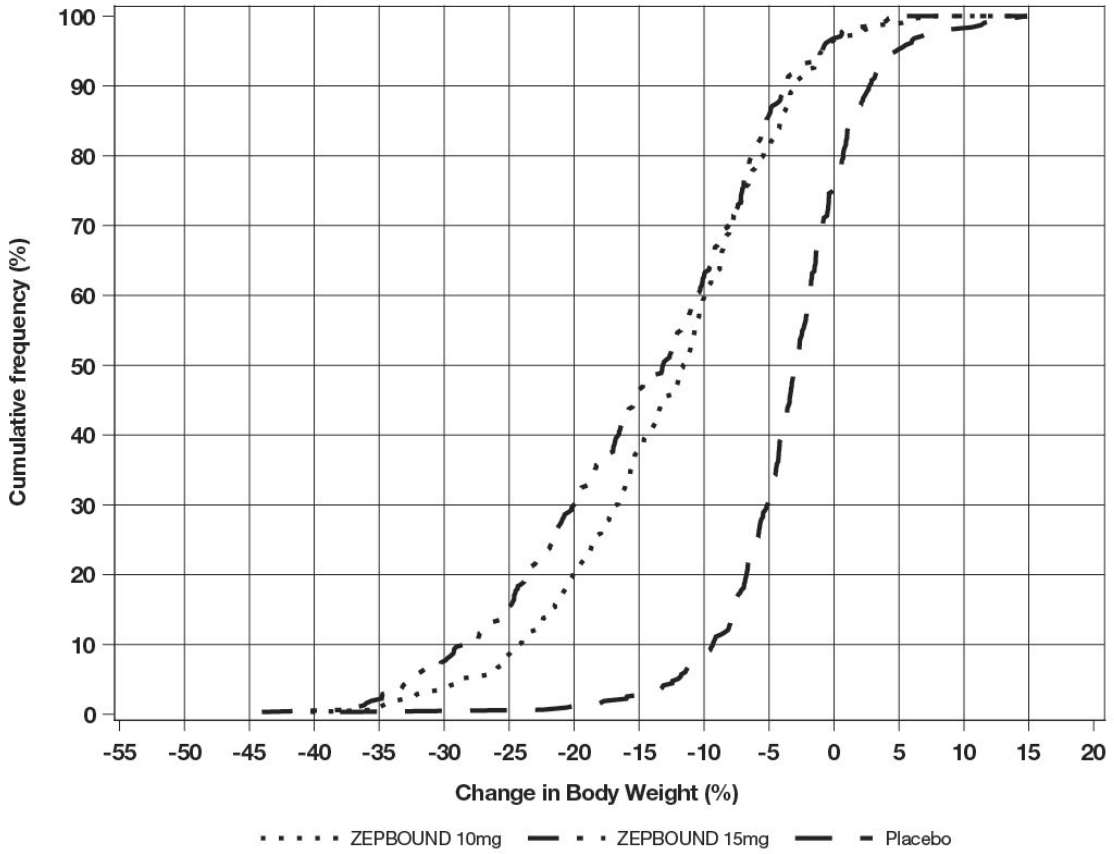
The cumulative frequency distributions of change in body weight are shown in Figure 1 for Study 1 and Figure 2 for Study 2. One way to interpret this figure is to select a change in body weight of interest on the horizontal axis and note the corresponding proportions of patients (vertical axis) in each treatment group who achieved at least that degree of weight reduction. For example, note that the vertical line arising from -10% in Figure 1 intersects the ZEPBOUND 15 mg and placebo curves at approximately 83.5%, and 18.8%, respectively, which correspond to the values shown in Table 2.

Figure 1: Changes in Body Weight (%) from Baseline to Week 72 in Study 1 in Patients with Obesity or Overweight (without Type 2 Diabetes)



Note: Based on average percent weight change of each randomized patient within each specific treatment arm from 100 imputed datasets including observed data and imputed data using hybrid approach for missing values.

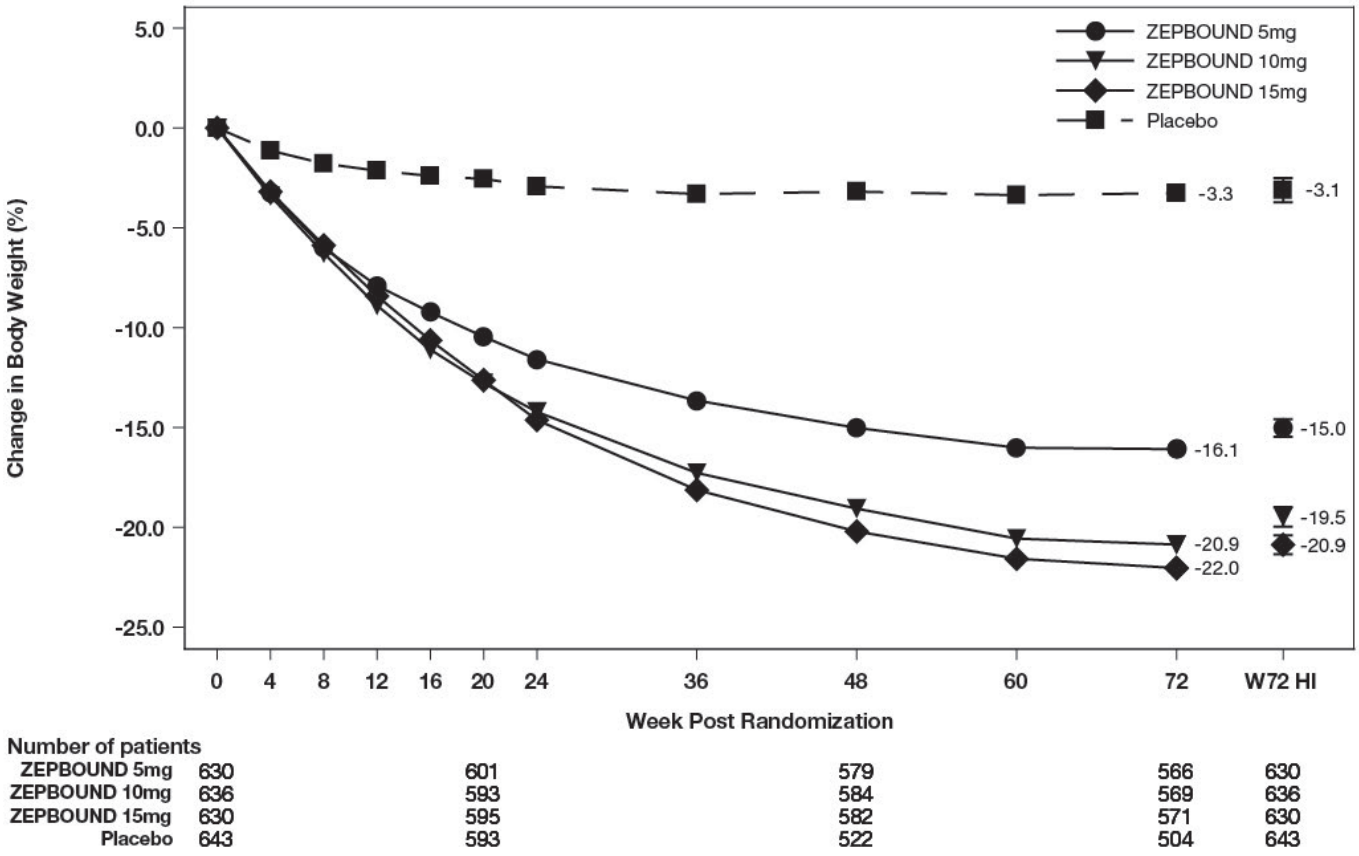
Figure 2: Changes in Body Weight (%) from Baseline to Week 72 in Study 2 in Patients with Obesity or Overweight and Type 2 Diabetes



Note: Based on average percent weight change of each randomized patient within each specific treatment arm from 100 imputed datasets including observed data and imputed data using hybrid approach for missing values.

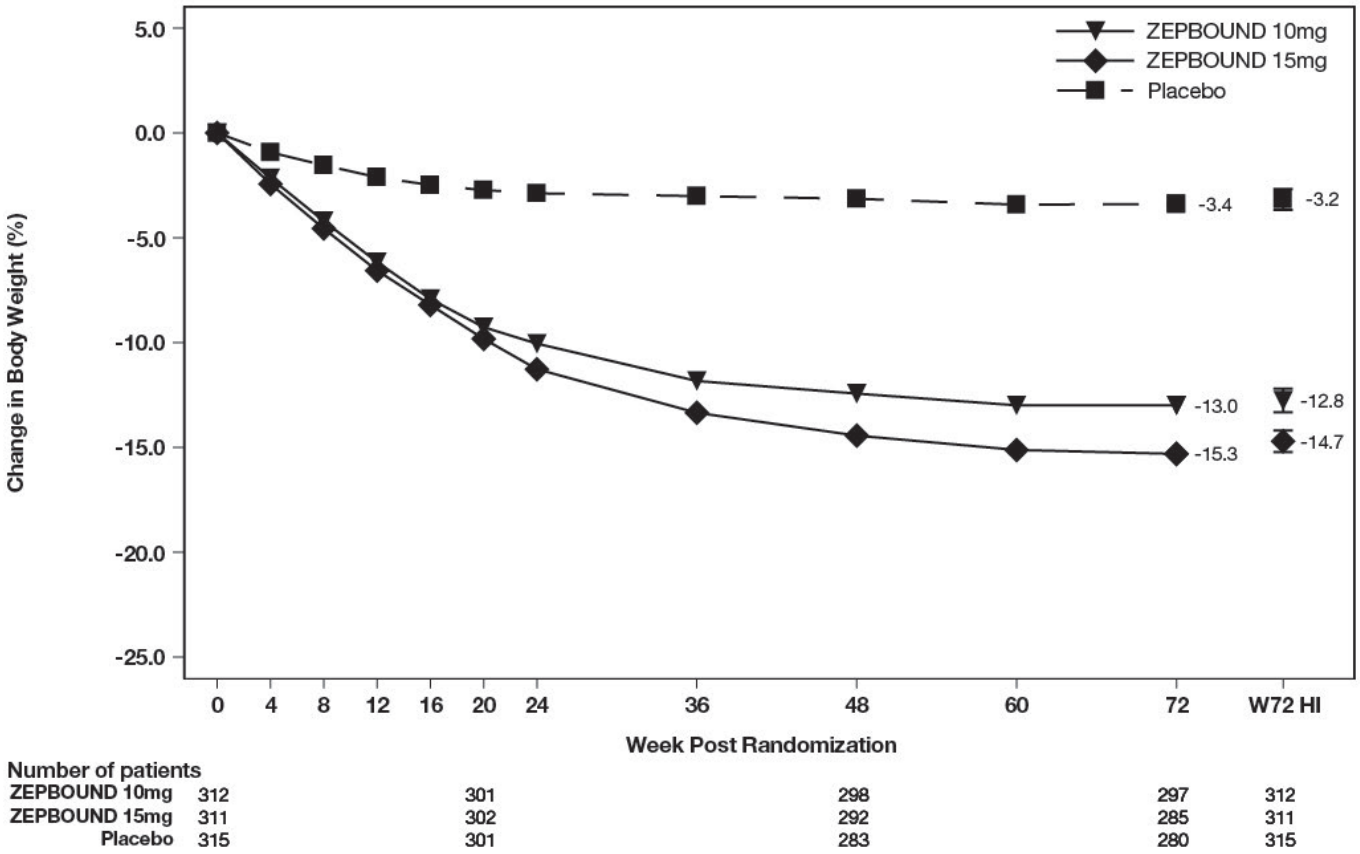
The time courses of weight reduction with ZEPBOUND and placebo from baseline through Week 72 are depicted in Figure 3 for Study 1 and Figure 4 for Study 2.

Figure 3: Change from Baseline (%) in Body Weight in Study 1 in Patients with Obesity or Overweight (without Type 2 Diabetes)



Note: Displayed results are from the Intent-to-Treat Population. (1) Observed mean value from Week 0 to Week 72, and (2) least-squares mean ± standard error at Week 72 hybrid imputation (HI).

Figure 4: Change from Baseline (%) in Body Weight in Study 2 in Patients with Obesity or Overweight and Type 2 Diabetes



Note: Displayed results are from the Intent-to-Treat Population. (1) Observed mean value from Week 0 to Week 72, and (2) least squares mean ± standard error at Week 72 hybrid imputation (HI).

Changes in waist circumference and cardiometabolic parameters with ZEPBOUND are shown in Table 3 for Study 1 and Study 2.

Table 3: Changes in Anthropometry and Cardiometabolic Parameters at Week 72 in Studies 1 and 2 in Patients with Obesity or Overweight

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

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

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

[a] The intention-to-treat population includes all randomly assigned patients. The missing values were imputed by a hybrid approach using retrieved dropouts from the same treatment group (if missing not due to COVID-19) or using all non-missing data assuming missing at random (for missing solely due to COVID-19).

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

[c] Analyzed using log-transformed data.

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

[e] Not controlled for type I error rate.

[f] Least-squares mean from mixed model for repeated measures adjusted for baseline value and other stratification factors.

[g] Baseline value is the geometric mean.

Weight Reduction Following Intensive Lifestyle Intervention in Adults with Obesity or Overweight (Study 3)

Overview of Study 3

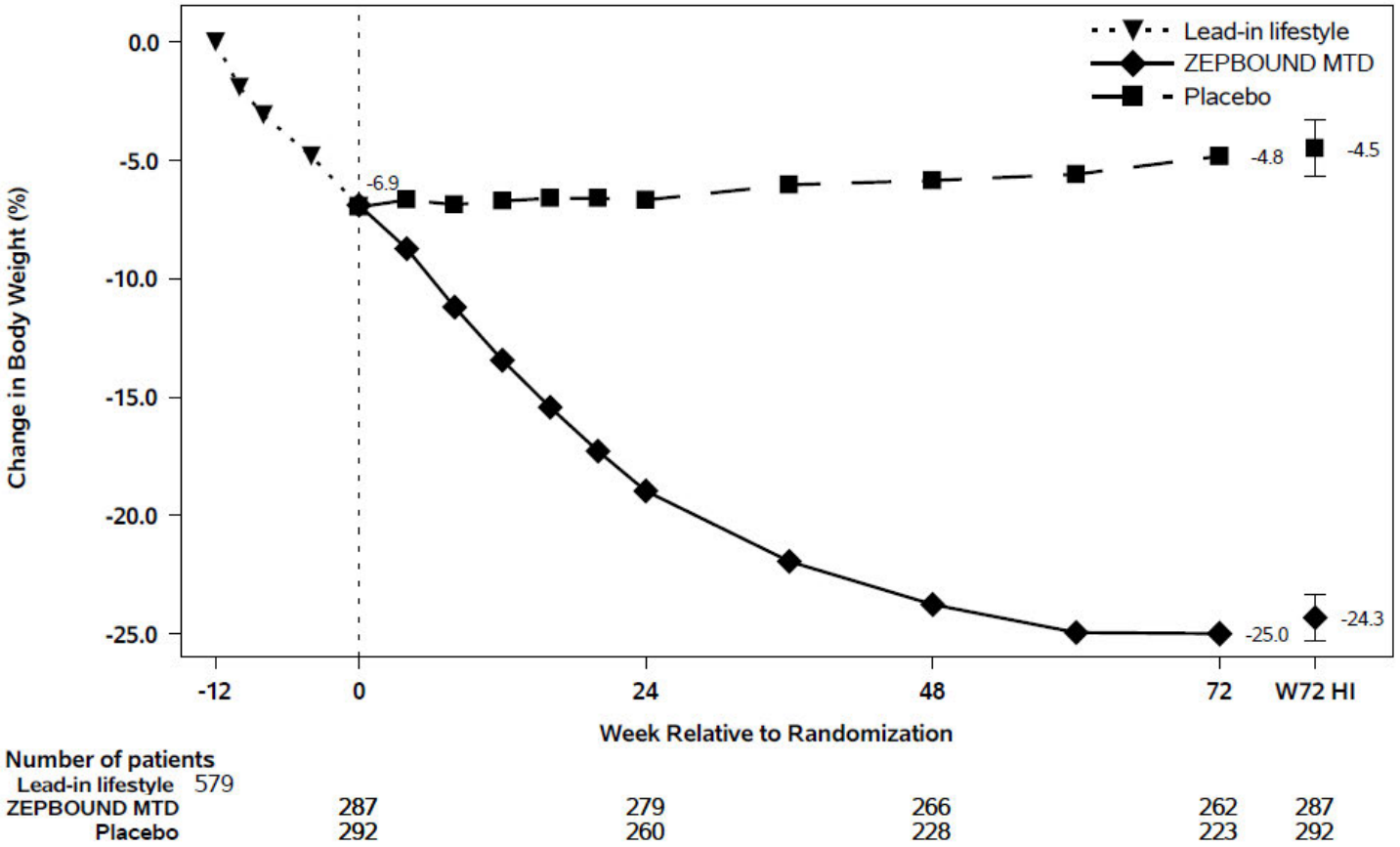
Study 3 (NCT04657016) was an 84-week trial with a 12-week intensive lifestyle intervention lead-in period (Week -12 to Week 0), followed by a 72-week randomized treatment period of ZEPBOUND versus placebo (Week 0 to Week 72) with a standard lifestyle intervention. Only patients who lost ≥5% body weight during the 12-week intensive lifestyle lead-in period entered the 72-week randomized treatment period. The trial initially enrolled 806 adult patients (aged 18 years and older) with obesity (BMI ≥30 kg/m^2), or with overweight (BMI 27 to <30 kg/m^2) and at least one weight-related comorbid condition, such as dyslipidemia, hypertension, obstructive sleep apnea, or cardiovascular disease; patients with type 2 diabetes mellitus were excluded. During the intensive lifestyle intervention lead-in period, lifestyle instruction was delivered 8 times over 12 weeks by a dietician or dietician-equivalent, with all patients receiving instruction to exercise for at least 150 minutes per week and to reduce their caloric intake to approximately 1,200 kcal/day (females) or 1,500 kcal/day (males). Patients also received counseling on behavior modification strategies to adhere to diet and exercise recommendations. At the end of the 12-week intensive lifestyle intervention lead-in period, 579 patients who achieved ≥5% weight reduction were randomized in a 1:1 ratio to ZEPBOUND or placebo for 72 weeks. ZEPBOUND dosages were escalated over a period of up to 20 weeks to a maximum tolerated dosage (MTD) of 10 mg or 15 mg subcutaneous once weekly. During the randomized treatment period, patients received a standard lifestyle instruction every 12 weeks on reduced-calorie diet (approximately 500 kcal/day deficit) and increased physical activity (recommended minimum of 150 min/week) that began with the first dose of ZEPBOUND or placebo and continued throughout the 72-week treatment period; behavior modification strategies were recommended as needed. Weight reduction was assessed after 72 weeks of treatment (at least 52 weeks at maintenance dose).

For the 579 patients who were randomized, mean body weight at enrollment prior to entering the 12-week lifestyle lead-in period (Week -12) was 109.5 kg and mean BMI was 38.6 kg/m^2. At randomization (Week 0), after the 12-week intensive lifestyle lead-in period, mean body weight was 101.9 kg and mean BMI was 35.9 kg/m^2. The mean age of patients randomized to treatment was 46 years (range 18-77 years), 63% were female, 86% were White, 11% were Black or African American, and 1% were Asian. A total of 54% were Hispanic or Latino ethnicity. Baseline characteristics for the 579 randomized patients included 34% with hypertension, 26% with dyslipidemia, 10% with obstructive sleep apnea, and 2% with cardiovascular disease.

Results for Study 3

At the end of the 12-week intensive lifestyle intervention lead-in, for patients who subsequently entered the randomized treatment period (n=579), the average body weight loss due to lifestyle was 6.9% (Week -12 to Week 0). Eighty-six percent (86%) of ZEPBOUND-treated patients had a maximum tolerated dosage of 15 mg weekly based on their final dose during the double-blind treatment period. The time course of weight reduction during the lead-in and from Week 0 to Week 72 with ZEPBOUND and placebo are depicted in Figure 5.

Figure 5: Change in Body Weight (%) After 12-Week Intensive Lifestyle Intervention Lead-In Followed by Randomized Treatment and a Standard Lifestyle Intervention (Study 3) in Patients with Obesity or Overweight



Note: Displayed results are from the randomized Population. (1) Observed mean value from Week -12 to Week 72, and (2) least squares mean ± standard error at Week 72 hybrid imputation (HI). Change from Week -12 is not a primary endpoint in Study 3.

The proportions of patients who discontinued study drug after randomization were 21.3% for the ZEPBOUND-treated group and 30.5% for the placebo-treated group.

For Study 3, the primary efficacy parameters were mean percent change in body weight from randomization (Week 0) to Week 72 and the percentage of patients achieving ≥5% weight reduction from randomization (Week 0) to Week 72. Amongst randomized patients who already lost ≥5% body weight during the 12-week intensive lifestyle lead-in period, subsequent treatment with ZEPBOUND resulted in a statistically significant reduction in body weight compared to placebo from randomization (Week 0) to Week 72. A greater proportion of patients treated with ZEPBOUND achieved at least 5%, 10%, 15%, and 20% weight reduction from Week 0 to Week 72 compared to placebo (see Table 4).

Table 4: Changes in Body Weight After 12-Week Intensive Lifestyle Intervention Lead-In Followed by Randomized Treatment and a Standard Lifestyle Intervention (Study 3) in Patients with Obesity or Overweight

	Study 3 N = 579[a]	
Body weight		
Mean (kg) at Week -12	109.5	
Intention-to-Treat (ITT) Population[a,b]	**Placebo N = 292**	**ZEPBOUND MTD (10 mg or 15 mg) N = 287**
Body Weight		
Mean (kg) at Week 0	101.3	102.5

% Change from randomization at Week 72[c]	2.5	-18.4
% Difference from placebo, at Week 72[c] (95% CI)		-20.8 (-23.2, -18.5)[e]
% of Patients losing ≥5% body weight	16.5	87.5
% Difference from placebo (95% CI)		71.1 (63.6, 78.5)[d,e]
% of Patients losing ≥10% body weight	8.9	76.7
% Difference from placebo (95% CI)		67.9 (60.7, 75.1)[d,e]
% of Patients losing ≥15% body weight	4.2	65.4
% Difference from placebo (95% CI)		61.3 (54.5, 68.1)[d,e]
% of Patients losing ≥20% body weight	2.2	44.7
% Difference from placebo (95% CI)		42.6 (36.0, 49.1)[d,e]

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

[a] The intent-to-treat population included only randomized patients with ≥5% weight loss at Week 0 after 12 weeks of intensive lifestyle intervention. During the 12-week lead-in period, 227 of 806 patients (28.2%) discontinued from the study. Of these 141 (17.5%) discontinued due to not achieving the randomization criteria of ≥5% weight reduction.

[b] The intent-to-treat population includes all randomly assigned patients. For Study 3 at Week 72, body weight was missing for 23.6% and 8.7% of patients randomly assigned to placebo and ZEPBOUND MTD (10 or 15 mg). The missing values were imputed by a hybrid approach using retrieved dropouts from the same treatment group (if missing not due to COVID-19) or using all non-missing data assuming missing at random (for missing solely due to COVID-19).

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

[d] Analyzed using logistic regression adjusted for baseline value.

[e] p-value<0.001 (unadjusted 2-sided) for superiority, controlled for type I error rate.

Changes in waist circumference and cardiometabolic parameters are shown in Table 5.

Table 5: Changes in Anthropometry and Cardiometabolic Parameters After 12-Week Intensive Lifestyle Intervention Lead-In Followed by Randomized Treatment and a Standard Lifestyle Intervention (Study 3) in Patients with Obesity or Overweight

	All Randomized Patients N=579		Placebo N=292		ZEPBOUND MTD (10 mg or 15 mg) N=287		
Intention-to-Treat (ITT) Population[a]	Baseline (Week -12)	Change from Week -12 to Week 0	Randomization (Week 0)	Change from Week 0 to Week 72	Randomization (Week 0)	Change from Week 0 to Week 72	Difference from placebo, Week 0 to Week 72 (95% CI)
Waist circumference (cm)[h]	116.1	-6.7	109.6	0.2[b]	109.3	-14.6[b]	-14.8[b] (-17.2, -12.5)[d]
Systolic Blood Pressure (mmHg)[h]	126.2	-5.0	120.8	3.5[b]	121.7	-5.1[b]	-8.6[b] (-11.3, -6.0)[e]
Diastolic Blood Pressure (mmHg)[h]	81.7	-2.9	78.3	2.1[b]	79.3	-3.2[b]	-5.3[b] (-6.9, -3.7)[e]
Pulse Rate (beats per minute)[h]	73.0	-1.6	70.7	0.9[f]	72.2	2.7[f]	1.8[f] (0.3, 3.4)[e]
HbA1c (%)[h]	5.5	-0.1	5.4	0.0[b]	5.3	-0.4[b]	-0.4[b] (-0.5, -0.3)[e]

Total Cholesterol (mg/dL)[g,h]	190.2	-8.6	181.6	4.3	181.7	-2.4	-6.4[b] (-9.0, -3.6)[c,e]
LDL Cholesterol (mg/dL)[g,h]	111.6	-3.5	107.5	4.4	108.0	-5.6	-9.6[b] (-13.7, -5.4)[c,e]
HDL Cholesterol (mg/dL)[g,h]	48.4	-1.2	47.8	5.4	46.9	15.2	9.3[b] (4.5, 14.2)[c,e]
Non-HDL Cholesterol (mg/dL)[g,h]	139.2	-7.4	131.5	4.4	132.4	-8.8	-12.6[b] (-15.9, -9.3)[c,e]
Triglycerides (mg/dL)[g,h]	123.1	-19.8	108.8	2.1	111.7	-23.5	-25.1[b] (-30.9, -18.9)[c,e]

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

[a] The intent-to-treat population included all randomly assigned patients. The missing values were imputed by a hybrid approach using retrieved dropouts from the same treatment group (if missing not due to COVID-19) or using all non-missing data assuming missing at random (for missing solely due to COVID-19).

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

[c] Analyzed using log-transformed data.

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

[e] Not controlled for type I error rate.

[f] Least-squares mean from mixed model for repeated measures adjusted for baseline value and other stratification factors.

[g] Baseline and randomization values are the geometric mean.

[h] Observed means are shown for change from Week -12 to Week 0. Least-square means are shown for change from Week 0 to Week 72.

Weight Reduction Following Randomized Withdrawal in Adults with Obesity or Overweight (Study 4)

Overview of Study 4

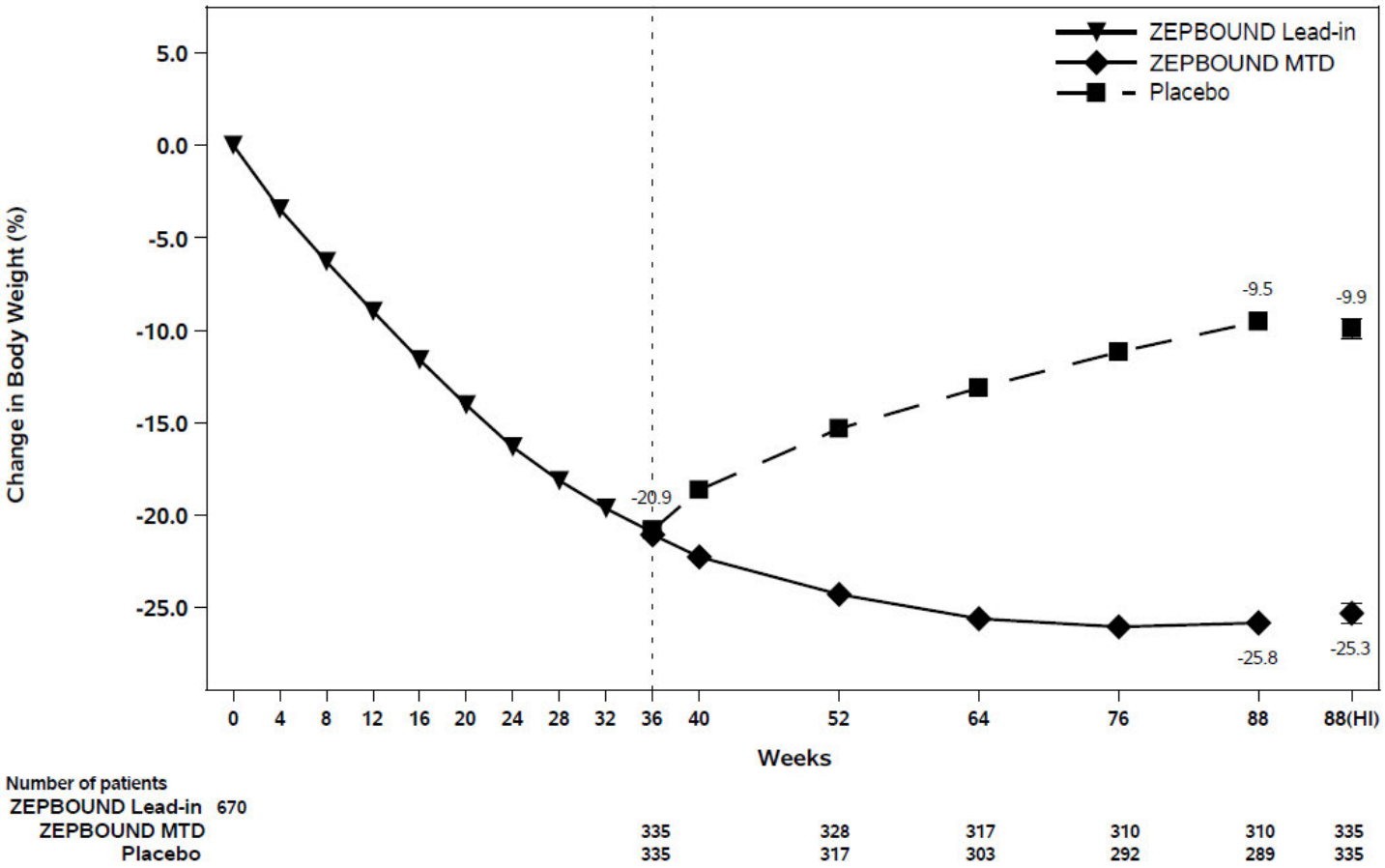
Study 4 (NCT04660643) was an 88-week randomized withdrawal trial in which all patients received open-label ZEPBOUND during a 36-week lead-in period, followed by randomization to either continue ZEPBOUND or switch to placebo for 52 weeks. The trial enrolled 783 adult patients (aged 18 years and older) with obesity (BMI ≥30 kg/m^2), or with overweight (BMI 27 to <30 kg/m^2) and at least one weight-related comorbid condition, such as dyslipidemia, hypertension, obstructive sleep apnea, or cardiovascular disease; patients with type 2 diabetes mellitus were excluded. All patients received a standard lifestyle intervention which included instruction on a reduced-calorie diet (approximately 500 kcal/day deficit) and increased physical activity counseling (recommended minimum of 150 min/week) that began with the first dose of ZEPBOUND, during the lead-in period, and continued throughout the trial. During the 36-week open-label ZEPBOUND lead-in period, ZEPBOUND dosages were escalated over a period of up to 20 weeks to an MTD of 10 mg or 15 mg subcutaneous once weekly. After the lead-in period, patients were randomized at Week 36 to continue ZEPBOUND or switch to placebo for 52 weeks.

Of the 783 patients who started ZEPBOUND at Week 0, 14.4% discontinued treatment before randomization at Week 36, and adverse events were the most common reason for discontinuation (6.8%). At Week 36, a total of 670 patients were randomized in a 1:1 ratio to ZEPBOUND MTD or placebo for 52 weeks. For the 670 randomized patients, at study entry (Week 0) mean body weight was 107.3 kg and mean BMI was 38.4 kg/m^2, and at randomization (Week 36, after the open-label ZEPBOUND lead-in period) mean body weight was 85.2 kg and mean BMI was 30.5 kg/m^2. Among the randomized patients, the mean age was 49 years (range 19-81 years), 71% were female, 80% were White, 11% were Black or African American, and 7% were Asian. A total of 44% were Hispanic or Latino ethnicity. Baseline characteristics for the 670 randomized patients included 35% with hypertension, 32% with dyslipidemia, 12% with obstructive sleep apnea, and 6% with cardiovascular disease.

Results for Study 4

At the end of the 36-week open-label ZEPBOUND lead-in period, of the 670 randomized patients, 93% were on ZEPBOUND MTD of 15 mg weekly and 7% were on MTD of 10 mg weekly. After open-label ZEPBOUND treatment, randomized patients (n=670) had an average body weight loss of 20.9% (Week 0 to Week 36). The time course of weight reduction from Week 0 through Week 88 is depicted in Figure 6.

Figure 6: Change in Body Weight (%) After 36-Week Open-Label Treatment Followed by Randomized Withdrawal (Study 4) in Patients with Obesity or Overweight



Note: Displayed results are from the randomized population. (1) Displayed results are observed mean value from Week 0 to Week 88 and (2) least squares mean ± standard error at Week 88 hybrid imputation (HI). Change from Week 0 was not a primary endpoint in Study 4.

The proportions of patients who discontinued study drug after randomization at Week 36 were 10.4% for the ZEPBOUND-treated group and 17.9% for the placebo-treated group.

For Study 4, the primary efficacy parameter was mean percent change in body weight from randomization (Week 36) to Week 88. After weight loss with ZEPBOUND treatment during the open-label lead-in period (Week 0 to Week 36), continued treatment with ZEPBOUND from randomization (Week 36) to Week 88 resulted in a statistically significant reduction in body weight compared with placebo (see Table 6).

Table 6: Changes in Body Weight After 36-Week Open-Label Treatment Followed by Randomized Withdrawal (Study 4) in Patients with Obesity or Overweight

	Study 4 N=670[a]	
Body weight		
Mean at Week 0 (kg)	107.3	
Intention-to-Treat (ITT) Population[a]	**Placebo N=335**	**ZEPBOUND (MTD 10 mg or 15 mg) N=335**
Body Weight		
Mean at Week 36 (kg)	85.8	84.6

% change from Week 36 at Week 88[b]	14.0	-5.5
% difference from placebo at Week 88 (95% CI)[b]		-19.4 (-21.2, -17.7)[d]

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

[a] The intent-to-treat population included all randomly assigned patients and did not include 113 patients who were enrolled but not randomized. At Week 88, body weight was missing for 13.7% and 7.5% of patients randomly assigned to placebo and ZEPBOUND MTD (10 or 15 mg), respectively. The missing values were imputed by a hybrid approach using retrieved dropouts from the same treatment group (if missing not due to COVID-19) or using all non-missing data assuming missing at random (for missing solely due to COVID-19).

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

[c] Analyzed using logistic regression adjusted for baseline value.

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

Changes in waist circumference and cardiometabolic parameters in Study 4 are shown in Table 7.

Table 7: Mean Changes in Anthropometry and Cardiometabolic Parameters After 36-Week Open-Label Treatment Followed by Randomized Withdrawal (Study 4) in Patients with Obesity or Overweight

	All Randomized Patients N=670		**Placebo N=335**		**ZEPBOUND MTD (10 mg or 15 mg) N=335**		
Intention-to-Treat (ITT) Population[a]	**Baseline (Week 0)**	**Change from Week 0 to Week 36**	**Randomization (Week 36)**	**Change from Week 36 to Week 88**	**Randomization (Week 36)**	**Change from Week 36 to Week 88**	**Difference from placebo, Week 36 to Week 88 (95% CI)**
Waist circumference (cm)[h]	115.2	-17.8	98.2	7.8[b]	96.8	-4.3[b]	-12.1[b] (-13.5, -10.6)[d]
Systolic Blood Pressure (mmHg)[h]	126.1	-11.2	114.8	8.2[b]	115.0	2.0[b]	-6.2[b] (-8.2, -4.3)[e]
Diastolic Blood Pressure (mmHg)[h]	80.9	-5.1	76.2	3.2[b]	75.4	-0.7[b]	-3.8[b] (-5.2, -2.4)[e]
Pulse Rate (beats per minute)[h]	72.5	5.0	77.8	-5.2[f]	77.1	-2.1[f]	3.1[f] (1.9, 4.3)[e]
HbA1c (%)[h]	5.5	-0.5	5.0	0.3[b]	5.1	-0.0[b]	-0.3[b] (-0.3, -0.2)[e]
Total Cholesterol (mg/dL)[g,h]	188.3	-12.4	176.1	8.0	175.9	2.7	-4.9[b] (-7.4, -2.4)[c,e]
LDL Cholesterol (mg/dL)[g,h]	108.6	-1.9	107.6	3.2	105.9	-3.5	-6.5[b] (-10.0, -2.9)[c,e]
HDL Cholesterol (mg/dL)[g,h]	49.9	-2.7	47.3	14.8	47.7	18.7	3.4[b] (0.2, 6.6)[c,e]
Non-HDL Cholesterol (mg/dL)[g,h]	135.8	-9.8	126.3	5.1	126.0	-3.4	-8.1[b] (-11.3, -4.8)[c,e]
Triglycerides (mg/dL)[g,h]	121.4	-40.4	85.5	13.5	90.9	-4.8	-16.1[b] (-21.7, -10.0)[c,e]

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

[a] The intent-to-treat population included all randomly assigned patients. The missing values were imputed by a hybrid approach using retrieved dropouts from the same treatment group (if missing not due to COVID-19) or using all non-missing data assuming missing at random (for missing solely due to COVID-19).

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

[c] Analyzed using log-transformed data.

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

[e] Not controlled for type I error rate.

[f] Least-squares mean from mixed model for repeated measures adjusted for baseline value and other stratification factors.

[g] Baseline and randomization values are the geometric mean.

[h] Observed means are shown for change from Week 0 to Week 36. Least-square means are shown for change from Week 36 to Week 88.

14.2 Obstructive Sleep Apnea Studies in Adults with Obesity

Overview of Study 5 and Study 6

The efficacy of ZEPBOUND for moderate to severe obstructive sleep apnea (OSA) (apnea-hypopnea index [AHI] ≥15) in patients with obesity (BMI ≥30 kg/m^2) was evaluated in a master protocol clinical trial (NCT05412004) that included two randomized, double-blind, placebo-controlled trials (Study 5 and Study 6) of 52 weeks duration. The two trials enrolled a total of 469 adult patients.

In Studies 5 and 6, patients were randomized in a 1:1 ratio to receive ZEPBOUND or placebo for 52 weeks. ZEPBOUND dosages were escalated over a period of up to 20 weeks to maximum tolerated dosage (MTD) of 10 mg or 15 mg subcutaneous once weekly *[see Dosage and Administration (2.1, 2.2)]*. Patients with type 2 diabetes mellitus were excluded and all patients received instruction on a reduced-calorie diet and increased physical activity counseling throughout the study.

Study 5 enrolled 234 adult patients with moderate to severe OSA and obesity who were unable or unwilling to use Positive Airway Pressure (PAP) therapy. Patients had a mean age of 48 years (range: 20 to 76 years), 67% were male, 66% were White, 20% were Asian, 8% were American Indian/Alaska Native, and 6% were Black or African American. A total of 42% were Hispanic or Latino ethnicity.

Study 6 enrolled 235 adult patients with moderate to severe OSA and obesity who were on PAP therapy. Patients had a mean age of 52 years (range: 26 to 79 years), 72% were male, 73% were White, 14% were Asian, 8% were American Indian/Alaska Native, and 5% were Black or African American. A total of 32% were Hispanic or Latino ethnicity.

Table 8 describes the baseline disease characteristics of patients in Studies 5 and 6.

Table 8: Baseline Disease Characteristics of Patients with OSA and Obesity in Study 5 and Study 6

	Study 5 (N=234)	**Study 6 (N=235)**
Baseline AHI (events/hour), mean (SD)	51.5 (31)	49.5 (26.7)
Moderate OSA, %[a]	35.2	30.9
Severe OSA, %[b]	63.1	68.2
ESS Total, mean (SD)	10.5 (5.2)	10 (4.6)
Total Hypoxic Burden (% min/hour), mean (SD)	208.4 (189.1)	193 (174.6)
BMI (kg/m^2), mean (SD)	39.1 (7)	38.7 (6)
Pre-diabetes, %	65	56.6
Hypertension, %	75.6	77.4
Cardiac disorders, %	10.3	11.1
Dyslipidemia, %	80.8	83.8

Abbreviations: AHI = Apnea-Hypopnea Index; BMI = body-mass index; ESS = Epworth Sleepiness Score; OSA = obstructive sleep apnea; SD = standard deviation.

[a] Moderate OSA was defined as an AHI ≥15 – 30 events/hour on polysomnogram at baseline.

[b] Severe OSA was defined as an AHI ≥30 events/hour on polysomnogram at baseline.

Results for Study 5 and Study 6

The primary endpoint for Studies 5 and 6 was the change from baseline in the apnea-hypopnea index (AHI) at Week 52. Patients in Study 5 were unable or unwilling to use PAP therapy, and patients in Study 6 were on PAP therapy and instructed to suspend PAP for 7 days prior to assessment of the primary endpoint. The clinical studies for OSA did not evaluate the timing or appropriateness of PAP discontinuation in patients who were previously compliant with PAP therapy.

In Studies 5 and 6, treatment with ZEPBOUND for 52 weeks resulted in a statistically significant reduction in AHI compared with placebo, and greater proportions of patients treated with ZEPBOUND achieved remission or mild non-

symptomatic OSA compared to placebo. Table 9 provides the efficacy results for Studies 5 and 6. A reduction in AHI was observed with ZEPBOUND irrespective of age, sex, ethnicity, baseline BMI, or baseline OSA severity. In both Studies 5 and 6, patients treated with ZEPBOUND achieved a greater reduction in systolic blood pressure and high-sensitivity C-reactive protein levels compared to placebo.

Table 9: Changes in Apnea-Hypopnea Index (AHI), Hypoxic Burden, and Body Weight at Week 52 in Study 5 and Study 6

Modified Intent-to-Treat (mITT) Population[a]	Study 5		Study 6	
	Placebo N = 120	ZEPBOUND MTD (10 mg or 15 mg) N = 114	Placebo N = 114	ZEPBOUND MTD (10 mg or 15 mg) N = 119
AHI (events/hr)				
Baseline mean	50.1	52.9	53.1	46.1
Change from baseline[b]	-5.3	-25.3	-5.5	-29.3
Difference from placebo[b] (95% CI)	-20 (-25.8, -14.2)[e]		-23.8 (-29.6, -17.9)[e]	
% change in AHI				
% change from baseline[b]	-3	-50.7	-2.5	-58.7
% difference from placebo[b] (95% CI)	-47.7 (-65.8, -29.6)[e]		-56.2 (-73.7, -38.7)[e]	
% of patients with ≥50% reduction in AHI[d]	19	61.2	23.3	72.4
% difference from placebo (95% CI)	42.8 (30.8, 54.8)[e]		48.6 (36.6, 60.7)[e]	
Remission or mild non-symptomatic OSA				
% of Patients with AHI <5 or AHI 5-14 and ESS≤10[d]	15.9	42.2	14.3	50.2
% difference from placebo (95% CI)	28.7 (18.3, 39.2)[e]		33.2 (22.1, 44.3)[e]	
Sleep apnea-specific hypoxic burden (% min/h)				
Baseline mean[f]	137.8	153.6	142.1	132.2
Change from baseline[b]	-25.1	-95.2	-41.7	-103
Difference from placebo[b] (95% CI)	-70.1 (-90.9, -49.3)[c,e]		-61.3 (-84.7, -37.9)[c,e]	
Body weight (kg)				
Baseline mean	112.8	116.7	115.1	115.8
% change from baseline[b]	-1.6	-17.7	-2.3	-19.6
% difference from placebo[b] (95% CI)	-16.1 (-18, -14.2)[e]		-17.3 (-19.3, -15.3)[e]	

Abbreviations: AHI = Apnea-Hypopnea Index; ANCOVA = analysis of covariance; CI = confidence interval; ESS = Epworth Sleepiness Scale; h = hour; MTD = maximum tolerated dose; N = number of participants randomly assigned and received at least 1 dose of study drug.

[a] Analyses were based on the modified intent-to-treat population which was defined as randomly assigned participants who were exposed to at least 1 dose of study intervention; two participants in Study 6 were randomized but did not receive study drug.

[b] Least-squares mean from ANCOVA adjusted for baseline values and stratification factors, with multiple imputation for missing data at Week 52.

[c] Analyzed using log transformed data.

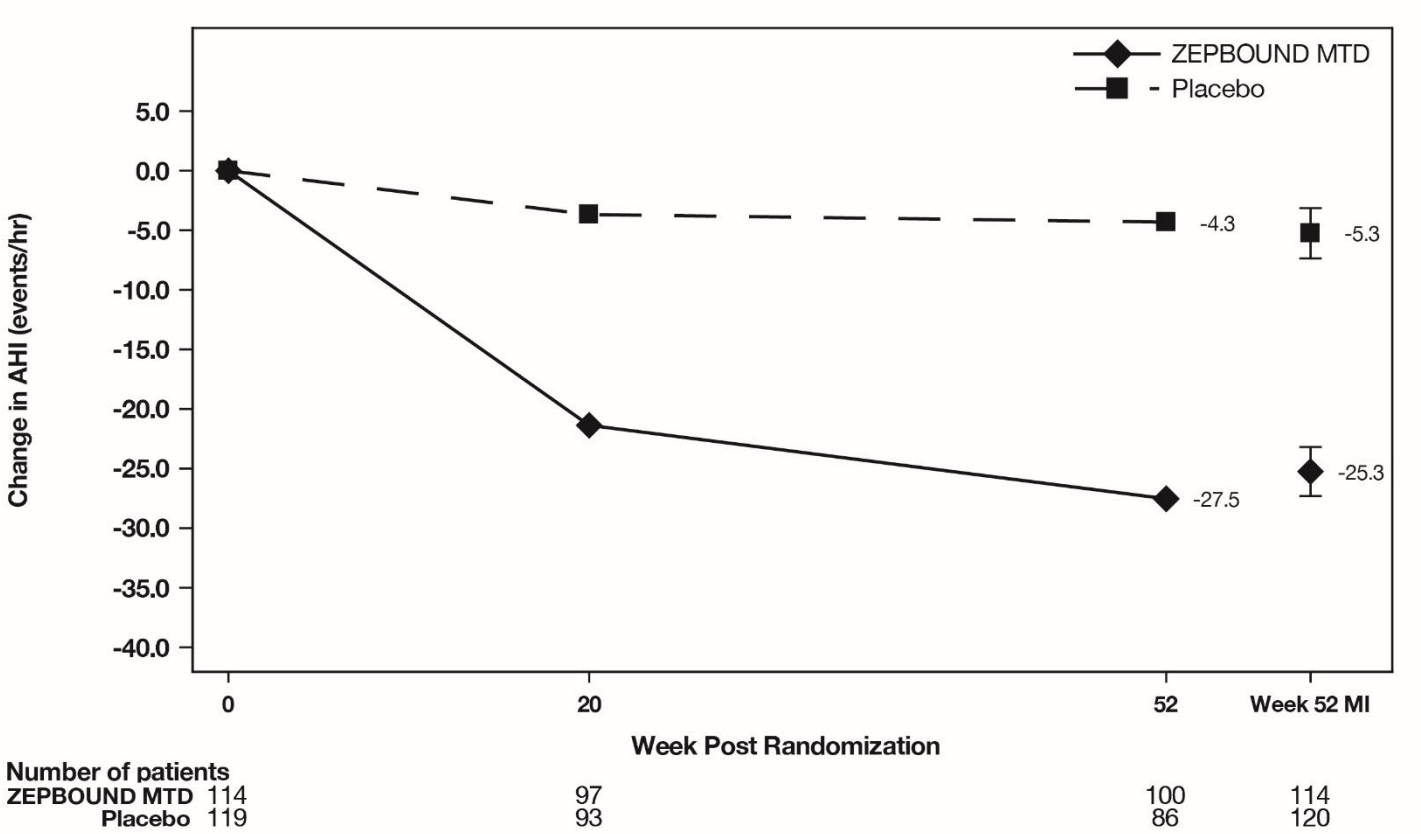
[d] Calculated by combining proportion of participants achieving target in imputed datasets.

[e] p-value <0.001 (unadjusted 2-sided) for superiority, controlled for multiplicity.

[f] Baseline value is the geometric mean.

The time course of change in AHI with ZEPBOUND and placebo from baseline through Week 52 are shown in Figure 7 for Study 5. Similar results were demonstrated for Study 6.

Figure 7: Change from Baseline in Apnea-Hypopnea Index (AHI) Through Week 52 (Study 5)



Abbreviations: AHI = Apnea-Hypopnea Index; ANCOVA = analysis of covariance; MI = multiple imputation; MTD = maximum tolerated dose.

Note: Displayed results are from modified Intent-to-Treat Population. (1) Observed mean value from Week 0 through Week 52, and (2) least squares mean ± standard error at Week 52 from ANCOVA adjusted for baseline values and stratification factors, with multiple imputation of missing data.

Sleep-Related Impairment

In OSA clinical studies (Study 5 and Study 6), ZEPBOUND-treated patients showed improvement in sleep-related impairment compared to those who received placebo. Sleep-related impairment was assessed using the Patient-Reported Outcomes Measurement Information System® (PROMIS) Short Form Sleep-Related Impairment 8a.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

ZEPBOUND (tirzepatide) is a clear, colorless to slightly yellow solution available in cartons containing 4 pre-filled single-dose pens or 1 single-dose vial as follows:

Total Strength per Total Volume	Pen NDC	Vial NDC
2.5 mg/0.5 mL	0002-2506-80	0002-0152-01
5 mg/0.5 mL	0002-2495-80	0002-0243-01
7.5 mg/0.5 mL	0002-2484-80	0002-1214-01
10 mg/0.5 mL	0002-2471-80	0002-1340-01
12.5 mg/0.5 mL	0002-2460-80	0002-1423-01
15 mg/0.5 mL	0002-2457-80	0002-2002-01

16.2 Storage and Handling

- Store ZEPBOUND in a refrigerator at 2°C to 8°C (36°F to 46°F).
- If needed, each single-dose pen or single-dose vial can be stored unrefrigerated at temperatures not to exceed 30°C (86°F) for up to 21 days. If ZEPBOUND is stored at room temperature, it should not be returned to the refrigerator.
- Discard if not used within 21 days after removing from the refrigerator.
- Do not freeze ZEPBOUND. Do not use ZEPBOUND if frozen.
- Store ZEPBOUND in the original carton to protect from light.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling *(Medication Guide and Instructions for Use)*.

Risk of Thyroid C-Cell Tumors

Inform patients that ZEPBOUND causes thyroid C-cell tumors in rats and that the human relevance of this finding has not been determined. Counsel patients to report symptoms of thyroid tumors (e.g., a lump in the neck, persistent hoarseness, dysphagia, or dyspnea) to their healthcare provider *[see Boxed Warning and Warnings and Precautions (5.1)]*.

Severe Gastrointestinal Adverse Reactions

Inform patients of the potential risk of severe gastrointestinal adverse reactions. Instruct patients to contact their healthcare provider if they have severe or persistent gastrointestinal symptoms *[see Warnings and Precautions (5.2)]*.

Acute Kidney Injury

Advise patients treated with ZEPBOUND of the potential risk of dehydration due to gastrointestinal adverse reactions and take precautions to avoid fluid depletion. Inform patients of the potential risk for worsening renal function and explain the associated signs and symptoms of renal impairment, as well as the possibility of dialysis as a medical intervention if renal failure occurs *[see Warnings and Precautions (5.3)]*.

Acute Gallbladder Disease

Inform patients of the risk of acute gallbladder disease. Instruct patients to contact their healthcare provider for appropriate clinical follow-up if gallbladder disease is suspected *[see Warnings and Precautions (5.4)]*.

Acute Pancreatitis

Inform patients of the potential risk for pancreatitis. Instruct patients to discontinue ZEPBOUND promptly and contact their healthcare provider if pancreatitis is suspected (severe abdominal pain that may radiate to the back, and which may or may not be accompanied by vomiting) *[see Warnings and Precautions (5.5)]*.

Hypersensitivity Reactions

Inform patients that serious hypersensitivity reactions have been reported with use of tirzepatide. Advise patients on the symptoms of hypersensitivity reactions and instruct them to stop taking ZEPBOUND and seek medical advice promptly if such symptoms occur *[see Warnings and Precautions (5.6)]*.

Hypoglycemia

Inform patients of the risk of hypoglycemia and educate patients on the signs and symptoms of hypoglycemia. Advise patients on insulin or insulin secretagogue therapy that they may have an increased risk of hypoglycemia when using ZEPBOUND and to report signs and/or symptoms of hypoglycemia to their healthcare provider *[see Warnings and Precautions (5.7)]*.

Diabetic Retinopathy Complications

Inform patients with type 2 diabetes mellitus to contact their healthcare provider if changes in vision are experienced during treatment with ZEPBOUND *[see Warnings and Precautions (5.8)]*.

Suicidal Behavior and Ideation

Advise patients to report emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior. Inform patients that if they experience suicidal thoughts or behaviors, they should stop taking ZEPBOUND *[see Warnings and Precautions (5.9)]*.

Pulmonary Aspiration During General Anesthesia or Deep Sedation

Inform patients that ZEPBOUND may cause their stomach to empty more slowly which may lead to complications with anesthesia or deep sedation during planned surgeries or procedures. Instruct patients to inform healthcare providers prior to any planned surgeries or procedures if they are taking ZEPBOUND *[see Warnings and Precautions (5.10)]*.

Pregnancy

Advise a pregnant patient of the potential risk to a fetus. Advise patients to inform their healthcare provider if they are pregnant or intend to become pregnant during treatment with ZEPBOUND. Advise patients that there will be a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to ZEPBOUND during pregnancy *[see Use in Specific Populations (8.1)]*.

Contraception

Use of ZEPBOUND may reduce the efficacy of oral hormonal contraceptives. Advise patients using oral hormonal contraceptives to switch to a non-oral contraceptive method or add a barrier method of contraception for 4 weeks after initiation with ZEPBOUND and for 4 weeks after each dose escalation *[see Drug Interactions (7.2), Use in Specific Populations (8.3), and Clinical Pharmacology (12.3)]*.

Administration

Instruct patients how to prepare and administer the correct dose of ZEPBOUND and assess their ability to inject subcutaneously to ensure the proper administration of ZEPBOUND. Instruct patients using the single-dose vial to use a syringe appropriate for dose administration (e.g., a 1 mL syringe capable of measuring a 0.5 mL dose) *[see Dosage and Administration (2.4)]*.

Missed Doses

Inform patients if a dose is missed, it should be administered as soon as possible within 4 days after the missed dose. If more than 4 days have passed, the missed dose should be skipped and the next dose should be administered on the regularly scheduled day. In each case, inform patients to resume their regular once weekly dosing schedule *[see Dosage and Administration (2.3)]*.

Marketed by: Lilly USA, LLC, Indianapolis, IN 46285, USA

B4.0-NL-ZEP-0004-USPI-YYYYMMDD

Medication Guide
ZEPBOUND® (ZEHP-bownd)
(tirzepatide)
injection, for subcutaneous use

What is the most important information I should know about ZEPBOUND?

ZEPBOUND may cause serious side effects, including:

- **Possible thyroid tumors, including cancer.** Tell your healthcare provider if you get a lump or swelling in your neck, hoarseness, trouble swallowing, or shortness of breath. These may be symptoms of thyroid cancer. In studies with rats, ZEPBOUND and medicines that work like ZEPBOUND caused thyroid tumors, including thyroid cancer. It is not known if ZEPBOUND will cause thyroid tumors, or a type of thyroid cancer called medullary thyroid carcinoma (MTC) in people.
- Do not use ZEPBOUND if you or any of your family have ever had a type of thyroid cancer called MTC, or if you have an endocrine system condition called Multiple Endocrine Neoplasia syndrome type 2 (MEN 2).

What is ZEPBOUND?

- ZEPBOUND is an injectable prescription medicine that may help adults with:
  - obesity, or some adults with overweight who also have weight-related medical problems, to lose excess body weight and keep the weight off.
  - moderate to severe obstructive sleep apnea (OSA) and obesity to improve their OSA.
- ZEPBOUND should be used with a reduced-calorie diet and increased physical activity.
- ZEPBOUND contains tirzepatide and should not be used with other tirzepatide-containing products or any GLP-1 receptor agonist medicines.
- It is not known if ZEPBOUND is safe and effective for use in children.

Do not use ZEPBOUND if:

- you or any of your family have ever had a type of thyroid cancer called MTC or if you have an endocrine system condition called MEN 2.
- you have had a serious allergic reaction to tirzepatide or any of the ingredients in ZEPBOUND. See the end of this Medication Guide for a complete list of ingredients in ZEPBOUND.

Before using ZEPBOUND, tell your healthcare provider about all of your medical conditions, including if you:

- have or have had problems with your pancreas or kidneys.
- have severe problems with your stomach, such as slowed emptying of your stomach (gastroparesis) or problems with digesting food.
- have a history of diabetic retinopathy.
- are scheduled to have surgery or other procedures that use anesthesia or deep sleepiness (deep sedation).
- are pregnant or plan to become pregnant. ZEPBOUND may harm your unborn baby. Tell your healthcare provider if you become pregnant while using ZEPBOUND.
  - **Pregnancy Exposure Registry:** There will be a pregnancy exposure registry for women who have taken ZEPBOUND during pregnancy. The purpose of this registry is to collect information about the health of you and your baby. Talk to your healthcare provider about how you can take part in this registry, or you may contact Eli Lilly and Company at 1-800-LillyRx (1-800-545-5979).
  - **Birth control pills by mouth may not work as well while using ZEPBOUND.** If you take birth control pills by mouth, your healthcare provider may recommend another type of birth control for 4 weeks after you start ZEPBOUND and for 4 weeks after each increase in your dose of ZEPBOUND. Talk to your healthcare provider about birth control methods that may be right for you while using ZEPBOUND.
- are breastfeeding or plan to breastfeed. It is not known if ZEPBOUND passes into your breast milk. Talk to your healthcare provider about the best way to feed your baby while using ZEPBOUND.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. ZEPBOUND may affect the way some medicines work, and some medicines may affect the way ZEPBOUND works.

Before using ZEPBOUND, tell your healthcare provider if you are taking medicines to treat diabetes including an insulin or sulfonylurea which could increase your risk of low blood sugar. Talk to your healthcare provider about low blood sugar levels and how to manage them.

Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

How should I use ZEPBOUND?

- Read the **Instructions for Use** that comes with ZEPBOUND.
- Use ZEPBOUND exactly as your healthcare provider tells you to. A healthcare provider should show you how to prepare to inject your dose of ZEPBOUND before injecting the first time.
- Use ZEPBOUND with a reduced-calorie diet and increased physical activity.
- ZEPBOUND is injected under the skin (subcutaneously) of your stomach (abdomen), thigh, or upper arm.
- **Use ZEPBOUND 1 time each week, at any time of the day.**
- You may change the day of the week you use ZEPBOUND as long as the time between the 2 doses is at least **3** days (72 hours).
- If you miss a dose of ZEPBOUND, take the missed dose as soon as possible within 4 days (96 hours) after the missed dose. If more than 4 days have passed, skip the missed dose and take your next dose on the regularly scheduled day. **Do not** take **2** doses of ZEPBOUND within **3** days (72 hours) of each other.
- ZEPBOUND may be taken with or without food.
- Change (rotate) your injection site with each weekly injection. You may use the same area of your body but be sure to choose a different injection site in that area. **Do not** use the same site for each injection.
- In case of overdose, get medical help or contact a Poison Center expert right away at 1-800-222-1222. Advice is also available online at poisonhelp.org.

What are the possible side effects of ZEPBOUND?

ZEPBOUND may cause serious side effects, including:

- See **"What is the most important information I should know about ZEPBOUND?"**
- **severe stomach problems.** Stomach problems, sometimes severe, have been reported in people who use ZEPBOUND. Tell your healthcare provider if you have stomach problems that are severe or will not go away.
- **kidney problems (kidney failure).** Diarrhea, nausea, and vomiting may cause a loss of fluids (dehydration) which may cause kidney problems. It is important for you to drink fluids to help reduce your chance of dehydration.
- **gallbladder problems.** Gallbladder problems have happened in some people who use ZEPBOUND. Tell your healthcare provider right away if you get symptoms of gallbladder problems which may include:
  - pain in your upper stomach (abdomen)
  - fever
  - yellowing of skin or eyes (jaundice)
  - clay-colored stools
- **inflammation of your pancreas (pancreatitis).** Stop using ZEPBOUND and call your healthcare provider right away if you have severe pain in your stomach area (abdomen) that will not go away, with or without vomiting. You may feel the pain from your abdomen to your back.
- **serious allergic reactions.** Stop using ZEPBOUND and get medical help right away if you have any symptoms of a serious allergic reaction including:
  - swelling of your face, lips, tongue or throat
  - problems breathing or swallowing
  - severe rash or itching
  - fainting or feeling dizzy
  - very rapid heartbeat
- **low blood sugar (hypoglycemia).** Your risk for getting low blood sugar may be higher if you use ZEPBOUND with medicines that can cause low blood sugar, such as an insulin or sulfonylurea. **Signs and symptoms of low blood sugar may include:**
  - dizziness or light-headedness
  - sweating
  - confusion or drowsiness
  - headache
  - blurred vision
  - slurred speech
  - shakiness
  - fast heartbeat
  - anxiety, irritability, or mood changes
  - hunger
  - weakness
  - feeling jittery

- **changes in vision in patients with type 2 diabetes.** Tell your healthcare provider if you have changes in vision during treatment with ZEPBOUND.
- **depression or thoughts of suicide.** You should pay attention to any changes in your mood, behaviors, feelings, or thoughts. Call your healthcare provider right away if you have any changes to your mental health that are new, worse, or worry you.
- **food or liquid getting into the lungs during surgery or other procedures that use anesthesia or deep sleepiness (deep sedation).** ZEPBOUND may increase the chance of food getting into your lungs during surgery or other procedures. Tell all your healthcare providers that you are taking ZEPBOUND before you are scheduled to have surgery or other procedures.

The most common side effects of ZEPBOUND include:

- nausea
- diarrhea
- vomiting
- constipation
- stomach (abdominal) pain
- indigestion
- injection site reactions
- feeling tired
- allergic reactions
- belching
- hair loss
- heartburn

Talk to your healthcare provider if you have any side effect that bothers you or that does not go away. These are not all the possible side effects of ZEPBOUND. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store ZEPBOUND?

- Store ZEPBOUND in the refrigerator between 36°F to 46°F (2°C to 8°C). Store ZEPBOUND in the original carton until use to protect it from light.
- If needed, each single-dose pen or single-dose vial can be stored at room temperature up to 86°F (30°C) for up to 21 days. If ZEPBOUND is stored at room temperature, it should not be returned to the refrigerator.
- Discard if not used within 21 days after removing from the refrigerator.
- Do not freeze ZEPBOUND. Do not use ZEPBOUND if frozen.

Keep ZEPBOUND and all medicines out of the reach of children.

General information about the safe and effective use of ZEPBOUND.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use ZEPBOUND for a condition for which it was not prescribed. Do not give ZEPBOUND to other people, even if they have the same condition you have. It may harm them. You can ask your pharmacist or healthcare provider for information about ZEPBOUND that is written for health professionals.

What are the ingredients in ZEPBOUND?

Active ingredient: tirzepatide

Inactive ingredients: sodium chloride, sodium phosphate dibasic heptahydrate, and water for injection. Hydrochloric acid solution and/or sodium hydroxide solution may have been added to adjust the pH.

Marketed by: Lilly USA, LLC, Indianapolis, IN 46285, USA

For more information, go to www.zepbound.com or call 1-800-545-5979.

This Medication Guide has been approved by the U.S. Food and Drug Administration. Revised: 12/2024

B2.0-NL-ZEP-0003-MG-YYYYMMDD

INSTRUCTIONS FOR USE

ZEPBOUND™ (ZEHP-bownd)

(tirzepatide)

injection, for subcutaneous use

2.5 mg/0.5 mL single-dose pen

5 mg/0.5 mL single-dose pen

7.5 mg/0.5 mL single-dose pen

10 mg/0.5 mL single-dose pen

12.5 mg/0.5 mL single-dose pen

15 mg/0.5 mL single-dose pen

use 1 time each week

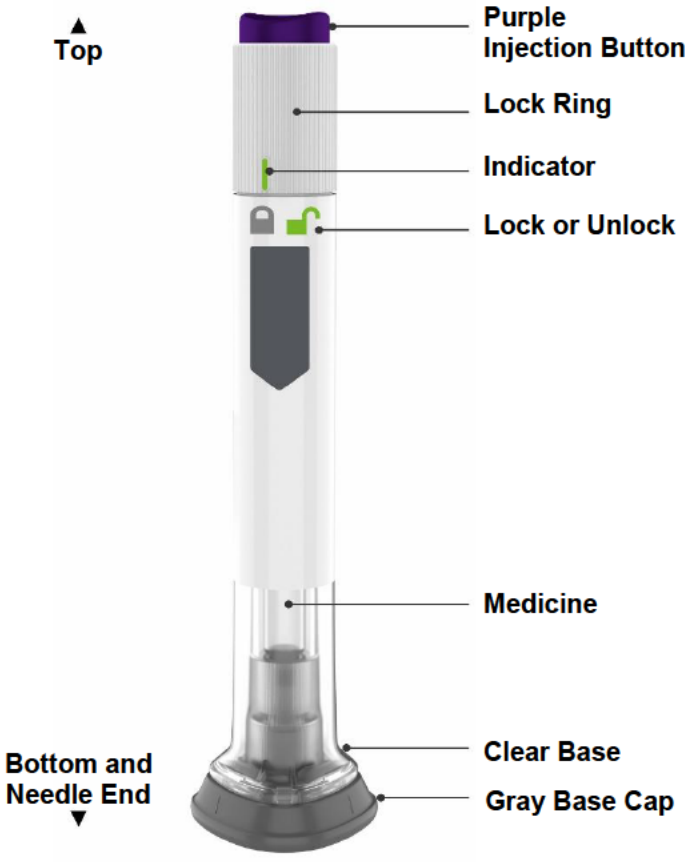
Important information you need to know before injecting ZEPBOUND

Read this Instructions for Use and the Medication Guide before using your ZEPBOUND pen and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or treatment.

Talk to your healthcare provider about how to inject ZEPBOUND the right way.

- ZEPBOUND is a single-dose prefilled pen.
- ZEPBOUND is used 1 time each week.
- Inject under the skin (subcutaneously) only.
- You or another person can inject into your stomach (abdomen) or thigh.
- Another person can inject into the back of your upper arm.

Guide to parts



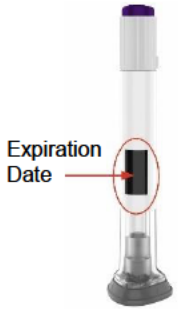
Preparing to inject ZEPBOUND

Remove the pen from the refrigerator.

Leave the gray base cap on until you are ready to inject.

Check the pen label to make sure you have the right medicine and dose, and that it has not expired.

Inspect the pen to make sure that it is not damaged.



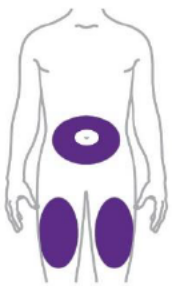
Make sure the medicine:

- is not frozen
- is colorless to slightly yellow
- is not cloudy
- does not have particles

Wash your hands.

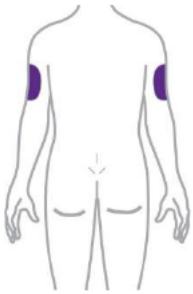
Step
1

Choose your injection site



Your healthcare provider can help you choose the injection site that is best for you.

You or another person can inject the medicine in your stomach (abdomen) or thigh.



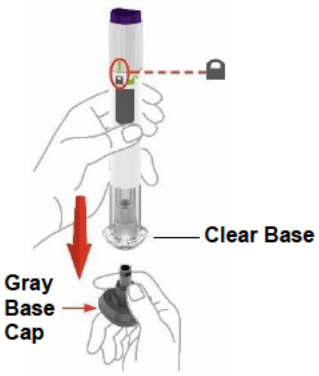
Another person should give you the injection in the back of your upper arm.

Change (rotate) your injection site each week.

You may use the same area of your body but be sure to choose a different injection site in that area.

Step
2

Pull off the gray base cap



Make sure the pen is **locked**.

Do not unlock the pen until you place the clear base on your skin and are ready to inject.

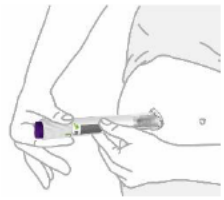
Pull the gray base cap straight off and throw it away in your household trash.

Do not put the gray base cap back on – this could damage the needle.

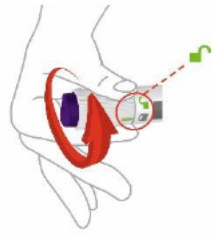
Do not touch the needle.

Step
3

Place clear base on skin, then unlock

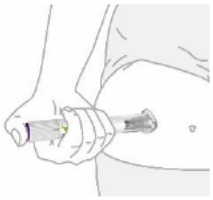


Place the clear base flat against your skin at the injection site.



Unlock by turning the lock ring.

Step 4 **Press and hold up to 10 seconds**



Press and hold the purple injection button for up to 10 seconds.

Listen for:

- First click = injection started
- Second click = injection completed

You will know your injection is complete when the gray plunger is visible.

After your injection, place the used pen in a sharps container.

See **Disposing of your used pen.**

Disposing of your used pen

- Put your used pen in an FDA-cleared sharps disposal container right away after use. **Do not** throw away (dispose of) pens in your household trash.
- If you do not have an FDA-cleared sharps disposal container, you may use a household container that is:
  - made of a heavy-duty plastic,
  - can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out,
  - upright and stable during use,
  - leak-resistant, and
  - properly labeled to warn of hazardous waste inside the container.
- When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used needles and syringes. For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: http://www.fda.gov/safesharpsdisposal.
- **Do not** recycle your used sharps disposal container.

Storage and handling

- Store your pen in the refrigerator between 36°F to 46°F (2°C to 8°C).
- You may store your pen at room temperature up to 86°F (30°C) for up to 21 days. If you store the pen at room temperature, do not return the pen to the refrigerator.
- Discard the pen if not used within 21 days after removing from the refrigerator.
- **Do not** freeze your pen. If the pen has been frozen, throw the pen away and use a new pen.
- Store your pen in the original carton to protect your pen from light.
- The pen has glass parts. Handle it carefully. If you drop the pen on a hard surface, **do not** use it. Use a new pen for your injection.
- Keep your ZEPBOUND pen and all medicines out of the reach of children.

Commonly asked questions

What if I see air bubbles in my pen?

Air bubbles are normal.

What if my pen is not at room temperature?

It is not necessary to warm the pen to room temperature.

What if I unlock the pen and press the purple injection button before pulling off the gray base cap?

Do not remove the gray base cap. Throw away the pen and get a new pen.

What if there is a drop of liquid on the tip of the needle when I remove the gray base cap?

A drop of liquid on the tip of the needle is normal. **Do not** touch the needle.

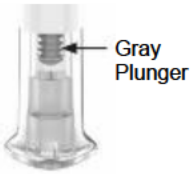
Do I need to hold the injection button down until the injection is complete?

This is not necessary, but it may help you keep the pen steady against your skin.

I heard more than 2 clicks during my injection—2 loud clicks and 1 soft one. Did I get my complete injection?

Some people may hear a soft click right before the second loud click. That is the normal operation of the pen. **Do not** remove the pen from your skin until you hear the second loud click.

I am not sure if my pen worked the right way.



Check to see if you have received your dose. Your dose was delivered the right way if the gray plunger is visible. Also, see **Step 4** of the instructions.

If you do not see the gray plunger, contact Lilly at 1-800-Lilly-Rx (1-800-545-5979) for further instructions. Until then, store your pen safely to avoid an accidental needle stick.

What if there is a drop of liquid or blood on my skin after my injection?

This is normal. Press a cotton ball or gauze over the injection site. **Do not** rub the injection site.

Other information

- If you have vision problems, **do not** use your pen without help from a person trained to use the ZEPBOUND pen.

Where to learn more

- If you have questions or problems with your ZEPBOUND pen, contact Lilly at 1-800-Lilly-Rx (1-800-545-5979) or call your healthcare provider.
- For more information about the ZEPBOUND pen, visit our website at www.zepbound.com.

Scan this code to launch
www.zepbound.com

Marketed by:
Lilly USA, LLC
Indianapolis, IN 46285, USA

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

Revised: November 2023

ZEP-0002-PEN-IFU-20231109

INSTRUCTIONS FOR USE

ZEPBOUND® [ZEHP-bownd]

(tirzepatide)

injection, for subcutaneous use

2.5 mg/0.5 mL single-dose vial

5 mg/0.5 mL single-dose vial

7.5 mg/0.5 mL single-dose vial

10 mg/0.5 mL single-dose vial

12.5 mg/0.5 mL single-dose vial

15 mg/0.5 mL single-dose vial

Important information you need to know before injecting ZEPBOUND

Read this Instructions for Use before you start taking ZEPBOUND and each time you get a new vial. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or your treatment.

Do not share your needles or syringes with other people. You may give other people a serious infection or get a serious infection from them.

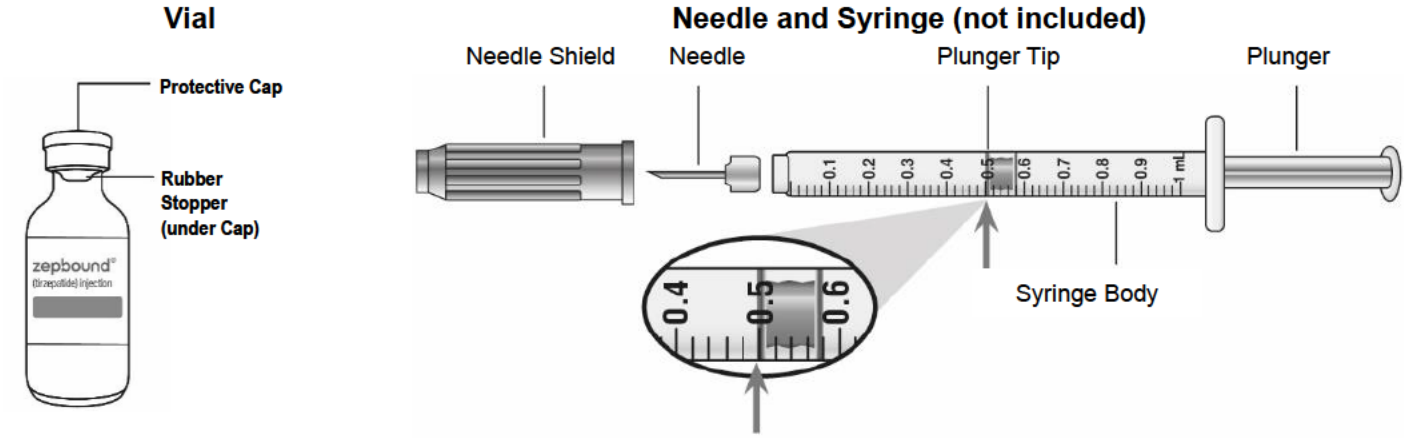
Talk to your healthcare provider about how to inject ZEPBOUND the right way.

- ZEPBOUND is a single-dose vial.
- ZEPBOUND is used 1 time each week.
- Inject under the skin (subcutaneously) only.
- You or another person may inject into your stomach (abdomen) or thigh.
- Another person can inject into the back of your upper arm.

Gather supplies needed to give your injection

- 1 single-dose ZEPBOUND vial
- 1 syringe and 1 needle, supplied separately (for example, use a 1 mL syringe and needle as recommended by your healthcare provider)
- 1 alcohol swab
- gauze
- 1 sharps container for throwing away used needles and syringes. **See** “Disposing of used needles and syringes” at the end of these instructions.

Guide to parts



Note: The needle and syringe are not included. The needle and syringe recommended by your healthcare provider may look different than the needle and syringe in this Instructions for Use.

Preparing to inject ZEPBOUND

Remove the vial from the refrigerator.

Check the vial label to make sure you have the right medicine and dose, and that it has not expired.

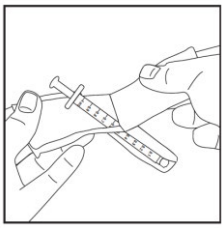
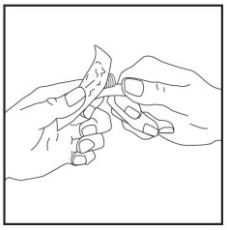
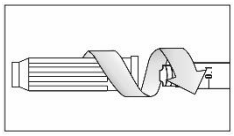
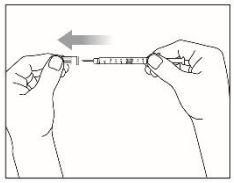
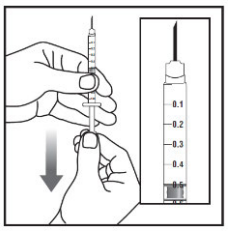
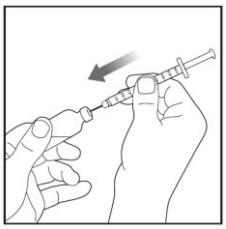
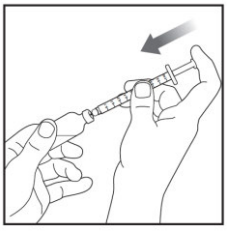
Make sure the medicine:

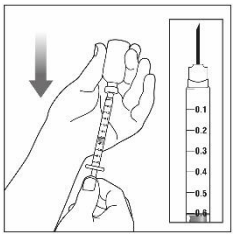
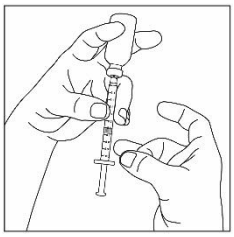
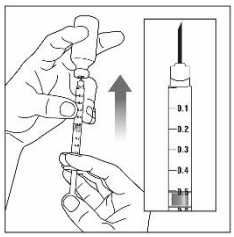
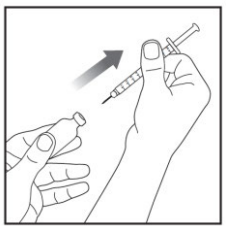
- is not frozen
- is colorless to slightly yellow
- is not cloudy
- does not have particles

Always use a new syringe and needle for each injection to prevent infections and blocked needles. Do not reuse or share your syringes or needles with other people. You may give other people a serious infection or get a serious infection from them.

Wash your hands with soap and water.

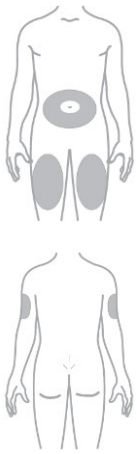
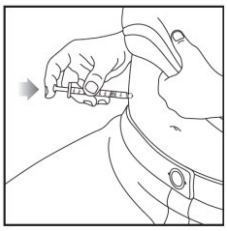
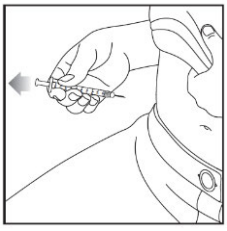
Step 1: Pull off the plastic protective cap. **Do not** remove the rubber stopper.	
Step 2: Wipe the rubber stopper with an alcohol swab.	

Step 3: Remove the outer wrapping from the syringe.	
Step 4: Remove the outer wrapping from the needle. The syringe that your healthcare provider recommended may have a pre-attached needle. If the needle is attached, skip to step 6.	
Step 5: Place the needle on top of the syringe and turn until it is tight and firmly attached.	
Step 6: Remove the needle shield by pulling straight off.	
Step 7: Hold the syringe in one hand with the needle pointing up. With the other hand pull down on the plunger until the plunger tip reaches the line on the syringe indicating that 0.5 mL of air has been drawn into the syringe.	
Step 8: Push the needle through the rubber stopper of the vial.	
Step 9: Push the plunger all the way in. This puts air into the vial and makes it easier to pull the solution from the vial.	

Step 10: Turn the vial and syringe upside down. Make sure that the tip of the needle is in the liquid and slowly pull the plunger down until the plunger tip is past the 0.5 mL line. If there are air bubbles, tap the syringe gently a few times to let any air bubbles rise to the top.	 
Step 11: Slowly push the plunger up until the plunger tip reaches the 0.5 mL line.	
Step 12: Pull the syringe out of the rubber stopper of the vial.	

Injecting ZEPBOUND

- Inject exactly as your healthcare provider has shown you. Your healthcare provider should tell you if you should pinch the skin before injecting.
- **Change (rotate) your injection site within the area you choose for each dose** to reduce your risk of getting lipodystrophy (pits in skin or thickened skin) and localized cutaneous amyloidosis (skin with lumps) at the injection sites.
- **Do not** inject where the skin has pits, is thickened, or has lumps.
- **Do not** inject where the skin is tender, bruised, scaly or hard, or into scars or damaged skin.
- **Do not** mix ZEPBOUND with any other medicine.
- **Do not** inject ZEPBOUND in the same injection site used for other medicines.

Step 13: Choose your injection site. You can inject ZEPBOUND under the skin (subcutaneously) of your stomach area (abdomen) or thighs. Someone else can inject in your stomach area, thighs, or the back of the upper arms.	
Step 14: Insert the needle into your skin.	
Step 15: Push down on the plunger to inject your dose. The needle should stay in your skin for at least 5 seconds to make sure you have injected all of your dose.	
Step 16: Pull the needle out of your skin. • If you see blood after you take the needle out of your skin, press the injection site with a piece of gauze or an alcohol swab. **Do not** rub the area. • **Do not** recap the needle. Recapping the needle can lead to a needle stick injury.	

Disposing of used needles and syringes

- Put your used needle and syringe in an FDA-cleared sharps disposal container right away after use. **Do not** throw away (dispose of) loose needles and syringes in your household trash.
- If you do not have an FDA-cleared sharps disposal container, you may use a household container that is:
  - made of a heavy-duty plastic,
  - can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out,
  - upright and stable during use,
  - leak-resistant, and
  - properly labeled to warn of hazardous waste inside the container.
- When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you

should throw away used needles and syringes. For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: http://www.fda.gov/safesharpsdisposal.

- **Do not** dispose of your used sharps disposal container in your household trash unless your community guidelines permit this. **Do not** recycle your used sharps disposal container.

Storing ZEPBOUND

- Store all unopened vials in the refrigerator at 36°F to 46°F (2°C to 8°C).
- You may store the unopened vial at room temperature up to 86°F (30°C) for up to 21 days.
- **Do not** freeze. **Do not** use if ZEPBOUND has been frozen.
- Store the vial in the original carton to protect from light.
- Throw away all opened vials after use, even if there is medicine left in the vial.

Keep ZEPBOUND vials, syringes, needles, and all medicines out of the reach of children.

If you have any questions or problems with your ZEPBOUND, contact Lilly at 1-800-Lilly-Rx (1-800-545-5979) or call your healthcare provider for help.

Marketed by:
Lilly USA, LLC
Indianapolis, IN 46285, USA

ZEP-0001-VL-IFU-20240328

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

Issued: March 2024

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

217806Orig1s013

MULTI-DISCIPLINE REVIEW

Summary Review
Office Director
Cross Discipline Team Leader Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

NDA Multi-Disciplinary Review and Evaluation

Application Type	Supplemental NDA
Application Number(s)	217806 S-013
Priority or Standard	Priority
Submit Date(s)	June 21, 2024
Received Date(s)	June 21, 2024
PDUFA Goal Date	December 21, 2024
Division/Office	Division of Pulmonology, Allergy, and Critical Care Office of New Drugs
Review Completion Date	December 18, 2024
Established/Proper Name	Tirzepatide
(Proposed) Trade Name	Zepbound
Pharmacologic Class	Glucose-dependent insulinotropic polypeptide (GIP) receptor and glucagon-like peptide-1 (GLP-1) receptor agonist
Applicant	Eli Lilly and Company (Lilly)
Dosage form	Injection 2.5 mg/0.5 mL in a single-dose pen or single-dose vial Injection 5 mg/0.5 mL in a single-dose pen or single-dose vial Injection 7.5 mg/0.5 mL in a single-dose pen or single-dose vial Injection 10 mg/0.5 mL in a single-dose pen or single-dose vial Injection 12.5 mg/0.5 mL in a single-dose pen or single-dose vial Injection 15 mg/0.5 mL in a single-dose pen or single-dose vial
Applicant proposed Dosing Regimen	The recommended starting dosage of Zepbound is 2.5 mg injected subcutaneously once weekly. After 4 weeks, increase the dosage to 5 mg injected subcutaneously once weekly. Continue to increase the dosage in 2.5 mg increments after at least 4 weeks on the current dose. The maximum dosage of Zepbound is 15 mg injected subcutaneously once weekly.
Applicant Proposed Indication(s)/Population(s)	treatment for moderate to severe obstructive sleep apnea (OSA) in adults with an initial body mass index (BMI) of 30 kg/m^2 or greater (obesity)
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s)	treat moderate to severe obstructive sleep apnea (OSA) in adults with obesity
Recommended Dosing Regimen	Unchanged

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APPEARS THIS WAY ON ORIGINAL

Reviewers of Multi-Disciplinary Review and Evaluation

Regulatory Project Manager	Linda Ebonine
Nonclinical Reviewer	Anup Srivastava
Nonclinical Team Leader	Carol Galvis
Office of Clinical Pharmacology Reviewer(s)	Liping (Cindy) Pan
Office of Clinical Pharmacology Team Leader(s)	Yunzhao Ren, Jingyu Yu
Clinical Reviewer	Shivani Klauer
Clinical Team Leader	Elisabeth Boulos
Statistical Reviewer(s)	Ping Li, Dong-Hyun Ahn, Xin Yuan, Monica Morell
Statistical Team Leader	Yongman Kim
Cross-Disciplinary Team Leader	Elisabeth Boulos
Statistical Supervisor (OB)	Weiya Zhang
Division Director (or designated signatory authority)	Banu Karimi-Shah

Additional Reviewers of Application

DCOA	Ji Li / Onyeka Illoh
OPQ	Sarah Zimmerman / Rohit Kolhatkar
OPDP	Quynh Capasso
OSI	Suyong Tina Chang / Phillip Kronstein
ADL	Jessica Lee
OSE/DMEPA	Lissa Owens / Damon Birkemeier / Matthew Barlow

DCOA=Division of Clinical Outcome Assessment
OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
ADL=Associate Director for Labeling
DMEPA=Division of Medication Error Prevention and Analysis

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Nonclinical Reviewer	Anup Srivastava	Office of New Drugs (OND)/Office of Immunology and Inflammation (OII)/Division of Pharmacology/Toxicology for Immunology and Inflammation (DPTII)	Sections: 5	**Select one:** _X__ Authored ___ Approved
	Signature:			
Nonclinical Supervisor	Carol Galvis	OND/OII/DPTII	Sections: 5	**Select one:** _X__ Authored __X_ Approved
	Signature:			
Clinical Pharmacology Reviewer and Pharmacometrics Reviewer	L. Cindy Pan	Office of Translational Sciences (OTS)/Office of Clinical Pharmacology (OCP)/Division of Inflammation and Immune Pharmacology (DIIP)	Sections: 6, 14	**Select one:** _X__ Authored ___ Approved
	Signature:			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Pharmacology Master Pharmacokineticist	Yunzhao Ren	OTS/OCP/DIIP	Sections: 6, 14	**Select one:** _X__ Authored _X__ Approved
	Signature:			
Pharmacometrics Team Leader	Jingyu (Jerry) Yu	OTS/OCP/DPM	Section: 14	**Select one:** ___ Authored _X__ Approved
	Signature:			
Clinical Reviewer	Shivani Klauer	OND/OII/Division of Pulmonology, Allergy, and Critical Care (DPACC)	Sections: 1, 2, 3, 7, 8, 9, 10, 11, 12, 14.5	**Select one:** __X_ Authored ___ Approved
	Signature:			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Team Leader	Elisabeth Boulos	OND/OII/DPACC	Sections: All	**Select one:** __X_ Authored __X_ Approved
	Signature:			
Deputy Division Director (Clinical)	Banu Karimi-Shah	OND/OII/DPACC	Sections: All	**Select one:** ___ Authored _X__ Approved
	Signature:			
Statistical Analyst	Ping Li	OTS/Office of Biostatistics (OB)/Division of Analytics and Informatics (DAI)	Sections: 8.1, 8.3, 14.5	**Select one:** _X__ Authored ___ Approved
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Statistical Team Leader	Yongman Kim	OTS/OB/DBIII	Sections: 8.1, 8.3, 14.5	**Select one:** ___ Authored _X__ Approved
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PFSS Reviewer	Xin Yuan	OTS/OB/DBIII/Patient-Focused Statistical Scientists (PFSS)	Sections: 8.1.3, 14.4	**Select one:** _X__ Authored ___ Approved
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PFSS Secondary Reviewer	Monica Morell	OTS/OB/DBIII/PFSS	Sections: 8.1.3, 14.4	**Select one:** ___ Authored __X_ Approved
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DCOA Reviewer	Ji Li	OND/ODES (Office of Drug Evaluation Sciences)/DCOA (Division of Clinical Outcome Assessment)	Sections: 8.1.1, 8.1.3, 14.4.1, 14.4.4	**Select one:** _X__ Authored ___ Approved
	Signature:			
DCOA Team Leader	Onyeka Illoh	OND/ODES/DCOA	Sections: 8.1.1, 8.1.3, 14.4.1, 14.4.4	**Select one:** ___ Authored _X__ Approved
	Signature:			
Statistical Supervisor (OB)	Weiya Zhang	OTS/OB/DBIII	Sections: 8.1, 8.3, 14.4, 14.5	**Select one:** ___ Authored __X_ Approved
	Signature:			

Glossary

ADA	antidrug antibody
AE	adverse event
AHI	apnea-hypopnea index
AR	adverse reaction
AUC	area under the concentration-time curve
Bt	biotinylated
BW	body weight
CDER	Center for Drug Evaluation and Research
C_{max}	maximum plasma concentration
CPAP	continuous positive airway pressure
CRF	case report form
CRP	serum C-reactive peptide
CSR	clinical study report
C-SSRS	Columbia Suicide-Severity Rating Scale
CWM	chronic weight management
CYP	cytochrome P450 enzyme
DB	double-blind
DBP	diastolic blood pressure
eCDF	empirical cumulative distribution function
ECG	electrocardiogram
ECL	electrochemiluminescence
ED	early discontinuation
ESS	Epworth Sleepiness Scale
FDA	Food and Drug Administration
GI	gastrointestinal
GIP	glucose-dependent insulinotropic polypeptide
GLP-1	glucagon-like peptide-1

GPI1	Trial 18F-MC-GPI1, OSA trial 1
GPI2	Trial 18F-MC-GPI2, OSA trial 2
GPIF	Trial 18F-MC-GPIF, master protocol
IND	Investigational New Drug
IS	internal standard
ITT	intent to treat
LC/MS	liquid chromatography with mass spectrometry
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
MSD	Meso Scale Discovery
MTC	medullary thyroid carcinoma
MTD	maximum tolerated dose
Nab	neutralizing antibodies
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OSA	obstructive sleep apnea
OSI	Office of Scientific Investigation
PAP	positive airway pressure
PD	pharmacodynamics
PFS	pre-filled syringe
PGIS-OSA	Patient Global Impression of Status - OSA
PHQ-9	Patient Health Questionnaire
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
popPK	population pharmacokinetic

PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PROMIS	Patient-Reported Outcome Measurement Information System
PROMIS-SD	PROMIS Short Form v1.0 Sleep Disturbance 8a
PROMIS-SRI	PROMIS Short Form v1.0 Sleep-related Impairment 8a
QW	once weekly
RDI	respiratory disturbance index
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SASHB	sleep apnea specific hypoxic burden
SBP	systolic blood pressure
SC	subcutaneously
sNDA	supplemental New Drug Application
SOC	standard of care
T2DM	type 2 diabetes mellitus
TEAE	treatment emergent adverse event
t_{max}	time of maximum observed drug concentration
US/OUS	United Sates of America/outside of the United States of America
VRS	verbal rating scale

1. Executive Summary

1.1. Product Introduction

Tirzepatide is a selective dual agonist of the glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) receptors. By binding to these receptors, tirzepatide enhances first- and second-phase insulin secretion and reduces glucagon serum concentrations, both in a glucose-dependent manner. Although there is limited direct evidence of the mechanism of action of tirzepatide in patients with obstructive sleep apnea (OSA), it is likely that tirzepatide exerts its effect in OSA by decreasing overall body weight and reducing oropharyngeal and abdominal fat deposits (Peng et al. 2024). Reductions in body weight correlate with reductions in the apnea-hypopnea index (AHI), an important objective measure of the severity of OSA (Malhotra et al. 2024).

Tirzepatide was first approved May 13, 2022 as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM). Tirzepatide was then approved November 8, 2023, to be used in combination with a reduced-calorie diet and increased physical activity to reduce excess body weight and maintain weight reduction long term in adults with obesity or adults with overweight in the presence of at least one weight-related comorbid condition. The single-dose vial is to be administered by a healthcare provider. The pre-filled syringe (PFS) may be administered by patients or caregivers.

With this supplemental New Drug Application (sNDA), Eli Lilly and Company provides data to support the proposed indication of tirzepatide as a treatment for adult patients with moderate to severe OSA with obesity at a dosage strength of 10 or 15mg subcutaneously (SC) weekly (QW). The Division granted tirzepatide Breakthrough Designation and this sNDA was reviewed on a priority timeline. There are currently no FDA-approved pharmacologic therapies for OSA.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The recommended regulatory action is **Approval** for tirzepatide 10 or 15mg SC QW for use in adult patients with moderate to severe OSA with obesity.

Obstructive sleep apnea is a breathing disorder that causes recurrent episodes of partial or complete collapse of the upper airway, which impairs normal ventilation during sleep. This disorder is associated with high rates of morbidity and mortality, primarily related to cardiovascular disease.

Substantial evidence of effectiveness for tirzepatide in subjects with moderate to severe OSA with obesity is established with two, adequate, and well-controlled trials (GPI1 and GPI2). Both trials were conducted under a master protocol (NCT05412004: SURMOUNT-OSA [GPIF]). GPI1

and GPI2 were two randomized, double-blind, multi-center, placebo-controlled trials of 52 weeks duration conducted under a basket-type master protocol that evaluated the efficacy and safety of tirzepatide at the maximum tolerated dose (MTD) (10 or 15mg) QW compared to placebo in 469 subjects with obesity and moderate to severe OSA. GPI1 enrolled subjects unable to tolerate positive airway pressure (PAP) therapy. GPI2 enrolled subjects using PAP, the standard of care for moderate to severe OSA. Subjects were randomized to receive either tirzepatide or placebo and were required to have a diagnosis of moderate to severe OSA with an AHI ≥15 events/hour, obesity (BMI of 30 kg/m^2 or greater), and a history of at least one self-reported unsuccessful dietary effort to lose body weight. The primary endpoint for both GPI1 and GPI2 was the absolute change in AHI from baseline to Week 52. Tirzepatide demonstrated statistically significant superiority with highly persuasive results when compared to placebo with a substantial reduction in AHI in both trials.

In GPI1 and GPI2, tirzepatide demonstrated substantial weight loss in patients with obesity leading to a significant reduction in AHI, thereby distinguishing tirzepatide as a novel pharmacotherapy for the treatment of OSA. There are several studies in the literature that have demonstrated a positive correlation between weight loss and reduction in AHI. Most of the weight loss in these studies was achieved through bariatric surgery. Although cross study comparisons should be explored with caution, we note that the magnitude of effect on AHI with tirzepatide is similar to that observed, on average, with bariatric surgery (Malhotra et al. 2024).

Tirzepatide compared to placebo also resulted in statistically significant improvements across all key secondary endpoints, which also contributed to substantial evidence of effectiveness. Tirzepatide compared to placebo demonstrated improvement in percent change in AHI, percent of subjects with OSA remission or mild non-symptomatic OSA (defined as percent of subjects with AHI <5 or AHI 5-14 events/hour with Epworth Sleepiness Scale (ESS) ≤10), change in sleep apnea specific hypoxic burden (SASHB), percent change in body weight, change in serum C-reactive peptide (CRP) concentration, and change in systolic blood pressure (SBP). Since the AHI has well-described limitations as a predictive measure of clinically meaningful outcomes in OSA (2019; Azarbarzin et al. 2019) and as a measurement of patient symptoms (Weaver et al. 2005), these key secondary endpoints provided valuable additional information about the effectiveness of tirzepatide for patients with moderate-to-severe OSA and obesity.

The improvement in SASHB in subjects treated with tirzepatide compared to placebo provides particularly clinically meaningful data. Emerging literature suggests that SASHB more strongly predicts cardiovascular mortality compared to other polysomnography (PSG) metrics (i.e., AHI alone). In addition, improvements in SASHB may better correlate with patient quality of life (Azarbarzin et al. 2019). Therefore, the robust improvement in the key secondary endpoint of SASHB contributed to our understanding of the clinical meaningfulness of the treatment effect of tirzepatide in this population.

The composite key endpoint evaluating the percent of subjects with OSA remission or mild non-symptomatic OSA identified subjects who achieved a wider definition of OSA remission. These patients, who have an AHI <5 or AHI 5-14 events/hour and ESS ≤10, are typically not indicated for further treatment in clinical practice. Tirzepatide compared to placebo demonstrated a large and statistically significant treatment difference in the percent of subjects achieving a wider definition of OSA remission in both trials.

To address uncertainty about whether patients with an AHI 5-14 events/hour and ESS ≤10 should be treated for OSA, additional exploratory analyses were conducted to identify the proportion of subjects who achieved the stricter definition of OSA remission of AHI <5 events/hour. With this definition, there is significantly less uncertainty about whether patients should be treated for their OSA, thus, this represents a more clinically meaningful endpoint. The results of this ad hoc analysis showed that when each component of the composite endpoint was evaluated separately, the percentage of patients achieving OSA remission (AHI <5 events/hour) contributed substantially to the composite endpoint.

In addition, tirzepatide appears to clinically resolve OSA in some patients, even those with severe disease at baseline. An exploratory analysis was conducted which showed that a significant proportion of subjects treated with tirzepatide who had severe OSA at baseline (AHI >30 events/hour) were able to achieve even the strict definition of OSA remission (AHI <5 events/hour) compared to subjects treated with placebo in both trials. Although interpretation is limited by the exploratory nature of these analyses, these analyses contributed substantively to our understanding of the effectiveness of tirzepatide.

Tirzepatide also demonstrated improvement in patient quality of life measures related to sleep impairment, specifically. The pre-specified multiplicity-controlled endpoint for the patient-reported outcome (PRO) was the change in baseline from Week 52 in both the PROMIS Short Form v1.0 Sleep-related Impairment 8a (PROMIS-SRI) and the PROMIS Short Form v1.0 Sleep Disturbance 8a (PROMIS-SD) pooled across both GPI1 and GPI2. The Division did not agree with pooling the efficacy results across GPI1 and GPI2 because of clinical differences in the populations that may confound PRO outcomes (i.e., PAP use) and because pooled analyses lack validation of independent substantiation, which is necessary to demonstrate substantial evidence of effectiveness. Additional secondary endpoints included analyses of the PRO endpoints independently for both GPI1 and GPI2. These analyses took into consideration the full distribution of PROMIS T-scores and selected meaningful change thresholds that minimized the misclassification of subjects who reported no improvement or worsening, as well as subjects' baseline global symptom severity. Based on this evaluation, the Agency concluded that the observed treatment effects on the PROMIS-SRI T-scores substantiated an improvement in subjects receiving tirzepatide as compared to placebo in both GPI1 and GPI2. This result demonstrates that tirzepatide not only causes robust improvement in objective markers of OSA, but also improves symptoms that subjects have related to sleep impairment.

In conclusion, the trial design of GPI1 and GPI2 was robust and the results were both highly statistically significant and clinically meaningful, providing strong support for the efficacy of tirzepatide in treating adults with obesity and moderate-to-severe OSA. Given the strength of the trial design and the persuasiveness of the results from the GPIF trials, along with the strength of the exploratory analyses, substantial evidence of effectiveness has been demonstrated and the recommended regulatory action is **Approval.**

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Obstructive sleep apnea (OSA) is a breathing disorder that causes recurrent episodes of partial or complete collapse of the upper airway, which impair normal ventilation during sleep. This disorder is associated with high rates of morbidity and mortality, primarily caused by cardiovascular disease. The prevalence of OSA is strongly associated with overweight and obesity, and obesity is the predominant modifiable risk factor for OSA. Significant weight loss, either through lifestyle interventions or as a result of bariatric surgery, can improve OSA. OSA remission is considered to occur when patients no longer qualify for OSA treatment and symptoms have resolved.

There are currently no approved pharmacologic therapies for the treatment of OSA that address the underlying pathophysiology or relieve the airway obstruction. The standard of care for moderate to severe OSA is positive airway pressure (PAP) therapy, most often administered in a continuous mode at a fixed pressure (CPAP). However, some patients are intolerant to PAP therapy. Patients intolerant to PAP therapy could use medical devices, such as oral mandibular-advancement splints. Surgical procedures for the management of OSA include uvulopalatopharyngoplasty or other soft tissue procedures, maxillomandibular advancement, and hypoglossal-nerve stimulation. Bariatric surgery is available for patients with severe obesity and can dramatically improve OSA; however, these surgical procedures are associated with the risk of perioperative and postoperative complications. Therefore, options for treatment that do not require surgery or wearing a device, such as medications that produce similar or greater improvements in sleep apnea parameters, would represent a significant advancement in treatment.

Data from two adequate and well-controlled GPIF trials, GPI1 and GPI2, demonstrate the efficacy of tirzepatide for the treatment of moderate-to-severe OSA and obesity. In these trials, tirzepatide demonstrated superiority compared to placebo with a substantial reduction in AHI in both trials. Secondary endpoints of percent change in AHI, percent of subjects in OSA remission or mild non-symptomatic OSA (defined as percent of subjects with AHI <5 or AHI 5-14 events/hour with ESS ≤ 10), change in SASHB, percent change in body weight also contributed to substantial evidence of effectiveness. Trials GPI1 and GPI2 were well-designed, well-conducted trials, and the results were both highly statistically significant and clinically meaningful, providing strong support for the efficacy of tirzepatide in treating adults with obesity and moderate to severe OSA. In addition, exploratory analyses demonstrated that a higher proportion of subjects treated with tirzepatide compared to placebo achieved OSA remission (AHI <5 events/hour), improved from severe OSA to OSA remission and/or improved severity category (e.g., severe to

mild), and showed an improvement in sleep-related impairment as measured by the PROMIS-SRI, all of which provided additional robustness to the trial results. Substantial evidence of effectiveness for the use of tirzepatide for the treatment of moderate to severe OSA with obesity has been demonstrated.

The safety profile for tirzepatide is well-established since its approval in 2022 and includes several warning and precautions statements, such as risks for acute kidney injury and acute pancreatitis. Common adverse reactions include nausea, diarrhea, and vomiting, particularly during dose escalation. No new safety concerns are seen in the moderate to severe OSA with obesity population compared to the known safety profile established with the same doses in subjects with overweight or obesity. The safety concerns for tirzepatide are well-established for the class of incretin drugs and can be appropriately mitigated in the post-market setting through labeling and no additional post-marketing risk mitigation strategies specific to this population are required.

Given the demonstration of substantial evidence of effectiveness and identification of no new safety findings, our assessment is that the data support a favorable benefit risk profile for tirzepatide for the treatment of moderate to severe OSA with obesity. As a result, the recommended regulatory action for this sNDA is **Approval**.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Obstructive sleep apnea is a breathing disorder that causes recurrent episodes of partial or complete collapse of the upper airway, which impair normal ventilation during sleep. • Obstructive sleep apnea affects approximately 25% of the US adult population with approximately 40% of these patients experiencing moderate-to-severe disease. • The prevalence of OSA is strongly associated with overweight and obesity, and obesity is the predominant modifiable risk factor for OSA. The rates of OSA are much higher in individuals with obesity than healthy weight individuals.	Obstructive sleep apnea is associated with high rates of morbidity and mortality, primarily related to cardiovascular disease.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Significant weight loss, either through lifestyle interventions, or as a result of bariatric surgery can substantially improve OSA.	
Current Treatment Options	• The goal of OSA therapy is to relieve the underlying airway obstruction. • There are several studies in the literature that have demonstrated a positive correlation between weight loss and reduction in AHI. Most of the weight loss is achieved through bariatric surgery. • Positive airway pressure (PAP) is the primary therapy for individuals with symptomatic OSA of any severity. PAP therapy acts as a pneumatic splint that prevents collapse of the upper airway during inspiration. Both auto-adjusting PAP (APAP) and continuous PAP (CPAP) deliver noninvasive positive airway pressure and PAP therapy normalizes AHI in more than 90% of patients while wearing the device. • There are no currently approved pharmacologic therapies for the management of OSA that relieve the underlying airway obstruction.	There are no pharmacologic therapies approved to treat OSA. Some patients are intolerant to or noncompliant with PAP therapy. Bariatric surgery is available for patients with severe obesity and can dramatically improve OSA; however, surgical procedures are associated with the risk of perioperative and postoperative complications. The availability of additional treatment options that address the underlying cause of the disease would be beneficial to this patient population.
Benefit	• Data from two adequate and well-controlled trials, GPI1 and GPI2, demonstrate the efficacy of tirzepatide for the treatment of moderate to severe OSA and obesity. • Tirzepatide demonstrated clinically meaningful and statistically significant superiority compared to placebo with a substantial reduction in AHI in both trials, as well as improvements across all secondary endpoints, percent change in AHI, percent of subjects in OSA remission or mild non-symptomatic OSA	GPI1 and GPI2 were well-designed and well-conducted trials, and the results were both highly statistically significant and clinically meaningful. The effectiveness of tirzepatide for the treatment of moderate to severe OSA with obesity is demonstrated in this development program.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	(defined as percent of subjects with AHI <5 or AHI 5-14 events/hour with ESS ≤ 10), change in SASHB, percent change in body weight, change in CRP concentration and SBP. • An improvement in sleep-related impairment as measured by the PROMIS-SRI score compared to placebo provided additional robustness to the trial results.	
Risk and Risk Management	• Tirzepatide is an approved and marketed agonist of the GLP-1 and GIP receptors. The safety profile for tirzepatide is well-established since its approval in 2022 and includes several warning and precautions statements, such as risks for acute kidney injury and severe gastrointestinal adverse reactions. Common adverse reactions include nausea, diarrhea, and vomiting, particularly during dose escalation. • No new safety concerns are seen in the moderate to severe OSA with obesity population compared to the known safety profile established with the same doses in subjects with overweight or obesity.	Tirzepatide does not present any safety findings that outweigh the efficacy benefit in this patient population, when tirzepatide is used as labeled. No new REMS or safety related PMR/PMC will be attached to this approval.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application

X	**The patient experience data that were submitted as part of the application include:**			Section of review where discussed, if applicable
	X	Clinical outcome assessment (COA) data, such as		
		X	Patient reported outcome (PRO)	8.1.3, 14.4, 14.5
		□	Observer reported outcome (ObsRO)	
		□	Clinician reported outcome (ClinRO)	
		□	Performance outcome (PerfO)	
	X	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		14.4
	□	Patient-focused drug development or other stakeholder meeting summary reports		
	□	Observational survey studies designed to capture patient experience data		
	□	Natural history studies		
	□	Patient preference studies (e.g., submitted studies or scientific publications)		
	□	Other: (Please specify):		
□	**Patient experience data that were not submitted in the application, but were considered in this review:**			
	□	Input informed from participation in meetings with patient stakeholders		
	□	Patient-focused drug development or other stakeholder meeting summary reports		
	□	Observational survey studies designed to capture patient experience data		
	X	Other: (Please specify):		Patient-Focused Drug Development Program report describing patient perspectives on symptoms that matter most, impact of the disease on their daily lives, and their experiences with currently available treatments.

□	**Patient experience data was not submitted as part of this application.**

2. Therapeutic Context

2.1. Analysis of Condition

Obstructive sleep apnea is a breathing disorder that causes recurrent episodes of partial or complete collapse of the upper airway that impairs normal ventilation during sleep. Obstructive sleep apnea affects approximately 25% of the US adult population with approximately 40% of these patients experiencing moderate to severe disease. OSA is characterized by impaired airway patency, which results in absent (apnea) or reduced (hypopnea) airflow that is associated with large changes in intrathoracic pressure, intermittent hypoxia, and arousal from sleep (Gottlieb and Punjabi 2020). Narrowing of the upper airway in patients with OSA can result from ectopic fat deposition in the soft palate, pharyngeal fat pads, and an enlarged tongue, in addition to other anatomic abnormalities (Sutherland et al. 2011).

In-lab polysomnography (PSG) remains the gold standard for OSA diagnosis. Examination with PSG generates an AHI or a respiratory disturbance index (RDI). An apnea is the absence of airflow for more than 10 seconds, and a hypopnea is a reduction in respiratory effort with greater than 4% oxygen desaturation. The AHI is the sum of the total number of apneas and hypopneas over the total hours of sleep. Based on the American Academy of Sleep Medicine (AASM) International Classification of Sleep Disorders (AASM 2017), a diagnosis of OSA is confirmed when (Kapur et al. 2017):

1) AHI/RDI ≥ 15
2) AHI/RDI ≥ 5 with one or more of the following
    a. Sleepiness, nonrestorative sleep, fatigue, or insomnia symptoms
    b. Waking up with breath holding, gasping, or choking
    c. Habitual snoring, breathing, interruptions
    d. Hypertension, mood disorder, cognitive dysfunction, coronary artery disease, stroke, congestive heart failure, atrial fibrillation, or type 2 diabetes

In addition, three different OSA severity classes are defined by AHI (Kapur et al. 2017):

1) Mild (5 to 14 events/hour)
2) Moderate (15 to 30 events/hour)
3) Severe (>30 events/hour)

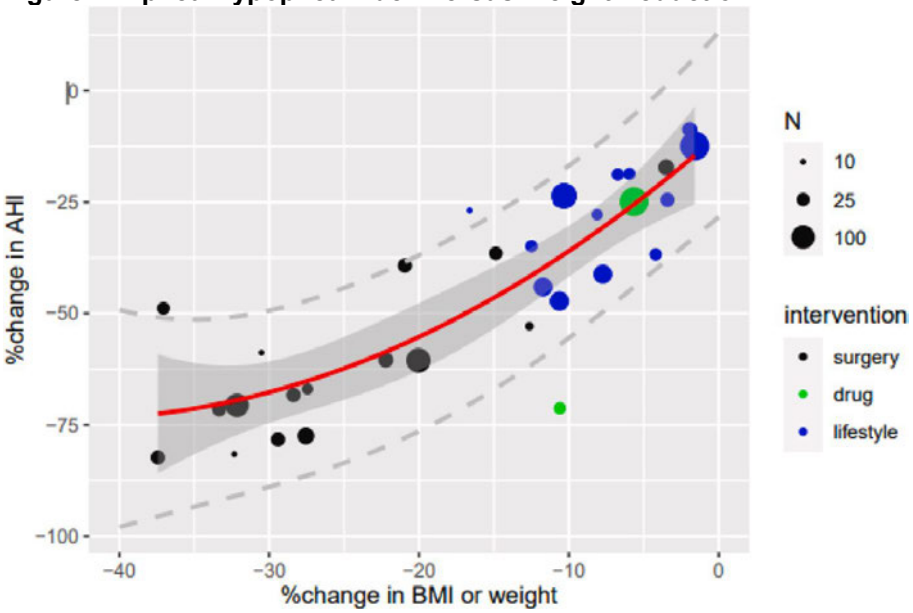
The severity of OSA is a predictor of disease outcomes, including renal outcomes, atrial

fibrillation, hypertension, stroke, coronary artery disease, and congestive heart failure (Peppard et al. 2000; Budhiraja et al. 2010; Cadby et al. 2015; Hwu et al. 2017).

The Centers for Medicare and Medicaid Services approves the use of PAP therapy in patients with moderate or severe OSA (AHI ≥ 15) and in patients with mild OSA (AHI ≥ 5 – 14) who have documentation of excessive daytime sleepiness or OSA-related comorbid conditions (Goyal and Johnson 2017). Significant weight loss, either through lifestyle interventions or as a result of bariatric surgery, may allow patients to attain OSA remission. OSA remission is considered to occur when patients no longer qualify for OSA treatment and symptoms have resolved (Currie et al. 2021; Carneiro-Barrera et al. 2022). As discussed in Section 2.2, the standard of care for moderate-severe OSA is PAP, most often administered as continuous positive airway pressure (CPAP).

The prevalence of OSA is strongly associated with overweight and obesity, and obesity is the predominant modifiable risk factor for OSA. The rates of OSA are much higher in individuals with obesity than healthy weight individuals (Punjabi 2008). There are several studies in the literature that have demonstrated a positive correlation between weight loss and reduction in AHI. Most of the weight loss is achieved through bariatric surgery or obesity pharmacotherapy. A study conducted at the University of Iowa demonstrated a mathematical relationship between BMI and AHI, suggesting that for every 7 pounds that are lost in weight, there is a 7% decrease in AHI (Fattal et al. 2022). In a systematic review and meta-analysis conducted in 2024, Malhotra et al. found that weight reduction in people with OSA and obesity was associated with improvements in the severity of OSA. A BMI reduction of 20% was associated with an AHI reduction of 57%, while further weight reduction beyond 20% in BMI was associated with a smaller effect on AHI (Malhotra et al. 2024) (Figure 1).

Figure 1: Apnea-Hypopnea Index Versus Weight Reduction



Source: Malhotra et al. 2024.
Drug refers to obesity pharmacotherapies, including incretins and phentermine/topiramate.

OSA is also an independent risk factor for cardiovascular disease, including coronary artery disease and stroke (Punjabi 2008). Men with severe untreated OSA are at an increased risk of fatal and non-fatal cardiovascular events compared to healthy men. AHI, although the standard metric of sleep apnea severity, may poorly predict adverse outcomes of OSA, particularly cardiovascular outcomes and symptoms of sleepiness. This may be because AHI is a frequency measure that does not adequately capture the full extent of disease burden, including depth and duration of ventilatory disturbances or blood gas changes.

The sleep apnea-specific hypoxic burden is a measure that encapsulates frequency, duration, and depth of the respiratory-event contribution to arterial hypoxemia, specifically the oxygen desaturation “area under the curve” in association with individual apneas or hypopneas. There is evidence supporting that the SASHB may strongly predict cardiovascular mortality (Azarbarzin et al. 2019). A SASHB greater than 60 %min/hour (i.e., 15 minutes of 4% desaturations every hour) appears to identify patients who are at increased risk of cardiovascular morbidity and mortality (Martinez-Garcia et al. 2023).

Positive airway pressure therapy improves AHI and OSA-related symptoms, such as excessive daytime sleepiness; however, its overall effectiveness can be limited by variable adherence to therapy. In addition, randomized-controlled trials have failed to demonstrate that PAP improves cardiovascular morbidity and mortality (Peker et al. 2006; McEvoy et al. 2016; Sánchez-de-la-Torre et al. 2020).

2.2. Analysis of Current Treatment Options

The goal of OSA therapy is to relieve the underlying airway obstruction. Positive airway pressure is the primary therapy for individuals with symptomatic OSA of any severity (Gottlieb and Punjabi 2020). Positive airway pressure therapy acts as a pneumatic splint that prevents collapse of the upper airway during inspiration (Goyal and Johnson 2017). Both APAP and CPAP deliver noninvasive positive airway pressure, and PAP therapy normalizes AHI in more than 90% of patients while wearing the device (Patil et al. 2019).

There are currently no FDA-approved pharmacologic therapies for the management of OSA that are able to relieve the underlying airway obstruction; however, there are medications approved for the treatment of excessive daytime sleepiness that is caused by underlying OSA (Table 1). All of these medications have limitations of use and do not address the underlying pathophysiology in OSA. Patients are recommended to continue using primary OSA therapy devices when taking these medications. Both modafinil and armodafinil are chemically similar in structure and have warnings and precaution statements for risks such as serious skin rash, including Stevens-Johnson syndrome, angioedema or anaphylaxis, psychiatric symptoms, including mania, delusions, hallucinations, and suicidal ideation, and cardiovascular events, including arrhythmias and chest pain.

Table 1. FDA-Approved Pharmacologic Therapies for the Management of Excessive Daytime Sleepiness Related to OSA

Product Name	Relevant Indication	Year of Approval	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
Modafinil	Improve wakefulness in adult patients with excessive daytime sleepiness associated with OSA	1998	200 mg once daily in the morning	Improved maintenance of wakefulness compared to placebo and improved ESS or CGI-C scale compared to placebo	Serious skin rash (Stevens-Johnson Syndrome) Angioedema, anaphylaxis Psychiatric symptoms (mania, delusions, hallucinations, suicidal ideation) Cardiovascular events (arrhythmias, chest pain)	Continue on primary OSA therapy device before and during treatment
Armodafinil		2007	150 to 250 mg once daily in the morning			
Solriamfetol		2019	37.5 mg once daily upon awakening. Maximum dose 150 mg once daily		Increased hypertension and tachycardia Psychiatric symptoms (anxiety, insomnia, irritability)	

Source: Drugs@FDA
Abbreviations: OSA, obstructive sleep apnea; ESS, Epworth Sleepiness Scale; CGI-C, clinical global impression of change;

For those patients with mild disease, treatments include behavioral measures such as abstinence from alcohol, avoiding supine sleep position, regular aerobic exercise, and weight loss.

Patients intolerant to PAP therapy may qualify for medical devices, such as oral mandibular-advancement splints. Surgical procedures for the management of OSA include uvulopalatopharyngoplasty or other soft tissue procedures, maxillomandibular advancement, and hypoglossal-nerve stimulation (Gottlieb and Punjabi 2020).

Bariatric surgery is available for patients with severe obesity and can dramatically improve OSA; however, these surgical procedures are associated with the risk of perioperative and postoperative complications (Fritscher et al. 2007). Therefore, options for management that do not require surgery or wearing a device, such as medications that produce similar improvements in sleep apnea parameters, would represent a significant advancement in the treatment of OSA.

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Tirzepatide was approved as Mounjaro on May 13, 2022, under NDA 215866, as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes (T2DM). There are three ongoing post-marketing requirement (PMR) studies for under NDA 215866:

1. A randomized, double-blind, placebo-controlled trial in pediatric T2DM patients ages 10 to 17 years (inclusive)
2. A milk-only lactation trial
3. A medullary thyroid carcinoma (MTC) registry-based case series trial.

Tirzepatide was approved as Zepbound on November 8, 2023, under NDA 217806, as an adjunct to diet and exercise for chronic weight management (CWM) in adults with obesity or overweight in the presence of at least one weight-related comorbid condition. There are six ongoing PMR studies for under NDA 217806:

1. A randomized, double-blind, placebo-controlled trial for CWM in pediatric patients ages 12 to 17 years (inclusive) with obesity
2. A safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) trial for CWM in pediatric patients ages 6 to 11 years (inclusive) with obesity
3. A randomized, double-blind, placebo-controlled trial for CWM in pediatric patients ages 6 to 11 years (inclusive) with obesity
4. A prospective pregnancy registry to compare the maternal, fetal, and infant outcomes of women exposed to tirzepatide for CWM during pregnancy with an unexposed comparator population
5. A pregnancy trial that uses a different design from the pregnancy exposure registry to compare the risks and prevalence of pregnancy and infant outcomes between women exposed to tirzepatide for CWM during pregnancy and an unexposed comparator population
6. An MTC registry-based case series trial

Refer to Section 8.2.13 for details on post-marketing safety surveillance for tirzepatide.

In addition to T2DM (NDA 215866) and CWM (NDA 217806), tirzepatide (b) (4)

(b) (4)

(b) (4)

3.2. Summary of Presubmission/Submission Regulatory Activity

Table 2 summarizes topics related to the OSA clinical development program that were discussed during key interactions between the Applicant and the FDA. Tirzepatide for moderate to severe OSA with obesity was developed under IND 157090.

Table 2: Summary of Regulatory Activity Relevant To This sNDA

Date	Meeting Type	Comments
10/27/2021	Type B	The Division recommended two adequate and well controlled trials to provide substantial evidence of effectiveness. The Applicant confirmed that each study in the basket protocol would not share a placebo arm and that data would not be pooled from both studies during analysis. The Division emphasized that meeting statistical significance on both an AHI-based primary endpoint and a PRO-based secondary endpoint would be critical to support review and registration.
2/15/2022	Opening IND submitted	IND 157090: Trial GPIF "A Master Protocol for Tirzepatide in Participants with OSA and Obesity" • GPI1 will enroll patients intolerant or incapable of using PAP • GPI2 will enroll patients compliant with PAP
9/26/2022	Agreed iPSP	The FDA and the Applicant agreed to grant a pediatric trial waiver for patients 0-5 years of age (inclusive) and a deferral for patients 6-17 years of age (inclusive).
11/3/2022	Fast Track	Fast track determination was granted for OSA.
7/26/2023	Type D	The FDA found that the FOSQ did not have content validity to be a PRO for the proposed context of use. The Division recommended that the Applicant obtain supplemental qualitative and quantitative evidence for the PROMIS-SRI and PROMIS-SD scales to see if these measure are fit-for-purpose.
12/8/2023	Type D	The FDA agreed that the PROMIS-SRI and PROMIS-SD scales are content validated and recommended that they should be prioritized in the multiplicity testing hierarchy as key secondary endpoints over FOSQ, which should be exploratory. The Applicant stated that the trial would have enough power to test PROMIS endpoints.
1/19/2024	Type C	The FDA expressed agreement with the Applicant's proposed presentation for efficacy analyses and agreed with their plan not to pool data across the trials.
2/26/2024	Type C	The Applicant submitted a proposal for a trial in adolescents with obesity, (b) (4) (b) (4) to measure change in AHI. (b) (4) (b) (4)
4/5/2024	SAP submitted	The Applicant submitted version 4.0 of the SAP, which detailed a hierarchical testing strategy in which the PROMIS-SRI and PROMIS-SD PRO results were pooled across ISAs.

Date	Meeting Type	Comments
4/18/2024	Information Request	The Division submitted an information request to the Applicant providing feedback on the SAP. The Division requested justification for the interpretability of the PROMIS-SRI and PROMIS-SD data when pooled and requested unpooled data be submitted for all efficacy assessments. The Division noted that the treatment effect on PROs based on the unpooled data will be the focus of the review.
7/3/2024	Breakthrough Therapy Designation	The submission was granted Breakthrough Therapy Designation.

Abbreviations: AHI, apnea-hypopnea index, ODI, oxygen desaturation index, PRO, patient reported outcome, PSG, polysomnogram, ISA, intervention-specific appendices; FOSQ, functional outcomes of sleep questionnaire; PROMIS-SRI, patient-reported outcomes measurement information system – sleep related impairment; PROMIS-SD, patient-reported outcomes measurement information system – sleep disturbance; SAP, statistical analysis plan

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

4.1. Office of Scientific Investigations (OSI)

OSI inspections were conducted for this supplement and no issues were identified. Three inspection sites were chosen based on high enrollment numbers and a small efficacy difference favoring tirzepatide (that was greater than the mean results). Site 39296 enrolled 11 subjects for GPI1 and 10 subjects for GP2. Site 57558 enrolled six subjects for GPI1 and site 27507 enrolled nine subjects for GPI2. A sensitivity analysis determined that subjects enrolled at these sites did not impact efficacy conclusions.

4.2. Product Quality

With this supplement, the Applicant proposed to use the same presentation of tirzepatide that has been approved for use and is commercially available in the United States, a 2.5 mg, 5 mg, 7.5 mg, 10 mg, 12.5 mg, or 15 mg per 0.5 mL injection in a pre-filled syringe (PFS).

The current approved dose for CWM is 2.5 mg SC weekly followed by an increase in 2.5 mg increments every 4 weeks to a maintenance dose of 5 mg, 10 mg, or 15 mg SC weekly. A maintenance dose of 10 mg or 15 mg SC weekly is recommended for the treatment of moderate-to-severe OSA with obesity using the current commercially available product. Cross-reference is made to the original NDA for the chemistry, manufacturing, and control drug substance information as there are no changes to the drug substance with this application.

4.3. Devices and Companion Diagnostic Issues

No new device information was submitted since the PFS was previously approved under the original NDA approval on May 13, 2022. The PFS was originally developed by the Applicant for

its GLP-1 receptor agonist dulaglutide (Trulicity, BLA 125429). The Applicant submitted a use related risk analysis for the proposed indication of moderate-to-severe OSA with obesity, and the Human Factors review team found the justification for not conducting an additional human factors validation study to be acceptable. The patient populations of T2DM and CWM are similar to the OSA patient population, and there are no clinical features of OSA that are anticipated to affect the use of the PFS.

5. Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

No new nonclinical pharmacology/toxicology data was submitted or reviewed with this supplement. For an assessment of the nonclinical data, refer to NDA 215866 (tradename Mounjaro) review.

6. Clinical Pharmacology

6.1. Executive Summary

Tirzepatide is a 39-amino acid peptide based on the GIP sequence including a C20 fatty diacid moiety attached via a linker at lysine residue at position 20, and containing aminoisobutyric acid (Aib, a non-proteinogenic amino acid) at positions 2 and 13. As a dual agonist of the GIP and GLP-1 receptors, tirzepatide was first approved in 2022 under NDA 215866 (tradename Mounjaro) as an adjunct to diet and exercise to improve glycemic control in adults with T2DM. It was later approved in 2023 under NDA 217806 (tradename Zepbound) for CWM in adults with obesity or overweight with weight-related comorbidities. Tirzepatide drug product is presented as pre-filled single-dose pens (i.e., an autoinjector) or vials, each available as one of six dosing strengths (2.5, 5, 7.5, 10, 12.5, and 15 mg) in a 0.5 mL volume. The approved administration route is SC injection.

In this efficacy supplement (S-013) of NDA 217806 submitted on June 21, 2024, the Applicant is seeking approval of tirzepatide as a treatment for moderate-to-severe OSA in adults with obesity. The proposed dose regimen including dose escalation schedule and route of administration, and to-be-marketed drug products (i.e., strength, formulation, presentation, etc.) for the proposed new indication of OSA are identical to that currently approved in the U.S. for the treatment of T2DM (NDA 215866) and CWM (NDA 217806).

In support of this efficacy supplement, the Applicant conducted two phase 3 trials, GPI1 and GPI2 under Master Protocol GPIF, in subjects with moderate to severe OSA and obesity with

(GPI2) or without (GPI1) PAP therapy. The same proposed dose regimen for the OSA indication was investigated in both trials (Table 3). Additional studies or reports that were submitted to this supplemental NDA (sNDA) include a new population PK (popPK) and PK/PD reports in which popPK models were developed with the PK, PD, efficacy and/or safety data obtained from the two phase 3 trials in subjects with OSA. Of note, no new stand-alone PK studies were conducted under this supplement as the clinical pharmacology of tirzepatide was well-characterized in the previous T2DM and CWM programs and are cross referenced to this sNDA. Refer to Office of Clinical Pharmacology Reviews of tirzepatide in DARRTS[1,2] for more information.

The key clinical pharmacology review findings and comments are summarized in Table 3.

Table 3. Summary of Clinical Pharmacology Review

Review Issues	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	Two pivotal phase 3 trials (GPI1 and GPI2) provide supportive evidence of effectiveness of tirzepatide for the treatment of moderate to severe OSA in adults with obesity.
General dosing instructions	• Starting dosage is 2.5 mg injected SC QW for 4 weeks in the abdomen, thigh, or upper arm at any time of day, with or without meals. • Followed by stepwise dose escalation in 2.5 mg increments every 4 weeks (QWx4), to attain tirzepatide doses of up to 15 mg, as maintenance dose. • A lower maintenance dose of 10 mg may be selected if a full dose escalation to 15 mg cannot be achieved or tolerated. • During the first 24 weeks of the treatment period, only one cycle of dose de-escalation and re-escalation is permitted. After the first 24 weeks of treatment period, dose modifications are not permitted.
Dosing in patient subgroups (intrinsic and extrinsic factors)	No dosage adjustment to the proposed dose regimen is needed based on intrinsic factors like age, gender, race, body weight, or disease states, i.e., renal impairment, or hepatic impairment.

[1] NDA 215866, Reference ID of 4954959 dated 3/18/2022

[2] NDA 217806, Reference ID of 5258712 dated 10/11/2023

Review Issues	Recommendations and Comments
Drug interactions (from the approved label of NDA 217806)	• In vitro studies suggest that tirzepatide is neither an inhibitor of cytochrome P450 (CYP) enzymes and drug transporters nor an inducer of CYP enzymes. • Tirzepatide delays gastric emptying and thereby has the potential to affect the absorption of concomitantly administered oral medications (i.e., acetaminophen, contraceptive)
Tirzepatide PK	The tirzepatide mean trough concentrations observed in patients with OSA were comparable to the mean values in patients with obesity or overweight from the CWM clinical program.
Immunogenicity	• The incidence of anti-drug antibodies (ADA) was similar in patients with OSA and patients with obesity or overweight from the CWM clinical program. • The incidences of cross-reactive ADA with native GIP or GLP-1 were similar in patients with OSA and patients with obesity or overweight from CWM clinical program. • Subjects who developed ADA showed minimal impact on tirzepatide PK and efficacy (i.e., change in AHI from baseline) • Subjects who developed ADA (ADA^+) appeared to be more likely to experience hypersensitivity and injection-site-related reactions compared to subjects who were ADA negative (ADA^-).
Bridge between the to-be-marketed and clinical trial products	The to-be-marketed products are the currently approved products under NDA 215866 and NDA 217806, which were used in the pivotal OSA trials.

6.1.1. Recommendations

The Office of Clinical Pharmacology, Division of Inflammation and Immune Pharmacology (DIIP) and Division of Pharmacometrics (DPM), has reviewed the clinical pharmacology data submitted under NDA 217806/S-013. From a Clinical Pharmacology perspective, this application is recommended for **Approval** for the treatment of moderate to severe OSA in adults with obesity.

6.1.2. Post-Marketing Requirements and Commitments (PMR/PMC)

None.

6.2. Summary of Clinical Pharmacology Assessment

The PK of tirzepatide is well-characterized in the T2DM (NDA 215866) and CWM (NDA 217806) programs. In the NDA 217806/S-013, tirzepatide trough concentrations were collected from OSA GPI1 and GPI2 trials to build the tirzepatide popPK model. The OSA popPK model structure and parameters were informed by the final T2DM popPK model. In addition, tirzepatide exposure-response relationship for efficacy (AHI and body weight) and safety (gastrointestinal tolerability) were also developed based on the data obtained from two OSA phase 3 trials GPI1 and GPI2.

6.2.1. Pharmacology and Clinical Pharmacokinetics

6.2.1.1. Mechanism of action of pharmacodynamics

Tirzepatide is a GIP receptor and GLP-1 receptor agonist. It contains a C20 fatty diacid that enables albumin binding and prolongs the half-life. Tirzepatide selectively binds to and activates both the GIP and GLP-1 receptors, the targets for native GIP and GLP-1.

GLP-1 is a physiological regulator of appetite and caloric intake. Nonclinical studies suggest the addition of GIP may further contribute to the regulation of food intake.

Tirzepatide lowers body weight with greater fat mass loss than lean mass loss. Tirzepatide decreases calorie intake, and the effects are likely mediated by affecting appetite.

Tirzepatide stimulates insulin secretion in a glucose-dependent manner and reduces glucagon secretion. Tirzepatide increases insulin sensitivity, as demonstrated in a hyperinsulinemic euglycemic clamp study in patients with type 2 diabetes mellitus after 28 weeks of treatment. These effects can lead to a reduction of blood glucose.

Tirzepatide delays gastric emptying. The delay is largest after the first dose and this effect diminishes over time.

6.2.1.2. Pharmacokinetics of tirzepatide

The following PK information for tirzepatide is from the approved label of NDA 217806:

Absorption

Following subcutaneous administration, the median time (range) to maximum plasma concentration of tirzepatide is 24 hours (8 to 72 hours). The mean absolute bioavailability of tirzepatide following subcutaneous administration is 80%. Similar exposure was achieved with subcutaneous administration of tirzepatide in the abdomen, thigh, or upper arm.

Distribution

The mean (CV%) apparent steady-state volume of distribution of tirzepatide following subcutaneous administration in patients with overweight or obesity is approximately 9.7 L (28.5%). Tirzepatide is highly bound to plasma albumin (99%).

Elimination

The apparent population mean clearance (CV%) of tirzepatide in patients with overweight or obesity is 0.056 L/h (20.9%) with an elimination half-life of approximately 5 days.

Metabolism

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

Excretion

The primary excretion routes of tirzepatide metabolites are via urine and feces. Intact tirzepatide is not observed in urine or feces.

Specific Populations

The intrinsic factors of age, sex, race, ethnicity, or body weight do not have a clinically relevant effect on the PK of tirzepatide. Renal and/or hepatic impairment does not impact the PK of tirzepatide.

Overall, the PK of tirzepatide is comparable in subjects with T2DM, overweight or obesity, or with OSA and obesity based on the observed trough concentrations and popPK analysis.

The statistical descriptions of observed tirzepatide trough concentrations from OSA GPI1 and GPI2 trials are summarized in Table 4 and Table 5, respectively. Of note, the summary includes subjects on all different dosing levels. Based on the studied dosing regimen (Figure 2), tirzepatide steady state PK is expected to be reached about 4 weeks after the last dose escalation (Week 20). In Trial GPI1, 96 (84.2%) and 8 (7.6%) subjects were on stabilized 15 mg and 10 mg once weekly treatment, respectively. In Trial GPI2, 112 (94.1%) and 3 (2.5%) subjects were on stabilized 15 mg and 10 mg once weekly treatment, respectively.

Table 4. Summary of Tirzepatide Plasma Concentration (ng/mL) by Visit or Week Following SC Administration of Tirzepatide Once Weekly (Trial GPI1)

	Treatment Phase				Follow-Up
Visit	3	5	8	11	801
Week	4	12	24	52	-
N	105	100	98	89	90
n	107	102	98	89	90
Mean	152	556	1080	1290	98.6
SD	78.3	275	557	679	227
Minimum	2.40	2.86	2.20	38.9	2.42
Median	141	494	1030	1230	36.7
Maximum	505	1320	2450	3110	1510

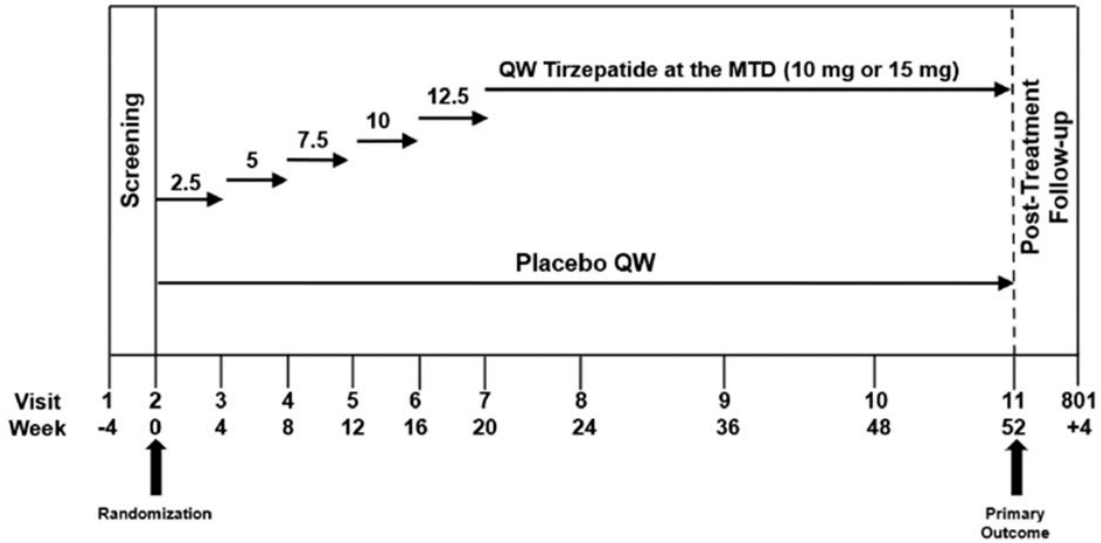
Source: Full Clinical Study Report of 18F-MC-GPI1, page 1020, Table GPI1.8.81.

Table 5. Summary of Tirzepatide Plasma Concentration (ng/mL) by Visit or Week Following SC Administration of Tirzepatide Once Weekly (Trial GPI2)

	Treatment Phase				Follow-Up
Visit	3	5	8	11	801
Week	4	12	24	52	-
N	114	108	107	101	97
n	114	108	107	101	99
Mean	180	542	1150	1180	70.7
SD	133	221	550	614	102
Minimum	6.20	9.24	9.81	5.11	2.22
Median	156	500	1040	1070	35.0
Maximum	1340	1290	3260	2710	603

Source: Full Clinical Study Report of 18F-MC-GPI2, page 1092, Table GPI2.8.89.

Figure 2. Illustration of Dose Escalation and Visit Schema for Master Protocol GPIF



Source: Full Clinical Study Report of 18F-MC-GPI1, page 46, Figure GPI13.2.

The mean steady state C_{trough} values of tirzepatide on Week 24 and Week 52 by doses pooled from GPI1 and GPI2 are summarized in Table 6. The mean C_{trough} values following 10 mg and 15

mg tirzepatide were comparable to the mean values obtained from CWM program (GPHL and GPHK). The sample size following 5 mg in the OSA program is too small for comparison.

Table 6. Comparison of Tirzepatide Trough Plasma Concentration (ng/mL) between OSA and CWM programs

Indication	OSA (GPI1 + GPI2)				CWM (Week 24)			
	Week 24		Week 52		GPHK		GPHL	
Dose	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N
5 mg	296 (148)	2	38.9	1	406 (202)	567	N/A	N/A
10 mg	950 (454)	11	804 (310)	2	815 (382)	568	695 (309)	277
15 mg	1126 (571)	191	1197 (679)	185	1226 (586)	566	1079 (486)	273

Source: pc.xpt and ADEC.xpt from 18F-MC-GPI1 and 18F-MC-GPI1; Table GPHK.8.139, Table GPHK.8.140, Table GPHK.8.141 from CSR GPHK; Table GPHL.8.151 and Table GPHK.8.152 from CSR GPHL.

Based on popPK analysis, the mean apparent steady-state volume of distribution (%CV) of tirzepatide is 10.3 L (23.8%) in subjects with T2DM, 9.7 L (28.5%) in subjects with overweight or obesity, and 11.8 L (37.2%) in subjects with OSA and obesity. These mean values are comparable across three indications. Tirzepatide is highly bound to plasma albumin (99%).

The mean apparent clearance (%CV) and terminal elimination half-life ($t_{1/2}$) (%CV) of tirzepatide are 0.061 L/hr (23.1%) and 18.1%) in subjects with T2DM, 0.056 L/hr (20.9%) and 5.69 hr (20.9%) in subjects with overweight or obesity, and 0.062 L/hr (19.4%) and (34.5%) in subjects with OSA and obesity, respectively. These mean values are comparable across the three indications.

6.2.1.3. Drug interactions

The potential risk of enzyme- or transporter-mediated drug-drug interaction is low for tirzepatide as either a substrate or an inhibitor/inducer. Tirzepatide is metabolized by proteolytic cleavage of the peptide backbone, beta-oxidation of the C20 fatty diacid moiety, and amide hydrolysis. In vitro studies suggest that tirzepatide doesn't clinically inhibit or induce CYP enzymes (i.e., CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and/or 3A4/5) and is not an inhibitor of drug transporters examined, i.e., organic anion-transporting polypeptide (OATP)1B1, OATP1B3, OAT1, OAT3, organic cation transporter (OCT)1, OCT2, P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), multidrug and toxin extrusion protein (MATE)1, and MATE2K.

The impact of tirzepatide on gastric emptying delay was evaluated in healthy subjects and subjects with T2DM using acetaminophen as a probe (Study 18F-MC-GPGA). The results suggested that a first SC dose of 5 mg tirzepatide reduced acetaminophen maximum plasma concentration (C_{max}) by approximately 50% and delayed the time of maximum observed drug concentration (t_{max}) by about an hour, but had no impact on the area under the concentration-time curve (AUC). After coadministration of tirzepatide QW over 4 weeks, the impact of tirzepatide on acetaminophen C_{max} and t_{max} was not meaningful.

The impact of tirzepatide on PK of oral contraceptive (OC) was also assessed in healthy female subject (Study 18F-MC-GPGR). Following administration of a combined OC (0.035 mg ethinyl estradiol and 0.25 mg norgestimate) in the presence of a single SC dose of 5 mg tirzepatide, the mean C_{max} of ethinyl estradiol, norgestimate, and norelgestromin, a main active metabolite of norgestimate, was reduced by 59%, 66%, and 55%, respectively. For estradiol, norgestimate, and norelgestromin, the mean AUC was reduced by approximately 20%, and a delay in t_{max} of 2.5 to 4.5 hours was observed.

Refer to Clinical Pharmacology Review authored by Dr. Kronfol, et al. in DARRTS[3] for more information.

6.2.1.4. Immunogenicity

Incidences of Anti-Drug Antibodies (ADA) and Neutralizing Antibodies

The immunogenicity analysis was primarily conducted in subjects with one baseline evaluation and at least one post-dose evaluation (i.e., evaluable for treatment-emergent (treatment-induced or boosted) ADA). The immunogenicity results were pooled from GPI1 and GPI2. Among 234 subjects in the placebo group from two trials, 222 subjects were evaluable for treatment-emergent (TE) ADA. Among these 222 subjects, 18 (8.1%) and 6 (2.7%) of subjects were ADA^+ at baseline and developed TE ADA^+ by Week 52, respectively.

Among 233 subjects in tirzepatide group from the two trials, 226 subjects were evaluable for TE ADA. Among these 233 subjects, 15 (6.6%) and 137 (60.6%) of subjects were ADA^+ at baseline and developed TE ADA^+ by Week 52, respectively. Of the 137 subjects who developed ADA, 84 (61%) were positive for cross-reactive ADA against native GIP (nGIP) and 44 (32%) were positive for cross-reactive ADA against native GLP-1 (nGLP-1). The TE ADA incidence following tirzepatide treatment in the OSA program (60.6%) was similar to the result from the CWM program (64.5%).

The ADA titer in 15 baseline ADA^+ subjects from tirzepatide group ranged from 1:10 to 1:320 (median 1:40). The ADA titer in 137 TE ADA^+ subjects from tirzepatide group ranged from 1:20 to 1:5120 (median 1:320).

Among the subjects who developed ADA post-dose, none had neutralizing antibodies (NAb) against tirzepatide activity on the GIP or GLP-1 receptors; none developed NAb against nGIP or nGLP-1.

The clinical pharmacology review team listed an immunogenicity comment in the 74-day letter dated August 21, 2024. The comment conveyed the concern of potential clinical impact of

[3] NDA 215866, Reference ID: 4954959

cross-reactive ADA+ subjects who discontinue the tirzepatide treatment, as anti-native GIP or GLP-1 antibody may worsen the disease or even trigger a new disease (such as T2DM) when there is not enough tirzepatide in the human body to mitigate the effect of these antibodies.

The Applicant responded on September 9, 2024 with the following justifications:

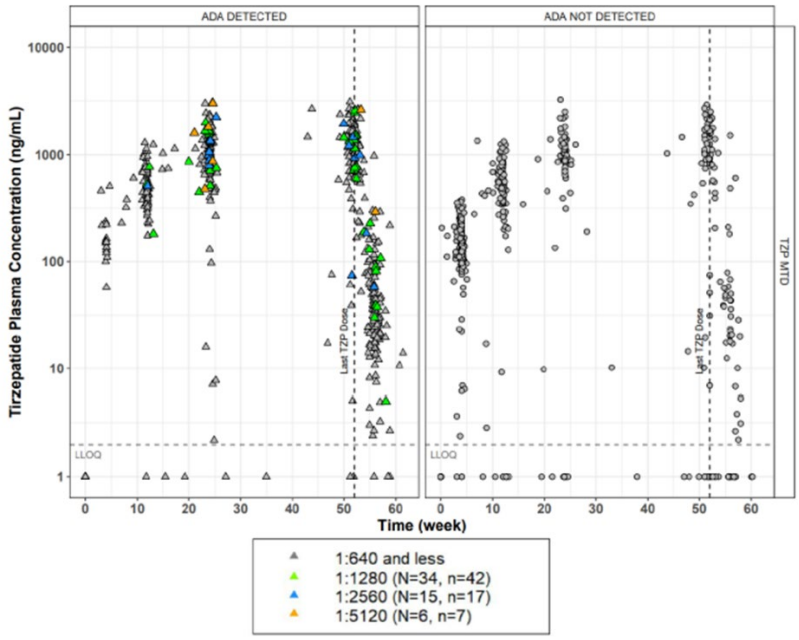
1. Both obesity and OSA are conditions that require chronic long-term therapy.
2. Although a small proportion of subjects (25/450) in GPI1 and GPI2 were positive for cross-reactive ADAs (3.8% for GIP and 1.8% for GLP-1) at baseline, there is no trend showing that cross-reactive ADA+ subjects have more severe OSA compared to cross-reactive ADA- subjects at baseline. The Applicant acknowledged the limitation of small sample size for this exploratory assessment.
3. No tirzepatide-treated participants developed T2DM during the post-baseline period, including the safety follow up period.

The clinical pharmacology review teams acknowledge that GPIF was not designed to assess the potential relationship between cross-reactive ADA status and weight regain, worsening of OSA parameters, or emergence of new diseases following treatment discontinuation. Given the limitations of the currently available information, the review teams agree that currently there is no compelling signal indicating that cross-reactive ADA$^+$ subjects who discontinue tirzepatide treatment may progress in disease or get newly diagnosed with GIP- and/or GLP-1-insufficiency-related diseases.

Effect of Immunogenicity on PK

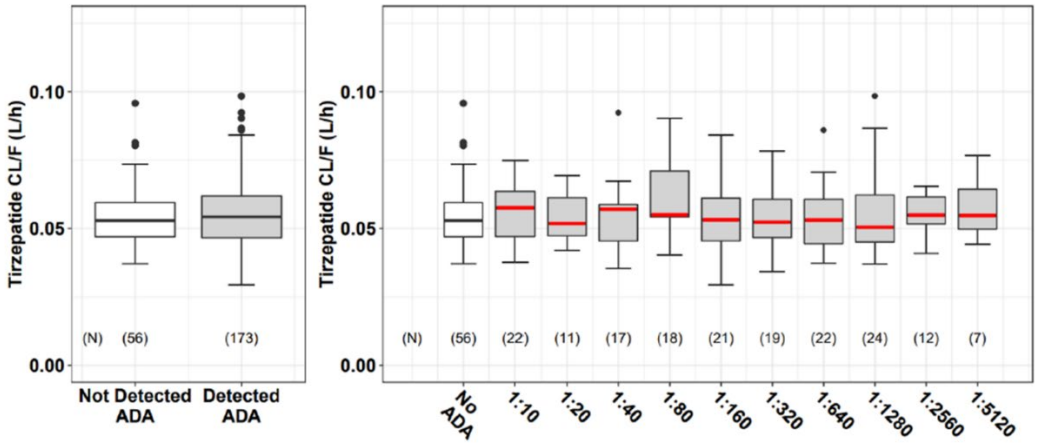
No apparent effect of ADA on observed tirzepatide trough concentrations was noted from GPI1 and GPI2 (Figure 3). No apparent relationship between ADA status/titers and tirzepatide clearance (CL/F) was detected (Figure 4).

Figure 3. Comparison of Tirzepatide Trough Concentrations from Participants with Detected (left panel) and Undetected (right panel) ADA in GPI1 and GPI2



Source: 18F-MC-GPIF Population PK/PD Report, Figure 9.1.

Figure 4. Tirzepatide Clearance (CL/F) by ADA Status (left panel) or ADA Titers (right panel) in GPI1 and GPI2

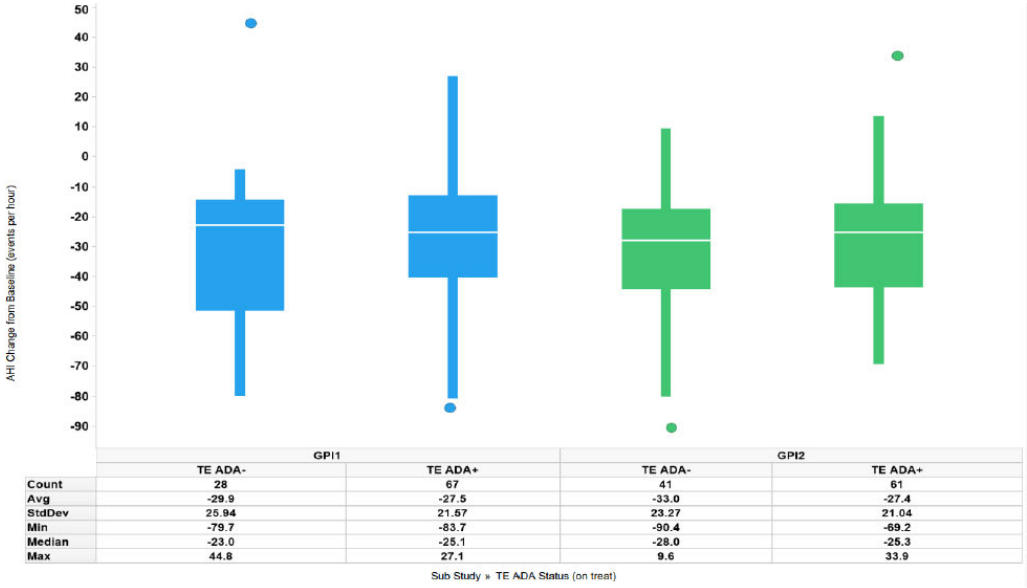


Source: Integrated Summary of Immunogenicity, Figure ISI.8.4.

Effect of Immunogenicity on Efficacy

No apparent effect of treatment-emergent ADA status on AHI change from baseline was observed (Figure 5).

Figure 5. Change in AHI from Baseline *vs.* TE ADA Status for Tirzepatide-Treated Participants in GPI1 and GPI2



	GPI1		GPI2	
	TE ADA-	TE ADA+	TE ADA-	TE ADA+
Count	28	67	41	61
Avg	-29.9	-27.5	-33.0	-27.4
StdDev	25.94	21.57	23.27	21.04
Min	-79.7	-83.7	-90.4	-69.2
Median	-23.0	-25.1	-28.0	-25.3
Max	44.8	27.1	9.6	33.9

Abbreviations: Avg = average; AHI = Apnea-Hypopnea Index; GPI1 = I8F-MC-GPI1; GPI2 = I8F-MC-GPI2; Max = maximum; Min = minimum; StdDev = standard deviation; TE ADA = treatment-emergent anti-drug antibody; TZP = tirzepatide.

Source: Integrated Summary of Immunogenicity, Figure ISI.8.6.

Effect of Immunogenicity on Hypersensitivity and Injection Site Reactions

Subjects who were TE ADA$^+$ in tirzepatide group were more likely to experience hypersensitivity and injection-site related reaction compared to TE ADA$^-$ subjects. The incidence of hypersensitivity and injection-site reaction was 4.4% (6/137) vs 1.1% (1/89) and 13.9% (19/137) vs 1.1% (1/89), respectively, in ADA$^+$ and ADA$^-$ subjects. Refer to Section 8.2.11.8 for details on these reactions.

Effect of Preexisting Anti-Drug Antibodies

The incidence rate of TE ADA$^+$ during the planned treatment period was similar between participants with and without preexisting ADA (60% *vs*. 60.7% [Table 7]), i.e., 9 out 15 (60%) participants with ADA$^+$ at baseline experienced titer increase and 128 out of 211 (60.7%) subjects with ADA$^-$ at baseline developed ADA after tirzepatide treatment. Thus, preexisting ADA do not appear to predispose subjects to developing TE ADA.

Table 7. Effect of Preexisting Antibodies

Category	TZP_ALL (N = 233) n (%)
Participants evaluable for TE ADA*[a]	226
Evaluable participants with ADA present at baseline	15 (6.6%)
Participants postbaseline TE ADA positive*[b]	137 (60.6%)
Treatment-induced TE ADA positive	128 (56.6%) [60.7%]*[c]
Treatment-boosted TE ADA positive	9 (4.0%) [60%]*[d]

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

*[a] A participant is TE ADA evaluable if there is at least 1 nonmissing test result for TZP ADA for each of the baseline period and the postbaseline period. All percentages are relative to the total number of TE ADA-evaluable participants in each treatment group.

*[b] A TE ADA-evaluable participant is considered to be TE ADA-positive if the participant has at least 1 postbaseline titer that is a 4-fold or greater increase in titer from baseline measurement (treatment-boosted). If the baseline result is ADA not present, then the participant is TE ADA-positive if there is at least 1 postbaseline result of ADA present with titer ≥1:20 (treatment-induced). A TE ADA-evaluable participant is TE ADA inconclusive if ≥20% of the participant's postbaseline samples, drawn predose, are ADA inconclusive and the participant is not otherwise TE ADA-positive. A TE ADA-evaluable participant is TE ADA negative if not TE ADA-positive and not TE ADA inconclusive.

*[c] TE ADA-positive rate in tirzepatide-treated participants without preexisting antibodies (treatment-induced) calculated as (TE ADA-positive treatment-induced) / (TE ADA-evaluable participants with ADA not present at baseline).

*[d] TE ADA-positive rate in tirzepatide-treated participants with preexisting antibodies (treatment-boosted) calculated as (TE ADA-positive treatment-boosted)/(TE ADA-evaluable participants with ADA present at baseline).

Source: Integrated Summary of Immunogenicity, Table ISI.8.4.

6.2.2. General Dosing and Therapeutic Individualization

6.2.2.1. General Dosing

The totality of clinical safety and efficacy data observed in the OSA phase 3 trials and the results of exposure-response model-based analyses overall support the acceptability of the stepwise dose-escalation approach starting at 2.5 mg SC QW for 4 weeks with 2.5-mg increments every 4 weeks to attain dose levels up to 15 mg tirzepatide for the treatment of moderate to severe OSA in adult subjects with obesity.

6.2.2.2. Therapeutic Individualization

Therapeutic individualization based on intrinsic or extrinsic factors is not necessary. PopPK analysis identified body weight (BW) as only statistically significant covariate on tirzepatide PK. The model projected that tirzepatide exposure (AUC) decreased with increasing BW in about 1.1% per Kg over a BW range of 80 to 130 kg in subjects with obesity or overweight and in subjects with OSA and obesity. However, dose adjustment based on BW is not clinically relevant and not necessary based on the available efficacy data from the OSA phase 3 trials. See Section 6.3.2.3.

6.2.2.3. Outstanding Issues

There are no outstanding issues that would preclude the approval of tirzepatide from a Clinical Pharmacology perspective

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

General clinical pharmacology, pharmacokinetics, and immunogenicity of tirzepatide are summarized in Table 8.

Table 8. Summary of Clinical Pharmacology and Immunogenicity of Tirzepatide

Pharmacology	
Mechanism of Action	Tirzepatide, a peptide, is a GIP receptor and GLP-1 receptor agonist.
Pharmacodynamics	Tirzepatide enhances the first- and second-phase insulin secretion. Tirzepatide increases insulin sensitivity. Tirzepatide reduces fasting and postprandial glucagon concentrations. Tirzepatide delays gastric emptying.
General Information	
Bioanalysis	Tirzepatide concentrations in human plasma were quantified using two fully validated liquid chromatography with mass spectrometry (LC/MS) methods Tirzepatide method at (b) (4) with the sensitivity of 2 ng/mL was used to analyze human plasma samples obtained from the global study participants outside of China. Tirzepatide method at (b) (4) with the sensitivity of 4 ng/mL was used to analyze human plasma samples obtained from the study participants in China.
PK model	The popPK model comprised 2 compartments with first-order absorption and interindividual variability on absorption rate (ka), clearance (CL), central volume of distribution (Vc), and proportional residual error.
Healthy vs. Patients	The PK of tirzepatide is similar between healthy subjects and subjects with T2DM or with overweight or obesity.
Drug Exposure at Steady State	Steady-state plasma concentrations of tirzepatide were achieved following 4 weeks of SC QW administration. The average steady state concentrations (C_{ss}) after QW SC administration of 5 mg, 10 mg or 15 mg of tirzepatide in the OSA phase 3 trials (GPIF) (n=229) were 483 ng/mL, 967 ng/mL, 1450 ng/mL, respectively. The inter-individual variability (%CV) for C_{ss} was 19.4% for all doses. The average C_{ss} values in the OSA program are similar to those in the T2DM and CWM programs.
Dose Proportionality	Tirzepatide exposure increased proportionally with dose increases across 2.5 to 15 mg. With multiple-dose administration, the drug accumulation ratio ranged from 1.7 to 1.9 in subjects with T2DM, overweight or obesity, or OSA and obesity.

Pharmacology	
Body weight	PopPK analysis identified BW as a statistically significant covariate affecting tirzepatide concentrations. Tirzepatide exposure decreases with increasing BW by ~ 1.1% per Kg over a BW range of 80 to 130 kg. At the BW >130 kg, the slope between tirzepatide exposure and BW is shallower.
ADME	
Absorption	Following SC administration, the median time to maximum plasma concentration of tirzepatide is 24 hours (range: 8 to 72 hours). The absolute bioavailability following SC administration was estimated to be 80%.
Distribution	The mean (%CV) apparent steady-state volume of distribution (V_d/F) of tirzepatide following SC administration was 10.3 L (23.8%), 9.7 L (28.5%), and 11.8 L (37.2%) in subjects with T2DM, overweight or obesity, or OSA and obesity, respectively. After 0.5 mg intravenous bolus administration, the mean of distribution (V_z) was 5.52 L, suggesting that tirzepatide distributes primarily in the blood volume. Tirzepatide is highly bound to plasma albumin (99%).
Elimination	The mean apparent clearance (%CV) and terminal elimination $t_{1/2}$ (%CV) of tirzepatide are 0.061 L/hr (23.1%) and 5.41 days (18.1%) in subjects with T2DM, 0.056 L/hr (20.9%) and 5.69 days (20.9%) in subjects with overweight or obesity, and 0.062 L/hr (19.4%) and 6.33 days (34.5%) in subjects with OSA and obesity, respectively.
Metabolism	Tirzepatide was mainly eliminated by metabolism with no intact tirzepatide observed in human urine or feces. The primary metabolic pathways were proteolytic cleavage of the peptide backbone, beta-oxidation of the C20 fatty diacid moiety, and amide hydrolysis. The formed metabolites of tirzepatide were eliminated via urine and feces in a ~2:1 ratio.
Excretion	The renal excretion of unchanged tirzepatide was not observed in the human mass balance study. However, the renal excretion was the primary route for the metabolites of tirzepatide.
Immunogenicity	
Bioanalysis	ADA were determined using a validated ligand-binding method. NAb were determined using validated cell-based assays. Cross-reactive NAb against nGIP and nGLP-1 were determined using in-silico classification methods
Incidence	Among 226 evaluable subjects in the OSA phase 3 studies, 137 subjects (60.6%) treated with tirzepatide developed ADA during the treatment period up to 52-week, in which 128 (56.6%) were classified as treatment-induced and 9 (4.0%) were classified as treatment-boosted. Of the 137 ADA-positive subjects, 84 (61.3%) were positive for cross-reactive ADA against nGIP and 44 (32.1%) were positive for cross-reactive ADA against nGLP-1. Of the subjects who developed ADA, none had NAb against tirzepatide activity on the GIP or GLP-1 receptors. Likewise, none of them developed NAb against nGIP or nGLP-1. Immunogenicity incidence in the OSA phase 3 trials is generally comparable to that observed in the T2DM and CWM clinical trials.

Pharmacology	
Clinical Impact	ADA and ADA titer had no discernable impact no tirzepatide PK. cacy: The development of ADA and ADA titer had no apparent impact on the change in AHI from baseline. ety: Subjects who developed ADA to tirzepatide were more likely to experience hypersensitivity and injection-site reactions compared to subjects who were ADA negative. ›ersensitivity reaction: 4.4% (ADA^+) *vs* 1.1% (ADA^-) ction-site reaction: 13.9% (ADA^+) *vs* 1.1% (ADA^-)

Source: Clinical pharmacology reviewer.
Abbreviations: ADME, absorption, distribution, metabolism, excretion

6.3.2. Clinical Pharmacology Questions

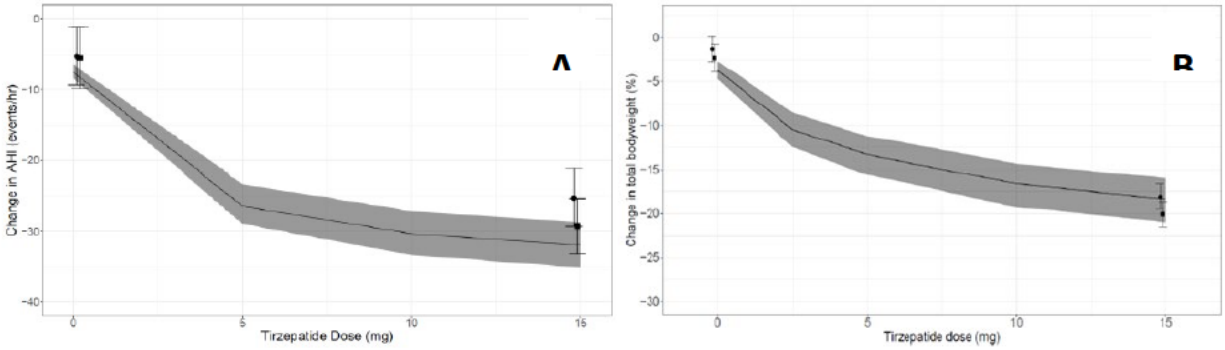
6.3.2.1. Does the clinical pharmacology program provide supportive evidence of effectiveness?

Yes. The overall data from the OSA phase 3 trials provides evidence that tirzepatide is effective for the treatment of adult subjects with OSA and obesity. The dose/exposure-response relationship for efficacy provides supportive evidence of effectiveness. See Section 8 of this multi-discipline review for details of the study design and efficacy/safety results of the phase 3 trials.

The Applicant used a nonlinear mixed effects modeling program, NONMEM®, with the measured plasma concentrations of tirzepatide, AHI, and BW data in the OSA phase 3 trials to describe the dose/exposure-response relationships for AHI and BW reduction after 52-week treatment of tirzepatide (see Section 14.3.2). The results demonstrated dose/exposure-response relationships for the two efficacy variables, i.e., AHI and BW reduction (Figure 6). The model predictions of reductions in AHI and BW corresponded well with observed data from the OSA phase 3 trials and the degree of AHI improvement was associated with the magnitude of BW reduction (Table 9).

Additionally, model-based analysis demonstrates tirzepatide 5 mg, 10 mg, and 15 mg QW treatment is associated with AHI reduction and that AHI reduction occurs across the range of baseline OSA severity (Figure 7). Of note, 10 mg and 15 mg were the target maintenance doses investigated in Trials GPI1 and GPI2.

Figure 6. Dose/Exposure-Response for AHI (A) or BW (B) Reduction after 52-week Treatment of Tirzepatide in Subjects with Moderate to Severe OSA and Obesity



Note: The line is the median and shaded area is the 95% confidence interval of model prediction. The circles and rectangles are observed least square means and the error bars are the 95% confidence interval of the observations in GPI1 and GPI2
Source: 2.7.2 Summary of Clinical Pharmacology, Figure 2.7.2.4 and Figure 2.7.2.3

Table 9. Relationship between Change in BW and Change in AHI

Weight measured as % change from baseline	GPIF Observed Change in AHI[a] Mean (1.96*SEM) [n, n_{tzp}]	PK/PD Model Predicted Change in AHI[b] Median (95% CI)
Weight neutral or weight gain	3.42 (-0.340, 7.19) [126, 5]	0 (-1.67, 1.68)
Weight loss		
0.1% to 4.9%	-8.06 (-11.2, -4.89) [184, 24]	-6.52 (-12.4, -0.170)
5% to 9.9%	-13.7 (-17.0, -10.4) [155, 90]	-17.2 (-22.0, -12.1)
10% to 14.9%	-24.1 (-27.6, -20.7) [120, 110]	-25.1 (-29.1, -21.0)
≥15%	-32.2 (-35.3 -29.2) [196, 187]	-31.4 (-35.2, -27.6)

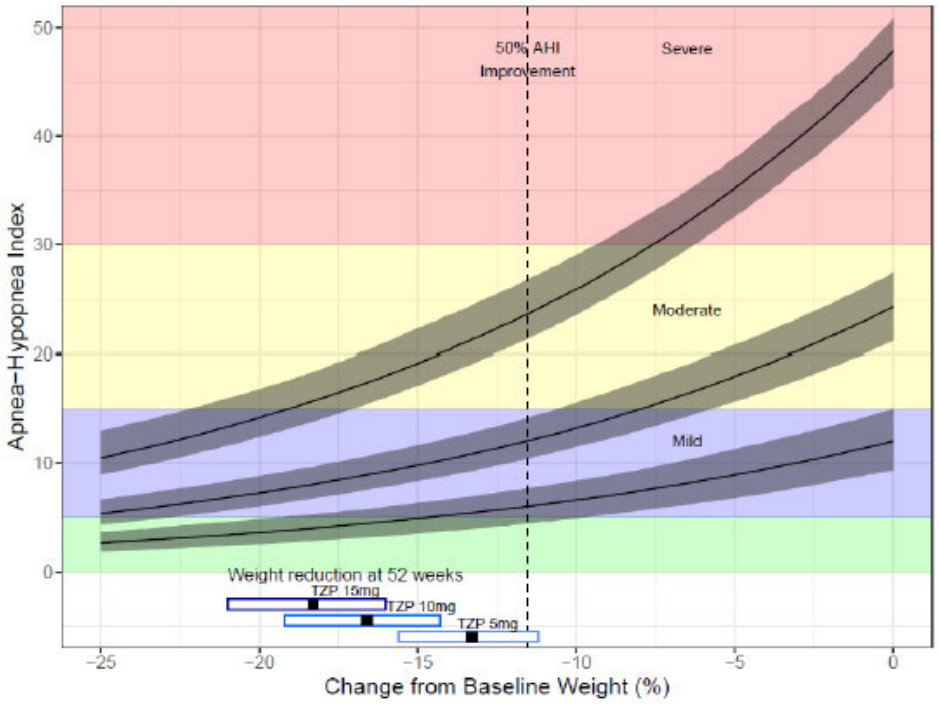
Abbreviations: AHI = apnea-hypopnea index; CI = confidence interval; GPIF = I8F-MC-GPIF; n = number of observations from both placebo and tirzepatide treatment arms; n_{tzp} = number of observations from tirzepatide treatment arm; PK/PD = pharmacokinetic/pharmacodynamic; SEM = standard error of the mean.

[a] Mean baseline AHI was 50 events/h for GPIF..

[b] Mean baseline AHI was 48 events/h for simulation. Simulation was performed with 200 replicates.

Source: 2.7.2 Summary of Clinical Pharmacology, Table 2.7.2.4

Figure 7. Model-Predicted AHI Improvement and BW Reduction at 52 Weeks with Tirzepatide Treatment in Subjects with Mild, Moderate or Severe OSA and Obesity



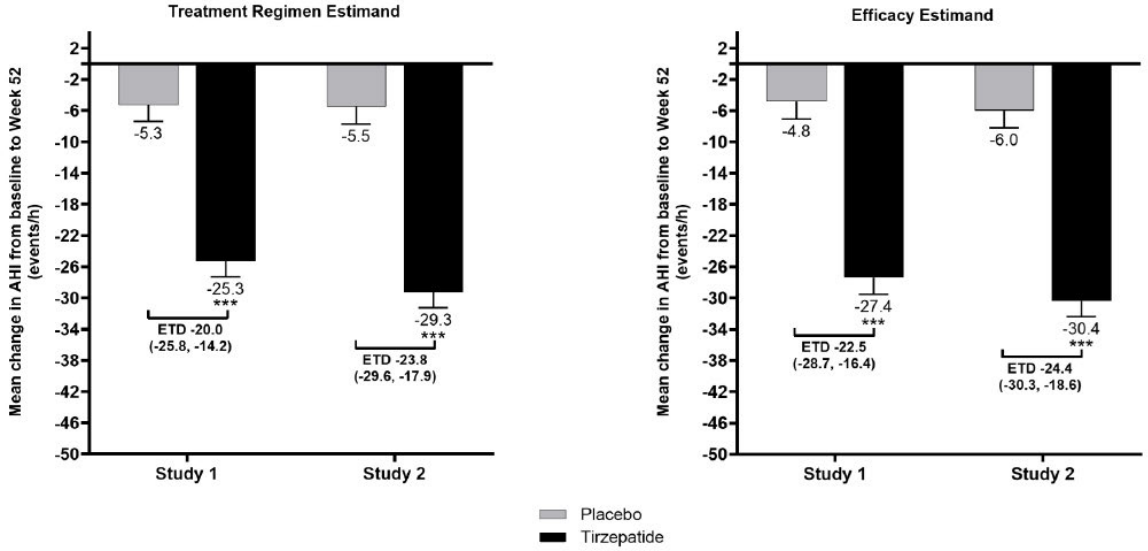
TZP=tirzepatide
Source: 2.7.2 Summary of Clinical Pharmacology, Figure 2.7.2.5

6.3.2.2. Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes. The efficacy and safety data from the OSA phase 3 trials support that the proposed dosing regimen (starting dosage is 2.5 mg SC QW, increase the dosage in 2.5 mg increments after at least 4 weeks on the current dose, up to 15 mg) is appropriate for the general patient population.

Using treatment-regimen and efficacy estimands, the tirzepatide treatment group with the proposed dosing regimen demonstrated superiority compared with placebo from mean change in AHI (improvement) from baseline to Week 52 ($p<0.001$) in GPI1 and GPI2 (Figure 8). See Section 8 of this multidisciplinary review for details of the efficacy data. Exposure-response analysis indicates that the proposed dosage regimen has achieved the plateau of efficacy and higher doses would not result in a meaningful reduction in AHI (Figure 6).

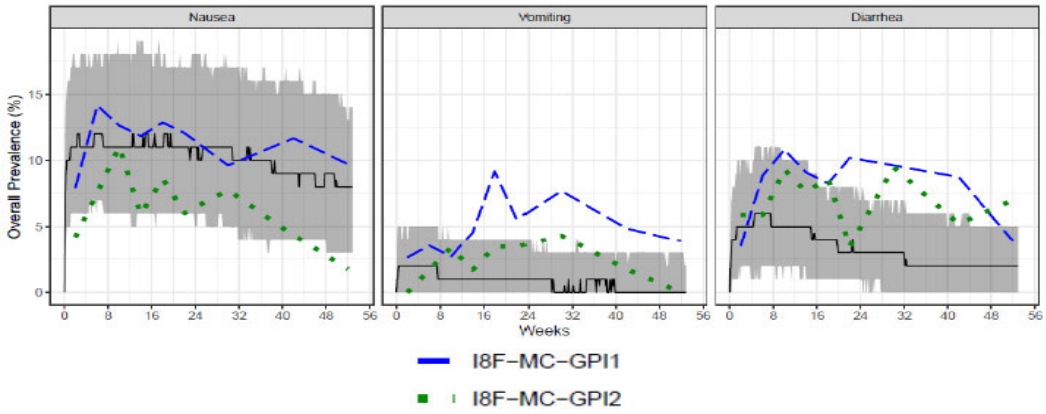
Figure 8. Change in AHI from Baseline to Week 52 in GPI1 and GPI2: mITT Population, Full Analysis Set (left) and Efficacy Analysis Set (right)



ETD=estimated treatment difference, Study 1=18F-MC-GPI1, Study 2=18F-MC-GPI2
***p-value<0.001 versus placebo, controlled for type I error
Source: 2.7.3 Summary of Clinical Efficacy, Figure 2.7.3.3

The exposure-response relationship for the gastrointestinal tolerability (e.g., nausea, vomiting or diarrhea adverse events [AEs]) were characterized in subjects with OSA and obesity. The observed prevalences of nausea, vomiting and diarrhea AEs from the two OSA phase 3 trials were generally comparable to those from the popPK analysis (Figure 9) and consistent with the results from the prior phase 3 trials (i.e., T2DM and CWM programs) with the same dose-escalation scheme. The majority of nausea, vomiting, and diarrhea AEs were reported during the dose-escalation phase, and their incidence decreased with time with a prevalence <10% once steady-state concentrations for the maintenance doses were attained (after 24 weeks). Thus, alternative dose titration doesn't appear to be required. Refer also to Section 8.2 for additional information on gastrointestinal AEs.

Figure 9. Model-Predicted Tirzepatide 15 mg QW Prevalence of Nausea, Vomiting and Diarrhea with Overlaid Observed Prevalence from the OSA Phase 3 Trials

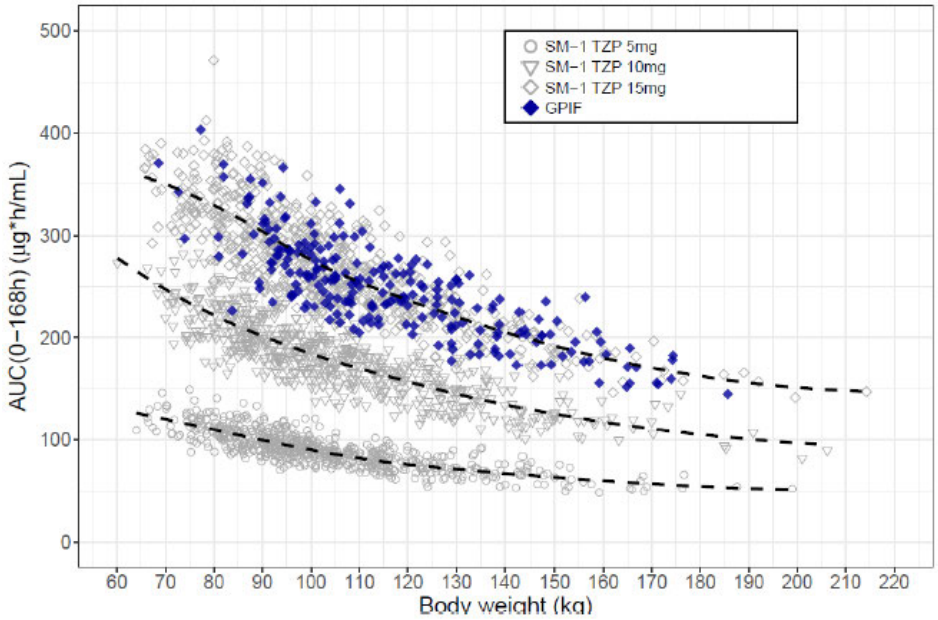


Black lines denote median of model predictions, Gray bands represent 90% confidence intervals.
Blue long dashed and green dotted lines are observed prevalence of event in population without and with continuous positive airway pressure (CPAP) device use, respectively.
Source: 2.7.2 Summary of Clinical Pharmacology, Figure 2.7.2.6

6.3.2.3. Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

No. An alternative dosing regimen or management strategy is not necessary for subpopulations based on intrinsic factors (i.e., age, gender, BW, race, renal or hepatic impairment, as well as ADA). PopPK analysis identified BW as a significant baseline covariate on tirzepatide PK. Over a BW range of 80 to 130 kg, tirzepatide exposure decreases with increasing BW by approximately 1.1% per Kg. When the BW is >130 kg, the slope between tirzepatide exposure and BW is shallower (Figure 10). However, a dose adjustment based on BW is not necessary based on the available efficacy data and exposure-BW analyses from the OSA phase 3 trials. Notably, BW is also a time-varying covariate as the treatment of tirzepatide is associated with significant reduction in BW over time.

Figure 10. Relationship between Plasma Concentrations of Tirzepatide and BW in the OSA Phase 3 Trials



Abbreviations: AUC(0-168h) = area under the concentration versus time curve from time 0 to 168 hours after dose at steady state; GPIF = I8F-MC-GPIF; SM-1 = SURMOUNT-1; TZP = tirzepatide.
Note: Symbols denote individual values. The dashed lines are the loess smoothing fit for the tirzepatide 5-mg, 10-mg, and 15-mg treatment arms from SM-1.

Source: 2.7.2 Summary of Clinical Pharmacology, Figure 2.7.2.2

6.3.2.4. Are there clinically relevant drug-drug interactions, and what is the appropriate management strategy?

The potential risk of enzyme- or transporter-mediated drug-drug interaction is low for tirzepatide. However, tirzepatide has the potential to influence the absorption of concomitantly administered oral medications by delaying gastric emptying. See Section 6.2.1.3 of this review for details.

7. Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

To support the proposed indication, the Applicant submitted clinical data from the SURMOUNT-OSA (GPIF) trials. GPIF is the master protocol that supported two pivotal independent trials, GPI1 and GPI2. Each trial was a multicenter, randomized, parallel-arm, double-blind, placebo-controlled phase 3 trial. Trial details are summarized in Table 10.

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Table 10. Clinical Trials Submitted in Support of Efficacy and Safety Determination

Trial Identity	NCT no.	Trial Design	Regimen/ Schedule/ Route	Trial Endpoints	Treatment Duration/ Follow Up	No. of Patients Enrolled	Trial Population	No. of Centers and Countries
Controlled Phase 3 Studies to Support Efficacy and Safety								
18F-MC-GPI1	NCT No: NCT05412004	Multicenter, randomized, parallel-arm, DB, placebo controlled trial in participants who are unable or unwilling to use PAP therapy	Tirzepatide MTD (10 mg or 15 mg); SC QW Dose escalation to maintenance dose: 2.5, 5, 7.5, 10, and 12.5 mg; each dose for 4 weeks, followed by a maintenance dose of 15 mg or highest MTD by the participant (10 mg or 15 mg) Placebo; SC QW	Primary: Change in AHI from baseline to Week 52	52 weeks	234 randomized	Adult male or female participants, with obesity, diagnosed with moderate to severe OSA with an AHI ≥15, who are unable or unwilling to use PAP therapy	57 sites, 9 countries (Australia, Brazil, China, Czech Republic, Germany, Japan, Mexico, Taiwan, United States)

Trial Identity	NCT no.	Trial Design	Regimen/ Schedule/ Route	Trial Endpoints	Treatment Duration/ Follow Up	No. of Patients Enrolled	Trial Population	No. of Centers and Countries
18F-MC-GPI2	NCT No: NCT05412004	Multicenter, randomized, parallel-arm, DB, placebo controlled trial in participants who are on PAP therapy for at least 3 months at time of screening and plan to continue PAP therapy during the trial	Tirzepatide MTD (10 mg or 15 mg); SC QW Dose escalation to MTD: 2.5, 5, 7.5, 10, and 12.5 mg; each dose for 4 weeks, followed by a maintenance dose of 15 mg or highest MTD tolerated by the participant (10 mg or 15 mg) Placebo; SC QW	Primary: Change in AHI from baseline to Week 52	52 weeks	235 randomized	Adult male or female participants, with obesity, diagnosed moderate-to-severe OSA with an AHI ≥15, and on PAP therapy	58 sites, 9 countries (Australia, Brazil, China, Czech Republic, Germany, Japan, Mexico, Taiwan, United States)

Source: Generated by clinical reviewer.
Abbreviations: DB, double blind; AHI, apnea-hypopnea index; OSA, obstructive sleep apnea; SC, subcutaneous; QW, once weekly; PAP, positive airway pressure

7.2. Review Strategy

The Applicant submitted clinical data from the two SURMOUNT-OSA trials to support the efficacy and safety of tirzepatide for the proposed indication of treatment of adult patients with moderate-to-severe OSA and obesity. The protocol design and trial results are outlined in Sections 8.1.1. The safety data are reviewed in Section 8.2. A detailed review of the clinical pharmacology program for tirzepatide is located in Section 6.

Data from GPI1 and GPI2 provide the primary evidence evaluating the efficacy of tirzepatide for the treatment of adult patients moderate-to-severe OSA and obesity. These data are presented in Section 8.1.2 by FDA biostatistician, Dong-Hyun Ahn, Ph.D., who confirmed the Applicant's efficacy analyses and generated tables and figures for this review.

For the evaluation of safety, FDA medical officer, Shivani Klauer, M.D., analyzed data from GPI1 and GPI2 using JMP, JMP Clinical, and the Office of Computational Science Analysis Toolbox. The safety results presented in 8.2 represent the medical officer reviewer's own analyses.

7.3. Data Sources

Data were submitted by the Applicant to the CDER electronic data room in SAS transport format and included protocols, statistical analysis plans, clinical study reports, correspondence, and data listings. The submitted datasets were of acceptable quality and were adequately documented or became so upon information request. We were able to reproduce the results of all key analyses.

8. Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. SURMOUNT-OSA Trial (Trial 18F-MC-GPIF)

The SURMOUNT-OSA trial (Trial GPIF) was the master protocol that supported two pivotal independent studies, GPI1 and GPI2. Each trial was a multicenter, randomized, parallel-arm, double -blind, placebo-controlled phase 3 trial to evaluate the efficacy and safety of tirzepatide compared to placebo in patients with moderate-to-severe OSA with obesity. The primary efficacy endpoint was assessed at Week 52. The two trials were identical in their trial design with regard to exclusion criteria, duration of the double-blind period, and trial endpoints. The primary difference between the two trials was the inclusion criteria. The inclusion criteria of GPI1 allowed only subjects who were unable or unwilling to use PAP therapy prior to screening, and GPI2 included only subjects who had been on PAP therapy and planned to continue PAP therapy during the trial.

8.1.1.1. Administrative Information

- **Trial Title:** A Master Protocol to Investigate the Efficacy and Safety of Tirzepatide Once Weekly in Participants who Have Obstructive Sleep Apnea and Obesity: A Randomized, Double-Blind, Placebo-Controlled Trial (SURMOUNT-OSA)

– **Trial 1 (Trial 18F-MC-GPI1):** Participants with OSA unable or unwilling to use PAP therapy

  - **Trial Dates:** First subject enrolled: (b) (6); last subject last visit in Double-blind period: (b) (6)

– **Trial 2 (Trial 18F-MC-GPI2):** Participants with OSA on PAP therapy

  - **Trial Dates:** First subject enrolled: (b) (6); last subject last visit in Double-blind period: (b) (6)

- **Trial Sites:** GPI1 was performed in 57 sites in 9 countries and GPI2 was performed in 58 sites in 9 countries.
- **Trial Report Date:** June 21, 2024

8.1.1.2. Objectives

Primary Objective

- To demonstrate that tirzepatide at the MTD (10 mg or 15 mg) SC QW was superior to placebo for decrease in AHI

Key Secondary Objectives

To demonstrate that tirzepatide at the MTD (10 mg or 15 mg) SC QW was superior to placebo for

- Change in patient-reported sleep-related impairment and sleep disturbance
- Percent change in AHI
- Clinically meaningful change in AHI
- Achieving OSA remission or mild non-symptomatic OSA
- Hypoxic burden
- Change in body weight
- Change in inflammatory status
- Change in systolic blood pressure (SBP)

Other Secondary Objectives

To demonstrate that tirzepatide at the MTD (10 mg or 15 mg) SC QW was superior to placebo for:

- Change in excessive daytime sleepiness assessed by ESS
- Changed in patient-reported functional status as assessed by FOSQ (30 items)
- Change in body weight
- Change in lipid parameters
- Change in patient reported outcomes (PROs)
- Insulin
- Change in diastolic blood pressure (DBP)

Exploratory Objectives

To demonstrate that tirzepatide at the MTD (10 mg or 15 mg) SC QW was superior to placebo for

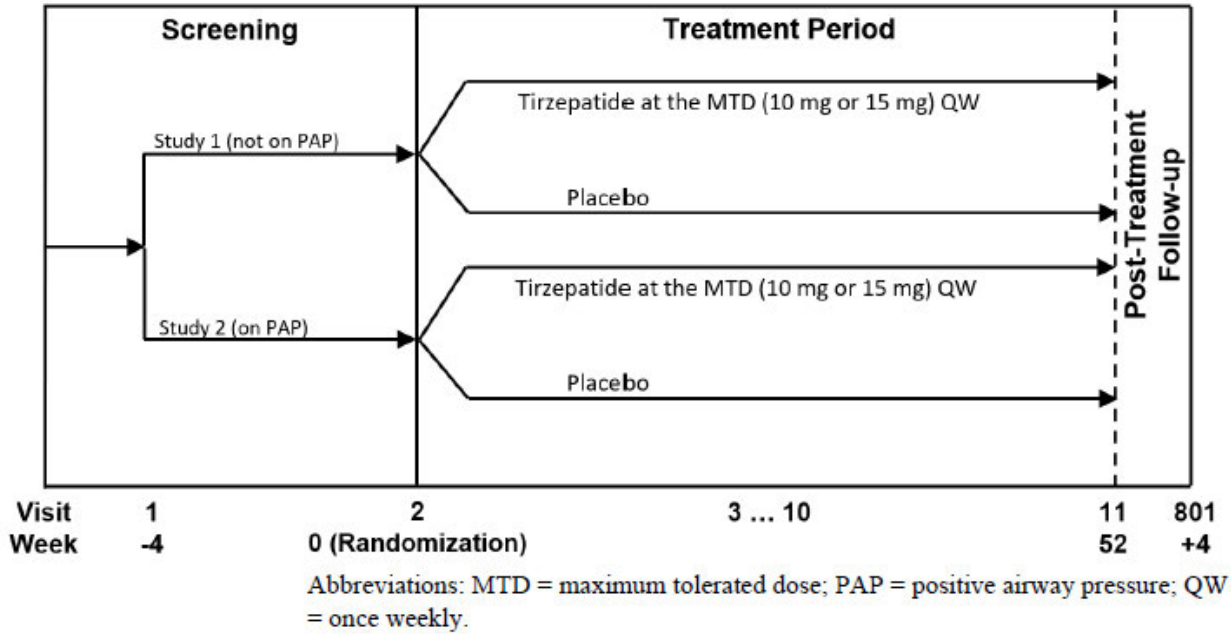
- Change in exploratory PROs
- To evaluate the effect on sleep parameters as measured by WatchPAT300

8.1.1.3. Trial Design

The GPIF trials were multicenter, randomized, parallel-arm, double-blind, placebo-controlled Phase 3 trials designed to evaluate the efficacy and safety of tirzepatide at the MTD (10 mg or

15mg) SC QW versus placebo in participants who have obesity and moderate-to-severe OSA. The basket-type master protocol investigated two patient populations in two pivotal independent studies, GPI1 and GPI2. Each trial consisted of an up to 4 week screening period, a 52-week trial treatment period, and a post-treatment follow-up of 4 weeks. Subjects were assigned to either GPI1 or GPI2 depending on whether they used PAP therapy. After enrollment, subjects were randomized 1:1 to receive either tirzepatide QW or placebo QW (Figure 11).

Figure 11. Trial Design Schematic: Master Protocol 18F-MC-GPIF



Abbreviations: MTD = maximum tolerated dose; PAP = positive airway pressure; QW = once weekly.

Source: GPI1 Trial CSR, Figure GPI1.3.1, p. 46

In both studies, tirzepatide was administered SC QW, with dose-escalation for improved gastrointestinal (GI) tolerability, starting at 2.5 mg weekly and increasing the dose by 2.5 mg every four weeks (to 5, 7.5, 10, 12.5 and 15 mg). The MTD of 10 mg and 15 mg was reached at Week 12 and Week 20, respectively (Table 11).

Table 11. Tirzepatide Dose-Escalation Scheme in Trial GPI1 and Trial GPI2

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

Note: Tirzepatide dose was either 10 mg or 15 mg. If participants did not tolerate 12.5 or 15 mg, then their dose was 10 mg for the remainder of the study. The lowest maintenance dose was tirzepatide 10 mg; participants who did not tolerate at least 10 mg were discontinued from the study drug.

Source: GPIF Clinical Overview, Table 2.5.4.2, p. 21

The 2.5, 7.5, and 12.5 mg doses were only used for four week periods during dose escalation and were not used for maintenance nor for dose reduction as described below.

Does modification was permitted for management of intolerable GI symptoms. Only one cycle of dose de-escalation and re-escalation was permitted during the first 24 weeks of the treatment period. Subjects who did not tolerate at least 10 mg even after one de-escalation and re-escalation attempt were discontinued from the trial intervention but remained in the trial for continued follow up. Subjects who tolerated:

- 10 mg, but did not tolerate 12.5 mg or 15 mg even following 1 de-escalation and re-escalation attempt, were continued on 10 mg as their maintenance dose;
- 12.5 mg, but did not tolerate 15 mg even after 1 de-escalation and re-escalation attempt, were continued on 10 mg as their maintenance dose;
- 15 mg, were continued on 15 mg as their maintenance dose.

Interventions to optimize tolerance included brief temporary interruptions and use of additional medications to manage GI symptoms (e.g., antiemetic or antidiarrheal medications).

Subjects continued concomitant medications that they required during the trial except certain medications that could interfere with assessment of efficacy and safety characteristics of trial treatments (e.g., DPP-4 inhibitors, stimulants, medications that may cause weight loss etc.).

The primary efficacy assessment in the trial was AHI, and AHI measurements were collected via PSG. PSG measurements were collected during single night, overnight clinic stays at baseline, during the screening period, at Week 20, and at the end of the trial at Week 52. For subjects who had been on PAP therapy prior to study enrollment and were continued on PAP therapy through the trial, a 7-day PAP washout period was implemented at both baseline and Week 52 assessments. The complete schedule of activities is located in Section 14.6.1.

8.1.1.4. Trial Population

The trial populations for both GPI1 and GPI2 included male and female subjects aged ≥18 years with a documented diagnosis of moderate-to-severe OSA with an AHI ≥15, as diagnosed by PSG,

and a history of obesity (BMI ≥ 30 kg/m^2) with at least one previously self-reported unsuccessful dietary effort to lose weight.

Subjects were assigned to either GPI1 if they were previously unwilling or unable to use PAP therapy. Subjects were assigned to GPI2 if they had been on PAP therapy for at least three months at the time of screening, and if they planned to continue PAP therapy during the trial. Subjects tolerant of PAP could not discontinue PAP for enrollment. The following inclusion and exclusion criteria were the same for both studies.

Key Inclusion Criteria:

1. Previously diagnosed moderate-to-severe OSA with an AHI ≥ 15, as diagnosed with PSG or home sleep apnea test
2. AHI ≥ 15 on PSG as part of the trial at Visit 1
3. BMI ≥ 30 kg/m^2
4. Have a history of at least 1 self-reported unsuccessful dietary effort to lose body weight

Key exclusion criteria:

1. Type 1 or type 2 diabetes mellitus, history of ketoacidosis, or hyperosmolar state/coma
2. Hemoglobin A1c (HbA1c) level ≥ 6.5% at Visit 1
3. Any previous or planned surgery for sleep apnea or major ear, nose, or throat surgery
4. Active device treatment of OSA other than PAP therapy
5. Reported change in body weight > 5 kg within 3 months prior to Visit 1
6. A prior or planned surgical treatment for obesity
7. Have obesity induced by other endocrinologic disorders or diagnosed monogenic or syndromic forms of obesity
8. At significant risk for suicide
9. Uncontrolled hypertension (SBP ≥ 160 mmHg and/or diastolic blood pressure (DBP) ≥ 100 mmHg) at Visit 1
10. Acute or chronic hepatitis, signs and symptoms of any other liver disease other than nonalcoholic fatty liver disease
11. Require the use of supplemental oxygen

The trial had typical exclusion requirements based on known safety issues of incretins (detailed in Section 8.2):

1. Severe GI disease including gastroparesis
2. History of pancreatitis
3. Elevated calcitonin, or personal or family history of medullary thyroid cancer or multiple endocrine neoplasia type 2 (MEN2, a rare familial cancer syndrome that includes medullary thyroid cancer)

In general, these inclusion and exclusion criteria are appropriate. A small minority of the treatment population of obese adults with OSA in the U.S. is likely excluded from this trial population (for example, because of the renal, psychiatric, liver, and pancreatic criteria).

8.1.1.5. Trial Endpoints

The primary and key secondary endpoints were the same for both GPI1 and GPI2.

Primary Endpoint:

The primary endpoint was the change in AHI from baseline to Week 52.

Key Secondary Endpoints (Controlled for Type 1 Error):

1. Percent change from baseline in AHI at Week 52
2. Percent of subjects with ≥50% AHI reduction from baseline at Week 52
3. Percent of subjects at Week 52 with:
    a. AHI < 5 events/hour or
    b. AHI 5-14 events/hour with ESS ≤ 10
4. Change from baseline in sleep apnea hypoxic burden (SASHB) concentration at Week 52 (% min/hour)
5. Percent change from baseline in body weight at Week 52
6. Change from baseline in high-sensitivity C-reactive protein (hsCRP) concentration at Week 52 (mg/L)
7. Change from baseline in SBP at Week 48
8. Change from baseline to Week 52 in:
    a. PROMIS- SRI
    b. PROMIS-SD

The Applicant specified that PROMIS-related endpoints were subject to submission-wise type 1 error control. They were outside of the multiple testing procedure in each individual trial. See details under the Type I Error Rate Control Strategy in Section 8.1.1.8. The blood pressure assessment was conducted at Week 48 because PAP withdrawal at Week 52 could confound BP assessment.

Safety Endpoints:

Safety and tolerability were evaluated based on adverse events (AEs), vital signs, physical exam, clinical laboratory, and electrocardiogram (ECG). The PK and immunogenicity of tirzepatide were evaluated based on serum tirzepatide concentrations and presence of anti-GIP antibodies and neutralizing antibodies. Refer to Section 6 for details on PK and immunogenicity. Baseline assessment of suicidal ideation and behavior/intervention emergent suicidal ideation and behavior were monitored using the Columbia Suicide-Severity Rating Scale (C-SSRS) and Patient

Health Questionnaire (PHQ-9).

8.1.1.6. Key Efficacy Measurements

Objective Efficacy Assessments:

The pivotal efficacy assessments in the trial relied on PSG assessments, including AHI, blood oxygen saturation parameters, pulse rate, and other sleep parameters. In-lab PSGs were performed during one night, overnight clinic stays. Data from the PSGs were read and scored centrally using the American Academy of Sleep Medicine (AASM) 1B scoring criteria.

An apnea required both of the following criteria to be met: (1) a drop in the peak breathing excursion by ≥ 90% of pre-event baseline is detected using a sensor, and (2) the duration of the ≥90% drop in the sensor signal is ≥10 seconds. A hypopnea required both of the following criteria to be met: (1) peak respiratory excursion drops by ≥30% of pre-event baseline, detected using a sensor, and (2) duration of the ≥30% drop in signal excursion is ≥10 seconds. In addition, a ≥4% oxygen desaturation from the pre-event baseline was used as an additional criterion to identify hypopneas.

The AHI was defined as the sum of the total number of apneas and hypopneas divided by the total sleep time (hours). The hypoxic burden was defined as the total area under the respiratory event-related desaturation curve for each individually identified apnea or hypopnea. The SASHB was then obtained by adding these individual desaturation areas and dividing the total area by the sleep duration, with the units of hypoxic burden being (%min)/h. For example, a hypoxic burden of 20 (%min)/h is equivalent to 20 min of 1% desaturation per hour or 5 min of 4% desaturation per hour.

Patient-Reported Outcomes (PROs):

The PROMIS-SRI is a PRO measure to assess self-reported perceptions of alertness, sleepiness, and tiredness during usual waking hours, as well as the perceived functional impairments associated with sleep problems or impaired alertness. The PROMIS-SRI consists of 8 items each rated on a 5-point verbal rating scale (VRS) ranging from “not at all” to “very much”, with a recall period of “in the past 7 days” (Figure 12), referred to as the PROMIS-SF-SRI 8a (Northwestern University 2016). Response pattern scoring was used to calculate T-scores with a mean of 50 and a standard deviation (SD) of 10. A higher PROMIS-SF-SRI 8a T-score indicates greater sleep related impairment. The PROMIS-SRI was completed electronically at screening (-4 weeks from randomization) and at Weeks 4, 12, 20, and 52 or early discontinuation (ED). Trial GPI2 subjects were required to withdraw from PAP therapy for 7 days prior to PRO completion at baseline and Weeks 20 and 52 to minimize the possible confounding effect of PAP on PRO assessments.

Figure 12. PROMIS-Sleep Related Impairment – Short Form

Sleep Related Impairment – Short Form 8a

Please respond to each item by marking one box per row.

	In the past 7 days...	Not at all	A little bit	Somewhat	Quite a bit	Very much
Sleep10	I had a hard time getting things done because I was sleepy	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Sleep119	I felt alert when I woke up	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Sleep18	I felt tired	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Sleep25	I had problems during the day because of poor sleep	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Sleep27	I had a hard time concentrating because of poor sleep	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Sleep30	I felt irritable because of poor sleep.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Sleep6	I was sleepy during the daytime.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Sleep7	I had trouble staying awake during the day	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Source: Attachment 2, Module 5.3.5.3 PRO-Dossier

The PROMIS-SD is a PRO measure to assess self-reported perceptions of sleep quality, sleep depth, and restoration associated with sleep, including perceived difficulties and concerns with getting to sleep or staying asleep, as well as subject's perceptions of sleep adequacy and satisfaction. The PROMIS-SD consists of 8 items (PROMIS-SF-SD 8b) each rated on a 5-point VRS ranging from "not at all" to "very much", "never" to "always", and "very poor" to "very good", with a recall period of "in the past 7 days" (Figure 13). Response pattern scoring was used to calculate T-scores with a mean of 50 and a standard SD of 10. A higher PROMIS-SF-SD 8b T-score indicates greater sleep disturbance. The PROMIS-SD was also completed electronically at screening and at Weeks 4, 12, 20, and 52 or ED with the same PAP interruption schedule for subjects in GPI2.

Figure 13. PROMIS-Sleep Disturbance – Short Form

Sleep Disturbance – Short Form 8b

Please respond to each item by marking one box per row.

	In the past 7 days...	**Not at all**	**A little bit**	**Somewhat**	**Quite a bit**	**Very much**
Sleep108	My sleep was restless.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Sleep115	I was satisfied with my sleep	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Sleep116	My sleep was refreshing	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Sleep44	I had difficulty falling asleep	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
	In the past 7 days…	**Never**	**Rarely**	**Sometimes**	**Often**	**Always**
Sleep87	I had trouble staying asleep.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Sleep90	I had trouble sleeping.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Sleep110	I got enough sleep	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
	In the past 7 days…	**Very poor**	**Poor**	**Fair**	**Good**	**Very good**
Sleep109	My sleep quality was	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

Source: Module 5.3.5.3 PRO-Dossier

8.1.1.7. Exploratory Efficacy Measurements

The Epworth Sleepiness Scale (ESS) is a self-administered 8-item questionnaire to assess daytime sleepiness in a variety of sleep disorders. This tool is used frequently in clinical practice. The ESS was analyzed as an exploratory endpoint and also evaluated as part of the multiplicity-controlled composite endpoint of OSA remission/achievement of mild non-symptomatic disease. The items ask subjects' usual chances of dozing in 8 different daytime situations with a recall period of "in recent times" based on a 4-point Likert scale ranging from 0 (would never doze) to 3 (high chance of dozing). The ESS total score is the sum of the 8-item

scores and ranges from 0 to 24, with higher scores indicating greater daytime sleepiness (Johns 1991).

The Patient Global Impression of Status - OSA (PGIS-OSA) scales were included to assess patient-perceived overall severity of OSA symptoms. Specifically, the PGIS-OSA Fatigue is a single item assessing subject's overall level of fatigue related to OSA over the past 7 days based on a 4-point VRS ranging from "No fatigue" to "Severe fatigue". The PGIS-OSA Sleepiness is a single item assessing subject's overall level of sleepiness during waking hours related to OSA over the past 7 days based on a 4-point VRS ranging from "Not at all sleepy" to "Very sleepy". Item 8 of the PROMIS-SD is used as the PGIS Sleep Quality which asks subjects to assess their sleep quality in the past 7 days using a 5-point VRS ranging from "Very poor" to "Very good". The PGIS-OSA Snoring consists of two items. The first item is a self-rated assessment of overall severity of subject's snoring related to OSA over the past 7 days, with respect to how much their snoring has affected their sleep based on a 4-point VRS ranging from "Not at all affected" to "Very affected". The second item asks subjects if they have ever been told by someone else that they snore in their sleep using a 3-point VRS ("Not at all" to "All the time").

8.1.1.8. Statistical Analysis Plan

This statistical analysis plan (SAP) is based on amendment (c) of the protocol for I8F-MC-GPIF (GPIF) approved on June 2, 2023. This SAP was approved prior to the first unblinding of the treatment assignments for the primary outcome lock.

Analysis Populations

- Randomized: All participants who were randomly assigned a trial treatment (double-blind).
- Modified intent-to-treat (mITT): All randomized participants who were exposed to at least 1 dose of trial intervention.
- Safety analysis set (SS): Data obtained during treatment and safety follow-up period of set of participants from the mITT population, regardless of adherence to study intervention.

Estimands

The applicant specified that the primary and each key secondary efficacy analysis were guided by the "treatment regimen" estimand and the "efficacy" estimand to support global regulatory submissions and publications (see details in Appendix 14.5.3). A focus of this review was the efficacy results based on the "treatment regimen" estimand.

The "treatment regimen" estimand was used as the primary estimand to support a marketing application for the FDA. The clinical question of interest for the treatment regimen estimand was the treatment difference between tirzepatide and placebo after 52 weeks of intervention in treated subjects with obesity and OSA, regardless of intervention discontinuation for any reason.

The "treatment regimen" estimand attributes are shown below. The analysis data set to be used for this estimand was data obtained during the treatment period of the set of participants from the mITT population, regardless of adherence to study intervention.

- Population: Adult subjects with obesity and OSA who received at least 1 dose of study treatment.
- Treatment condition: On- or off-randomized-treatment.
  - Tirzepatide at the MTD (10 mg or 15 mg) QW
  - Placebo
- Endpoints: The primary and key secondary endpoints
- Population level summary: The difference in mean change from baseline to 52 weeks was used for continuous endpoints, and the difference in proportion (absolute or relative, as appropriate) was used for dichotomous endpoints.
- Intercurrent events (handling strategy):
  - Treatment discontinuation (treatment policy strategy)
  - Initiation of PAP therapy in GPI1 (treatment policy strategy)

Sample Size Calculation

Approximately 206 subjects per trial were to be randomly assigned to either tirzepatide or placebo in a 1:1 ratio (approximately 103 subjects per treatment arm), and the statistical power was to be evaluated for the primary efficacy endpoint and key secondary combination PRO endpoint at a 2-sided significance level of 0.05. This sample size was to provide the following:

- at least 90% power to demonstrate superiority of tirzepatide at the MTD (10 mg or 15 mg) to placebo for the mean percent change from baseline in AHI, assuming 50% improvement, with a common standard deviation of 50% and a dropout rate of 25%, and
- at least 90% power to demonstrate superiority of tirzepatide at the MTD (10 mg or 15 mg) to placebo for the hierarchical combination PRO endpoint using the Finkelstein-Schoenfeld method (Finkelstein and Schoenfeld 1999), with a dropout rate of 25%.

An upper limit of approximately 70% enrollment of male subjects was used to ensure a sufficiently large sample of female participants.

The Applicant had initially proposed the percent change from baseline in AHI at Week 52 as the primary endpoint and later changed the primary endpoint to the absolute change from baseline per the Division's recommendation. Despite this change, the trial sample size and power calculations were not updated based on the final primary endpoint of the absolute change from baseline in AHI at Week 52. The studies were not underpowered with respect to the current primary endpoint.

Primary Efficacy Analysis

For each trial, the primary objective was to demonstrate that tirzepatide at the MTD (10 mg or 15 mg) is superior to placebo in treating subjects with OSA with respect to the change in AHI. The treatment effect was defined as the difference between the estimates of the mean change from baseline at 52 weeks for tirzepatide at the MTD (10 mg or 15 mg) and placebo. For AHI analyses, baseline was defined as the last nonmissing measurement prior to the first dose.

Unless otherwise noted, all tests of treatment effects were conducted at a 2-sided alpha level of 0.05, and the confidence interval was calculated at a 2-sided 95% level.

For the primary analysis guided by the "treatment regimen" estimand, the analysis was conducted using the data on- and off- randomized treatment. Missing values were imputed based on the strategy to handle intercurrent events described in Table 12. After imputation, the primary efficacy comparison was based on the contrast between tirzepatide at the MTD (10 mg or 15 mg) and placebo from the ANCOVA analysis of mean change from baseline to Week 52 in AHI. The ANCOVA model included treatment and strata (geographic region [United Sates of America/outside of the United States of America (US/OUS)] and gender) as fixed effects and baseline AHI as a fixed covariate. Statistical inference over multiple imputed data set was guided by Rubin (1987).

Table 12: Imputation Approaches to Handle Missing/Invalid Data for Treatment Regimen Estimand

Missing/Invalid Data	Strategy to Handle Missing/Invalid Data	Assumptions for Missing Values	Methods to Handle Missing Values
Data missing at baseline, invalid data collected or missing data after treatment DC due to the COVID-19 pandemic (after other reasons for missing data are ruled out), technical issues (that is, sensor error on PSG) leading to invalid measurements ascertained while on treatment, missing data from participants completing the treatment period on the study drug intervention, or missing data after study DC due to inadvertent enrollment.	Hypothetical	MAR	Multiple imputation assuming MAR
Missing data due to any other reason (for example, study DC due to any reason other than COVID-19 or inadvertent enrollment).	Treatment policy	MNAR	Retrieved dropout imputation[a]. If there are not enough retrieved dropouts to provide a reliable imputation model, placebo-based multiple imputation will be used.

Abbreviations: COVID-19 = coronavirus disease-2019; DC = discontinuation; MAR = missing at random; MNAR = missing not at random; PSG = polysomnography; SBP = systolic blood pressure.

[a] Retrieved dropout imputation utilizes observed data from participants in the same treatment group who had outcome measures at Week 52 (or Week 48 for SBP) after early DC of study drug to impute the missing value.

Source: I8F-MC-GPIF Statistical Analysis Plan Version 4 Table GPIF.4.2., p.30

A two-way tipping point analysis was to be utilized for the primary endpoint. This analysis was to begin with the primary analysis aligned to the treatment regimen estimand and then adding positive and negative penalties simultaneously to both the tirzepatide MTD arm and the placebo arm, considering when results tip from superiority to inconclusive, and then considering the clinical plausibility of such scenarios.

The following subgroups were to be considered if there was an adequate number of participants in each treatment by subgroup (for example, 10%):

- Age (<50 years, ≥50 years)
- Baseline OSA severity (not severe, severe)
- Race
- Ethnicity
- Region of enrollment (US/OUS)
- Gender (male or female)

- Baseline BMI (<35, ≥35 and <40, ≥40 kg/m^2), and
- Baseline ESS (ESS ≤10, ESS >10).

Key Secondary Efficacy Analyses

Analysis of percent change in AHI, percent change from baseline to Week 52 in body weight, change from baseline to Week 52 in log of high-sensitivity C-reactive protein, change from baseline to Week 48 in SBP, change from baseline to Week 52 in PROMIS SRI, change from baseline to Week 52 in PROMIS SD, and change from baseline to Week 52 in log of hypoxic burden were conducted in a manner similar to the primary efficacy analyses using an ANCOVA model with treatment, strata (geographic region [US/OUS], AHI stratum [not severe (AHI <30), severe (AHI ≥30)], and gender), and baseline of the corresponding variable as a covariate for the treatment regimen estimand. If the hypoxic burden was reported to be 0, log (0.01) was to be used in place of the log of hypoxic burden.

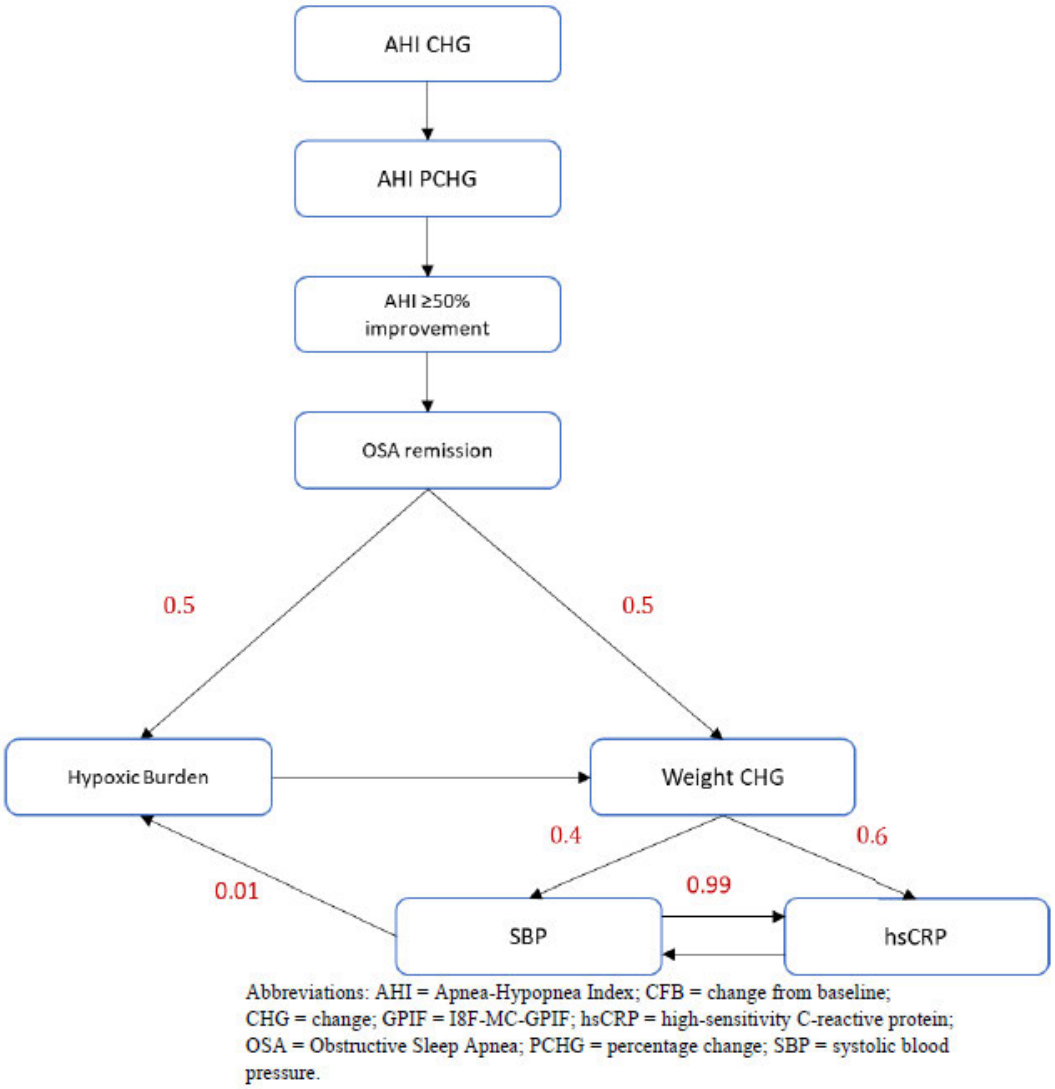
Comparisons at the 52-week visit between the treatments relative to the proportion of subjects achieving ≥50% AHI reduction and AHI<5 or (AHI 5 through 14 and ESS ≤10) were conducted using logistic regression analysis including the following terms as a covariate: treatment, geographic region (US/OUS), baseline AHI, and gender. Unconditional risk differences were also to be provided for these endpoints using logistic regression (Ye et al. 2023).

The analysis method utilizing data from both trials for change from baseline to Week 52 in PROMIS-SRI and PROMIS-SD is described in Appendix 14.5.1.

Type I Error Rate Control Strategy

All primary and key secondary hypotheses were tested with the overall family-wise Type 1 error rate at a 2-sided alpha level of 0.05 through the multiplicity control approach based on the graphical multiple testing procedure. The primary endpoint hypothesis was tested at a 2-sided alpha level of 0.05 for statistical significance. If the primary efficacy endpoint was significant, the alpha of 0.05 was to be propagated to the key secondary efficacy endpoints. The detailed graphical testing scheme is outlined in Figure 14.

Figure 14. Graphical Testing Scheme for Study GPIF



Abbreviations: AHI = Apnea-Hypopnea Index; CFB = change from baseline; CHG = change; GPIF = I8F-MC-GPIF; hsCRP = high-sensitivity C-reactive protein; OSA = Obstructive Sleep Apnea; PCHG = percentage change; SBP = systolic blood pressure.

Source: I8F-MC-GPIF Statistical Analysis Plan Version 4 Table GPIF.2.1., p.24

The Applicant planned that the analysis for change in PROMIS-SRI and PROMIS-SD was specified in the integrated efficacy analysis plan (Appendix 14.5.1) to be tested subject to the submission wise error rate control strategy by conducting a pooled analysis across the trials. During the IND review, the review team indicated that results based on pooled data may not be meaningful from a clinical perspective because of the difference in use of PAP between the study populations and its potential impact on these PROs. In addition, pooling of a key efficacy endpoint is not consistent with independent substantiation of efficacy from more than one investigation. A focus of the review is on PROMIS endpoints in the individual trials.

8.1.1.9. Compliance with Good Clinical Practice

A statement of compliance with Good Clinical Practice is in the Clinical Study Report.

8.1.1.10. Financial Disclosure

The Applicant has adequately disclosed that there were no financial interests with any of the clinical investigators as recommended in the guidance for industry Financial Disclosure (February 2013) by Clinical Investigators (see Appendix 14.2)

8.1.2. Trial Results

8.1.2.1. Protocol Amendments

The original clinical trial protocol for the master protocol GPIF was approved January 27, 2022. Protocols for GPI1 and GPI2 were approved on January 28, 2022. The first amendments were on February 10, 2022. The terminology used in the protocols for GPIF, GPI1, and GPI2 were corrected and selected clarifications were added. On September 30, 2022 the GPIF protocol was amended to include the addition of the key secondary objective "change in AHI". The endpoint for key secondary objective "change in SBP" and other secondary objective "change in DBP" were updated to Week 48 from Week 52. Changes were made to the schedule of activities to reflect synchronization of timing of C-SSRS to PHQ-9. The protocol for GPI1 was updated with additional instructions for the use of PAP therapy. On June 2, 2023 the protocol for GPIF was amended to include changes made to the primary and key secondary endpoints for change in AHI and clarification around the timing of PHQ-9 assessment. Revisions were made to clarify the role of central reading of PSG scores.

8.1.2.2. Protocol Violations/Deviations

In GPI1 a total of 107 subjects (46%) had at least one important protocol deviation. The number of protocol deviations were balanced between the tirzepatide group (51 subjects, 45%) and the placebo group (56 subjects, 47%). The most frequently reported category of protocol deviations were related to the investigational product (19%), compliance with trial procedures (18%), and informed consent (16%). A total of 22 subjects (9%) had a protocol deviation related to eligibility criteria.

In GPI2 a total of 116 participants (50%) had at least one important protocol deviation. The number of protocol deviations were balanced between the tirzepatide group (56 subjects, 47%) and the placebo group (60 subjects, 52%). The most frequently reported category of protocol deviations were related to compliance with trial procedures (25%), informed consent (14%), and investigational product (14%). A total of 15 subjects (6%) had a protocol deviation related to eligibility criteria.

Many of the protocol deviations related to the investigational product or compliance with trial procedures were a result of user errors with the electronic Clinical Outcome Assessment (eCOA) device associated with missing, partial, or duplicate completion of PRO assessments. Additionally, many subjects failed to reliably document dosing with the trial investigative product using an eCOA. Since analyses aligned to efficacy estimand and treatment-regimen

estimand did not rely on compliance data from eCOA, and safety analysis utilized all the available data, the ability to draw conclusions and interpret trial results was not affected by the protocol deviations.

8.1.2.3. Review of Efficacy

8.1.2.3.1. *Subject Disposition*

Subject disposition for Trial GPI1 is summarized in Table 13. Among the 234 randomized subjects (114 in the tirzepatide arm and 120 in the placebo arm), the overall trial discontinuation rate was 20%. The discontinuation rate was higher in the placebo arm (28% vs 11%). The primary reasons for discontinuation were “withdrawal by subject” in 23 subjects, with 4 (4%) in the tirzepatide arm and 19 (16%) in the placebo arm, and “assigned treatment by mistake” in 9 subjects, with 4 (4%) in the tirzepatide arm and 5 (4%) in the placebo arm.

The overall treatment discontinuation rate was 23%, and the discontinuation rate was higher in the placebo arm (30% vs 15%). The primary reasons for discontinuation were “withdrawal by subject” in 23 subjects, with 2 (2%) in the tirzepatide arm and 21 (18%) in the placebo arm, and “assigned treatment by mistake” in 15 subjects, with 5 (4%) in the tirzepatide arm and 10 (8%) in the placebo arm.

Table 13: Subject Disposition (Randomized Population), Trial GPI1

	TZP MTD (N=114)	Placebo (N=120)	Total (N=234)
Trial disposition, n(%)			
Completed	101 (88.6)	86 (71.7)	187 (79.9)
Discontinued	13 (11.4)	34 (28.3)	47 (20.1)
Adverse event	0	2 (1.7)	2 (<1)
Assigned treatment by mistake	4 (3.5)	5 (4.2)	9 (3.8)
Lost to follow-up	3 (2.6)	0	3 (1.3)
Other	1 (<1)	6 (5.0)	7 (3.0)
Physician decision	0	1 (<1)	1 (<1)
Pregnancy	0	1 (<1)	1 (<1)
Protocol deviation	1 (<1)	0	1 (<1)
Withdrawal by subject	4 (3.5)	19 (15.8)	23 (9.8)
Treatment disposition, n(%)			
Completed	97 (85.1)	84 (70.0)	181 (77.4)
Discontinued	17 (14.9)	36 (30.0)	53 (22.6)
Adverse event	5 (4.4)	2 (1.7)	7 (3.0)
Assigned treatment by mistake	5 (4.4)	10 (8.3)	15 (6.4)
Lack of efficacy	1 (<1)	0	1 (<1)
Lost to follow-up	3 (2.6)	0	3 (1.3)
Non-compliance with drug	0	1 (<1)	1 (<1)
Physician decision	0	1 (<1)	1 (<1)
Pregnancy	0	1 (<1)	1 (<1)
Protocol deviation	1 (<1)	0	1 (<1)
Withdrawal by subject	2 (1.8)	21 (17.5)	23 (9.8)

Abbreviations: N = number of subjects in analysis populations; n = number of subjects within category; MTD = maximum tolerated dose; TZP = tirzepatide.
Source: Full Clinical Study Report (pages 279-280); results reproduced by statistical analyst using adsl.xpt and adds.xpt

Subject disposition for GPI2 is summarized in Table 14. Among the 235 randomized participants (120 in the tirzepatide arm and 115 in the placebo arm), the overall trial discontinuation rate was 14% and the discontinuation rate was higher in the placebo arm (23% vs 6%). The primary reasons for discontinuation were “withdrawal by subject” in 18 subjects, with 4 (3%) in the tirzepatide arm and 14 (12%) in the placebo arm, and “adverse event” in 6 subjects, with 1 (<1%) in the tirzepatide arm and 5 (4%) in the placebo arm.

The overall treatment discontinuation rate was 18%, and the discontinuation rate was higher in the placebo arm (26% vs 10%). The primary reasons for discontinuation were “withdrawal by subject” in 19 subjects, with 4 (3%) in the tirzepatide arm and 15 (13%) in the placebo arm, and “adverse event” in 12 subjects, with 4 (3%) in the tirzepatide arm and 8 (7%) in the placebo arm. The relatively high discontinuation rates were clarified via an Information Requestion to the Applicant and are likely driven by perceived lack of efficacy. These rates are similar to those observed in the CWM program.

Table 14: Subject Disposition (Randomized Population), Trial GPI2

	TZP MTD (N=120)	Placebo (N=115)	Total (N=235)
Trial Disposition			
Completed	113 (94.2)	89 (77.4)	202 (86.0)
Discontinued	7 (5.8)	26 (22.6)	33 (14.0)
Adverse Event	1 (<1)	5 (4.3)	6 (2.6)
Assigned Treatment By Mistake	0	3 (2.6)	3 (1.3)
Other	2 (1.7)	3 (2.6)	5 (2.1)
Screen Failure	0	1 (<1)	1 (<1)
Withdrawal By Subject	4 (3.3)	14 (12.2)	18 (7.7)
Treatment Disposition			
Completed	108 (90.0)	85 (73.9)	193 (82.1)
Discontinued	12 (10.0)	30 (26.1)	42 (17.9)
Adverse Event	4 (3.3)	8 (7.0)	12 (5.1)
Assigned Treatment By Mistake	2 (1.7)	4 (3.5)	6 (2.6)
Non-Compliance With Trial Drug	0	1 (<1)	1 (<1)
Other	1 (<1)	1 (<1)	2 (<1)
Physician Decision	1 (<1)	0	1 (<1)
Screen Failure/Not Treated	0	1 (<1)	1 (<1)
Withdrawal By Subject	4 (3.3)	15 (13.0)	19 (8.1)

Abbreviations: MTD = maximum tolerated dose; N = number of subjects in analysis populations; n = number of subjects within category; TZP = tirzepatide.
Note: One subject was inadvertently randomized and later deemed to be screen failed. This patient did not receive any treatment and is marked as discontinued treatment due to screen failure/not treated.
Source: Full Clinical Study Report (pages 292-293); results reproduced by statistical reviewer using adsl.xpt and adds.xpt

8.1.2.3.2. *Demographics and Other Baseline Characteristics*

Demographics and other baseline characteristics are summarized in Table 15**.** The population enrolled had a higher proportion of males(70%) and the majority were White (69%). The mean age was 50 years. This trial was conducted in nine countries, among which U.S. sites enrolled 149 (32%) of the randomized population. These demographics generally reflect the overall global OSA population.

Table 15. Demographics (Randomized Population), Trial GPI1 and GPI2

	GPI1 (N=234)		GPI2 (N=235)		GPI1 and GPI2
Characteristic	**TZP MTD[a] (N=114) n (%)**	**Placebo (N=120) n (%)**	**TZP MTD[a] (N=120) n (%)**	**Placebo (N=115) n (%)**	**Total (N = 469) n (%)**
Age					
Mean (SD)	47.3 (11)	48.4 (12)	50.8 (11)	52.7 (11)	49.8 (11.39)
Median (Min, Max)	48.0 (20, 72)	49.0 (21, 76)	51.0 (26, 75)	54.0 (27, 79)	50.0 (20, 79)
Age Category					
<50	63 (55)	62 (52)	54 (45)	45 (39)	224 (48)
≥50	51 (45)	58 (48)	66 (55)	70 (61)	245 (52)
Sex					
F	36 (32)	41 (34)	33 (28)	32 (28)	142 (30)
M	78 (68)	79 (66)	87 (73)	83 (72)	327 (70)
Country/Region					
Australia	1 (1)	5 (4)	10 (8)	9 (8)	25 (5)
Brazil	24 (21)	25 (21)	18 (15)	17 (15)	84 (18)
China	14 (12)	14 (12)	4 (3)	5 (4)	37 (8)
Czech Republic	5 (4)	6 (5)	6 (5)	6 (5)	23 (5)
Germany	7 (6)	7 (6)	16 (13)	16 (14)	46 (10)
Japan	3 (3)	4 (3)	7 (6)	6 (5)	20 (4)
Mexico	20 (18)	19 (16)	14 (12)	16 (14)	69 (15)
Taiwan	5 (4)	4 (3)	4 (3)	3 (3)	16 (3)
United States	35 (31)	36 (30)	41 (34)	37 (32)	149 (32)
Race					
Missing	0	0	0	1 (1)	37 (8)
American Indian or Alaska Native	9 (8)	9 (8)	10 (8)	9 (8)	80 (17)
Asian	23 (20)	24 (20)	17 (14)	16 (14)	24 (5)
Black or African American	6 (5)	7 (6)	8 (7)	3 (3)	1 (0)
Multiple	2 (2)	0	0	0	2 (0)
White	74 (65)	80 (67)	85 (71)	86 (75)	325 (69)
Ethnicity					
Hispanic or Latino	51 (45)	47 (39)	38 (32)	38 (33)	174 (37)
Not Hispanic or Latino	63 (55)	69 (58)	82 (68)	76 (66)	290 (62)
Not reported	0	4 (3.3)	0	1 (1)	5 (1)

Source: OCS Analysis Studio, Custom Table Tool.
[a]TZP MTD is tirzepatide 10 or 15 mg once weekly
Abbreviations: MTD, maximum tolerated dose; SD, standard deviation

Baseline disease characteristics were generally well balanced between the treatment arms for each trial and are shown below in Table 16.

Table 16: Baseline Characteristics (Randomized Population), Trial GPI1 and GPI2

	GPI1 (N=234)		GPI2 (N=235)		GPI1 and GPI2
Characteristic	**TZP MTD[a] (N=114) n (%)**	**Placebo (N=120) n (%)**	**TZP MTD[a] (N=120) n (%)**	**Placebo (N=115) n (%)**	**Total (N = 469) n (%)**
AHI – events/h					
Mean (SD)	52.9 (31)	50.1 (31)	46.1 (22)	53.1 (30)	50.5 (28.88)
Median (Min, Max)	49.8 (9, 127)	44.0 (3, 147)	43.5 (15, 96)	43.4 (7, 121)	45.0 (3.2, 146.9)
ESS Total					
Mean (SD)	10.3 (5)	10.8 (5)	10.8 (5)	9.5 (4)	10.4 (4.89)
Median (Min, Max)	9.5 (0, 22)	10.0 (2, 24)	11.0 (1, 22)	9.0 (0, 19)	10.0 (0, 24)
OSA Severity					
Missing	0	1 (1)	1 (1)	1 (1)	5 (1)
Mild	1 (1)	2 (2)	0	2 (2)	3 (1)
Moderate	39 (34)	43 (36)	35 (29)	37 (32)	154 (33)
Severe	74 (65)	73 (61)	84 (70)	75 (65)	306 (65)
No Apnea	0	1 (1)	0	0	1 (0)
Weight (kg)					
Mean (SD)	116.7 (25)	112.8 (23)	115.8 (21)	115.1 (23)	115.1 (22.84)
Median (Min, Max)	110.1 (69, 186)	110.2 (74, 191)	112.4 (77, 174)	110.5 (66, 168)	110.5 (65.5, 191)
Height (cm)					
Mean (SD)	171.2 (9)	170.8 (10)	173.0 (10)	172.1 (10)	171.8 (9.72)
Median (Min, Max)	171.0 (144, 197)	171.0 (151, 195)	173.1 (145, 191)	172.9 (147, 195)	172.0 (144, 197)
BMI (kg/m^2)					
Mean (SD)	39.7 (7)	38.6 (7)	38.6 (6)	38.7 (6)	38.9 (7)
Median (Min, Max)	37.6 (28, 60)	36.5 (29, 67)	37.3 (28, 61)	37.8 (30, 61)	37.2 (28, 67)
BMI Categories (kg/m^2)					
<35	33 (29)	44 (37)	33 (28)	33 (29)	143 (30)
≥35 and <40	39 (34)	35 (29)	47 (39)	41 (36)	162 (35)
≥40	42 (37)	41 (34)	39 (33)	40 (35)	162 (35)
Missing	0	0	1 (1)	1 (1)	2 (0)
Waist Circumference (cm)					
Mean (SD)	122.6 (17)	119.8 (15)	120.7 (13)	121.0 (14)	121.0 (14.63)
Median (Min, Max)	120.0 (91, 183)	118.0 (90, 162)	119.5 (97, 166)	122.0 (84, 149)	120.0 (84, 183)

Characteristic	GPI1 (N=234)		GPI2 (N=235)		GPI1 and GPI2
	TZP MTD[a] (N=114) n (%)	Placebo (N=120) n (%)	TZP MTD[a] (N=120) n (%)	Placebo (N=115) n (%)	Total (N = 469) n (%)
Neck Circumference (cm)					
Mean (SD)	44.4 (5)	43.4 (4)	44.9 (5)	44.7 (5)	44.3 (4.65)
Median (Min, Max)	44.0 (34, 56)	43.6 (33, 53)	45.0 (32, 64)	45.0 (27, 55)	44.3 (27, 63.5)
Prediabetes					
N	40 (35)	42 (35)	51 (43)	51 (44)	184 (39)
Y	74 (65)	78 (65)	69 (58)	64 (56)	285 (61)
Dyslipidemia					
N	23 (20)	22 (18)	20 (17)	18 (16)	83 (18)
Y	91 (80)	98 (82)	100 (83)	97 (84)	386 (82)
HbA1C (%)					
Mean (SD)	5.7 (0)	5.6 (0)	5.6 (0)	5.6 (0)	5.6 (0.38)
Median (Min, Max)	5.7 (5, 7)	5.6 (5, 7)	5.5 (5, 7)	5.6 (4, 7)	5.6 (4, 6.7)
HbA1C Categories (%)					
<6.5%	113 (99)	119 (99)	117 (98)	108 (94)	457 (97)
≥6.5%	1 (1)	1 (1)	2 (2)	6 (5)	10 (2)
Missing	0	0	1 (1)	1 (1)	2 (0)
Hypertension					
N	30 (26)	27 (23)	29 (24)	24 (21)	110 (23)
Y	84 (74)	93 (78)	91 (76)	91 (79)	359 (77)
PROMIS-SD t-score					
Mean (SD)	53.8 (6)	53.5 (7)	56.0 (8)	55.7 (8)	55.0 (7.45)
Median (Min, Max)	54.3 (36, 69)	54.3 (29, 69)	55.3 (38, 77)	56.3 (40, 77)	55.0 (29, 76.5)
PROMIS-SRI t-score					
Mean (SD)	53.2 (7)	54.3 (9)	55.3 (8)	55.0 (9)	54.7 (8.87)
Median (Min, Max)	52.9 (30, 71)	55.1 (30, 71)	56.1 (39, 77)	55.1 (35, 77)	55.0 (30, 77.5)
Total Hypoxic Burden (% min/hour)					
Mean (SD)	221.0 (203)	196.4 (174)	173.7 (141)	213.1 (203)	200. 7 (181.9)
Median (Min, Max)	135.7 (30, 977)	131.4 (12, 936)	128.1 (38, 666)	118.1 (19, 929)	129.4 (12, 977)

Source: OCS Analysis Studio, Custom Table Tool.
[a]TZP MTD is tirzepatide 10 or 15 mg once weekly
Abbreviations: AHI, apnea-hypopnea index, BMI, body-mass index; ESS, Epworth Sleepiness Score; OSA, obstructive sleep apnea; SD, standard deviation

All subjects had moderate or severe OSA at baseline as defined by the inclusion criteria for the master protocol, except for 9 subjects (2%) who had no apnea, mild apnea, or their OSA severity was not reported. These subjects were "randomized in error" and discontinued from the trial; however, they were included in all safety analyses. Because the inclusion of these subjects did not have an impact on trial results or interpretation, they were not considered important protocol deviations. Two subjects in GPI2 were randomized but did not receive study drug and were withdrawn from the trial.

The GPIF trials were designed to enroll OSA subjects with either moderate or severe OSA. However, on average, across both GPI1 and GPI2, subjects had a mean baseline AHI of 50 events/hour (severe), and the majority of subjects (306, 65%) had severe disease as categorized by AHI. The average hypoxic burden was 200 % minutes/hour, which corresponds to 50 minutes of 4% desaturations every hour. These parameters describe a population with objectively severe disease and high physiologic burden at baseline. The minimum AHI is listed as 3, which reflects a total of four subjects who had an AHI <15 at baseline and did not meet the inclusion criteria for the trial.

The average BMI across both trials was 39 kg/m^2 and 35% of subjects had a BMI > 40 kg/m^2. Most patients had prediabetes (61%), dyslipidemia (82%) and hypertension (77%). Subjects were excluded from the trial if they had an HbA1c ≥6.5% at baseline. A total of 10 subjects (2%) had a HbA1c ≥6.5%; as the inclusion of these subjects did not have an impact on trial results or interpretation, they were not considered important protocol deviations.

The average ESS across both trials was 10.4, which corresponds to a normal or mild level of excessive daytime sleepiness (EDS). Similarly, the average PROMIS-SRI T-score and PROMIS-SD T-score were 55, which reflect that these subjects had a normal or mild level of sleep impairment or sleep disturbance. The trial populations were not enriched to capture subjects who had symptoms of EDS, sleep impairment, or sleep disturbance at baseline, but rather enriched for heavier BMI and worse PSG parameters (e.g., AHI). Despite the severe baseline obstructive impairments, most subjects were relatively asymptomatic as measured by the PROs. Possible reasons for the discrepancy between the objective and subjective impairments and the impact of that discrepancy on the PRO efficacy endpoints are discussed in detail in Section 8.1.3.

8.1.2.3.3. *Primary Endpoint*

Efficacy Results – Primary Endpoint

The primary and key secondary efficacy endpoint analyses were conducted using the mITT population. For the primary analysis, the analysis data set used was the data on- and off-randomized treatment targeting the "treatment regimen" estimand.

Table 17 summarizes the primary endpoint results. In both trials, tirzepatide MTD met statistical significance for the primary endpoint demonstrating an improvement over placebo in

change from baseline to Week 52 in AHI with the difference in LS means of -20.0 [95% CI:-25.8, -14.2; p-value <0.01] and -23.8 [95% CI: -29.6, -17.9; p-value < 0.01] in GPI1 and GPI2, respectively.

Table 17: Change from Baseline in AHI at Week 52 (mITT), Trials GPI1 and GPI2

	GPI1		GPI2	
	TZP MTD (N=114)	Placebo (N=120)	TZP MTD (N=119)	Placebo (N=114)
Baseline, mean (SD)	52.9 (30.5)	50.1 (31.5)	46.1 (22.4)	53.1 (30.2)
Value at 52 Weeks, mean (SD)	25.6 (26.7)	45.1 (32.0)	17.1 (18.1)	46.5 (31.8)
Missing, n(%)	14 (12.3)	34 (28.3)	9 (7.6)	27 (23.7)
Change from Baseline, mean[1] (SE)	-25.3 (2.1)	-5.3 (2.1)	-29.3 (2.0)	-5.5 (2.2)
Difference from Placebo, mean[1] (CI)	-20.0 (-25.8, -14.2)	-	-23.8 (-29.6, -17.9)	-
Between-treatment p-value[2]	<0.01	-	<0.01	-

Abbreviations: AHI=Apnea Hypopnea Index, ANCOVA=analysis of covariance, CI=confidence interval, MTD=maximum tolerated dose, N = number of subjects in treatment arm, n = number of subjects with missing value at the specified time point, SD = standard deviation, SE = standard error, TZP = tirzepatide.
Analysis Population is Modified Intent-to-Treat (mITT): Number of participants randomly assigned and received at least 1 dose of study drug.
Model: ANCOVA with Multiple Imputation by Treatment for Missing Data at 52 Weeks.
[1] Shown are least squares means.
[2] Region, sex, and baseline AHI were included in the model.
Note: Imputed baseline AHI values were restricted to be between the minimum value of AHI to be included in the study and the 97.5th quantile of observed values of visits included in the imputation. Imputed week 52 AHI values were restricted to be between 0.01 and the 97.5th quantile of observed values of visits included in the imputation. Calculated change in AHI from imputed values were restricted to be between the 2.5th and 97.5th quantile of observed values of visits included in the imputation.
Source: Full Clinical Study Report (pages 82 and 86 for I8F-MC-GPI1 and I8F-MC-GPI2, respectively); results reproduced by statistical analyst using adpsg.xpt, adds.xpt, and adsl.xpt

Although there is no well-established meaningful within patient change threshold for AHI, the magnitude of treatment effect observed was substantial. As explored in the key secondary and exploratory analyses discussed in this section, the magnitude of change in AHI for subjects treated with tirzepatide was large enough to result in categorical shifts in disease severity and even in disease remission for a large portion of subjects. Since there are limitations to the predictive value of AHI for cardiovascular outcomes and limitations to its correlation with quality of life (Weaver et al. 2005), the size of the treatment difference observed in both trials is important for understanding the clinical meaningfulness of the treatment effect.

For the primary endpoint, the pre-defined subgroups were analyzed on change in AHI values from baseline to Week 52 by age, baseline OSA severity, race, ethnicity, region of enrollment, gender, baseline BMI, and baseline ESS. Results for the evaluated subgroups were generally consistent with the overall population for both trials as shown in Table 18.

Table 18: Change from Baseline in AHI at Week 52 by Subgroups (mITT), Trials GPI1 and GPI2

	GPI1			
Subgroup	**TZP MTD (N=114) n**	**Placebo (N=120) n**	**LS Mean Difference**	**95% CI**
Age				
<50	59	42	-20.68	-29.18, -12.19
≥50	41	44	-19.52	-27.67, -11.36
Baseline OSA Severity				
Not Severe	34	32	-10.11	-16.51, -3.71
Severe	66	54	-26.49	-35.24, -17.73
Race				
American Indian or Alaska Native	9	9	-30.70	NA, NA
Asian	20	18	-25.96	-38.00, -13.91
Black or African American	6	5	-6.45	-43.13, 30.23
White	64	54	-18.23	-25.44, -11.02
Ethnicity				
Hispanic or Latino	45	37	-18.46	-26.85, -10.08
Not Hispanic or Latino	55	46	-21.29	-29.48, -13.09
Geographic Region				
US	31	24	-20.57	-31.77, -9.36
OUS	69	62	-19.83	-26.67, -12.99
Gender				
Male	70	55	-21.73	-28.87, -14.58
Female	30	31	-16.57	-26.70, -6.45
Baseline BMI				
<35	30	30	-17.18	-26.35, -8.01
≥35 and <40	35	28	-22.48	-31.32, -13.64
≥ 40	35	28	-21.42	-33.22, -9.61
Baseline ESS				
≤10	45	38	-25.44	-33.75, -17.14
>10	30	32	-17.48	-27.59, -7.37

Abbreviations: CI = confidence interval, LSMean = least squares mean, MTD = maximum tolerated dose, n = number of subjects with value at Week 52, NA = not available, TZP = tirzepatide.
Model: ANCOVA with Multiple Imputation by Treatment for Missing Data at 52 Weeks. The ANCOVA model included treatment and strata (geographic region [US/OUS] and gender) as fixed effects and baseline AHI as a fixed covariate. When analyzing OSA severity (not severe, severe) as a subgroup, the baseline AHI was not included as a covariate.
Source: Statistical Analyst using adsl.xpt and adpsg.xpt.

Table 18 continued

	GPI2			
Subgroup	**TZP MTD (N=114) n**	**Placebo (N=120) n**	**LS Mean Difference**	**95% CI**
Age				
<50	48	35	-28.88	-38.98, -18.78
≥50	62	52	-20.58	-27.67, -13.49
Baseline OSA Severity				
Not Severe	34	27	-15.97	-24.70, -7.24
Severe	76	60	-21.50	-29.27, -13.73
Race				
American Indian or Alaska Native	10	8	-38.73	-60.36, -17.10
Asian	14	15	-23.88	-42.14, -5.62
Black or African American	7	1	-2.55	-57.24, 52.13
White	79	62	-23.40	-29.99, -16.81
Ethnicity				
Hispanic or Latino	36	29	-29.06	-39.57, -18.56
Not Hispanic or Latino	74	57	-21.17	-28.26, -14.08
Geographic Region				
US	39	22	-22.51	-32.78, -12.25
OUS	71	65	-24.62	-31.73, -17.52
Gender				
Male	79	61	-24.42	-31.59, -17.26
Female	31	26	-22.28	-31.69, -12.87
Baseline BMI				
<35	31	28	-23.97	-34.20, -13.73
≥35 and <40	42	31	-25.76	-35.60, -15.92
≥ 40	37	28	-21.76	-32.50, -11.02
Baseline ESS				
≤10	44	43	-22.05	-30.67, -13.44
>10	48	31	-28.08	-37.84, -18.33

Abbreviations: CI = confidence interval, LSMean = least squares mean, MTD = maximum tolerated dose, n = number of subjects with value at Week 52, NA = not available, TZP = tirzepatide.
Model: ANCOVA with Multiple Imputation by Treatment for Missing Data at 52 Weeks. The ANCOVA model included treatment and strata (geographic region [US/OUS] and gender) as fixed effects and baseline AHI as a fixed covariate. When analyzing OSA severity (not severe, severe) as a subgroup, the baseline AHI was not included as a covariate.
Source: Statistical Analyst using adsl.xpt and adpsg.xpt.

Data Quality and Integrity

The clinical and statistical reviewers assessed the data quality and integrity of the submitted GPI1 and GPI2 datasets. No data quality and integrity issues were raised by the submission.

8.1.2.3.4. *Secondary and other relevant endpoints*

This section summarizes the key secondary endpoint results.

In both trials, tirzepatide MTD demonstrated a statistically significant improvement over placebo in percent change from baseline to Week 52 in AHI with the difference in LS means of -47.7 [95% CI:-65.8, -29.6; p-value <0.01] and -56.2 [95% CI: -73.7, -38.7; p-value < 0.01] in GPI1 and GPI2, respectively (Table 19). The larger effect observed in GPI2 may be related to lingering

effects from PAP, despite the washout period, but the clinical meaning of that difference is not clear.

Table 19: Percent Change from Baseline in AHI at Week 52 (mITT), Trials GPI1 and GPI2

	GPI1		GPI2	
	TZP MTD (N=114)	**Placebo (N=120)**	**TZP MTD (N=119)**	**Placebo (N=114)**
Baseline, mean (SD)	52.9 (30.5)	50.1 (31.5)	46.1 (22.4)	53.1 (30.2)
Value at 52 Weeks, mean (SD)	25.6 (26.7)	45.1 (32.0)	17.1 (18.1)	46.5 (31.8)
Missing, n(%)	14 (12.3)	34 (28.3)	9 (7.6)	27 (23.7)
Percent Change from Baseline, mean[1] (SE)	-50.7 (5.9)	-3.0 (7.1)	-58.7 (5.3)	-2.5 (7.0)
Difference from Placebo, mean[1] (CI)	-47.7 (-65.8, -29.6)	-	-56.2 (-73.7, -38.7)	-
Between-treatment p-value[2]	<0.01	-	<0.01	-

Abbreviations: AHI=Apnea Hypopnea Index, ANCOVA=analysis of covariance, CI=confidence interval, MTD=maximum tolerated dose, **N = number of subjects in treatment arm, n = number of subjects with missing value at the specified time point, SD = standard deviation, SE = standard error, TZP = tirzepatide.**
Analysis Population is Modified Intent-to-Treat (**mITT): Number of participants randomly assigned and received at least 1 dose of study drug.**
Model: ANCOVA with Multiple Imputation by Treatment for Missing Data at 52 Weeks.
[1] **Shown are least squares means.**
[2] **Region, sex, and baseline AHI were included in the model.**
Source: Full Clinical Study Report (pages **360-361and 393-395 for I8F-MC-GPI1 and I8F-MC-GPI2, respectively); results reproduced by statistical analyst using adpsg.xpt, adds.xpt, and adsl.xpt.**

In both trials, tirzepatide MTD demonstrated a statistically significant improvement over placebo in percentage of subjects achieving ≥50% AHI reduction from baseline to Week 52 with the odds ratio of 7.3 [95% CI: 3.8, 14.3; p-value <0.01] and 8.2 [95% CI: 4.3, 15.5; p-value <0.01] in GPI1 and GPI2, respectively, as shown in Table 20. Similarly, the treatment effect is numerically larger in GPI2, possibly related to PAP use. For both trials, tirzepatide-treated subjects had significantly larger odds of reducing their OSA severity, as measured by AHI, by at least half.

Table 20: Percentage of Subjects with ≥50% AHI Reduction from Baseline at Week 52 (mITT), Trials GPI1 and GPI2

	GPI1		GPI2	
	TZP MTD (N=114)	Placebo (N=120)	TZP MTD (N=119)	Placebo (N=114)
Achieve ≥50% AHI Reduction, m(%)	70 (61.2)	23 (19.0)	86 (72.4)	27 (23.2)
Odds Ratio (95% CI)[1]	7.3 (3.8,14.3)	-	8.2 (4.3,15.5)	-
Risk Difference (95% CI)[1]	42.8 (30.8, 54.8)		48.6 (36.6, 60.7)	
p-value[1]	<0.01	-	<0.01	-
Missing, n(%)	14 (12.3)	34 (28.3)	9 (7.6)	27 (23.7)

Abbreviations: AHI=Apnea Hypopnea Index, CI=confidence interval, MTD=maximum tolerated dose, m = number of subjects achieving target in imputed data, N = number of subjects in treatment arm, n = number of subjects with missing value at the specified time point, TZP = tirzepatide.
Analysis Population is Modified Intent-to-Treat (mITT): Number of participants randomly assigned and received at least 1 dose of study drug.
[1] Odd ratio, risk difference, CIs, and p-value are from logistic regression model using imputed data with baseline AHI, geographic region, sex, and treatment as factors.
Source: Full Clinical Study Report (pages 89 and 94 for I8F-MC-GPI1 and I8F-MC-GPI2, respectively); results reproduced by statistical analyst using adpsg.xpt, adds.xpt, and adsl.xpt.

In both trials, tirzepatide MTD demonstrated a statistically significant improvement over placebo in percentage of subjects achieving OSA remission or mild non-symptomatic OSA (AHI <5 or AHI 5-14 with ESS ≤10) at Week 52 with the odds ratio of 7.3 [95% CI: 3.2, 17.0; p-value <0.01] and 6.6 [95% CI: 3.1, 14.0; p-value <0.01] in GPI1 and GPI2, respectively (Table 21).

Table 21: Percentage of Subjects with OSA Remission (AHI<5) or Mild Non-symptomatic OSA (AHI 5-14 with ESS≤ 10) at Week 52 (mITT), Trials GPI1 and GPI2

	GPI1		GPI2	
	TZP MTD (N=114)	Placebo (N=120)	TZP MTD (N=119)	Placebo (N=114)
AHI<5 or AHI 5-14 with ESS<=10, m(%)	48 (42.2)	19 (15.9)	60 (50.2)	16 (14.3)
Odds Ratio (95% CI)[1]	7.3 (3.2, 17.0)	-	6.6 (3.1,14.0)	-
Risk Difference (95% CI)[1]	28.7 (18.3, 39.2)		33.2 (22.1, 44.3)	
p-value[1]	<0.01	-	<0.01	-
Missing, n(%)	14 (12.3)	34 (28.3)	9 (7.6)	27 (23.7)

Abbreviations: AHI=Apnea Hypopnea Index, CI=confidence interval, ESS=Epworth Sleepiness Scale, MTD=maximum tolerated dose, OSA=obstructive sleep apnea, m = number of subjects achieving target in imputed data, N = number of subjects in treatment arm, n = number of subjects with missing value at the specified time point, TZP = tirzepatide.
Analysis Population is Modified Intent-to-Treat (mITT): Number of participants randomly assigned and received at least 1 dose of study drug.
[1] Odd ratio, Risk Difference, CIs, and p-value are from logistic regression model using imputed data with baseline AHI, geographic region, sex, and treatment as factors.
Note: Imputed baseline AHI values were restricted to be between the minimum value of AHI to be included in the study and the 97.5th quantile of observed values of visits included in the imputation. Imputed week 52 AHI values were restricted to be between 0.01 and the 97.5th quantile of observed values of visits included in the imputation. Calculated change in AHI and ESS from imputed values were restricted to be between the 2.5th and 97.5th quantile of observed values of visits included in the imputation. Imputed baseline and week 52 of ESSTOTAL values were restricted to the 0 and 24, the min and max participants can theoretically score on the test.
Source: Full Clinical Study Report (pages 92 and 97 for I8F-MC-GPI1 and I8F-MC-GPI2, respectively); results reproduced by statistical analyst using adess.xpt, adpsg.xpt, adds.xpt, and adsl.xpt.

This endpoint is particularly clinically meaningful because patients within these parameters (AHI <5 or AHI 5-14 with ESS ≤10) typically do not require treatment in clinical practice. Withdrawal

of PAP was not assessed in GPIF, and the available data do not answer the questions of when or whether patients requiring PAP may discontinue it when treated with tirzepatide. Regardless, these results support that the magnitude of the treatment effect on AHI with tirzepatide is clinically meaningful.

In both trials, tirzepatide MTD demonstrated a statistically significant improvement over placebo in change from baseline to Week 52 in SASHB concentration with the difference in LS means of -70.1 [95% CI: -90.9, -49.3; p-value <0.01] and -61.3 [95% CI: -84.7, -37.9; p-value < 0.01] in GPI1 and GPI2, respectively (Table 22).

Table 22: Change from Baseline in SASHB Concentration at Week 52 (mITT), Trials GPI1 and GPI2

	GPI1		GPI2	
	TZP MTD (N=114)	Placebo (N=120)	TZP MTD (N=119)	Placebo (N=114)
Baseline, mean[1] (CV)	153.6 (1.0)	137.8 (1.0)	132.2 (0.8)	142.1 (1.1)
Value at 52 Weeks, mean[1] (CV)	50.1 (2.2)	116.6 (1.5)	30.3 (3.0)	104.0 (1.7)
Change from Baseline, mean[2] (SE)	-95.2 (4.1)	-25.1 (9.8)	-103.0 (3.8)	-41.7 (11.3)
Difference from Placebo, mean[2] (CI)	-70.1 (-90.9, -49.3)	-	-61.3 (-84.7, -37.9)	-
Between-treatment p-value[2]	<0.01	-	<0.01	-

Abbreviations: ANCOVA=analysis of covariance, CI=confidence interval, CV=coefficient of variation, N = number of subjects in treatment arm, SASHB=Sleep Apnea-specific Hypoxic Burden, SE = standard error, TZP = tirzepatide.
Analysis Population is Modified Intent-to-Treat (mITT): Number of participants randomly assigned and received at least 1 dose of study drug.
Model: ANCOVA with Multiple Imputation by Treatment for Missing Data at 52 Weeks.
[1] Shown are geometric means. Log transformations were applied to raw data.
[2] log (baseline SASHB), region, sex, baseline OSA severity group were included in the model.
Note: Imputed baseline and week 52 SASHB values and their calculated change were restricted to be between the log(0.01) and 97.5th quantile of observed values at visits included in the imputation. Calculated change from imputed values of SASHB were restricted to be between the 2.5th quantile and 97.5th quantile of observed values at visits included in the imputation.
Source: Full Clinical Study Report (pages 95 and 100 for I8F-MC-GPI1 and I8F-MC-GPI2, respectively); results reproduced by statistical analyst using adspg.xpt, adds.xpt, adsl.xpt, and vs.xpt

The treatment effect demonstrated on SASHB is clinically meaningful since it measures an important physiologic improvement in sleep disordered ventilation. As discussed in Section 1, SASHB and measures of nocturnal hypoxic burden are strongly associated with long-term morbidity and mortality, such as major adverse cardiac events, and may better correlate with patient quality of life. The magnitude of the treatment effect observed, as with the AHI-related endpoints, is also numerically substantial.

In both phase 3 trials, tirzepatide MTD demonstrated a statistically significant improvement over placebo in percent change from baseline in body weight (%) at Week 52 with the difference in LS means of -16.1 [95% CI: -18.0, -14.2; p-value <0.01] and -17.3 [95% CI: -19.3, -15.3; p-value < 0.01] in GPI1 and GPI2, respectively (Table 23). The changes observed are consistent with those from the CWM program. The substantial reduction in body weight, as well as oropharyngeal and abdominal wall fat deposits, is likely the primary mechanism by which tirzepatide exerts its effect in OSA.

Table 23: Percent Change from Baseline in Body Weight (%) at Week 52 (mITT), Trials GPI1 and GPI2

	GPI1		GPI2	
	TZP MTD (N=114)	**Placebo (N=120)**	**TZP MTD (N=119)**	**Placebo (N=114)**
Baseline, mean (SD)	116.7 (24.6)	112.8 (22.6)	115.8 (21.5)	115.1 (22.7)
Value at 52 Weeks, mean (SD)	95.5 (23.6)	109.6 (24.5)	92.3 (19.5)	111.5 (24.3)
Percent Change from Baseline, mean[1] (SE)	-17.7 (0.7)	-1.6 (0.7)	-19.6 (0.7)	-2.3 (0.7)
Difference from Placebo, mean[1] (CI)	-16.1 (-18.0, -14.2)	-	-17.3 (-19.3, -15.3)	-
Between-treatment p-value[2]	<0.01	-	<0.01	-

Abbreviations: ANCOVA=analysis of covariance, CI=confidence interval, MTD=maximum tolerated dose, OSA=obstructive sleep apnea, N = number of subjects in treatment arm, SD = standard deviation, SE = standard error, TZP = tirzepatide.
Analysis Population is Modified Intent-to-Treat (mITT): Number of participants randomly assigned and received at least 1 dose of study drug.
Model: ANCOVA with Multiple Imputation by Treatment for Missing Data at 52 Weeks.
[1] Shown are least squares means.
[2] Region, sex, baseline OSA severity group, and baseline weight were included in the model.
Note: Imputed baseline and week 52 body weight values were restricted to be between the 2.5th and 97.5th quantile of observed values of visits included in the imputation. Calculated change in body weight from imputed values were restricted to be between the 2.5th and 97.5th quantile of observed values of visits included in the imputation.
Source: Full Clinical Study Report (pages 104 and 109 for I8F-MC-GPI1 and I8F-MC-GPI2, respectively); results reproduced by statistical analyst using advs.xpt, adds.xpt, and adsl.xpt.

In both phase 3 trials, tirzepatide MTD demonstrated a statistically significant improvement over placebo in change from baseline in SBP at Week 48 with the difference in LS means of -7.6 [95% CI: -10.5, -4.8; p-value < 0.01] and -3.7 [95% CI: -6.8, -0.7; p-value < 0.01] in GPI1 and GPI2, respectively (Table 24). These results are consistent with those observed in previous clinical trials with tirzepatide and demonstrate another improvement in a comorbidity closely associated with OSA, hypertension.

Table 24: Change from Baseline in SBP at Week 48 (mITT), Trials GPI1 and GPI2

	GPI1		GPI2	
	TZP MTD (N=114)	Placebo (N=120)	TZP MTD (N=119)	Placebo (N=114)
Baseline, mean (SD)	128.4 (12.2)	130.3 (10.7)	130.5 (14.3)	130.5 (12.8)
Value at 48 Weeks, mean (SD)	118.3 (11.9)	127.9 (11.6)	123.1 (13.4)	126.4 (12.1)
Missing, n(%)	14 (12.3)	31 (25.8)	7 (5.9)	23 (20.2)
Change from Baseline, mean[1] (SE)	-9.5 (1.02)	-1.8 (1.0)	-7.6 (1.0)	-3.9 (1.2)
Difference from Placebo, mean[1] (CI)	-7.6 (-10.5, -4.8)	-	-3.7 (-6.8, -0.7)	-
Between-treatment p-value[2]	<0.01	-	0.02	-

Abbreviations: AHI=Apnea Hypopnea Index, ANCOVA=analysis of covariance, CI=confidence interval, MTD=maximum tolerated dose, N = number of subjects in treatment arm, OSA=obstructive sleep apnea, SBP=systolic blood pressure, SD = standard deviation, SE = standard error, TZP = tirzepatide.
Analysis Population is Modified Intent-to-Treat (MITT): Number of participants randomly assigned and received at least 1 dose of study drug.
Model: ANCOVA with Multiple Imputation by Treatment for Missing Data at 48 Weeks.
[1] Shown are least squares means.
[2] Region, sex, baseline OSA severity group, and baseline SBP were included in the model.
Note: Imputed baseline and week 48 systolic blood pressure values were restricted to be between the 2.5 and 97.5th quantile of observed values of visits included in the imputation. Calculated change in systolic blood pressure from imputed values were restricted to be between the 2.5th and 97.5th quantile of observed values of visits included in the imputation.
Source: Full Clinical Study Report (pages 403-404 and pages 441-443 for I8F-MC-GPI1 and I8F-MC-GPI2, respectively); results reproduced by statistical analyst using advs.xpt, adds.xpt, and adsl.xpt.

In both phase 3 trials, tirzepatide MTD demonstrated a statistically significant improvement over placebo in change from baseline to Week 52 in hsCRP concentration with the difference in LS means of -0.7 [95% CI: -1.2, -0.2; p-value =<0.01] and -1.0 [95% CI: -1.6, -0.5; p-value < 0.01] in GPI1 and GPI2, respectively (Table 25). These results are also consistent with changes observed in previous clinical trials with tirzepatide.

Table 25: Change from Baseline in hsCRP Concentration at Week 52 (mITT), Trials GPI1 and GPI2

	GPI1		GPI2	
	TZP MTD (N=114)	Placebo (N=120)	TZP MTD (N=119)	Placebo (N=114)
Baseline, mean[1] (CV)	3.5 (1.2)	3.6 (1.3)	3.0 (1.2)	2.7 (1.3)
Value at 52 Weeks, mean[1] (CV)	2.1 (1.7)	3.2 (1.2)	1.5 (1.7)	2.4 (1.3)
Change from Baseline, mean[2] (SE)	-1.4 (0.2)	-0.7 (0.2)	-1.4 (0.1)	-0.3 (0.2)
Difference from Placebo, mean[2] (CI)	-0.7 (-1.2, -0.2)	-	-1.0 (-1.6, -0.5)	-
Between-treatment p-value[2]	<0.01	-	<0.01	-

Abbreviations: ANCOVA=analysis of covariance, CI=confidence interval, CV=coefficient of variation, hsCRP=high-sensitivity C-reactive protein, N = number of subjects in treatment arm, SE = standard error, TZP = tirzepatide.
Analysis Population is Modified Intent-to-Treat (MITT): Number of participants randomly assigned and received at least 1 dose of study drug.
Model: ANCOVA with Multiple Imputation by Treatment for Missing Data at 52 Weeks.
[1] Shown are geometric means.
[2] log(baseline CSRP), region, sex, baseline OSA severity group were included in the model.
Note: Imputed baseline and week 52 hsCRP values and their calculated change were restricted to be between the 2.5th and 97.5th quantile of the observed values at visits included in the imputation.
Source: Full Clinical Study Report (pages 397-398 and 434-435 for I8F-MC-GPI1 and I8F-MC-GPI2, respectively); results reproduced by statistical analyst using adlb.xpt, adds.xpt, adsl.xpt, and vs.xpt

Efficacy Results – Secondary or Exploratory COA (PRO) Endpoints

Evaluation of the key secondary PROMIS endpoints based on the unpooled individual trial data are provided in Table 26 and Table 27. As discussed in Section 8.1.1.8, the Applicant prespecified pooling of the PROs, with which the Division did not agree for clinical reasons, mainly that PAP use at baseline may confound PRO assessments. In addition, pooling of a key efficacy endpoint is not consistent with independent substantiation of efficacy from more than one investigation. As such, we focused our review on the individual trial results. Refer to Section 14.5.2 for the pooled PRO analysis results.

In both trials, tirzepatide MTD demonstrated a nominally significant improvement in change from baseline to Week 52 in PROMIS-SRI compared to the placebo arm with the difference in LS means of-3.4 [95% CI: -5.7,-1.2] and -4.3 [95% CI: -7.90,-1.6] in GPI1 and GPI2, respectively, as shown in Table 24. These analyses were not controlled in the pre-specified multiplicity testing hierarchy and were, therefore, considered exploratory.

Table 26: Summary and Analysis of Change in PROMIS-SRI T-Scores (mITT), Trials GPI1 and GPI2

	GPI1		GPI2	
	TZP MTD (N=114)	Placebo (N=120)	TZP MTD (N=119)	Placebo (N=114)
Baseline, mean (SD)	53.5 (7.7)	54.7 (8.9)	55.6 (8.7)	55.2 (10.0)
Value at 52 Weeks, mean (SD)	46.9 (9.1)	51.2 (8.6)	47.0 (9.0)	51.3 (10.4)
Missing, n(%)	4 (3.5)	24 (20.0)	9 (7.6)	17 (14.9)
Change from Baseline, mean[1] (SE)	-6.6 (0.8)	-3.1 (0.8)	-8.2 (1.0)	-3.9 (1.0)
Difference from Placebo, mean[1] (CI)	-3.4 (-5.7, -1.2)	-	-4.3 (-7.0, -1.6)	-

Abbreviations: ANCOVA=analysis of covariance, CI=confidence interval, MTD=maximum tolerated dose, OSA=obstructive sleep apnea, PROMIS=Patient-Reported Outcomes Measurement Information System, SRI=sleep related impairment, TZP = tirzepatide.
Analysis Population is Modified Intent-to-Treat (mITT): Number of participants randomly assigned and received at least 1 dose of study drug.
Model: ANCOVA with Multiple Imputation by Treatment for Missing Data at 52 Weeks.
[1] Shown are least squares means. Region, sex, baseline OSA severity group, and baseline SRIT were included in the model.
Note: Imputed baseline and week 52 SRIt-scores were restricted to be between the minimum of SRI t-scores and the maximum value of the observed SRIt-scores from values of visits included in the imputation.
Calculated change in SRI t-scores from imputed values were restricted to be between the maximum and minimum of observed change in SRI t-scores from values of visits included in the imputation.
Source: Full Clinical Study Report (pages 373-374); Full Clinical Study Report (pages 409-410); results reproduced by statistical analyst using adpromis.xpt, adds.xpt, and adsl.xpt.

Similarly, in both phase 3 trials, tirzepatide MTD demonstrated a nominally significant improvement in change from baseline to Week 52 in PROMIS-SD compared to the placebo arm with the difference in LS means of -2.0 [95% CI: -4.0, -0.1] and -3.9 [95% CI: -6.2, -1.6] in Trial 1 and Trial 2, respectively (Table 27). These analyses were not controlled in the pre-specified multiplicity testing hierarchy and were considered exploratory.

Table 27: Summary and Analysis of Change in PROMIS-SD T-Scores (mITT), Trials GPI1 and GPI2

	GPI1		GPI2	
	TZP MTD (N=114)	**Placebo (N=120)**	**TZP MTD (N=119)**	**Placebo (N=114)**
Baseline, mean (SD)	53.9 (6.1)	53.8 (7.5)	56.2 (8.0)	56.1 (7.8)
Value at 52 Weeks, mean (SD)	49.2 (6.9)	51.4 (7.8)	49.0 (7.4)	53.0 (8.7)
Missing, n(%)	4 (3.5)	25 (20.8)	12 (10.1)	19 (16.7)
Change from Baseline, mean[1] (SE)	-4.5 (0.7)	-2.4 (0.7)	-7.0 (0.8)	-3.1 (0.9)
Difference from Placebo, mean[1] (CI)	-2.0 (-4.0, -0.1)	-	-3.9 (-6.2, -1.6)	-

Abbreviations: ANCOVA=analysis of covariance, CI=confidence interval, MTD=maximum tolerated dose, OSA=obstructive sleep apnea, PROMIS=Patient-Reported Outcomes Measurement Information System, SD=sleep disturbance, TZP = tirzepatide.
Analysis Population is Modified Intent-to-Treat (mITT): Number of participants randomly assigned and received at least 1 dose of study drug.
Model: ANCOVA with Multiple Imputation by Treatment for Missing Data at 52 Weeks.
[1] Shown are least squares means. Region, sex, baseline OSA severity group, and baseline SDTS were included in the model.
Note: Imputed baseline and week 52 SD t-scores were restricted to be between the minimum of SD t-scores and the maximum of the observed SD t-scores from values of visits included in the imputation.
Calculated change in SD t-scores from imputed values were restricted to be between the maximum and minimum of observed change in SD t-scores from values of visits included in the imputation.
Source: Source: Full Clinical Study Report (pages 406-408); results reproduced by statistical analyst using adpromis.xpt, adds.xpt, and adsl.xpt.

Interpretation of the changes observed for the PROMIS-SRI and PROMIS-SD and the content validity of these instruments are discussed in Section 8.1.3.

Additional Analyses Conducted

OSA Remission or Mild Non-Symptomatic OSA Endpoint

The prespecified secondary endpoint of OSA remission or mild non-symptomatic OSA, defined as the proportion of subjects who achieved either AHI <5 events/h or AHI 5-14 events/h with ESS ≤10, was intended to identify those who achieved a wider definition of OSA remission and are typically not indicated for further treatment. As there is uncertainty about whether patients with an AHI 5-14 events/h and ESS ≤10 should be treated for their OSA, additional exploratory analyses were conducted to identify the proportion of subjects who achieved the stricter definition of OSA remission of AHI <5 events/h. In clinical practice, patients with an AHI<5 events/h do not are not treated for OSA, and thus represents a more clinically meaningful endpoint.

Table 28 shows that when each component of the composite endpoint of OSA remission or mild non-symptomatic OSA is evaluated separately, the percentage of patients achieving OSA remission (AHI <5 events/h) contributes substantially to the observed effect on the composite endpoint. In GPI1, 22.5% of tirzepatide-treated subjects achieved AHI <5 events/h at Week 52 compared to 4.9% of placebo-treated subjects and. In GPI2, 33.1% of tirzepatide-treated subjects achieved OSA remission compared to 6.9% of placebo-treated subjects.

Table 28: Percentage of Subjects with Individual Components of the Remission (AHI<5) or Mild Nonsymptomatic OSA (AHI 5-14 with ESS≤10) (mITT), Trials GPI1 and GPI2

	GPI1		GPI2	
Week 52 (Visit 11)	**TZP MTD (N=114)**	**Placebo (N=120)**	**TZP MTD (N=119)**	**Placebo (N=114)**
Achieve AHI<5, n[1] (%)	26 (22.53)	6 (4.87)	39 (33.13)	8 (6.93)
Risk Difference (95% CI)[2]	18.57 (9.83, 27.30)		24.68 (14.50, 34.86)	
Achieve AHI 5 to 14 with ESS≤10, n[1] (%)	22 (19.64)	13 (11.01)	20 (17.11)	8 (7.40)
Risk Difference (95% CI)[2]	10.35 (1.09, 19.60)		8.92 (0.56, 17.29)	

Abbreviations: AHI=Apnea Hypopnea Index, CI=confidence interval, ESS=Epworth Sleepiness Scale, MTD=maximum tolerated dose, OSA=obstructive sleep apnea, N = number of subjects in treatment arm, TZP = tirzepatide.
Analysis Population is Modified Intent-to-Treat (mITT): Number of participants randomly assigned and received at least 1 dose of study drug.
[1] Counts are based on imputed data.
[2] Risk difference (%) and CI for endpoint measures are from logistic regression model using imputed data with Baseline AHI, Geographic Region, Sex and Treatment as factors.
Source: Tables APP3-APP6 Information Request Regulatory response-19 sept-2024

Categorical Shifts in OSA Disease Severity

An exploratory analysis was conducted to identify the proportion of subjects who underwent categorical shifts in their OSA severity (e.g., subjects who began the trial with severe OSA and had improvement at Week 52 to mild OSA) (Table 29).

Table 29: Proportion of Subjects who Underwent Categorical Shifts from Baseline to Week 52 in OSA Severity (mITT), Trials GPI1 and GPI2

GPI1				GPI2			
TZP MTD		Placebo		TZP MTD		Placebo	
OSA Severity				OSA Severity			
Baseline	Week 52	Baseline	Week 52	Baseline	Week 52	Baseline	Week 52
Moderate (N=34)	AHI<5 16 (47%) Mild 15 (44%) Moderate 2 (6%) Severe 1 (3%)	Moderate (N = 32)	AHI<5 1 (3%) Mild 14 (44%) Moderate 14 (44%) Severe 3 (9%)	Moderate (N=34)	AHI<5 17 (50%) Mild 10 (29%) Moderate 3 (9%) Severe 4 (12%)	Moderate (N = 27)	AHI<5 1 (4%) Mild 7 (26%) Moderate 10 (37%) Severe 9 (33%)
Severe (N=66)	No apnea 7 (11%) Mild 14 (21%) Moderate 16 (42%) Severe 29 (44%)	Severe (N=54)	No apnea 1 (2%) Mild 2 (4%) Moderate 8 (15%) Severe 43 (80%)	Severe (N=76)	No apnea 21 (28%) Mild 14 (18%) Moderate 24 (32%) Severe 17 (22%)	Severe (N=60)	No apnea 4 (7%) Mild 1 (2%) Moderate 9 (15%) Severe 46 (77%)

Abbreviations: AHI=Apnea Hypopnea Index, MTD=maximum tolerated dose, OSA=obstructive sleep apnea, N = number of subjects with non-missing value at baseline and week 52, TZP = tirzepatide.
Analysis Population is Modified Intent-to-Treat (mITT): Number of participants randomly assigned and received at least 1 dose of study drug.
Note: Values are number of observed subjects (proportion) who underwent categorical shifts from baseline at Week 52 in their OSA severity. Moderate and severe OSA severity are defined as (AHI≥15 and AHI<30) and (AHI≥30), respectively.
Source: Statistical Reviewer

A significant proportion of subjects treated with tirzepatide in both GPI1 and GPI2 underwent a 'categorical shift' in their disease severity, compared to those on placebo. In addition, a significant proportion who had severe OSA at baseline (AHI >30 events/h) were able to achieve OSA remission (AHI <5 events/h) compared to subjects treated with placebo in these two trials. In this way, tirzepatide appears to clinically resolve OSA for some patients, even those with severe disease at baseline.

Proportion of Symptomatic Subjects with Symptom Improvement by the ESS

There are limitations to the regulatory utility of the ESS as a PRO because of concerns about its content validity for OSA, but the ESS is used in the practice of medicine to assess OSA symptom severity or screen for OSA. As such, an exploratory analysis was conducted to assess the proportion of subjects who had an ESS >10 at baseline and were able to achieve an ESS ≤10 at Week 52. There was a greater proportion of tirzepatide-treated subjects compared to placebo who achieved this endpoint in both trials, but the sample size was small and interpretation is limited by the exploratory nature.

In practice, a patient meeting criteria for asymptomatic OSA, with an AHI <14, would unlikely be started on therapy for OSA, such as PAP. We acknowledge that there is uncertainty about

whether subjects who achieve this definition of remission should be weaned off PAP therapy, and the GPIF trials were not designed to assess the appropriateness of discontinuation of PAP therapy in subjects who were previously compliant.

Dose Response

The GPIF trials were not intended to compare differences in efficacy between tirzepatide doses, but rather to compare the MTD to the placebo comparator. In GPI1, the distribution of the final dose of tirzepatide, including in subjects who discontinued the study drug, was 15mg SC QW for 84.2% of subjects and 10mg SC QW for 7% of subjects. In GPI2, the distribution of the final dose of tirzepatide, including in subjects who discontinued the study drug, was 15mg SC QW for 94.1% of subjects and 10mg SC QW for 2.5% of subjects. Given the known efficacy of both doses in the CWM program and the small proportion of subjects on the 10mg dose in both GPI1 and GPI2, additional exploratory analyses to evaluate the primary endpoint by dose were not conducted. Refer to Section 6 for clinical pharmacology assessment of exposure-response.

Integrated Review of Effectiveness

8.1.3. Integrated Assessment of Effectiveness

Polysomnography endpoints and other objective outcomes

Subjects on tirzepatide in both GPI1 and GPI2 achieved a substantial and statistically significant reduction in the primary endpoint of change in AHI from baseline to Week 52. All secondary endpoints based on AHI metrics further supported that the magnitude of change was clinically meaningful. Reduction in AHI by approximately 50% or greater and achievement of remission or mild asymptomatic disease demonstrate treatment effects similar to those often observed with surgical interventions (Malhotra et al. 2024). The achievement of remission, particularly the strict definition of AHI <5 and for patients with severe disease at baseline, represents a clinically meaningful improvement in disease. The magnitude of improvement in SASHB also represents a clinically meaningful change for patients. Since the AHI has limitations as a predictive measure of clinically meaningful outcomes in OSA, these additional endpoints also contributed to the demonstration of substantial evidence of effectiveness (Azarbarzin et al. 2019).

The reduction in AHI of tirzepatide compared to placebo, and most PSG-based endpoints, was slightly greater in GPI2 than in GPI1, indicating that the use of PAP therapy may have contributed slightly to the additional improvements in GPI2, despite the washout periods. However, given the small treatment difference between the two trials, it is difficult to make conclusions regarding the effect of tirzepatide in combination with PAP therapy. The clinical trials for OSA did not evaluate the timing or appropriateness of PAP discontinuation in subjects who were previously compliant with PAP therapy. This uncertainty will be communicated in labeling and may only be clarified with postmarketing experience or additional studies.

The percent change in body weight, reduction in SBP and hsCRP, were similar in GPI1 and GPI2 and consistent with the effects of tirzepatide demonstrated in CWM. The reduction in body weight is likely the primary mechanism by which tirzepatide improves PSG parameters and OSA. There are several studies in the literature that have demonstrated a positive correlation between weight loss and reduction in AHI. Most of the weight loss in these published studies was achieved through bariatric surgery. Although cross study comparisons should be explored with caution, we note that the magnitude of effect with tirzepatide is similar to that observed, on average, with bariatric surgery (Malhotra et al. 2024). In GPI1 and GPI2, tirzepatide demonstrated substantial weight loss in patients with obesity leading to a significant reduction in AHI, thereby distinguishing tirzepatide as a novel pharmacotherapy for the treatment of OSA.

Both the clinical and statistical reviews of this sNDA find that the data from the GPIF trials, GPI1 and GPI2, provide convincing support for the efficacy of tirzepatide as a treatment for moderate to severe OSA with obesity.

PROMIS-SRI and PROMIS-SD

In Trials GPI1 and GPI2, aspects of sleep-related impairment and sleep disturbance were assessed by the PROMIS-SRI and PROMIS-SD, respectively. The Applicant's standalone patient interviews and within-trial exit interviews confirmed that both sleep-related impairment and sleep disturbance are relevant and important impairments associated with OSA and obesity in the target patient population. The Applicant also provided sufficient evidence from the literature, as well as qualitative and quantitative research, to support the content validity and other psychometric properties (i.e., internal consistency, test-retest reliability, construct validity, and ability to detect change) of the PROMIS-SRI and PROMIS-SD T-scores for the context of use in this drug development program. The Applicant conducted anchor-based analyses supplemented with empirical cumulative distribution function (eCDF) curves to evaluate the clinically meaningful changes in the multiplicity-controlled endpoints derived from PROMIS-SRI and PROMIS-SD, separately.

Several PGIS-OSA scales were included in Trials GPI1 and GPI2 to facilitate meaningful change analyses. Refer to Section 8.1.1.7 for detailed descriptions of the PGIS-OSA scales. The Applicant also included corresponding 5-point Patient Global Impression of Change-OSA scales measuring change in subjects' overall level of fatigue, sleepiness, sleep quality, and snoring related to their condition since subjects started taking study medication. Based on correlations between anchor scales and target PROs, the Applicant determined that the primary anchor scales for PROMIS-SRI were PGIS-OSA Sleepiness in Trial GPI1 and PGIS-OSA Fatigue in GPI2, respectively. The Applicant determined that the primary anchor scale for PROMIS-SD was PGIS Sleep Quality in both trials. However, the review team recommended the Applicant conduct additional anchor-based analyses using multiple PGIS items, i.e., PGIS-OSA Sleepiness, PGIS-OSA Fatigue, and PGIS Sleep Quality, to provide an accumulation of evidence to help derive a range

of clinically meaningful within-patient score change in the PROMIS-SF-SRI and PROMIS-SF-SD scores.

The pre-specified multiplicity controlled endpoint for the PRO was the change in baseline from Week 52 in both the PROMIS-SRI and the PROMIS-SD pooled across both GPI1 and GPI2. The Division did not agree with pooling the efficacy results across GPI1 and GPI2, because of clinical differences in the populations that may affect PRO outcomes (i.e., PAP use) and because pooled analyses lack validation of independent substantiation, which is necessary to demonstrate substantial evidence of effectiveness. Therefore, exploratory analyses were performed to evaluate each PRO endpoint independently for both GPI1 and GPI2. These analyses took into consideration the full distribution of PROMIS T-scores and selected meaningful change thresholds that minimized the misclassification of subjects who reported no improvement or worsening, as well as subjects' baseline global symptom severity. Based on this evaluation, the Agency concluded that the observed treatment effects on the PROMIS-SRI 8a T-scores substantiated a clinically meaningful improvement in subjects receiving tirzepatide as compared to placebo in both GPI1 and GPI2. This result demonstrates that tirzepatide not only causes robust improvement in objective markers of OSA, but also improves symptoms that subjects have related to sleep impairment. (b) (4)

In reviewing the PRO endpoints, an additional issue was noted, which may have limited our interpretation of the clinical meaningfulness of the PROMIS-SRI and PROMIS-SD endpoint results. The baseline scores of 55.0 for the PROMIS-SRI and 54.7 for the PROMIS-SD are similar to the general population mean of 50, such that it appears subjects did not have sufficient sleep impairment or sleep disturbance at baseline for an adequate assessment of improvement. Reasons for this inconsistency in symptoms of sleepiness and objective measures of sleep disordered breathing are unclear but are consistent with uncertainties and knowledge gaps described in the literature, including prior studies that have demonstrated limitations to measures such as AHI/RDI in capturing or quantifying quality of life associated with OSA and sleep-related symptoms (Cheshire et al. 1992; Walter et al. 2002; Macey et al. 2010; Soori et al. 2022). These studies demonstrate a weak relationship between AHI and subjective experience of excessive daytime sleepiness, suggesting that either the severity of excessive daytime sleepiness is influenced by factors other than polysomnographic variables or the measures used to assess excessive daytime sleepiness are not sensitive enough (Walter et al. 2002). Future clinical development programs for the treatment of OSA may want to consider strategies to enrich their patient population with subjects who are symptomatic with sleep impairment or sleep disturbance.

Refer to Section 14.4 for additional details on the interpretation of the meaningfulness of the PROMIS-SRI and PROMIS-SD endpoint results.

8.2. Review of Safety

8.2.1. Safety Review Approach

The safety of tirzepatide 10 or 15 mg once weekly SC in subjects with moderate-to-severe OSA and obesity is primarily informed by the results of the SURMOUNT-OSA trials, GPI1 and GPI2. Safety data from subjects enrolled in previous CWM and T2DM trials (SURMOUNT-1 [18F-MC-GPHK], SURMOUNT-2 [18F-MC-GPHL], SURPASS-1 [18F-MC-GPGK], and SURPASS-2 [18F-MC-GPGL]) provide supplemental support. The enrolled populations in the CWM and T2DM trials are sufficiently similar to the enrolled population in GPIF to rely on the safety profile of tirzepatide among subjects with overweight, obesity or T2DM as supplemental support. This safety review compares differences in the safety signals to those observed in the CWM program, since the CWM and OSA populations are most similar.

Both pooled and unpooled safety analyses were provided for this sNDA. The safety results were evaluated by this reviewer both individually for each trial and pooled. This safety review focuses on the pooled safety population of GPI1 and GPI2 given the similarities of the populations. This safety review includes all subjects who received at least one dose of trial drug.

8.2.2. Review of the Safety Database

Overall Exposure

The safety analysis set included all randomized subjects who were exposed to at least one dose of study drug. GPI1 randomized 234 subjects: 114 subjects to tirzepatide MTD QW and 120 subjects to placebo QW. All subjects were included in the safety analysis set. The mean duration of exposure during the double-blind period of GPI1 was 43.3 weeks for placebo and 47.8 weeks for tirzepatide MTD. GPI2 randomized 235 subjects: 120 subjects to tirzepatide MTD QW and 115 subjects to placebo QW, 119 subjects in the tirzepatide arm and 115 subjects in the placebo arm were included in the safety analysis. The mean duration of exposure during the DB period of GPI2 was 44.1 weeks for placebo and 50 weeks for tirzepatide MTD. This difference in duration of treatment exposure between the placebo and tirzepatide arms in both trials was driven by the higher discontinuation rate in the placebo arm of each trial.

Adequacy of the Safety Database

Tirzepatide is an approved product with an established safety profile for the same doses (10 and 15 mg SC QW) in two other populations: subjects with overweight or obesity and subjects with T2DM. A MTD of 10 or 15mg SC QW is recommended for patients with moderate-to-severe OSA and obesity; this dose was previously studied in pivotal phase 3 trials (SURMOUNT-1, SURMOUNT-2, SURPASS-1, and SURPASS-2). Approximately 10,813 individuals with BMI ≥27

kg/m^2 have been exposed to tirzepatide through controlled trials conducted across related indications (Table 30).

Table 30: Safety Database for Tirzepatide

Safety Database for Tirzepatide **N =** 10,813 individuals exposed to tirzepatide treatment			
Clinical Trial Groups	**Tirzepatide as the New Drug**	**Tirzepatide as the Active Control[3]**	**Placebo**
Healthy volunteers	0	0	0
Controlled trials conducted for OSA indication[1]	233	0	234
Controlled trials conducted for other indications[2]	8,759	1,821	1,203

Source: NDA 217806 Unireview and Applicant adsl.xpt datasets for pooled analysis for GPIF
[1] Trials GPI1 and GPI2
[2] Includes Trials GPHK, GPHL (SURMOUNT -1 and -2), GPHN (SURMOUNT-4) open-label treatment lead-in period, ten trials for T2DM (two phase 2 trials and eight phase 3 SURPASS trials), limited to trial subjects with BMI ≥ 27 kg/m^2
[3] Tirzepatide was administered in the active control arm for three phase 3 trials for T2DM under IND 139721

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

No data integrity or submission quality issues that hinder the safety review of this sNDA were identified.

Categorization of Adverse Events

The Applicant provided accurate definitions of AEs and serious adverse events (SAEs) in the protocols. Adverse events and SAEs were collected from the signing of informed consent until the end of trial participation. The Applicant coded AEs into system organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA) Version 26.1. The Applicant's coding of verbatim terms to PTs was appropriate. Adverse events of special interest (AESIs) included severe hypoglycemia, major adverse cardiovascular events (MACE) (cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, hospitalization for unstable angina, and hospitalization for heart failure, treatment-emergent arrhythmias and cardiac conduction disorders), hepatobiliary disorders (biliary colic, cholecystitis, and other gallbladder diseases, severe GI events), acute renal events, Major Depressive Disorder and suicidal behavior and ideation, pancreatitis, c-cell hyperplasia and thyroid malignancies, and allergic or hypersensitivity reactions.

Routine Clinical Tests

A central laboratory analyzed all protocol-required clinical laboratory parameters. Safety assessments consisted of routine reporting of all AEs, SAEs, relationship to the drug,

concomitant medications, and pregnancies. Subjects also underwent regular monitoring of blood work (hematology, chemistry, urine analysis), vital signs and physical exams. Subjects underwent additional laboratory testing including HbA1c levels, hsCRP, c-peptide, free fatty acids, cystatin-C, calcitonin, pancreatic amylase, lipase, and TSH. Blood samples were obtained regularly to assess for immunogenicity. A 12-lead ECG was obtained at screening, Week 52 and if early discontinuation occurred during the trial. If a clinically significant increase in the QT/QTc interval from baseline or other significant changes from baseline were observed on ECG, the subject was assessed for symptoms of palpitations, near syncope or syncope and a determination was made about whether the subject could continue in the trial.

8.2.4. Safety Results

8.2.5. Deaths

There were no deaths reported during the GPIF trials.

8.2.6. Serious Adverse Events

There was no clinically meaningful difference in the frequency of SAEs occurring in two or more subjects between the tirzepatide and placebo arms of GPIF (Table 31). Overall, there were 15 subjects (6.4%) in the tirzepatide arm and 18 subjects (7.7%) in the placebo arm who reported at least one SAE. The most common SAEs in GPIF were in the infections and infestations SOC. There were four (1.7%) events in the tirzepatide arm and one (0.4%) event in the placebo arm. Given the small number of events (one event) for each PT (e.g., appendicitis, Dengue fever, gastroenteritis, pneumonia), it is difficult to draw meaningful conclusions from this pattern. Infections and infestations was also the most common SOC with SAEs in the CWM trials, with the most common PTs being COVID-19 related. However, the events were balanced across treatment arms and there was no apparent dose effect of tirzepatide on the event rate; therefore, this was not considered a significant safety concern and was not included in the prescribing information (PI) for tirzepatide.

Serious adverse events in the neoplasms benign, malignant and unspecified (including cysts and polyps) SOC were the most common SAEs in the placebo arm (five subjects (2.1%) vs one subject (0.4%) in the tirzepatide arm). Neoplasms also occurred more frequently in the placebo group of the CWM trials. An exploratory endpoint in the phase 3b trial GPIJ (SURMOUNT-MMO) will evaluate whether tirzepatide reduces the incidence of obesity-associated malignancies. The current PI of tirzepatide has a warning and precaution statement related to the risk of thyroid c-cell tumors (medullary thyroid cancer [MTC]), and there is a Boxed Warning for those with a personal or family history of MTC or in those with Multiple Endocrine Neoplasia Type 2 (MEN 2). There were no malignant thyroid neoplasms or thyroid c-cell hyperplasia events during the trial. The remaining SAEs that occurred in only one subject (not shown in table) did not reveal any concerning signals or patterns.

Table 31: Summary of Serious TEAEs Affecting ≥2 Subjects in Any Treatment Arm (MITT – Safety Analysis Set), GPIF Trial

	TZP MTD[a] N = 233		Placebo N = 234	
Preferred Term	**n**	**(%)[b]**	**n**	**(%)**
Any SAE	15	(6.4)	18	(7.7)
Nephrolithiasis	2	(0.9)	0	(0.0)
Diarrhea	2	(0.9)	0	(0.0)
Suicide attempt	2	(0.9)	0	(0.0)
Atrial fibrillation	1	(0.4)	2	(0.9)
Cholelithiasis	0	(0.0)	2	(0.9)

Source: OCS Analysis Studio, Safety Explorer.
[a]TZP MTD is tirzepatide 10 or 15 mg once weekly
[b] Number (%) of subjects with TEAEs, sorted on descending frequency for PT according to total frequency in the TZP MTD arm. Subjects with multiple events in the same PT were counted only once in that PT. Subjects with events in more than one PT were counted once in each of these categories. Percentages were based upon number of subjects in the treatment group within the Safety Analysis Set.
Abbreviations: SAE, serious adverse event; TZP MTD, tirzepatide maximum tolerated dose

In GPI1, there were two events that were in the CSR as SAEs but did not appear in this reviewer's safety review. Both records had a start date prior to the start date of trial treatment and were**,** therefore, not flagged as treatment emergent in my review. These events did not impact the overall safety analysis of GPI1 or GPI2.

Dropouts and/or Discontinuations Due to Adverse Effects

In the phase 3 trials for CWM, GI symptoms of nausea and diarrhea were the most common AEs in the tirzepatide arm that led to discontinuation from trial treatment. For the GPIF trial, investigators were permitted to initiate one cycle of dose de-escalation and re-escalation during the first 24 weeks of the treatment period to mitigate GI symptoms. In GPIF, a total of 19 subjects (8.2%) permanently discontinued from the trial drug due to an AE, which included nine subjects (3.9%) in the tirzepatide arm and 10 subjects (4.3%) in the placebo arm. Adverse events in the GI disorders SOC were the most common AEs that led to trial drug discontinuation, with five subjects (2.1%) in the tirzepatide arm discontinuing trial drug compared to one subject (0.4%) in the placebo arm.

In GPI1, a total of two subjects (0.9%) discontinued the trial due to an AE. Both subjects were in the placebo group. One of the subjects was discontinued from trial participation after testing positive on a home pregnancy test, and the other subject had an SAE of metastatic tonsillar cancer. In GPI2, a total of six subjects (2.6%) discontinued the trial due to an AE. The number of subjects discontinuing the trial due to an AE was lower in the tirzepatide group (one subject) compared with the placebo group (five subjects).

8.2.7. Significant Adverse Events

Investigators in the GPIF trials graded both AEs and SAEs as mild, moderate, or severe. In GPIF, AEs graded as severe had a slightly higher incidence in the tirzepatide arm (10.3%) than the placebo arm (6%). This imbalance was predominantly related to severe GI AEs, which occurred

in 3% of subjects in the tirzepatide arm and in no subjects in the placebo arm. Included PTs were diarrhea, nausea, gastroesophageal reflux disease, and acute pancreatitis. This finding is consistent with the phase 3 CWM trials, where a similar rate was seen in the frequency of severe GI AEs.

8.2.8. Treatment Emergent Adverse Events and Adverse Reactions

Preferred terms that occurred in ≥5% of subjects in GPIF in either treatment arm and with a risk difference between tirzepatide and placebo that was ≥1% are presented in Table 32. A review of all AEs in GPIF did not reveal any new safety concerns compared to the known safety profile of tirzepatide. Gastrointestinal disorders such as nausea, diarrhea, and vomiting are the most common AEs associated with the use of tirzepatide. The current PI of tirzepatide notes that these events are more likely to occur early on after treatment initiation during dose escalation and resolve over time. As such, in the GPIF trials, the most frequently observed AEs were in the GI disorders SOC, with substantially more events in the tirzepatide arm (54.9%) compared to the placebo arm (23.5%). For the remaining SOCs, small differences were observed between the treatment groups for the most common AEs; however, no specific trends could be identified. The tirzepatide arm had a higher rate of injection site reactions (6%) and alopecia (4.3%) compared to the placebo arm (0.6% and 0.9%, respectively). These imbalances were also seen in the CWM trials, and both AEs are described in the current PI. Overall, the common AEs in the tirzepatide arm of both trials are similar to the AEs described for the CWM population in the current PI.

Table 32: Summary of TEAEs Affecting ≥5% of Subjects in Any Treatment Arm and if Risk Difference Between Tirzepatide and Placebo was ≥1% (MITT – Safety Analysis Set), GPIF Trial

System Organ Class Preferred Term	TZP MTD[a] N = 233 n	 (%)[b]	Placebo N = 234 n	 (%)
Any AE	190	(81.5)	175	(74.8)
Gastrointestinal disorders	**128**	**(54.9)**	**55**	**(23.5)**
Diarrhea	56	(24.0)	25	(10.7)
Nausea	55	(23.6)	18	(7.7)
Constipation	36	(15.5)	8	(3.4)
Vomiting	31	(13.3)	6	(2.6)
Eructation	19	(8.2)	1	(0.4)
Dyspepsia	16	(6.9)	3	(1.3)
Gastroesophageal reflux disease	15	(6.4)	1	(0.4)
Abdominal pain	12	(5.2)	6	(2.6)
General disorders and administration site conditions	**35**	**(15.0)**	**21**	**(9.0)**
Injection site reaction	14	(6.0)	1	(0.4)
Investigations	**30**	**(12.9)**	**26**	**(11.1)**
Lipase increased	7	(3.0)	0	(0.0)
Heart rate increased	6	(2.6)	2	(0.9)
Sars-cov-2 test positive	3	(1.3)	0	(0.0)
Blood creatine phosphokinase increased	2	(0.9)	7	(3.0)
Blood pressure increased	1	(0.4)	3	(1.3)

Source: OCS Analysis Studio, Safety Explorer.
Analysis Population is Modified Intent-to-Treat (MITT): Number of participants randomly assigned and received at least 1 dose of study drug.
[a]TZP MTD is tirzepatide 10 or 15 mg once weekly
[b] Number (%) of subjects with TEAEs, sorted on descending frequency order for SOC and descending frequency for PT according to total frequency in the TZP MTD arm. Subjects with multiple events in the same PT were counted only once in that PT. Subjects with events in more than one PT were counted once in each of these categories. Percentages were based upon number of subjects in the treatment group within the Safety Analysis Set.
Abbreviations: TEAE, treatment-emergent adverse event.

8.2.9. Laboratory Findings

There were no new safety concerns regarding clinical laboratory evaluations identified in the GPIF trials. The current PI of tirzepatide has a warning and precaution statement regarding the risk of hypoglycemia in subjects treated with tirzepatide. In the GPIF trials, subjects on placebo had a higher incidence of elevated fasting serum glucose levels (17.1%), elevated serum insulin levels (32.2%), and elevated serum c-peptide levels (37.3%) compared to subjects treated with tirzepatide (2.3%, 11.5%, and 15.2%, respectively), which is consistent with effects of tirzepatide on glycemic control.

Increases in serum amylase and lipase levels are also known AEs associated with the use of tirzepatide, and the risk of acute pancreatitis is included as a warning and precaution statement in the PI. In the GPIF trials, subjects on tirzepatide had a higher incidence of elevated lipase levels (34.7%) and elevated amylase levels (12.7%) compared to placebo (9.2% and 6.1%, respectively). However, the clinical meaning of increases in amylase and lipase levels without other signs of pancreatitis is unclear. The incidence of acute pancreatitis in GPIF is discussed in Section 8.2.11.6.

The current PI of tirzepatide also has a warning and precaution statement related to the risk of thyroid c-cell tumors (medullary thyroid cancer [MTC]), and there is a Boxed Warning for those with a personal or family history of MTC or in those with Multiple Endocrine Neoplasia Type 2 (MEN 2). Increased levels of serum calcitonin can be used to detect MTC. Subjects treated with tirzepatide had a higher incidence of elevated calcitonin levels (5.5%) compared to subjects treated with placebo (0.5%). The current PI does not recommend routine monitoring of serum calcitonin levels for the early detection of MTC in patients being treated with tirzepatide as this can increase the risk of unnecessary procedures. The frequency of other AEs related to laboratory parameters were comparable between the tirzepatide and placebo arms.

8.2.10. Vital Signs and ECGs

Increases in heart rate are a known class effect of GLP-1R agonists, and in the phase 3 trials for CWM, treatment with tirzepatide resulted in an average increase in heart rate of 1-3 beats per minute compared to no increase in subjects who received placebo. Consistent with this finding, in the GPIF trials, there was no change in pulse rate from baseline to Week 52 for subjects in the placebo group, but subjects in the tirzepatide group had a mean increase of 1-2 beats per minute from baseline. At the safety follow up visit, subjects treated with tirzepatide had reductions in heart rate to below baseline levels. The average pulse rate for subjects in the tirzepatide group decreased by 4-5 beats per minute from baseline at the safety follow up visit. Eight subjects in the tirzepatide group met the criteria for abnormally high pulse rate post-baseline (defined as pulse rate >100 beats per minute or change from baseline >15) and there were more subjects who met this criteria in the tirzepatide group compared to the placebo group.

Hypotension also occurred more frequently in the phase 3 trials for CWM in subjects treated with tirzepatide (1.6%) compared to subjects taking placebo (0.1%). Hypotension was more frequently seen in tirzepatide-treated subjects on concomitant antihypertensive therapy and also occurred in association with GI AEs and dehydration. In the GPIF trials, there was a mean decrease in SBP from baseline to Week 52 for subjects in both the tirzepatide and placebo groups. The effect was greater in the tirzepatide group and on average resulted in 9.6 mmHg decrease in SBP. At the safety follow up visit, the effect of tirzepatide on SBP was diminishing and the SBP for subjects treated with tirzepatide had decreased 6.7 mmHg from baseline. No subjects in the tirzepatide group met the criteria for abnormally low SBP post-baseline (defined as SBP ≤ 90 mmHg and change from baseline ≤-20).

There were no meaningful differences in ECGs over time in either treatment group, and no meaningful trends in ECGs parameters between groups during the treatment period. This is consistent with the ECG sub-study that was conducted for the T2DM indication (NDA 215866), for which the Applicant performed in vitro evaluations and a concentration-QTc analysis of ECG data.

For additional details on arrhythmias, refer to Section 8.2.11.4.

8.2.11. Analysis of Submission-Specific Safety Issues

Adverse events of special interest specified by the Applicant included severe GI AEs, severe hypoglycemia, MACE (cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, hospitalization for unstable angina, and hospitalization for heart failure, treatment-emergent arrhythmias and cardiac conduction disorders), hepatobiliary disorders (biliary colic, cholecystitis, and other gallbladder diseases), acute renal events, Major Depressive Disorder and suicidal behavior and ideation, pancreatitis, c-cell hyperplasia and thyroid malignancies, and allergic or hypersensitivity reactions. With the exceptions of MACE and cardiac conduction disorders, each of these is included as warning and precaution statement in the tirzepatide PI.

There were no cases of thyroid malignancies in the GPIF trials. There was 1 subject in the placebo arm of trial GPI2 who had two events related to MACE. These events were an acute myocardial infarction and coronary artery disease that resulted in hospitalization.

The tirzepatide PI also has a warning and precaution statement for an increased risk of diabetic retinopathy complications in patients with T2DM; this AESI was not assessed in the GPIF trials, as subjects with T2DM were excluded from the trial population. Each of the remaining AESIs are discussed below.

8.2.11.1. Gastrointestinal Adverse Events

Gastrointestinal AEs are common within the incretin class of drugs, and the PI for tirzepatide includes a warning and precaution for severe GI AEs. Dose escalation strategies are typically used to improve GI tolerability. The protocol for GPIF included strategies to mitigate and manage GI symptoms, including recommendations to eat small meals, temporary use of symptomatic antidiarrheal or antiemetic medications, and trial drug interruption, dose reduction, or discontinuation. To assess for severe or serious GI AEs in this application, AEs of GI disorders were defined from a Custom MedRA Query (CMQ) that captured both “severe” and “serious” GI events. This reviewer evaluated the list of included/excluded terms and found this list to be reasonable. Reported PTs included diarrhea, nausea, and gastroesophageal reflux disease. This list also included acute pancreatitis, which is discussed further in Section 8.2.5.6. This CMQ list identified eight subjects with treatment-emergent GI related AEs in GPIF and all subjects identified were in the tirzepatide arm (Table 33). The rates of such AEs are comparable to the frequency in the CWM trials.

Table 33: Summary of Serious and Severe Gastrointestinal Adverse Events (MITT – Safety Analysis Set), GPIF Trial

	TZP MTD[a] N = 233		Placebo N = 234	
Preferred Term	**n**	**(%)**	**n**	**(%)**
Any AE	8	(3.4)	0	(0.0)
Diarrhea	5	(2.1)	0	(0.0)
Nausea	3	(1.3)	0	(0.0)
Gastroesophageal reflux disease	1	(0.4)	0	(0.0)
Pancreatitis acute	1	(0.4)	0	(0.0)

Source: OCS Analysis Studio, Safety Explorer
Analysis Population is Modified Intent-to-Treat (MITT): Number of participants randomly assigned and received at least 1 dose of study drug.
[a]TZP MTD is tirzepatide 10 or 15 mg once weekly
Abbreviations: AE, adverse event

8.2.11.2. Severe Hypoglycemia

Hypoglycemia episodes were recorded on a specific case report form (CRF) and were not recorded as AEs or SAEs unless the event met serious criteria. Glucose levels ≥54 to <70 mg/dL were considered Level 1 hypoglycemia and could be self-treated with fast-acting carbohydrates. Glucose levels <54 mg/dL were considered Level 2 hypoglycemia and were noted as clinically relevant regardless of the presence or absence of symptoms of hypoglycemia. A severe hypoglycemic event was characterized by altered mental and/or physical status requiring assistance for the treatment of hypoglycemia. In GPI1, there were three hypoglycemia events reported in three subjects during the study; however, none of these events met severe criteria. One event was in a subject in the placebo group and two events were in tirzepatide-treated subjects. One event in a tirzepatide-treated subject was reported as a treatment-emergent adverse event (TEAE). This subject had a blood glucose level of 59 mg/dL and was reported as "asymptomatic hypoglycemia," mild in severity. There were no Level 2 or severe hypoglycemia events reported in GPI2.

8.2.11.3. Hepatobiliary Disorders

Both obesity and incretin drugs are associated with an increased risk for gallstone formation and related disorders, including cholelithiasis and cholecystitis. To assess for hepatobiliary events in this application, the Applicant used the following SMQs to identify hepatobiliary cases:

- Liver-related investigations, signs and symptoms (broad and narrow terms)
- Cholestasis and jaundice of hepatic origin (broad and narrow terms)
- Hepatitis non-infections (broad and narrow terms)
- Hepatic failure, fibrosis and cirrhosis and other liver damage (broad and narrow terms)
- Liver-related coagulation and bleeding disturbances (narrow terms)

- Gallbladder-related disorders (narrow terms)
- Biliary tract disorders (narrow terms)
- Gallstone-related disorders (narrow terms)

This reviewer evaluated the list of included/excluded terms and found that the list to be reasonable. A total of 11 subjects (4.7%) experienced at least 1 TEAE and there was a slightly greater number of hepatobiliary events in the placebo arm (7, 3.0%) compared to the tirzepatide arm (4, 1.7%) (Table 34). There were no serious or severe hepatic events reported in either GPI1 or GPI2. There were two serious gallbladder TEAEs (cholelithiasis), and both events were in the placebo group.

Table 34: Summary of Hepatobiliary Adverse Events (MITT – Safety Analysis Set), GPIF Trial

	TZP MTD[a] N = 233		Placebo N = 234	
Preferred Term	**n**	**(%)[b]**	**n**	**(%)[b]**
Any AE	4	(1.7)	7	(3.0)
Hepatic steatosis	3	(1.3)	3	(1.3)
Cholelithiasis	2	(0.9)	2	(0.9)
Alanine aminotransferase increased	0	(0.0)	1	(0.4)
Blood alkaline phosphatase increased	0	(0.0)	1	(0.4)
Gamma-glutamyltransferase increased	0	(0.0)	1	(0.4)
Hepatic function abnormal	0	(0.0)	1	(0.4)
Transaminases increased	0	(0.0)	1	(0.4)

Source: OCS Analysis Studio, Safety Explorer
Analysis Population is Modified Intent-to-Treat (MITT): Number of participants randomly assigned and received at least 1 dose of study drug.
[a]TZP MTD is tirzepatide 10 or 15 mg once weekly
[b] Number (%) of subjects with TEAEs, sorted on descending frequency order for SOC and descending frequency for PT according to total frequency in the TZP MTD arm. Subjects with multiple events in the same PT were counted only once in that PT. Subjects with events in more than one PT were counted once in each of these categories. Percentages were based upon number of subjects in the treatment group within the Safety Analysis Set.
Abbreviations: AE, adverse event

8.2.11.4. Arrhythmias and Cardiac Conduction Disorders

In trials GPI1 and GPI2, 12-lead ECGs were performed at baseline, Week 52, and if early discontinuation from the study occurred. If a clinically significant increase in the QT/QTc interval from baseline or other clinically significant quantitative or qualitative change from baseline was identified, the subject was assessed by the investigator for symptoms (palpitations, near syncope, syncope) and a determination was made about whether the subject could continue in the study.

To assess for arrhythmias and cardiac conduction disorder AEs in this application, the Applicant used the following SMQs to identify these cases:

- Arrhythmias

– For symptoms: Arrhythmia related investigations, signs and symptoms (broad and narrow terms)
– For supraventricular arrhythmias: Cardiac arrhythmia SMQ, under tachyarrhythmia sub SMQ
    - Supraventricular tachyarrhythmia (broad and narrow terms)
    - Tachyarrhythmia terms, nonspecific (narrow terms)
    - Ventricular tachyarrhythmia (narrow terms)

- Cardiac conduction disorders

– Conduction defects (narrow terms)
– Cardiac conduction disorders (high level terms, all PTs)

There was no meaningful imbalance in the proportion of subjects on tirzepatide or placebo with AEs related to arrhythmias or cardiac conduction disorders (Table 35). Increases in pulse rate, which were more common in subjects on tirzepatide, are discussed in Section 8.2.4.7. With the exception of (b) (4), adverse reactions related to cardiac conduction disorders and arrhythmias are not included in the USPI for tirzepatide. Given the low frequency of other arrhythmias or cardiac conduction disorder events and similar rate of occurrence in the tirzepatide and placebo arms of GPI1 and GPI2, additional labeling for these adverse events is not warranted.

Table 35: Summary of Arrhythmias and Cardiac Conduction Disorder Adverse Events (MITT – Safety Analysis Set), GPIF Trial

	TZP MTD[a] N = 233		Placebo N = 234	
Preferred Term	**n**	**(%)[b]**	**n**	**(%)[b]**
Any AE	13	(5.6)	11	(4.7)
Heart rate increased	6	(2.6)	2	(0.9)
Bundle branch block right	1	(0.4)	0	(0.0)
Extrasystoles	1	(0.4)	0	(0.0)
Tachycardia	2	(0.9)	1	(0.4)
Bradycardia	1	(0.4)	1	(0.4)
Supraventricular extrasystoles	1	(0.4)	1	(0.4)
Syncope	1	(0.4)	1	(0.4)
Ventricular extrasystoles	1	(0.4)	1	(0.4)
Atrioventricular block second degree	0	(0.0)	1	(0.4)
Supraventricular tachycardia	0	(0.0)	1	(0.4)
Atrial fibrillation	1	(0.4)	3	(1.3)

Source: OCS Analysis Studio, Safety Explorer
Analysis Population is Modified Intent-to-Treat (MITT): Number of participants randomly assigned and received at least 1 dose of study drug.
[a]TZP MTD is tirzepatide 10 or 15 mg once weekly
[b] Number (%) of subjects with TEAEs, sorted on descending frequency order for SOC and descending frequency for PT according to total frequency in the TZP MTD arm. Subjects with multiple events in the same PT were counted only once in that PT. Subjects with events in more than one PT were counted once in each of these categories. Percentages were based upon number of subjects in the treatment group within the Safety Analysis Set.
Abbreviations: AE, adverse event

8.2.11.5. Acute Renal Events

The PI for tirzepatide includes a warning and precaution statement regarding the risk of acute kidney injury, which can result from dehydration from gastrointestinal adverse reactions to tirzepatide (e.g., nausea, vomiting, diarrhea). There have also been postmarketing reports of acute kidney injury and worsening of chronic renal failure, which may sometimes require hemodialysis.

To assess for arrhythmias and cardiac conduction disorder adverse events in this application, the Applicant used the following SMQs to identify these cases:

- Acute renal failure (narrow terms)
- Chronic kidney disease (narrow terms)

In GPI2, there was one event of acute kidney injury in the tirzepatide arm. This event was severe in severity and led to discontinuation of the study drug. This subject also experienced dehydration, hypokalemia, and gastroenteritis. Symptoms resolved after the drug was withdrawn. This risk is captured by the current language in the PI.

8.2.11.6. Acute Pancreatitis

Exocrine pancreas safety, including concerns about acute pancreatitis, have been an area of interest with incretin drugs. However, as the Applicant notes, both obesity and T2DM raise the risk of acute pancreatitis, and it remains uncertain whether incretin therapy affects this risk. In addition, GLP-1R agonists increase amylase and lipase through an unclear mechanism as a class effect. In the clinical trials for T2DM and CWM, increases of 30-40% in amylase and lipase levels were noted. The increases were dose-dependent and were maintained until the end of treatment, with levels declining at the safety follow-up visit.

Post-marketing reports of acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis with incretin drugs have led to warning and precaution statement in labeling for the class. An imbalance in acute pancreatitis was reported in clinical trials (T2DM and CWM) for liraglutide, but not for semaglutide.

The Applicant's nonclinical program did not find evidence of pancreatitis, pancreatic cancer or tirzepatide-related pancreatic pathology in mice, rats, or monkeys. Subjects with a history of pancreatitis were excluded from this trial and clinical trials of tirzepatide for CWM and T2DM, so it is unknown whether a history of pancreatitis increases the risk of pancreatitis in subjects taking tirzepatide. Subjects in this trial who developed TEAEs of acute or chronic pancreatitis were also required to discontinue study drug.

In order to evaluate causes of acute pancreatitis comprehensively in the tirzepatide clinical development program for OSA, the Applicant used broad criteria to capture events sent for adjudication. These criteria included:

- all suspected cases of acute or chronic pancreatitis

- AEs of severe or serious abdominal pain of unknown etiology
- cases of pancreatic amylase or lipase values ≥ 3 times the upper limit of normal (ULN) with symptoms
- asymptomatic cases of amylase or lipase values ≥3 times the ULN that underwent additional diagnostic follow-up.

All suspected cases of acute or chronic pancreatitis were adjudicated by a committee blinded to treatment assignment. The criteria the Applicant used to diagnosis acute pancreatitis (two of the following three features: abdominal pain, characteristic of acute pancreatitis with pain often associated with nausea and vomiting, serum amylase and/or lipase ≥3 times the ULN and characteristic findings of acute pancreatitis on CT scan or MRI) appeared reasonable and consistent with standard of care. There were two cases in the tirzepatide arm of GPI2 of suspected pancreatitis that were reviewed for adjudication. Both cases had elevated amylase or lipase values ≥3 times the ULN and characteristic abdominal pain, but only one had a CT scan with characteristic findings of acute pancreatitis. Initially, only one event was reported as a TEAE; however, upon review by the adjudication committee, both events were positively adjudicated as a TEAEs of acute pancreatitis, both mild in severity.

8.2.11.7. Major Depressive Disorder and Suicidal Ideation

Suicidality and depression are safety issues of concern for all centrally acting obesity drugs including (b) (4) lorcaserin (NDA 22529), phentermine/topiramate (NDA 22580), and naltrexone/bupropion (NDA 200063). In addition, patients with OSA are more likely to experience major depressive disorder (MDD) compared to those without sleep apnea (Lu et al. 2017).

The protocol for the GPIF trials included scheduled baseline assessments of suicidal ideation and behavior and intervention emergent suicidal ideation and behavior were monitored using the Columbia Suicide-Severity Rating Scale (C-SSRS) and PHQ-9 screening tools. To assess for Major Depressive Disorder or Suicidal Ideation or Behavior adverse events in this application, the Applicant used the following SMQs to identify these cases:

- Depression, excluding suicide and self-injury (narrow terms)
- Suicide/self-injury (narrow terms)

This reviewer evaluated the list of included/excluded terms and found that preferred terms such as memory impairment and mood altered were included in the broad Depression excluding suicide and self-injury SMQ but excluded from the SMQ narrow terms list. These adverse events appeared relevant to capture; therefore, they are included in Table 36 below. There were two adverse events of suicide attempt in the tirzepatide arm (0.9%) compared to no events in the placebo arm. Adverse events of depression were similar between the two arms.

Table 36: Summary of Major Depressive Disorder or Suicidal Ideation or Behavior Adverse Events (MITT – Safety Analysis Set), GPIF Trial

	TZP MTD[a] N = 233		Placebo N = 234	
Preferred Term	**n**	**(%)[b]**	**n**	**(%)[b]**
Any AE	6	(2.6)	5	(2.1)
Depression	3	(1.3)	4	(1.7)
Suicide attempt	2	(0.9)	0	(0.0)
Mood altered	1	(0.4)	0	(0.0)
Memory impairment	0	(0.0)	1	(0.4)

Source: OCS Analysis Studio, Safety Explorer.
Analysis Population is Modified Intent-to-Treat (MITT): Number of participants randomly assigned and received at least 1 dose of study drug.
[a]TZP MTD is tirzepatide 10 or 15 mg once weekly
[b] Number (%) of subjects with TEAEs, sorted on descending frequency order for SOC and descending frequency for PT according to total frequency in the TZP MTD arm. Subjects with multiple events in the same PT were counted only once in that PT. Subjects with events in more than one PT were counted once in each of these categories. Percentages were based upon number of subjects in the treatment group within the Safety Analysis Set.
Abbreviations: TEAE, treatment-emergent adverse event.

8.2.11.8. Allergic or Hypersensitivity Reactions

Incretin drugs are associated with an increased risk of serious hypersensitivity reactions (e.g., anaphylaxis, angioedema), and the PI for tirzepatide contains a warning and precaution statement describing the occurrence of hypersensitivity following use of the medication. In addition, class labeling for incretin drugs includes a contraindication statement that contraindicates use for individuals with a history of a serious hypersensitivity reaction to the specific labeled drug. To assess for hypersensitivity events in this application, the Applicant used the following SMQs to identify hypersensitivity cases:

- Anaphylactic reaction (narrow and algorithm terms). (The anaphylaxis algorithm requires an Anaphylactic reaction SMQ narrow term, or that there be two Anaphylactic reaction SMQ broad terms from distinct categories occurring on the day of the same study drug administration.)
- Angioedema (narrow terms)
- Severe cutaneous adverse reactions (narrow terms)
- Hypersensitivity (narrow terms)

This reviewer evaluated the list of included/excluded terms and found that the list to be reasonable. The list did not include injection site reactions, which were reported separately. Reported preferred terms included urticaria, rash and angioedema. Preferred terms, such as cough, wheezing, asthma and seasonal allergy were included in the broad Hypersensitivity SMQ list but excluded from the Hypersensitivity SMQ narrow terms list.

Hypersensitivity events were classified as immediate if the TEAE occurred from the start of study drug administration up to 24 hours after end of study drug administration. Hypersensitivity events were classified as nonimmediate if the TEAE occurred more than 24

hours after the end of study drug administration, but prior to subsequent drug administration. In GPI1 a total of two (0.9%) subjects, one subject in the placebo group and one subject in the tirzepatide group, experienced at least 1 TEAE of potential, immediate hypersensitivity reactions within 24 hours following study drug administration. No subjects experienced an immediate hypersensitivity reaction in GPI2. There were no severe or serious immediate hypersensitivity reactions reported during the study period of GPI1 or GPI2.

One severe nonimmediate hypersensitivity reaction was reported during the study period of GPI1 for a subject in the tirzepatide group. This subject reported an event of a severe anaphylactic reaction occurring on study day 67 and resolving the same day. The most recent dose of tirzepatide 7.5 mg was reported on study day 64. This subject had a medical history of anaphylactic reaction to food due to food allergy. No actions were taken with regard to study medication. Table 37 summarizes hypersensitivity events during GPIF.

Table 37: Summary of Hypersensitivity Adverse Events (MITT – Safety Analysis Set), GPIF Trial

Preferred Term	TZP MTD[a] N = 233		Placebo N = 234	
	n	(%)[b]	n	(%)[b]
Any AE	7	(3.0)	5	(2.1)
Urticaria	3	(1.3)	0	(0.0)
Conjunctivitis	2	(0.9)	2	(0.9)
Mouth ulceration	1	(0.4)	0	(0.0)
Anaphylactic reaction	1	(0.4)	0	(0.0)
Dermatitis allergic	1	(0.4)	1	(0.4)
Drug hypersensitivity	1	(0.4)	0	(0.0)
Injection related reaction	1	(0.4)	0	(0.0)
Injection site rash	1	(0.4)	0	(0.0)
Angioedema	0	(0.0)	1	(0.4)
Hand dermatitis	0	(0.0)	1	(0.4)
Injection site urticaria	0	(0.0)	1	(0.4)
Rash pruritic	0	(0.0)	1	(0.4)
Rhinitis allergic	0	(0.0)	1	(0.4)

Source: OCS Analysis Studio, Safety Explorer.
Analysis Population is Modified Intent-to-Treat (MITT): Number of participants randomly assigned and received at least 1 dose of study drug.
[a]TZP MTD is tirzepatide 10 or 15 mg once weekly
[b] Number (%) of subjects with TEAEs, sorted on descending frequency order for SOC and descending frequency for PT according to total frequency in the TZP MTD arm. Subjects with multiple events in the same PT were counted only once in that PT. Subjects with events in more than one PT were counted once in each of these categories. Percentages were based upon number of subjects in the treatment group within the Safety Analysis Set.
Abbreviations: TEAE, treatment-emergent adverse event.

Injection site reactions were assessed using TEAEs of injection site reactions (using MedDRA PTs of high level terms of injection site reaction, administration site reaction and infusion site reaction) and details of injection site reactions collected in eCRF, including location of the reaction, timing of the reaction relative to study drug administration, and characteristics of the injection site reaction. At the time of AE occurrence in the tirzepatide group, samples were collected for measurement of tirzepatide ADAs and tirzepatide concentration. Overall, 26 subjects (11.2%) experienced a TEAE of injection site reaction (Table 38). Injection site reactions

were more common in the tirzepatide group (20, 8.6%) compared to placebo (6, 2.6%) and the most frequently reported injection site reaction PT was injection site reaction. Most events were mild in severity and most subjects experienced the most immediate onset of an injection site reaction even within the first 24 hours following study drug administration.

Table 38: Summary of Injection Site Reactions Adverse Events (MITT – Safety Analysis Set), GPIF Trial

Preferred Term	TZP MTD[a] N = 233		Placebo N = 234	
	n	(%)[b]	n	(%)[b]
Any AE	20	(8.6)	6	(2.6)
Injection site reaction	14	(6.0)	1	(0.4)
Injection site bruising	3	(1.3)	4	(1.7)
Injection site pruritus	3	(1.3)	0	(0.0)
Injection site erythema	2	(0.9)	0	(0.0)
Administration site reaction	1	(0.4)	0	(0.0)
Injection site rash	1	(0.4)	0	(0.0)
Injection site pain	0	(0.0)	1	(0.4)
Injection site urticaria	0	(0.0)	1	(0.4)

Source: OCS Analysis Studio, Safety Explorer.
Analysis Population is Modified Intent-to-Treat (MITT): Number of participants randomly assigned and received at least 1 dose of study drug.
[a]TZP MTD is tirzepatide 10 or 15 mg once weekly
[b] Number (%) of subjects with TEAEs, sorted on descending frequency order for SOC and descending frequency for PT according to total frequency in the TZP MTD arm. Subjects with multiple events in the same PT were counted only once in that PT. Subjects with events in more than one PT were counted once in each of these categories. Percentages were based upon number of subjects in the treatment group within the Safety Analysis Set.
Abbreviations: TEAE, treatment-emergent adverse event.

8.2.12. Additional Safety Explorations

Human Reproduction and Pregnancy

In GPIF, subjects were required to use appropriate contraception to avoid pregnancy in women of child-bearing potential who are subjects or partners of male subjects. Pregnancy was not excluded. Pregnancy during maternal or paternal exposure to the study drug did not meet the definition of an AE; however, these subjects were discontinued from study drug in the event of pregnancy. In GPI1, 1 subject in the placebo group and no subjects in the tirzepatide group reported maternal exposure before or during pregnancy and 1 subject in the tirzepatide group reported paternal exposure before or during pregnancy. Of these subjects, no tirzepatide-treated female subject reported a case of premature birth or spontaneous abortion. In GPI2, no subject reported maternal or paternal exposure to tirzepatide before or during pregnancy.

8.2.13. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Tirzepatide was first approved on May 13, 2022 in the US as an adjunct to diet and exercise to improve glycemic control in adults with T2DM. Since then, tirzepatide has been approved for

T2DM in over 50 countries. Tirzepatide was also approved in the US on November 8, 2023 as an adjunct to a reduced-calorie diet and increased physical activity for weight management in adults with obesity, or overweight with weight-related comorbidities. Tirzepatide has been authorized in the European Union and the United Kingdom and is approved or under review in other countries for weight management. An estimated 4,450,200 patients have been exposed to tirzepatide (any dose) since first approval.

To identify post-marketing safety issues, the Office of Pharmacovigilance and Epidemiology, Division of Pharmacovigilance I (DPV I), documented their Postmarket Drug Safety Surveillance Summary for tirzepatide (tradename Mounjaro) on October 13, 2023. DPV I conducted a search of the FAERS database over the period covering May 13, 2022, to August 3, 2023, a search of the medical literature, a review of the Periodic Safety Update Reports and Periodic Adverse Drug Experience Reports submitted for tirzepatide. Based on this review, DPV I identified several New Identified Safety Signals (NISS) for tirzepatide, including hypoglycemia, impaired gastric emptying, alopecia, aspiration, suicidal ideation, ileus, dysgeusia, eosinophilia, hypersensitivity, and cutaneous amyloidosis.

Since that time, DPV I has conducted two additional reviews relevant to this application. DPV I published a review on December 13, 2023 evaluating the relationship between GLP-1 receptor agonists and the safety signal of regurgitation and pulmonary aspiration of gastric contents during general anesthesia and deep sedation. A FAERS database search was conducted for all reports through July 31, 2023. DPV I also published a review on May 8, 2023 evaluating the relationship between GLP-1 receptor agonists and the safety signal of suicidal ideation and behavior. In this review, DPV I conducted a FAERS database search over the period covering January 1, 2013 to August 27, 2023. For both reviews, DPV I also conducted a search of the medical literature, review of the Periodic Safety Update Reports submitted for tirzepatide, and information requests were sent to the Applicants for their respective GLIP-1 receptor agonist products requesting a cumulating review of all relevant cases.

With regards to the safety signal of regurgitation and pulmonary aspiration, DPV I found the presence of postmarketing aspiration cases with plausible causality to support that the risk is more than theoretical. The Office of Pharmacovigilance and Epidemiology recommended an addition to the Warning and Precaution section of the USPI for all GLP-1 receptor agonist products informing of the risk of aspiration of gastric contents during general anesthesia and deep sedation. The PI for tirzepatide was updated to include this information on October 18, 2024, in accordance with a Safety Labeling Change (SLC) issued by DDLO.

For the safety signal of suicidal ideation and behavior, DPV I was unable to draw substantive conclusions about a potential causal association of GLP-1 receptor agonists and suicidal ideation and behavior.

Expectations on Safety in the Postmarket Setting

We expect the safety in the OSA population in the postmarket setting to be comparable to that

of the chronic weight management population. We anticipate capturing additional events through routine pharmacovigilance.

8.2.14. Integrated Assessment of Safety

Tirzepatide is an approved therapy with a well-characterized safety profile in populations closely related to the moderate-to-severe OSA and obesity population. The safety of tirzepatide among subjects with moderate-to-severe OSA and obesity was similar to the safety of tirzepatide among subjects in the CWM trials. Therefore, it is reasonable to rely on the safety profile of tirzepatide among subjects in the CWM trials as supplemental support.

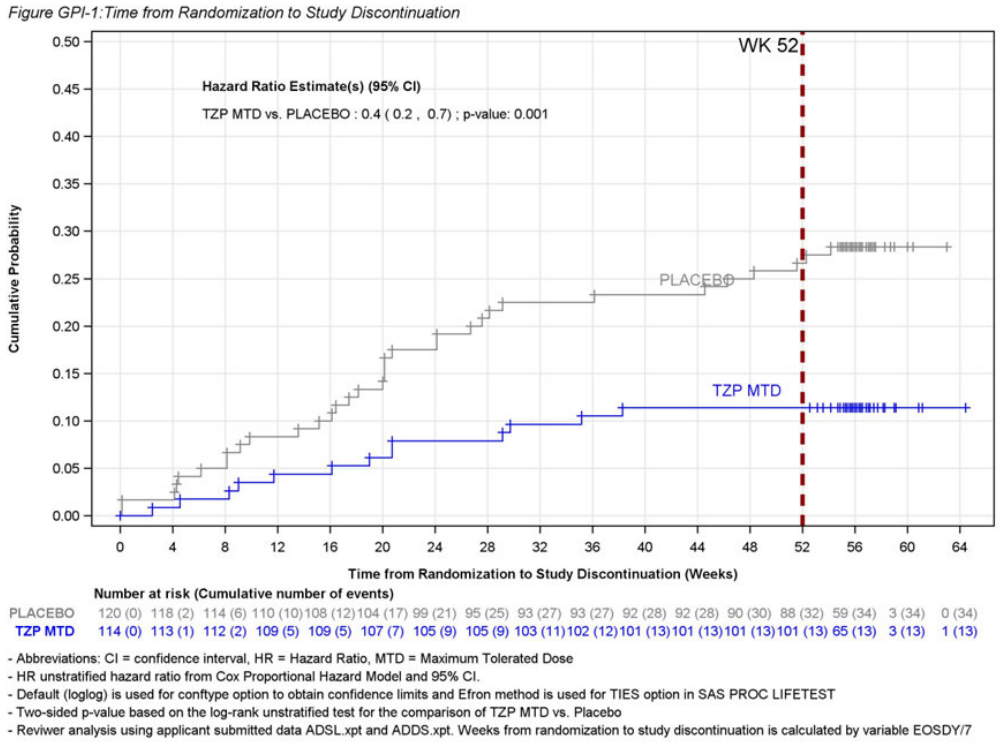
The safety experience based on the GPIF trials was limited to 233 subjects. There were no new safety concerns identified in the GPIF trials that alter the risk-benefit profile of tirzepatide for the moderate-to-severe OSA with obesity population when used as labeled. Generally, the frequency and type of AEs were consistent with previous studies in CWM. There were no deaths in the GPIF trials. The frequency of SAEs and AESIs were also consistent with previous studies in CWM. The most commonly reported TEAEs were related to GI disturbances of nausea, vomiting, and diarrhea, and most of these TEAEs were mild or moderate in severity. There were no new safety concerns regarding clinical laboratory evaluations identified in the GPIF trials. All potential risks can be managed through updates to the product label and routine pharmacovigilance.

8.3. Statistical Issues

- Robustness of Primary Efficacy Data

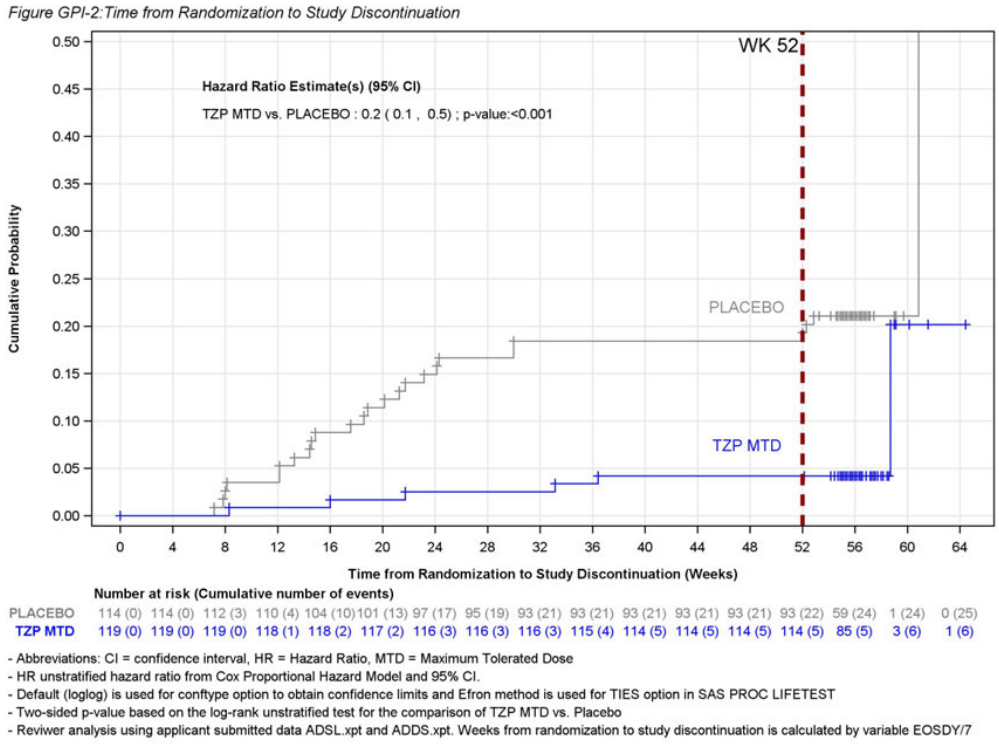
The Kaplan-Meier curves (Figure 15, Figure 16) indicate that the probability of study discontinuation in the placebo arm was higher than the probability of study discontinuation in the tirzepatide arm over time in both trials.

Figure 15. Kaplan-Meier Plot of Time from Randomization to Study Discontinuation from Randomization to Week 52 (mITT), Trial GPI1



Source: Statistical Analyst, SAS 9.4, ADSL.xpt and ADDS.xpt

Figure 16. Kaplan-Meier Plot of Time from Randomization to Study Discontinuation from Randomization to Week 52 (mITT), Trial GPI2



Source: Statistical Analyst, SAS 9.4, ADSL.xpt and ADDS.xpt

For the primary efficacy analysis of change from baseline in AHI at Week 52, there were 47 subjects with missing data in Trial GPI1, 14 (12.3%) in the tirzepatide arm and 34 (28.3%) in the placebo arm, and 36 subjects with missing data in Trial GPI2, 9 (7.6%) in the tirzepatide arm and 27 (23.7%) in the placebo arm. For the missing data handling, per the SAP, the retrieved dropout imputation was to be used to handle the missing data due to any other reason (for example, study discontinuation due to any reason other than COVID-19 or inadvertent enrollment) assuming missing not at random (MNAR); however, since there were not enough retrieved dropouts to provide a reliable imputation model, placebo-based multiple imputation was used.

A breakdown of the imputation methods and the reasons for missing data are given in Table 39. The table shows that there were a higher proportion of subjects with missing data that were imputed using the placebo-based multiple imputation in the placebo arms (20.0% and 18.4%) compared with the tirzepatide arms (7.0% and 3.4%) in both trials. Therefore, the statistical review team was initially concerned that the statistically significant treatment effect for the primary endpoint could have been driven by the higher placebo-based multiple imputed data in the placebo arm in both trials. In order to assess the impact of missing data imputation method on the robustness of the primary endpoint outcome measure, the planned tipping point analysis performed by the Applicant was carefully reviewed.

Table 39: Distribution of Missing Data in Primary Endpoint Analysis, Trials GPI1 and GPI2

	GPI 1			GPI 2		
	TZP MTD (N=114)	Placebo (N=120)	Total (N=234)	TZP MTD (N=119)	Placebo (N=114)	Total (N=233)
Missing Data, n (%)	**14 (12.3)**	**34 (28.3)**	**48 (20.5)**	**9 (7.6)**	**27 (23.7)**	**36 (15.5)**
Imputation methods and reasons for missing, n (%)						
Multiple imputation (MAR)	**6 (5.3)**	**10 (8.3)**	**16 (6.8)**	**5 (4.2)**	**6 (5.3)**	**11 (4.7)**
2. Data at Week 52 is missing and subject discontinued study on or prior due to inadvertent enrollment	5 (4.4)	10 (8.3)	15 (6.4)	2 (1.7)	4 (3.5)	6 (2.6)
7. Missing data at Week 52 but subject completed study treatment	1 (0.9)	0 (0)	1 (0.4)	3 (2.5)	2 (1.8)	5 (2.1)
Placebo-based multiple imputation	**8 (7.0)**	**24 (20.0)**	**32 (13.7)**	**4 (3.4)**	**21 (18.4)**	**25 (10.7)**
4. Missing data at Week 52 due to all other reasons	8 (7.0)	24 (20.0)	32 (13.7)	4 (3.4)	21 (18.4)	25 (10.7)

Abbreviations: MAR=Missing-at-random, MTD=maximum tolerated dose, TZP=tirzepatide.
Source: Statistical Analyst, SAS 9.4, ADSL.xpt and ADPSG.xpt

The tipping point analysis for Trial GPI1 indicates that, in order for the significant result to be tipped, the tirzepatide arm should be penalized at least 100 AHI episodes per hour for missingness when the placebo arm is not penalized for missingness (Table 40). Similarly, in order for the significant result to be tipped for Trial GPI2, the tirzepatide arm should be penalized at least 170 AHI episodes per hour for missingness when placebo arm is not penalized for missingness (Table 41). As these scenarios appear to be clinically implausible, the reviewer concludes that the primary analysis results in both trials are robust to the main missing data imputation method.

Table 40: Tipping Point Analysis: LS mean Difference (p-value) Between MTD TZP and Placebo in Change From Baseline in AHI at Week 52 (mITT), Trial GPI1

Delta for TZP	Delta for Placebo 0	Delta for Placebo -5	Delta for Placebo -10	Delta for Placebo -15	Delta for Placebo -20	Delta for Placebo -25	Delta for Placebo -30
0	-20.01 (<.0001)	-18.58 (<.0001)	-17.15 (<.0001)	-15.73 (<.0001)	-14.30 (<.0001)	-12.88 (<.0001)	-11.45 (0.0004)
10	-18.77 (<.0001)	-17.34 (<.0001)	-15.92 (<.0001)	-14.49 (<.0001)	-13.07 (<.0001)	-11.64 (0.0003)	-10.22 (0.0019)
20	-17.53 (<.0001)	-16.11 (<.0001)	-14.68 (<.0001)	-13.26 (<.0001)	-11.83 (0.0003)	-10.41 (0.0016)	-8.98 (0.0077)
30	-16.30 (<.0001)	-14.87 (<.0001)	-13.44 (<.0001)	-12.02 (0.0003)	-10.59 (0.0015)	-9.17 (0.0070)	-7.74 (0.0258)
40	-15.06 (<.0001)	-13.63 (<.0001)	-12.21 (0.0003)	-10.78 (0.0016)	-9.36 (0.0070)	-7.93 (0.0246)	-6.51 (0.0708)
50	-13.82 (<.0001)	-12.40 (0.0004)	-10.97 (0.0020)	-9.55 (0.0076)	-8.12 (0.0250)	-6.69 (0.0688)	-5.27 (0.1596)
60	-12.59 (0.0006)	-11.16 (0.0025)	-9.73 (0.0088)	-8.31 (0.0266)	-6.88 (0.0695)	-5.46 (0.1559)	-4.03 (0.3025)
70	-11.35 (0.0035)	-9.92 (0.0107)	-8.50 (0.0296)	-7.07 (0.0724)	-5.65 (0.1557)	-4.22 (0.2948)	-2.80 (0.4944)
80	-10.11 (0.0133)	-8.69 (0.0338)	-7.26 (0.0773)	-5.84 (0.1585)	-4.41 (0.2910)	-2.98 (0.4800)	-1.56 (0.7160)
90	-8.88 (0.0391)	-7.45 (0.0837)	-6.02 (0.1636)	-4.60 (0.2905)	-3.17 (0.4696)	-1.75 (0.6935)	-0.32 (0.9427)
100	-7.64 (0.0916)	-6.21 (0.1705)	-4.79 (0.2926)	-3.36 (0.4624)	-1.94 (0.6744)	-0.51 (0.9125)	0.91 (0.8461)

Abbreviations: AHI=Apnea Hypopnea Index, ANCOVA=analysis of covariance, MTD=maximum tolerated dose, TZP=tirzepatide.
Analysis Population is Modified Intent-to-Treat (mITT): Number of participants randomly assigned and received at least 1 dose of study drug.
Model: ANCOVA with Multiple Imputation by Treatment for Missing Data at 52 Weeks. Region, sex, and baseline AHI were included in the model. Delta penalties were applied to values imputed under the MNAR and MAR assumption.
Source: Full Clinical Study Report (page 427-430); results reproduced by statistical analyst using adpsg.xpt, adds.xpt, and adsl.xpt.

Table 41: Tipping Point Analysis: LS mean Difference (p-value) Between MTD TZP and Placebo in Change From Baseline in AHI at Week 52 (mITT), Trial GPI2

Delta for TZP	Delta for Placebo 0	Delta for Placebo -5	Delta for Placebo -10	Delta for Placebo -15	Delta for Placebo -20	Delta for Placebo -25	Delta for Placebo -30
0	-23.77 (<.0001)	-22.54 (<.0001)	-21.32 (<.0001)	-20.09 (<.0001)	-18.87 (<.0001)	-17.64 (<.0001)	-16.42 (<.0001)
10	-22.99 (<.0001)	-21.77 (<.0001)	-20.54 (<.0001)	-19.32 (<.0001)	-18.10 (<.0001)	-16.87 (<.0001)	-15.65 (<.0001)
20	-22.22 (<.0001)	-21.00 (<.0001)	-19.77 (<.0001)	-18.55 (<.0001)	-17.32 (<.0001)	-16.10 (<.0001)	-14.87 (<.0001)
30	-21.45 (<.0001)	-20.22 (<.0001)	-19.00 (<.0001)	-17.77 (<.0001)	-16.55 (<.0001)	-15.32 (<.0001)	-14.10 (<.0001)
40	-20.67 (<.0001)	-19.45 (<.0001)	-18.23 (<.0001)	-17.00 (<.0001)	-15.78 (<.0001)	-14.55 (<.0001)	-13.33 (<.0001)
50	-19.90 (<.0001)	-18.68 (<.0001)	-17.45 (<.0001)	-16.23 (<.0001)	-15.00 (<.0001)	-13.78 (<.0001)	-12.55 (0.0004)
60	-19.13 (<.0001)	-17.90 (<.0001)	-16.68 (<.0001)	-15.46 (<.0001)	-14.23 (<.0001)	-13.01 (0.0003)	-11.78 (0.0012)
70	-18.36 (<.0001)	-17.13 (<.0001)	-15.91 (<.0001)	-14.68 (<.0001)	-13.46 (0.0003)	-12.23 (0.0010)	-11.01 (0.0035)
80	-17.58 (<.0001)	-16.36 (<.0001)	-15.13 (<.0001)	-13.91 (0.0002)	-12.69 (0.0009)	-11.46 (0.0030)	-10.24 (0.0090)
90	-16.81 (<.0001)	-15.59 (<.0001)	-14.36 (0.0003)	-13.14 (0.0009)	-11.91 (0.0028)	-10.69 (0.0079)	-9.46 (0.0200)
100	-16.04 (<.0001)	-14.81 (0.0003)	-13.59 (0.0009)	-12.36 (0.0027)	-11.14 (0.0072)	-9.92 (0.0178)	-8.69 (0.0400)
110	-15.27 (0.0003)	-14.04 (0.0010)	-12.82 (0.0027)	-11.59 (0.0069)	-10.37 (0.0164)	-9.14 (0.0359)	-7.92 (0.0721)
120	-14.49 (0.0011)	-13.27 (0.0029)	-12.04 (0.0069)	-10.82 (0.0156)	-9.59 (0.0331)	-8.37 (0.0651)	-7.15 (0.1188)
130	-13.72 (0.0031)	-12.50 (0.0071)	-11.27 (0.0153)	-10.05 (0.0313)	-8.82 (0.0600)	-7.60 (0.1078)	-6.37 (0.1812)
140	-12.95 (0.0074)	-11.72 (0.0153)	-10.50 (0.0302)	-9.27 (0.0564)	-8.05 (0.0994)	-6.82 (0.1652)	-5.60 (0.2586)
150	-12.17 (0.0156)	-10.95 (0.0297)	-9.72 (0.0539)	-8.50 (0.0930)	-7.28 (0.1524)	-6.05 (0.2367)	-4.83 (0.3489)
160	-11.40 (0.0296)	-10.18 (0.0522)	-8.95 (0.0881)	-7.73 (0.1421)	-6.50 (0.2187)	-5.28 (0.3208)	-4.05 (0.4489)
170	-10.63 (0.0511)	-9.40 (0.0845)	-8.18 (0.1340)	-6.95 (0.2038)	-5.73 (0.2970)	-4.51 (0.4146)	-3.28 (0.5549)

Abbreviations: AHI=Apnea Hypopnea Index, ANCOVA=analysis of covariance, MTD=maximum tolerated dose, TZP=tirzepatide.
Analysis Population is Modified Intent-to-Treat (mITT): Number of participants randomly assigned and received at least 1 dose of study drug.
Model: ANCOVA with Multiple Imputation by Treatment for Missing Data at 52 Weeks. Region, sex, and baseline AHI were included in the model.
Source: Full Clinical Study Report (page 466-473); results reproduced by statistical analyst using adpsg.xpt, adds.xpt, and adsl.xpt.

8.4. Conclusions and Recommendations

This efficacy supplement (S-13) for tirzepatide proposes a new indication "for the treatment of moderate-to-severe OSA with obesity." To support the efficacy and safety of tirzepatide for the proposed indication, the Applicant submitted data from GPI1 and GPI2,two randomized, double-blind (DB), multi-center, placebo-controlled trials of 52 weeks duration conducted

under a basket-type master protocol that evaluated the efficacy and safety of tirzepatide at the MTD of 10 or 15 mg QW compared to placebo in 469 subjects with obesity and moderate-to-severe OSA.

The MTD of 10 or 15 mg was supported by adequate justification and clinical data from the CWM programs. There is also adequate nonclinical support for the proposed dose. No new nonclinical pharmacology or toxicology study reports were provided in the current supplement. No new presentations or devices were introduced with this supplement.

GPI1 and GPI2 were well-designed and well-conducted trials, and the results were both highly statistically significant and clinically meaningful, providing strong support for the efficacy of tirzepatide in treating adults with obesity and moderate-to-severe OSA. The primary endpoint for both GPI1 and GPI2 was the absolute change in AHI from baseline to Week 52. Tirzepatide demonstrated statistically significant superiority compared to placebo with a substantial reduction in AHI in both trials. Tirzepatide compared to placebo also resulted in statistically significant improvements across all key secondary endpoints, which included: percent change in AHI, percent of subjects with OSA remission or mild non-symptomatic OSA, change in SASHB, percent change in body weight, change in serum CRP concentration, and change in SBP. Since the AHI has limitations as a predictive measure of clinically meaningful outcomes in OSA (2019; Azarbarzin et al. 2019), these additional endpoints also contributed to the demonstration of substantial evidence of effectiveness.

In addition, exploratory analyses demonstrated that a higher proportion of subjects treated with tirzepatide compared to placebo achieved OSA remission (AHI <5 events/hour), improved from severe OSA to OSA remission and/or improved severity category (e.g., severe to mild), and showed an improvement in the PROMIS-SRI, all of which provided additional robustness to the trial results. Substantial evidence of effectiveness for the use of tirzepatide for the treatment of moderate-to-severe OSA with obesity has been demonstrated.

The safety profile for tirzepatide is well-established since its approval in 2022 and includes several warning and precautions statements, such as risks for acute kidney injury and acute pancreatitis. Common adverse reactions include nausea, diarrhea and vomiting, particularly during dose escalation. No new safety concerns are seen in the moderate-to-severe OSA with obesity population compared to the known safety profile established with similar doses in subjects with overweight or obesity. The safety concerns for tirzepatide are well-established for the class of incretin drugs and can be appropriately mitigated in the post-market setting mainly via labeling and routine pharmacovigilance.

Given the demonstration of substantial evidence of effectiveness and identification of no new safety findings, a favorable benefit-risk assessment for tirzepatide for the treatment of moderate-to-severe OSA with obesity has been established. As a result, the recommended regulatory action for this sNDA is **Approval**.

9. Advisory Committee Meeting and Other External Consultations

An Advisory Committee meeting was not convened for this sNDA. Tirzepatide is an approved and marketed drug product with a well-characterized safety profile, and efficacy in this patient population was adequately demonstrated by the completed trials.

10. Pediatrics

There was no pediatric data included in this submission. Tirzepatide is not approved for any pediatric indications at the time of this review. Refer to Section 12 regarding pediatric post-marketing studies.

11. Labeling Recommendations

11.1. Prescription Drug Labeling

The supplement proposed to add a new indication to include the treatment of adult patients with moderate to severe OSA and obesity based on the results of two adequate and well controlled trials. Refer to the Labeling Information Request dated November 22, 2024, December 6, 2024, and December 13, 2024 for the labeling revisions conveyed to the Applicant. The Applicant incorporated our revisions, and the agreed upon labeling is dated December 18, 2024. The labeling changes are summarized in Table 42.

Table 42: Labeling Changes

Full Prescribing Information Sections	Rationale for Major Changes Incorporated into the Finalized Prescribing Information (PI)
1 INDICATIONS AND USAGE	Zepbound® is indicated in combination with a reduced-calorie diet and increased physical activity to treat moderate to severe obstructive sleep apnea (OSA) in adults with obesity. *The OSA indication was added as a second bullet following the Weight Reduction and Long-Term Maintenance indication to reduce redundancy because the reduced calorie diet and increase physical activity also applied to the OSA indication.*
2 DOSAGE AND ADMINISTRATION	**Recommended Dose Escalation Schedule** subsection was created to separate the dose escalation schedule from Recommended Dosage. **Recommended Dose Escalation Schedule** subsection was added to Section 2 to include the specific dosage increments and frequency to escalate the dosage until a maintenance dosage is achieved.

	The Recommended Dosage was revised to **Recommended Maintenance and Maximum Dosage** with headings to clarify the maintenance dosage for each indication and the maximum dosage for all indications. The following is the recommended maintenance dosage for OSA: The recommended maintenance dosage are 10 mg or 15 mg injected subcutaneously once weekly.
4 CONTRAINDICATIONS	N/A
5 WARNINGS AND PRECAUTIONS	Similar adverse reaction (AR) rates for Zepbound were observed from the review of clinical studies for Weight Reduction and Long-Term Maintenance and OSA. Language to convey the similarity of ARs in the following Warnings and Precautions subsections were updated: Severe Gastrointestinal Adverse Reactions, Acute Gallbladder Disease, Acute Pancreatitis, and Hypersensitivity Reactions.
6 ADVERSE REACTIONS	Language that conveys that similar adverse reactions were observed with Zepbound from the OSA trials to those reported in the weight reduction trials was added under the heading of Adverse Reactions in Patients with Obstructive Sleep Apnea.
7 DRUG INTERACTIONS	N/A
8 USE IN SPECIFIC POPULATIONS (e.g., Pregnancy, Lactation, Females and Males of Reproductive Potential, Pediatric Use, Geriatric Use, Renal Impairment, Hepatic Impairment)	The Geriatric Use subsection was updated with information from the OSA clinical trials.
10 OVERDOSAGE	N/A
12 CLINICAL	The **Pharmacokinetics** subsection was updated with values

PHARMACOLOGY	reported for distribution and clearance of tirzepatide in patients with OSA and obesity. The **Immunogenicity** subsection was updated with ADA values from OSA clinical studies.
13 NONCLINICAL TOXICOLOGY	N/A
14 CLINICAL STUDIES	• Obstructive Sleep Apnea Studies in Adults with Obesity subsection was added that provides the efficacy of Zepbound for patients with moderate to severe obstructive sleep apnea and obesity. Zepbound was evaluated in a master protocol that included two randomized, double-blind, placebo-controlled trials (Study 5 and Study 6) for 52 weeks. Each study population is described in text and the patients' baseline disease characteristics are presented in a Table 8 of the PI. Study 5 included patients with OSA and obesity who were unable or unwilling to use Positive Airway Pressure (PAP) therapy and Study 6 included patients with OSA and obesity who were on PAP therapy. The primary endpoint was the change from baseline in the apnea-hypopnea index (AHI) at Week 52. The efficacy results are provided in Table 9 of the PI. • Figure depicting change in AHI through Week 52 added to label (Figure 7) to provide prescribers a visual understanding of the time course of improvements in AHI (Appendix Figure 24). • Included a descriptive statement summarizing the results of the assessment of sleep-related impairment using the Patient Reported Outcomes Measurement Information System (PROMIS) Short Form Sleep-Related Impairment 8a. The PROMIS-SRI endpoint results demonstrated meaningful improvements in both GPI1 and GPI2; (b) (4)
17 PATIENT COUNSELING	N/A

INFORMATION	
Product Quality Sections (i.e., DOSAGE FORMS AND STRENGTHS, DESCRIPTION, HOW SUPPLIED/STORAGE AND HANDLING)	N/A

Source: Labeling Discussion Comments dated November 22, 2024, December 6, 2024, and December 13, 2024.

12. Postmarketing Requirements and Commitment

Below in bold are the two postmarketing requirements (PMRs) that will be issued for tirzepatide; no postmarketing commitments (PMCs) are recommended for this application. As part of the agreed initial Pediatric Study Plan (iPSP) for tirzepatide for OSA under IND 157090, the Division agreed to waiving the pediatric study requirement for ages 0 through 5 years (inclusive), and to deferring the studies in ages 6 years to 17 years (inclusive). The Applicant's deferred pediatric studies are required as postmarketing studies in accordance with the Pediatric Research Equity Act (PREA). As detailed in the iPSP, the phase 3 OSA trial in pediatric subjects should be initiated once preliminary safety and efficacy are established in adults aged ≥18 years, by trials GPI1 and GPI2 in the current NDA and once safety and PK data is available from pediatric trials of CWM.

PMR-1 **Conduct a 72-week randomized, double-blind, placebo-controlled, parallel-group clinical study in adolescents 12 to 17 years of age (inclusive) with obesity-related obstructive sleep apnea (OSA) to assess the safety, efficacy, and pharmacokinetics of tirzepatide.**

Draft Protocol Submission:	**June 2031**
Final Protocol Submission:	**December 2031**
Study Completion:	**April 2036**
Final Report Submission:	**October 2036**

PMR-2 **Conduct a 72-week randomized, double-blind, placebo-controlled, parallel-group clinical study in children 6 to 11 years of age (inclusive) with obesity-related OSA to assess the safety, efficacy, and pharmacokinetics of tirzepatide.**

Draft Protocol Submission:	**June 2031**
Final Protocol Submission:	**December 2031**
Study Completion:	**November 2039**
Final Report Submission:	**May 2040**

13. Division Director (Clinical) Comments

Eli Lily and Company (The Applicant) has submitted a supplemental new drug application (NDA 217806/S-013) for tirzepatide, a dual agonist of the glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) receptors, for the treatment of moderate to severe obstructive sleep apnea (OSA) in adults with obesity. Tirzepatide is currently approved for the treatment of type 2 diabetes mellitus and to reduce excess body weight and maintain weight reduction long term in adults with obesity or adults with overweight in the presence of at least one weight-related comorbid condition.

The Applicant has provided the results of two, adequate and well-controlled trials to demonstrate substantial evidence of effectiveness of tirzepatide in the treatment of patients with moderate to severe OSA. GPI1 and GPI2 were randomized, double-blind, multi-center, placebo-controlled trials of 52 weeks duration conducted under a basket-type master protocol that evaluated the efficacy and safety of tirzepatide at the maximum tolerated dose (MTD) (10 or 15mg) QW compared to placebo in 469 subjects with obesity and moderate to severe OSA. GPI1 enrolled subjects unable to tolerate positive airway pressure (PAP) therapy. GPI2 enrolled subjects using PAP, the standard of care for moderate to severe OSA. Subjects were required to have a diagnosis of moderate to severe OSA with an AHI ≥15 events/hour, obesity (BMI of 30 kg/m^2 or greater), and a history of at least one self-reported unsuccessful dietary effort to lose body weight.

Efficacy

The primary endpoint for both GPI1 and GPI2 was the absolute change in AHI from baseline to Week 52. In both trials, tirzepatide MTD demonstrated a statistically significant improvement when compared with placebo in change from baseline to Week 52 in AHI with the difference in LS means of -20.0 [95% CI:-25.8, -14.2; p-value <0.01] and -23.8 [95% CI: -29.6, -17.9; p-value < 0.01] in GPI1 and GPI2, respectively.

In order to interpret the clinical significance of this reduction in AHI, the review team examined the results of various secondary and exploratory analyses. The magnitude of change in AHI for subjects treated with tirzepatide was large enough to result in categorical shifts in disease severity and even in disease remission for a large portion of subjects. To illustrate this point, in both trials, tirzepatide MTD demonstrated a statistically significant improvement over placebo in percentage of subjects achieving OSA remission or mild non-symptomatic OSA (AHI <5 or AHI 5-14 with ESS ≤10) at Week 52 with the odds ratio of 7.3 [95% CI: 3.2, 17.0; p-value <0.01] and 6.6 [95% CI: 3.1, 14.0; p-value <0.01] in GPI1 and GPI2, respectively. This endpoint is particularly clinically meaningful because patients within these parameters (AHI <5 or AHI 5-14 with ESS ≤10) typically do not require treatment in clinical practice. In addition, the sleep apnea specific hypoxic burned (SASHB), an important physiologic measure of sleep disordered ventilation

associated with long-term cardiovascular morbidity and mortality in patients with OSA, was also significantly improved at Week 52 in tirzepatide treated patients. The results from these additional endpoints are highly persuasive and support the clinical significance of the magnitude of AHI improvement in both trials.

Patient-reported outcomes to investigate sleep-related impairment (PROMIS-SRI) and sleep disturbance (PROMIS-SD) were also evaluated in trials GPI1 and GPI2. Although both instruments were deemed to have content validity, only the PROMIS-SRI was determined to have demonstrated a clinically meaningful improvement in patients treated with tirzepatide, as analyzed in each individual trial. It was notable that baseline scores with both PROs were similar to the general population, indicating subjects did not have sufficient sleep impairment or sleep disturbance at baseline for an adequate assessment of improvement. Future clinical development programs for the treatment of OSA may want to consider strategies to enrich their patient population with subjects who are symptomatic with sleep impairment or sleep disturbance.

Safety

Tirzepatide is an approved therapy with a well-characterized safety profile in populations closely related to the moderate to severe OSA and obesity population. The safety of tirzepatide among subjects with moderate to severe OSA and obesity was similar to the safety of tirzepatide among subjects in the CWM trials. No new safety signals were noted.

Benefit Risk Assessment and Regulatory Action

The review team has determined that the submitted efficacy data have provided substantial evidence of effectiveness (SEE) to support tirzepatide to treat moderate to severe OSA in patients with obesity, and I agree with their conclusions. The magnitude of treatment effect observed in AHI was substantial. The magnitude of the change in AHI for subjects treated with tirzepatide was large enough to result in categorical shifts in disease severity and even in disease remission for a large portion of subjects, which was also supported by improvement in other physiologic measures, such as SASHB. It is notable that patients lost ~16-17% of their body weight. The substantial reduction in body weight, as well as oropharyngeal and abdominal wall fat deposits, is likely the primary mechanism by which tirzepatide exerts its effect in OSA. No new safety signals were noted with this supplemental new drug application, resulting in a favorable benefit-risk assessment. The Division and the Applicant have agreed upon the final labeling language, and the content of post-marketing requirements.

There are currently no FDA-approved drugs approved for the treatment of OSA. Approval of tirzepatide for the indicated patient population would represent the first approval of a pharmacotherapy in OSA and will be a significant addition to the armamentarium for providers who treat these patients. The action for this application will be **Approval.**

14. Appendices

14.1. References

Guidances

Draft guidance for industry *Patient-Focused Drug Development: Incorporating Clinical Outcome Assessments Into Endpoints for Regulatory Decision-Making* (April 2023)

Guidance for Clinical Investigators, Industry, and FDA Staff *Financial Disclosure by Clinical Investigators* (February 2013)

Literature

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14.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): 18F-MC-GPI1, 18F-MC-GPI2

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 287		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in trial: 0 Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		

Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

14.3. OCP Appendices (Technical documents supporting OCP recommendations)

The Applicant did not conduct any stand-alone clinical pharmacology studies to support this efficacy supplement (NDA217,806/S-013) as the clinical pharmacology of tirzepatide had been well characterized in the T2DM and CWM development programs. To date, the completed clinical pharmacology studies of tirzepatide are summarized in Table 43 and Table 44.

Refer to Office of Clinical Pharmacology Reviews of tirzepatide in DARRTS with the Reference ID of 4954959 dated 3/18/2022 under NDA 215866 and the Reference ID of 5258712 dated 10/11/2023 under NDA 217806 for more information.

Table 43. Completed Clinical Pharmacology Studies Submitted with the Original T2DM Application

Study	Description	Population	Reference
I8F-MC-GPHX	Disposition of radioactivity and PK	Healthy males	Summary of Clinical Pharmacology Studies Section 2.7.2.2.1.1.1 of the original application
I8F-MC-GPGA	Single- and multiple-dose safety, PK, and PD	Healthy participants and participants with T2DM[a]	Summary of Clinical Pharmacology Studies Section 2.7.2.2.1.2.1 of the original application
I8F-JE-GPGC	Multiple-dose safety, PK, PD	Japanese T2DM[b]	Summary of Clinical Pharmacology Studies Section 2.7.2.2.1.2.2 of the original application
I8F-MC-GPGS	Effect of injection device	Healthy participants	Biopharmaceutic Studies and Associated Analytical Methods Section 2.7.1.2 of the original application.
I8F-MC-GPHI	Effect of injection site and BMI	Healthy participants; low and high BMI	Summary of Clinical Pharmacology Studies Section 2.7.2.2.1.3.1 of the original application
I8F-MC-GPGG	Effect of renal impairment	Normal or impaired renal function	Summary of Clinical Pharmacology Studies Section 2.7.2.2.1.3.2 of the original application
I8F-MC-GPGQ	Effect of hepatic impairment	Normal or impaired hepatic function	Summary of Clinical Pharmacology Studies Section 2.7.2.2.1.3.3 of the original application
I8F-MC-GPGR	Effect on combined OC	Healthy women eligible to use OC	Summary of Clinical Pharmacology Studies Section 2.7.2.2.1.4.1 of the original application
I8F-MC-GPGT	Effect on pancreatic α- and β-cell function, insulin sensitivity, food intake, and appetite	Participants with T2DM[c]	Summary of Clinical Pharmacology Studies Section 2.7.2.2.1.5.1 of the original application and in Section 2.7.2.2.1.4

Source: 2.7.2 Summary of Clinical Pharmacology Studies (CWM), Table 2.7.2.2.

Table 44. Completed Clinical Pharmacology Studies Submitted with the CWM Application

Study	Description	Population	SC Dosing Regimen	Key Messages
I8F-MC-GPHU	Impact of TZP on gastric emptying	Obesity or overweight with or without T2DM	Total dosing duration: 6 weeks Dose-escalation scheme: TZP QW: 5 mg (2 weeks), 10 mg (3 weeks), 15 mg (1 week) Acetaminophen dosing: Days -1, 2, and 37	• Overall in participants with obesity or overweight, acetaminophen PK was impacted in a similar manner as presented in Study GPGA, and the effect tachyphylaxed faster in participants without T2DM compared to participants with T2DM.
I8F-MC-GPHT	Multiple-dose safety, PK, PD	Native Chinese with T2DM[a]	Total dosing duration: 16 to 24 weeks TZP QW dose range: 2.5 to 15 mg [1] 2.5 mg (4 weeks), 5 mg (4 weeks), 7.5 mg (4 weeks), 10 mg (4 weeks) [2] 2.5 mg (4 weeks), 5 mg (4 weeks), 7.5 mg (4 weeks), 10 mg (4 weeks), 12.5 mg (4 weeks), 15 mg (4 weeks) or Placebo	• TZP safety and PK profiles in Chinese participants with T2DM was consistent with findings from Study GPGA. • Mean body weight change from baseline in the 10-mg treatment group at Week 16 was -4.2 kg (-6.8%) and in the 15-mg treatment group at Week 24 was -6.7 kg (-10.1%).
I8F-MC-GPHG	Effect on the counter-regulatory response to hypoglycemia	T2DM[b]	Total dosing duration: 12 weeks Dose-escalation scheme: TZP QW: 2.5 mg (2 weeks), 5 mg (2 weeks), 10 mg (4 weeks), 15 mg (4 weeks) or Placebo	• The primary analysis of glucagon response during the induced hypoglycemia showed no statistically significant difference in the change in glucagon concentration from the target PG plateau of 100 mg/dL (5.5 mmol/L) to the target PG nadir plateau of 45 mg/dL (2.5 mmol/L) when receiving tirzepatide 15 mg QW compared to placebo.

Source: 2.7.2 Summary of Clinical Pharmacology Studies (CWM), Table 2.7.2.3.

14.3.1. Summary of Bioanalytical Method Validation and Performance

14.3.1.1. PK assays: bioanalytical methods for determination of tirzepatide concentrations in human plasma

The Applicant developed and validated liquid chromatography with mass spectrometry (LC/MS) methods for detecting tirzepatide intact mass, comprising the full-length peptide plus the linker and acyl side chain. Two LC/MS methods developed and validated by (b) (4) and (b) (4) were used to analyze human plasma samples obtained from the global study participants outside of China and from the study participants in China, respectively. Both analytical methods were used in the CWM program of tirzepatide. Briefly, tirzepatide was extracted from human plasma using immunoaffinity in a 96-well format and LSN3316897 (stable isotope-labeled tirzepatide) as the internal standard (IS). Then, tirzepatide and IS were quantified using a Q Exactive or Q Exactive Plus quadrupole-orbitrap mass spectrometer equipped with Heated Electrospray Ionization and High Mass Resolution, Accurate Mass Monitoring detection. Liquid chromatography was performed with an LC/MS system consisting of a Supelco Discovery BioWide Pore C5-3 chromatography column and Dionex UltiMate 3000 system. The concentrations were calculated using peak area ratios, and the linearity of the calibration curve was determined using linear regression analysis employing a $1/x^2$ weighting. The standard curve range was 2.00 ng/mL or 4.00 ng/mL to 500 ng/mL. The validation parameters and performance of LC/MS for measurement of tirzepatide concentrations in human plasma by (b) (4) are summarized in Table 45 and Table 46, respectively.

Table 45. Summary of Validation Parameters of the LC/MS for Measurement of Tirzepatide Concentrations in Human Plasma ((b) (4))

Bioanalytical method validation report name, amendments, and hyperlinks	Report 191444 (b) (4) _EII_R3 (b) (4)		
Method description	Partial Method Validation for the Quantitation of LY3298176 (GIP707) in Human Plasma by HRAM LC/MS		
Materials used for standard calibration curve and concentration	Tirzepatide lot RS1058 Internal standard (IS): LSN3316897 lot BCA-BE03935-132 Citrate buffer solution		
Validated assay range	2.00 to 500 ng/mL		
Material used for quality controls (QCs) and concentration	Tirzepatide lot RS1058 Internal standard (IS): LSN3316897 lot BCA-BE03935-132 Citrate buffer solution		
Minimum required dilutions (MRDs)	Not applicable		
Source and lot of reagents	Not applicable		
Regression model and weighting	Weighted $1/x^2$ least squares linear regression		
Validation parameters	**Method validation summary**		**Source location**
Standard calibration curve performance during accuracy and precision runs	Number of standard calibrators from LLOQ to ULOQ	8	191444 (b) (4) _EII_R3 Section 5.3.1.4
	Cumulative accuracy (%bias) from LLOQ to ULOQ Tirzepatide	-2.8% to 4.8%	191444 (b) (4) _EII_R3 Section 5.3.1.4
	Cumulative precision (%CV) from LLOQ to ULOQ Tirzepatide	≤4.8%	191444 (b) (4) _EII_R3 Section 5.3.1.4
Performance of QCs during accuracy and precision runs	Cumulative accuracy (%bias) in 3 QCs QCs: Tirzepatide	-2.1% to 2.8%	191444 (b) (4) _EII_R3 Section 5.3.1.4
	Inter-batch %CV QCs: Tirzepatide	≤12.9%	191444 (b) (4) _EII_R3 Section 5.3.1.4
	Total error (TE) QCs:	Not applicable	
Selectivity & matrix effect	Number of total lots tested. Range of observed bias. State any issue		Six lots of blank plasma were tested. Response was ≤12.3% of LLOQ.
Interference & specificity	Number of total lots tested. Range of observed bias. State any issue		Not applicable
Hemolysis effect	Number of total lots tested. Range of observed bias. State any issue		One lot of 2% hemolytic plasma was tested. Response was 6.9% of LLOQ.
Lipemic effect	Number of total lots tested. Range of observed bias. State any issue		One lot of lipemic plasma was tested. Response was 7.3% of LLOQ.
Dilution linearity & hook effect	100-fold dilution validated. Hook effect not applicable.		

Bench-top/process stability	Plasma: 24 hours at room temperature Extracted plasma: 177 hours at room temperature	
Freeze-Thaw stability	5 freeze-thaw cycles at -20°C and -70°C	
Long-term storage	680 days at -20°C and 842 days at -70°C	
Parallelism	Not applicable	
Carry over	There was no significant carryover.	
Method performance in Study		
Assay passing rate	GPIF (GPI1): 11 out of 11 runs passed (100%) GPIF (GPI2): 11 out of 13 runs passed (85%)	GPIF (GPI1) GPIF (GPI2)
Standard curve performance	• Cumulative bias range: GPIF (GPI1): -2.4% to 2.4% GPIF (GPI2): -2.0% to 1.0% • Cumulative precision: GPIF (GPI1): ≤10.4% CV GPIF (GPI2): ≤11.0% CV	GPIF (GPI1) GPIF (GPI2)
QC performance	• Cumulative bias range: GPIF (GPI1): -2.2% to -0.6% GPIF (GPI2): -7.7% to -2.0% • Cumulative precision: GPIF (GPI1): ≤10.7% CV GPIF (GPI2): ≤11.2% CV	GPIF (GPI1) GPIF (GPI2)
Method reproducibility	GPIF (GPI1): 11% of samples were run in ISR and 97% passed criteria. GPIF (GPI2): 10% of samples were run in ISR and 97% passed criteria.	GPIF (GPI1) GPIF (GPI2)
Study sample analysis/ stability	Samples were kept at -70°C for up to 479 days. Stability was established for 842 days at -70°C.	GPIF (GPI1) GPIF (GPI2)

Abbreviations: CV = coefficient of variation; GPI1 = Study I8F-MC-GPI1; GPI2 = Study I8F-MC-GPI2; GPIF = Study I8F-MC-GPIF; HRAM = high resolution accurate mass; ISR = incurred sample reanalysis; LBA = ligand-binding assay; LC/MS = liquid chromatography with tandem mass spectrometry; LLOQ = lower limit of quantitation; ULOQ = upper limit of quantitation.

Source: 2.7.1.4 Appendix to the Summary of Biopharmaceutic Studies and Associated Analytical Methods, Table App 2.7.1.4.2.

Table 46. Summary of Validation Parameters of the LC/MS for Measurement of Tirzepatide Concentrations in Human Plasma (b) (4)

Bioanalytical method validation report name, amendments, and hyperlinks	Report 400008-191850- (b) (4) R1-R2 (b) (4)		
Method description	Quantification of LY3298176 in Human Plasma by LC/MS		
Materials used for standard calibration curve and concentration	Tirzepatide lot # RS1058 Internal standard: LSN3316897 lot # BCA-BE03935-132		
Validated assay range	4.00 to 500 ng/mL		
Material used for quality controls (QCs) and concentration	Tirzepatide lot # RS1058 Internal standard: LSN3316897 lot # BCA-BE03935-132		
Minimum required dilutions (MRDs)	Not applicable		
Source and lot of reagents (LBA)	Not applicable		
Regression model and weighting	Weighted $1/x^2$ quadratic regression		
Validation parameters	**Method validation summary**		**Source location**
Standard calibration curve performance during accuracy and precision runs	Number of standard calibrators from LLOQ to ULOQ	8	400008-191850 (b) (4) -R1-R2 Section 5.3.1.4
	Cumulative accuracy (%bias) from LLOQ to ULOQ Tirzepatide	-3.4% to 4.0%	400008-191850- (b) (4) -R1-R2 Section 5.3.1.4
	Cumulative precision (%CV) from LLOQ to ULOQ Tirzepatide	≤5.8%	400008-191850 (b) (4) -R1-R2 Section 5.3.1.4
Performance of QCs during accuracy and precision runs	Cumulative accuracy (%bias) in 3 QCs QCs: Tirzepatide	-1.9% to 2.7%	400008-191850- (b) (4) -R1-R2 Section 5.3.1.4
	Inter-batch %CV QCs: Tirzepatide	≤8.9%	400008-191850 (b) (4) -R1-R2 Section 5.3.1.4
	Total error (TE) QCs:	Not applicable	
Selectivity & matrix effect	Number of total lots tested. Range of observed bias. State any issue		Six lots of blank plasma were tested for selectivity. Response was 0.0% of LLOQ. Matrix effect was tested at 3 concentrations and passed the acceptance criteria for matrix effect.
Interference & specificity	Number of total lots tested. Range of observed bias. State any issue		Interference was evaluated in all batches. No interference effects were observed.
Hemolysis effect	Number of total lots tested. Range of observed bias. State any issue		Six lots of 2% hemolytic plasma were tested. Response was 1.7% of LLOQ.
Lipemic effect	Number of total lots tested. Range of observed bias. State any issue		Six lots of lipemic plasma were tested. Response was 2.4% of LLOQ.

Dilution linearity & hook effect	100-fold dilution validated. Hook effect not applicable.	
Bench-top/process stability	Plasma: 24 hours at room temperature Extracted plasma: 179 hours at 6°C	
Freeze-Thaw stability	5 freeze-thaw cycles at -20°C and -70°C	
Long-term storage	804 days at -20°C and -70°C	
Parallelism	Not applicable	
Carry over	There was no significant carryover.	
Method performance in Studies		
Assay passing rate	GPIF (GPI1): 3 out of 3 runs passed (100%) GPIF (GPI2): 2 out of 2 runs passed (100%)	GPIF (GPI1) GPIF (GPI2)
Standard curve performance	• Cumulative bias range: GPIF (GPI1): -4.4% to 3.7% GPIF (GPI2): -3.6% to 2.4% • Cumulative precision: GPIF (GPI1): ≤6.8% CV GPIF (GPI2): ≤6.6% CV	GPIF (GPI1) GPIF (GPI2)
QC performance	• Cumulative bias range: GPIF (GPI1): 4.3% to 5.6% GPIF (GPI2): -0.8% to 4.5% • Cumulative precision: GPIF (GPI1): ≤8.1% CV GPIF (GPI2): ≤4.9% CV	GPIF (GPI1) GPIF (GPI2)
Method reproducibility	GPIF (GPI1): 29% of samples were run in ISR and 88% passed criteria. GPIF (GPI2): 77% of samples were run in ISR and 100% passed criteria.	GPIF (GPI1) GPIF (GPI2)
Study sample analysis/ stability	Samples were kept at -70°C for up to 525 days. Stability was established for 804 days at -70°C.	GPIF (GPI1) GPIF (GPI2)

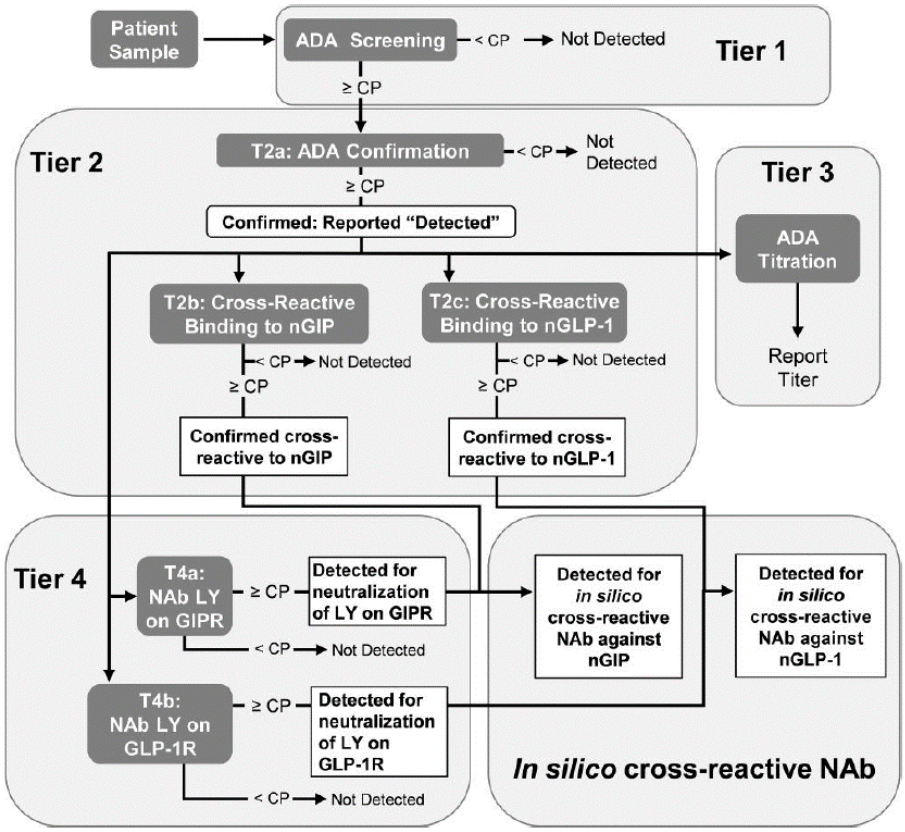
Abbreviations: CV = coefficient of variation; GPI1 = Study I8F-MC-GPI1; GPI2 = Study I8F-MC-GPI2; GPIF = Study I8F-MC-GPIF; HRAM = high resolution accurate mass; ISR = incurred sample reanalysis; LBA = ligand-binding assay; LC/MS = liquid chromatography with tandem mass spectrometry; LLOQ = lower limit of quantitation; ULOQ = upper limit of quantitation.

Source: 2.7.1.4 Appendix to the Summary of Biopharmaceutic Studies and Associated Analytical Methods, Table App 2.7.1.4.2.

14.3.1.2. Immunogenicity assays: methods for testing anti-drug antibodies and neutralizing anti-drug antibodies

To characterize the potential immune response of tirzepatide in humans, the Applicant has developed a multi-tiered immunogenicity testing strategy with ligand-binding method used for several ADA assays, cell-based method used for NAb assays, and an in-silico classification method used to detect cross-reactive NAb (Figure 17).

Figure 17. Tirzepatide Immunogenicity Sample Testing Paradigm



ADA=anti-drug antibodies; CP=cut point; GIP=glucose-dependent insulinotropic polypeptide; GLP-1=glucagon-like peptide-1; LY=LY3298176 (tirzepatide); NAb=neutralizing antibody; R=receptor
Source: 1) Method History Report Version 3 Figure 5.1 (with modification)
2) Mullins GR, et.al J Clin Endocrinol Metab, 2024, 109(2):361-369

ADA Assays

An affinity capture elution bridge electrochemiluminescence (ECL) immunosorbent assay developed and validated in the T2DM and CWM programs of tirzepatide was used for detection of ADA against tirzepatide in human serum from the OSA phase 3 trials.

Briefly, human ADA in patients' sera were detected by an affinity capture elution assay on the Meso Scale Discovery (MSD) platform. A Streptavidin plate previously was coated with biotinylated (Bt)-peptides, GIP735 and GIP740 (GIP707 with and without the fatty acid group). Analytical samples were then diluted to the assay minimum required dilution and captured overnight at 4°C by the Bt-peptide-coated on the Streptavidin plate. The captured ADA were eluted from the plate by acid treatment, neutralized in a fresh MSD plate, and allowed to bind. After the plate was blocked, ADA were detected by Streptavidin-Ruthenium using an MSD plate reader. After a wash step, a tripropylamine-containing buffer (MSD®, MD) was added to the plate. Ruthenium emits light at 620 nm when electrically stimulated and co-reacts with the tripropylamine buffer to enhance the ECL signal. The ECL units are directly proportional to the

amount of tirzepatide-specific ADA bound by the initial capture present in the well. The assay was used to determine the specificity of antibodies detected, as well as to measure the titer of specific human ADA against tirzepatide. Table 47 summarizes the validation assay parameters, acceptance criteria, and results summary.

Table 47. Validation Assay Parameters, Acceptance Criteria, and Results Summary

Assay Parameter	A Priori Acceptance Criteria	Pass/Fail	Results
MRD	Confirm performance of the MRD identified during assay development and verified in the global validation (1:10)	Pass	Confirmed MRD = 1:10
Assay Controls	The assay controls must generate a mean signal (ECLU) according to their prepared levels: NC<LPC<MPC<HPC. The HPC must provide a mean signal in the assay corresponding to the upper range of linearity of the assay. The MPC must approximate the mid-point (on a log scale) of the LPC and HPC signal. The target LPC value is fall within the target range identified above. The NC must be within ±40% of the mean signal (minimum ±40 ECLU) from quality controls during the cut point experiment.	Pass	Uninhibited Control Ranges Assay Control / Mean Signal (ECLU) / %CV / -40% (-40ECLU) / +40% (+40 ECLU) NC / 84 / 17.1 / 44 / 124 LPC / 207 / 12.6 / 124 / 290 MPC / 1616 / 15.3 / 970 / 2262 HPC / 10443 / 17.1 / 6266 / 14620
Screening (Tier 1) Assay Cut Point and Specificity	Data will be considered acceptable if the floating cut point factor multiplied by the NC mean is < 200 ECLU.	Pass	Floating cut point factor: 1.14 Floating cut point factor multiplied by NC mean (ECLU value): 80
	Specificity will be considered acceptable if the mean ECLU of the LPC, MPC, and HPC is ≥ the calculated Screening cut point.	Pass	Assay Control / Signal (ECLU) NC / 71 LPC / 188 MPC / 1526 HPC / 10107
Assay Specificity Confirmatory (Tier 2a) Cut Point	Specificity will be considered acceptable if the MPC and HPC demonstrate ≥ 50% inhibition and the LPC demonstrates inhibition ≥ the Confirmatory cut point with the addition of 50 µg/mL LY3298176. The confirmatory assay cut point will be considered acceptable if it is < 50%.	Pass	Assay Control / Percent Inhibition (%) / %CV LPC / 64.7 / 5.2 MPC / 95.2 / 0.6 HPC / 98.8 / 0.2 Confirmatory (Tier 2a) cut point = 17.5 %
Cross-Reactivity to $GIP_{(1-42)}$ (Tier 2b) Cut Point	The cross reactivity to $GIP_{(1-42)}$ cut point is expected to be <50% inhibition. If the cross reactivity to $GIP_{(1-42)}$ assay cut point is ≥50% inhibition, justification will be included, if this cut point is to be accepted, along with sponsor approval.	Pass	Confirmatory (Tier 2b) cut point = 14.5 %
Cross-Reactivity to $GLP_{(7-36)}$ (Tier 2c) Cut Point	The cross reactivity to $GLP_{(7-36)}$ cut point is expected to be <50% inhibition. If the cross reactivity to $GLP_{(7-36)}$ assay cut point is ≥50% inhibition, justification will be included, if this cut point is to be accepted, along with sponsor approval.	Pass	Confirmatory (Tier 2c) cut point = 14.5 %
Titration (Tier 3) Cut Point	The Titration (Tier 3) cut point will be considered acceptable if it is ≥ the Screening cut point in NHS. If the Titration cut point is < the Screening cut point, the Screening cut point will be utilized as the Titration cut point as well.	Pass	Titration (Tier 3) Cut Point = 1.25
Sensitivity	Sensitivity will be considered acceptable if the interpolated value (based on Screening cut point) is ≤ 100 ng/mL AP-HIMS	Pass	Sensitivity = 2.2 ng/mL

<table>
<tr><th>Assay Parameter</th><th>A Priori Acceptance Criteria</th><th>Pass/Fail</th><th>Results</th></tr>
<tr><td>Drug Tolerance to LY3298176</td><td>Drug tolerance will be considered acceptable if the data demonstrates a drug tolerance ≥ 100 µg/mL LY3298176 is tolerated in the presence of 100 ng/mL AP-HIMS</td><td>Pass</td><td><table><tr><th>AP-HIMS (ng/mL)</th><th>LY Tolerance (µg/mL)</th></tr><tr><td>100</td><td>>250</td></tr><tr><td>25</td><td>125.7</td></tr><tr><td>12.5</td><td>58.7</td></tr></table></td></tr>
<tr><td>Intra-Assay and Inter-Assay Precision</td><td>Intra- and inter-assay precision will be considered acceptable if the calculated CV is ≤ 25% for each PC in the absence (naïve) and presence (Confirmatory) of 50 µg/mL final concentration of LY3298176.</td><td>Pass</td><td><table><tr><th rowspan="2">Assay Control</th><th rowspan="2">Intra-assay (CV %)</th><th colspan="2">Inter-assay (CV %)</th></tr><tr><th>Screening</th><th>Confirmatory</th></tr><tr><td>LPC</td><td>6.1</td><td>12.6</td><td>5.2</td></tr><tr><td>MPC</td><td>7.6</td><td>15.3</td><td>0.6</td></tr><tr><td>HPC</td><td>8.1</td><td>17.1</td><td>0.2</td></tr></table></td></tr>
<tr><td>Titration (Tier 3) Verification</td><td>To be considered acceptable, it must be demonstrated that a PC can be diluted with a NHS pool to a level which falls below the Titration (Tier 3) cut point.</td><td>Pass</td><td>MPC was able to be titrated below the titration assay cut point. The MPC demonstrated a titer of 1:64.</td></tr>
<tr><td>Robustness</td><td>The assay will be considered robust if assay controls pass the assay control acceptance criteria for each variable assessed.</td><td>Pass</td><td><table><tr><th>Variable</th><th>Pass/Fail</th></tr><tr><td>Incubation Time +</td><td>Pass</td></tr><tr><td>Incubation Time -</td><td>Pass</td></tr></table></td></tr>
</table>

Abbreviations: AP-HIMS = affinity-purified hyperimmune monkey serum; CV = coefficient of variation; ECLU = electrochemiluminescence units; HPC = high positive control; LPC = low positive control; MPC = mid positive control; MRD = minimum required dilution; NC = negative control; NHS = normal human serum; PC = positive control

Note: Due to rounding differences between spreadsheet applications and calculators some data may contain minor differences when checked using an alternative method.

Source: Anti-LY3298176 Antibody Assay Validation Reprot (Study Number: 400008-192224-AMV),Table 1

Neutralizing Antibody (NAb) Assays

Two cell-based NAb assays developed and validated in the T2DM and CWM programs of tirzepatide were applied to support the OSA development program. Briefly, in the NAb assay methods, anti-tirzepatide antibodies in ADA$^+$ samples were first captured on a Streptavidin plate coated with a mixture of two differently Bt-tirzepatide molecules (GIP740 and GIP735). In the next step, the anti-tirzepatide antibodies were eluted, and pH neutralized in the presence of tirzepatide to allow ADA binding to the study drug. The resulting mixtures were finally added to reporter cell lines to assess the ability of ADA to inhibit tirzepatide signaling via GIP receptor (GIPR) or GLP-1 receptor (GLP-1R) expressed by the reporter cells. Human embryonic kidney 293 cells stably transfected with either GIPR or GLP-1R were used in these assays. Binding of tirzepatide to corresponding cell surface receptors led to cAMP production, which was reduced or abolished in the presence of neutralizing antibodies present in the sample.

See Immunogenicity Review authored by Dr. Sheikh in Office of Biotechnology Products dated 10/10/2023, under NDA 217806 in DARRTS (Reference ID 5258476) for details.

14.3.2. Pharmacometric Review

An initial population PK model (T2DM PK model) of tirzepatide was developed based on tirzepatide PK data from 19 clinical studies, which included data from healthy subjects in clinical pharmacology studies, subjects with renal or hepatic impairment, and data from subjects with T2DM in phase 1, phase 2, and phase 3 clinical trials. The model structure and parameter estimates from the final T2DM PK model were used to inform the base model for developing a

CWM population PK model. The final PK model for CWM (SURMOUNT-1) was used to evaluate the PK data from subjects who have obesity and moderate to severe OSA in Study GPIF. For details of pharmacometrics assessment of tirzepatide in the T2DM and CWM programs, refer to the Clinical Pharmacology Reviews in DARRTS (NDA 215866 dated 8/3/2022 and NDA 217806 dated 10/10/2023).

Overall, the popPK model adequately captured the PK of tirzepatide and is acceptable in deriving individual exposures for PK/PD modeling for OSA. The final PK/PD model adequately described the effect of tirzepatide exposure on AHI and BW reduction, GI tolerability, and/or safety events in adult subjects with OSA and obesity.

14.3.2.1. Objective, data, and model development strategy

- The objectives of the population PK and PK/PD analyses of data from subjects who have obesity and moderate to severe OSA are to:

– Characterize the PK of tirzepatide following weekly SC injections of tirzepatide
– Identify intrinsic and extrinsic factors, including immunogenicity, which may influence tirzepatide disposition
– Derive individual PK parameters and exposure metrics for assessment of exposure-response relationships
– Characterize the relationship between tirzepatide exposure and efficacy responses, such as changes in AHI and body weight
– Characterize the relationship between tirzepatide exposure and tolerability and safety response (such as nausea, vomiting, diarrhea)

- Data collected from healthy subjects, participants with T2DM (Population PK/PD Report for T2DM), and participants with obesity or overweight (Population PK/PD Report for CWM) were incorporated into the development and evaluation of the population PK model. The data collected from GPI1 and GPI2 were used in the exposure-response analyses (Table 48).

Table 48. Summary of Study with Tirzepatide Included in PK/PD Analyses for SOA

Study	Description	Population	Tirzepatide Dose Amount, Frequency & Route of Administration	Estimated Number of Participants	Analysis Population
Global Phase 3 Studies (OSA)					
I8F-MC-GPIF	A multicenter, randomized, parallel-arm, placebo-controlled, double-blinded study under a basket-design in participants who have moderate-to-severe OSA and obesity One master protocol with 2 studies/intervention-specific appendices (ISA): ISA 1 (GPI1) participants unwilling or unable to use PAP therapy; ISA 2 (GPI2) participants who are on PAP therapy	Obesity and moderate-to-severe OSA (non-T2DM)	• All SC route of administration QW with 52-week treatment duration • TZP TITR to the maximum tolerated dose (10 mg or 15 mg)	103 per arm (planned) Trough PK from all participants (except placebo)	PopPK & Exp-Resp

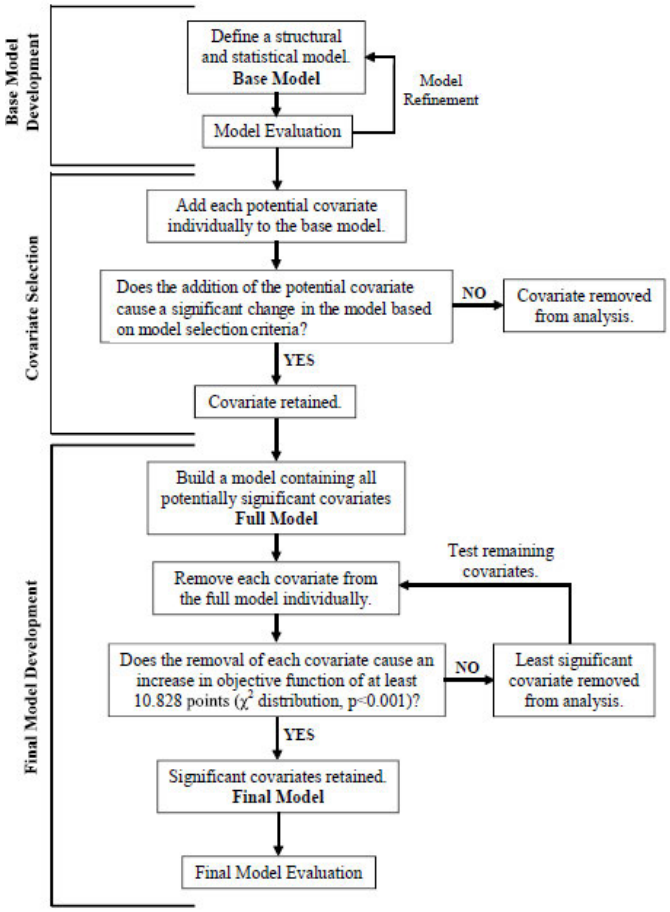
Abbreviations: Exp-Resp = exposure response; OSA = obstructive sleep apnea; PAP = positive airway pressure; PD = pharmacodynamics; PK = pharmacokinetics; PopPK = population pharmacokinetics; QW = once weekly schedule; SC=subcutaneous; T2DM = participants with Type 2 diabetes mellitus; TITR = titrated; TZP = tirzepatide.

Source: 18F-MC-GPIF Population PK/PD Report, Attachment 2, Table 1.

Population PK analyses of tirzepatide concentration-time data were performed using the nonlinear mixed-effects modeling program, NONMEM 7.4.2. First order conditional estimation with interaction was used as the estimation method. The general process for population PK modeling development is presented in Figure 18. Effect of two potential covariates (BW and ADA titer) on the PK of tirzepatide was assessed as most of covariates have been evaluated in the T2DM and CWM programs and did not show a relationship with tirzepatide PK.

The PK/PD modeling strategy was similar to the strategy described in the PK model. The BW PK/PD model and nausea, vomiting and diarrhea (N/V/D) model were performed in the CWM program of tirzepatide.

Figu e 18. General Process for PK Modeling Development



Source: 18F-MC-GPIF Population PK/PD Report, Attachment 2, Figure 2.

14.3.2.2. Results

Pharmacokinetic Results

The observed tirzepatide concentrations from subjects with obesity and OSA in Study GPIF were adequately described by the same model structure and parameter estimates from the population PK model previously developed from studies of tirzepatide for treatment of T2DM and weight management.

The final model for analysis of Study GPIF tirzepatide concentrations has 2 compartments, with first-order absorption and I on Ka, CL, Vc, and proportional residual error. Parameters were fixed to values estimated from SURMOUNT-1 (Table 49). A summary of the post hoc PK parameters from Study GPIF is provided in Table 50.

Table 49. Pharmacokinetic and Covariate Parameters in Tirzepatide Population Models

Parameter	T2DM PK Model Population Estimate Bootstrap Median (95% CI)[a]	SURMOUNT-1 PK Model Population Estimate Bootstrap Median (95% CI)[a]
Bioavailability (F, fraction)	0.8 fixed	0.8 fixed
Absorption rate (ka, 1/h)	0.0373 0.0370 (0.0289, 0.0460)	0.0318 0.0321 (0.0280, 0.0395)
Clearance (CL, L/h/70kg)	0.0329 0.0329 (0.0313, 0.0342)	0.0371 0.0371 (0.0359, 0.0382)
Intercompartmental clearance (Q, L/h/70kg)	0.126 0.125 (0.101, 0.144)	0.0934 0.0930 (0.0851, 0.101)
Central volume of distribution (Vc, L/70kg)	2.47 2.46 (2.05, 2.92)	2.88 2.90 (2.45, 3.74)
Peripheral volume of distribution (Vp, L/70kg)	3.98 3.98 (3.56, 4.21)	4.05 4.03 (3.62, 4.31)
Covariate Effects		
Covariate effect on F[b]		
Relative study effect	-0.181 -0.181 (-0.220, -0.147)	NA[c]
Covariate effect on CL and Q[d]		
Body weight (kg)	0.8 fixed	0.8 fixed
Fraction of fat mass	1 fixed	0.711 0.712 (0.638, 0.800)
Covariate effect on Vc and Vp[e]		
Body weight (kg)	1 fixed	1 fixed
Fraction of fat mass	0.482 0.483 (0.447, 0.524)	0.417 0.416 (0.315, 0.526)
Covariate effect on ka[f]		
Lyophilized formulation	-0.161 -0.161 (-0.207, -0.107)	NA[g]
Interindividual variability CV%		
ka	22.5% 22.1 (14.9, 28.7)	15.2% 15.2 (14.4, 16.3)
CL	14.2% 14.2 (13.7, 14.7)	12.3% 12.3 (11.6, 13.0)
Vc	49.0% 49.5 (38.3, 62.3)	61.5% 61.1 (47.5, 71.2)
Proportional residual	58.1% 58.0 (56.1, 60.0)	65.2% 65.1 (62.0, 68.3)
Residual variability		
Proportional (%)	20.6% 20.6 (20.3, 21.0)	20.6% 20.6 (20.0, 21.3)

Abbreviations: CI = confidence interval; CL = clearance; CV = coefficient of variation; F = bioavailability; FFM = fat-free mass (kg); ka = absorption rate constant; Q = intercompartmental clearance; T2DM = type 2 diabetes mellitus; Vc = central volume of distribution; Vd = volume of distribution; Vp = peripheral volume of distribution; NA = not applicable.

[a] Median and 95% CI derived from bootstrap analysis.

[b] $F = \Theta_1 * (1 + \Theta_{10})$, where Θ_1 is the bioavailability value from Study GPGE and Θ_{10} is the relative fraction.

[c] A scalar for F in SURMOUNT-1 relative to 0.8 was tested and did not have an impact on the objective function.

[d] iCL = pCL * [(FFM + fat mass* Θ_8)/70)]^0.8, where iCL is an individual's CL, pCL is the population CL, FFM is an individual's FFM, and Θ_8 is a fraction. The described structure was applied to CL and Q.

[e] iVd = pVd * [(FFM + fat mass* Θ_9)/70]^1, where iVd is an individual's Vd, pVd is the population Vd, FFM is an individual's FFM, and Θ_9 is a fraction. The described structure was applied to Vc and Vp.

[f] ika = pka * $(1 + \Theta_{11})$, where ika is an individual's ka, pka is the population ka, and Θ_{11} is a fraction.

[g] The solution formulation of tirzepatide was administered in SURMOUNT-1.

Source: 18F-MC-GPIF Population PK/PD Report, Attachment 4, Table ATT.4.1

Table 50. Summary of Tirzepatide Population PK Post Hoc Parameters from Participants in OSA, Clinical Pharmacology, T2DM, and Weight Management Studies

	Geometric Mean (CV%)					
PK Parameter	GPI1 GPIF (n = 111)	GPI2 GPIF (n = 118)	Overall GPIF (n = 229)	Non-T2DM[a] in T2DM Program (n = 307)	T2DM in T2DM Program (n = 5495)	Non-T2DM GPHK (SURMOUNT-1) (n = 1880)
Baseline weight (kg) Arithmetic mean (SD)	117 (24.8)	115 (21.2)	116 (23.0)	79.8 (15.9)	90.0 (20.5)	105 (22.4)
Absorption rate (ka, 1/h)	0.0317 (3.38)	0.0316 (3.55)	0.0317 (3.47)	0.0378 (23.7)	0.0366 (9.51)	0.0319 (4.83)
Apparent clearance (CL/F, L/h)	0.0619 (20.8)	0.0613 (18.1)	0.0616 (19.4)	0.0489 (22.3)	0.0606 (23.1)	0.0564 (20.9)
Apparent volume of distribution (Vd/F, L)	11.2 (36.8)	12.4 (37.1)	11.8 (37.2)	7.94 (21.3)	10.3 (23.8)	9.66 (28.5)
Half-life (t1/2, days)	6.05 (34.0)	6.60 (34.5)	6.33 (34.5)	5.28 (12.7)	5.41 (18.1)	5.69 (20.9)
Accumulation ratio	1.84 (24.7)	1.95 (25.4)	1.89 (25.1)	1.67 (7.8)	1.70 (11.5)	1.75 (14.2)
5 mg average steady state concentration (Css, ng/mL)	481 (20.8)	486 (18.1)	483 (19.4)	609 (22.3)	491 (23.1)	528 (20.9)
10 mg average steady state concentration (Css, ng/mL)	962 (20.8)	972 (18.1)	967 (19.4)	1220 (22.3)	983 (23.1)	1060 (20.9)
15 mg average steady state concentration (Css, ng/mL)	1440 (20.8)	1460 (18.1)	1450 (19.4)	1830 (22.3)	1470 (23.1)	1580 (20.9)

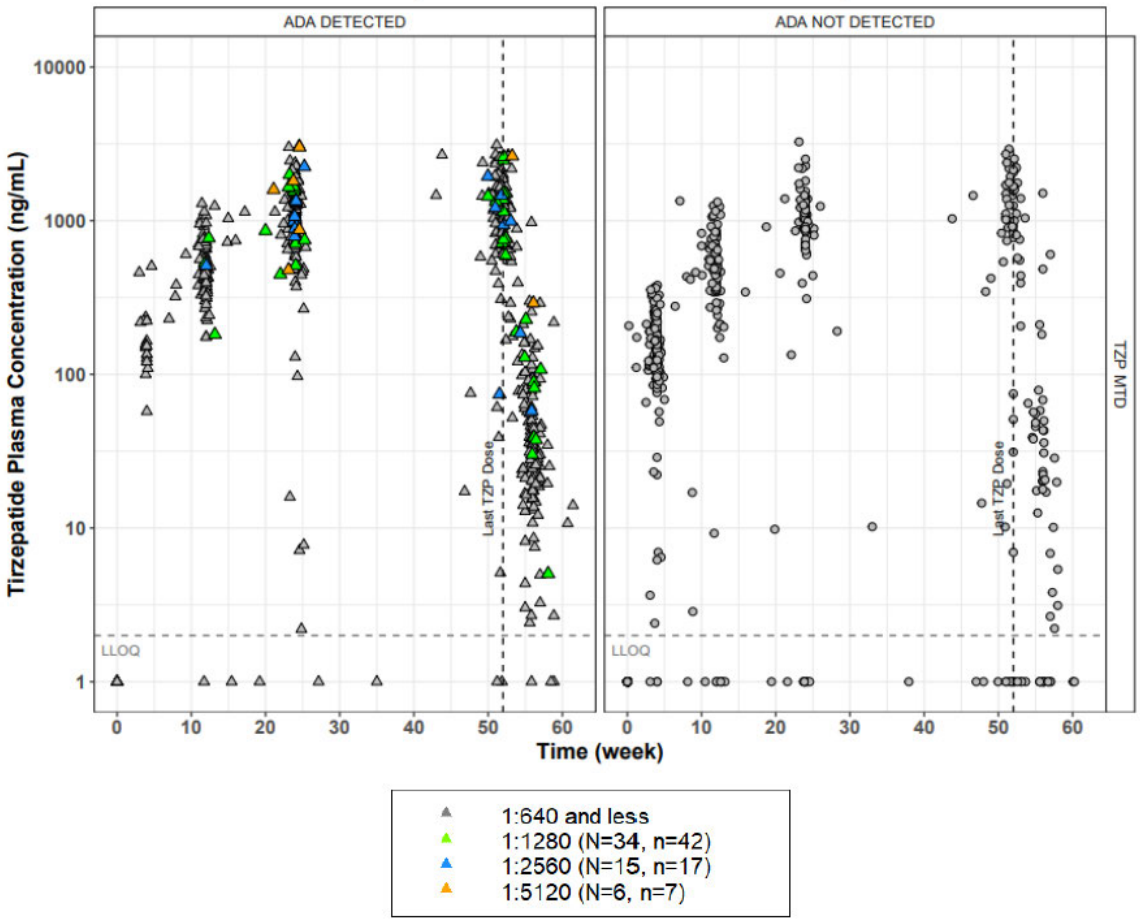
Abbreviations: CPAP = continuous positive airway pressure; CV = geometric coefficient of variation; GPIF = Study I8F-MC-GPIF; GPI1 = I8F-MC-GPIF participants without CPAP device use; GPI2 = I8F-MC-GPIF participants with CPAP device use; n = number of participants; Non-T2DM = without T2DM; OSA = obstructive sleep apnea; PK = pharmacokinetics; SD = standard deviation; T2DM = type 2 diabetes mellitus.

[a] The non-T2DM participants in the T2DM program were subjects from Phase 1 biopharmaceutical and clinical pharmacology studies.

Source: 18F-MC-GPIF Population PK/PD Report, Table 10.1.

The potential impact of immunogenicity on tirzepatide PK was investigated. The range of observed tirzepatide concentrations was comparable in subjects with and without ADA (Figure 19) and there were no obvious time-dependent trends (Figure 20). No statistically significant difference was observed in tirzepatide CL/F across the range of observed ADA titer values (Figure 21).

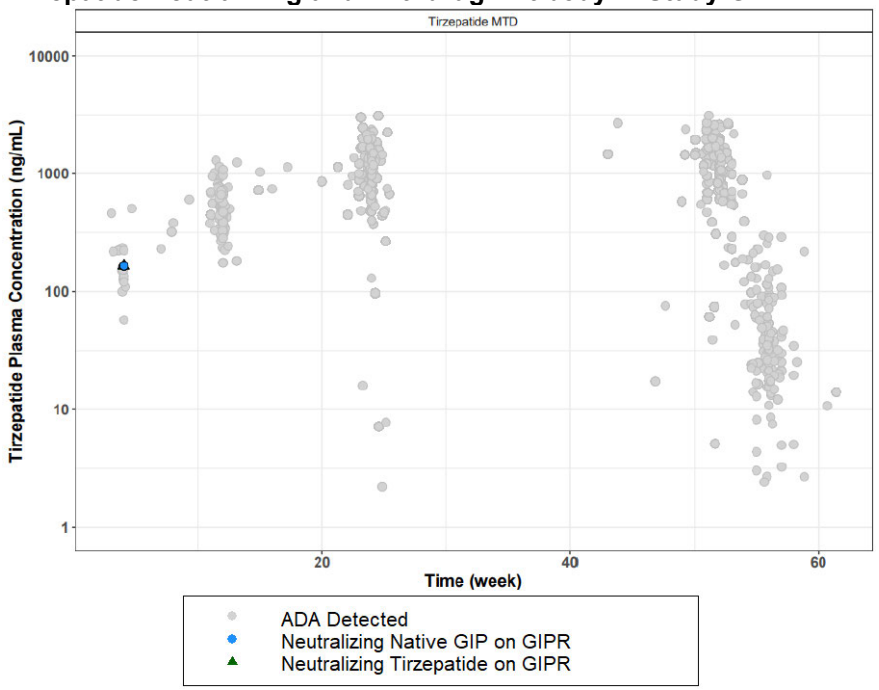
Figure 19. Comparison of Observed Tirzepatide Concentrations from Participants with Detected (left panel) and Undetected (right panel) Tirzepatide Anti-drug Antibody in Study GPIF



Abbreviations: ADA = anti-drug antibody; LLOQ = lower limit of quantitation (2 ng/mL); MTD = maximum tolerated dose; N = number of participants; n = number of observations; TZP = tirzepatide.
Note: Results below LLOQ were included in the plot with an assigned value of 1 ng/mL.

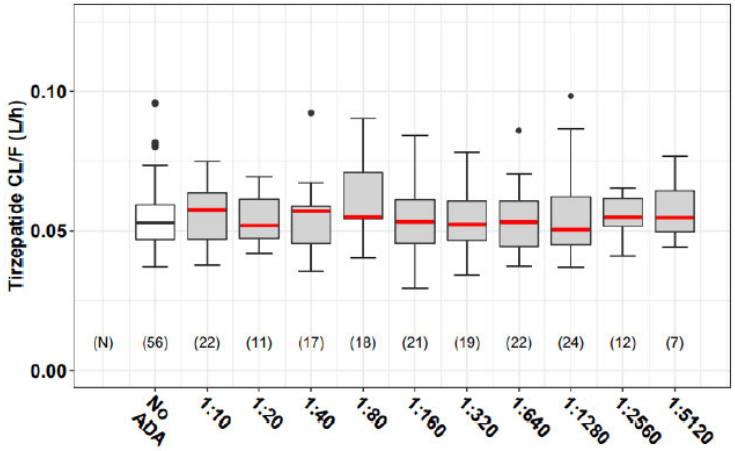
Source: 18F-MC-GPIF Population PK/PD Report, Figure 9.1.

Figure 20. Comparison of Observed Tirzepatide Concentrations from Participants with Detected Tirzepatide Neutralizing and Anti-drug Antibody in Study GPIF



ADA=anti-drug antibody; GIP=glucose-dependent insulinotropic polypeptide; GIPR= glucose-dependent insulinotropic polypeptide receptor, LLOQ=low limit of quantitation; MTD=maximum tolerated dose
Note: LLOQ=2 ng/mL; One sample with neutralizing antibodies detected was from a participant with ADA detected, but treatment-emergent ADA negative
Source: 18F-MC-GPIF Population PK/PD Report, Figure 9.2.

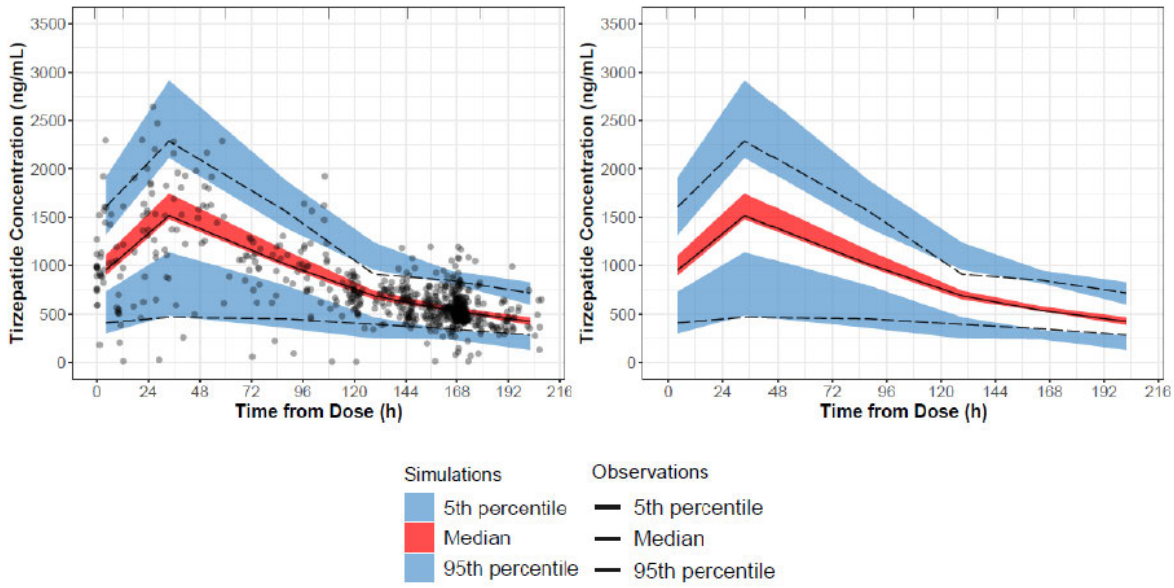
Figure 21. Tirzepatide CL/F across Each Participant's Maximum ADA Titer in Study GPIF



ADA=anti-drug antibody; CL/F=apparent clearance; N=number of participants
Note: Solid circles denote individual values outside the whisker range; the top and bottom margins of the boxplot represent the 75th and 25th percentiles, and the middle line of the boxplot represent the median; the whiskers extend to ±1.5-times interquartile range.
Source: 18F-MC-GPIF Population PK/PD Report, Figure 9.3.

The prediction-corrected visual predictive check for the final population PK model showed good agreement between observed and model-predicted tirzepatide concentrations overall (Figure 22).

Figure 22. pcVPC of the Final Population PK Model with (left) and without (right) Overlaid Observed Data after Tirzepatide



Abbreviations: pcVPC = prediction-corrected visual predictive check; PK = pharmacokinetics.
Note: Solid circles denote individual values, shaded areas denote 95% confidence interval of simulation percentiles, and the dashed lines denote the observation percentiles.

Source: 18F-MC-GPIF Population PK/PD Report, Figure 9.4.

Pharmacodynamic Results

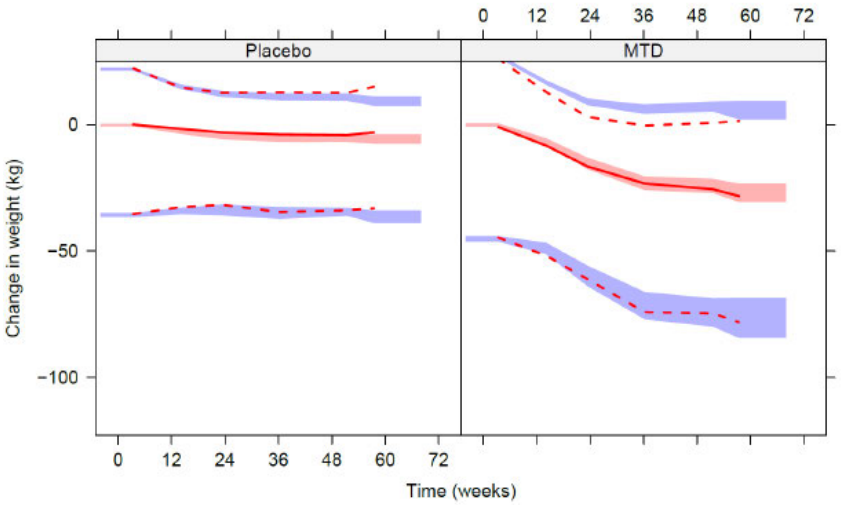
Body Weight Model

The VPCs of exposure-response for weight reduction in Study GPIF showed good agreement between model prediction and the observed fat-free mass (FFM), fat mass, and body weight (Figure 23). The model-predicted weight reductions at 52 weeks were consistent with the results of Study GPIF (Figure 6B). Parameter estimates for the final model are show in Table 51.

Apnea-Hypopnea Index Model

AHI data collected at baseline, Week 20, and end of study at Week 52 from participants who received placebo or tirzepatide treatment were pooled together (Figure 24). A direct exponential relationship between BW reduction and AHI reduction adequately described the data, suggesting that AHI improvement corresponds with time course of BW loss.

Figure 23. Prediction and Variability-Corrected Visual Predictive Check for Final Weight Reduction Model-Change from Baseline for Total Body Weight



Abbreviation: MTD = maximum tolerated dose of tirzepatide treatment arm.
Note: The upper dotted line represents the 95th percentile of the observed data. The middle continuous line represents the 50th percentile of the observed data. The lower dotted line represents the 5th percentile of the observed data. The shaded areas represent the model-predicted 95% confidence interval of the corresponding percentiles. Due to their high density, the observed data points have been removed from the plot to increase the clarity of the percentiles.

Source: 18F-MC-GPIF Population PK/PD Report, Figure 9.7

Table 51. Parameter Estimates of Tirzepatide Weight Reduction Model

Population Parameter	SURMOUNT-1 Estimate (95% CI)[a]	Study GPIF Estimate (95% CI)[a]
Baseline fat-free mass (kg)	73.5 (72.6, 74.3)	75.3 (74.4, 76.1)
Baseline fat mass (kg)	45.0 (43.4, 46.3)	47.5 (46.1, 48.9)
First-order elimination rate constant, Kout ($week^{-1}$)	0.0314 (0.0295, 0.0348)	Fixed
Maximum effect for drug inhibiting formation of fat-free mass	0.144 (0.119, 0.176)	Fixed
Maximum effect for drug inhibiting formation of fat mass	0.319 (0.266, 0.385)	Fixed
IC50 for drug inhibiting formation of fat-free mass (ng/mL)	1760 (1490, 2030)	Fixed
IC50 for drug inhibiting formation of fat mass (ng/mL)	518 (390, 678)	Fixed
Placebo fractional reduction in fat-free mass Kin	0.0658 (0.0594, 0.0698)	0.0377 (0.0324, 0.0430)
Placebo fractional reduction in fat mass Kin	0.213 (0.192, 0.228)	0.13 (0.110, 0.148)
Half-life of waning placebo effect (weeks)	40.3 (34.6, 54.4)	57.9 (47.5, 122)[b]

Covariate Effects		
Fractional change in baseline fat-free mass in females	-0.312 (-0.322, -0.302)	Fixed
Fractional change in fat mass in females	0.0539 (0.0170, 0.0994)	Fixed
Fractional change in drug maximum effect for fat-free mass in females	1.78 (1.37, 2.33)	Fixed
Fractional change in drug maximum effect for fat mass in females	0.809 (0.528, 1.12)	Fixed
Fractional change in drug IC50 effect for fat-free mass in females	1.14 (0.836, 1.55)	Fixed
Fractional change in drug IC50 effect for fat mass in females	2.05 (1.31, 3.19)	Fixed
Fractional change in baseline fat-free mass in Asians	-0.110 (-0.128, -0.0905)	Fixed
Fractional change in baseline fat mass in Asians	-0.254 (-0.291, -0.214)	Fixed
Interindividual variability (CV%)		
Baseline fat-free mass	11.0 (10.5, 11.5)	11.8 (11.1, 12.6)
Baseline fat mass	29.3 (28.1, 30.4)	30.1 (28.3, 31.7)
Correlation between the random effects for baseline fat and fat-free mass	0.851 (0.835, 0.864)	0.869 (0.777, 0.980)
Correlation between the random effects for baseline fat-free mass and Kout	-0.140 (-0.212, -0.0667)	-0.187 (-0.330, -0.0424)
Correlation between the random effects for baseline fat mass and Kout	-0.172 (-0.246, -0.0936)	-0.254 (-0.386, -0.103)
First-order elimination rate constant, Kout	124 (110, 140)	135 (120, 168)
Maximum drug effect on fat-free mass	84.5 (68.4, 102)	Fixed
Maximum drug effect on fat mass	69.6 (54.4, 85.1)	Fixed
Correlation between the random effects for maximum effect (IMAX)	0.993 (0.988, 0.994)	Fixed
IC50 for drug inhibiting formation of fat-free mass	25.7 (19.4, 34.7)	Fixed
IC50 for drug inhibiting formation of fat mass	47.4 (35.3, 66.1)	Fixed
Correlation between the random effects for IC50	0.9994 (0.9986, 0.9998)	Fixed
Placebo effect for fat-free mass	96.6 (87.5, 107)	124 (105, 152)
Placebo effect on fat mass	94.7 (86.3, 106)	132 (107, 162)
Correlation between the random effects for placebo	0.977 (0.972, 0.985)	0.988 (0.652, 1.45)
Residual error		
Proportional for fat-free mass (%)	0.985 (0.910, 1.04)	0.920 (0.788, 1.14)
Proportional for fat mass (%)	3.35 (3.08, 3.54)	3.56 (3.06, 4.38)
Correlation between residual error (%)	98.4 (98.4, 98.6)	99.5 (72.8, 151)

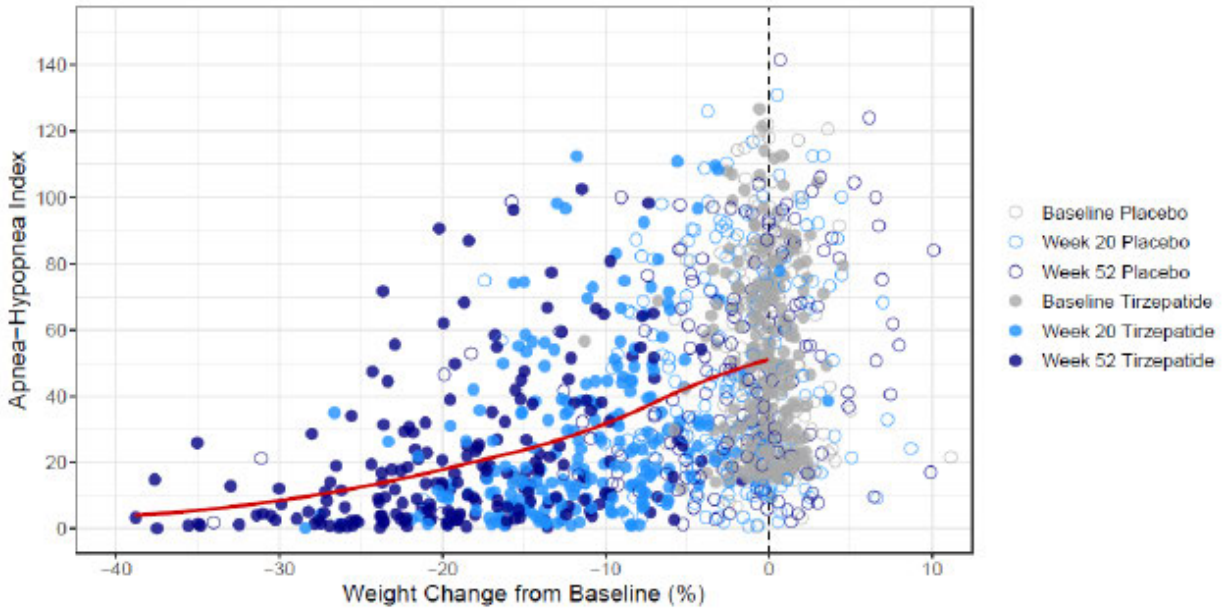
Abbreviations: CI = confidence interval; CV = coefficient of variation; IC50 = drug concentration that produces 50% of IMAX; IMAX = maximum inhibitory effect; Kin = formation rate; Kout = first-order elimination rate constant.

[a] Confidence interval obtained from a bootstrap analysis.

[b] Estimated for the placebo arm only.

Source: 18F-MC-GPIF Population PK/PD Report, Table 9.1.

Figure 24. Relationship between Percent Change from Baseline BW and AHI Response for Participants with Obesity and Moderate to Severe OSA in Study GPIF



Abbreviations: AHI = apnea-hypopnea index; OSA = obstructive sleep apnea; QW = once weekly.

Note: The circles represent observed data. The solid red line denotes a loess smoothing fit. The dashed line denotes a reference line for 0% weight change from baseline. At Week 20, tirzepatide 15 mg QW was initiated for those participants who tolerated dose escalation. The majority of participants in Study GPIF were on tirzepatide 15 mg QW at Week 52.

Source: 18F-MC-GPIF Population PK/PD Report, Figure 9.8

With tirzepatide treatment, reduction in AHI was observed at Week 20 following dose escalation and at the beginning of the maintenance dose period. Further reduction in AHI was observed at Week 52 when subjects were on the maximum tolerated dose (10 mg or 15 mg) QW of tirzepatide.

The model-predicted a 50% improvement from baseline AHI with a change from baseline BW reduction of 11.5%. This means that the population average baseline AHI of 48 would decrease to 24 with at least a weight reduction of 11.5%.

Sex was a significant covariate and was included in the final model. Females had a 35% lower baseline AHI than males. No statistically significant influences of age, race, ethnicity, baseline BW, or use of continuous positive airway pressure (CPAP) device were detected for AHI baseline or for the rate constant of AHI change with weight reduction.

Parameter estimates for the final model are summarized in Table 52.

Table 52. Parameter Estimates of Tirzepatide AHI Model

Parameter	Final Model Population Estimate (95% CI)[a]
Baseline AHI (events/hour)	47.8 (44.3, 51.2)
First-order rate constant for AHI across weight reduction[b]	0.0601 (0.0540, 0.0673)
Covariate Effects	
Fractional change in baseline AHI for females	-0.348 (-0.416, -0.261)
Interindividual Variability (%)	
Baseline AHI	54.7 (48.4, 60.2)
Correlation between the random effects for baseline AHI and rate constant	-0.551 (-0.786, -0.337)
Rate constant	66.2 (50.5, 86.8)
Residual Error	
Additive (events/hour)	2.58 (0.570, 6.29)
Proportional (%)	33.0 (27.2, 37.9)

Abbreviations: AHI = apnea-hypopnea index; CI = confidence interval PCWT = percent change from baseline body weight.

[a] Median and 95% CI derived from bootstrap analysis.

[b] AHI = Baseline AHI × exp(PCWT × θ), where θ was the estimated first-order rate constant.

Source: 18F-MC-GPIF Population PK/PD Report, Table 9.2.

Nausea, Vomiting and Diarrhea Models

The SURMOUNT-1 models were used to simulate nausea, vomiting, and diarrhea prevalence to compare to the observed nausea, vomiting, and diarrhea prevalence in the Study GPIF. Parameters describing the relationship between tirzepatide exposure and probabilities of nausea, vomiting, and diarrhea state and tolerance rate constant were fixed to the estimates from SURMOUNT-1 analysis. The influence of population characteristics on PK and PD were taken into consideration by random sampling with replacement from the sets of baseline demographics from subjects in Study GPIF to preserve correlation of demographics in the simulations. Since most participants in Study GPIF reached tirzepatide 15 mg QW, the simulation was implemented with dose escalation up to tirzepatide 15 mg QW.

The exposure-response relationship and observed nausea, vomiting, and diarrhea events from Study GPIF are shown to be comparable with those from the SURMOUNT-1 analysis (Figure 9). The results from Study GPIF confirmed the stepwise dose escalation scheme, starting at 2.5 mg dose for 4 weeks, followed by increases in doses by 2.5 mg increments every 4 weeks to attain maintenance dose levels of 10 mg or 15 mg, have mitigated GI adverse events in participants with obesity and moderate to severe OSA.

Parameter estimates for the final model are summarized in Table 53 and Table 54.

Table 53. Parameter Estimates from the Final Tirzepatide Nausea and Vomiting Markov Model for SURMOUNT-1

Population Parameter	Estimate (95% CI)[a]
Baseline transition probability from no to mild nausea, NP10 (logit)	-9.70 (-10.2, -9.23)
Baseline transition probability from no to moderate/severe nausea, NP20 (logit)	-10.6 (-11.6, -9.92)
Baseline transition probability from mild to no nausea and from moderate/severe to no nausea, NP01 and NP02 (logit)	-4.05 (-4.29, -3.75)
Baseline transition probability from mild to moderate/severe nausea and from moderate/severe to mild nausea, NP21 and NP12 (logit)	-7.71 (-8.33, -7.37)
Baseline transition probability from no to mild vomiting, VP10 (logit)	-12.1 (-13.4, -11.5)
Baseline transition probability from no to moderate/severe vomiting, VP20 (logit)	-13.0 (-14.1, -12.1)
Baseline transition probability from mild to no vomiting and from moderate/severe to no vomiting, VP01 and VP02 (logit)	-3.33 (-3.68, -2.94)
Baseline transition probability from mild to moderate/severe vomiting and from moderate/severe to mild vomiting, VP21 and VP12 (logit)	-30 FIX
Slope of drug effect with tolerance on NP10, SLPN10	1.33 (0.856, 1.78)
Slope of drug effect with tolerance on NP20, SLPN20	1.21 (0.784, 1.69)
Slope of drug effect on NP01 and NP02, SLPN012 (log)	-8.65 (-87.5, -7.35)
Slope of drug effect with tolerance on VP10, SLPV10	1.56 (1.01, 2.95)
Slope of drug effect with tolerance on VP20, SLPV20	1.60 (0.971, 2.715)
Power model exponent for nausea drug effects with tolerance, HILLN (log)	-0.889 (-0.989, -0.770)
Power model exponent for vomiting drug effects with tolerance, HILLV (log)	-0.973 (-1.18, -0.825)
Tolerance rate constant, K_{TOL} (log) (h^{-1})	-8.21 (-8.81, -7.77)
First event effect on NP10 and NP20	-0.226 (-0.257, -0.185)
First event effect on VP10 and VP20	-0.271 (-0.302, -0.233)
Current nausea effect on VP10 and VP20	-0.182 (-0.216, -0.147)
Covariate Effects	
Hispanic ethnicity effect on K_{TOL}	-0.175 (-0.351, 0.154)
Japanese subrace effect on K_{TOL}	0 FIX
Gender effect on K_{TOL}	-0.413 (-0.603, -0.175)
Caucasian race effect on NP10	-0.425 (-0.680, -0.177)
Japanese subrace effect on NP20	-30 FIXED
Japanese subrace effect on VP10	0 FIXED
Japanese subrace effect on VP20	-30 FIXED

Source: 18F-MC-GPIF Population PK/PD Report, Attachment 4, Table ATT.4.3.
CI=confidence interval
[a]: CI obtained from a bootstrap analysis

Table 54. Parameter Estimates from the Final Tirzepatide Diarrhea Markov Model for SURMOUNT-1

Population Parameter	Estimate (95% CI)[a]
Baseline transition probability from no to mild diarrhea, DP10 (logit)	-9.63 (-10.8, -9.20)
Baseline transition probability from no to moderate/severe diarrhea, DP20 (logit)	-11.0 (-11.3, -9.42)
Baseline transition probability from mild to no diarrhea and from moderate/severe to no diarrhea, DP01 and DP02 (logit)	-3.40 (-4.36, -3.64)
Baseline transition probability from mild to moderate/severe diarrhea and from moderate/severe to mild diarrhea, DP21 and DP12 (logit)	-8.44 (-60.9, -8.09)
Slope of drug effect with tolerance on DP10, SLPD10	0.352 (0.0411, 1.14)
Slope of drug effect with tolerance on DP20, SLPD20	0.365 (0.0323, 1.08)
Power model exponent for diarrhea drug effects with tolerance, HILLD (log)	-0.580 (-0.875, -0.101)
Tolerance rate constant, K_{TOL} (log) (h^{-1})	-10.4 (-11.2, -8.58)
First event effect on DP10 and DP20	-0.230 (-0.278, -0.164)
Covariate Effects	
Japanese subrace effect on DP20	-30 FIX

Abbreviation: CI = confidence interval.

[a] CI obtained from a bootstrap analysis.

Source: 18F-MC-GPIF Population PK/PD Report, Attachment 4, Table ATT.4.4.

14.4. Additional Clinical Outcome Assessment Analyses

14.4.1. Qualitative Data from Exit Interviews

The Applicant conducted within-trial exit interviews with 82 subjects with moderate-to-severe OSA and obesity (n=40 from GPI1 and n=42 from GPI2), who were mostly male (61%), White (92%), and college-educated (56%), with a mean age of 52.7 years. Exit interview subjects most frequently reported sleep-related impairment (n=75/82, 92%) followed by sleep disturbance (n=66/82, 81%) as OSA-related impact experienced prior to participating in GPI1 and GPI2; they also endorsed these as most bothersome impacts related to OSA in subjects.

Approximately 83% to 95% of subjects in the tirzepatide arms reported improvement in sleep-related impairment and sleep disturbance as compared to those in the placebo arms (43% to 56%) in both trials. Majority of the subjects reporting improvement considered the change meaningful. In addition, greater proportions of subjects from the placebo group reported “no change” as compared to the tirzepatide group; worsening of sleep-related impairment and sleep disturbance was only reported by a few subjects from the placebo group in Trial GPI1.

Furthermore, a 1-point change at the item-level of the PROMIS-SRI and PROMIS-SD items was deemed meaningful from the patient perspective. However, it is challenging to translate changes in item-level raw scores to T-scores as T-scores were calculated through response pattern scoring.

14.4.1.1. Conclusion

Data from the exit interviews indicated that a greater proportion of subjects receiving tirzepatide treatment experienced a clinically meaningful improvement in sleep-related impairment and sleep disturbance as compared to the placebo group in both the GPI1 and GPI2 trials, which helps provide contextual information for the interpretation of the treatment effect.

The following section details analyses conducted to evaluate the meaningfulness of the observed treatment effects for the change from baseline in PROMIS-SF-SRI 8a T-scores and PROMIS-SF-SD 8b T-scores at the end of treatment (Week 52) using data from GPI1 and GPI2.

14.4.2. Anchor Assessments in GPI1 and GPI2

Anchor assessments that were used to establish the clinically meaningful change of PROMIS-SF-SRI 8a and PROMIS-SF-SD 8b T-scores include PGIS-OSA Sleepiness, PGIS-OSA Fatigue, and PGIS Sleep Quality (see Section 8.1.1.7 for details on these measures). Table 55 presents the correlations between the endpoint scores and anchor scores for PROMIS-SF-SRI 8a and PROMIS-SF-SD 8b by study.

Table 55. Correlations Between Change in PROMIS-SF-SRI 8a and PROMIS-SF-SD 8b and Anchor Assessments For Trials GPI1 and GPI2

		GPI1		GPI2	
Score	**Anchor Assessment**	n	r	n	r
PROMIS-SF-SRI 8a	PGIS-OSA Sleepiness	145	0.54	152	0.68
	PGIS-OSA Fatigue	145	0.48	152	0.70
	PGIS Sleep Quality	147	0.49	156	0.60
PROMIS-SF-SD 8b	PGIS-OSA Sleepiness	145	0.40	152	0.58
	PGIS-OSA Fatigue	145	0.43	152	0.60
	PGIS Sleep Quality	148	0.75	159	0.83

Source: Table 27 in the Attachment 10 of the "Clinical Outcome Assessment Evidence Dossier – PROMIS-Short Form (v1.0) Sleep-Related Impairment 8a" and Table 17 in the Attachment 10 of the "Clinical Outcome Assessment Evidence Dossier – PROMIS-Short Form (v1.0) Sleep Disturbance 8b". Analyses were verified by reviewer using datasets adpromis.xpt and adpgis.xpt.
Abbreviations: PROMIS-SF-SRI 8a = Patient-Reported Outcomes Measurement Information System Short Form – Sleep Related Impairment, PROMIS-SF-SD 8b = Patient-Reported Outcomes Measurement Information System Short Form – Sleep Disturbance, PGIS-OSA = patient global impresion of severity – obstructive sleep apnea

14.4.3. Anchor-Based Analyses

The Applicant and FDA independently conducted meaningful change analyses using anchor-based methods supplemented with empirical cumulative distribution function (eCDF) curves to support the interpretation of the change from baseline to Week 52 in PROMIS-SF-SRI 8a T-scores and PROMIS-SF-SD 8b T-scores. The anchor-based analyses were conducted using pooled data (across treatment arms) in GPI 1 and GPI 2 separately by both the Applicant and FDA.

14.4.4. Target Anchor Change Category

Based on patient input from the qualitative interviews conducted by the Applicant, the Applicant prespecified and used a 1-category improvement on each of the three anchors as the target anchor change category to support anchor-based meaningful change analyses (Section 14.4.5 and 14.4.6). The Applicant's proposed 1-category improvement on the 4-category PGIS-OSA Sleepiness scale, 4-category PGIS-OSA Fatigue scale, and 5-category PGIS Sleep Quality scale was deemed acceptable by the FDA review team to support the anchor-based meaningful change analyses. Table 56, Table 57, and Table 58 show the distribution of change patterns in global symptom severity between baseline and Week 52 using data pooled across treatment arms for GPI1 and GPI2 separately, for PGIS-OSA Sleepiness, PGIS-OSA Sleep Quality, and PGIS-OSA Fatigue, respectively.

Most subjects started with a "Slightly sleepy" or "Moderately sleepy" status at baseline in both Trials GPI1 and GPI2 (Table 56). For subjects who reported slightly sleepy at baseline, over half experienced no change at Week 52 in both trials (51.32% in GPI1 and 55.07% in GPI2), while over 30% reported a 1-category improvement to "Not at all sleepy" at Week 52 in both trials (38.16% in Trial GPI1 and 34.78% in Trial GPI2). For subjects who had "Moderately sleepy" at baseline, 63.16% experienced a 1-category improvement to "Slightly sleepy" in Trial GPI1, and 46.67% of them reported a 1-category improvement in Trial GPI2.

Table 56. Category Change (n (%)) in PGIS-OSA Sleepiness from Baseline to Week 52 by Baseline PGIS-OSA Sleepiness (Trial GPI1 and Trial GPI2)

		PGIS-OSA Sleepiness at Week 52			
PGIS-OSA Sleepiness at baseline		Not at all sleepy	Slightly sleepy	Moderately sleepy	Very sleepy
Trial GPI1	Not at all sleepy (n=18)	13 (72.22%)	3 (16.67%)	0 (0%)	2 (11.11%)
	Slightly sleepy (n=76)	29 (38.16%)	39 (51.32%)	6 (7.89%)	2 (2.63%)
	Moderately sleepy (n=38)	8 (21.05%)	24 (63.16%)	5 (13.16%)	1 (2.63%)
	Very sleepy (n=13)	0 (0%)	6 (46.15%)	3 (23.08%)	4 (30.77%)
Trial GPI2	Not at all sleepy (n=18)	10 (55.56%)	8 (44.44%)	0 (0%)	0 (0%)
	Slightly sleepy (n=69)	24 (34.78%)	38 (55.07%)	5 (7.25%)	2 (2.9%)
	Moderately sleepy (n=45)	9 (20%)	21 (46.67%)	14 (31.11%)	1 (2.22%)
	Very sleepy (n=20)	4 (20%)	11 (55%)	2 (10%)	3 (15%)

Source: Reviewer generated tables using datasets adpromis.xpt and adpgis.xpt.
Abbreviations: PGIS-OSA = Patient Global Impression of Severity-obstructive sleep apnea

In both trials, more subjects had mild fatigue at baseline, followed by moderate fatigue (Table 57). For subjects who reported mild fatigue at baseline, over half of them experienced no change at Week 52 in both trials (50.72% in GPI1 and 54.29% in GPI2). In GPI1, 40.58% of subjects had a 1-category improvement to "No fatigue", and 25.71% had a 1-category improvement at Week 52 in Trial GPI2. For subjects with "Moderate fatigue" at baseline, most of them experienced a 1-category improvement to "Mild fatigue" at Week 52 (61.22% in GPI1 and 50% in GPI2).

Table 57. Category Change (n (%)) in PGIS-OSA Fatigue from Baseline to Week 52 by Baseline PGIS-OSA Fatigue (Trial GPI1 and Trial GPI2)

		PGIS-OSA Fatigue at Week 52			
PGIS-OSA Fatigue		No fatigue	Mild fatigue	Moderate fatigue	Severe fatigue
Trial GPI1	No fatigue (n=20)	14 (70%)	5 (25%)	0 (0%)	1 (5%)
	Mild fatigue (n=69)	28 (40.58%)	35 (50.72%)	5 (7.25%)	1 (1.45%)
	Moderate fatigue (n=49)	7 (14.29%)	30 (61.22%)	11 (22.45%)	1 (2.04%)
	Severe fatigue (n=7)	0 (0%)	4 (57.14%)	3 (42.86%)	0 (0%)
Trial GPI2	No fatigue (n=21)	14 (66.67%)	7 (33.33%)	0 (0%)	0 (0%)
	Mild fatigue (n=70)	18 (25.71%)	38 (54.29%)	12 (17.14%)	2 (2.86%)
	Moderate fatigue (n=64)	18 (28.13%)	32 (50%)	14 (21.88%)	0 (0%)
	Severe fatigue (n=11)	3 (27.27%)	3 (27.27%)	4 (36.36%)	1 (9.09%)

Source: Reviewer generated tables using datasets adpromis.xpt and adpgis.xpt.
Abbreviations: PGIS-OSA = Patient Global Impression of Severity-obstructive sleep apnea

Regarding subjects' baseline sleep quality, the majority of subjects reported fair sleep quality at baseline in GPI1 (Table 58). Over half of them (56.47%) did not experience changes in their sleep quality, with 34.12% experiencing a 1-category improvement at Week 52 in GPI1. Similarly, in GPI2, over half (51.47%) of the subjects reported no change in their sleep quality, while 35.29% of them experienced a 1-category improvement at Week 52.

Table 58. Category Change (n (%)) in PGIS Sleep Quality from Baseline to Week 52 by Baseline PGIS Sleep Quality (Trial GPI1 and Trial GPI2)

		PGIS Sleep Quality at Week 52				
PGIS Sleep Quality at Baseline		Very good	Good	Fair	Poor	Very Poor
Trial GPI1	Very good (n=3)	3 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	Good (n=27)	2 (7.41%)	15 (55.56%)	8 (29.63%)	2 (7.41%)	0 (0%)
	Fair (n=85)	1 (1.18%)	29 (34.12%)	48 (56.47%)	6 (7.06%)	1 (1.18%)
	Poor (n=22)	2 (9.09%)	1 (4.55%)	14 (63.64%)	3 (13.64%)	2 (9.09%)
	Very Poor (n=11)	0 (0%)	4 (36.36%)	4 (36.36%)	3 (27.27%)	0 (0%)
Trial GPI2	Very good (n=1)	0 (0%)	1 (100%)	0 (0%)	0 (0%)	0 (0%)
	Good (n=27)	3 (11.11%)	16 (59.26%)	6 (22.22%)	2 (7.41%)	0 (0%)
	Fair (n=68)	3 (4.41%)	24 (35.29%)	35 (51.47%)	5 (7.35%)	1 (1.47%)
	Poor (n=56)	4 (7.14%)	17 (30.36%)	21 (37.5%)	12 (21.43%)	2 (3.57%)
	Very Poor (n=21)	3 (14.29%)	3 (14.29%)	6 (28.57%)	5 (23.81%)	4 (19.05%)

Source: Reviewer generated tables using datasets adpromis.xpt and adpgis.xpt.
Abbreviations: PGIS-OSA = Patient Global Impression of Severity-obstructive sleep apnea

14.4.5. Clinically Meaningful Change in PROMIS-SF-SRI 8a T-score Results

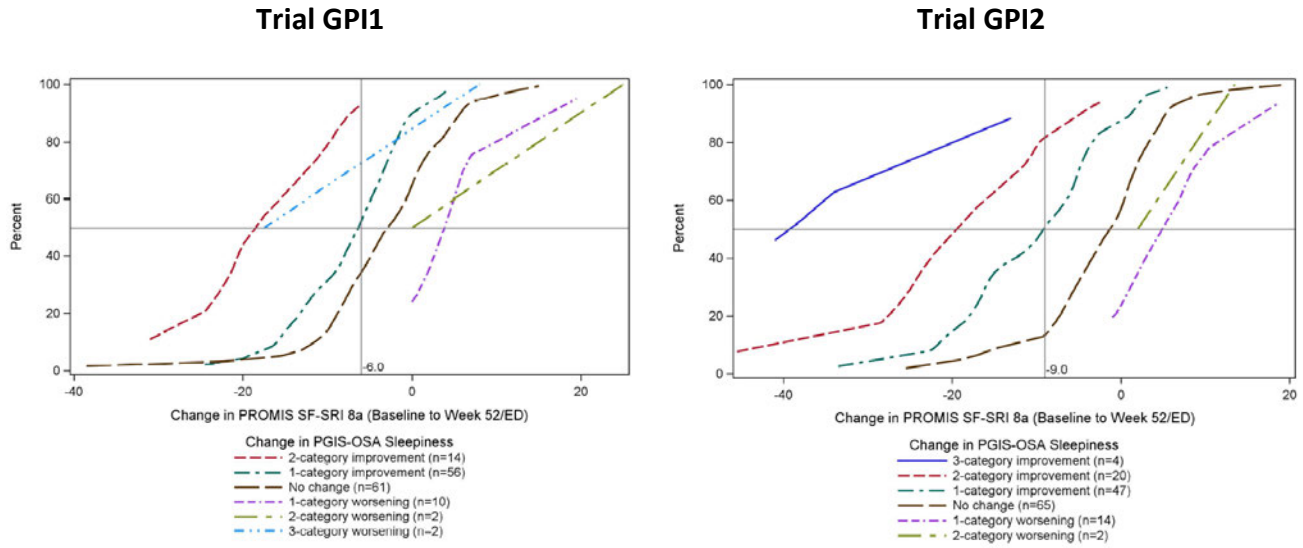
As stated in the "Clinical Outcome Assessment Evidence Dossier –PROMIS-Short Form (v1.0) Sleep-Related Impairment 8a", the Applicant proposed meaningful change thresholds for the PROMIS-SF-SRI 8a T-score for the individual trials, based on a triangulation of the median values of the change scores for 1-category improvement of their proposed primary anchor scales, supported by distribution-based analyses:

- For GPI1, a change of -6.0 in PROMIS-SF-SRI 8a T-scores is suggested to define the meaningful change threshold, based on their proposed primary anchor (change in PGI-OSA Sleepiness).
- For GPI2, a change of -9.5 in PROMIS-SF-SRI 8a T-scores is suggested to define the meaningful change threshold, based on their proposed primary anchor (change in PGI-OSA Fatigue).

The Applicant's proposed single values as the meaningful change thresholds for the two trials appeared to be based on their proposed primary anchor scales only. However, FDA recommends multiple approaches, including multiple anchor scales, be used when assessing meaningful change (April 2023). Furthermore, the Applicant's thresholds resulted in misclassifying >20% of subjects who reported no change or worsening on the PGIS-OSA Sleepiness anchor scale in GPI1 as experiencing meaningful change. Additionally, what subjects consider to be clinically meaningful improvement may be affected by their baseline global symptom severity. The Applicant's analyses did not consider subjects' baseline symptom severity when determining clinically meaningful improvement thresholds. As such, FDA does not agree with the Applicant's proposed meaningful change thresholds.

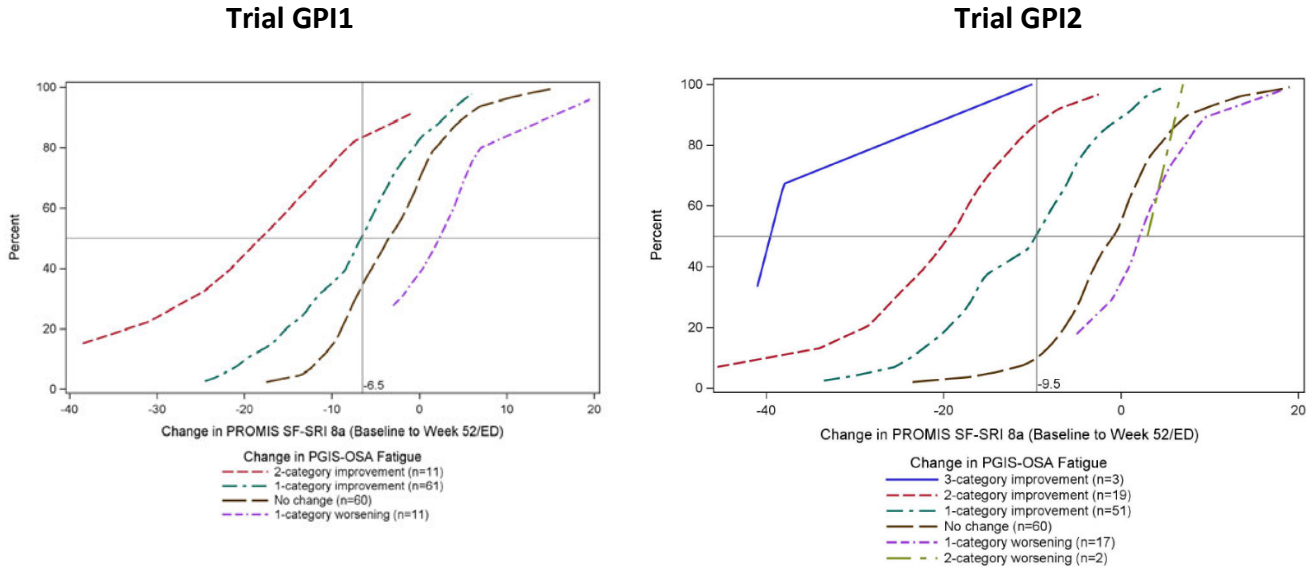
FDA conducted anchor-based analyses using all the 3 PGIS anchor scales. Figures 10, 11, and 12 below show the eCDF curves of change from baseline in PROMIS-SF-SRI 8a T-scores at Week 52 by PGIS category of change from baseline for Trial GPI1 and Trial GPI2 for PGIS-OSA Sleepiness, PGIS-OSA Fatigue, and PGIS-OSA Sleep Quality, respectively. As discussed in Section 14.5.4, the review team found the Applicant's proposed 1-category improvement on the 4-category PGIS-OSA Sleepiness scale, 4-category PGIS-OSA Fatigue scale, and 5-category PGIS Sleep Quality scale acceptable to support further anchor-based meaningful change analyses.

Figure 25. eCDF Curves of Change from Baseline in PROMIS-SF-SRI 8a T-scores at Week 52 by PGIS-OSA Sleepiness Category of Change from Baseline for Trial GPI1 and Trial GPI2



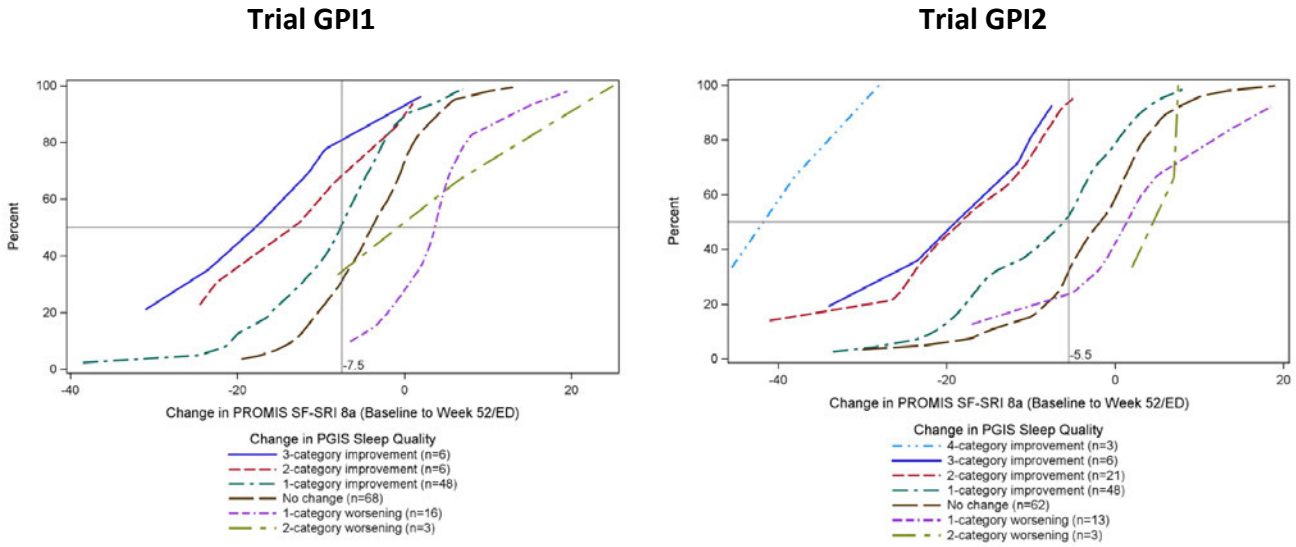
Source: Appendices 3 and 4 of the Applicant's response to FDA IR dated Oct 11, 2024. Analyses were verified by reviewer using datasets adpromis.xpt and adpgis.xpt.
Abbreviations: eCDF = empirical cumulative distribution function, PROMIS-SF-SRI 8a = Patient-Reported Outcomes Measurement Information System Short Form – Sleep Related Impairment, PGIS-OSA = patient global impression of severity – obstructive sleep apnea, ED = early discontinuation.

Figure 26. eCDF Curves of Change from Baseline in PROMIS-SF-SRI 8a T-scores at Week 52 by PGIS-OSA Fatigue Category of Change from Baseline for Trial GPI1 and Trial GPI2



Source: Source: Appendices 3 and 4 of the Applicant's response to FDA IR dated Oct 11, 2024. Analyses were verified by reviewer using datasets adpromis.xpt and adpgis.xpt.
Abbreviations: eCDF = empirical cumulative distribution function, PROMIS-SF-SRI 8a= Patient-Reported Outcomes Measurement Information System Short Form – Sleep Related Impairment, PGIS-OSA = patient global impression of severity – obstructive sleep apnea, ED = early discontinuation.

Figure 27. eCDF Curves of Change from Baseline in PROMIS-SF-SRI 8a T-scores at Week 52 by PGIS Sleep Quality Category of Change from Baseline for Trial GPI1 and Trial GPI2



Source: Appendices 3 and 4 of the Applicant's response to FDA IR dated Oct 11, 2024. Analyses were verified by reviewer using datasets adpromis.xpt and adpgis.xpt.
Abbreviations: eCDF = empirical cumulative distribution function, PROMIS-SF-SRI 8a = Patient-Reported Outcomes Measurement Information System Short Form – Sleep Related Impairment, PGIS = patient global impression of severity, ED = early discontinuation.

FDA derived a plausible range of meaningful change thresholds based on the median values of change in PROMIS-SF-SRI 8a T-scores for subjects who experienced the target anchor change category of a 1-category improvement on the PGIS anchor assessments, minimizing the misclassification subjects who experienced no change in the anchors as experiencing meaningful change (i.e., ≤20% of subjects) and subjects' baseline global symptom severity as measured by the PGIS anchors for each of the two trials (Table 59, Table 60, and Table 61).

The tables below show the distribution of PROMIS-SF-SRI 8a change scores among subjects who experienced 1-category improvement on PGIS scales between baseline and Week 52, stratified by their PGIS baseline status in Trial GPI1 and Trial GPI2.

Table 59. Distribution of PROMIS-SF-SRI 8a Change Scores among Subjects Who Experienced 1-Category Improvement on PGIS-OSA Sleepiness between Baseline and Week 52, Stratified by PGIS-OSA Sleepiness Baseline Status

PGIS-OSA Sleepiness at baseline		n (%)	10th	25th	50th	75th	90th
Study 1	Slightly sleepy	29 (51.79%)	-19.50	-13.50	-8.00	-5.50	0.00
	Moderately sleepy	24 (42.86%)	-12.50	-7.75	-2.75	-1.00	1.50
	Very sleepy	3 (5.36%)	-6.00	-6.00	-3.00	-3.00	-3.00
Study 2	Slightly sleepy	24 (51.06%)	-21.00	-17.75	-14.50	-6.00	-3.50
	Moderately sleepy	21 (44.68%)	-20.00	-10.00	-5.50	-2.50	2.50
	Very sleepy	2 (4.26%)	-5.50	-5.50	-1.25	3.00	3.00

Source: Appendices 7 and 8 of the Applicant's response to FDA IR dated Oct 11, 2024. Analyses were verified by reviewer using datasets adpromis.xpt and adpgis.xpt.
Note: PGIS-OSA = Patient Global Impression of Status – Obstructive Sleep Apnea. n = Group sample size.

Table 60. Distribution of PROMIS-SF-SRI 8a Change Scores among Subjects Who Experienced 1-Category Improvement on PGIS-OSA Fatigue between Baseline and Week 52, Stratified by PGIS-OSA Fatigue Baseline Status

PGIS-OSA Fatigue at baseline		n (%)	10th	25th	50th	75th	90th
Study 1	Mild fatigue	28 (45.9%)	-21.00	-15.50	-7.75	-4.50	-2.00
	Moderate fatigue	30 (49.18%)	-16.50	-12.50	-6.50	0.50	4.25
	Severe fatigue	3 (4.92%)	-3.00	-3.00	-3.00	-3.00	-3.00
Study 2	Mild fatigue	18 (35.29%)	-30.00	-22.00	-16.75	-8.00	2.50
	Moderate fatigue	30 (58.82%)	-19.50	-15.50	-7.75	-5.00	0.25
	Severe fatigue	3 (5.88%)	-10.50	-10.50	-5.50	3.50	3.50

Source: Appendices 7 and 8 of the Applicant's response to FDA IR dated Oct 11, 2024. Analyses were verified by reviewer using datasets adpromis.xpt and adpgis.xpt.
Note: PGIS-OSA = Patient Global Impression of Status – Obstructive Sleep Apnea. n = Group sample size.

Table 61. Distribution of PROMIS-SF-SRI 8a Change Scores among Subjects Who Experienced 1-Category Improvement on PGIS Sleep Quality between Baseline and Week 52, Stratified by PGIS Sleep Quality Baseline Status

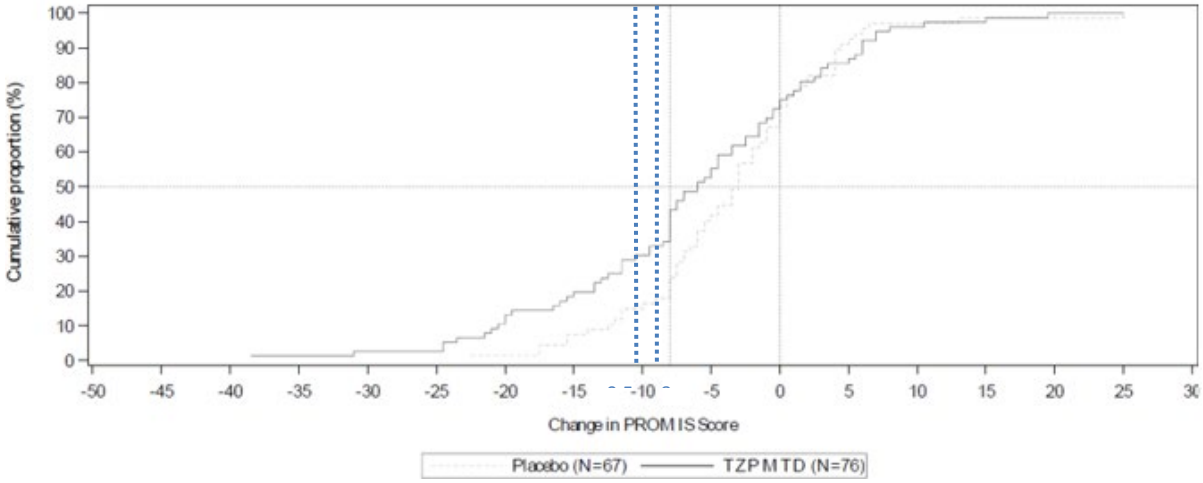
PGIS Sleep Quality at baseline		n (%)	10th	25th	50th	75th	90th
Study 1	Good	2 (4.17%)	-6.00	-6.00	-4.75	-3.50	-3.50
	Fair	29 (60.42%)	-21.50	-16.00	-10.50	-7.00	-3.00
	Poor	14 (29.17%)	-15.50	-6.00	-2.75	4.00	6.00
	Very poor	3 (6.25%)	-7.50	-7.50	-1.00	0.00	0.00
Study 2	Good	2 (4.17%)	-16.00	-16.00	-4.25	7.50	7.50
	Fair	23 (47.92%)	-22.00	-18.00	-7.50	0.50	2.50
	Poor	19 (39.58%)	-21.00	-15.50	-6.50	-3.00	2.50
	Very poor	4 (8.33%)	-5.50	-5.25	-3.75	0.50	3.50

Source: Appendices 7 and 8 of the Applicant's response to FDA IR dated Oct 11, 2024. Analyses were verified by reviewer using datasets adpromis.xpt and adpgis.xpt.
Note: PGIS-OSA = Patient Global Impression of Status – Obstructive Sleep Apnea. n = Group sample size.

Based on the results of the anchor-based analyses using the PGIS-OSA Sleepiness, PGIS-OSA Fatigue, and PGIS-OSA Sleep Quality, the Agency concluded that a plausible meaningful improvement threshold range should be between an 8-point and 10.5-point improvement in PROMIS-SF-SRI 8a for GPI1 and between 7-point and 16.75-point improvement in PROMIS-SF-SRI 8a for GPI2. Figure 28 and Figure 29 show the eCDF plots of changes in PROMIS-SF-SRI 8a T-score from baseline to Week 52 by treatment arm for GPI1 and GPI2, respectively. Both figures

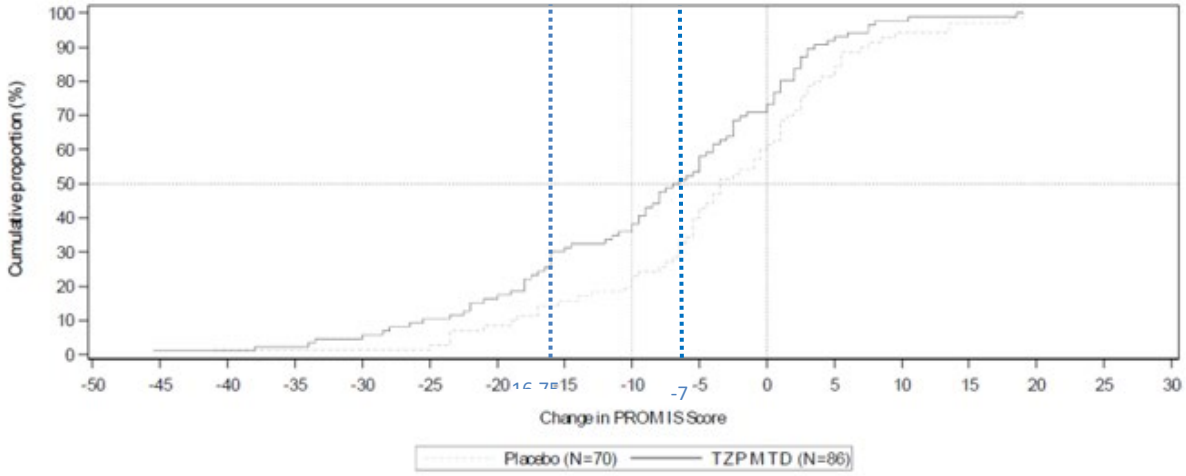
show a clear and consistent separation between treatment arms based on visual inspection in the FDA-proposed meaningful change range of 8-point and 10.5-point improvement for GPI1 and between 7-point and 16.75-point improvement for GPI2.

Figure 28. eCDF of Change on PROMIS-SF-SRI 8a at Week 52 Modified Intent-to-Treat – Trial GPI1 Full Analysis Set



Source: Adapted from Figure GPI1.8.1. of the CSR of GPI1. Analyses were verified by reviewer using data of adsl.xpt and adspromis.xpt.
Abbreviations: eCDF = empirical cumulative distribution function, PROMIS-SF-SRI 8a = Patient-Reported Outcomes Measurement Information System Short Form – Sleep Related Impairment.

Figure 29. eCDF of Change on PROMIS-SF-SRI 8a at Week 52 Modified Intent-to-Treat – Trial GPI2 Full Analysis Set



Source: Adapted from Figure GPI2.8.1. of the CSR of GPI1. Analyses were verified by reviewer using data of adsl.xpt and adspromis.xpt.
Abbreviations: eCDF = empirical cumulative distribution function, PROMIS-SF-SRI 8a = Patient-Reported Outcomes Measurement Information System Short Form – Sleep Related Impairment.

14.4.5.1 Conclusion

Taking into consideration the full distribution of PROMIS-SF-SRI 8a T-scores and selecting meaningful change thresholds that not only minimize the misclassification of subjects who reported no improvement or worsening, but also take into account subjects' baseline global symptom severity, the Agency concludes that a plausible range of clinically meaningful change thresholds is between 8 and 10.5-point improvement in GPI1 and between 7 and 16.75-point improvement in GPI2. The observed treatment effects on the PROMIS-SF-SRI 8a T-scores substantiated a clinically meaningful improvement in subjects receiving tirzepatide as compared to placebo in both GPI1 and Trial GPI2.

14.4.6. Clinically Meaningful Change in PROMIS-SF-SD 8b T-score Results

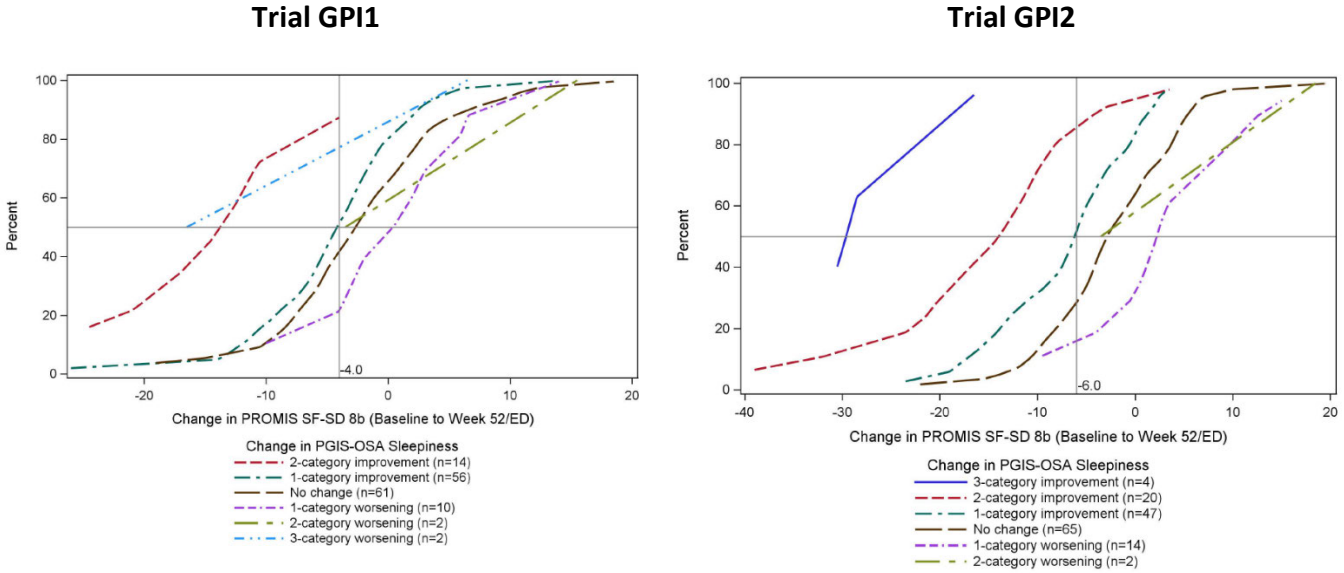
As stated in the "Clinical Outcome Assessment Evidence Dossier – PROMIS-Short Form (v1.0) Sleep Disturbance 8b", the Applicant proposed a single meaningful change threshold for the PROMIS-SF-SD 8b T-score for both trials, based on a triangulation of the median values of the change scores for 1-category improvement of their proposed primary anchor scale, supported by distribution-based analyses:

- For both GPI1 and GPI2, a change of -7.5 in PROMIS-SF-SD 8b T-scores is suggested to define the clinically meaningful change threshold, based on the primary anchor (change in PGIS Sleep Quality).

The Applicant's proposed single value as the meaningful change threshold for the two trials was based on their proposed primary anchor scale only. However, FDA recommends multiple approaches, including multiple anchor scales, be used when assessing meaningful change (April 2023). Furthermore, what subjects consider to be clinically meaningful improvement may be affected by their baseline global symptom severity. The Applicant's analyses did not consider subjects' baseline symptom severity when determining clinically meaningful improvement thresholds. As such, FDA does not agree with the Applicant's proposed meaningful change thresholds.

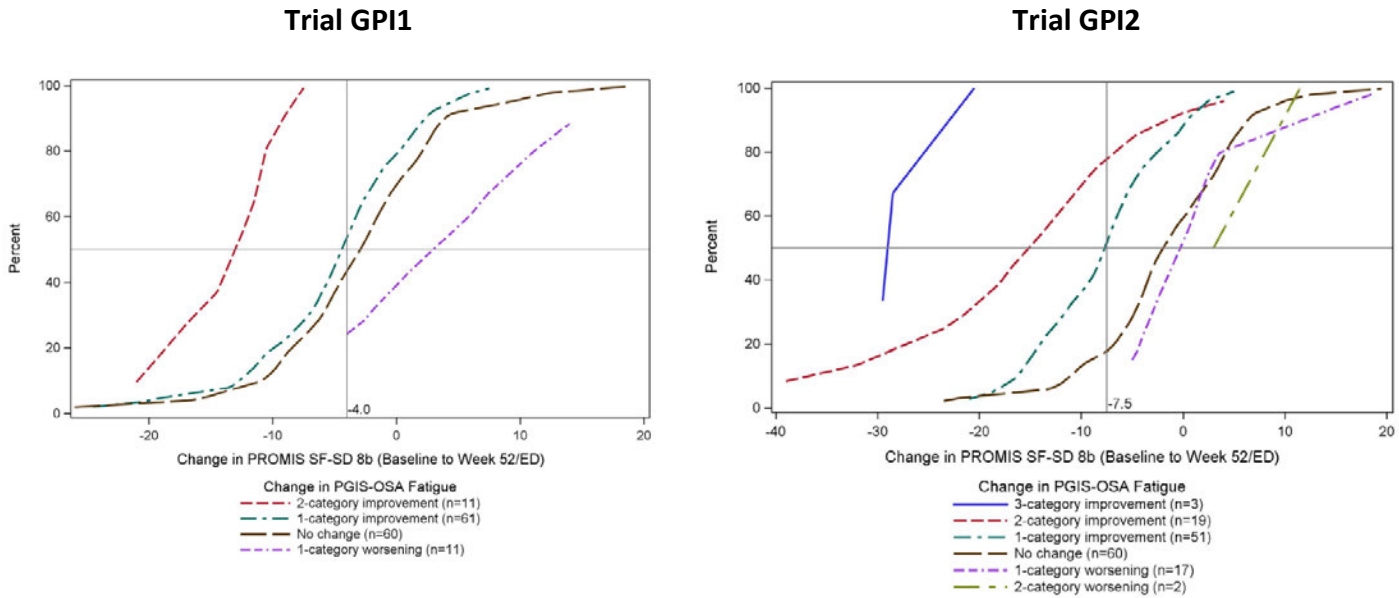
FDA conducted anchor-based analyses using all the 3 PGIS anchor scales. The figures below (Figure 30, Figure 31, and Figure 32) show the eCDF curves of change from baseline in PROMIS-SF-SD 8b T-scores at Week 52 by PGIS category of change from baseline for GPI1 and GPI2 for PGIS-OSA Sleepiness, PGIS-OSA Fatigue, and PGIS-OSA Sleep Quality, respectively. As discussed in Section 14.5.4, the review team found the Applicant's proposed 1-category improvement on the 4-category PGIS-OSA Sleepiness scale, 4-category PGIS-OSA Fatigue scale, and 5-category PGIS Sleep Quality scale acceptable to support further anchor-based meaningful change analyses.

Figure 30. eCDF Curves of Change from Baseline in PROMIS-SF-SD 8b T-scores at Week 52 by PGIS-OSA Sleepiness Category of Change from Baseline for Trial GPI1 and Trial GPI2



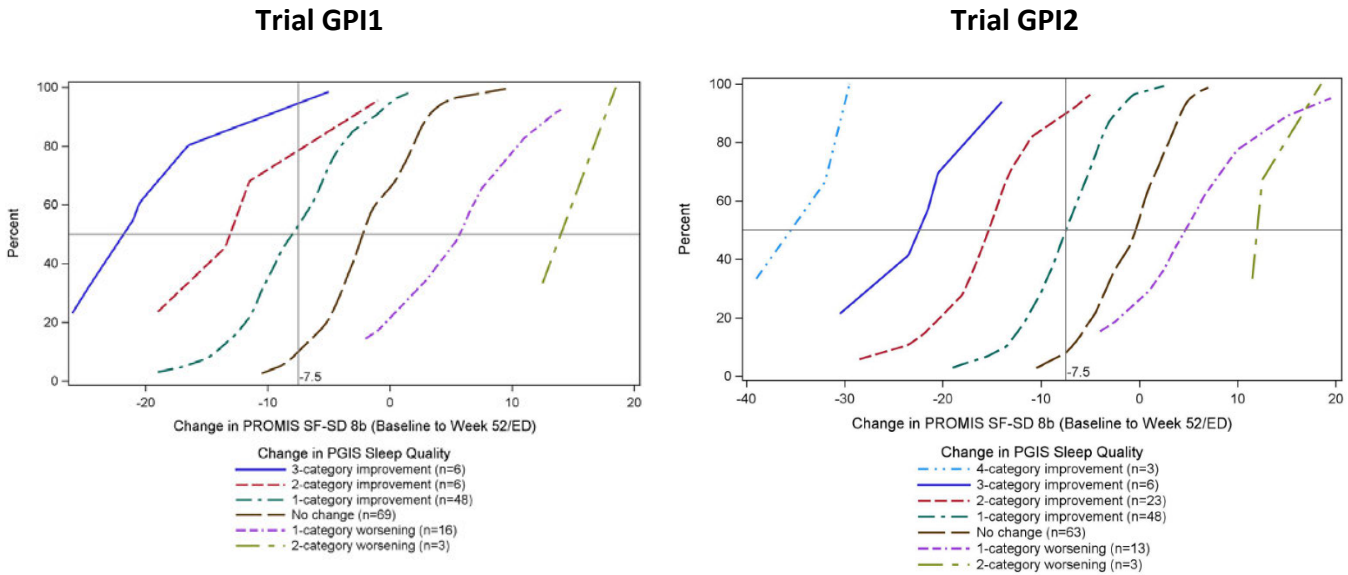
Source: Appendices 5 and 6 of the Applicant's response to FDA IR dated Oct 11, 2024. Analyses were verified by reviewer using datasets adpromis.xpt and adpgis.xpt.
Abbreviations: eCDF = empirical cumulative distribution function, PROMIS-SF-SD 8b = PROMIS-Short-Form Sleep Disturbance 8b, PGIS-OSA = patient global impresion of severity – obstructive sleep apnea, ED = early discontinuation.

Figure 31. eCDF Curves of Change from Baseline in PROMIS-SF-SD 8b T-scores at Week 52 by PGIS-OSA Fatigue Category of Change from Baseline for Trial GPI1 and Trial GPI2



Source: Appendices 5 and 6 of the Applicant's response to FDA IR dated Oct 11, 2024. Analyses were verified by reviewer using datasets adpromis.xpt and adpgis.xpt.
Abbreviations: eCDF = empirical cumulative distribution function, PROMIS-SF-SD 8b = PROMIS-Short-Form Sleep Disturbance 8b, PGIS-OSA = patient global impresion of severity – obstructive sleep apnea, ED = early discontinuation.

Figure 32. eCDF Curves of Change from Baseline in PROMIS-SF-SD 8b T-scores at Week 52 by PGIS Sleep Quality Category of Change from Baseline for Trial GPI1 and Trial GPI2



Source: Appendices 5 and 6 of the Applicant's response to FDA IR dated Oct 11, 2024. Analyses were verified by reviewer using datasets adpromis.xpt and adpgis.xpt.
Abbreviations: eCDF = empirical cumulative distribution function, PROMIS-SF-SD 8b = PROMIS-Short-Form Sleep Disturbance 8b, PGIS = patient global impresion of severity, ED = early discontinuation.

FDA derived a plausible range of meaningful change thresholds based on the median values of change in PROMIS-SF-SD 8b T-scores for participants who experienced the target anchor change category of a 1-category improvement on the PGIS anchor assessments, minimizing the misclassification subjects who experienced no change in the anchors as experiencing meaningful change (i.e., ≤20% of subjects), and subjects' baseline global symptom severity as measured by the PGIS anchors for each of the two trials.

The tables below (Table 62, Table 63, and Table 64) show the description of distribution of PROMIS-SF-SD 8b change scores among subjects who experienced 1-category improvement on PGIS scales between baseline and Week 52, stratified by PGIS baseline status in GPI1 and GPI2.

Table 62. Distribution of PROMIS-SF-SD 8b Change Scores among Subjects Who Experienced 1-Category Improvement on PGIS-OSA Sleepiness between Baseline and Week 52, Stratified by PGIS-OSA Sleepiness Baseline Status

PGIS-OSA Sleepiness at baseline		n (%)	10th	25th	50th	75th	90th
Trial GPI1	Slightly sleepy	24 (51.06%)	-16.00	-12.75	-7.00	-4.00	0.50
	Moderately sleepy	24 (42.86%)	-11.50	-3.75	-2.25	0.00	2.50
	Very sleepy	3 (5.36%)	-6.50	-6.50	-6.00	-0.50	-0.50
Trial GPI2	Slightly sleepy	24 (51.06%)	-21.00	-17.75	-14.50	-6.00	-3.50
	Moderately sleepy	21 (44.68%)	-18.00	-9.50	-5.00	-2.50	0.00
	Very sleepy	2 (4.26%)	2.50	2.75	2.50	3.00	3.00

Source: Appendices 7 and 8 of the Applicant's response to FDA IR dated Oct 11, 2024. Analyses were verified by reviewer using datasets adpromis.xpt and adpgis.xpt.
Note: PGIS-OSA = Patient Global Impression of Status – Obstructive Sleep Apnea. n = Group sample size.

Table 63. Distribution of PROMIS-SF-SD 8b Change Scores among Subjects Who Experienced 1-Category Improvement on PGIS-OSA Fatigue between Baseline and Week 52, Stratified by PGIS-OSA Fatigue Baseline Status

PGIS-OSA Fatigue at baseline		n (%)	10th	25th	50th	75th	90th
Trial GPI1	Mild fatigue	28 (45.90%)	-11.50	-9.75	-5.25	-1.00	5.50
	Moderate fatigue	30 (49.18%)	-13.25	-6.00	-3.00	-1.00	2.25
	Severe fatigue	3 (4.92%)	-6.50	-6.50	-6.00	3.00	3.00
Trial GPI2	Mild fatigue	18 (35.29%)	-16.00	-11.00	-7.00	-0.50	0.50
	Moderate fatigue	30 (58.82%)	-16.00	-12.50	-7.75	-4.50	-1.25
	Severe fatigue	3 (5.88%)	-13.50	-13.50	-7.00	2.50	2.50

Source: Appendices 7 and 8 of the Applicant's response to FDA IR dated Oct 11, 2024. Analyses were verified by reviewer using datasets adpromis.xpt and adpgis.xpt.
Note: PGIS-OSA = Patient Global Impression of Status – Obstructive Sleep Apnea. n = Group sample size.

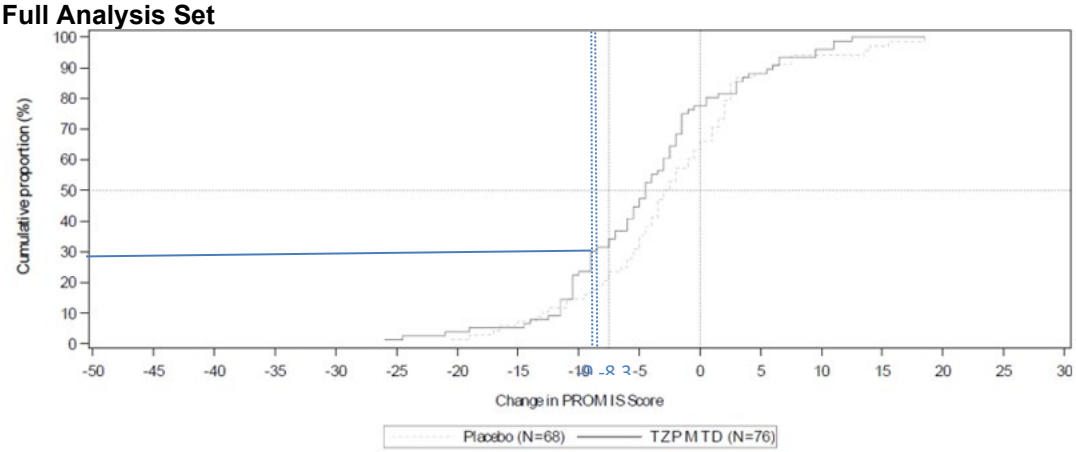
Table 64. Distribution of PROMIS-SF-SD 8b Change Scores among Subjects Who Experienced 1-Category Improvement on PGIS Sleep Quality between Baseline and Week 52, Stratified by PGIS Sleep Quality Baseline Status

PGIS Sleep Quality at baseline		n (%)	10th	25th	50th	75th	90th
Trial GPI1	Good	2 (4.17%)	-7.00	-7.00	-6.00	-5.00	-5.00
	Fair	29 (60.42%)	-15.00	-11.50	-9.00	-5.50	-3.00
	Poor	14 (29.17%)	-10.50	-7.00	-4.75	-3.00	-0.50
	Very poor	3 (6.25%)	-11.00	-11.00	-7.50	0.50	0.50
Trial GPI2	Good	2 (4.17%)	-11.50	-11.50	-10.50	-9.50	-9.50
	Fair	23 (47.92%)	-13.00	-11.00	-7.50	-5.00	-3.00
	Poor	19 (39.58%)	-13.50	-10.00	-7.50	-4.00	-1.00
	Very poor	4 (8.33%)	-7.00	-6.75	-5.25	-3.75	-3.50

Source: Appendices 7 and 8 of the Applicant's response to FDA IR dated Oct 11, 2024. Analyses were verified by reviewer using datasets adpromis.xpt and adpgis.xpt.
Note: PGIS-OSA = Patient Global Impression of Status – Obstructive Sleep Apnea. n = Group sample size.

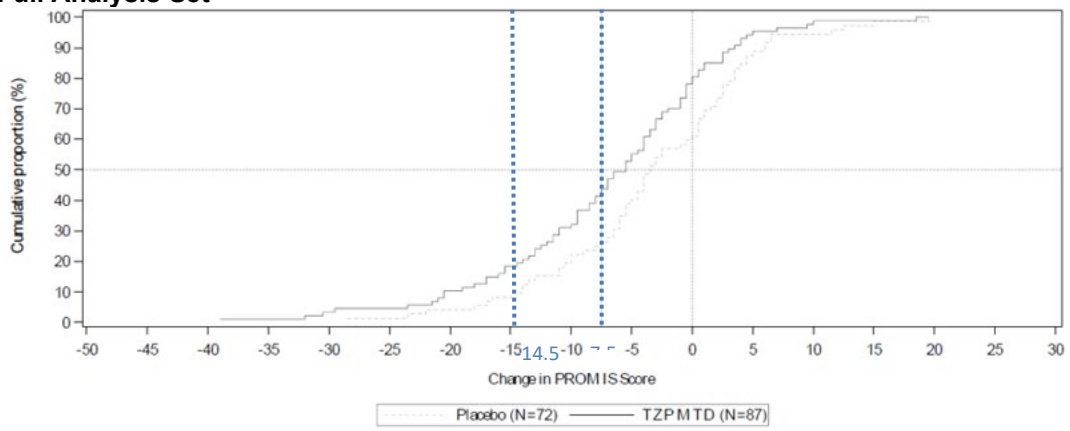
Based on the results of the anchor-based analyses using the PGIS-OSA Sleepiness, PGIS-OSA Fatigue, and PGIS-OSA Sleep Quality, the Agency concluded that a plausible meaningful improvement threshold range should be between an 8.3-point and 9-point improvement in PROMIS-SF-SD 8b for GPI1 and between 7.5-point and 14.5-point improvement in PROMIS-SF-SD 8b for GPI2. Figure 33 and Figure 34 show the eCDF plots of changes in PROMIS-SF-SD 8b T-score from baseline to Week 52 by treatment arm for GPI1 and GPI2, respectively. Figure 34 shows a consistent separation between treatment arms in GPI2 between 7.5-point and 14.5-point improvement for GPI2. While some separation between treatment arms is observed in Figure 33 in the FDA-proposed meaningful change range of 8.3-point and 9-point improvement for Trial GPI1 based on visual inspection, the eCDF curves cross at PROMIS change scores of approximately 11 to 17 points indicating more placebo patients saw improvements in PROMIS-SF-SD 8b scores in this range than patients treated with tirzepatide.

Figure 33. eCDF of Change on PROMIS-SF-SD 8b at Week 52 Modified Intent-to-Treat – Trial GPI1 Full Analysis Set



Source: Adapted from Figure GPI1.8.3. of the CSR of GPI1. Analyses were verified by reviewer using data of adsl.xpt and adspromis.xpt.
Abbreviations: eCDF = empirical cumulative distribution function, PROMIS-SF-SRI 8a = Patient-Reported Outcomes Measurement Information System Short Form – Sleep Related Impairment.

Figure 34. eCDF of Change on PROMIS-SF-SD 8b at Week 52 Modified Intent-to-Treat – Trial GPI2 Full Analysis Set



Source: Adapted from Figure GPI2.8.3. of the CSR of GPI1. Analyses were verified by reviewer using data of adsl.xpt and adspromis.xpt.
Abbreviations: eCDF = empirical cumulative distribution function, PROMIS-SF-SRI 8a = Patient-Reported Outcomes Measurement Information System Short Form – Sleep Related Impairment.

14.4.7. Conclusion

Taking into consideration the full distribution of PROMIS-SF-SD 8b T-scores and selecting meaningful change thresholds that not only minimize the misclassification of subjects who reported no improvement or worsening, but also take into account subjects' baseline global symptom severity, the Agency concludes that a plausible range of clinically meaningful change thresholds is between 8.3 and 9-point improvement in GPI1 and between 7.5 and 14.5-point improvement in GPI2. The observed treatment effect on the PROMIS-SF-SD 8b T-scores is suggestive of a clinically meaningful improvement in subjects receiving tirzepatide as compared to placebo in GPI2. (b) (4)

(b) (4)

14.5. OB Appendices

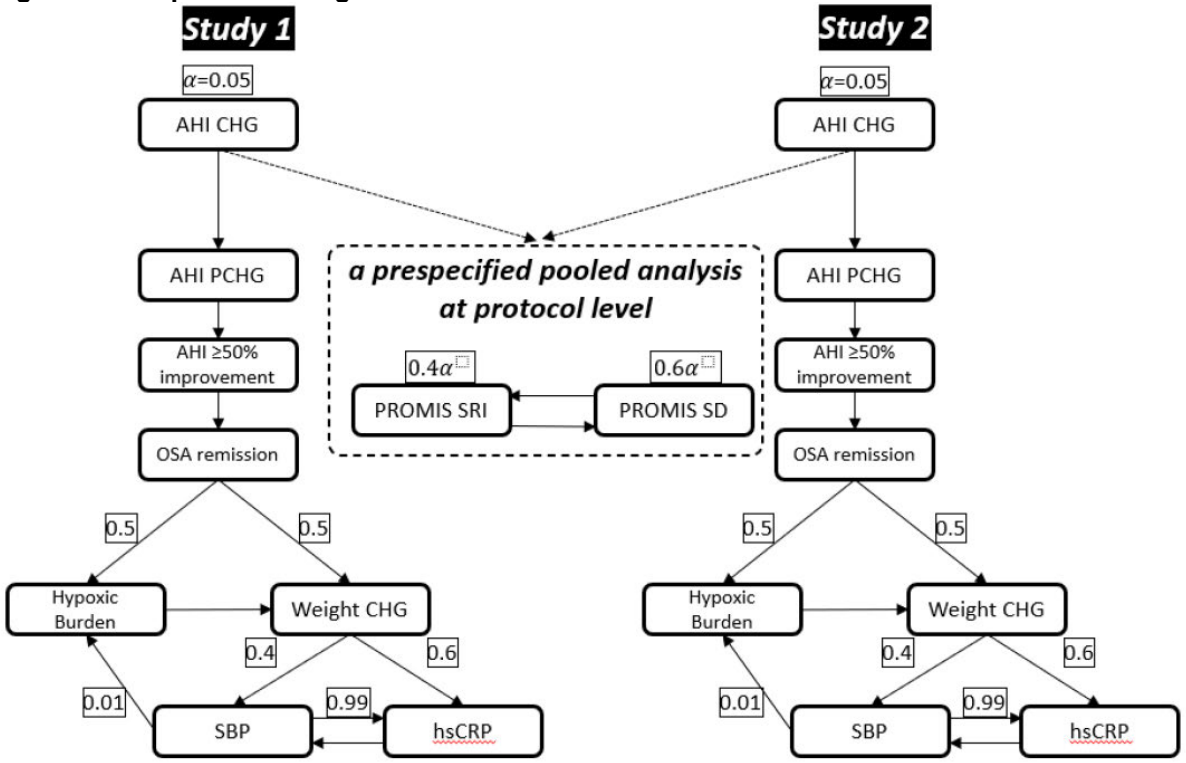
14.5.1. Integrated Efficacy Analysis Plan

The Applicant planned an integrated analysis for selected efficacy parameters potentially not adequately powered within each trial using pooled data from GPI1 and GPI2, while controlling the submission-wise type 1 error rate (Vandemeulebroecke et al. 2024). Pooled analyses were to be conducted using the same analysis set as used in the individual trials. A pooled analysis was conducted for the key secondary endpoints of change from baseline in PROMIS-SRI and PROMIS-SD, respectively.

All analyses were planned to be performed and aligned to the "treatment regimen" estimand. Analysis methods and imputation approaches for handling missing/invalid data were in line with the individual trials. These endpoints were to be analyzed from the ANCOVA model with treatment, trial (GPI1/GPI2), geographic region (US/OUS), AHI stratum (not severe [AHI <30]/severe [AHI ≥30]), and gender as fixed effects, with baseline as a covariate, using the pooled study populations.

The applicant proposed graphical testing schema for the pooled analyses of the secondary PRO endpoints from the Summary of Clinical Efficacy in Figure 35.

Figure 35. Graphical Testing Scheme for GPI1 and GPI2.



Abbreviations: AHI = Apnea-Hypopnea Index; CHG = change; hsCRP = high-sensitivity C-reactive protein; OSA = obstructive sleep apnea; PCHG = percent change; PRO = patient-reported outcome; PROMIS = Patient-Reported Outcomes Measurement Information System; SD = Sleep Disturbance; SRI = Sleep-Related Impairment; SBP = systolic blood pressure.

Note: Study 1 and Study 2 represent Trial GPI1 and Trial GPI2, respectively. The pooled analyses are subject to the SWER of α`= 0.04875 = 2 × (0.025- 0.025^2) if the primary endpoint is achieved under the family wise error rate (FWER) control in both trials, and α= 0.05 if all endpoints subject to the FWER control of endpoint is achieved in both trials.
Source: NDA Summary of Clinical Efficacy Figure 2.7.3.2., p.22

During the IND review, the review team indicated that results based on pooled data may not be meaningful from a clinical perspective because of the difference in use of PAP between the study populations and its potential impact on these PROs and that a focus of our review would be the treatment effect on PROs based on the unpooled individual trial data. Refer to Section

8.1.3 for more discussion of the PROs. For the completeness of the review, the results from the Applicant's pooled analysis are presented in the following section.

14.5.2. Pooled PROMIS PRO Endpoints Results

In the pooled GPIF phase 3 trials, the LS mean difference in change from baseline to Week 52 in PROMIS-SD T-Scores between Tirzepatide MTD and placebo was -3.0 [95% CI: -4.48, -1.54] (Table 65); the LS mean difference in change from baseline to Week 52 in PROMIS-SRI T-Scores between Tirzepatide MTD and placebo was -3.9 [95% CI: -5.69, -2.16] (Table 66).

Table 65: Change from Baseline in PROMIS-SD T-Score at Week 52 (mITT), Pooled Trials GPI1 and GPI2

	TZP MTD (N=233)	Placebo (N=234)
Baseline, mean (SD)	55.1 (7.22)	54.9 (7.71)
Value at **52 Weeks, mean (Standard Deviation)**	49.1 (7.13)	52.2 (8.26)
Missing, n(%)	16 (6.9)	44 (18.8)
Change from Baseline, mean[1] **(SE)**	-5.7 (0.53)	-2.7 (0.56)
Difference from Placebo, mean[1] **(CI)**	-3.0 (-4.48, -1.54)	-
Between-treatment p-value[2]	<0.01	-

Abbreviations: ANCOVA=analysis of covariance, CI=confidence interval, MTD=maximum tolerated dose, OSA=obstructive sleep apnea, PROMIS=Patient-Reported Outcomes Measurement Information System, SD=sleep disturbance, N = number of subjects in treatment arm, TZP = tirzepatide.
Analysis Population is Modified Intent-to-Treat (mITT): Number of participants randomly assigned and received at least 1 dose of study drug.
Model: ANCOVA with Multiple Imputation by Treatment for Missing Data at 52 Weeks.
[1] Shown are least squares means.
[2] Region, sex, substudy identifier, baseline OSA severity group, and baseline SDTS were included in the model.
Note: Imputed baseline and Week 52 SD t-scores were restricted to be between the minimum value of SD t-scores and the maximum value of the observed SD t-scores from values of visits included in the imputation.
Calculated change in SD t-scores from imputed values were restricted to be between the maximum and minimum of observed change in SD t-scores from values of visits included in the imputation.
Source: Integrated Summary of Effectiveness Data (pages 7-8); results reproduced by statistical analyst using adpro.xpt (from gpi1 and gpi2), adds.xpt, and adsl.xpt.

Table 66: Summary and Analysis of Change in PROMIS-SRI T-Score (mITT), Pooled Trials GPI1 and GPI2

	TZP MTD (N=233)	Placebo (N=234)
Baseline, mean (SD)	54.6 (8.28)	54.9 (9.41)
Value at **52 Weeks, mean (SD)**	46.9 (9.00)	51.2 (9.50)
Missing, n(%)	13 (5.6)	41 (17.5)
Change from Baseline, mean[1] **(SE)**	-7.5 (0.63	-3.6 (0.68)
Difference from Placebo, mean[1] **(CI)**	-3.9 (-5.69, -2.16)	-
Between-treatment p-value[2]	<0.01	-

Abbreviations: ANCOVA=analysis of covariance, CI=confidence interval, MTD=maximum tolerated dose, OSA=obstructive sleep apnea, PROMIS=Patient-Reported Outcomes Measurement Information System, SD = standard deviation, SRI=sleep related impairment, TZP = tirzepatide.
Analysis Population is Modified Intent-to-Treat (mITT): Number of participants randomly assigned and received at least 1 dose of study drug.
Model: ANCOVA with Multiple Imputation by Treatment for Missing Data at 52 Weeks.
Note: Imputed baseline and Week 52 SRI t-scores were restricted to be between the minimum value of SRI t-scores and the maximum value of the observed SRI t-scores from values of visits included in the imputation. Calculated change in SRI t-scores from imputed values were restricted to be between the maximum and minimum of observed change in SRI t-scores from values of visits included in the imputation.
[1] Shown are least squares means.
[2] Region, sex, substudy identifier, baseline OSA severity group, and baseline SRIT were included in the model.
Source: Integrated Summary of Effectiveness Data (pages 9-10); results reproduced by statistical analyst using adpro.xpt (from gpi1 and gpi2), adds.xpt, and adsl.xpt.

14.5.3. Efficacy Estimand

The applicant specified that the primary and each key secondary efficacy analysis were guided by the "treatment regimen" estimand and the "efficacy" estimand to support global regulatory submissions and publication. Compared to the attributes of the "treatment regimen" estimand, the "efficacy" estimand specified different strategies handling intercurrent events. The difference was that the intercurrent events of treatment discontinuation and use of PAP therapy for subjects in GPI1 were addressed by the hypothetical strategy. The potential outcome of interest was the response in the efficacy measurement if subjects remained on their randomly assigned treatment for 52 weeks and did not initiate PAP therapy during the study. The analysis data set used for the "efficacy" estimand was data obtained during the treatment period of the mITT population, excluding data after discontinuation of study intervention (last dose + 7 days) and for GPI1, excluding data after initiating PAP therapy.

The efficacy results based on the "efficacy" estimand are not presented in this review.

14.6. Clinical Appendices

14.6.1. Schedule of Activities

Figure 36. Schedule of Activities

	Study Period I - Screening	Study Period II - Treatment											Study Period III - Post-Treatment Follow-up	Comments
Visit number	1	2	3	4	5	6	7	8	9	10	11	ED	801	
Weeks from randomization	-4	0	4	8	12	16	20	24	36	48	52	-	See footnote a	
Visit interval tolerance (days)	-14 to +21	–	±3	±3	±3	±3	±7	±3	±7	±3	±7	±7	±3	
Fasting Visit		X	X	X	X	X	X	X	X	X	X	X	X	See footnote b. If V10 is remote, then the visit will not be fasting.
Informed consent	X													The informed consent must be signed before any protocol-specific tests/procedures are performed.
Inclusion and exclusion criteria, review and confirm	X	X												Inclusion/Exclusion criteria should be confirmed prior to drug assignment and administration of first dose of study intervention.
Demographics	X													Includes ethnicity, year of birth, gender (sex), and race.
Preexisting conditions and medical history, including relevant surgical history	X													All conditions ongoing and relevant past surgical and medical history should be collected.
Prespecified medical history	X													Should include, but not be limited to, collecting diagnosis of OSA and obesity-related health problems.
Prior treatments for indication	X													Include OSA and obesity.
Substance use (alcohol, caffeine, tobacco use)	X													
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	
AEs	X	X	X	X	X	X	X	X	X	X	X	X	X	Any events that occur after signing the informed consent are considered AEs as defined in Section 8.3.1. Additional data are collected for certain AEs.
Physical Evaluation														
Height	X													
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	Weight measurements should be obtained per the instructions in 10.8. If V10 is remote, then weight will not be obtained at the visit.
Waist circumference		X					X				X	X	X	Waist circumference should be obtained per the instructions in Section 10.8.
Hip circumference		X					X				X	X	X	Hip circumference should be obtained per the instructions in Section 10.8.
Neck circumference		X					X				X	X	X	Neck circumference should be obtained per the instructions in Section 10.8.
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	Includes PR and BP. Measured after participant has been sitting at least 5 minutes. Vital-sign measurements should be taken before obtaining an ECG tracing and before collection of blood samples for laboratory testing. See Sections 8.2.2 and 10.8. If V10 is remote, vital signs will not be obtained at the visit.

	Study Period I - Screening	Study Period II - Treatment											Study Period III - Post-Treatment Follow-up	Comments
Visit number	1	2	3	4	5	6	7	8	9	10	11	ED	801	
Weeks from randomization	-4	0	4	8	12	16	20	24	36	48	52	-	See footnote a	
Visit interval tolerance (days)	-14 to +21	–	±3	±3	±3	±3	±7	±3	±7	±3	±7	±7	±3	
Fasting Visit		X	X	X	X	X	X	X	X	X	X	X	X	See footnote b. If V10 is remote, then the visit will not be fasting.
Complete physical examination	X													The complete physical examination is performed (excludes pelvic, rectal, and breast examinations unless clinically indicated).
Symptom-directed physical assessment		X	X	X	X	X	X	X	X	X	X	X	X	As indicated based on participant status and standard of care. May be performed by qualified personnel per local regulations. If V10 is remote, then symptom-directed physical assessment will not be done at the visit.
12-lead ECG (local)	X										X	X		ECG measurements should be obtained per the instructions in Section 8.2.3.
Wearable Devices and PSG Assessments														
Schedule Sleep Center Study for PSG	X					X				X		X		PSG results must be reviewed to confirm eligibility prior to randomization.
Sleep Center Study for PSG	X						X				X	X		PSG at V7 and 11 may be scheduled for any day +/- 14 days.
Participant wears the WatchPat300	X		X		X		X				X			Applicable only to participants in GPI1 (off PAP). Training documents will detail information on the dispensation, wearing, and return process.
Participant wears actigraphy (AX6) device	X		X		X		X				X			Training documents will detail information on the dispensation, wearing, and return process.
Participant Education and Supplies														
eDiary education	X													Additional training can be repeated, as needed.
Train participant on study intervention administration		X												Re-training is available anytime.
Review Lifestyle Program instructions		X	X	X	X	X	X	X	X	X	X	X		
Review diet and exercise goals		X	X	X	X	X	X	X	X	X	X	X		All training should be repeated as needed to ensure participant compliance. Study personnel to provide reinforcement and encouragement for lifestyle modifications.
Participant Diary (Electronic)														
Participant diary dispensed	X													Includes the following: Sleep diary; Dosing diary; Hypoglycemic events (when applicable), Patient Diet and Exercise diary, PAP adherence (for GPI2 only).
Diary compliance check		X	X	X	X	X	X	X	X	X	X	X		
Diary return											X	X		

	Study Period I - Screening	Study Period II - Treatment											Study Period III - Post-Treatment Follow-up	Comments
Visit number	1	2	3	4	5	6	7	8	9	10	11	ED	801	
Weeks from randomization	-4	0	4	8	12	16	20	24	36	48	52	-	See footnote a	
Visit interval tolerance (days)	-14 to +21	–	±3	±3	±3	±3	±7	±3	±7	±3	±7	±7	±3	
Fasting Visit		X	X	X	X	X	X	X	X	X	X	X	X	See footnote b. If V10 is remote, then the visit will not be fasting.
Patient-Reported Outcomes (Electronic) *Complete prior to any clinical-administered assessments*														
ESS	X		X		X		X				X	X		When the PROs are scheduled for visits at which the PSG will be done, they should be completed in the following order (FOSQ, ESS, PROMIS Short Form v1.0 Sleep Disturbance 8b, PROMIS Short Form v1.0 Sleep-related Impairment 8a, PGIS, PGIC, SF-36v2 acute form, and EQ-5D-5L) before the PSG is conducted, and should be done at the same time of day for each of those visits.
EQ-5D-5L	X										X	X		
FOSQ	X				X		X				X	X		
PGIS (OSA Symptom Scales)	X		X		X		X				X	X		
PGIC (OSA Symptom Scales)			X		X		X				X	X		
PROMIS Short Form v1.0 Sleep Disturbance 8b	X		X		X		X				X	X		
PROMIS Short Form v1.0 Sleep-related Impairment 8a	X		X		X		X				X	X		
SF-36v2, acute	X						X				X	X		
PHQ-9	X	X					X				X	X		The PHQ-9 should be administered after assessment of AEs.
Clinician-Administered Assessments (Paper)														
C-SSRS screening/baseline	X													The C-SSRS should be administered after assessment of AEs. The C-SSRS since last visit is adapted for the assessment of the ideation and behavior categories only. The Intensity of Ideation and Lethality of Behavior sections are removed.
C-SSRS (since last visit version)		X	X	X	X	X	X	X	X	X	X	X	X	
Laboratory Tests and Sample Collections														
Hematology	X				X			X	X		X	X	X	
HbA1c	X	X			X			X	X		X	X	X	
Clinical chemistry (includes glucose)	X	X			X			X	X		X	X	X	
Lipid panel		X						X			X	X	X	
hsCRP		X						X			X	X		
Serum pregnancy	X													Only for WOCBP and females with a history of tubal ligation. See Section 10.4, Appendix 4.

	Study Period I - Screening	Study Period II - Treatment											Study Period III - Post-Treatment Follow-up	Comments
Visit number	1	2	3	4	5	6	7	8	9	10	11	ED	801	
Weeks from randomization	-4	0	4	8	12	16	20	24	36	48	52	-	See footnote a	
Visit interval tolerance (days)	-14 to +21	–	±3	±3	±3	±3	±7	±3	±7	±3	±7	±7	±3	
Fasting Visit		X	X	X	X	X	X	X	X	X	X	X	X	See footnote b. If V10 is remote, then the visit will not be fasting.
Urine pregnancy (local)		X			X			X	X		X	X		A urine pregnancy test must be performed at V2 with the result available prior to first dose/injection of study intervention for WOCBP only. Additional pregnancy tests (beyond those required per the SoA) should be performed at any time during the trial if a menstrual period is missed, there is clinical suspicion of pregnancy, or as required by local law or regulation.
FSH	X													Optional; performed as needed to confirm postmenopausal status. See Section 10.4, Appendix 4.
Insulin		X						X			X	X	X	
C-Peptide		X						X			X	X	X	
Free fatty acids		X						X			X	X	X	
Cystatin-C	X							X			X	X	X	
Calcitonin	X										X	X	X	
Pancreatic amylase	X				X			X			X	X	X	
Lipase	X				X			X			X	X	X	
TSH	X													
eGFR	X	X			X			X	X		X	X	X	Calculated using CKD-EPI method.
UACR	X	X			X			X	X		X	X	X	
PK samples		X	X		X			X			X	X	X	PK samples to be collected predose and close to ADA samples.
Immunogenicity (ADA) samples		X	X		X			X			X	X	X	In the event of systemic drug hypersensitivity reactions (immediate or nonimmediate), additional unscheduled samples should be collected as detailed in Section 10.3.7.2 (Hypersensitivity Reactions). Immunogenicity samples and PK samples for immunogenicity must be predose.
Stored Samples														
Genetics sample		X												Sample can be obtained at or after the specified visit.
Exploratory biomarker samples		X						X			X	X	X	
Randomization and Dosing														
Register visit with IWRS	X	X	X	X	X	X	X	X	X	X	X	X	X	
ISA assignment via IWRS	X													
ISA treatment randomization via IWRS		X												

	Study Period I - Screening	Study Period II - Treatment											Study Period III - Post-Treatment Follow-up	Comments
Visit number	1	2	3	4	5	6	7	8	9	10	11	ED	801	
Weeks from randomization	-4	0	4	8	12	16	20	24	36	48	52	-	See footnote a	
Visit interval tolerance (days)	-14 to +21	–	±3	±3	±3	±3	±7	±3	±7	±3	±7	±7	±3	
Fasting Visit		X	X	X	X	X	X	X	X	X	X	X	X	See footnote b. If V10 is remote, then the visit will not be fasting.
Observe participant administer study intervention		X												Participants should administer their first dose of study intervention at the end of the V2, after other study procedures are completed.
Dispense study drug via IWRS		X	X	X	X	X	X	X	X	X				
Dispense study drug to participant (for at home dosing)		X	X	X	X	X	X	X	X	X				
Dispense ancillary supplies to participant		X												Dispensation of ancillary supplies may vary beyond V2 based on expiry dating of applicable supplies and/or participant needs.
Participant returns all unused study intervention			X	X	X	X	X	X	X	X	X	X		If V10 is remote, participant will return any unused study intervention dispensed at V9 during the V11 visit.
Assess study intervention compliance			X	X	X	X	X	X	X	X	X	X		If V10 is remote, the next study intervention compliance will be done at V11.

Abbreviations: ADA = antidrug antibody; AEs = adverse events; AX6 = Axivity 6; CKD EPI = Chronic Kidney Disease Epidemiology; hsCRP = high sensitivity C-reactive protein; C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; ED = early discontinuation; eGFR = estimated glomerular filtration rate; EQ-5D-5L = EuroQol - 5 Dimension - 5 Level; ESS = Epworth Sleepiness Scale; FOSQ = Functional Outcomes of Sleep Questionnaire; FSH = follicle-stimulating hormone; HbA1c = hemoglobin A1c; ISA = indication-specific appendix; IWRS = interactive web-response system; OSA = obstructive sleep apnea; PHQ = Patient Health Questionnaire-9; PGIC = Patient Global Impression of Change; PGIS = Patient Global Impression of Status; PK = pharmacokinetic; PSG = polysomnography; PR = pulse rate; PRO = patient reported outcome; PROMIS = Patient-Reported Outcomes Measurement Information System; SF-36v2 = Short-Form 36 version 2; SoA = schedule of activities; TSH = thyroid-stimulating hormone; UACR = urinary albumin/creatinine ratio; V = visit; WOCBP = woman of childbearing potential.

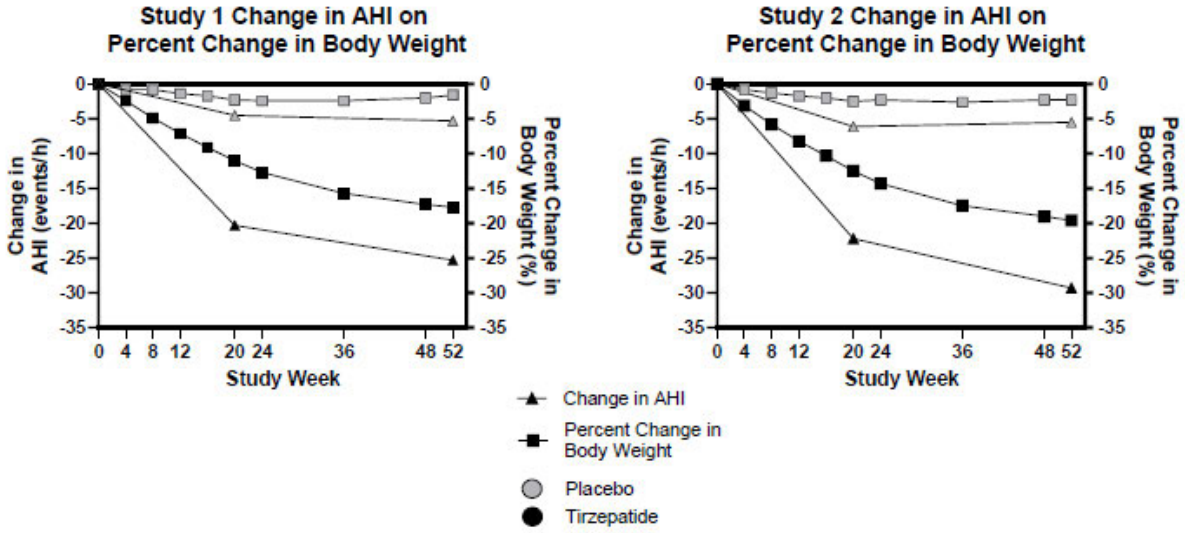
a Post-treatment follow-up occurs approximately 4 weeks after the participant's final treatment period visit.

b Fasting visit: On all office visits, study participants should be reminded to report to the site before taking study intervention in a fasting condition, after a period of approximately 8 hours without eating, drinking (except minimal amount of water, as needed), or any significant physical activity.

Source: GPIF Protocol OSA, Schedule of Activities, p. 13-22

14.6.2. Change in AHI and Percent Change in Body Weight

Figure 37. Change in AHI (events/h) on Percent Change in Body Weight (mITT), Trials GPI1 and GPI2



Source: Figure 4.3 Information Request Regulatory response-19 sept-2024

Consistent with previous literature on the relationship between change in body weight and change in AHI (Fattal et al. 2022; Malhotra et al. 2024), the GPIF trials also showed a strong correlation between decreases in body weight and improvements in AHI (Appendix Figure 37). In both GPI1 and GPI2, subjects treated with tirzepatide achieved approximately 10% change in body weight from baseline at Week 20, which correlated with a change in AHI of 20 events/h.

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/

BANU A KARIMI SHAH
12/20/2024 07:26:14 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

217806Orig1s013

STATISTICAL REVIEW(S)

STATISTICAL REVIEW AND EVALUATION
FILING REVIEW OF AN NDA/BLA

NDA/BLA #:	NDA 217806
Supplement #:	SUPPL-13
Related IND #:	IND 157090
Product Name:	Zepbound (tirzepatide)
Indication(s):	Treatment of moderate-to-severe OSA in patients with a BMI ≥ 30kg/m^2
Applicant:	Eli Lilly and Company
Dates:	Submit Date: 06/21/2024 PDUFA Goal Date: 12/21/2024
Review Priority:	Priority
Biometrics Division:	Division of Biometrics (DB) III
Statistical Reviewer:	Dong-Hyun Ahn, PhD; Nathan Janus (Analyst), MS
Concurring Reviewers:	Yongman Kim (TL), PhD
Medical Division:	Division of Pulmonology, Allergy, and Critical Care (DPACC)
Clinical Team:	Shivani Klauer, MD; Elisabeth Boulos (TL), MD
Project Manager:	Linda Ebonine

1. Summary of Efficacy/Safety Clinical Trials to be Reviewed

Tirzepatide is a long-acting glucose-dependent insulinotropic polypeptide (GIP) receptor and glucagon-like peptide-1 (GLP-1) receptor agonist. It is an amino acid sequence including a C20
fatty diacid moiety that enables albumin binding and prolongs the half-life. Tirzepatide selectively binds to and activates both the GIP and GLP-1 receptors, the targets for native GIP
and GLP-1. Tirzepatide is approved as an adjunct to diet and exercise to improve glycemic control in adults with Type 2 diabetes mellitus in the US, EU, Japan, and China with applications approved or
under review in other regions. It is also approved for weight management in adults with obesity
or overweight with weight-related comorbidities in the US and EU with applications approved or
under review in other regions.

The present application is for the use of tirzepatide to treat moderate-to-severe obstructive sleep
apnea in adults with obesity.
This application presents the evidence from Protocol I8F-MC-GPIF (SURMOUNT-OSA), a master protocol that supported 2 studies:

- Study GPI1 (Study 1) included participants who were unable or unwilling to use positive airway pressure (PAP) therapy.
- Study GPI2 (Study 2) included participants who were on PAP therapy for at least 3 months at the time of screening and planned to continue PAP therapy during the study.

Table 1 provides the key design elements of Study 1 and Study 2.

Table 1: Summary of Phase 3 Trials to be Assessed in the Statistical Review

Trial ID	Design*	Treatment/ Sample Size (randomized)	Endpoint/Analysis (for both trials)	Preliminary Findings
Study 1	MC, R, DB, PG, PC trial (52 weeks + 4-week safety follow-up) Patient Population: Participants who were unable or unwilling to use PAP therapy and had not used PAP for at least 4weeks prior to Visit 1	Tirzepatide/ N_T =114 Placebo/ N_P = 120 Randomization Ratio: 1:1	Primary: Change from baseline in AHI at Week 52 Key Secondary: Percent change in AHI at Week 52 Percent of participants with ≥50% AHI reduction at Week 52 Percent of participants at Week 52 with AHI <5 or (AHI 5 through 14 and ESS ≤10)	Tirzepatide had statistically significant improvements compared with placebo for all the key efficacy endpoints using "treatment-regimen" estimand.
Study 2	MC, R, DB, PG, PC trial (52 weeks + 4-week safety follow-up) Patient Population: Participants on PAP therapy for at least 3 months at the time of Visit 1 and planned to continue PAP therapy during the study	Tirzepatide/ N_T = 120 Placebo/ N_P = 115 Randomization Ratio: 1:1	Percent change from baseline to Week 52 in body weight Change from baseline to Week 48 in SBP Change from baseline to Week 52 in C-reactive protein Change in sleep apnea-specific hypoxic burden Change in PROMIS	Tirzepatide had statistically significant improvements compared with placebo for all the key efficacy endpoints using "treatment-regimen" estimand.

		Sleep-related impairment short form 8a (pooled across Studies 1 and 2) Change in PROMIS Sleep disturbance short form 8b (pooled across Studies 1 and 2)

* AHI: Apnea-Hypopnea Index, ESS: Epworth Sleepiness Scale, MC: multi-center, R: randomized, DB: double-blind, PAP: positive airway pressure, PG: parallel group, PC: placebo controlled, PROMIS: Patient-Reported Outcomes Measurement Information System, SBP: systolic blood pressure, Study 1: I8F-MC-GPI1; Study 2: I8F-MC-GPI2.

2. Assessment of Protocols and Study Reports

Table 2: Summary of Information Based Upon Review of the Protocol(s) and the Study Report(s)

Content Parameter	Response/Comments
Designs utilized are appropriate for the indications requested.	**Yes**
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	**Yes**
Interim analyses (if present) were pre-specified in the protocol with appropriate adjustments in significance level. DSMB meeting minutes and data are available.	**NA**
Appropriate details and/or references for novel statistical methodology (if present) are included (e.g., codes for simulations).	**Yes** **(Submission-wise Error Rate approach)**
Investigation of effect of missing data and discontinued follow-up on statistical analyses appears to be adequate.	**Yes**

3. Electronic Data Assessment

Table 3: Information Regarding the Data

Content Parameter	Response/Comments
Dataset location	\\CDSESUB1\evsprod\NDA217806\0241\m5\datasets\i8f-mc-gpi1\analysis \\CDSESUB1\evsprod\NDA217806\0241\m5\datasets\i8f-mc-gpi2\analysis
Were analysis datasets provided?	Yes
Dataset structure (e.g., SDTM or ADaM)	SDTM & ADaM
Are the define files sufficiently	Yes

Content Parameter	Response/Comments
detailed?	
List the dataset(s) that contains the primary endpoint(s)	ADPSG
Are the *analysis datasets* sufficiently structured and defined to permit analysis of the primary endpoint(s) without excess data manipulation? *	Yes
Are there any initial concerns about site(s) that could lead to inspection? If so, list the site(s) that you request to be inspected and the rationale.	No
Safety data are organized to permit analyses across clinical trials in the NDA/BLA.	Yes

* This might lead to the need for an information request or be a refuse to file issue depending on the ability to review the data.

4. Filing Issues

Table 4: Initial Overview of the NDA/BLA for Refuse-to-file (RTF):

Content Parameter	Yes	No	NA	Comments
Index is sufficient to locate necessary reports, tables, data, etc..	✓			
ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.).	✓			
Safety and efficacy were investigated for gender, racial, and geriatric subgroups.	✓			
Data sets are accessible, sufficiently documented, and of sufficient quality (e.g., no meaningful data errors).	✓			
Application appears to be free from any other deficiency that render the application unreviewable, administratively incomplete, or inconsistent with regulatory requirements.	✓			

IS THE APPLICATION FILEABLE FROM A STATISTICAL PERSPECTIVE? Yes

5. Comments to be Conveyed to the Applicant

5.1. Refuse-to-File Issues

None

5.2. Information Requests/Review Issues

Your submission to NDA 217806 S-013 (tirzepatide) dated June 21, 2024, is under review. We have the following comments and requests for information.

Patient Reported Outcomes (PROs)

1. (b) (4) As noted in the Type C pre-NDA Meeting Minutes dated 1/19/2024, to support substantial evidence of effectiveness for tirzepatide in the treatment of OSA the expectation was for independent substantiation of efficacy results in two adequate and well-controlled investigations.

   We acknowledge the justification you provide regarding insufficient power in each study for these PROs. We also acknowledge the clinical rationale you provide to support pooling: that the 7-day washout period prior to polysomnogram (PSG) assessment at both baseline and Week 52 likely reduces the potential impact of PAP on PRO outcomes in Study 2; therefore, the populations of the two studies can be considered homogenous and suitable for pooling in the context of PRO assessment. However, the literature on the effects and timing of PAP withdrawal on clinical symptoms is not conclusive[1-5]. The extent and duration of the PAP washout effect can be highly variable and potentially confounded by issues of night-to-night variability in measurement of sleep-disordered breathing. Therefore, it is not clear that the populations of the two studies can be pooled when assessing the PROMIS-SRI and PROMIS-SD. There is uncertainty whether baseline use of PAP therapy may have a cumulative benefit that is captured by the PRO assessment and may be responsible for driving the pooled analysis outcome.

   Provide additional justification for why pooling these two study populations is appropriate. Whether the pooled PRO data will be sufficient to support efficacy will be a review issue.

2. Provide the score manual that includes the following details regarding the scoring algorithm for the PROMIS-SD and PROMIS-SRI T-scores. Provide the following specific information:

   a. Formula that was used to calculate the T-scores through item scores,
   b. How missing item-level data was handled and how many non-missing items were required to calculate the T-scores.

3. Provide a subgroup analysis of the efficacy of tirzepatide on the change from baseline in the PRO to Week 52 for PROMIS-SRI and PROMIS-SD using data from

Study 1 and Study 2 separately, as well as pooled data from the two studies. To define the subgroup(s), we recommend that you explore creating meaningful score regions (MSRs) for the PROMIS-SRI and PROMIS-SD scores. MSRs can be created by examining the distribution of the PROMIS-SRI and PROMIS-SD scores corresponding to each response category of an anchor scale (e.g., Patient Global Impression of Severity [PGIS]). Then, the MSRs can be used to identify the range of scores that is representative of moderate/severe symptom severity. We have the following recommendations for your analyses to establish MSRs; however, we are open to alternative well-justified approaches.

a. You should use the same primary anchor scales (i.e., PGIS Sleep Quality for the PROMIS-SD, PGIS Sleepiness [Study 1] and PGIS Fatigue [Study 2] for the PROMIS-SRI) to define MSRs as you used to conduct anchor-based analyses.
b. You should use the 75th percentiles of the score distributions corresponding to the target PGIS response category that is representative of at least moderate symptom severity to define the cutoff scores that represent a moderate/severe symptom severity. For more guidance on how to define a meaningful score region, we refer you to Section III.B of the *Draft Guidance for Industry, Food and Drug Administration Staff, and Other Stakeholders Patient-Focused Drug Development: Incorporating Clinical Outcome Assessments Into Endpoints for Regulatory Decision-Making (April 2023)*[1].

4. We acknowledge that the ESS and FOSQ-10 are PROs that were not deemed fit for purpose. However, given the limitations of the PROMIS-SRI and PROMIS-SD analyses, these PROs may provide additional insights for understanding subjects' symptoms of sleepiness and response to intervention. The following analyses are exploratory in nature to assist us with our review process.

a. Provide the mean changes in FOSQ-10 and ESS from baseline to Week 52 using the treatment-regimen estimand for both Study 1 and Study 2 for each study individually and pooled for both studies.
b. Provide meaningful within patient change (MWPC) thresholds (e.g., from the literature or using data from Study 1 and Study 2) for both FOSQ-10 and ESS. Provide the percentage of subjects who met these thresholds for each study and pooled for both studies for both the tirzepatide arm and the placebo arm using the treatment-regimen estimand.
c. Provide a subgroup analysis of the efficacy of tirzepatide on the change from baseline in the PRO to Week 52 for the ESS and FOSQ-10. Divide the subgroups into categories based on symptom severity. Provide a definition of the subgroup categories and provide justification for the level of symptom severity of each subgroup category.

Efficacy Analysis

5. Derive the difference in proportion (i.e., population-level responder difference) for the following endpoints using the treatment-regimen estimand:

a. Percentage of Participants with ≥50% AHI Reduction from Baseline to Week 52,

b. Percentage of Participants Achieving OSA Remission or Mild, Non-symptomatic OSA (AHI <5 Events/h or AHI 5-14 Events/h with ESS ≤10) at Week 52,
c. Percentage of Participants Achieving Meaningful Within-Patient Change in PROMIS SRI Score from Baseline to Week 52(for each study individually and pooled for both studies),
d. Percentage of Participants Achieving Meaningful Within-Patient Change in PROMIS SD Score from Baseline to Week 52 (for each study individually and pooled for both studies).

6. According to the schedule of activities, a blinded PSG was performed at Week 20. Provide analyses on the key primary and secondary efficacy endpoints using the data from the Week 20 PSG. Provide information on whether patients had changes made to their PAP settings at that time.

7. Provide plots for both Study 1 and Study 2 that show the change from baseline in AHI (using Week 20 PSG data) over time through Week 52 and, on the same graph, show the change from baseline in percent body weight over time through Week 52.

Patient Disposition

8. We note that both Study 1 and Study 2 have high study discontinuation rates in the placebo arms. The majority of these events are attributed to “withdrawal by subject”. Provide additional details for subjects who withdrew for this reason and an explanation for the high discontinuation rates. In addition, provide details on the timing of patients who withdrew from study treatment and, where available, specific reasons for each discontinuation.

9. We note that “assigned treatment by mistake” is one of the reasons given for study and treatment discontinuation in both Study 1 and Study 2. Provide further clarification and details on this discontinuation reason and timing of discontinuation.

Immunogenicity

10. We acknowledge that approximately 60% of subjects on tirzepatide treatment developed anti-drug antibodies (ADA) in the OSA clinical program. Although in vitro binding assay indicates that only about 2.8% of ADA+ cases cross-react with the endogenous GIP, the clinical meaning is unclear. Provide the following justifications:

    a. Whether OSA patients are expected to be on (life-) long-term treatment of tirzepatide.
    b. The prevalence of endogenous anti-GIP or anti-GLP1 antibodies in subjects who have never received a GIP/GLP-1 agonist treatment (such as in placebo groups or pre-dose evaluation in tirzepatide groups in your clinical programs) and whether the baseline antibodies levels are associated with the severity of the diseases (e.g., diabetes, obesity, OSA, etc.) compared to ADA- patients at baseline.

c. Whether ADA+ patients experienced higher magnitude of rebound or gained new diagnosis of diseases (e.g., diabetes, obesity, or OSA) when compared to ADA- patients after they discontinued tirzepatide treatment.

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/s/

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WEIYA ZHANG
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Signed it for Yongman Kim as the secondary reviewer while he is on leave.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

217806Orig1s013

OTHER REVIEW(S)

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:	December 13, 2024
To:	Linda Ebonine, PA-C Senior Regulatory Project Manager **Division of Pulmonology, Allergy, and Critical Care (DPACC)**
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)** Quynh-Nhu Capasso, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	ZEPBOUND (tirzepatide)
Dosage Form and Route:	injection, for subcutaneous use
Application Type/Number:	NDA 217806
Supplement Number:	S-013
Applicant:	Eli Lilly and Company

1 INTRODUCTION

On June 21, 2024, Eli Lilly and Company submitted for the Agency's review an Efficacy Supplemental New Drug Application (Snda) 217806 S-013 for ZEPBOUND (tirzepatide). The purpose of this supplement is to propose revisions to the Prescribing Information (PI) to reflect the following new indication for ZEPBOUND (tirzepatide): to treat moderate to severe obstructive sleep apnea (OSA) in adults with obesity.

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 Pulmonary, Allergy, and Critical Care (DPACC) on August 28, 2024, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for ZEPBOUND (tirzepatide) injection, for subcutaneous use.

2 MATERIAL REVIEWED

- Draft ZEPBOUND (tirzepatide) injection, for subcutaneous use MG received on June 21, 2024, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on December 6, 2024.
- Draft ZEPBOUND (tirzepatide) injection, for subcutaneous use Prescribing Information (PI) received on June 21, 2024, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on December 6, 2024.

3 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.

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.

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the PI
- removed unnecessary or redundant information
- ensured that the MG 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 meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG is consistent with the approved comparator labeling where applicable

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG 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.

Please let us know if you have any questions.

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/s/

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MARCIA B WILLIAMS
12/13/2024 01:25:53 PM

LASHAWN M GRIFFITHS
12/13/2024 01:46:41 PM

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

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

Memorandum

Date: December 12, 2024

To: Linda Ebonine, Senior Regulatory Project Manager
Division of Pulmonology, Allergy, and Critical Care (DPACC)

From: Quynh-Nhu Capasso, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Adewale Adeleye, Team Leader, OPDP

Subject: OPDP Labeling Comments for ZEPBOUND® (tirzepatide) injection, for subcutaneous use

NDA: 217806, S-013

Background:
In response to DPACC's consult request dated August 28, 2024, OPDP has reviewed the proposed Prescribing Information (PI) and Medication Guide for supplement S-013 for ZEPBOUND® (tirzepatide) injection, for subcutaneous use (Zepbound). While we were consulted to review the Instructions for Use (IFU), no changes were made to the IFU for this supplement and it was not sent to OPDP. This labeling supplement proposes the addition of a new indication, treatment of moderate to severe obstructive sleep apnea in adults with obesity, in combination with a reduced-calorie diet and increased physical activity.

PI/Medication Guide:
OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on December 5, 2024, 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 comments will be sent under separate cover.

Thank you for your consult. If you have any questions, please contact Quynh-Nhu Capasso at quynh-nhu.capasso@fda.hhs.gov.

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The Clinical Inspection Summary

Date	November 19, 2024
From	Tina Chang, M.D., Medical Officer Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	Shivani Klauer, M.D., Clinical Reviewer, DPACC Elisabeth Boulos, M.D., Clinical Team Leader, DPACC Linda Ebonine, Sr. Regulatory Health Project Manager, DPACC Division of Pulmonary, Allergy, and Critical Care (DPACC)
NDA #	217806 S-013
Applicant	Eli Lilly & Company (Lilly)
Drug	Zepbound (tirzepatide)
NME (Yes/No)	No
Proposed Indication	Treatment of obstructive sleep apnea
Consultation Request Date	July 25, 2024
Summary Goal Date	November 21, 2024
Action Goal Date	December 21, 2024
PDUFA Date	December 21, 2024

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Drs. Blair Brengle, Raj Karunakara, and John Hudson were inspected in support of NDA 217806 S-013, covering Studies I8F-MCGPI1 and I8F-MCGPI2. There were two unreported protocol deviations involving two subjects who took opioids during Study I8F-MCGPI2. Subject (b) (6), randomized to tirzepatide, took morphine for a single day due to a kidney stone, and Subject (b) (6), randomized to placebo, took hydrocodone for a week due to a cochlear implant placement. Opioids were listed by the Sponsor under prohibited medications. These protocol deviations are unlikely to impact the overall safety or efficacy results of Study I8F-MCGPI2. Both prohibited medications were reported by the Sponsor under the listing of concomitant medications. However, they were not reported as protocol deviations, so we are presenting this information here for the review division's consideration.

Based on the inspection results, Studies I8F-MCGPI1 and I8F-MCGPI2 appear to have been conducted adequately, and the data generated by the clinical investigator sites appear acceptable in support of this sNDA.

II. BACKGROUND

Tirzepatide was approved in 2022 as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. The brand name for this diabetes indication is Mounjaro. Tirzepatide was also approved in 2023 as an adjunct to a reduced-calorie diet and

increased physical activity for chronic weight management in adults with an initial body mass index of 30 kg/m^2 or greater, or 27 kg/m^2 or greater 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 brand name for weight loss indication is Zepbound.

According to the sponsor, tirzepatide is an agonist to both long-acting glucose-dependent insulinotropic polypeptide (GIP) receptor and glucagon-like peptide 1 (GLP-1) receptor that may have the potential to provide benefit to patients with obstructive sleep apnea (OSA) who have obesity by reducing weight. The sponsor submitted an efficacy supplement, sNDA 217806 S-013, for the treatment of moderate to severe obstructive sleep apnea (OSA) in adults with obesity based on the safety and efficacy results from a Master Protocol 18F-MC-GPIF that supported two Phase 3 studies, I8F-MCGPI1 and I8F-MCGPI2. Both Phase 3 studies were the same in study design and included their own placebo groups and treatment arms, except that Study I8F-MCGPI1 included subjects who were unwilling or unable to use positive airway pressure (PAP) therapy and Study I8F-MCGPI2 included subjects who used PAP therapy. The following describes Studies I8F-MCGPI1 and I8F-MCGPI2:

18F-MC-GPIF: "A Master Protocol to Investigate the Efficacy and Safety of Tirzepatide Once Weekly in Participants who have Obstructive Sleep Apnea and Obesity: A Randomized, Double-Blind, Placebo-Controlled Trial (SURMOUNT-OSA)."

1) **Study I8F-MCGPI1:** Participants with OSA unwilling or unable to use PAP therapy
2) **Study I8F-MCGPI2:** Participants with OSA on PAP therapy

Studies I8F-MCGPI1 and **I8F-MCGPI2** were Phase III, randomized, double-blind, parallel-arm, placebo-controlled, safety and efficacy studies. The primary objective for both studies was to demonstrate that tirzepatide at the maximum tolerated dose once weekly is superior to placebo for mean decrease in Apnea-Hypopnea Index (AHI).

Both studies consisted of a 4-week Screening Period, a 52-week Treatment Period, and a 4-week Post-treatment Follow-up Period. Subjects were randomized 1:1 to tirzepatide or placebo and administered the investigational product subcutaneously once weekly via a single-dose pen. Subjects followed a schedule to titrate the dose up once monthly, beginning with tirzepatide 2.5 mg once weekly to reach a maximum tolerated dose (10 or 15 mg) once weekly.

Key inclusion criteria: Male or female subjects had to be at least 18 years of age and previously diagnosed with moderate-to-severe OSA with an AHI of at least 15 events/hour prior to Visit 1 and on polysomnography at Visit 1, body mass index of at least 30 kg/m^2, and at least one self-reported unsuccessful dietary effort to lose body weight. The inclusion criteria were the same for both studies, and the only difference was whether subjects were on or off positive airway pressure (PAP) therapy. For Study 18F-MCGIP1, subjects were unable or unwilling to use PAP therapy and must not have used PAP therapy for at least 4 weeks prior to Visit 1. For Study I8F-MCGPI2, subjects used PAP therapy for at least 3 months at time of screening and planned to continue PAP therapy. Please see protocols for complete eligibility criteria.

Primary efficacy endpoint: Change in AHI from Baseline to Week 52.

Data flow of primary efficacy endpoint: Each subject was sent to a sleep lab to have polysomnography (PSG) performed. A PSG is a sleep study test that measures several parameters, including the AHI. A sleep lab technician uploaded the PSG data to a PSG central reader portal. A blinded PSG central reader read, scored the PSG data, and sent the PSG scoring report to the Lab Vendor ((b) (4)), clinical investigator, and the sleep lab technician. The Lab Vendor transferred the full database to the Sponsor's database. Clinical investigator sites were provided password protected USBs for them to access all data with audit trails from the electronic data capture systems.

1) Study I8F-MCGPI1: Participants with OSA unwilling or unable to use PAP therapy

Sites: A total of 57 centers in Australia, Brazil, China, Czech Republic, Germany, Japan, Mexico, Taiwan, and United States.

Subjects: A total of 234 subjects were randomized (i.e., 114 subjects received tirzepatide, 120 subjects received placebo), and 187 subjects completed Treatment Period (i.e., 101 who received tirzepatide, 86 who received placebo).

Study initiation date: (b) (6) (first patient, first visit); (b) (6) (last patient, last visit)

Database lock date and study unblinding date: April 10, 2024 (database lock date and study unblinding date)

Note: Subjects who participated in Study I8F-MCGPI1 had subjects IDs beginning with "10".

2) I8F-MCGPI2: Participants with OSA on PAP therapy

Site: A total of 58 centers in Australia, Brazil, China, Czech Republic, Germany, Japan, Mexico, Taiwan, and United States.

Subjects: A total of 235 subjects were randomized (i.e., 120 subjects received tirzepatide, 115 subjects received placebo), and 202 subjects completed Treatment Period (i.e., 113 who received tirzepatide, 89 who received placebo).

Study initiation date: (b) (6) (first patient, first visit); (b) (6) (last patient, last visit)

Database lock date and study unblinding date: April 10, 2024 (database lock date and study unblinding date)

Note: Subjects who participated in Study I8F-MCGPI2 had subject ID's beginning with "20".

III. RESULTS (by site):

1. **Dr. Blair Brengle**
   Site # 39296
   Protocols I8F-MCGPI1 and I8F-MCGPI2
   8803 N Meridian Street
   Suite 350
   Indianapolis, IN, 46260-5386
   PDUFA Inspection Dates: August 26-29, 2024

For Protocol I8F-MCGPI1, 16 subjects were screened, 11 subjects were randomized, and 8 subjects completed the study. Two subjects withdrew consent because they believed they were receiving placebo and preferred not to remain in the study. One subject discontinued due to pregnancy.

For Protocol I8F-MCGPI2, 14 subjects were screened, 10 subjects were randomized, and 9 subjects completed the study. One subject withdrew consent.

An audit of the study records was conducted for all subjects who were screened for both studies. Records reviewed included, but were not limited to, protocol versions of Protocols I8F-MCGPI1, I8F-MCGPI2, and the Master Protocol I8F-MCGPIF, eligibility criteria, informed consent forms, subjects' charts, medical records, data listings, case report forms, sponsor and IRB communications, regulatory documents, FDA 1572, financial disclosures, monitoring, investigational product accountability, training records, adverse event reporting, and source documents for verification of the primary efficacy endpoint. Source records for subjects were in paper and electronic format.

For Studies I8F-MCGPI1 and I8F-MCGPI2, the number of AHI events at baseline and Visit 11 (Week 52) recorded in the subject data line listings were compared with the source documents. No discrepancies were noted.

For Study I8F-MCGPI1, there were three unreported adverse events for one subject. According to the adverse event log, Subject (b) (6) (randomized to placebo on (b) (6)) had mild intermittent dizziness from (b) (6), that completely resolved by (b) (6), and intermittent diarrhea from (b) (6), that completely resolved by (b) (6). Additionally, the clinical investigator documented in the progress notes on (b) (6), that this subject was experiencing worsening erectile dysfunction.

Reviewer's comment: The three unreported adverse events for a single subject who received placebo is unlikely to impact the safety profile of the drug.

For Study I8F-MCGPI2, there was one unreported adverse event. According to the adverse event log, Subject (b) (6) (randomized to tirzepatide on (b) (6) had intermittent constipation of moderate severity (well-controlled with Metamucil) that started on (b) (6), and completely resolved by (b) (6), before the last dose of study treatment was received on (b) (6).

Reviewer's comment: The unreported adverse event of constipation (well-controlled with Metamucil) for a single subject who received tirzepatide and resolving prior to the end of the study does not appear to be serious in nature. Constipation is already reported in the sponsor's label, so this adverse event is unlikely to impact the safety profile of the drug.

2. **Dr. John Hudson**
   Site # 27507
   Protocol I8F-MCGPI2
   1600 W 38th Street
   Ste. 404
   Austin, TX 78731
   PDUFA Inspection Dates: September 9-13, 2024

For Protocol I8F-MCGPI2, 17 subjects were screened, 9 subjects were randomized, and 8 subjects completed the study. One subject withdrew due to noncompliance.

An audit of the study records was conducted for all randomized subjects. Records reviewed included, but were not limited to, protocol versions of Protocol I8F-MCGPI2 and the Master Protocol I8F-MCGPIF, eligibility criteria, informed consent forms, subjects' charts, medical records, case report forms, data listings, sponsor and IRB communications, regulatory documents, FDA 1572, financial disclosures, monitoring, investigational product accountability, training records, use of concomitant medications, protocol deviations, adverse event reporting, and source documents for verification of the primary efficacy endpoint. Source records for subjects were in paper format.

For Study I8F-MCGPI2, the number of AHI events at baseline and Visit 11 (Week 52) recorded in the subject data line listings were compared with the source documents. No discrepancies were noted. There was no evidence of under-reporting of adverse events.

There were two unreported protocol deviations involving two subjects who received opioids, which were listed as prohibited concomitant medications in Section 6 of the Master Protocol. Subject (b) (6) randomized to tirzepatide on (b) (6), took morphine on (b) (6), for a kidney stone. Subject (b) (6), randomized to placebo on (b) (6), took hydrocodone from (b) (6), following a cochlear implant placement.

Reviewer's comment: The unreported protocol deviation of a single subject, randomized to tirzepatide, who took morphine for a one day, and the unreported protocol deviation of a single subject, randomized to placebo, who took hydrocodone for a week, are unlikely to impact the overall safety or efficacy results of Study I8F-MCGPI2. Both prohibited medications were reported by the Sponsor under the listing of concomitant medications. However, since they were not documented as protocol deviations, we present this information here for the review division's consideration.

3. **Dr. Raj Karunakara**
   Site #57558
   Protocol I8F-MCGPI1
   21 Ne 1st Avenue
   Ocala, FL 34470
   PDUFA Inspection Dates: September 23-25, 2024

For Protocol I8F-MCGPI1, 10 subjects were screened, 6 subjects were randomized, and 4 subjects completed the study. Subject (b) (6) (randomized to placebo) discontinued due to a moderate hypersensitivity reaction at the injection site, characterized by hives and vomiting. Subject (b) (6) (randomized to placebo) discontinued due to being dissatisfied with the lack of weight loss.

All subject records were audited to verify informed consent. An audit of the study records was conducted for all 6 randomized subjects. Records reviewed included, but were not limited to, protocol versions of I8F-MCGPI1 and the Master Protocol I8F-MCGPIF, eligibility criteria, informed consent forms, subjects' charts, medical records, case report forms, data listings, sponsor and IRB communications, regulatory documents, FDA 1572, financial disclosures, monitoring, investigational product accountability, use of concomitant medications, training records, protocol deviations, adverse event reporting, and source documents for verification of the primary efficacy endpoint. Source records for subjects were in paper format.

For Study I8F-MCGPI1, the number of AHI events at baseline and Visit 11 (Week 52) recorded in the subject data line listings were compared with the source documents. No discrepancies were noted. There was no evidence of under-reporting of adverse events.

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Suyoung Tina Chang, M.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Phillip Kronstein, M.D.
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.
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Office of Scientific Investigations

CC:

Central Doc. Rm.
Review Division /Division Director/
Review Division /Medical Team Leader/
Review Division /Project Manager/
Review Division/MO/
OSI/Office Director/
OSI/DCCE/ Division Director/
OSI/DCCE/Branch Chief/
OSI/DCCE/Team Leader/
OSI/DCCE/GCP Reviewer/
OSI/ GCP Program Analysts/
OSI/Database PM/

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JENN W SELLERS
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NDA:	217806-0241
Subject:	Immunogenicity Consult
Review Date:	10/09/2024
Primary Reviewer:	Svetlana Petrovskaya, Ph.D
Secondary Reviewer:	Mohanraj Manangeeswaran, Ph.D
Applicant:	Eli Lilly and Company
Dosage regimen:	once a week
Indication:	Treatment for moderate to severe obstructive sleep apnea (OSA) on adults with obesity
Route:	Subcutaneous injection
Requesting Office:	CDER/OPQ/OPRO/DRBPMII
Requestor:	

Purpose of the memo:

The sponsor would like to add a new indication to Zepbound as a treatment for moderate-to-severe obstructive sleep apnea (OSA) in adults with obesity. Sponsor has submitted an efficacy supplement for the new indication that included immunogenicity data. The consult request was to review the adequacy of ADA assays that were used for this supplement.

Recommendation:

Overall strategy and the ADA assays presented as part of this supplement was already reviewed by the Agency and found suitable. Data provided by the Sponsor using in-study samples show that the cut-point is appropriate for use in OSA patients. The assays presented in the supplement are appropriate.

Review:

The current application seeks approval of tirzepatide as an adjunct to a reduced-calorie diet and increased physical activity to treat moderate-to-severe obstructive sleep apnea (OSA) in adults with obesity.

Tirzepatide (TZP) is a long-acting glucose-dependent insulinotropic polypeptide (GIP) receptor and glucagon-like peptide-1 (GLP-1) receptor agonist that is chemically synthesized based on GIP sequence. TZP includes a C20 fatty diacid moiety that enables albumin binding and prolongs the half-life. Tirzepatide selectively binds to and activates both the GIP and GLP-1 receptors, the targets for native GIP (nGIP) and GLP-1 (nGLP-1). Tirzepatide stimulates insulin secretion by β cells in a glucose-dependent manner and reduces glucagon secretion.

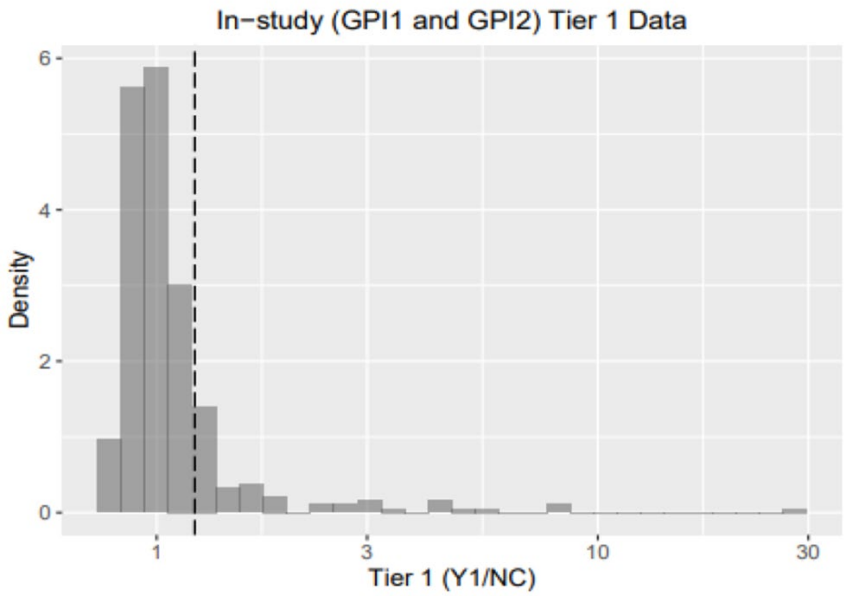
The sponsor has developed a multi-tiered immunogenicity testing strategy with a ligand-binding screening assay (Tiers 1 through 3), 4 cell-based neutralizing antibody (cNAb) assays, and 2 *in silico* assessments to detect and characterize ADA against tirzepatide.

The overall immunogenicity assay strategy was submitted in the T2DM tirzepatide licensing application in 2018 and approved by the FDA in 2022. The Sponsor used a tiered immunogenicity strategy as detailed below.

Tier	Acronym	Assay type
Tier 1 (screening)	T1	Ligand binding assay
Tier 2a (confirmation)	T2a	Ligand binding assay
Tier 2b (cross-reactive binding to nGIP)	T2b	Ligand binding assay-native GIP
Tier 2c (cross-reactive binding to nGLP-1)	T2c	Ligand binding assay-native GLP-1
Tier 3 (titer assessment)	T3	Dilution and ligand binding assay
Tier 4a (NAb against tirzepatide activity on GIPR)	T4a	Cell based neutralization activity-GIPR
Tier 4b (NAb against tirzepatide activity on GLP-1R)	T4b	Cell based neutralization activity-GLP-1R

The immunogenicity assay strategy and validation package for all the assays used for this NDA supplement was submitted under NDA217806 (for chronic weight management) and was determined to be suitable. Previously, the same assay strategy was also used for NDA 215866 (Tirzepatide for T2DM) and the licensing application was approved by FDA in 2022. Lilly has requested to incorporate the ADA assay information by cross-reference.

The Sponsor provided data on the qualitative assessment of the Tier 1 signal and the quantitative assessment of the tier 1 putative positive rate and the tier 1 false positive error rate using in-study (18F-MC-GPI1 & 18F-MC-GPI2) samples. Tier 1 data from in-study samples is plotted in the graph below.



Assessor comments:

The cut-point established previously and used for T2DM and CWM was 1.22. Data provided by the Sponsor demonstrate that obesity disease-state cut points are appropriate for use in OSA trials. Although the indications are different, clinical studies for both chronic weight management and obstructive sleep apnea were conducted on obese patients. Therefore, it is reasonable that the cut-point for CWM is suitable for the OSA study.

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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:	October 29, 2024
Requesting Office or Division:	Division of Pulmonology, Allergy, and Critical Care (DPACC)
Application Type and Number:	NDA 217806/S-013
Product Name, Dosage Form, and Strength:	Zepbound (tirzepatide) Injection, 2.5 mg/0.5 mL, 5 mg/0.5 mL, 7.5 mg/0.5 mL, 10 mg/0.5 mL, 12.5 mg/0.5 mL, 15 mg/0.5 mL
Product Type:	Combination Product (Drug-Device)
Rx or OTC:	Prescription (Rx)
Applicant Name:	Eli Lilly and Company (Lilly)
FDA Received Date:	June 21, 2024; September 25, 2024
TTT ID #:	2024-10683
DMEPA 1 Safety Evaluator:	Lissa C. Owens, PharmD
DMEPA 1 Team Leader:	Damon Birkemeier, PharmD, FISMP, NREMT
DMEPA 1 Human Factors Team Leader	Matthew Barlow, RN, BSN

1 INTRODUCTION

Eli Lilly and Company submitted an Efficacy Supplement for Zepbound (tirzepatide) Injection to propose a new indication to treat moderate to severe obstructive sleep apnea (OSA) in adults with obesity. Subsequently, the Division of Pulmonology, Allergy, and Critical Care (DPACC) requested that we review the proposed Zepbound Prescribing Information (PI) and Medication Guide (MG) for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

This section lists the materials considered for our review of NDA 217806/S-013.

Table 1. Materials Considered for this Label and Labeling Review

Materials Reviewed	Appendix Section
Relevant Product Information	A
Labeling	B
Previous DMEPA Reviews	C
Information Request (IR)	D

3 HUMAN FACTORS DISCUSSION

On September 19, 2024, we issued an information request (IR) requesting Lilly confirm that there have been no modifications to the user interface, intended users, uses, or use environments or use-related risk analysis (URRA). On September 25, 2024, Lilly responded to the IR confirming that there have been no modifications to the user interface, intended users, uses or use environments or URRA. Additionally, our clinical colleagues confirmed that the obstructive sleep apnea patient population is comparable to the patient populations for the currently approved indications of Zepbound. As such, we have no additional human factors (HF) data needs or recommendations at this time.

4 CONCLUSION

Our evaluation of the proposed Zepbound Prescribing Information (PI) and Medication Guide (MG) did not identify areas of vulnerability that may lead to medication errors. We have no recommendations at this time.

From an HF perspective, we have no additional human factors (HF) data needs or recommendations at this time.

APPENDICES: METHODS AND RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. RELEVANT PRODUCT INFORMATION

Table 2 presents relevant product information for Zepbound received on June 21, 2024 from Eli Lilly and Company.

Table 2. Relevant Product Information for Zepbound	
Initial Approval Date	November 8, 2023
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: o 30 kg/m² or greater (obesity) or o 27 kg/m²or greater (overweight) in the presence of at least one weight-related comorbid condition (e.g., hypertension, dyslipidemia, type 2 diabetes mellitus, obstructive sleep apnea or cardiovascular disease) • Treat moderate to severe obstructive sleep apnea (OSA) in adults with obesity (proposed)
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, 15 mg/0.5 mL
Route of Administration	subcutaneous
Dose and Frequency	• The recommended starting dosage is 2.5 mg injected subcutaneously once weekly. • After 4 weeks, increase to 5 mg injected subcutaneously once weekly. • Increase the dosage in 2.5 mg increments after at least 4 weeks on the current dose. • The recommended maintenance dosages are 5 mg, 10 mg, or 15 mg injected subcutaneously once weekly. • The maximum dosage is 15 mg subcutaneously once weekly.

<table>
<tr><th colspan="2">Table 2. Relevant Product Information for Zepbound</th></tr>
<tr><td>How Supplied</td><td>A clear, colorless to slightly yellow solution available in cartons containing 4 pre-filled single-dose pens or 1 single-dose vial as follows:
<table>
<tr><th>Total Strength per Total Volume</th><th>Pen NDC</th><th>Vial NDC</th></tr>
<tr><td>2.5 mg/0.5 mL</td><td>0002-2506-80</td><td>0002-0152-01</td></tr>
<tr><td>5 mg/0.5 mL</td><td>0002-2495-80</td><td>0002-0243-01</td></tr>
<tr><td>7.5 mg/0.5 mL</td><td>0002-2484-80</td><td>0002-1214-01</td></tr>
<tr><td>10 mg/0.5 mL</td><td>0002-2471-80</td><td>0002-1340-01</td></tr>
<tr><td>12.5 mg/0.5 mL</td><td>0002-2460-80</td><td>0002-1423-01</td></tr>
<tr><td>15 mg/0.5 mL</td><td>0002-2457-80</td><td>0002-2002-01</td></tr>
</table></td></tr>
<tr><td>Storage</td><td>Refrigerator at 2°C to 8°C (36°F to 46°F).
If needed, each single-dose pen or single-dose vial can be stored unrefrigerated at temperatures not to exceed 30°C (86°F) for up to 21 days. If ZEPBOUND is stored at room temperature, it should not be returned to the refrigerator.</td></tr>
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APPENDIX B. LABELS AND LABELING

B.1 List of Labels and Labeling Reviewed

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

- Prescribing Information received on June 21, 2024, available from \\CDSESUB1\EVSPROD\nda217806\0241\m1\us\annotated.pdf
- Medication Guide received on June 21, 2024, available from \\CDSESUB1\EVSPROD\nda217806\0241\m1\us\proposed-medguide.docx

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

APPENDIX C. PREVIOUS DMEPA REVIEWS

On October 7, 2024, we searched for previous DMEPA reviews relevant to this current review using the terms, Zepbound. Our search identified 1 previous review[b], since the date of our last search on December 27, 2023, and we considered our previous recommendations to see if they are applicable for this current review.

[b] Patel. V. Label and Labeling Review for Zepbound (NDA 217806/S-003). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2024 JAN 03. TTT ID No.: 2023-7331.

APPENDIX D. Information Request (IR)

Information Request response, received on September 25, 2024, available from \\CDSESUB1\EVSPROD\nda217806\0775\m5\53-clin-stud-rep\535-rep-effic-safety-stud\osa\5354-other-stud-rep\human-factors-engineering-report\rpt-924743-supplementary-information-osa.pdf.

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