EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

12 December 2024
EMA/14848/2025
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Mounjaro

International non-proprietary name: Tirzepatide

Procedure No. EMEA/H/C/005620/II/0027

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Table of contents

List of abbreviations

Abbreviation or Term	Definition/Explanation
ADA	Anti-drug antibodies
AE	adverse event
AESI	adverse event of special interest
AF	atrial fibrillation
AHI	apnoea-hypopnoea index
AKI	acute kidney injury
ALT	alanine aminotransferase
AR	adverse reaction
BMI	body mass index
BP	blood pressure
CAD	coronary artery disease
CEC	clinical endpoint committee
CSR	clinical study report
C-SSRS	Columbia-Suicide Severity Rating Scale
CV	cardiovascular
CVD	cardiovascular disease
DBP	diastolic blood pressure
EDS	excessive daytime sleepiness
eGFR	estimated glomerular filtration rate
EMA RP	European Medicines Agency Reflection Paper
EoI	extension of indication
ESS	Epworth Sleepiness Scale
FDA	Food and Drug Administration
FOSQ	Functional Outcomes of Sleep Questionnaire
GCP	Good clinical practice
GI	gastrointestinal
GIP	glucose-dependent insulinotropic polypeptide
GLP-1	glucagon-like peptide-1
HDL	high-density lipoprotein
HF	heart failure
HR	heart rate
HSAT	home sleep apnoea testing
hsCRP	high-sensitivity C-reactive protein
ICSD	International Classification of Sleep Disorders
ISA	Intervention-specific appendix
ISR	injection-site reaction
MA	marketing authorization
MACE	major adverse cardiovascular event
MAH	Marketing authorization holder
MASLD	Metabolic dysfunction-associated steatotic liver disease
MDD	Major depressive disorder
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed model repeated measures
MMO	morbidity and mortality in adults with obesity
MRD	Minimum required dilution
MTC	medullary thyroid carcinoma
MTD	maximum tolerated dose
MWPC	meaningful within-patient change
OSA	obstructive sleep apnoea
PAP	positive airway pressure
PGIC	Patient Global Impression of Change
PHQ-9	Patient Health Questionnaire-9

PR	Pulse rate
PRO	patient-reported outcome
PROMIS SD	patient-reported outcomes measurement information system short form sleep disturbance 8b
PROMIS SRI	patient-reported outcomes measurement information system short form sleep-related impairment 8a
PSG	polysomnography
QW	once weekly
RDI	respiratory disturbance index
REI	respiratory event index
SA	scientific advice
SAE	serious adverse event
SASHB	sleep apnoea-specific hypoxic burden
SBP	systolic blood pressure
SC	subcutaneous(ly)
SF-36v2	Short-Form-36 Health Survey, Version 2
SMQ	standardised MedDRA query
SmPC	Summary of Product Characteristics
SOC	system organ class
T2DM	type 2 diabetes mellitus
TE ADA	treatment-emergent antidrug antibody
TEAE	treatment-emergent adverse event
UACR	urine albumin-to-creatinine ratio
ULN	upper limit of normal

1. Background information on the procedure

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Eli Lilly Nederland B.V. submitted to the European Medicines Agency on 1 July 2024 an application for a variation.

The following changes were proposed:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include, as an adjunct to diet and exercise, the treatment of moderate to severe obstructive sleep apnoea (OSA) in adults with obesity for MOUNJARO based on final results from studies I8F-MC-GPI1 and I8F-MC-GPI2. These are multicentre, randomized, parallel-arm, double-blind, placebo-controlled studies investigating the effects of tirzepatide compared with placebo in adult participants with moderate-to-severe OSA and obesity. As a consequence, sections 4.1, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 3.1 of the RMP has also been submitted.

The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included (an) EMA Decision(s) P/0478/2023 adopted on 1 December 2023 for tirzepatide (EMEA-002360-PIP02-22-M02) the agreement of a paediatric investigation plan (PIP). In particular, PDCO agreed with the applicant's position, that the proposed indication "treatment of obstructive sleep apnoea (OSA) in paediatric patients with obesity", falls under the scope of the above mentioned Decision, as the indication is considered to be covered by the condition "treatment of obesity" listed in the Agency Decision.

At the time of submission of the application, the PIP was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The applicant applied for Scientific Advice from CHMP for tirzepatide in relation to the non-clinical and clinical development plan to support registration of tirzepatide for the treatment of type 2 diabetes mellitus (T2DM) in adults. Scientific Advice (Ref EMA/CHMP/SAWP/689326/2018) was received from the CHMP on 18-October-2018. Some aspects of the non-clinical development plan apply also to the OSA

indication. A copy of the Scientific Advice was already provided in the initial MAA application for T2DM.

2. Recommendations

Based on the review of the submitted data, this application regarding the following change:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Update of sections 4.1, 4.8 and 5.1 of the SmPC based on final results from studies I8F-MC-GPI1 and I8F-MC-GPI2. These are multicentre, randomized, parallel-arm, double-blind, placebo-controlled studies investigating the effects of tirzepatide compared with placebo in adult participants with moderate-to-severe OSA and obesity. The Package Leaflet is updated accordingly.

☒is recommended for approval.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I and IIIB are recommended.

3. EPAR changes

The table in Module 8b of the EPAR will be updated as follows:

Scope

Please refer to the Recommendations section above

Summary

Please refer to Scientific Discussion 'Mounjaro-H-C-005620-II-0027'

4. Scientific discussion

4.1. Introduction

Tirzepatide is a long-acting GIP and GLP-1 receptor agonist. Both receptors are present on the pancreatic α and β endocrine cells, heart, vasculature, immune cells (leukocytes), gut and kidney. GIP receptors are also present on adipocytes. In addition, both GIP and GLP-1 receptors are expressed in the areas of the brain important to appetite regulation.

It improves glycaemic control by lowering fasting and postprandial glucose concentrations in patients with type 2 diabetes (T2DM) through several mechanisms. Furthermore, it interferes with appetite regulation and energy metabolism. Body weight and body fat mass are lowered. The mechanisms associated with body weight and body fat mass reduction involve decreased food intake through the regulation of appetite. Clinical studies show that tirzepatide reduces energy intake and appetite by increasing feelings of satiety and fullness, and decreasing feelings of hunger.

On a pharmacodynamics level, tirzepatide increases pancreatic β-cell glucose sensitivity. It enhances first- and second-phase insulin secretion in a glucose dependent manner and improves insulin sensitivity.

As a consequence of tirzepatide administration, gastric emptying is delayed which may slow post meal glucose absorption and can lead to a beneficial effect on postprandial glycaemia.

Based on a number of large randomised, controlled, phase 3 studies, a MA was granted for tirzepatide, Mounjaro for the treatment of T2DM (SURPASS 1-5 studies) and weight management (Surmount-1 study).

The present extension-of-indication (EoI) Variation procedure is intended to support the use of tirzepatide, as an adjunct to diet and exercise, in the treatment of moderate to severe obstructive sleep apnoea (OSA) in adults with obesity (BMI $\geq$ 30 kg/m^2).

4.1.1. Problem statement

Disease or condition

OSA is characterized by recurrent episodes of upper airway collapse during sleep leading to complete or partial cessation of airflow, i.e., apnoea or hypopnoea. If left untreated, the fragmented sleep and intermittent hypoxia in addition to the increased sympathetic nervous activity can lead to wide ranging consequences and impairment of the quality of life in these patients. Disturbances in gas exchange during sleep result in oxygen desaturation, and sleep fragmentation, which contribute to the consequences of OSA, e.g. cardiovascular, metabolic, and neurocognitive effects. Individuals with OSA have an associated increased risk of CV and metabolic comorbidities such as hypertension, T2DM, AF, HF, coronary heart disease, stroke, and death (Xie et al. 2017; Somers et al. 2008; Punjabi 2008; Dempsey et al. 2010; Javaheri et al. 2017).

Excessive daytime sleepiness (EDS) is a leading symptom in many OSA patients where they feel drowsy and sluggish most days, and these symptoms often interfere with work, school, activities, or relationships. However, as shown by large cohort studies (Ulander et al. 2022) and the European Sleep Apnoea Database (Hedner et al. 2011), not all OSA patients complain about EDS. In up to half of affected subjects, daytime sleepiness remains in the upper normal range.

State the claimed the therapeutic indication

The MAH initially requested an extension of indication to include the treatment of moderate to severe obstructive sleep apnoea (OSA) in adults with obesity as an adjunct to diet and exercise.

Following the assessment of all data provided, the CHMP concluded that a separate indication is not acceptable. The CHMP does, however, support the addition of relevant data of the OSA trials in SmPC section 5.1, and a reference to these data in SmPC section 4.1 (see section 'Scientific discussion' below).

The final weight management indication, as accepted by CHMP, is as follows (new text in bold):

Weight management

Mounjaro is indicated as an adjunct to a reduced-calorie diet and increased physical activity for weight management, including weight loss and weight maintenance, in adults with an initial Body Mass Index (BMI) of

- ≥ 30 kg/m^2 (obesity) or
- ≥ 27 kg/m^2 to < 30 kg/m^2 (overweight) in the presence of at least one weight-related comorbid condition (e.g., hypertension, dyslipidaemia, obstructive sleep apnoea, cardiovascular disease, prediabetes, or type 2 diabetes mellitus).

For trial results with respect to obstructive sleep apnoea (OSA), see section 5.1.

Epidemiology and risk factors

Figures on OSA prevalence vary greatly, partly as a function of evolution of diagnostic criteria and an increase in associated risk factors, like e.g. obesity.

The prevalence of OSA varies also depending on the definition of hypopnoeas. The oxyhaemoglobin desaturation threshold (e.g., 3% or 4%) used for defining hypopnoeas can lead to varying estimates of disease severity (Punjabi 2008). Using the conservative definition, requiring a 4% decline in blood oxygen saturation to define hypopnoea, the Wisconsin Sleep Cohort Study estimated that 17.4% of women and 33.9%of men in the US aged 30 to 70 years had at least mild OSA, defined as an AHI of 5 to 14.9 events per hour of sleep, while 5.6% of women and 13.0% of men had moderate (AHI of 15-29.9) or severe (AHI ≥ 30) OSA. The prevalence of OSA increased by approximately 30% between 1990 and 2010, with absolute increases of 4.2% in women and 7.5% in men.

In the US, the prevalence of OSA is approximately 26.6% in men and 8.7% in women among individuals aged 30 to 49 years and approximately 43.2% in men and 27.8% in women among individuals aged 50 to 70 years. The prevalence of OSA increases with age and is approximately twice as common in men as in women (Gottlieb & Punjabi 2020).

The prevalence of OSA is closely connected with obesity and obesity-related metabolic disorders. Some 60% to 90% of adults with OSA are overweight, and the relative risk of OSA in obesity (BMI > 29 kg/m^2) is ≥ 10 (Pillar and Shehadeh 2008). As compared with the general population (17%), the prevalence of OSA is higher among individuals with obesity (40% to 70%) and with T2DM (58% to 86%) (Pugliese et al. 2020).

Clinical presentation, diagnosis

An essential tool in the diagnosis and severity grading of OSA conventionally is the apnoea-hypopnoea index (AHI), which reflects the number of apnoeas and hypopnoeas as events per hour of

electroencephalography (EEG) -measured sleep during a full night polysomnography (PSG). Both PSG and home sleep apnoea testing (HSAT) can be used to support the diagnosis of OSA, per current clinical guidelines (Kapur et al. 2017). While PSG remains the gold standard for diagnosis of OSA, HSAT has decreased costs and greater accessibility.

According to ICSD-3 criteria [2014], the diagnosis requires either signs/symptoms (e.g., associated sleepiness, fatigue, insomnia, snoring, subjective nocturnal respiratory disturbance, or observed apnoea) or associated medical or psychiatric disorder (i.e., hypertension, coronary artery disease, atrial fibrillation, congestive heart failure, stroke, diabetes, cognitive dysfunction, or mood disorder) coupled with five or more predominantly obstructive respiratory events (obstructive and mixed apnoeas, hypopnoeas, or respiratory effort-related arousals, as defined by the AASM scoring manual) per hour of sleep during PSG.

Alternatively, a frequency of obstructive respiratory events $\geq$ 15/h satisfies the criteria, even in the absence of associated symptoms or disorders (Sateia 2014).

Based on ICSD-3, a diagnosis of OSA is confirmed when

- AHI/RDI/REI is >15, or
- AHI/RDI/REI is ≥5, with 1 or more of the following:
    - sleepiness, nonrestorative sleep, fatigue, or insomnia symptoms
    - waking up with breath holding, gasping, or choking
    - habitual snoring or breathing interruptions, and
    - hypertension, mood disorder, cognitive dysfunction, CAD, stroke, congestive HF, AF, or T2DM.

Three different OSA severity categories are defined by AHI:

- mild (AHI ≥5 and AHI <15 events/h)
- moderate (AHI ≥15 and AHI <30 events/h), and
- severe (AHI ≥30 events/h).

Management

The most effective therapy to reduce obstructive sleep apnoea is positive airway pressure (PAP) applied with a tight seal to the nose or mouth (or both) serving to stent open the upper airway. Continuous positive airway pressure (CPAP) provides a constant level of positive pressure across inspiration and expiration. Although PAP is highly effective in reducing the AHI (to <5 events per hour in most patients) when assessed in the sleep laboratory, it requires tremendous effort on the patient's part to position the mask properly and maintain the machine and supplies. When adherence is defined as use for more than 4 hours per night for more than 70% of nights, PAP adherence rates of 75% have been reported. A far smaller percentage of patients use PAP during all sleep (Veasey & Rosen 2019).

Patients with mild OSA who decline or are unable to use PAP therapy may be candidates for an oral appliance to advance the mandible, positional therapy (avoiding a supine sleep position), or surgical correction of a collapsible pharynx (Veasey & Rosen 2019).

To date, no pharmacotherapies are approved for the treatment of OSA. No available therapeutic approaches have addressed the underlying pathophysiology of the disease. Stimulant medications (modafinil, solriamfetol, and pitolisant) have been used to treat EDS as the most burdensome and dangerous symptom of OSA. Following a merely symptom-oriented approach, solriamfetol (Sunosi) and pitolisant (Wakix, Ozawade) are approved in the EU to improve EDS in patients with either OSA or

narcolepsy with or without cataplexy. The use of modafinil has been restricted to narcolepsy patients with EDS following a Referral procedure in 2010.

4.1.2. About the product

Tirzepatide (Mounjaro) is approved as an adjunct to diet and exercise to improve glycaemic control in adults with T2DM 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.

Mounjaro is presented as solution for subcutaneous (sc) injection in the abdomen, thigh or upper arm. The regular dosing interval is once a week (QW). During the dose titration process, dose increments of 2.5 mg are recommended after a minimum of 4 weeks on the current dose. Six tirzepatide dose strengths (2.5, 5, 7.5, 10, 12.5, and 15 mg) are available. The starting dose of tirzepatide is 2.5 mg QW. After 4 weeks, the dose should be increased to 5 mg QW. The dose should be selected with consideration of treatment response and tolerability. Regardless of the indication (either approved T2DM / weight management, or proposed OSA), the maximum dose of tirzepatide is 15 mg QW.

4.1.3. The development programme/compliance with CHMP guidance/scientific advice

The design of the tirzepatide OSA registration program was informed by available clinical guidance documents (ICH 2017) as well as advice from the FDA.

Having received approval for the T2DM and weight management indication, the MAH did not seek further scientific advice (SA) from the EMA in preparation of the OSA registration program. Instead, regulatory advice was provided from the FDA between November 2021 and December 2023. During the advice, the MAH sought alignment with the FDA on revision of the endpoint strategy.

4.1.4. General comments on compliance with GCP

See Section 4.3.1

4.2. Non-clinical aspects

A comprehensive package of non-clinical pharmacology, PK, and toxicology studies was conducted to support the T2DM application. Additional non-clinical pharmacology studies were conducted to support the weight management application. The MAH has not conducted any new non-clinical studies specifically to support the OSA indication.

4.2.1. Ecotoxicity/environmental risk assessment (ERA)

The ERA provided is considered complete and acceptable. No ERA studies are required with respect to the chemical nature of the molecule. Tirzepatide is administered in parenteral form and has been described to be not excreted in unchanged form. It consists of 39 amino acids, two of them non-coded (aminoisobutyric acid, Aib in positions 2 and 13). The backbone of the peptide contains 2 methylated amid bonds, which are protected from cleavage by standard metabolic peptidases. However, the remaining amid-bonds are susceptible to peptidase activity. Therefore, the peptide part is not expected to pose a risk to the environment. Also, the 1,20-eicosanedioic acid moiety are identical to naturally

occurring substances. The fate of the linker (γ-Glu and two 8-amino-3,6-dioxaoctanoic acid moieties) is not known.

Tirzepatide is not expected to pose a risk to the environment.

4.2.2. Discussion on non-clinical aspects

N/A

4.2.3. Conclusion on the non-clinical aspects

The active substance is a protein covalently linked with a C20 fatty diacid moiety, excretion of the intact molecule from humans does not occur. Therefore, tirzepatide is not expected to pose a risk to the environment. There are no open issues left in the ERA. The ERA provided is considered complete and acceptable. No ERA studies are required with respect to the chemical nature of the molecule.

4.3. Clinical aspects

4.3.1. Introduction

Tirzepatide is a GIP receptor and 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. It selectively binds to and activates both the GIP and GLP-1 receptors, the targets for native GIP and GLP-1.

Having received approval via the centralised procedure for the treatment of T2DM and weight management, the present EoI variation was initially intended to support the additional use of tirzepatide, as an adjunct to diet and exercise, for the treatment of moderate to severe OSA in adults with obesity.

GCP

The MAH has provided a statement to the effect that:

All completed studies supporting this application were conducted under the supervision of an institutional review board, with adequate informed consent procedures, and in accordance with

i. consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki and the Council for International Organizations of Medical Sciences International Ethical Guidelines
ii. the International Council for Harmonisation GCP guideline [E6], and
iii. applicable laws and regulations.

Clinical studies conducted outside of the EU meet the ethical requirements of Directive 2001/20/EC.

Table 1 Tabular overview of clinical studies

Study Identifier, Report Type	Primary Objective	Study Design and Type of Control	Test Drug, Dosage Regimen, and Route of Administration	Number of Healthy Participants	Healthy Participants or Diagnosis of Patients	Duration of Treatment
5.3.5.1: Study Reports and Related Information of Controlled Clinical Studies Pertinent to the Claimed Indication						
I8F-MC-GPI1 Full CSR Synopsis: Appendix 1	To demonstrate that tirzepatide at the MTD QW is superior to placebo for mean decrease in AHI	Phase 3, multicenter, randomized, parallel-arm, double-blind, placebo-controlled study in participants who are unable or unwilling to use PAP therapy	**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 maintenance dose tolerated by the participant (10 mg or 15 mg) **Placebo; SC QW**	**Overall** Randomized: 234 Treated: 234 Completed: 187 **Tirzepatide MTD** Randomized: 114 Treated: 114 Completed: 101 **Placebo** Randomized: 120 Treated: 120 Completed: 86	Adult male or female participants, with obesity, diagnosed moderate-to-severe OSA with an AHI ≥15, who are unable or unwilling to use PAP therapy	52 weeks
I8F-MC-GPI2 Full CSR Synopsis: Appendix 2	To demonstrate that tirzepatide at the MTD QW is superior to placebo for mean decrease in AHI	Phase 3, multicenter, randomized, parallel-arm, double-blind, placebo-controlled study in participants who are on PAP therapy for at least 3 months at time of screening and plan to continue PAP therapy during the study	**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 maintenance dose tolerated by the participant (10 mg or 15 mg) **Placebo; SC QW**	**Overall** Randomized: 235 Treated: 233 Completed: 202 **Tirzepatide MTD** Randomized: 120 Treated: 119 Completed: 113 **Placebo** Randomized: 115 Treated: 114 Completed: 89	Adult male or female participants, with obesity, diagnosed moderate-to-severe OSA with an AHI ≥15, and on PAP therapy	52 weeks
I8F-MC-GPI1 *MRI Addendum* Included within the GPI1 full CSR	To compare the effect of tirzepatide QW at MTD vs placebo on the changes of soft tissues volumes, fat volumes, and fat content (%) in the upper airway structures and abdomen in participants with OSA and obesity	Phase 3, multicenter, randomized, parallel-arm, double-blind, placebo-controlled study in participants who are unable or unwilling to use PAP therapy	**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 maintenance dose tolerated by the participant (10 or 15 mg) **Placebo; SC QW**	**Overall** Randomized: 78 **Tirzepatide MTD** Randomized: 38 **Placebo** Randomized: 40	Participants enrolled in Study GPI1 at selected sites that have the technical capability of conducting specified MRI scans were included	52 weeks

Abbreviations: AHI = apnea-hypopnea index; CSR = clinical study report; GPI1 = I8F-MC-GPI1; MRI = magnetic resonance imaging; MTD = maximum tolerated dose; OSA = obstructive sleep apnea; PAP = positive airway pressure; QW = once weekly; SC = subcutaneous; vs = versus.

4.3.2. Pharmacokinetics

Since the previous submissions, no additional Phase 1 studies have been completed. A Population Pharmacokinetic/Pharmacodynamic Report is provided to support the OSA application.

Key findings from the clinical pharmacology program are as follows:

Table 2 Highlights of Tirzepatide Clinical Pharmacology

Dose range tested	Healthy participants • Single doses in the range of 0.25 to 8 mg studied • A 5-mg dose administered as single dose identified as MTD • Higher doses (up to 10 mg) attained through escalation Participants with T2DM and with obesity or overweight • Doses up to maximum of 15 mg attained via escalation. That is, tirzepatide dosing was initiated at 2.5 mg QW for 4 weeks, followed by stepwise dose escalation in 2.5-mg increments every 4 weeks, to attain tirzepatide doses of up to 15 mg as maintenance dose.
Exposures achieved at maximum tested dose	Single dose: 8 mg in healthy participants • Mean (%CV) C_{max}: 874 ng/mL (19%) • Mean (%CV) AUC: 169,000 ng·hour/mL (8%) Multiple dose: 15 mg QW in participants with T2DM • Mean (%CV) C_{max}: 1990 ng/mL (22%) • Mean (%CV) AUC: 250,000 ng·hour/mL (22%) Multiple dose: 15 mg QW in participants with obesity or overweight • Mean (%CV) C_{max}: 2120 ng/mL (20%) • Mean (%CV) AUC: 266,000 ng·hour/mL (20%)
Accumulation index	Accumulation index at steady state • Mean (%CV) = 1.70 (11%) in participants with T2DM • Mean (%CV) = 1.75 (14%) in participants with obesity or overweight
Dose proportionality	• Over the single dose range of 0.25 to 8 mg in healthy participants, ratios of dose-normalized geometric means and associated 90% CI for C_{max} and $AUC_{(0-\infty)}$ were 0.851 (0.68, 1.06) and 0.826 (0.706, 0.966), respectively, suggesting that increases in exposure were in an approximately dose-proportional manner.

	• Exposure to tirzepatide also appeared to increase proportionally across the dose range of 0.25 to 15 mg. The average C_{max} of tirzepatide at steady state after multiple 5-, 10-, and 15-mg tirzepatide doses in participants with obesity or overweight was 710, 1410, and 2120 ng/mL, respectively (19.5% to 21.2% CV). The average exposure AUC within a dosing interval at steady state for participants with obesity or overweight was 88,900, 177,000, and 266,000 ng·hour/mL, respectively (20.2% to 22.0% CV).
Absorption	Median (range) tirzepatide t_{max}: 24 hours (8 to 72 hours)
Distribution	Mean (%CV) V_d/F in • participants with T2DM = 10.3 L, and • participants with obesity or overweight = 9.7 L. Tirzepatide was highly bound in human plasma with a mean percentage bound of 99.1%.
Metabolism	Tirzepatide was the largest component in plasma accounting for approximately 80% of the circulating radioactivity. The 4 minor metabolites in plasma resulting from proteolytic cleavage of the peptide backbone each accounted for less than 5.7% of total circulating radioactivity. Tirzepatide was eliminated through metabolism. The primary metabolic pathways that contributed to the clearance of tirzepatide were proteolytic cleavages of the peptide backbone, β-oxidation of the C20 fatty diacid moiety, and amide hydrolysis.
Elimination	• Mean (%CV) $t_{1/2}$ = 5.4 days (18%) in participants with T2DM • Mean (%CV) $t_{1/2}$ = 5.7 days (21%) in participants with obesity or overweight • Mean (%CV) CL/F = 0.061 L/hour (23%) in participants with T2DM • Mean (%CV) CL/F = 0.056 L/hour (21%) in participants with obesity or overweight Renal excretion was the primary route of elimination for tirzepatide. From the human ^{14}C study, approximately 70% of the administered dose was recovered, approximately 50% of the administered radioactivity was excreted in the urine, and approximately 21% was excreted in feces. Tirzepatide was eliminated through metabolism with no intact tirzepatide observed in urine or feces.
Intrinsic factors	• No clinically meaningful effect of age, sex, race, renal impairment, or hepatic impairment was detected in the population PK analysis. • Body weight was the only statistically significant covariate on CL/F, and V_d/F, with overall exposure decreasing with an increase in body weight (based on baseline body weight of 90 kg for T2DM and 105 kg for participants with obesity or overweight). However, the extent of impact was within the known variability of tirzepatide PK and thereby is not a covariate requiring dose adjustment. • There were no clinically relevant effects on the PK of a single subcutaneous 5-mg tirzepatide dose in participants with mild, moderate, or severe renal impairment or ESRD compared to participants with normal renal function. Therefore, no adjustment to the dose of tirzepatide is recommended in participants with renal impairment or in participants undergoing dialysis. • There were no clinically relevant effects of varying degrees of hepatic impairment, based on Child-Pugh score, on PK of a single subcutaneous 5-mg tirzepatide dose. Therefore, adjustment to the dose of tirzepatide, based on PK, is not recommended in participants with hepatic impairment. • Tirzepatide exposure ($AUC_{[0-\infty]}$ and C_{max}) following administration of a 5-mg subcutaneous dose to the upper arm or thigh injection site was similar to exposures noted following administration to the abdomen as injection site.

Extrinsic factors	**Effect of other drugs on tirzepatide** • Tirzepatide is a synthetic amino acid sequence expected to be proteolytically degraded into component amino acids. Currently, there are no known factors that may cause a clinically meaningful increase in exposure of tirzepatide. **Effects of tirzepatide on concomitant drugs** Acetaminophen (gastric-emptying marker) with tirzepatide (within Study GPGA) • In healthy participants and in participants with T2DM, acetaminophen C_{max} decreased approximately 50% after first 5-mg dose of tirzepatide and t_{max} was delayed by about an hour, thereby suggesting delay in gastric emptying. • In healthy participants and in participants with T2DM, acetaminophen AUC was not altered by tirzepatide to a clinically meaningful extent. • Impact on acetaminophen PK was greatest after the first dose of tirzepatide and showed tachyphylaxis with repeated QW dosing. Acetaminophen (gastric-emptying marker) with tirzepatide (within Study GPHU) • In participants with obesity or overweight with or without T2DM, acetaminophen PK was impacted in a similar manner as presented in Study GPGA. • The effect showed faster tachyphylaxis in participants with obesity and without T2DM compared to participants with both obesity and T2DM. Combination OC (ethinyl estradiol + norgestimate) • Overall exposure to OC as measured through AUC was reduced by 16% to 23% when the OC was administered in the presence of 5 mg tirzepatide compared with dosing with OC alone. • Peak exposure to the OC as measured through C_{max} was reduced by 55% to 66% when the OC was administered in the presence of 5 mg tirzepatide compared with dosing with OC alone. • Delays in t_{max} of 2.5 to 4.5 hours were observed when the OC was administered in the presence of 5 mg tirzepatide. • Overall, while peak OC exposure was lower in the presence of tirzepatide, the overall exposure to OC in the presence of the maximum effect of gastric-emptying delay caused by 5-mg dose of tirzepatide was not considered to be clinically significant. • Given that the impact on OC PK under the conditions leading to greatest gastric emptying delay with 5 mg tirzepatide is approximately 20% on overall exposure, it is not expected that the OC PK would be significantly impacted by the intended clinical dosing scheme of tirzepatide starting at a dose of 2.5 mg followed by gradual stepwise dose escalation, knowing that gastric-emptying effect shows tachyphylaxis with time.

Abbreviations: AUC = area under the drug plasma concentration versus time curve; $AUC_{(0-\infty)}$ = AUC from time zero to infinity; CI = confidence interval; CL/F = apparent clearance; C_{max} = maximum observed drug plasma concentration; CV = coefficient of variation; ESRD = end-stage renal disease; GPGA = I8F-MC-GPGA; GPHU = I8F-MC-GPHU; MTD = maximum tolerated dose; OC = oral contraceptive; PK = pharmacokinetic(s); QW = once weekly; $t_{1/2}$ = terminal elimination half-life; T2DM = type 2 diabetes mellitus; t_{max} = time to maximum observed drug plasma concentration; V_d/F = apparent volume of distribution.

Population PK analysis

A population pharmacokinetic analysis was conducted to evaluate the data from Phase 3 study GPIF. In this study, sparse PK sample collection was performed, with 6 planned samples per participant. Predose PK and immunogenicity samples were collected at Weeks 0, 4, 12, 24, and 52. PK and immunogenicity samples were also collected at the posttreatment follow-up visit.

The model structure and parameter estimates from the previously developed T2DM model (5802 participants) were used to inform the base model for the population PK analysis of data from SURMOUNT-1 for weight management (1880 patients). The final model of this analysis was then used to evaluate the PK data from participants who have obesity and moderate-to-severe OSA in Study GPIF (1013 observations from 229 patients) after weekly s.c. dosing of tirzepatide.

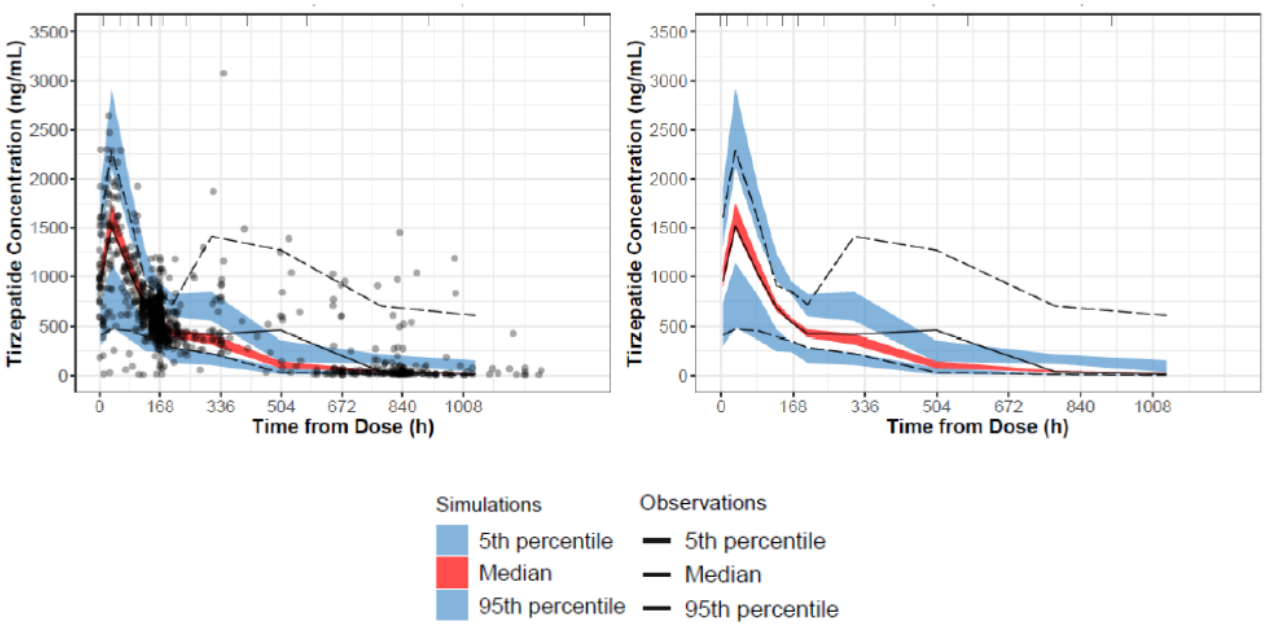
The participants with obesity and OSA in Study GPIF had comparable baseline demographics within the range of the populations evaluated in the previous population PK analyses for treatment of T2DM or weight management.

The key elements of the previously established tirzepatide PK model are listed as follows:

- The PK model has 2 compartments with first-order absorption and IIV on ka, CL, Vc, and proportional residual error.
- The mean absolute bioavailability of tirzepatide following a single-dose SC administration of a 5-mg dose was approximately 80% based on intravenous bolus data from biopharmaceutical Study GPGE.
- No significant change in bioavailability was associated with tirzepatide dose amount and tirzepatide exposure increases proportionally over the dose range of 2.5 to 15 mg.
- Body weight as a time varying factor was included on CL and Vd parameters.

Parameters were fixed to values estimated from SURMOUNT-1. Body weight related allometric exponents were included as fixed values on CL, Q, Vc, and Vp parameters (exponent 0.8 for clearance parameters and 1 for volume parameters) in the tirzepatide population PK base and final models.

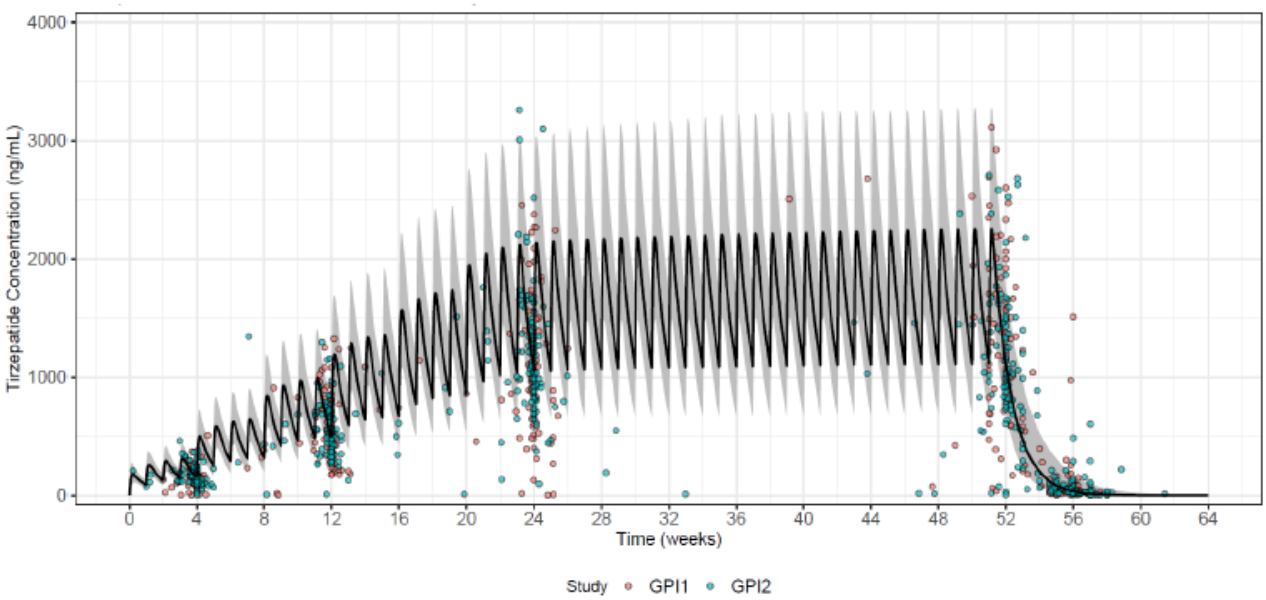
The evaluation of the previously developed model from SURMOUNT-1 on the GPIF dataset is based on a prediction-corrected visual predictive check (pcVPC, see figure below) and residual plots.



Abbreviations: h = hour; 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.

Figure ATT.4.5. Study GPIF: Tirzepatide population PK final model pcVPC with x-axis up to 6 weeks (1008 h).

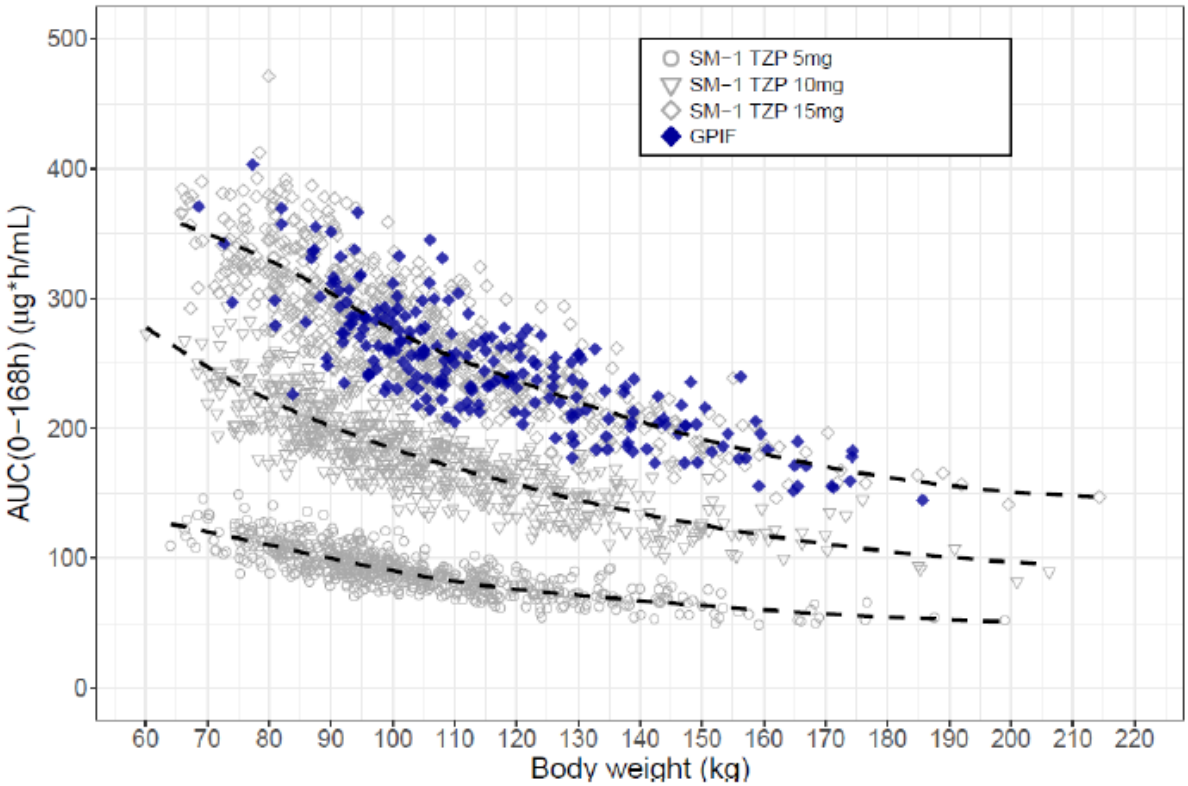
Concentrations of patients with and without CPAP device are compared in figure 10.1 (see below). Observed tirzepatide concentrations in populations without or with CPAP device use were consistent with the final population PK model predictions.



Abbreviations: CPAP = continuous positive airway pressure; GPI1 = Study I8F-MC-GPIF participants without CPAP device use; GPI2 = Study I8F-MC-GPIF participants with CPAP device use; LLOQ = lower limits of quantitation; PK = pharmacokinetic(s); QW = once weekly.

Note: Circles represent observed tirzepatide concentrations. Dose escalation started with 2.5 mg and dose amount was increased by a 2.5-mg increment every 4 weeks. Tirzepatide doses were administered QW during the study treatment period up to 52 weeks. Tirzepatide LLOQ is 2 ng/mL. The majority of participants were on tirzepatide 15 mg QW at Week 52. Simulation was performed with the population PK model. The solid line represents the median of the simulation, and the shaded area is the 90% prediction interval.

Figure 10.1. **Comparison of observed tirzepatide concentrations from participants without CPAP device use and with CPAP device use and population PK model-predicted tirzepatide concentrations.**



Abbreviation: AUC(0-168h) = area under the concentration versus time curve from time 0 to 168 hour after dose at steady state; GPIF = Study 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.

Figure 10.2. Relationship between tirzepatide exposure and body weight for tirzepatide.

The VPC indicates an adequate performance up to 168 h (1 week), but exposure seems underpredicted at later time points up to 6 weeks (figure ATT.4.5 above). Together with the diagnostic plots provided, there is an indication that there may be room for improvement of the model. Outliers are also seen in Figure 10.1. It is unclear, why it was not attempted to re-estimate the model parameters to potentially further improve the model performance.

Nevertheless, it is considered that improving model performance would not change the conclusion that there was no need for dose adjustments in specific subgroups. Therefore, this issue is not further pursued.

4.3.3. Pharmacodynamics

See tabulated highlights of tirzepatide clinical pharmacology above.

4.3.4. PK/PD modelling

PK/PD analyses were conducted related to different PD parameters related to efficacy and safety. The primary efficacy measure was AHI and was evaluated by polysomnography at screening and at Visits 7 and 11 (approximately Weeks 20 and 52). Body weight was measured during the study period at Weeks 0, 4, 8, 12, 16, 20, 24, 36, 48, and 52 and at the post-treatment follow-up visit. Adverse events of

special interest, such as nausea, vomiting, and diarrhoea were reported by participants and entered by study personnel into the electronic case report form at each study visit. PK, immunogenicity, and body weight data were additionally collected at early discontinuation visits.

Body Weight

The effect of tirzepatide on fat and fat-free mass is quantified using turn-over models. The previously developed model from the SURMOUNT-1 study was used, but variability parameters were re-estimated, but resulted in very similar estimates compared to the SURMOUNT-1 model. The model is considered adequate.

Apnoea-Hypopnoea Index

The apnoea-hypopnoea index (AHI) was modelled using post hoc PK parameters from the population PK model and individual post hoc PD parameters from the population body weight model. The relationship between a body weight reduction leading to an improvement in AHI seems credible and the presented model diagnostics indicate an adequate model performance.

Nausea, Vomiting, and Diarrhoea

The models from the SURMOUNT-1 study were used to simulate nausea, vomiting, and diarrhoea prevalence to compare to the observed nausea, vomiting, and diarrhoea prevalence in Study GPIF. The model seems to adequately predict nausea, while vomiting and diarrhoea are underpredicted by the model in the group with obesity and OSA without CPAP (continuous positive airway pressure) devices. It is unclear why the model was not re-estimated to better reflect the observed data.

The simulation on the tirzepatide effect on body weight and body composition can be followed. For, the simulations on the tirzepatide effect on AHI, 5, 10, and 15 mg are simulated. While for mild OSA, a dose of 5-10 may be sufficient, a higher dose of 15 mg appears to be required to reduce a severe into a mild OSA. Hence, the dose rationale suggesting an up titration to 15 mg is supported.

4.3.5. Discussion on clinical pharmacology

PK and PK/PD data have been evaluated with the previously developed models based on data from T2DM and weight management indications. Overall, this appears acceptable, but it would in general be preferred to re-estimate the parameters including patient data from the GPIF study. But since it is considered that this would not have changed the overall conclusion, this issue is not further pursued. Thus, popPK and PKPD analyses support the proposed dosing regimen.

4.3.6. Conclusions on clinical pharmacology

Overall, the popPK analysis and the PK/PD analyses support the dosing regimen for up-titration to 15 mg, if tolerable.

4.4. Clinical efficacy

4.4.1. Dose response study

No dose response study was conducted for the use of tizepatide in OSA. For dose and dose-escalation selection, see Subheading *Treatment* below.

4.4.2. Main studies

SURMOUNT-OSA

I8F-MC-GPIF (GPIF; SURMOUNT-OSA) is a master protocol that supported 2 studies. Each independent pivotal study was a multi-centre, randomized, parallel-arm, double-blind, placebo-controlled, Phase 3 study with a 52-week treatment duration and investigated the effects of treatment with QW tirzepatide at the MTD (10 mg or 15 mg) compared with placebo in participants who have moderate to severe OSA and obesity.

Table 3 Master Protocol I8F-MC-GPIF Amendment Summary

DOCUMENT HISTORY	
Document	**Date**
Amendment b	*30-Sep-2022*
Amendment a	*10-Feb-2022*
Original Protocol	*27-Jan-2022*

Protocol amendments were implemented in response to regulatory recommendation from the FDA. The primary endpoint was updated from "Percent change in AHI from baseline to Week 52" to "Change in AHI from baseline to Week 52 (events per hour)". The first Key Secondary Endpoint was updated from "Change in AHI" to "Percent change in AHI".

- **Study I8F-MC-GPI1 (GPI1; Study 1)** included participants who were unable or unwilling to use PAP therapy.
- **Study I8F-MC-GPI2 (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.

Participants were assigned to the study that reflected their current PAP usage. Each participant was then randomly assigned 1:1 to treatment or placebo.

Study I8F-MC-GPI1 (GPI1; Study 1)

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

Study 1: Participants with OSA Unable or Unwilling to use PAP Therapy (EudraCT Nr: 2021-004551-16)

Study Sponsor:	Eli Lilly and Company
Study Initiation Date:	21 June 2022 (first participant first visit)
Study Completion:	28 March 2024 (last participant last visit)

Number of Study Centers, Participants, and Countries	This study was conducted at 57 centers that randomly assigned 234 participants in Australia, Brazil, China, Czech Republic, Germany, Japan, Mexico, Taiwan, and United States.

The analyses presented in the CSR are based on database lock dates of 10 April 2024 for the primary outcome and 24 April 2024 for pharmacokinetics and immunogenicity data.

Study I8F-MC-GPI2 (GPI2; Study 2)

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

Study 2: Participants with OSA on PAP Therapy, i.e. participants who were on PAP therapy for at least 3 months at the time of Visit 1 and planned to continue PAP therapy during the study. (EudraCT Nr: 2021-004552-41)

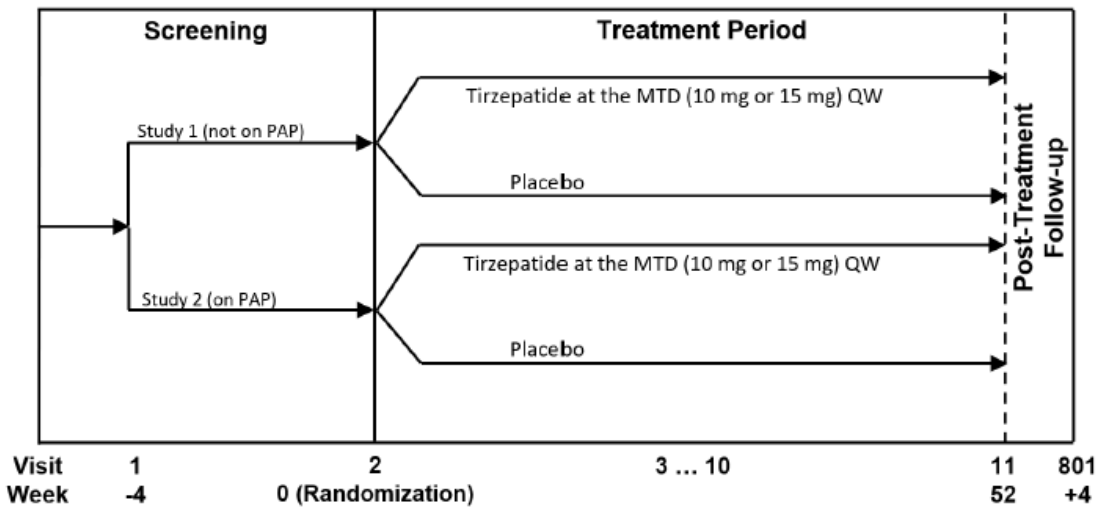
Name of Sponsor/Company	Eli Lilly and Company
Study Period	First participant visit: 23 June 2022 Last participant visit: 29 March 2024
Number of Study Centers, Participants, and Countries	This study was conducted at 58 centers that randomly assigned 235 participants in Australia, Brazil, China, Czech Republic, Germany, Japan, Mexico, Taiwan, and United States

The analyses presented in the CSR are based on database lock dates of 10 April 2024 for the primary outcome and 24 April 2024 for pharmacokinetics and immunogenicity data.

Methods

The tirzepatide treatment duration in Study 1 and Study 2 was 52 weeks. The standard dose-escalation period was 20 weeks. Both study 1 and 2 followed the same design illustrated below.

Figure 1 Illustration of master protocol design for Master Protocol I8F-MC-GPIF



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

Recommendations on lifestyle

All Study 1 and Study 2 participants in both tirzepatide and placebo groups consulted with study personnel experienced in diet and exercise counselling to receive lifestyle program instructions. The diet and exercise goals and the importance of adherence to the lifestyle program were reinforced at each trial contact (every 4 weeks). Dietary and lifestyle counselling consisted of advice on healthy food choices

with a focus on calorie restriction using a hypocaloric diet (500 kcal per day below individualized energy requirements) with appropriate macronutrient composition and increased physical activity (moderate intensity for at least 150 minutes per week).

Study participants

To be eligible for the study, participants

- were 18 years or older
- were previously diagnosed with moderate-to-severe OSA with an AHI of at least 15 events/h or prior to Visit 1
- had an AHI of at least 15 events/hour or on polysomnography as part of the trial at Visit 1
- had obesity, defined as having a BMI of at least 30 kg/m^2
- had a history of at least 1 self-reported unsuccessful dietary effort to lose body weight,

Participants were not eligible for the study if they had

- type 1 diabetes mellitus or type 2 diabetes mellitus, history of ketoacidosis, or hyperosmolar state/coma
- HbA1c level of at least 6.5% at Visit 1
- any previous or planned surgery for sleep apnoea or major ear, nose, or throat surgery
- active device treatment of OSA other than PAP therapy
- reported a change in body weight greater than 5 kg within 3 months prior to Visit 1
- a prior or planned surgical treatment for obesity
- history of chronic or acute pancreatitis
- have obesity induced by other endocrinologic disorders or diagnosed monogenetic or syndromic forms of obesity
- at significant risk for suicide
- uncontrolled hypertension (SBP of at least 160 mmHg and/or DBP of at least 100 mmHg) at Visit 1
- acute or chronic hepatitis, signs and symptoms of any other liver disease other than non-alcoholic fatty liver disease
- a family or personal history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2, or
- require the use of supplemental oxygen.

Other key eligibility criteria

Only Study 1: Enrolment was restricted to participants who were unable or unwilling to use PAP therapy during the study. In addition, the participants should not have used PAP for at least 4 weeks prior to Visit 1. However, PAP therapy could be initiated when urgent compensation for sleep-disordered breathing was needed based on the opinion of the investigator.

Only Study 2: Enrolment was restricted to participants who were on PAP therapy for at least 3 consecutive months prior to Visit 1 and planned to continue PAP therapy during the study.

Prohibited Concomitant Medications

The following medications are prohibited during the study:

- DPP-4 inhibitors
- Open-label GLP-1R agonists
- Stimulants (e.g. modafinil, solriamfetol, pitolisant, amphetamine, dextroamphetamine, dexmethylphenidate, methylphenidate, and lisdexamfetamine)

- medications that may cause significant weight gain (such as, but not limited to, paroxetine, tricyclic antidepressants, atypical antipsychotic and mood stabilizers).
- Medications that may cause weight loss (such as, but not limited to, liraglutide, semaglutide, orlistat, sibutramine, phenylpropanolamine, naltrexone/bupropion, phentermine/topiramate combination, zonisamide, and topiramate)
- hypnotics, mirtazapine, opioids, trazodone, pramlintide, sibutramine, orlistat, and zonisamide
- Systemic glucocorticoid therapy, per discussion with sponsor
- Use of any over-the-counter or prescription medications that could affect the evaluation of excessive sleepiness, per investigator discretion (such as, but not limited to, CBD oil, THC, etc.)
- Any glucose-lowering medication, including metformin

Treatments

Dose and dose-escalation selection

The dose-escalation scheme used in Study 1 and Study 2 was 2.5 mg QW, with subsequent dose escalations every 4 weeks until the participants achieved the MTD of 10 mg or 15 mg QW.

Tirzepatide doses of 10 mg or 15 mg as MTD were selected based on the following criteria:

- each dose provided substantial body weight reduction relative to placebo (in previous trials)
- the percentage of participants achieving ≥10% body weight reduction was higher with 15 mg than 10 mg, and
- safety and tolerability were supported by Phase 3 results in T2DM and weight management studies.

The maximum dose of 15 mg is consistent with the maximum approved dose of tirzepatide used for weight management and T2DM.

Table 4 Tirzepatide Dose-Escalation Scheme in Study 1 and Study 2

	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.

Based on expected weight reduction and potential corresponding AHI reduction, the tirzepatide treatment duration in Study 1 and Study 2 of 52 weeks was chosen for all planned efficacy and safety assessments.

Outcomes/endpoints

Studies 1 and 2 have the same primary and key secondary objectives and endpoints and are listed below.

Table 5 Primary and Key Secondary Objectives and Endpoints Studies 1 and 2

Objectives	Endpoints
Primary	
To demonstrate that tirzepatide at the MTD (10 mg or 15 mg) QW is superior to placebo for decrease in AHI	Change in AHI from baseline to Week 52
Key secondary (controlled for type 1 error)	
To demonstrate that tirzepatide at the MTD (10 mg or 15 mg) QW is superior to placebo for	From baseline to Week 52
• Change in patient-reported sleep-related impairment and sleep disturbance	• Change in[a] o PROMIS SRI o PROMIS SD
• Percent change in AHI • Clinically meaningful change in AHI	• Percent change in AHI • Percent of participants with ≥50% AHI reduction
• Achieving OSA remission or mild non-symptomatic OSA	• Percent of participants with o AHI <5 events/h or o AHI 5-14 events/h with ESS ≤10
• Hypoxic burden • Change in body weight • Change in inflammatory status	• Change in SASHB (% min/hour) • Percent change in body weight • Change in hsCRP concentration
• Change in SBP	From baseline to Week 48[b] • Change in SBP
Other secondary	
To demonstrate that tirzepatide at the MTD (10 mg or 15 mg) QW is superior to placebo for	From baseline to Week 52
• Change in excessive daytime sleepiness	• Change in ESS score
• Change in patient-reported functional status as assessed by FOSQ	• Change in FOSQ-10 score • Change in FOSQ (30 items) score • Change in all FOSQ domain scores, specifically o general productivity o activity level o vigilance o social outcomes o intimate and sexual relationships
• Change in body weight	• Percent of participants who achieve o ≥10% body weight reduction o ≥15% body weight reduction o ≥20% body weight reduction
• Change in lipid parameters	• Change in o HDL-cholesterol o non-HDL-cholesterol o triglycerides

Objectives	Endpoints
• A hierarchical assessment of PRO change • Change in supportive secondary PROs • Insulin • Change in DBP	• A hierarchical combination of the following: o Change in PROMIS SRI o Change in PROMIS SD • Change in o SF-36v2 acute form domain and summary scores • Percent of participants with improved categorical shift in o PGIS-OSA Sleepiness o PGIS-OSA Fatigue o PGIS-OSA Snoring • Proportion of participants achieving clinically meaningful within-patent change in o PROMIS SRI o PROMIS SD • Change in fasting insulin From baseline to Week 48[b] • Change in DBP
Exploratory	
To demonstrate that tirzepatide at the MTD (10 mg or 15 mg) QW is superior to placebo for • Change in exploratory PROs	From baseline to Week 52 • Change in o EQ-5D-5L utility index o EQ-VAS scores • Percent of participants with improved categorical shift in o PGIC-OSA Sleepiness o PGIC-OSA Fatigue o PGIC-OSA Sleep quality o PGIC-OSA Snoring

Abbreviations: AHI = Apnea-Hypopnea Index; BP = blood pressure; DBP = diastolic blood pressure; EQ-5D-5L = EQ-5D-5 Level; EQ-VAS = EQ-Visual Analog Scale; ESS = Epworth Sleepiness Scale; FOSQ = Functional Outcomes of Sleep Questionnaire; HDL = high-density lipoprotein; hsCRP = high-sensitivity C-reactive protein; MTD = maximum tolerated dose; OSA = obstructive sleep apnea; PAP = positive airway pressure; PGIC-OSA = Patient Global Impression of Change – Obstructive Sleep Apnea; PGIS-OSA = Patient Global Impression of Status – Obstructive Sleep Apnea; PRO = patient-reported outcome; PROMIS = Patient-Reported Outcomes Measurement Information System; QW = once weekly; SASHB = sleep apnea-specific hypoxic burden; SBP = systolic blood pressure; SD = sleep disturbance; SF-36v2 = Short-Form 36 Version 2; SRI = sleep-related impairment.

[a] PROMIS-related endpoints are tested in the graphical testing scheme only as an integrated analysis subject to submission-wise type 1 error rate control (Vandemeulebroecke et al. 2024).

[b] BP was assessed at Week 48 because PAP withdrawal at Week 52 may confound BP assessment.

PAP withdrawal 7 days before primary endpoint measurement in study 2

Participants in Study 1 did not use PAP while in the study, and participants in Study 2 had withdrawn PAP for 7 days before PSG testing. PAP withdrawal for 7 days minimizes the PAP therapy influence on sleep-disordered breathing (Schwarz et al. 2018), and therefore, the results from both Study 1 and Study 2 are declared to show tirzepatide effects on sleep-disordered breathing.

Efficacy endpoints measured at week 52

All endpoints were assessed as a change from baseline to Week 52, except SBP and DBP, which were assessed at Week 48 to eliminate the confounding effect of PAP withdrawal in Study 2.

AHI Primary efficacy assessment

The primary efficacy assessment in this study is AHI. The AHI counts the number of apnoeas or hypopnoeas recorded during the study as events per hour of sleep (Gottlieb and Punjabi 2020). AHI measurements will be collected via polysomnography (PSG).

Polysomnography assessments (including AHI, blood oxygen saturation parameters, PR, sleep parameters) will be performed during 1-night, overnight clinic stays, per the SoA. Data from the PSGs will be read and scored centrally using the AASM 1B hypopnoea scoring method (when there is ≥4% oxygen desaturation from pre-event baseline; see Section 10.10, Appendix 10 for definitions).

For AHI event measurement the following definitions were applied.

Apnoea = decrease in airflow ≥90% from baseline for ≥10 seconds

Hypopnoea = an abnormal respiratory event lasting ≥10 seconds with ≥30% reduction in thoraco-abdominal movement or airflow as compared to baseline, and with ≥ 4% oxygen desaturation.

AHI is the standard clinical metric of OSA severity. However, the metric has limitations in predicting the adverse outcomes of sleep apnoea because it measures only frequency of events and may not adequately capture the disease burden. For further details, please refer to *Point and Counterpoint: Is the Apnoea-Hypopnoea Index the Best Way to Quantify the Severity of Sleep-disordered Breathing? Yes (Rapoport DM) / No (Punjabi NM), Chest Jan 2016).*

Since AHI only captures the rate of apnoea / hypopnoea events, the AHI incorporates severity of the individual events only to the extent that event severity correlates with frequency. There are other potentially independent axes of event severity (e.g., the depth and duration of desaturation, the extent and duration of arousal, the level of sympathetic activation) that could affect severity of the overall clinical syndrome.

In order to also capture the duration and degree of oxygen desaturation during periods of disturbed breathing the secondary endpoint of Hypoxic Burden was introduced.

Hypoxic Burden (HB)

The sleep apnoea specific hypoxic burden (SASHB) is a recent method of clinical measurement in OSA. It is determined by measuring the respiratory event–associated area under the curve for oxygen desaturation from pre-event baseline and represents the cumulative burden of intermittent hypoxia caused by OSA-related sleep-disordered breathing.

The change in SASHB (%min/hour) from baseline to Week 52 was obtained from PSG measurements.

There is literature pointing to higher predictability of cardiovascular mortality in OSA patients if based on HB as compared to AHI (Martinez-Garcia, et al. 2022; Azarbarzin et al. 2019).

Achievement of OSA remission or mild non-symptomatic OSA

OSA severity is typically quantified using the AHI. Based on expert consensus, an AHI less than 5 events per hour is considered normal, 5 to 14.9 is considered mild, 15 to 29.9 is considered moderate, and at least 30 is considered severe OSA (Gottlieb & Punjabi 2020). See also Section 4.1.1 Clinical presentation / Diagnosis.

However, it was argued that the AHI is useful at its extreme values (<5 corresponding to normal as opposed to > 30 events/h), but less so in the mid-range. The AHI was considered a poor assessment for the continuum of severity if the severity of the other sequelae are meant that are part of the syndrome (Rapoport & Punjabi 2016).

The secondary endpoint of achievement of OSA remission (i.e. AHI < 5) or mild OSA (AHI 5-14 events/h) with ESS ≤ 10 is intended to illustrate the clinical significance of AHI reduction. It provides percentages of patients with categorical improvement. For the mild OSA category, patients have also to present with daytime sleepiness in the higher normal range (i.e. not excessive daytime sleepiness), based on subjective Epworth Sleepiness Scale (ESS ≤ 10).

Patient reported outcomes

The US FDA and Eli Lilly and Company (Lilly) have had ongoing regulatory interactions and correspondence regarding the patient-reported outcome (PRO) evaluations used in the clinical development program for tirzepatide for obstructive sleep apnoea (OSA) and obesity.

As part of the research program, the Patient-Reported Outcomes Measurement Information System® (PROMIS) Short-form Sleep Disturbance 8b (PROMIS SD); and the PROMIS Short Form Sleep-Related Impairment 8a (PROMIS SRI) were included as key secondary (multiplicity controlled) endpoints.

PROMIS Short Form v1.0 Sleep-related Impairment 8a

The PROMIS Short Form v1.0 Sleep-related Impairment 8a assesses self-reported perceptions of alertness, sleepiness, and tiredness during usual waking hours, and the perceived functional impairments associated with sleep problems or impaired alertness. The PROMIS Short Form v1.0 Sleep-related Impairment 8a consists of 8 items each rated on a 5-point scale ranging from "not at all" to "very much." Items have a recall period of "in the past 7 days." Individual item scores are totalled to obtain a raw score, with higher scores indicating more sleep-related impairment. Raw scores can be converted to a T-score, which is standardized with a mean of 50 and a SD of 10. (Northwestern, 2016a)

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

9 May 2016

PROMIS Short Form v1.0 Sleep Disturbance 8b

The PROMIS Short Form v1.0 Sleep Disturbance 8b assesses 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 perceptions of the adequacy of and satisfaction with sleep. The PROMIS SD consists of 8 items each rated on a 5-point Likert scale. The measure contains three different Likert scales:

- Not at all, A little bit, Somewhat, Quite a bit, Very much (for 4 items)
- Never, Rarely, Sometimes, Often, Always (for 3 items)
- Very poor, Poor, Fair, Good, Very good (for 1 item)

Items have a recall period of "in the past 7 days." The outcome is presented as a T-score that standardizes the raw score to a distribution with a mean of 50 and standard deviation of 10.

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

The PROMIS SRI and PROMIS SD are participant, self-administered questionnaires that were completed on a provisioned electronic device at screening (-4 weeks from randomization) and at Weeks 4, 12, 20, and 52 or ED. When completion of the PROMIS SRI or PROMIS SD was scheduled for visits where PSG was completed, the PRO measures were completed on the same day as the PSG, in the following order: FOSQ, ESS, PROMIS SD, PROMIS SRI, PGIS, PGIC, SF-36v2 (acute form) and EQ-5D-5L.

Epworth sleepiness scale (ESS)

The ESS will be included to assess improvements in excessive daytime sleepiness from baseline to Week 52. The ESS is an 8-item participant-completed measure that asks the participant to rate on a scale of 0 (would never doze) to 3 (high chance of dozing), their usual chances of dozing in 8 different daytime situations, with a recall period of "in recent times." 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).

Functional Outcomes of Sleep Questionnaire (FOSQ)

The FOSQ was included to assess change in FOSQ domains and total score from baseline to Week 52. The FOSQ is a 30-item sleep-specific, participant-completed questionnaire used to assess the effect of disorders associated with excessive daytime sleepiness (EDS) on daily functioning in adults. It assesses the following 5 domains of

- General productivity (8 items)
- Activity level (9 items)

- Vigilance (7 items)
- Social outcomes (2 items)
- Intimate and sexual relationships (4 items)

The FOSQ items assess participant's current status with each item rated on a scale of 1 (extreme difficulty) to 4 (no difficulty), with an additional not applicable (0 = "I don't do this activity for other reasons") also available. Individual domain scores are calculated by taking the mean of answered, non-zero items within each domain and a total score can be calculated by first computing the mean score for each domain, then multiplying the mean of the domain scores by 5 (Weaver et al. 1997). The total score for the FOSQ 10-item short form (FOSQ-10) can also be calculated.

Patient Global Impression of Status – Obstructive Sleep Apnoea (PGIS-OSA)

Three patient global impression of status scales will be included to assess categorical shift in participant self-rated assessment of their OSA symptom severity from baseline to Week 52.

PGIS-OSA Fatigue
This is a single-item, participant self-rated assessment of their overall level of fatigue due to OSA, "over the past 7 days." The item is rated on a 4-point scale ranging from "No fatigue" to "Severe fatigue."

PGIS-OSA Sleepiness
This is a single-item, participant self-rated assessment of their overall level of sleepiness due to OSA during waking hours, "over the past 7 days." The item is rated on a 4-point scale ranging from "Not at all sleepy" to "Very sleepy."

PGIS-OSA Snoring
The PGIS-OSA Snoring scale consists of two items. The first item is a participant self-rated assessment of their overall perception of the severity of their snoring due to OSA, "over the past 7 days," with respect to how much their snoring has affected their sleep. The item is rated on a 4-point scale ranging from "Not at all affected" to "Very affected." For the second item, participants will be asked on a 3-point scale ("Not at all" to "All the time") if they have ever been told by someone else that they snore in their sleep.

Patient Global Impression of Change – Obstructive Sleep Apnoea (PGIC-OSA)

Four patient global impression of change scales were included to assess categorical shift in participant self-rated assessment of change in their OSA symptom severity from baseline to Week 52.

PGIC-OSA Fatigue
This is a single-item, participant self-rated assessment of the change in their overall level of fatigue due to OSA, "since you started taking the study medication." The item is rated on a 5-point scale ranging from "Much worse" to "Much better."

PGIC-OSA Sleepiness
This is a single-item, participant self-rated assessment of the change in their overall level of sleepiness due to OSA during waking hours, "since you started taking the study medication." The item is rated on a 5-point scale ranging from "Much more sleepy" to "Much less sleepy."

PGIC-OSA Sleep Quality
This is a single-item, participant self-rated assessment of the change in their overall sleep quality due to OSA, "since you started taking the study medication." The item is rated on a 5-point scale ranging from "Much worse" to "Much better."

PGIC-OSA Snoring

This is a single-item, participant self-rated assessment of the overall change in how their snoring has affected their sleep, "since you started taking the study medication." The item is rated on a 5-point scale ranging from "My sleep is much more affected" to "My sleep is much less affected."

OSA-Related CV Risk Factors

Obesity, chronic low-grade inflammation, hypertension, dyslipidemia, and insulin resistance are important CV risk factors associated with OSA, and therefore, it was assessed how the participants were affected by the treatment intervention. Assessed CV risk factors included

- SBP and DBP
- hsCRP
- HDL-C, non-HDL-C, triglycerides, and
- fasting insulin.

Statistical methods

Estimands

The primary and key secondary efficacy analyses were guided by 2 estimands: "treatment-regimen" and "efficacy" estimands.

The **"efficacy" estimand** provided an on-treatment assessment of efficacy without confounding the treatment effect from the data collected after treatment discontinuation. It represented on-treatment efficacy.

The **"treatment-regimen"** estimand estimated the treatment effect, including the effect of the study drug discontinuation to reflect clinical practice. It represented the efficacy irrespective of adherence to the study drug.

Treatment regimen estimand

The clinical question of interest for the treatment-regimen estimand is the treatment difference between tirzepatide and placebo after 52 weeks of intervention in treated participants with obesity and OSA, regardless of intervention discontinuation for any reason.

Treatment estimand attributes

- Population: Adult participants with obesity and OSA who received at least 1 dose of study drug.
- Treatment condition: On- or off-randomized-treatment.
- Endpoints: The primary and key secondary endpoints were studied. Further details on the endpoints are in the Objectives and Endpoints table (Table 5).
- Population-level summary: The difference in mean change from baseline to Week 52 was used for continuous endpoints, and the difference in proportion (absolute or relative, as appropriate) was used for dichotomous endpoints. The population-level summary was conducted using the FAS described in Table 6.
- Handling of intercurrent events: No intercurrent events since treatment adherence and the initiation of PAP therapy are part of the treatment condition. Methods to handle missing data are described in detail in Table 7.

Rationale: The treatment-regimen estimand estimates treatment effect, including the effect of intervention discontinuation to reflect clinical practice. It is used for submission and registration purpose with regulatory agencies.

Efficacy estimand

The clinical question of interest for the efficacy estimand is the treatment difference between tirzepatide and placebo after 52 weeks of intervention in treated participants with obesity and OSA, prior to study intervention discontinuation for any reason and prior to initiation of PAP therapy.

Efficacy estimand attributes

- Population: Adult participants with obesity and OSA who received at least 1 dose of study drug.
- Treatment condition: On randomized treatment.
- Endpoints: The primary and key secondary endpoints were studied. Further details on the endpoints can be found in the Objectives and Endpoints table (Table 5).
- Population-level summary: The difference in mean change from baseline to Week 52 was used for continuous endpoints; the difference in proportion (absolute or relative, as appropriate) was used for dichotomous endpoints. The population-level summary was conducted using the EAS described in Table 6.
- Handling of intercurrent events: The intercurrent events of treatment discontinuation, and use of PAP therapy for participants in Study 1, is addressed by the hypothetical strategy. The potential outcome of interest is the response in the efficacy measurement if participants would remain on their randomly assigned treatment for 52 weeks and would not initiate PAP therapy during the study.

Rationale: The efficacy estimand provides an on-treatment assessment without confounding the treatment effect from off-treatment data.

Analysis Population and Datasets

Table 6 Description of Analysis Populations and Datapoint Sets in Studies 1 and 2

Analysis Population	**Description**
Entered	All participants who signed informed consent
Randomized	All participants who were randomly assigned a study drug (double-blind)
mITT	All randomly assigned participants who were exposed to at least 1 dose of the study drug
Analysis Set	**Description**
FAS	Data obtained during treatment period of the set of participants from the mITT population regardless of adherence to the study drug. For AHI-related endpoints and PROs associated with PSG visits (ESS, FOSQ, PROMIS SRI, PROMIS SD, PGIS, PGIC, SF-36v2 acute form, and EQ-5D-5L), data obtained outside the anticipated window through to the end of the study were included as part of the treatment period.
EAS	Data obtained during treatment period of the set of participants from the mITT population, excluding data after discontinuation of the study drug (last dose +7 days), and for Study 1, excluding data after initiating PAP therapy. For AHI-related endpoints and PROs associated with PSG visits (ESS, FOSQ, PROMIS SRI, PROMIS SD, PGIS, PGIC, SF-36v2 acute form, and EQ-5D-5L), data obtained outside the anticipated window through the end of the study were included as part of the treatment period.

Abbreviations: AHI = Apnea-Hypopnea Index; EAS = efficacy analysis set; ESS = Epworth Sleepiness Scale; EQ-5D-5L = EuroQol-5 Dimension-5 Level; FAS = full analysis set; FOSQ = Functional Outcomes of Sleep Questionnaire; mITT = modified intent to treat; PAP = positive airway pressure; PGIC = Patient Global Impression of Change; PGIS = Patient Global Impression of Status; PROMIS = Patient-Reported Outcomes Measurement Information System; PRO = patient-reported outcome; PSG = polysomnography; SD = Sleep Disturbance; SF-36v2 = Short Form 36 version 2; SRI = Sleep-Related Impairment; Study 1 = I8F-MC-GPI1; Study 2 = I8F-MC-GPI2.

Statistical Analysis Methods

Treatment-regimen estimand analysis

The primary and key secondary analyses guided by the "treatment-regimen" estimand were conducted using the FAS as defined above. After imputation, the primary efficacy comparison was based on the contrast between tirzepatide and placebo from the ANCOVA analysis of mean change from baseline values to Week 52 in AHI. The ANCOVA model included treatment and strata (geographic region [US/OUS] and gender) as fixed effects and baseline AHI as a fixed covariate. Analyses of continuous secondary endpoints 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.

Analysis of percentage of participants achieving target thresholds used a logistic regression including the following terms as a covariate: treatment, geographic region (US/OUS), baseline AHI, and gender. For the pooled analysis of data from the two studies, all endpoints were analyzed from the analysis of covariance model with treatment, ISA [ISA1/ISA2], geographic region [US/OUS], Apnoea-Hypopnoea Index (AHI) stratum (not severe [AHI <30]/severe [AHI ≥30]), and gender as fixed effects, with baseline as a covariate, using the pooled full analysis set (FAS) in each ISA.

Efficacy estimand analysis

The primary and key secondary analyses guided by the "efficacy" estimand were conducted using efficacy analysis set (EAS) as defined above. The analysis was based on the contrast between tirzepatide and placebo from the MMRM analysis of mean change from baseline values to Week 52 in AHI, adjusted for baseline value, stratification factors, visit, and treatment-by-visit interaction, unless specified otherwise.

Handling of Dropouts or Missing Data

For the primary and key secondary efficacy endpoint analyses aligned to the **"treatment-regimen" estimand** and subject to type I error rate control, the missing data were imputed based on the reason for the missing values, as described in the Table below.

For analyses aligned to the **"efficacy" estimand**, the missing data were considered missing at random, and hence no explicit imputation was performed for continuous endpoints. For categorical endpoints, the corresponding continuous variable associated with the missing categorical data were considered missing at random, and multiple imputation assuming the data to be missing at random was performed.

For the purposes of this document, "randomized in error", "inadvertent enrolment", and "assigned treatment by mistake" are equivalent.

Table 7 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 discontinuation due to the COVID-19 pandemic (after other reasons for missing data were 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, or missing data after study discontinuation due to inadvertent enrollment	Hypothetical	MAR	Multiple imputation using MAR
Missing data due to any other reason (e.g., study discontinuation due to any reason other than COVID-19 or inadvertent enrollment)	Treatment policy	MNAR	Retrieved dropout imputation[a]. If there were not enough retrieved dropouts to provide a reliable imputation model, placebo-based multiple imputation was used.

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

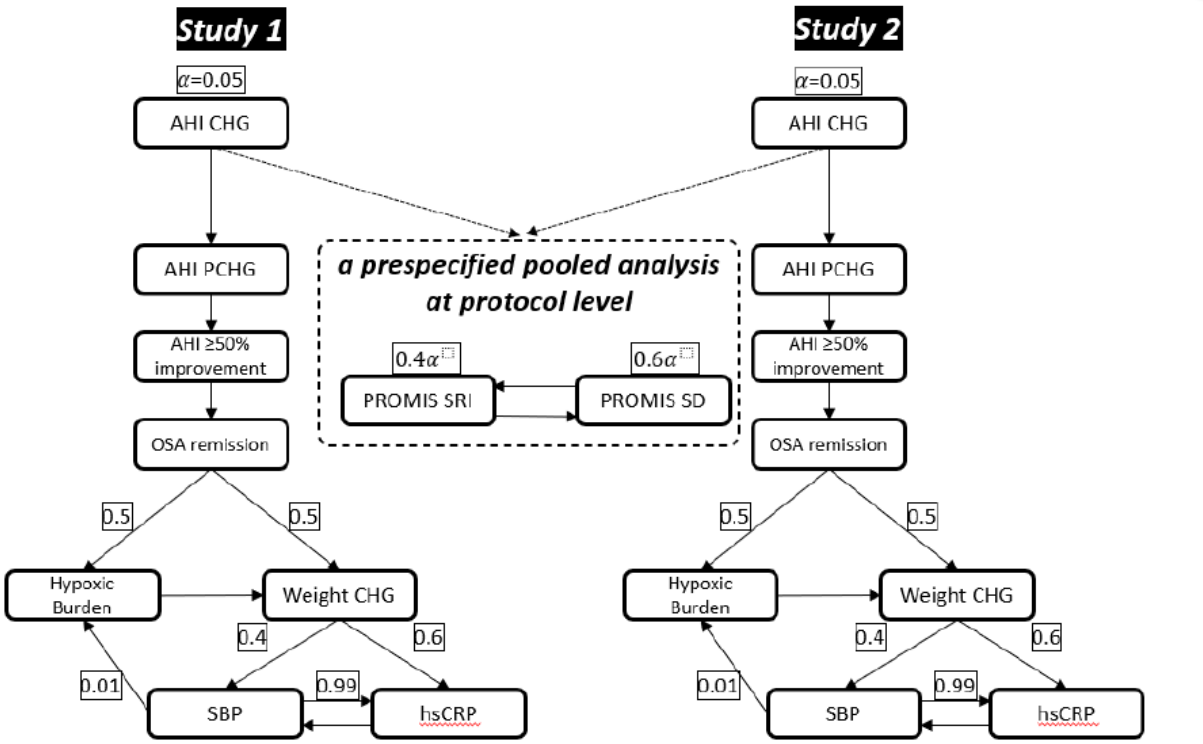
[a] Retrieved dropout imputation utilized observed data from participants in the same treatment group who had outcome measures at Week 52 (or Week 48 for SBP) after early discontinuation of the study drug to impute the missing value.

Graphical Testing Scheme

The Figure below presents the graphical testing procedure for both Studies 1 and 2. A pre-specified hypothesis testing plan was developed that employs Bretz's graphical approach (Bretz et al. 2009, 2011) to provide strong type I error rate control of the family-wise error rate control at 2-sided 0.05 significance

level, either within each study or within the submission by means of submission-wise error rate control. This approach was a closed testing procedure; hence, it strongly controlled the family-wise error rate across all hypotheses (Alosh et al. 2014). The graphical approach is conducted separately for each of the estimands, which are intended for different purposes; thus, no multiplicity adjustments are made for conducting separate analyses on the same objective.

Figure 2 Graphical testing scheme for Studies 1 and 2.



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.

Experience with PRO endpoints in prior OSA clinical trials varies (Winslow et al. 2012; Blackman et al. 2016; Schweitzer et al. 2023). In the course of conducting tirzepatide OSA Phase 3 studies, Eli Lilly included PRO measures, completed qualitative interviews in individuals living with OSA and obesity to identify symptoms that are most relevant and impactful to participants' disease experience, and consulted external experts and regulators to inform prioritization of PRO endpoints within the graphical testing strategy. Based on these inputs, PROMIS SRI and PROMIS SD were selected as prioritized endpoints for inclusion in the alpha-controlled testing strategy in SURMOUNT-OSA. Consequently, Lilly reassessed statistical power assumptions, given the uncertainty as to whether the newly selected key secondary PRO endpoints were sufficiently powered to allow inclusion in the individual study graphical testing strategy.

This uncertainty was mitigated by implementing a submission-wise error rate strategy as elucidated by Vandemeulebroecke et al. (2024). This methodology advocates for a pooled analysis across multiple trials with selected key secondary endpoints, aiming to maintain rigorous control of the family-wise error rate within each study for the primary endpoints while facilitating efficient statistical evaluation of secondary endpoints.

The pooled, multiplicity-controlled analysis was pre-specified and conducted only for the following 2 secondary PRO endpoints:

- change from baseline in PROMIS SRI at Week 52, and
- change from baseline in PROMIS SD at Week 52.

Studies 1 and 2 had identical inclusion and exclusion criteria, and the difference between the studies was the presence of background PAP therapy in Study 2. The potential effect of PAP on PRO outcomes in Study 2 was minimized by a 7-day PAP washout period, consistently implemented at both baseline and Week 52 assessment, and therefore, the populations of the 2 studies were considered homogenous and suitable for pooling in the context of PRO assessment.

Results

Participant flow

According to Protocol provisions, a distinction is made *Treatment discontinuation* and *Study discontinuation.*

When necessary, a participant may be permanently discontinued from study intervention. If so, the participant will remain in the study and follow procedures for remaining study visits, as shown in the SoA.

A participant who prematurely discontinues study intervention is strongly encouraged to remain in the study for safety and efficacy assessments through the treatment period and post-treatment follow-up.

Possible reasons leading to permanent discontinuation of study intervention are

- participant decision
- initiation of prohibited medication
- BMI $\leq$ 18.5 kg/m^2 is reached at any time during the treatment period
- TEAE
- Diagnosis of T1DM, thyroid C-cell hyperplasia, acute / chronic pancreatitis, pregnancy, suicidal ideation or behaviour and others

Discontinuation from the study is expected to be uncommon. A participant may withdraw from the study, e.g.

- At any time on own request
- At the discretion of the Investigator for safety, behavioural, compliance, or administrative reasons

Study 1

In Study 1, a total of 449 participants were screened. Overall, 234 participants screened were randomly assigned, and all randomly assigned participants received the study drug (placebo [n = 120]; tirzepatide [n = 114]). More participants randomly assigned to tirzepatide MTD completed the study (88.6%) and the study drug (85.1%) than participants randomly assigned to placebo (71.7% for study and 70.0% for study drug).

Study 2

In Study 2, a total of 416 participants were screened. Overall, 235 participants were randomly assigned, and 233 participants received the study drug (placebo [n = 114], tirzepatide [n = 119]). More participants randomly assigned to tirzepatide MTD completed the study (94.2%) and the study drug

(90.0%) than participants randomly assigned to placebo (77.4% for study, and 73.9%% for study drug).

Table 8 Summary of Disposition and Discontinuation All Randomized Population of Studies 1 & 2

Attribute	Study 1 (Total = 234)		Study 2 (Total = 235)	
Treatment Disposition	**Placebo (N = 120) n (%)**	**Tirzepatide (N = 114) n (%)**	**Placebo (N = 115) n (%)**	**Tirzepatide (N = 120) n (%)**
Discontinued	36 (30.0)	17 (14.9)	30 (26.1)	12 (10.0)
Completed	84 (70.0)	97 (85.1)	85 (73.9)	108 (90.0)
Reasons for treatment discontinuation				
Adverse event	2 (1.7)	5 (4.4)	8 (7.0)	4 (3.3)
Randomized in error	10 (8.3)	5 (4.4)	4 (3.5)	2 (1.7)
Lack of efficacy	0	1 (0.9)	0	0
Lost to follow-up	0	3 (2.6)	0	0
Noncompliance with study drug	1 (0.8)	0	1 (0.9)	0
Other	0	0	1 (0.9)	1 (0.8)
Physician decision	1 (0.8)	0	0	1 (0.8)
Pregnancy	1 (0.8)	0	0	0
Protocol deviation	0	1 (0.9)	0	0
Screen failure/not treated	0	0	1 (0.9)	0
Withdrawal by subject	21 (17.5)	2 (1.8)	15 (13.0)	4 (3.3)
Study disposition				
Discontinued	34 (28.3)	13 (11.4)	26 (22.6)	7 (5.8)
Completed	86 (71.7)	101 (88.6)	89 (77.4)	113 (94.2)
Reasons for study discontinuation				
Adverse event	2 (1.7)	0	5 (4.3)	1 (0.8)
Randomized in error	5 (4.2)	4 (3.5)	3 (2.6)	0
Lost to follow-up	0	3 (2.6)	0	0
Other	6 (5.0)	1 (0.9)	3 (2.6)	2 (1.7)
Physician decision	1 (0.8)	0	0	0
Pregnancy	1 (0.8)	0	0	0
Protocol deviation	0	1 (0.9)	0	0
Screen failure	0	0	1 (0.9)	0
Withdrawal by subject	19 (15.8)	4 (3.5)	14 (12.2)	4 (3.3)

Abbreviations: CSR = clinical stud report; n = number of participants in the specified category; N = number of participants in the population; Study 1 = I8F-MC-GPI1; Study 2 = I8F-MC-GPI2.

Baseline data

Study 1 and Study 2 were intended to represent a broad and diverse target treatment population of patients with moderate to severe OSA and obesity, including participants

- with moderate to severe OSA
- with Class 1, Class 2, and Class 3 (BMI 30-34.9; 35-39.9; 40-49.9 kg/m^2) obesity
- representing appropriately both male and female populations
- from demographic and ethnic groups impacted by OSA, and
- with a range of relevant intrinsic and extrinsic characteristics.

Table 9 Key Demographics and Clinical Characteristics Randomized Population, Study 1 & 2

Parameter	Study 1 (N = 234)	Study 2 (N = 235)
Age (years), mean ± SD	47.9 ± 11.5	51.7 ± 11.0
Age category, n (%)		
<50	125 (53.4)	99 (42.1)
≥50	109 (46.6)	136 (57.9)
Sex, n (%)		
Female	77 (32.9)	65 (27.7)
Male	157 (67.1)	170 (72.3)
Country/region, n (%)		
Australia	6 (2.6)	19 (8.1)
Brazil	49 (20.9)	35 (14.9)
China	28 (12.0)	9 (3.8)
Czech Republic	11 (4.7)	12 (5.1)
Germany	14 (6.0)	32 (13.6)
Japan	7 (3.0)	13 (5.5)
Mexico	39 (16.7)	30 (12.8)
Taiwan	9 (3.8)	7 (3.0)
United States	71 (30.3)	78 (33.2)
Race, n (%)		
American Indian or Alaska Native	18 (7.7)	19 (8.1)
Asian	47 (20.1)	33 (14.1)
Black or African American	13 (5.6)	11 (4.7)
White	154 (65.8)	171 (73.1)
Multiple	2 (0.9)	0
Missing	0	1

Ethnicity, n (%)		
Hispanic or Latino	98 (41.9)	76 (32.3)
Not Hispanic or Latino	132 (56.4)	158 (67.2)
Not reported	4 (1.7)	1 (0.4)
AHI – events/h, mean ± SD	51.5 ± 31.0	49.5 ± 26.7
Hypoxic burden (% min/h), mean ± SD	208.4 ± 189.1	193.0 ± 174.6
Sleep efficiency (%), mean ± SD	76.5 ± 14.0	75.0 ± 14.2
Sleep onset (min), mean ± SD	15.2 ± 18.1	16.6 ± 24.0
Wake after sleep onset (min), mean ± SD	94.7 ± 59.1	100.9 ± 60.2
Percentage of REM sleep, mean ± SD	13.8 ± 7.1	12.3 ± 7.0
OSA severity		
No apnea (AHI <5 events/h)[a]	1 (0.4)	0
Mild (≥5 events/h AHI <15 events/h)[a]	3 (1.3)	2 (0.9)
Moderate (≥15 events/h AHI <30 events/h)	82 (35.2)	72 (30.9)
Severe (AHI ≥30 events/h)	147 (63.1)	159 (68.2)

Parameter	Study 1 (N = 234)	Study 2 (N = 235)
Missing[b]	1	2
PROMIS Sleep Disturbance T-score, mean ± SD	53.6 ± 6.7	55.9 ± 7.6
PROMIS Sleep-Related Impairment T-score, mean ± SD	53.8 ± 8.1	55.2 ± 8.9
ESS, mean ± SD	10.6 ± 5.3	10.2 ± 4.5
Weight (kg), mean ± SD	114.7 ± 23.7	115.5 ± 22.0
Height (cm), mean ± SD	171.0 ± 9.7	172.6 ± 9.7
BMI (kg/m^2), mean ± SD	39.1 ± 7.0	38.7 ± 6.0
BMI categories, n (%)		
<35 kg/m^2	77 (32.9)	66 (28.3)
≥35 kg/m^2 and <40 kg/m^2	74 (31.6)	88 (37.8)
≥40 kg/m^2	83 (35.5)	79 (33.9)
Missing	0	2
Waist circumference (cm), mean ± SD	121.2 ± 15.7	120.9 ± 13.5
Neck circumference (cm), mean ± SD	43.9 ± 4.5	44.8 ± 4.8
Prediabetes, n (%)	152 (65.0)	133 (56.6)
HbA1c (%), mean ± SD	5.7 ± 0.4	5.6 ± 0.4
Hypertension, n (%)	177 (75.6)	182 (77.4)

Abbreviations: AHI = apnea-hypopnea index; BMI = body mass index; CSR = clinical study report; ESS = Epworth Sleepiness Scale; HbA1c = glycated hemoglobin A1c; n = number of participants in the specified category; N = number of participants in the population; OSA = obstructive sleep apnea; PROMIS = patient-reported outcomes measurement system; PSG = polysomnography; REM = rapid eye movement; SD = standard deviation; Study 1 = I8F-MC-GPI1; Study 2 = I8F-MC-GPI2.

Note: Presented are mean ± SD, except where noted.

[a] The 6 participants recorded for no apnea and mild apnea were enrolled in error and had no OSA or mild OSA when PSG results were received and verified. They began treatment, and then all were discontinued from study treatment due to "randomized in error" and were also discontinued from the study.

[b] One participant from Study 1 had an invalid PSG assessment and 2 participants from Study 2 were randomly assigned but not treated.

Outcomes and estimation

This section provides a side-by-side presentation of efficacy results from Studies 1 and 2. The key measures that provide efficacy support for this tirzepatide application for moderate to severe OSA in adults with obesity include

- sleep-disordered breathing assessments
- patient-reported outcomes, and
- OSA-related cardiometabolic parameters.

Efficacy on Sleep-Disordered Breathing

Change in AHI from Baseline to Week 52

Using treatment-regimen and efficacy estimands, the tirzepatide group demonstrated superiority compared with placebo for mean change in AHI (improvement) from baseline to Week 52 ($p<0.001$) in both Studies 1 and 2.

Table 10 Change in AHI from Baseline to Week 52 mITT Population – Full Analysis Set; Efficacy Analysis Set

	Study 1		Study 2	
Attribute	**Placebo N = 120**	**Tirzepatide N = 114**	**Placebo N = 114**	**Tirzepatide N = 119**
Treatment-regimen estimand[a]				
Mean AHI at baseline (events/h)	50.1	52.9	53.1	46.1
Mean change in AHI from baseline to Week 52 (events/h)	-5.3	-25.3	-5.5	-29.3
Mean difference vs placebo (95% CI)	N/A	-20.0*** (-25.8, -14.2)	N/A	-23.8*** (-29.6, -17.9)
Efficacy estimand[b]				
Mean AHI at baseline (events/h)	50.9	54.3	53.1	45.8
Mean change in AHI from baseline to Week 52 (events/h)	-4.8	-27.4	-6.0	-30.4
Mean difference vs placebo (95% CI)	N/A	-22.5*** (-28.7, -16.4)	N/A	-24.4*** (-30.3, -18.6)

Abbreviations: AHI = Apnea-Hypopnea Index; ANCOVA = analysis of covariance; CI = confidence interval; CSR = clinical study report; mITT = modified intent to treat; MMRM = mixed model repeated measures; N = number of randomly assigned participants who received at least 1 dose of the study drug; N/A = not applicable; Study 1 = I8F-MC-GPI1; Study 2 = I8F-MC-GPI2.

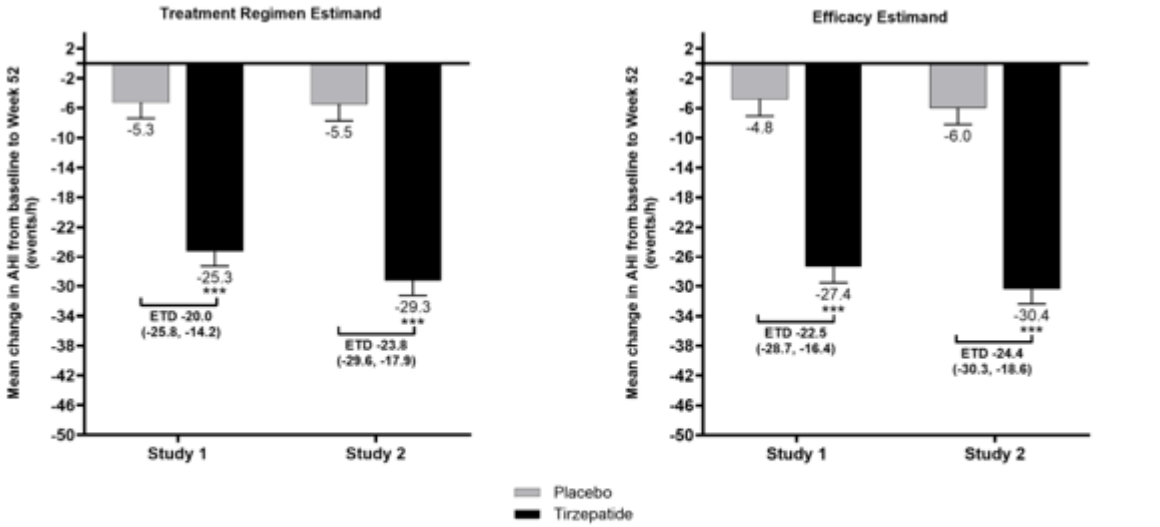
[a] ANCOVA with multiple imputation by treatment for missing data at Week 52.

[b] MMRM analysis.

Note: Shown are least squares means.

*** p-Value <0.001 versus placebo, controlled for type I error.

Figure 3 Change in AHI from baseline to Week 52 in Studies 1 and 2: mITT population, full analysis set (left), efficacy analysis set (right).



Abbreviations: AHI = Apnea-Hypopnea Index; ANCOVA = analysis of covariance; CI = confidence interval; CSR = clinical study report; ETD = estimated treatment difference; mITT = modified intent to treat; MMRM = mixed model repeated measures; Study 1 = I8F-MC-GPI1; Study 2 = I8F-MC-GPI2.
Note 1: ANCOVA analysis for the treatment-regimen estimand; MMRM analysis for the efficacy estimand.
Note 2: Shown are the least squares means ± standard errors and ETD (95% CI).
***p-Value <0.001 versus placebo, controlled for type I error.

Percent Change in AHI from Baseline to Week 52

Using treatment-regimen and efficacy estimands, the tirzepatide group demonstrated superiority compared with placebo for mean percent change in AHI from baseline to Week 52 ($p<0.001$) in both Studies 1 and 2.

Table 11 Percent Change in AHI from Baseline to Week 52 mITT Population – Full Analysis Set; Efficacy Analysis Set

	Study 1		Study 2	
Attribute	**Placebo N = 120**	**Tirzepatide N = 114**	**Placebo N = 114**	**Tirzepatide N = 119**
Treatment-regimen estimand[a]				
Percent AHI at baseline (%)	50.1	52.9	53.1	46.1
Mean percent change in AHI from baseline to Week 52 (%)	-3.0	-50.7	-2.5	-58.7
Mean difference vs placebo (%) (95% CI)	N/A	-47.7*** (-65.8, -29.6)	N/A	-56.2*** (-73.7, -38.7)
Efficacy estimand[b]				
Percent AHI at baseline (%)	50.9	54.3	53.1	45.8
Mean percent change in AHI from baseline to Week 52 (%)	-5.0	-55.0	-6.4	-62.8
Mean difference vs placebo (%) (95% CI)	N/A	-49.9*** (-62.8, -37.0)	N/A	-56.4*** (-70.7, -42.2)

Abbreviations: AHI = Apnea-Hypopnea Index; ANCOVA = analysis of covariance; CI = confidence interval; CSR = clinical study report; mITT = modified intent to treat; MMRM = mixed model repeated measures; N = number of randomly assigned participants who received at least 1 dose of the study drug; N/A = not applicable; Study 1 = I8F-MC-GPI1; Study 2 = I8F-MC-GPI2.

a ANCOVA with multiple imputation by treatment for missing data at Week 52.

b MMRM analysis.

Note: Shown are least squares means.

*** p-Value <0.001 versus placebo, controlled for type I error.

Percentage of Participants with ≥50% AHI Reduction

A 50% AHI improvement (reduction) has been proposed as a threshold for clinically significant outcomes in the literature (Ramar et al. 2015; Chang et al. 2023).

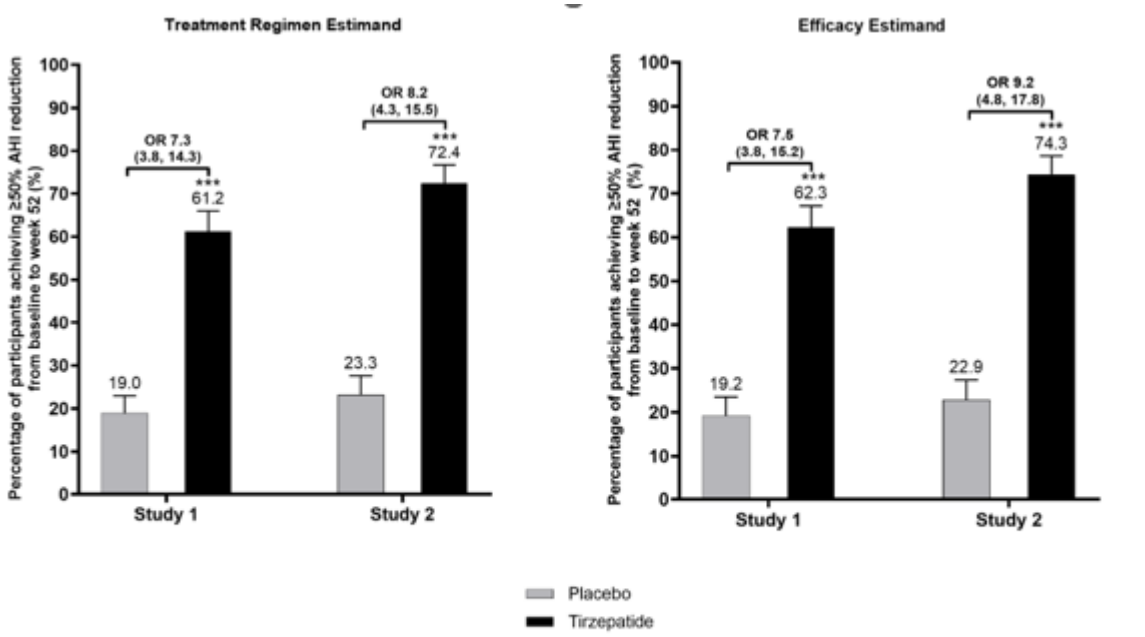
Using both the treatment-regimen and efficacy estimands, the tirzepatide group demonstrated superiority compared with placebo for percentage of participants achieving at least 50% AHI reduction from baseline to Week 52 in both Studies 1 and 2.

Table 12 Percentage of Participants with ⩾50% AHI Reduction from Baseline to Week 52 mITT Population – Full Analysis Set; Efficacy Analysis Set

	Study 1		Study 2	
Attribute	**Placebo N = 120**	**Tirzepatide N = 114**	**Placebo N = 114**	**Tirzepatide N = 119**
Treatment-regimen estimand				
Percentage of participants with ≥50% AHI reduction at Week 52	19.0	61.2	23.3	72.4
OR (95% CI)	NA	7.3*** (3.8, 14.3)	NA	8.2*** (4.3, 15.5)
Efficacy estimand				
Percentage of participants with ≥50% AHI reduction at Week 52	19.2	62.3	22.9	74.3
OR (95% CI)	NA	7.5*** (3.8, 15.2)	NA	9.2*** (4.8, 17.8)

Abbreviations: AHI = Apnea-Hypopnea Index; CI = confidence interval; CSR = clinical study report; mITT = modified intent to treat; N = number of randomly assigned participants who received at least 1 dose of the study drug; NA = not applicable; OR = odds ratio; Study 1 = I8F-MC-GPI1; Study 2 = I8F-MC-GPI2.
Note: OR, CI, and p-value are from logistic regression analysis.
*** p-Value <0.001 versus placebo, controlled for type I error.

Figure 4 Percentage of participants achieving ≥50% AHI reduction from baseline at Week 52 in Study 1 and Study 2: mITT population, full analysis set (left) and efficacy analysis set (right).



Abbreviations: AHI = Apnea-Hypopnea Index; CI = confidence interval; CSR = clinical study report; mITT = modified intent to treat; OR = odds ratio; Study 1 = I8F-MC-GPI1; Study 2 = I8F-MC-GPI2.
Note 1: Shown are the estimated means ± standard errors and OR (95% CI).
Note 2: OR, CI, and p-value are from logistic regression analysis.
***p-Value <0.001 versus placebo, controlled for type I error.

Percentage of Participants with AHI <5 or AHI 5-14 with ESS ≤10

The participants who reached AHI<5 or AHI<15 without EDS (ESS ≤10) represent those who achieved a wider definition of OSA remission and are not typically indicated for further treatment.

Using both the treatment-regimen and efficacy estimands, the tirzepatide group demonstrated superiority compared with placebo for percentage of participants achieving OSA remission or mild OSA without EDS (AHI <5 events/h or AHI 5-14 events/h with ESS ≤10) at Week 52 in both Studies 1 and 2.

Table 13 Percentage of Participants with AHI <5 or AHI 5-14 with ESS ⩽10 at Week 52: mITT Population – Full Analysis Set; Efficacy Analysis Set

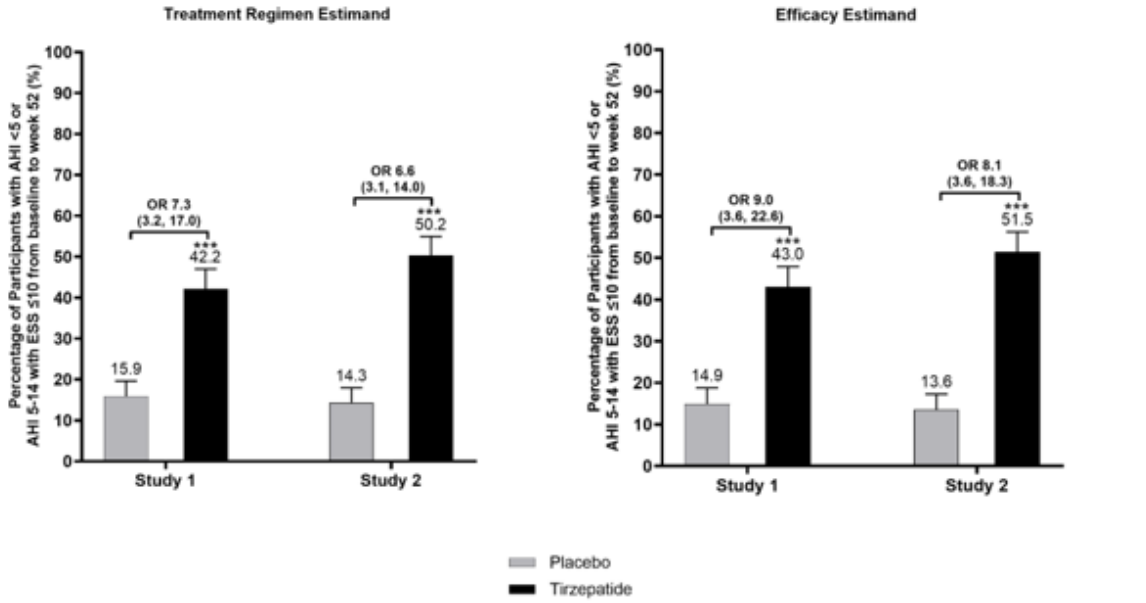
	Study 1		Study 2	
Attribute	**Placebo N = 120**	**Tirzepatide N = 114**	**Placebo N = 114**	**Tirzepatide N = 119**
Treatment-regimen estimand				
Percentage of participants with AHI <5 or AHI 5-14 with ESS ≤10 at Week 52	15.9	42.2	14.3	50.2
OR (95% CI)	NA	7.3*** (3.2, 17.0)	NA	6.6*** (3.1, 14.0)
Efficacy estimand				
Percentage of participants with AHI <5 or AHI 5-14 with ESS ≤10 at Week 52	14.9	43.0	13.6	51.5
OR (95% CI)	NA	9.0*** (3.6, 22.6)	NA	8.1*** (3.6, 18.3)

Abbreviations: AHI = Apnea-Hypopnea Index; CI = confidence interval; CSR = clinical study report; ESS = Epworth Sleepiness Scale; OR = odds ratio; mITT = modified intent to treat; N = number of randomly assigned participants who received at least 1 dose of the study drug; NA = not applicable; OR = odds ratio; Study 1 = I8F-MC-GPI1; Study 2 = I8F-MC-GPI2.

Note: OR, CI, and p-value are from logistic regression analysis.

*** p-Value <0.001 versus placebo, controlled for type I error.

Figure 5 Percentage of participants with AHI <5 events/h or AHI 5-14 events/h with ESS ⩽10 at Week 52: mITT population, full analysis set (left) and efficacy analysis set (right).



Abbreviations: AHI = Apnea-Hypopnea Index; CI = confidence interval; CSR = clinical study report; ESS = Epworth Sleepiness Scale; mITT = modified intent to treat; OR = odds ratio; Study 1 = I8F-MC-GPI1; Study 2 = I8F-MC-GPI2.
Note 1: Shown are the estimated means ± standard errors and OR (95% CI).
Note 2: OR, CI, and p-value are from logistic regression analysis.
***p-Value <0.001 versus placebo, controlled for type I error.

Hypoxic Burden

Using both the treatment-regimen and efficacy estimands, the tirzepatide group demonstrated superiority compared with placebo for mean percent change in SASHB from baseline to Week 52 in both Studies 1 and 2 (p<0.001).

Table 14 Change in SASHB from Baseline to Week 52: mITT Population – Full Analysis Set, Efficacy Analysis Set

Attribute	Study 1		Study 2	
	Placebo N = 120	Tirzepatide N = 114	Placebo N = 114	Tirzepatide N = 119
Treatment-regimen estimand[a]				
Baseline geometric mean (% min/h)	137.8	153.6	142.1	132.2
Mean change from baseline to Week 52 (% min/h)	-25.1	-95.2	-41.7	-103.0
Mean percent change from baseline to Week 52 (%)	-17.3	-65.5	-30.4	-75.2
Mean difference vs placebo (%) (95% CI)	N/A	-58.3*** (-66.8, -47.7)	N/A	-64.3*** (-74.1, -50.9)
Efficacy estimand[b]				
Baseline geometric mean (% min/h)	148.2	156.6	139.1	129.9
Mean change from baseline to Week 52 (% min/h)	-21.1	-103.1	-40.7	-103.0
Mean percent change from baseline to Week 52 (%)	-13.8	-67.6	-30.4	-76.9
Mean difference vs placebo (%) (95% CI)	N/A	-62.4*** (-70.6, -51.9)	N/A	-66.8*** (-76.5, -53.1)

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; CSR = clinical study report; mITT = modified intent to treat; MMRM = mixed model repeated measures; N = number of randomly assigned participants who received at least 1 dose of the study drug; N/A = not applicable; SASHB = sleep apnea-specific hypoxic burden; Study 1 = I8F-MC-GPI1; Study 2 = I8F-MC-GPI2.

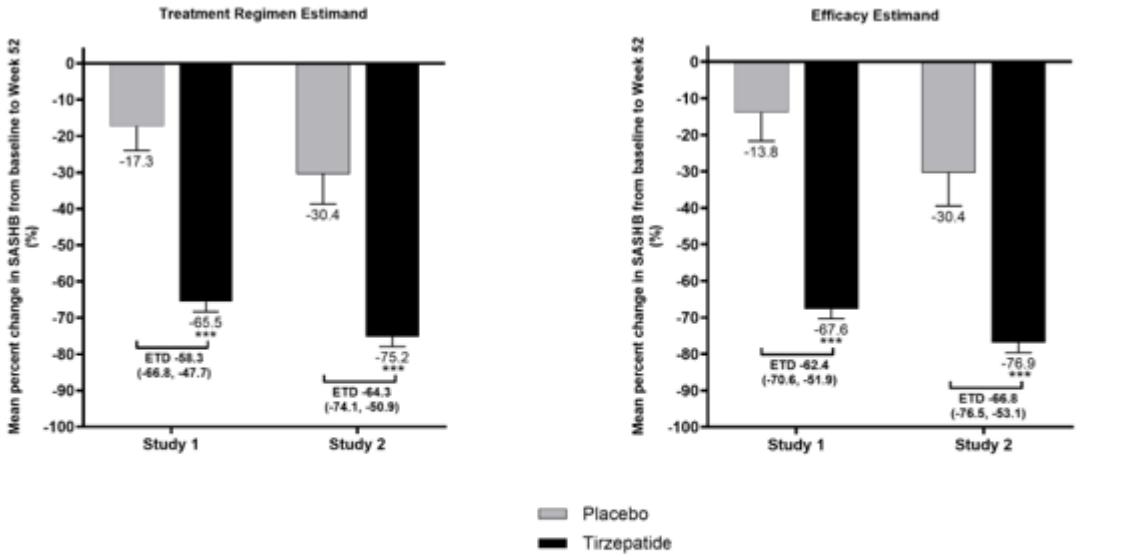
[a] ANCOVA with multiple imputation by treatment for missing data at Week 52.

[b] MMRM analysis.

Note: Shown are estimated means. Log transformations were applied to raw data.

*** p-Value <0.001 versus placebo, controlled for type I error.

Figure 6 Percent change in SASHB from baseline to Week 52 in Study 1 and Study 2: mITT population, full analysis set (left) and efficacy analysis set (right).



Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; CSR = clinical study report; ETD = estimated treatment difference; mITT = modified intent to treat; MMRM = mixed model for repeated measures; SASHB = sleep apnea-specific hypoxic burden; Study 1 = I8F-MC-GPI1; Study 2 = I8F-MC-GPI2.
Note 1: ANCOVA analysis for the treatment-regimen estimand; MMRM analysis for the efficacy estimand.
Note 2: Shown are the estimated means ± standard errors and ETD (95% CI).
Note 3: Log transformations were applied to raw data.
***p-Value <0.001 versus placebo, controlled for type I error.

Patient-Reported Outcomes

PROMIS Sleep-Related Impairment

Pooled Analyses of PROMIS SRI Scores

The pooled analyses of the secondary PRO endpoints from Studies 1 and 2 were controlled for submission-wise type I error. Using both treatment-regimen and efficacy estimands, pooled tirzepatide demonstrated superiority compared with placebo for mean PROMIS SRI scores (improvement) from baseline to Week 52 ($p<0.001$) in the pooled analyses from Studies 1 and 2 ($p<0.001$).

Table 15 Results of the Pooled Analyses of PROMIS SRI Study 1 and Study 2: mITT Population – Full Analysis Set; Efficacy Analysis Set

Attribute	Pooled Study 1 and Study 2[a]	
	Placebo N = 234	Tirzepatide N = 233
Treatment-regimen estimand[b]		
Baseline T-scores	54.9	54.5
Mean change in T-scores from baseline to Week 52	-3.6	-7.5
Mean change difference from placebo at Week 52 (95% CI)	N/A	-3.9*** (-5.7, -2.2)
Efficacy estimand[c]		
Baseline T-scores	54.8	54.5
Mean change in T-scores from baseline to Week 52	-3.5	-7.3
Mean change difference from placebo at Week 52 (95% CI)	N/A	-3.8*** (-5.8, -1.9)

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; ISE = integrated summary of efficacy; mITT = modified intent to treat; MMRM = mixed model repeated measures; N = number of randomly assigned participants who received at least 1 dose of the study drug; N/A = not applicable; PROMIS = Patient-Reported Outcomes Measurement Information System; SRI = Sleep-Related Impairment; Study 1 = I8F-MC-GPI1; Study 2 = I8F-MC-GPI2.

a Controlled for submission-wise type I error.

b ANCOVA with multiple imputation by treatment for missing data at Week 52.

c MMRM analysis.

Note: Shown are least squares means.

*** p-Value <0.001 versus placebo, controlled for submission-wise type I error.

The pooled PROMIS SRI T-scores from Studies 1 and 2 were controlled for submission-wise type I error. Additionally, the individual studies included mean change in PROMIS SRI scores from baseline to Week 52 as a secondary endpoint not controlled for type I error.

Using the treatment-regimen estimand, the tirzepatide group showed a statistically significant decrease (improvement) from baseline to Week 52 in mean PROMIS SRI T-scores compared with placebo in both studies.

Table 16 Change in PROMIS SRI From Baseline to Week 52: mITT Population – Full Analysis Set, Efficacy Analysis Set

Attribute	Study 1		Study 2	
	Placebo N = 120	Tirzepatide N = 114	Placebo N = 114	Tirzepatide N = 119
Treatment-regimen estimand[a]				
Baseline T-scores	54.7	53.5	55.2	55.6
Mean change in T-scores from baseline to Week 52	-3.1	-6.6	-3.9	-8.2
Mean change difference from placebo at Week 52 (95% CI)	N/A	-3.4## (-5.7, -1.2)	N/A	-4.3## (-7.0, -1.6)
Efficacy estimand[b]				
Baseline T-scores	54.2	53.3	55.3	55.7
Mean change in T-scores from baseline to Week 52	-3.1	-6.3	-3.8	-8.1
Mean change difference from placebo at Week 52 (95% CI)	N/A	-3.2# (-5.8, -0.6)	N/A	-4.3## (-7.2, -1.4)

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; CSR = clinical study report; mITT = modified intent to treat; MMRM = mixed model repeated measures; N = number of randomly assigned participants who received at least 1 dose of the study drug; N/A = not applicable; PROMIS = Patient-Reported Outcomes Measurement Information System; Study 1 = I8F-MC-GPI1; Study 2 = I8F-MC-GPI2.

[a] ANCOVA with multiple imputation for missing data at 52 weeks.

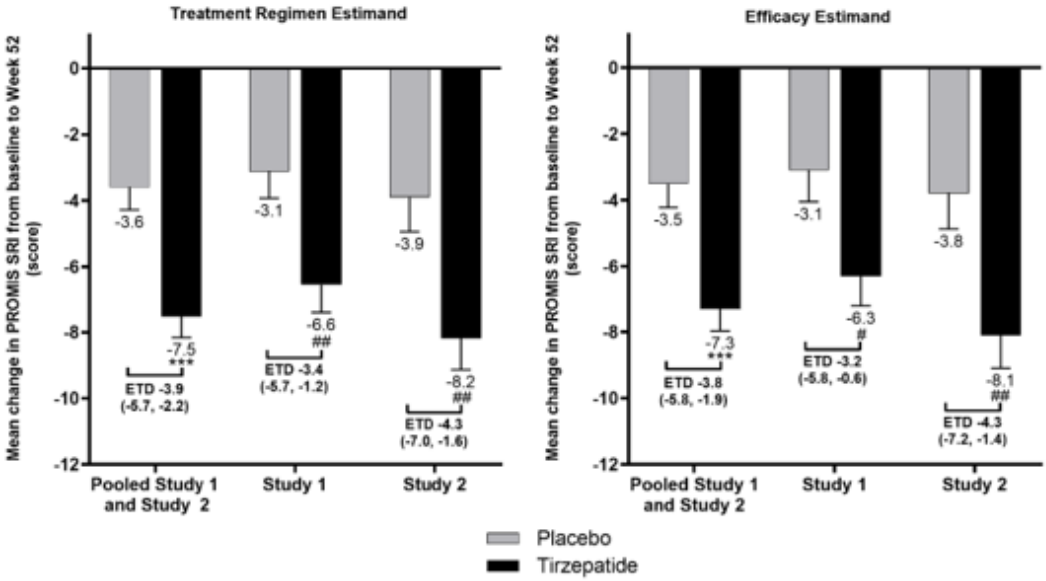
[b] MMRM analysis.

Note: Shown are the least squares means.

#p-Value <0.05 versus placebo, not controlled for type I error.

##p-Value <0.01 versus placebo, not controlled for type I error.

Figure 7 Change in PROMIS SRI from baseline to Week 52 in pooled Study 1 and Study 2, Study 1, and Study 2: mITT population, full analysis set (left) and efficacy analysis set (right).



Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; CSR = clinical study report; ETD = estimated treatment difference; ISE = integrated summary of efficacy; mITT = modified intent to treat; MMRM = mixed model for repeated measures; PROMIS = Patient-Reported Outcomes Measurement Information System; SRI = Sleep-Related Impairment; Study 1 = I8F-MC-GPI1; Study 2 = I8F-MC-GPI2.
Note 1: ANCOVA analysis for the treatment-regimen estimand; MMRM analysis for the efficacy estimand.
Note 2: Shown are the least squares means ± standard errors and ETD (95% CI).
*** p-Value <0.001 versus placebo, controlled for type I error.
# p-Value <0.05 versus placebo, not controlled for type I error.
p-Value <0.01 versus placebo, not controlled for type I error.

Pooled Analyses of PROMIS SD Scores

The pooled analyses of the results of the key secondary PRO endpoints from Studies 1 and 2 were controlled for submission-wise type I error. Using both treatment-regimen and efficacy estimands, pooled tirzepatide demonstrated superiority compared with placebo in mean PROMIS SD scores (improvement) from baseline to Week 52 ($p<0.001$) in the pooled analyses.

Table 17 Results of the Pooled Analyses of PROMIS SD Studies 1 and 2: mITT Population – Full Analysis Set; Efficacy Analysis Set

Attribute	Pooled Study 1 and Study 2[a]	
	Placebo N = 234	Tirzepatide N = 233
Treatment-regimen estimand[b]		
Baseline T-scores	54.9	55.0
Mean change in T-scores from baseline to Week 52	-2.7	-5.7
Mean change difference from placebo at Week 52 (95% CI)	N/A	-3.0*** (-4.5, -1.5)
Efficacy estimand[c]		
Baseline T-scores	55.0	55.0
Mean change in T-scores from baseline to Week 52	-2.9	-5.8
Mean change difference from placebo at Week 52 (95% CI)	N/A	-2.9*** (-4.5, -1.3)

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; ISE = integrated summary of efficacy; mITT = modified intent to treat; MMRM = mixed model repeated measures; N = number of randomly assigned participants who received at least 1 dose of the study drug; N/A = not applicable; PROMIS = Patient-Reported Outcomes Measurement Information System; SD = Sleep Disturbance; Study 1 = I8F-MC-GPI1; Study 2 = I8F-MC-GPI2.

a Controlled for submission-wise type I error.

b ANCOVA with multiple imputation by treatment for missing data at Week 52.

c MMRM analysis.

Note: Shown are least squares means.

*** p-Value <0.001 versus placebo, controlled for submission-wise type I error.

The pooled PROMIS SD T-scores from Studies 1 and 2 were controlled for submission-wise type I error. Additionally, the individual studies included mean change in PROMIS SD scores from baseline to Week 52 as a secondary endpoint not controlled for type I error.

Using the treatment-regimen estimand, the tirzepatide group showed a statistically significant decrease compared with placebo in mean PROMIS SD T-scores from baseline to Week 52 in both studies.

Table 18 Change in PROMIS SD from Baseline to Week 52: mITT Population – Full Analysis Set, Efficacy Analysis Set

Attribute	Study 1		Study 2	
	Placebo N = 120	Tirzepatide N = 114	Placebo N = 114	Tirzepatide N = 119
Treatment-regimen estimand[a]				
Baseline T-scores	53.8	53.9	56.1	56.2
Mean change in T-scores from baseline to Week 52	-2.4	-4.5	-3.1	-7.0
Mean change difference from placebo at Week 52 (95% CI)	N/A	-2.0# (-4.0, -0.1)	N/A	-3.9### (-6.2, -1.6)
Efficacy estimand[b]				
Baseline T-scores	53.6	53.9	56.3	56.0
Mean change in T-scores from baseline to Week 52	-2.5	-4.3	-3.1	-7.2
Mean change difference from placebo at Week 52 (95% CI)	N/A	-1.8 (-4.0, 0.4)	N/A	-4.1## (-6.5, -1.7)

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; CSR = clinical study report; mITT = modified intent to treat; MMRM = mixed model repeated measures; N = number of randomly assigned participants who received at least 1 dose of the study drug; N/A = not applicable; PROMIS = Patient-Reported Outcomes Measurement Information System; SD = Sleep Disturbance; Study 1 = I8F-MC-GPI1; Study 2 = I8F-MC-GPI2.

[a] ANCOVA with multiple imputation for missing data at 52 weeks.

[b] MMRM analysis.

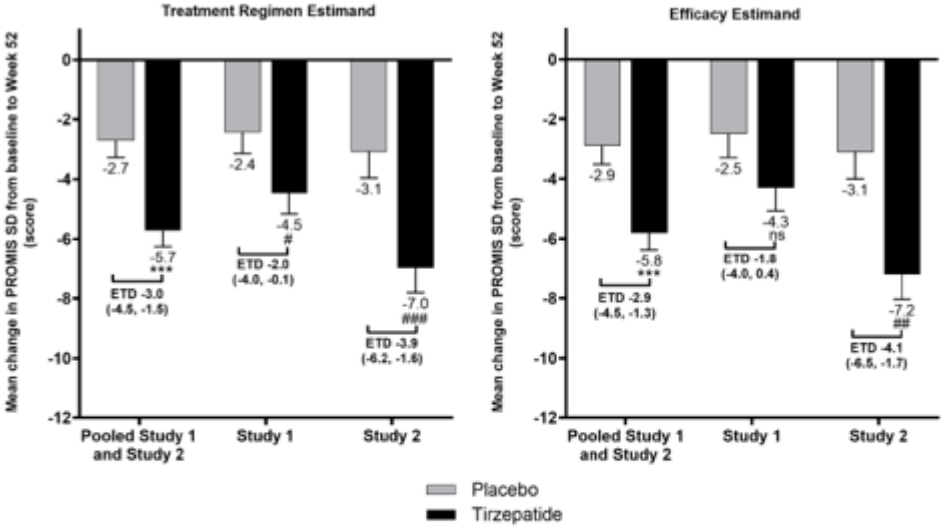
Note: Shown are the least squares means.

p-Value <0.001 versus placebo, not controlled for type I error.

p-Value <0.01 versus placebo, not controlled for type I error.

p-Value <0.05 versus placebo, not controlled for type I error.

Figure 8 Change in PROMIS SD from baseline to Week 52 in pooled Study 1 and Study 2, Study 1, and Study 2: mITT population, full analysis set (left) and efficacy analysis set (right).



Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; CSR = clinical study report; ETD = estimated treatment difference; ISE = integrated summary of efficacy; mITT = modified intent to treat; MMRM = mixed model for repeated measures; PROMIS = Patient-Reported Outcomes Measurement Information System; SD = Sleep Disturbance; Study 1 = I8F-MC-GPI1; Study 2 = I8F-MC-GPI2.
Note 1: ANCOVA analysis for the treatment-regimen estimand; MMRM analysis for the efficacy estimand.
Note 2: Shown are the least squares means ± standard errors and ETD (95% CI).
*** p-Value <0.001 versus placebo, controlled for type I error.
# p-Value <0.05 versus placebo, not controlled for type I error; ##p-value <0.01 versus placebo; ###p-value <0.001 versus placebo, not controlled for type I error.

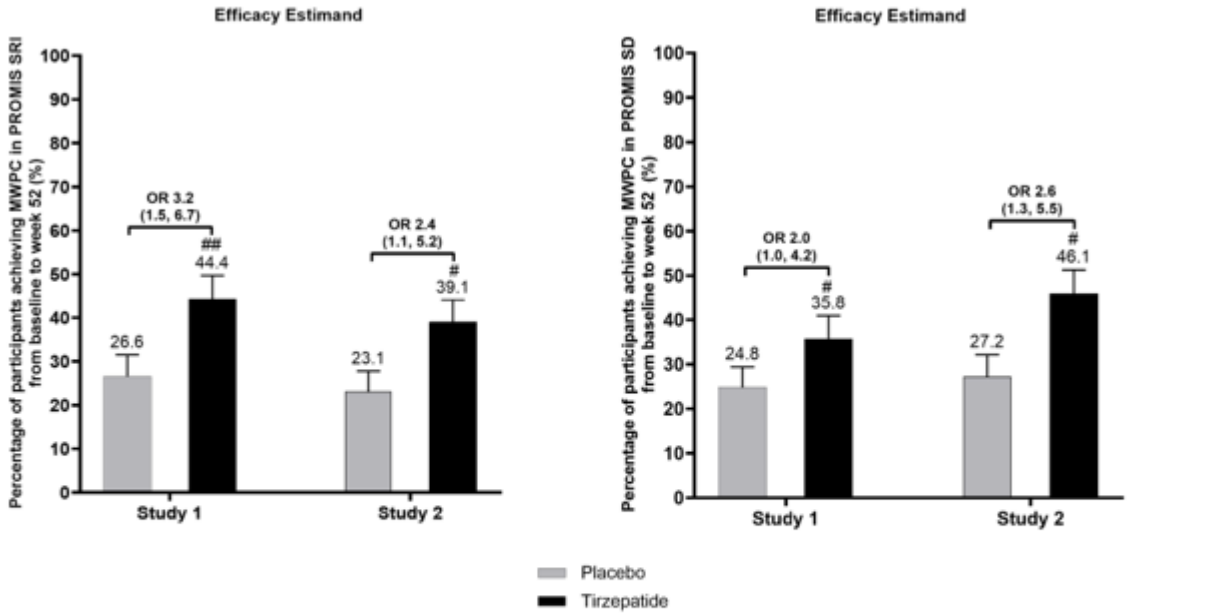
Meaningful Within-Patient Change Thresholds in PROMIS Scores

MWPC thresholds for improvement in PROMIS SRI and PROMIS SD T-scores were derived empirically based on data from participants in Studies 1 and 2. Using the anchor-based methodology described in the Psychometric Analyses Report, the estimated MWPC thresholds were

- ≤-8.0 change in PROMIS SRI for Study 1
- ≤-10.0 change in PROMIS SRI for Study 2, and
- ≤-7.5 change in PROMIS SD for Studies 1 and 2.

Using the efficacy estimand, the proportion of participants in Studies 1 and 2 tirzepatide groups that met or surpassed the MWPC thresholds for improvement in sleep-related impairment (PROMIS SRI) and sleep disturbance (PROMIS SD) from baseline to Week 52 was significantly greater than the proportion of participants that met the thresholds in the placebo groups.

Figure 9 Percentage of participants achieving meaningful within-patient change in PROMIS SD and PROMIS SRI scores from baseline to Week 52 in Study 1 and Study 2: mITT population, efficacy analysis set.



Abbreviations: CI = confidence interval; CSR = clinical study report; mITT = modified intent to treat; MWPC = meaningful within-person change; OR = odds ratio; PROMIS = Patient-Reported Outcomes Measurement Information System; SD = Sleep Disturbance; SRI = Sleep-Related Impairment; Study 1 = I8F-MC-GPI1; Study 2 = I8F-MC-GPI2.
Note 1: Shown are the estimated means ± standard errors and OR (95% CI).
Note 2: OR, CI, and p-value are from logistic regression analysis.
#p-Value <0.05 versus placebo, not controlled for type I error; ##p-value <0.01 versus placebo, not controlled for type I error.

ESS – Supportive secondary endpoint

Excessive daytime sleepiness was assessed with ESS (Epworth Sleepiness Scale), which is an 8-item self-completed measure that asks participants to rate on a scale of 0 (would never doze) to 3 (high chance of dozing) their usual chances of dozing in 8 different daytime situations.

In study 1, using the efficacy estimand, participants in the tirzepatide group had significant decrease in excessive daytime sleepiness (lower ESS scores) from baseline to Week 52 compared with the placebo group.

Table 19 Study 1. Summary and Analysis of Change in ESS Score MMRM by Treatment and Visit from Baseline to 52 Weeks Modified Intent-to-Treat – Efficacy Analysis Set

Parameters	Placebo (N=120)	TZP MTD (N=114)
ESS Total Score		
Baseline	10.70	10.27
Week 52: Change from Baseline	-1.62	-3.17
Within-treatment p-value	0.001	<0.001
Difference from Placebo (95% CI)	-	-1.55 (-2.90, -0.21)
Between-treatment p-value	-	0.024

Abbreviations: - = not applicable; CI = confidence interval; ESS = Epworth Sleepiness Scale; MMRM = mixed model repeated measures; MTD = maximum tolerated dose; N = number of participants randomly assigned and received at least 1 dose of study drug; TZP = tirzepatide
Note: Shown are least squares means.

In study 2, using the efficacy estimand, after the 52-week treatment period, both placebo and tirzepatide groups showed modest improvement with no significant differences between groups.

Table 20 Study 2. Summary and Analysis of Change in ESS Score MMRM by Treatment and Visit from Baseline to 52 Weeks Modified Intent-to-Treat – Efficacy Analysis Set

Parameters	Placebo (N=114)	TZP MTD (N=119)
ESS Total Score		
Baseline	9.47	10.76
Week 52: Change from Baseline	-2.91	-3.58
Within-treatment p-value	<0.001	<0.001
Difference from Placebo (95% CI)	-	-0.67 (-1.96, 0.62)
Between-treatment p-value	-	0.305

Abbreviations: - = not applicable; CI = confidence interval; ESS = Epworth Sleepiness Scale; MMRM = mixed model repeated measures; MTD = maximum tolerated dose; N = number of participants randomly assigned and received at least 1 dose of study drug; TZP = tirzepatide
Note: Shown are least squares means.

OSA-Related CV Risk Factors

The OSA-related CV risk factors including, SBP, DBP, hsCRP, HDL-C, non-HDL-C, triglycerides, and fasting insulin, were assessed in both Studies 1 and 2.

It has been documented that 7 days without PAP minimizes the effect of PAP on AHI and OSA-related PRO endpoints (Schwarz et al. 2016, 2018), which were measured at the end of the withdrawal period. Systolic and diastolic blood pressure were assessed outside of the PAP withdrawal periods, and time of hsCRP assessment in relation to PAP withdrawal period has not been specified.

Change in hsCRP Concentrations from Baseline to Week 52

Chronic low-grade inflammation, measured by hsCRP, is independently associated with OSA and represents an important risk factor for coronary artery disease development.

Using both the treatment-regimen and efficacy estimands, the tirzepatide group demonstrated superiority compared with placebo for the mean percent change in hsCRP concentration from baseline to Week 52 in both Studies 1 and 2.

Table 21 Percent Change in hsCRP Concentration from Baseline to Week 52: mITT Population – Full Analysis Set, Efficacy Analysis Set

Attribute	Study 1		Study 2	
	Placebo N = 120	Tirzepatide N = 114	Placebo N = 114	Tirzepatide N = 119
Treatment-regimen estimand[a]				
Baseline geometric mean (mg/L)	3.6	3.5	2.7	3.0
Mean change from baseline to Week 52 (mg/L)	-0.7	-1.4	-0.3	-1.4
Mean percent change from baseline to Week 52 (%)	-19.9	-40.1	-11.5	-48.2
Mean difference vs placebo (%) (95% CI)	N/A	-25.2** (-38.6, -8.9)	N/A	-41.5*** (-54.5, -24.8)
Efficacy estimand[b]				
Baseline geometric mean (mg/L)	3.8	3.6	2.7	3.0
Mean change from baseline to Week 52 (mg/L)	-0.8	-1.6	-0.3	-1.4
Mean percent change from baseline to Week 52 (%)	-21.4	-44.2	-10.4	- 50.7
Mean difference vs placebo (%) (95% CI)	N/A	- 28.9** (-43.4, -10.8)	N/A	-45.1*** (-58.8, -26.7)

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; CSR = clinical study report; hsCRP = high-sensitivity C-reactive protein; mITT = modified intent to treat; MMRM = mixed model repeated measures; N = number of randomly assigned participants who received at least 1 dose of the study drug; N/A = not applicable; Study 1 = I8F-MC-GPI1; Study 2 = I8F-MC-GPI2.

a ANCOVA with multiple imputation by treatment for missing data at Week 52.

b MMRM analysis.

Note: Shown are estimated means. Log transformations were applied to raw data.

*** p-Value <0.001 versus placebo, controlled for type I error.

**p-Value <0.01 versus placebo, controlled for type I error.

Change in SBP from Baseline to Week 48

OSA is independently associated with hypertension that represents an important CV risk factor.

Using both the treatment-regimen and efficacy estimands, the tirzepatide group demonstrated superiority compared with placebo for the mean change in SBP from baseline to Week 48 in both Studies 1 and 2.

Table 22 Change in SBP from Baseline to Week 48: mITT Population – Full Analysis Set, Efficacy Analysis Set

Attribute	Study 1		Study 2	
	Placebo N = 120	Tirzepatide N = 114	Placebo N = 114	Tirzepatide N = 119
Treatment-regimen estimand[a]				
SBP at baseline (mmHg)	130.3	128.4	130.5	130.5
Mean change from baseline to Week 48 (mmHg)	-1.8	-9.5	-3.9	-7.6
Mean change difference vs placebo (mmHg) (95% CI)	N/A	-7.6*** (-10.5, -4.8)	N/A	-3.7* (-6.8, -0.7)
Efficacy estimand[b]				
SBP at baseline (mmHg)	130.3	128.2	130.5	130.7
Mean change from baseline to Week 48 (mmHg)	-1.7	-9.6	-3.3	-7.6
Mean change difference vs placebo (mmHg) (95% CI)	N/A	-7.9*** (-11.0, -4.9)	N/A	-4.3** (-7.3, -1.2)

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; CSR = clinical study report; mITT = modified intent to treat; MMRM = mixed model repeated measures; N = number of randomly assigned participants who received at least 1 dose of the study drug; N/A = not applicable; SBP = systolic blood pressure; Study 1 = I8F-MC-GPI1; Study 2 = I8F-MC-GPI2.

a ANCOVA with multiple imputation by treatment for missing data at Week 48.

b MMRM analysis.

Note: Shown are least squares means.

*** p-Value <0.001 versus placebo, controlled for type I error.

** p-Value <0.01 versus placebo, controlled for type I error.

* p-Value <0.05 versus placebo, controlled for type I error.

Change in DBP from Baseline to Week 48

Using both the treatment-regimen and efficacy estimands, the tirzepatide group showed statistically significant decrease compared with placebo for mean change in DBP from baseline to Week 48 in Study 1. In Study 2, no statistically significant reductions in DBP were observed in the tirzepatide group at Week 48 using either of the estimands.

Table 23 Change in DBP from Baseline to Week 48: mITT Population – Full Analysis Set, Efficacy Analysis Set

Attribute	Study 1		Study 2	
	Placebo N = 120	Tirzepatide N = 114	Placebo N = 114	Tirzepatide N = 119
Treatment-regimen estimand[a]				
DBP at baseline (mmHg)	84.0	83.7	80.5	83.2
Mean change from baseline to Week 48 (mmHg)	-2.1	-4.9	-2.2	-3.3
Mean change difference vs placebo (mmHg) (95% CI)	N/A	-2.8## (-5.0, -0.7)	N/A	-1.1 (-3.2, 1.0)
Efficacy estimand[b]				
DBP at baseline (mmHg)	83.9	83.7	80.5	83.2
Mean change from baseline to Week 48 (mmHg)	-2.0	-5.2	-1.8	-3.0
Mean change difference vs placebo (mmHg) (95% CI)	N/A	-3.2## (-5.4, -1.0)	N/A	-1.2 (-3.4, 0.9)

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; CSR = clinical study report; DBP = diastolic blood pressure; mITT = modified intent to treat; MMRM = mixed model repeated measures; N = number of randomly assigned participants who received at least 1 dose of the study drug; N/A = not applicable; Study 1 = I8F-MC-GPI1; Study 2 = I8F-MC-GPI2.

[a] ANCOVA with multiple imputation by treatment for missing data at Week 48.

[b] MMRM analysis.

Note: Shown are least squares means ± standard errors.

##p-Value <0.01, not controlled for type I error.

Percent Change in Body Weight from Baseline to Week 52

Obesity is present in most patients with OSA; both OSA and obesity are associated with CV morbidity and mortality.

Using both the treatment-regimen and efficacy estimands, the tirzepatide group demonstrated superiority compared with placebo for the mean percent change in body weight from baseline to Week 52 ($p<0.001$) in both Studies 1 and 2.

Table 24 Percent Change in Body Weight from Baseline to Week 52: mITT Population – Full Analysis Set, Efficacy Analysis Set

	Study 1		Study 2	
Attribute	**Placebo N = 120**	**Tirzepatide N = 114**	**Placebo N = 114**	**Tirzepatide N = 119**
Treatment-regimen estimand[a]				
Mean body weight at baseline (kg)	112.8	116.7	115.1	115.8
Mean percent change in body weight from baseline to Week 52 (%)	-1.6	-17.7	-2.3	-19.6
Mean difference vs placebo (%) (95% CI)	N/A	-16.1*** (-18.0, -14.2)	N/A	-17.3*** (-19.3, -15.3)
Efficacy estimand[b]				
Mean body weight at baseline (kg)	112.7	117.0	115.0	115.8
Mean percent change in body weight from baseline to Week 52 (%)	-1.3	-18.1	-2.3	-20.1
Mean difference vs placebo (%) (95% CI)	N/A	-16.8*** (-18.8, -14.7)	N/A	-17.8*** (-19.9, -15.7)

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; CSR = clinical study report; mITT = modified intent to treat; MMRM = mixed model repeated measures; N = number of randomly assigned participants who received at least 1 dose of the study drug; N/A = not applicable; Study 1 = I8F-MC-GPI1; Study 2 = I8F-MC-GPI2.

[a] ANCOVA with multiple imputation by treatment for missing data at Week 52.

[b] MMRM analysis.

Note: Shown are least squares means.

*** p-Value <0.001 versus placebo, controlled for type I error.

Change in Lipid Levels

OSA is reported to be associated with dyslipidemia, which represents an increased risk for coronary artery disease.

Using the efficacy estimand, the tirzepatide group showed statistically significant decrease compared with placebo for mean change in non-HDL-C and triglyceride levels, and a statistically significant increase for mean change in HDL-C levels from baseline to Week 52 in both Studies 1 and 2 ($p<0.001$).

Table 25 Change in Lipid Levels from Baseline to Week 52: mITT Population –Efficacy Analysis Set

	Study 1		Study 2	
Attribute	**Placebo N = 120**	**Tirzepatide N = 114**	**Placebo N = 114**	**Tirzepatide N = 119**
HDL-C				
Baseline geometric mean (mmol/L)	1.2	1.1	1.2	1.1
Mean change from baseline to Week 52 (mmol/L)	0.04	0.1	0.1	0.2
Mean percent change from baseline to Week 52 (%)	3.1	10.6	4.5	15.0
Mean difference vs placebo (%) (95% CI)	N/A	7.2### (3.2, 11.4)	N/A	10.0### (4.6, 15.7)
Non-HDL-C				
Baseline geometric mean (mmol/L)	3.7	3.8	3.5	3.8
Mean change from baseline to Week 52 (mmol/L)	-0.1	-0.6	-0.1	-0.6
Mean percent change from baseline to Week 52 (%)	-2.3	-15.0	-1.8	-15.8
Mean difference vs placebo (%) (95% CI)	N/A	-13.0### (-19.0, -6.6)	N/A	-14.3### (-19.1, -9.2)
Triglycerides				
Baseline geometric mean (mmol/L)	1.7	1.7	1.7	1.7
Mean change from baseline to Week 52 (mmol/L)	0	-0.6	-0.1	-0.6
Mean percent change from baseline to Week 52 (%)	-1.0	-33.0	-5.4	-35.2
Mean difference vs placebo (%) (95% CI)	N/A	-32.2### (-39.2, -24.3)	N/A	-31.5### (-38.5, -23.8)

Abbreviations: CI = confidence interval; CSR = clinical study report; HDL-C = high-density lipoprotein-cholesterol; mITT = modified intent to treat; MMRM = mixed model repeated measures; N = number of randomly assigned participants who received at least 1 dose of the study drug; N/A = not applicable; Study 1 = I8F-MC-GPI1; Study 2 = I8F-MC-GPI2.

Note 1: MMRM analysis.

Note 2: Shown are estimated means. Log transformations were applied to raw data.

p-Value <0.001 versus placebo, not controlled for type I error.

Change in Fasting Insulin Levels

OSA is reported to be independently associated with insulin resistance (Ip et al. 2002). Treatment-emergent changes in fasting insulin in normoglycaemic people may signal improvement in insulin sensitivity.

Using the efficacy estimand, the tirzepatide group showed statistically significant reductions compared with placebo for mean percent change of fasting insulin levels at Week 52 in both Studies 1 and 2.

Table 26 Change of Fasting Insulin from Baseline to Week 52: mITT Population – Efficacy Analysis Set

	Study 1		Study 2	
Attribute	**Placebo N = 120**	**Tirzepatide N = 114**	**Placebo N = 114**	**Tirzepatide N = 119**
Mean fasting insulin at baseline (mU/L)	17.9	22.8	20.8	17.9
Mean change of fasting insulin from baseline to Week 52 (mU/L)	-1.0	-8.9	-1.1	-9.3
Mean percent change of fasting insulin from baseline to Week 52 (%)	-4.7	-44.2	-5.6	-48.5
Mean difference vs placebo (%) (95% CI)	N/A	-41.4### (-50.5, -30.6)	N/A	-45.4### (-55.1, -33.7)

Abbreviations: CI = confidence interval; CSR = clinical study report; mITT = modified intent to treat; MMRM = mixed model repeated measures; N = number of randomly assigned participants who received at least 1 dose of the study drug; N/A = not applicable; Study 1 = I8F-MC-GPI1; Study 2 = I8F-MC-GPI2.

Note: MMRM analysis.

Note 2: Shown are the estimated means.

Note 3: Log transformations were applied to raw data.

p-Value <0.001 versus placebo; not controlled for type I error.

Ancillary analyses

Comparison of Results in Subpopulations

Subgroup analyses on primary endpoint of change in AHI values from baseline to Week 52 were conducted for several participant characteristics (age: <50 vs ≥50 years; gender; OSA severity at baseline: not severe vs severe; region of enrolment: US vs, outside of US; race; ethnicity; baseline BMI: <35, ≥35 kg/m^2 and <40, ≥40 kg/m^2; ESS at baseline: ≤10 vs >10).

Using the efficacy estimand, all but Black or African American subgroup generally showed a significantly better AHI reduction in the tirzepatide group compared with the placebo group for both Studies 1 and 2. As expected, the treatment difference for mean change from baseline in AHI was lower in the "not severe" baseline AHI subgroup compared with the "severe" baseline AHI subgroup; the effect within all other subgroups was generally consistent with the overall treatment effect in both studies.

A p-value of 0.091 was reported for race by treatment interaction effect in Study 2. While the number of Black or African American participants was representative for the US population, the overall sample size was small and poorly balanced between the placebo and tirzepatide groups. Therefore, the insignificant result may not represent a signal of different treatment based on race or ethnicity.

Summary of main studies

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Title: Study 1 (I8F-MC-GPI1 A Master Protocol to Investigate the Efficacy and Safety of Tirzepatide Once Weekly in Participants who have Obstructive Sleep Apnoea and Obesity: A Randomized, Double-Blind, Placebo-Controlled Trial (SURMOUNT-OSA) In Participants with OSA Unable or Unwilling to use PAP Therapy		
Design	Multi-centre, randomized, parallel-arm, double-blind, placebo-controlled Phase 3 study to evaluate the efficacy and safety of tirzepatide at the MTD (10 mg or 15 mg) QW versus placebo in participants who have obesity and moderate-to-severe OSA. Study 1 included participants with OSA who were unable or unwilling to use PAP therapy and had not used PAP for at least 4 weeks prior to Visit 1.	
	Duration of Screening	4 weeks
	Duration of Treatment Period	52 weeks
	Duration of Posttreatment Follow-Up	4 weeks
Hypothesis	The primary objective is to demonstrate that tirzepatide at the MTD (10 mg or 15 mg) QW is superior to placebo in treating participants with OSA with respect to the change in AHI. Thus, the null hypotheses will be defined as below. • Null hypothesis: Tirzepatide at the MTD (10 mg or 15 mg) QW is not different from the placebo with respect to the mean change from baseline in AHI at 52 weeks.	
Treatment Groups	Placebo, QW	120 participants were randomized and received at least 1 dose of study drug
	Tirzepatide at the MTD (10 mg or 15 mg), QW	114 participants were randomized and received at least 1 dose of study drug
Endpoints and Definitions	Primary Endpoint	Change in AHI from baseline to Week 52
	Key Secondary Endpoints (controlled for Type 1 error for multiplicity)	Percent change in AHI (from baseline to Week 52)
		Percent of participants with ≥50% AHI reduction (from baseline to Week 52)
		Percent of participants with • AHI <5 events/h, or • AHI 5-14 events/h with ESS ≤10 (from baseline to Week 52)
		Change in SASHB (% min/h) (from baseline to Week 52)
		Percent change in body weight (from baseline to Week 52)

		Change in hsCRP concentration (from baseline to Week 52)		
		Change in SBP (from baseline to Week 48[a])		
		Change in[b]: (from baseline to Week 52) • PROMIS SRI • PROMIS SD		
	Other Secondary Endpoints	Proportion of participants achieving clinically meaningful within-patient change in (from baseline to Week 52): • PROMIS SRI • PROMIS SD		
		Change in ESS score (from baseline to Week 52)		
		Change in FOSQ-10 score (from baseline to Week 52) Change in FOSQ (30 items) score (from baseline to Week 52) Change in all FOSQ domain scores (from baseline to Week 52)		
		Change in (from baseline to Week 52) • HDL-cholesterol • non-HDL-cholesterol • triglycerides		
		Change in fasting insulin (from baseline to Week 52)		
Database Lock	10 April 2024 (primary outcome database lock)			
Results and Analysis				
1. Efficacy on Sleep-Disordered Breathing Endpoints				
Analysis Description	**Primary Endpoint: Change in AHI at Week 52**			
Analysis population and time point description	***Treatment-Regimen Estimand (Full Analysis Set), 52 weeks:*** The average treatment effect of tirzepatide relative to placebo after 52 weeks in treated participants with obesity and OSA, regardless of intervention discontinuation for any reason. Includes all available data obtained during the treatment period from randomly assigned participants who were exposed to at least 1 dose of study drug (mITT population; N=234) regardless of adherence to study drug.			
Descriptive statistics, estimate variability, and estimate of effect	**Treatment group[c] (number of participants)**	**Units**	**Placebo (N=120)**	**Tirzepatide MTD (N=114)**
	LS mean AHI at baseline	events/h	50.13	52.86
	LS mean change from baseline to Week 52	events/h	-5.25	-25.25
	Within-treatment p-value	-	0.013	<0.001

	LS mean difference from placebo (95% CI)	events/h	-	-20.01 (-25.82, -14.20)
	Between-treatment p-value	-	-	<0.001
Analysis Description	**Key Secondary Endpoint: Percent change in AHI at Week 52**			
Analysis population and time point description	***Treatment-Regimen Estimand (Full Analysis Set), 52 weeks***			
Descriptive statistics, estimate variability, and estimate of effect	**Treatment group[c] (number of participants)**	**Units**	**Placebo (N=120)**	**Tirzepatide MTD (N=114)**
	LS mean AHI at baseline	events/h	50.13	52.86
	LS mean percent change from baseline to Week 52	%	-3.03	-50.68
	Within-treatment p-value	-	0.668	<0.001
	LS mean percent difference from placebo (95% CI)	%	-	-47.65 (-65.76, -29.55)
	Between-treatment p-value	-	-	<0.001
Analysis Description	**Key Secondary Endpoint: Percentage of participants with ≥50% AHI reduction from baseline at Week 52**			
Analysis population and time point description	***Treatment-Regimen Estimand (Full Analysis Set), 52 weeks***			
Descriptive statistics, estimate variability, and estimate of effect	**Treatment group[e] (number of participants)**	**Units**	**Placebo (N=120)**	**Tirzepatide MTD (N=114)**
	Percentage of participants with ≥50% AHI reduction at Week 52	%	18.96	61.22
	OR (95% CI)[f]	-	-	7.33 (3.75, 14.34)
	Between-treatment p-value[f]	-	-	<0.001
Analysis Description	**Key Secondary Endpoint: Percentage of participants with AHI <5 or AHI 5-14 with ESS ≤10 at Week 52**			
Analysis population and time point description	***Treatment-Regimen Estimand (Full Analysis Set), 52 weeks***			
Descriptive statistics, estimate variability, and estimate of effect	**Treatment group[e] (number of participants)**	**Units**	**Placebo (N=120)**	**Tirzepatide MTD (N=114)**
	Percentage of participants with AHI <5 or AHI 5-14 with ESS ≤10	%	15.88	42.17
	OR (95% CI)[f]	-	-	7.32 (3.16, 16.95)

	Between-treatment p-value[f]	-	-	<0.001
Analysis Description	**Key Secondary Endpoint: Change in hypoxic burden (SASHB) at Week 52**			
Analysis population and time point description	***Treatment-Regimen Estimand (Full Analysis Set), 52 weeks***			
Descriptive statistics, estimate variability, and estimate of effect	**Treatment group[c,g] (number of participants)**	**Units**	**Placebo (N=120)**	**Tirzepatide MTD (N=114)**
	Baseline geometric mean	% min/h	137.80	153.60
	Mean change from baseline to Week 52	% min/h	-25.07	-95.19
	Difference from placebo (95% CI)	% min/h	-	-70.13 (-90.94, -49.31)
	Week 52: Percent change from baseline	%	-17.25	-65.52
	Within-treatment p-value	-	0.020	<0.001
	Difference from placebo (95% CI)	%	-	-58.33 (-66.80, -47.70)
	Between-treatment p-value	-	-	<0.001
2. Patient-Reported Outcomes				
Analysis Description	**Key Secondary Endpoint: Change in PROMIS SRI T-score at Week 52**			
Analysis population and time point description	***Treatment-Regimen Estimand (Full Analysis Set), 52 weeks***			
Descriptive statistics, estimate variability, and estimate of effect	**Treatment group[c] (number of participants)**	**Units**	**Placebo (N=120)**	**Tirzepatide MTD (N=114)**
	LS mean PROMIS SRI score at baseline	-	54.65	53.45
	LS mean change from baseline to Week 52	-	-3.13	-6.57
	Within-treatment p-value	-	<0.001	<0.001
	LS mean difference from placebo (95% CI)	-	-	-3.43 (-5.69, -1.17)
	Between-treatment p-value	-	-	0.003[h]
Analysis Description	**Key Secondary Endpoint: Change in PROMIS SD T-score at Week 52**			
Analysis population and time point description	***Treatment-Regimen Estimand (Full Analysis Set), 52 weeks***			

Descriptive statistics, estimate variability, and estimate of effect	**Treatment group[c] (number of participants)**	**Units**	**Placebo (N=120)**	**Tirzepatide MTD (N=114)**
	LS mean PROMIS SD score at baseline	-	53.76	53.87
	LS mean change from baseline to Week 52	-	-2.44	-4.47
	Within-treatment p-value	-	<0.001	<0.001
	LS mean difference from placebo (95% CI)	-	-	-2.03 (-3.95, -0.12)
	Between-treatment p-value	-	-	0.037[h]
Analysis Description	**Other Secondary Endpoint: MWPC in PROMIS SRI at Week 52**			
Analysis population and time point description	***Efficacy Estimand (Efficacy Analysis Set), 52 weeks***			
Descriptive statistics, estimate variability, and estimate of effect	**Treatment group[e] (number of participants)**	**Units**	**Placebo (N=120)**	**Tirzepatide MTD (N=114)**
	Percentage of participants with MWPC	%	26.58	44.41
	OR (95% CI)[f]	-	-	3.15 (1.5, 6.65)
	Between-treatment p-value[f]	-	-	0.003[h]
Analysis Description	**Other Secondary Endpoint: MWPC in PROMIS SD at Week 52**			
Analysis population and time point description	***Efficacy Estimand (Efficacy Analysis Set), 52 weeks***			
Descriptive statistics, estimate variability, and estimate of effect	**Treatment group[e] (number of participants)**	**Units**	**Placebo (N=120)**	**Tirzepatide MTD (N=114)**
	Percentage of participants with MWPC	%	24.83	35.76
	OR (95% CI)[f]	-	-	2.04 (1.00, 4.16)
	Between-treatment p-value[f]	-	-	0.049[h]
Analysis Description	**Other Secondary Endpoint: Change in ESS Score at Week 52**			
Analysis population and time point description	***Efficacy Estimand (Efficacy Analysis Set), 52 weeks***			
Descriptive statistics, estimate variability, and estimate of effect	**Treatment group[d] (number of participants)**	**Units**	**Placebo (N=120)**	**Tirzepatide MTD (N=114)**
	LS mean ESS score at baseline	-	10.70	10.27

	LS mean change from baseline to Week 52	-	-1.62	-3.17
	Within-treatment p-value	-	0.001	<0.001
	LS mean difference from placebo (95% CI)	-	-	-1.55 (-2.90, -0.21)
	Between-treatment p-value	-	-	0.024[h]
Analysis Description	**Other Secondary Endpoint: Change in FOSQ (30 item) Total and Domain Scores at Week 52**			
Analysis population and time point description	***Efficacy Estimand (Efficacy Analysis Set), 52 weeks***			
Descriptive statistics, estimate variability, and estimate of effect	**Treatment group[d] (number of participants)**	**Units**	**Placebo (N=120)**	**Tirzepatide MTD (N=114)**
	FOSQ (30 item) Total Score			
	LS mean score at baseline	-	15.7	16.3
	LS mean change from baseline to Week 52	-	0.8	1.5
	Within-treatment p-value	-	0.007	<0.001
	LS mean difference from placebo (95% CI)	-	-	0.7 (-0.1, 1.5)
	Between-treatment p-value	-	-	0.068[h]
Analysis Description	**Other Secondary Endpoint: Change in FOSQ-10 Score at Week 52**			
Analysis population and time point description	***Efficacy Estimand (Efficacy Analysis Set), 52 weeks***			
Descriptive statistics, estimate variability, and estimate of effect	**Treatment group[d] (number of participants)**	**Units**	**Placebo (N=120)**	**Tirzepatide MTD (N=114)**
	LS mean FOSQ-10 score at baseline	-	15.0	15.6
	LS mean change from baseline to Week 52	-	1.1	1.8
	Within-treatment p-value	-	<0.001	<0.001
	LS mean difference from placebo (95% CI)	-	-	0.7 (-0.1, 1.6)
	Between-treatment p-value	-	-	0.102[h]
3. OSA-Related Cardiovascular Risk Factors				
Analysis Description	**Key Secondary Endpoint: Change in hsCRP Concentration at Week 52**			

Analysis population and time point description	***Treatment-Regimen Estimand (Full Analysis Set), 52 weeks***			
Descriptive statistics, estimate variability, and estimate of effect	**Treatment group[c,g] (number of participants)**	**Units**	**Placebo (N=120)**	**Tirzepatide MTD (N=114)**
	Baseline geometric mean	mg/L	3.60	3.46
	Mean change from baseline to Week 52	mg/L	-0.70	-1.42
	Difference from placebo (95% CI)	mg/L	-	-0.71 (-1.21, -0.22)
	Week 52: Percent change from baseline	%	-19.85	-40.07
	Within-treatment p-value	-	0.002	<0.001
	Difference from placebo (95% CI)	%	-	-25.23 (-38.62, -8.92)
	Between-treatment p-value	-	-	0.004
Analysis Description	**Key Secondary Endpoint: Change in SBP at Week 48[a]**			
Analysis population and time point description	***Treatment-Regimen Estimand (Full Analysis Set), 48 weeks:*** The average treatment effect of tirzepatide relative to placebo after 48 weeks in treated participants with obesity and OSA, regardless of intervention discontinuation for any reason. Includes all available data obtained during the treatment period from randomly assigned participants who were exposed to at least 1 dose of study drug (mITT population; N=234) regardless of adherence to study drug.			
Descriptive statistics, estimate variability, and estimate of effect	**Treatment group[i] (number of participants)**	**Units**	**Placebo (N=120)**	**Tirzepatide MTD (N=114)**
	LS mean SBP at baseline	mmHg	130.33	128.44
	LS mean change from baseline to Week 48	mmHg	-1.84	-9.46
	Within-treatment p-value	-	0.074	<0.001
	LS mean difference from placebo (95% CI)	mmHg	-	-7.62 (-10.48, -4.77)
	Between-treatment p-value	-	-	<0.001
Analysis Description	**Other Secondary Endpoint: Change in Lipid Levels at Week 52**			
Analysis population and time point description	***Efficacy Estimand (Efficacy Analysis Set), 52 weeks***			
Descriptive statistics, estimate variability, and estimate of effect	**Treatment group[d,g] (number of participants)**	**Units**	**Placebo (N=120)**	**Tirzepatide MTD (N=114)**
	HDL-C			

	Baseline geometric mean	mmol/L	1.16	1.11
	Mean change from baseline to Week 52	mmol/L	0.04	0.12
	Difference from placebo (95% CI)	mmol/L	-	0.08 (0.04, 0.13)
	Week 52: Percent change from baseline	%	3.13	10.58
	Within-treatment p-value	-	0.031	<0.001
	Difference from placebo (95% CI)	%	-	7.22 (3.16, 11.44)
	Between-treatment p-value	-	-	<0.001[h]
	Non-HDL-C			
	Baseline geometric mean	mmol/L	3.66	3.79
	Mean change from baseline to Week 52	mmol/L	-0.09	-0.56
	Difference from placebo (95% CI)	mmol/L	-	-0.47 (-0.71, -0.23)
	Week 52: Percent change from baseline	%	-2.30	-14.97
	Within-treatment p-value	-	0.373	<0.001
	Difference from placebo (95% CI)	%	-	-12.97 (-18.95, -6.56)
	Between-treatment p-value	-	-	<0.001[h]
	Triglycerides			
	Baseline geometric mean	mmol/L	1.71	1.69
	Mean change from baseline to Week 52	mmol/L	-0.2	-0.56
	Difference from placebo (95% CI)	mmol/L	-	-0.54 (-0.70, -0.38)
	Week 52: Percent change from baseline	%	-1.02	-32.85
	Within-treatment p-value	-	0.799	<0.001
	Difference from placebo (95% CI)	%	-	-32.16 (-39.17, -24.34)
	Between-treatment p-value	-	-	<0.001[h]
Analysis Description	**Other Secondary Endpoint: Change in Fasting Insulin Levels at Week 52**			
Analysis population and time point description	***Efficacy Estimand (Efficacy Analysis Set), 52 weeks***			

Descriptive statistics, estimate variability, and estimate of effect	**Treatment group[d,g] (number of participants)**	**Units**	**Placebo (N=120)**	**Tirzepatide MTD (N=114)**
	Baseline geometric mean	mU/L	17.91	22.79
	Mean change from baseline to Week 52	mU/L	-0.96	-8.95
	Difference from placebo (95% CI)	mU/L	-	-7.99 (-10.67, -5.30)
	Week 52: Percent change from baseline	%	-4.74	-44.17
	Within-treatment p-value	-	0.436	<0.001
	Difference from placebo (95% CI)	%	-	-41.39 (-50.52, -30.57)
	Between-treatment p-value	-	-	<0.001[h]
Analysis Description	**Key Secondary Endpoint: Percent Change in Body Weight at Week 52**			
Analysis population and time point description	***Treatment-Regimen Estimand (Full Analysis Set), 52 weeks***			
Descriptive statistics, estimate variability, and estimate of effect	**Treatment group[c] (number of participants)**	**Units**	**Placebo (N=120)**	**Tirzepatide MTD (N=114)**
	LS mean body weight at baseline	kg	112.77	116.67
	LS mean percent change from baseline to Week 52	%	-1.56	-17.65
	Within-treatment p-value	-	0.021	<0.001
	LS mean percent difference from placebo (95% CI)	%	-	-16.09 (-17.99, -14.19)
	Between-treatment p-value	-	-	<0.001

Abbreviations: AHI = Apnoea-Hypopnoea Index; ANCOVA = analysis of covariance; BP = blood pressure; CI = confidence interval; ESS = Epworth Sleepiness Scale; FOSQ = Functional Outcomes of Sleep Questionnaire; HDL-C = high-density lipoprotein-cholesterol; hsCRP = high-sensitivity C-reactive protein; LS = least squares; mITT = modified intent-to-treat; MMRM = mixed model for repeated measures; MTD = maximum tolerated dose; MWPC = meaningful within-patient change; N = number of randomly assigned participants who received at least 1 dose of study drug; OR = odds ratio; OSA = obstructive sleep apnoea; PAP = positive airway pressure; PROMIS = Patient-Reported Outcomes Measurement Information System; QW = once weekly; SASHB = sleep apnoea-specific hypoxic burden; SBP = systolic blood pressure; SD = sleep disturbance; SRI = sleep-related impairment.

[a] BP was assessed at Week 48 to eliminate confounding effect of PAP withdrawal in Study 2.

[b] PROMIS-related endpoints are tested in the graphical testing scheme only as a pooled analysis, subject to submission-wise type 1 error rate control (Vandemeulebroecke et al. 2024).

[c] ANCOVA with multiple imputation by treatment for missing data at Week 52.

[d] MMRM analysis.

[e] Logistic regression with multiple imputation for missing data at 52 weeks.
[f] OR, CI, and p-value are from logistic regression analysis.
[g] Log transformations were applied to raw data.
[h] Not controlled for multiplicity.
[i] ANCOVA with multiple imputation by treatment for missing data at Week 48.

Title: Study 2 (I8F-MC-GPI2) A Master Protocol to Investigate the Efficacy and Safety of Tirzepatide Once Weekly in Participants who have Obstructive Sleep Apnoea and Obesity: A Randomized, Double-Blind, Placebo-Controlled Trial (SURMOUNT-OSA) In Participants with OSA on PAP Therapy		
Design	Multi-centre, randomized, parallel-arm, double-blind, placebo-controlled Phase 3 study to evaluate the efficacy and safety of tirzepatide at the MTD (10 mg or 15 mg) QW versus placebo in participants who have obesity and moderate-to-severe OSA. Study 2 included participants who were on PAP therapy for at least 3 months at the time of Visit 1 and planned to continue PAP therapy during the study.	
	Duration of Screening	4 weeks
	Duration of Treatment Period	52 weeks
	Duration of Posttreatment Follow-Up	4 weeks
Hypothesis	The primary objective is to demonstrate that tirzepatide at the MTD (10 mg or 15 mg) QW is superior to placebo in treating participants with OSA with respect to the change in AHI. Thus, the null hypotheses will be defined as below. • Null hypothesis: Tirzepatide at the MTD (10 mg or 15 mg) QW is not different from the placebo with respect to the mean change from baseline in AHI at 52 weeks..	
Treatment Groups	Placebo, QW	114 participants were randomized and received at least 1 dose of study drug
	Tirzepatide at the MTD (10 mg or 15 mg), QW	119 participants were randomized and received at least 1 dose of study drug
Endpoints and D efinitions	Primary Endpoint	Change in AHI from baseline to Week 52
	Key Secondary Endpoints (controlled for Type 1 error for multiplicity)	Percent change in AHI (from baseline to Week 52)
		Percent of participants with ≥50% AHI reduction (from baseline to Week 52)
		Percent of participants with • AHI <5 events/h, or • AHI 5-14 events/h with ESS ≤10 (from baseline to Week 52)
		Change in SASHB (% min/h) (from baseline to Week 52)
		Percent change in body weight (from baseline to Week 52)
		Change in hsCRP concentration (from baseline to Week 52)
		Change in SBP (from baseline to Week 48[a])

		Change in[b]: (from baseline to Week 52) • PROMIS SRI • PROMIS SD
	Other Secondary Endpoints	Proportion of participants achieving clinically meaningful within-patient change in (from baseline to Week 52): • PROMIS SRI • PROMIS SD
		Change in ESS score (from baseline to Week 52)
		Change in FOSQ-10 score (from baseline to Week 52) Change in FOSQ (30 items) score (from baseline to Week 52) Change in all FOSQ domain scores (from baseline to Week 52)
		Change in (from baseline to Week 52) • HDL-cholesterol • non-HDL-cholesterol • triglycerides
		Change in fasting insulin (from baseline to Week 52)
Database Lock	10 April 2024 (primary outcome database lock)	
Results and Analysis		
1. Efficacy on Sleep-Disordered Breathing Endpoints		

Analysis Description	**Primary Endpoint: Change in AHI at Week 52**			
Analysis population and time point description	***Treatment-Regimen Estimand (Full Analysis Set), 52 weeks:*** The average treatment effect of tirzepatide relative to placebo after 52 weeks in treated participants with obesity and OSA, regardless of intervention discontinuation for any reason. Includes all available data obtained during the treatment period from randomly assigned participants who were exposed to at least 1 dose of study drug (mITT population; N=233) regardless of adherence to study drug.			
Descriptive statistics, estimate variability, and estimate of effect	**Treatment group[c] (number of participants)**	**Units**	**Placebo (N=114)**	**Tirzepatide MTD (N=119)**
	LS mean AHI at baseline	events/h	53.10	46.08
	LS mean change from baseline to Week 52	events/h	-5.51	-29.27
	Within-treatment p-value	-	0.013	<0.001
	LS mean difference from placebo (95% CI)	events/h	-	-23.77 (-29.61, -17.93)

	Between-treatment p-value	-	-	<0.001
Analysis Description	**Key Secondary Endpoint: Percent change in AHI at Week 52**			
Analysis population and time point description	***Treatment-Regimen Estimand (Full Analysis Set), 52 weeks***			
Descriptive statistics, estimate variability, and estimate of effect	**Treatment group[c] (number of participants)**	**Units**	**Placebo (N=114)**	**Tirzepatide MTD (N=119)**
	LS mean AHI at baseline	events/h	53.10	46.08
	LS mean percent change from baseline to Week 52	%	-2.50	-58.72
	Within-treatment p-value	-	0.719	<0.001
	LS mean percent difference from placebo (95% CI)	%	-	-56.21 (-73.73, -38.70)
	Between-treatment p-value	-	-	<0.001
Analysis Description	**Key Secondary Endpoint: Percentage of participants with ≥50% AHI reduction from baseline at Week 52**			
Analysis population and time point description	***Treatment-Regimen Estimand (Full Analysis Set), 52 weeks***			
Descriptive statistics, estimate variability, and estimate of effect	**Treatment group[e] (number of participants)**	**Units**	**Placebo (N=114)**	**Tirzepatide MTD (N=119)**
	Percentage of participants with ≥50% AHI reduction at Week 52	%	23.25	72.40
	OR (95% CI)[f]	-	-	8.19 (4.32, 15.54)
	Between-treatment p-value[f]	-	-	<0.001
Analysis Description	**Key Secondary Endpoint: Percentage of participants with AHI <5 or AHI 5-14 with ESS ≤10 at Week 52**			
Analysis population and time point description	***Treatment-Regimen Estimand (Full Analysis Set), 52 weeks***			
Descriptive statistics, estimate variability, and estimate of effect	**Treatment group[e] (number of participants)**	**Units**	**Placebo (N=114)**	**Tirzepatide MTD (N=119)**
	Percentage of participants with AHI <5 or AHI 5-14 with ESS ≤10	%	14.33	50.24
	OR (95% CI)[f]	-	-	6.62 (3.14, 13.96)
	Between-treatment p-value[f]	-	-	<0.001

Analysis Description	**Key Secondary Endpoint: Change in hypoxic burden (SASHB) at Week 52**			
Analysis population and time point description	***Treatment-Regimen Estimand (Full Analysis Set), 52 weeks***			
Descriptive statistics, estimate variability, and estimate of effect	**Treatment group[c,g] (number of participants)**	**Units**	**Placebo (N=114)**	**Tirzepatide MTD (N=119)**
	Baseline geometric mean	% min/h	142.10	132.20
	Mean change from baseline to Week 52	% min/h	-41.69	-102.98
	Difference from placebo (95% CI)	% min/h	-	-61.29 (-84.66, -37.93)
	Week 52: Percent change from baseline	%	-30.44	-75.19
	Within-treatment p-value	-	0.002	<0.001
	Difference from placebo (95% CI)	%	-	-64.34 (-74.08, -50.94)
	Between-treatment p-value	-	-	<0.001
2. Patient-Reported Outcomes				
Analysis Description	**Key Secondary Endpoint: Change in PROMIS SRI T-score at Week 52**			
Analysis population and time point description	***Treatment-Regimen Estimand (Full Analysis Set), 52 weeks***			
Descriptive statistics, estimate variability, and estimate of effect	**Treatment group[c] (number of participants)**	**Units**	**Placebo (N=114)**	**Tirzepatide MTD (N=119)**
	LS mean PROMIS SRI score at baseline	-	55.17	55.60
	LS mean change from baseline to Week 52	-	-3.91	-8.18
	Within-treatment p-value	-	<0.001	<0.001
	LS mean difference from placebo (95% CI)	-	-	-4.26 (-6.97, -1.56)
	Between-treatment p-value	-	-	0.002[h]
Analysis Description	**Key Secondary Endpoint: Change in PROMIS SD T-score at Week 52**			
Analysis population and time point description	***Treatment-Regimen Estimand (Full Analysis Set), 52 weeks***			
	Treatment group[c] (number of participants)	**Units**	**Placebo (N=114)**	**Tirzepatide MTD (N=119)**

Descriptive statistics, estimate variability, and estimate of effect	LS mean PROMIS SD score at baseline	-	56.06	56.15
	LS mean change from baseline to Week 52	-	-3.08	-6.98
	Within-treatment p-value	-	<0.001	<0.001
	LS mean difference from placebo (95% CI)	-	-	-3.90 (-6.21, -1.58)
	Between-treatment p-value	-	-	<0.001[h]
Analysis Description	**Other Secondary Endpoint: MWPC in PROMIS SRI at Week 52**			
Analysis population and time point description	***Efficacy Estimand (Efficacy Analysis Set), 52 weeks***			
Descriptive statistics, estimate variability, and estimate of effect	**Treatment group[e] (number of participants)**	**Units**	**Placebo (N=114)**	**Tirzepatide MTD (N=119)**
	Percentage of participants with MWPC	%	23.09	39.08
	OR (95% CI)[f]	-	-	2.44 (1.13, 5.24)
	Between-treatment p-value[f]	-	-	0.023[h]
Analysis Description	**Other Secondary Endpoint: MWPC in PROMIS SD at Week 52**			
Analysis population and time point description	***Efficacy Estimand (Efficacy Analysis Set), 52 weeks***			
Descriptive statistics, estimate variability, and estimate of effect	**Treatment group[e] (number of participants)**	**Units**	**Placebo (N=114)**	**Tirzepatide MTD (N=119)**
	Percentage of participants with MWPC	%	27.22	46.06
	OR (95% CI)[f]	-	-	2.62 (1.25, 5.50)
	Between-treatment p-value[f]	-	-	0.011[h]
Analysis Description	**Other Secondary Endpoint: Change in ESS Score at Week 52**			
Analysis population and time point description	***Efficacy Estimand (Efficacy Analysis Set), 52 weeks***			
Descriptive statistics, estimate variability, and estimate of effect	**Treatment group[d] (number of participants)**	**Units**	**Placebo (N=114)**	**Tirzepatide MTD (N=119)**
	LS mean ESS score at baseline	-	9.47	10.76
	LS mean change from baseline to Week 52	-	-2.91	-3.58

	Within-treatment p-value	-	<0.001	<0.001
	LS mean difference from placebo (95% CI)	-	-	-0.67 (-1.96, 0.62)
	Between-treatment p-value	-	-	0.305[h]
Analysis Description	**Other Secondary Endpoint: Change in FOSQ (30 item) Total and Domain Scores at Week 52**			
Analysis population and time point description	***Efficacy Estimand (Efficacy Analysis Set), 52 weeks***			
Descriptive statistics, estimate variability, and estimate of effect	**Treatment group[d] (number of participants)**	**Units**	**Placebo (N=114)**	**Tirzepatide MTD (N=119)**
	FOSQ (30 item) Total Score			
	LS mean score at baseline	-	16.1	16.3
	LS mean change from baseline to Week 52	-	1.9	2.2
	Within-treatment p-value	-	<0.001	<0.001
	LS mean difference from placebo (95% CI)	-	-	0.3 (-0.2, 0.8)
	Between-treatment p-value	-	-	0.263[h]
Analysis Description	**Other Secondary Endpoint: Change in FOSQ-10 Score at Week 52**			
Analysis population and time point description	***Efficacy Estimand (Efficacy Analysis Set), 52 weeks***			
Descriptive statistics, estimate variability, and estimate of effect	**Treatment group[d] (number of participants)**	**Units**	**Placebo (N=114)**	**Tirzepatide MTD (N=119)**
	LS mean FOSQ-10 score at baseline	-	15.7	15.8
	LS mean change from baseline to Week 52	-	2.0	2.4
	Within-treatment p-value	-	<0.001	<0.001
	LS mean difference from placebo (95% CI)	-	-	0.5 (-0.1, 1.1)
	Between-treatment p-value	-	-	0.123[h]
3. OSA-Related Cardiovascular Risk Factors				
Analysis Description	**Key Secondary Endpoint: Change in hsCRP Concentration at Week 52**			
Analysis population and time point description	***Treatment-Regimen Estimand (Full Analysis Set), 52 weeks***			

Descriptive statistics, estimate variability, and estimate of effect	**Treatment group[c,g] (number of participants)**	**Units**	**Placebo (N=114)**	**Tirzepatide MTD (N=119)**
	Baseline geometric mean	mg/L	2.66	3.01
	Mean change from baseline to Week 52	mg/L	-0.33	-1.37
	Difference from placebo (95% CI)	mg/L	-	-1.04 (-1.57, -0.51)
	Week 52: Percent change from baseline	%	-11.47	-48.19
	Within-treatment p-value	-	0.195	<0.001
	Difference from placebo (95% CI)	%	-	-41.48 (-54.49, -24.75)
	Between-treatment p-value	-	-	<0.001
Analysis Description	**Key Secondary Endpoint: Change in SBP at Week 48[a]**			
Analysis population and time point description	***Treatment-Regimen Estimand (Full Analysis Set), 48 weeks:*** The average treatment effect of tirzepatide relative to placebo after 48 weeks in treated participants with obesity and OSA, regardless of intervention discontinuation for any reason. Includes all available data obtained during the treatment period from randomly assigned participants who were exposed to at least 1 dose of study drug (mITT population; N=233) regardless of adherence to study drug.			
Descriptive statistics, estimate variability, and estimate of effect	**Treatment group[i] (number of participants)**	**Units**	**Placebo (N=114)**	**Tirzepatide MTD (N=119)**
	LS mean SBP at baseline	mmHg	130.50	130.50
	LS mean change from baseline to Week 48	mmHg	-3.94	-7.64
	Within-treatment p-value	-	<0.001	<0.001
	LS mean difference from placebo (95% CI)	mmHg	-	-3.70 (-6.75, -0.65)
	Between-treatment p-value	-	-	0.017
Analysis Description	**Other Secondary Endpoint: Change in Lipid Levels at Week 52**			
Analysis population and time point description	***Efficacy Estimand (Efficacy Analysis Set), 52 weeks***			
Descriptive statistics, estimate variability, and estimate of effect	**Treatment group[d,g] (number of participants)**	**Units**	**Placebo (N=114)**	**Tirzepatide MTD (N=119)**
	HDL-C			
	Baseline geometric mean	mmol/L	1.16	1.10

	Mean change from baseline to Week 52	mmol/L	0.05	0.17
	Difference from placebo (95% CI)	mmol/L	-	0.12 (0.06, 0.18)
	Week 52: Percent change from baseline	%	4.51	14.98
	Within-treatment p-value	-	0.021	<0.001
	Difference from placebo (95% CI)	%	-	10.02 (4.61, 15.71)
	Between-treatment p-value	-	-	<0.001[h]
	Non-HDL-C			
	Baseline geometric mean	mmol/L	3.52	3.79
	Mean change from baseline to Week 52	mmol/L	-0.07	-0.58
	Difference from placebo (95% CI)	mmol/L	-	-0.51 (-0.71, -0.32)
	Week 52: Percent change from baseline	%	-1.80	-15.84
	Within-treatment p-value	-	0.406	<0.001
	Difference from placebo (95% CI)	%	-	-14.30 (-19.12, -9.18)
	Between-treatment p-value	-	-	<0.001[h]
	Triglycerides			
	Baseline geometric mean	mmol/L	1.66	1.68
	Mean change from baseline to Week 52	mmol/L	-0.09	-0.59
	Difference from placebo (95% CI)	mmol/L	-	-0.50 (-0.65, -0.35)
	Week 52: Percent change from baseline	%	-5.43	-35.24
	Within-treatment p-value	-	0.171	<0.001
	Difference from placebo (95% CI)	%	-	-31.52 (-38.49, -23.76)
	Between-treatment p-value	-	-	<0.001[h]
Analysis Description	**Other Secondary Endpoint: Change in fasting insulin levels at Week 52**			
Analysis population and time point description	***Efficacy Estimand (Efficacy Analysis Set), 52 weeks***			

Descriptive statistics, estimate variability, and estimate of effect	**Treatment group[d,g] (number of participants)**	**Units**	**Placebo (N=114)**	**Tirzepatide MTD (N=119)**
	Baseline geometric mean	mU/L	20.75	17.86
	Mean change from baseline to Week 52	mU/L	-1.07	-9.28
	Difference from placebo (95% CI)	mU/L	-	-8.21 (-11.09, -5.33)
	Week 52: Percent change from baseline	%	-5.59	-48.48
	Within-treatment p-value	-	0.430	<0.001
	Difference from placebo (95% CI)	%	-	-45.43 (-55.10, -33.67)
	Between-treatment p-value	-	-	<0.001[h]
Analysis Description	**Key Secondary Endpoint: Percent Change in Body Weight at Week 52**			
Analysis population and time point description	***Treatment-Regimen Estimand (Full Analysis Set), 52 weeks***			
Descriptive statistics, estimate variability, and estimate of effect	**Treatment group[c] (number of participants)**	**Units**	**Placebo (N=114)**	**Tirzepatide MTD (N=119)**
	LS mean body weight at baseline	kg	115.09	115.82
	LS mean percent change from baseline to Week 52	%	-2.34	-19.62
	Within-treatment p-value	-	0.002	<0.001
	LS mean percent difference from placebo (95% CI)	%	-	-17.28 (-19.29, -15.28)
	Between-treatment p-value	-	-	<0.001

Abbreviations: AHI = Apnoea-Hypopnoea Index; ANCOVA = analysis of covariance; BP = blood pressure; CI = confidence interval; ESS = Epworth Sleepiness Scale; FOSQ = Functional Outcomes of Sleep Questionnaire; HDL-C = high-density lipoprotein-cholesterol; hsCRP = high-sensitivity C-reactive protein; LS = least squares; mITT = modified intent-to-treat; MMRM = mixed model for repeated measures; MTD = maximum tolerated dose; MWPC = meaningful within-patient change; N = number of randomly assigned participants who received at least 1 dose of study drug; OR = odds ratio; OSA = obstructive sleep apnoea; PAP = positive airway pressure; PROMIS = Patient-Reported Outcomes Measurement Information System; QW = once weekly; SASHB = sleep apnoea-specific hypoxic burden; SBP = systolic blood pressure; SD = sleep disturbance; SRI = sleep-related impairment.

a BP was assessed at Week 48 to eliminate confounding effect of PAP withdrawal in Study 2.

b PROMIS-related endpoints are tested in the graphical testing scheme only as a pooled analysis, subject to submission-wide type 1 error rate control (Vandemeulebroecke et al. 2024).

c ANCOVA with multiple imputation by treatment for missing data at Week 52.

d MMRM analysis.

[e] Logistic regression with multiple imputation for missing data at 52 weeks.
[f] OR, CI, and p-value are from logistic regression analysis.
[g] Log transformations were applied to raw data.
[h] Not controlled for multiplicity.
[i] ANCOVA with multiple imputation by treatment for missing data at Week 48.

4.4.3. Discussion on clinical efficacy

Tirzepatide (Mounjaro) is currently approved for the treatment of insufficiently controlled T2DM and for weight management in adults with an initial BMI of $\geq$ 30 kg/m^2 (obesity) or $\geq$27 kg/m^2 in the presence of at least one weight-related comorbid condition (e.g. hypertension, dyslipidaemia, CV disease, obstructive sleep apnoea and others). The present EoI variation procedure was initially intended to introduce Mounjaro for the treatment of moderate to severe OSA in adults with obesity as an adjunct to diet and exercise.

No OSA-specific molecular mode of action is claimed for tirzepatide. The beneficial effect of tirzepatide on sleep-related disordered breathing and associated symptoms in OSA is assumed to secondarily result from tirzepatide's beneficial effects in terms of weight reduction and associated metabolic parameters (BP, lipid levels, CRP, fasting insulin levels and others), which have already been demonstrated for the established indications of Mounjaro. The use of tirzepatide in OSA was tested following the same dose range (maintenance treatment at 10-15 mg MTD) and the same titration (incremental steps of 2.5 mg every 4 weeks) and dosing intervals as already approved. Hence, no dedicated phase 1 studies were conducted in support of the present EoI, which is acceptable. On the other hand, the fact that the same posology is followed for tirzepatide's use in OSA as already established in treatment of T2DM / weight reduction further underlines the assumption that no OSA-specific molecular mechanism is involved.

Design and conduct of clinical studies

To support the use of tirzepatide in patients with moderate to severe OSA and obesity, the MAH conducted two phase 3 studies which shared the general design features in terms of duration and endpoints (the identical Master Protocol), however, differed as regards the study population. Study 1 (I8F-MC-GPI1) recruited subjects who were unable or unwilling to use PAP therapy and must not have used PAP for at least 4 weeks prior to Visit 1, while study 2 (I8F-MC-GPI2) included participants that had been on PAP therapy for at least 3 consecutive months prior to Visit 1 and planned to continue PAP therapy during the study.

Positive airway pressure therapy (often referred to as continuous PAP [cPAP], and administered via nasal appliances) constitutes first choice treatment in OSA of any severity. It prevents pharyngeal collapse during sleep and diminishes obstructive sleep disordered breathing (SDB) events by stabilizing the upper airway. However, adherence to PAP has been reported to be low in a portion of patients (Gottlieb & Punjabi 2020). Being the first-line OSA therapy, the general concept of testing tirzepatide in both PAP and non-PAP OSA patient populations is endorsed.

The primary interest would be to see whether tirzepatide can bring added benefit in PAP-compliant OSA patients. Unfortunately, however, study 2 was not designed to answer this question. Participants in study 2 were instructed to suspend PAP therapy for 7 days before polysomnographic and patient-reported outcome assessments at baseline, week 20, and week 52 to minimize the confounding effect of PAP therapy on SDB and PRO assessments. All endpoints were assessed from baseline to week 52 except for BP, which was measured at week 48 to prevent confounding the assessment due to PAP withdrawal. There is literature showing that short-term withdrawal of cPAP (patients randomized to a sub-therapeutic sham-cPAP device) in patients with prior optimal cPAP adherence results in recurrence of OSA and its consequences. Withdrawal of cPAP resulted in an increased AHI at 1 and 2 weeks to a comparable degree (mean increase in AHI +31.9 [95% CI: +20.1 to +43.7] and +33.5 [95% CI: +22.4 to +44.6], respectively; $p<0.001$ for both comparisons) compared to continuation of cPAP (Schwarz E et al. 2018). Hence, the 7-day pre-assessment PAP suspension period is adequately chosen, if it is intended to prevent PAP therapy from "confounding" the PSG and PRO assessments. From the regulatory perspective,

however, the 7-day suspension of PAP prior to endpoint assessment is a drawback in the clinical significance of study 2, since it does not allow to examine the added benefit of tirzepatide in OSA on top of PAP therapy. Besides, it remains unclear whether a minimum adherence to PAP therapy during study 2 was specified according to Protocol provisions. In the past, adequate adherence was defined as use for at least 4 hours per night for at least 5 nights per week (Gottlieb & Punjabi 2020).

In both parallel arm pivotal studies, eligible subjects were randomized 1:1 to receive either individually titrated tirzepatide up to MTD (10 mg or 15 mg) per once weekly subcutaneous injection or placebo for an overall double-blind treatment duration of 52 weeks. Medication has been approved for symptomatic relief of excessive daytime sleepiness (EDS) occurring in OSA or narcolepsy. Apart from symptomatic EDS treatment, no OSA-specific medication is available yet. Hence, placebo comparison and treatment duration are acceptable. Up to date, there is no EMA guideline on OSA.

It has been shown that excess body weight is positively associated with SDB (Peppard et al. 2000). Although not every OSA patient is overweight, obstructive sleep apnoea is strongly associated with obesity (Malhotra et al. 2024; Pugliese et al. 2020). Some 60-90% of adults with OSA are overweight, and the relative risk of OSA in obesity is $\geq$ 10 (Pillar & Shehadeh 2008). Tirzepatide is proposed for the use in OSA patients with obesity ($\geq$ 30 kg/m^2). According to Protocol, participants in both tirzepatide and placebo groups consulted with study personnel experienced in diet and exercise counselling to receive lifestyle program instructions at each trial contact. Dietary and lifestyle counselling consisted of advice on healthy food choices with a focus on calorie restriction using a hypocaloric diet (500 kcal per day below individualized energy requirements) and increased physical activity (moderate intensity for at least 150 minutes per week). Lifestyle counselling, concomitantly undertaken in both arms, is endorsed. According to current OSA Treatment Guidelines, weight-loss and comprehensive lifestyle interventions are associated with improvements in OSA severity, cardiometabolic comorbidities, and QoL (Hudgel et al. 2018).

Study inclusion criteria do not make formal reference to the International Classification of Sleep Disorders (ICSD-3) diagnostic criteria. To be eligible for study participation, adult subjects had to be previously diagnosed moderate-to-severe OSA with an AHI ≥15 (per PSG, or home sleep apnoea test (HSAT)) prior to Visit 1, present with AHI ≥15 on PSG as part of the trial at Visit 1, suffer from obesity (BMI ≥30 kg/m^2), and have a history of at least 1 self-reported unsuccessful dietary effort to lose body weight.

Based on the ICSD criteria, a diagnosis of OSA is confirmed when AHI is >15, or AHI is ≥5, with 1 or more of the following:

- o sleepiness, nonrestorative sleep, fatigue, or insomnia symptoms
- o waking up with breath holding, gasping, or choking
- o habitual snoring or breathing interruptions, and
- o hypertension, mood disorder, cognitive dysfunction, CAD, stroke, congestive HF, AF, or T2DM.

Hence, the decision about study eligibility selectively focussed on the AHI $\geq$ 15 criterion for diagnosis, along with the choice of the primary endpoint, i.e. reduction of AHI as compared from baseline. The clinical benefit of tirzepatide in OSA patients with AHI $\geq$ 5 (but < 15), and presenting with clinical features as listed in ICSD-3 criteria should be elucidated. One secondary endpoint was included combining AHI reduction with daytime sleepiness (percentage of participants with AHI < 5 or AHI 5 to 14 with ESS $\leq$ 10). However, daytime sleepiness was not excessive in the recruited study population. Baseline ESS scores (10.2 – 10.6) reflected daytime sleepiness around the higher normal range.

About two thirds of the study population were male (67.1 – 72.3%), which is in line with a higher prevalence of OSA in men reported in the literature (Punjabi 2008). Mean body weight at baseline was around 115 kg (mean around BMI 39 kg/m^2, with about 35% included subjects qualifying for class 3 obesity [BMI $\geq$ 40 mg/m^2]). Obesity was a requirement for participation as reflected by the proposed

indication, however, that does not mean that the population is somehow artificial, given the dramatic increases in the number of overweight and obese adults over the last 10-15 years and population-based studies confirming that excess body weight is uniformly associated with a graded increase in OSA prevalence (Punjabi 2008). Clinical sites were globally distributed with about 10-18% European (CZ, DE) and 30-33% US portions.

Diabetic patients were excluded, however, the majority of subjects presented with prediabetes (65.0 – 56.6%) and hypertension (75.6 – 77.4%) at baseline. In terms of OSA severity grading based on AHI, the majority of patients fulfilled criteria for moderate (AHI $\geq$ 15 and < 30 events/h; 35,2 – 30.9%) or severe OSA (AHI $\geq$ 30 events/h; 63.1 – 68.2%). Accordingly, the number of apnoea / hypopnoea events per hour was high across recruited subjects (51.5 in study 1, and 49.5 in study 2).

Due to non-eligibility of subjects with diabetes at study entry, provisions had to be specified for incident diabetes, since 56 – 65% of participants were pre-diabetic. Glucose lowering medication (e.g. metformin) was prohibited as concomitant medication. However, in case of incident diabetes, metformin could be initiated without subject exclusion. Absolute case numbers of patients that were initiated on metformin during the studies were low (4 subjects in study 1 and 2 subjects in study 2). Five out of these 6 patients was allocated to placebo. Hence, initiation of metformin is not expected to have impacted the study outcome in terms of metformin-induced weight reduction.

The primary efficacy endpoint was the change in AHI from baseline to week 52, collected via polysomnography. Polysomnography assessments (including AHI, blood oxygen saturation parameters, PR, sleep parameters) were performed during 1-night, overnight clinic stays.

Although established as a tool for OSA diagnosis and severity grading, the AHI has been criticised for not capturing relevant clinical OSA features (*Punjabi / Rapoport 2016, Is the Apnoea-Hypnea Index the Best Way to Quantify the Severity of Sleep-disordered Breathing? No – Yes*), and remains of topic of discussion (*Malhotra et al. 2020. Metrics of sleep apnoea severity: beyond the apnoea-hypopnoea index; Pevernagie et al. 2020. On the rise and fall of the apnoea-hypopnoea index: A historical review and critical appraisal*). There are three lines of AHI criticism:

a) The AHI is a count of the number of complete and partial obstructions that occur per hour of sleep. Only the rate is captured. However, there are other potentially independent axes of event severity (eg, the depth and duration of desaturation, the extent and duration of arousal, the level of sympathetic activation etc.).

b) The linear relation between AHI score and OSA symptomatology is questioned. Taking reference to past study results, the AHI was considered useful at its extremes (AHI < 5 means no OSA, while AHI scores > 15 are clear markers for disease), but less so in its midrange (5-15 events/h). Furthermore, the relation between hypertension and AHI may not be linear. A plateau of increased risk for hypertension was found at AHI >15, with little further increase above this AHI threshold.

c) There are varying definitions for the hypopnoea events, making across study comparisons difficult.

The Applicant has taken account of the structural shortcoming of the AHI (merely event rate counting without taking note of the degree of oxygen desaturation and duration of the event) by introducing the additional secondary endpoint of hypoxic burden SASHB (% min / hour). The SASHB endpoint measures the respiratory event–associated area under the curve for oxygen desaturation from pre-event baseline and represents the cumulative burden of intermittent hypoxia caused by OSA-related sleep-disordered breathing. Hence, SASHB is defined as the product of min desaturation by percent desaturation per hour. The change in SASHB (%min/hour) from baseline to Week 52 was obtained from PSG measurements.

Since the magnitude of hypoxic events during sleep is the underlying root cause in OSA, introduction of the SASHB endpoint as adjunct to the AHI primary is endorsed.

In studies 1 and 2, apnoea (decrease in airflow $\geq$ 90% from baseline for $\geq$ 10 sec) and hypopnoea events (an abnormal respiratory event lasting $\geq$ 10 sec with $\geq$ 30% reduction in airflow as compared to baseline, and with $\geq$ 4% oxygen desaturation) were adequately defined.

The questionable (linear) relationship between the lab AHI parameter and clinical symptomatology in OSA is a relevant issue. The most common symptom of OSA is unrefreshing sleep, with excessive sleepiness reported by up to 90% of patients with OSA referred to sleep clinics (Gottlieb & Punjabi 2020). However, according to ICSD-3, severity of OSA as determined by AHI and/or degree of desaturation correlates only poorly with symptomatic sleepiness. This is well illustrated by the population of studies 1 and 2, where AHI scores at baseline were high (> 50), however, daytime sleepiness was not excessive, but only in the upper normal range (ESS 10.2 -10.6). To contextualize, in study 14-003 supporting the use of solriamfetol as symptomatic treatment of EDS in OSA patients, subjects presented with mean ESS scores of 15 at baseline, corresponding to moderate excessive daytime sleepiness (Sunosi SmPC). One may assume that reactive (or comorbid) hypertension, present in > 75% of recruited subjects, may have contributed to counteract daytime sleepiness in the tirzepatide trials in obese OSA patients.

In order to associate reduction of AHI scores from baseline with clinical improvement, the Applicant introduced two key-secondary PRO endpoints, i.e. PROMIS-SRI for sleep-related impairment and PROMIS-SD for sleep disturbance, along with percent of participants with $\geq$ 50% AHI reduction, and non-OSA specific endpoints like change in body weight, change in hsCRP, or change in SBP (all type I error controlled). ESS, FOSQ, PGIS (OSA categorical shifts in sleepiness, fatigue, snoring) and PGIC (categorical shifts in sleepiness, fatigue, sleep quality, snoring) were assessed as other / exploratory secondary endpoints.

PROMIS-SRI assesses self-reported perceptions of alertness, sleepiness, and tiredness during usual waking hours, and the perceived functional impairments associated with sleep problems or impaired alertness. The **PROMIS-SD** assesses 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 perceptions of the adequacy of and satisfaction with sleep. For both PROs, questionnaires consist of 8 items (5-pt range) for a recall period of "in the past 7 days."

Overall, the entirety of endpoints is considered adequate to measure the efficacy of tirzepatide in obese OSA patients.

Statistics

The provided description of the estimand attributes is not fully in line with the idea of the estimand framework to disentangle the definition of the estimand (question of interest) and the specification of the study design and statistical analysis (how to address the question of interest). For example, the population attribute should describe the target population rather than the analysis sets and missing data handling is not part of the estimand definition. However, the overall description of the estimand attributes still allows to appropriately identify the estimand of interest that is targeted. As intercurrent events such as treatment discontinuation or initiation of PAP therapy (study 1) occur also in clinical practice, the "treatment regimen" estimand (treatment effect regardless of these events) is of primary regulatory interest, while the hypothetical effect if these events had not occurred (i.e. "efficacy estimand") is of less relevance.

For the "treatment regimen" estimand, treatment discontinuation due to COVID-19 or due to inadvertent enrolment was, on the one side, not considered an intercurrent event according to the estimand definition but, on the other side, handled by a hypothetical strategy according to the description of missing data

handling (and missing data replaced under a MAR assumption). As it may not always be unambiguously possible to identify the true reason for discontinuation, the number of patients that discontinue for these reasons should be given and, if non-negligible, a sensitivity analysis replacing missing data for these patients based on placebo multiple imputation was requested in a request for supplementary information (RSI). In the response to the RSI, the MAH clarified that all patients where missing data was replaced based on MAR after discontinuation were inadvertently enrolled. Replacing under a MAR assumption for a relevant number of patients who discontinued due to COVID-19 may have been more problematic but no patients discontinued for this reason. The numbers of inadvertently enrolled patients were small in both studies and the sensitivity analyses replacing these under MNAR (placebo-based multiple imputation) showed consistent results.

Patients that were not treated were excluded from the analysis, which is acceptable for this blinded study.

The stratified randomisation was appropriately taken into account by the primary analysis model by including the stratification factors as factors/covariate in the analysis.

For both studies, study 1 and study 2, a multiplicity strategy ensuring control of the study-wise type 1 error rate at the 0.05 significance level for primary and secondary endpoints was pre-specified. In addition, a multiplicity strategy aiming to provide control of the submission-wise type 1 error rate at the 0.05 significance level was pre-specified. This was to allow confirmatory conclusions for the endpoints PROMIS SD and PROMIS SRI based on a pre-specified analysis pooling studies 1 and 2, as no confirmatory tests were planned for these endpoints on a study-level (due to concerns on lack of power). However, the concept of a submission-wise type 1 error rate is not established and not well defined; particularly, there is no agreement on a submission-wise significance level such as 0.05. Regulatory decision-making (and support of regulatory claims) is generally based on the totality of evidence from the pivotal studies and supportive studies. Usually, two successful pivotal studies are required, which provides both statistical evidence stronger than a significance level of 0.05 and independent replication. A pre-specified meta-analysis of the studies may still be acceptable to support regulatory decision making depending on compelling nature of the data, which includes homogeneity of study populations, consistent treatment effects in single studies and precision of estimation.

While it is acknowledged that multiplicity adjustment is not necessarily required when several estimands are specified for different purposes, these purposes should have been clearly pre-specified in the study protocol. However, according to the SAP, the treatment regimen estimand was to be used for submission and registration purpose with regulatory agencies such that no multiplicity issue arises (anyway, both estimands lead to the same conclusions with regard to hypothesis testing).

For targeting the 'treatment regimen' estimand, all data were to be used as observed irrespectively of treatment discontinuation. Consequently, according to protocol, all patients were intended to be followed for efficacy and safety outcomes independently from treatment discontinuation and their values should have been used for estimating the 'treatment regimen' estimand. However, almost all patients who discontinued treatment also discontinued the study.
Data that were nevertheless missing were to be replaced in accordance with the estimand. Missing data for patients without intercurrent event were replaced by multiple imputation under a MAR assumption, which is generally acceptable (see above for patients who discontinued due to COVID-19 or inadvertent enrolment, which was not considered as intercurrent event). Missing data for patients who discontinued the study were intended to be replaced by retrieved drop-out imputation or, if there are not enough retrieved dropouts to provide a reliable imputation model, placebo-based multiple imputation was used. It appears to be obvious that placebo MI had to be used. To avoid ambiguity with regard to what are enough drop-outs for a reliable imputation model and as it may have been foreseeable that not enough drop-outs could be retrieved, it would have been preferable to uniquely pre-specify placebo multiple

imputation as primary analysis method (although it is acknowledged that retrieved drop-out imputation is theoretically an appealing approach).

For targeting the efficacy estimand, a MMRM under the assumption of MAR is appropriate, although sensitivity analyses to assess whether the results are robust to deviations from MAR may have been useful. However, from a regulatory perspective, the efficacy estimand is anyway of minor relevance.

Disposition

Study completion was high. More than 85% / 90% of subjects allocated to tirzepatide completed treatment in study 1 and 2. Also for placebo, the majority of subjects completed treatment (70.0 to 73.9%). The most common reasons for withdrawal were randomization in error or withdrawal by subject. Only 1 subject, allocated to tirzepatide discontinued for lack of efficacy across the two studies. It is plausible that completion rates were slightly higher in patients receiving PAP in study 2 as compared to study 1, regardless of treatment allocation.

Efficacy data and additional analyses

Efficacy on Sleep-Disordered Breathing

Tirzepatide demonstrated substantial AHI reduction. Mean AHI scores of about 50 at baseline were reduced by -50.7% in study 1 (placebo: -3.0%) and -58.7% in study 2 (placebo: -2.5%) after 52 week treatment, thereby achieving highly significant placebo superiority. AHI reduction also translates into reduction of hypoxic burden. Mean SASHB values, which reflect the degree and duration of oxygen desaturation during sleep (apart from event frequency), were reduced by -65.5% in study 1 (placebo: -17.3%) and by -75.2% in study 2 (placebo: -30.4%). In accordance with the reduction of hypoxic events and hypoxic burden, tirzepatide significantly increased the likelihood for participants to reach AHI < 5 or AHI < 15 without EDS (ESS ≤ 10) representing those who achieved a wider definition of OSA remission and are not typically indicated for further treatment (study 1: OR 7.3 [3.2, 17.0]; study 2: OR 6.6 [3.1, 14.0]). Overall, impaired breathing leading to hypoxic events during sleep is the underlying cause of OSA and related symptomatology. The beneficial effect of tirzepatide has consistently been shown across all sleep-disordered breathing related endpoints / reduction of the AHI from baseline to week 52 of treatment, which was measured as primary.

Patient-Reported Outcomes

As opposed to sleep-disordered breathing, the beneficial effect of tirzepatide on OSA symptoms, as expressed by PROs, is less clear.

Two 8-item questionnaires were introduced as key secondaries to reflect improvement in terms of sleep-related impairment during daytime (PROMIS-SRI) and sleep disturbance during night (PROMIS-SD). According to the Applicant's literature review, there is limited published evidence available to confirm the content validity and psychometric properties of the PROMIS SRI and PROMIS SD for the intended context of use, i.e. individuals with moderate-to-severe OSA and obesity. In addition, a MWPC threshold is not established.

The Applicant provided a qualitative research study to establish content validity of PROMIS SF-SRI 8a and PROMIS SF-SD 8b in the intended context of use. In addition, psychometric analysis was conducted using the data from the two pivotal SURMOUNT-OSA studies. The MWPC threshold was derived using anchor and distribution based methods using SURMOUNT-OSA data.

Overall, the qualitative study, psychometric analysis and MWPC derivation were in accordance with the usual requirements. However, in accordance with the EMA RP, as a general rule, the validation of HRQL instrument should preferably have been completed before its use in therapeutic confirmatory trials. In

principle, the same study should not be used to validate the HRQL instrument and to test for the HRQL change. In the present case, however, psychometric analyses and establishment of MWPC was based on the SURMOUNT-OSA study.

Different MWPCs for PROMIS SRI resulted from study 1 and study 2. The Applicant hypothesizes that those participants who were consistent and committed PAP users are likely to have appreciated the residual relief from PAP therapy, and needed a bigger improvement to consider meaningful. However, this post-hoc explanation appears not to be fully convincing, as the threshold for a meaningful worsening was also larger for consistent and committed PAP users, although it could be argued that these patients would tolerate only a smaller worsening. In addition, if it was accepted that the MWPC is indeed different for the two populations, this would raise concerns on the validity of pooling these populations for the analysis of PROMIS SRI, particularly with regard to the interpretation of results.

The mean difference to placebo was, although statistically significant, smaller than the MWPC for all analyses. I.e., the relevance of the effect that a patient can expect, is questionable. Still, there could be a meaningful difference in the proportion of patients experiencing a relevant improvement. Therefore, responder analyses to support the interpretation are meaningful. However, these were only provided for the efficacy estimand and the MAH was requested to also provide them for the treatment regimen estimand. In the response to the RSI, the responder analyses were provided as requested for the treatment regimen estimand. Results are similar as those previously presented for the efficacy estimand. It is acknowledged that clinical relevance should not only be assessed based on the difference in group means being smaller than the MWPC that translates to a direct, meaningful benefit to an individual patient. However, no new arguments or data were provided beyond what was presented before such that conclusions on validation status or relevance of the findings for PROMIS-SRI, PROMIS-SD remain unchanged.

Only the pooled analysis was pre-specified as confirmatory. However, the nominally statistically significant results in study 1 and study 2 can be considered as replication with overall statistically significant results (with p-value < 0.001).

Despite statistical significance, there are uncertainties about the clinical relevance of the key secondary PROMIS results. These are mainly based on unclear external validity of the questionnaires in the context of the obese OSA population and the effect size. Net effects over placebo consistently were clearly lower than MWPC for both sleep-related daytime impairment (Pooled PROMIS-SRI: T score mean change difference from placebo at week 52: -3.9 [MWPC: Study 1: $\leq$ -8.0, Study 2: $\leq$ -10.0]) and sleep disturbance during night (Pooled PROMIS-SD: T score mean change difference from placebo at week 52: -3.0 [MWPC: Studies 1 / 2: $\leq$ -7.5]).

Daytime sleepiness was not excessive across recruited subjects at baseline. Despite considerably disturbed breathing during sleep (AHI about 50), ESS scores were only in the higher normal range (ESS 10.2 – 10.6). ESS scores significantly improved in study 1 (net effect over placebo -1.6, p=0.024), however, only modestly improved in PAP participants of study 2 (net effect over placebo -0.7, p=0.305). PAP was discontinued 7 days prior to ESS assessment at week 52. However, the different results between study 1 and study 2 may still be influenced by the different populations (PAP use yes / no), since the ESS questionnaire does not specify sleepiness over a concrete recall period, but asks to retrospectively estimate the likelihood to doze or fall asleep in different daytime situations "in recent times".

Across studies 1 and 2, FOSQ (30 items) and FOSQ (10 items) between-treatment p values were not significant. PGIC Assessment of OSA symptom severity revealed for the efficacy estimand that a higher proportion of participants in the tirzepatide group compared with the placebo group shifted to an improved category from baseline to Week 52 for PGIC-OSA fatigue, sleepiness, snoring, and sleep quality in both Studies 1 and 2.

OSA-Related CV Risk Factors

In line with the outcome of clinical studies in support of the established tirzepatide indications like diabetes or weight management, considerable benefit in terms of CV risk factors could also be shown in OSA patients with obesity.

Chronic low-grade inflammation, measured by hsCRP, was shown to be independently associated with OSA and the levels decrease with cPAP therapy (Budhiraja et al. 2007). As a marker and a contributor to the vascular inflammatory process, CRP represents a risk factor for CAD development. Hs-CRP levels at baseline were in the range of 2.7 – 3.6 mg/L, thereby at the interface between predicting moderate (1.0 – 3.0 mg/L) to high (3.0 – 10.0) risk of heart disease. Across both studies, hsCRP values were reduced by > 40% achieving statistical significance over placebo for both estimands, The effect was slightly more pronounced in PAP patients of study 2 (-48.2%) as compared to PAP refusing patients of study 1 (-40.1%).

It could be shown that the degree of sleep-disordered breathing is associated with increased risk for hypertension and consequent CV morbidity in the general population (Peppard et al. 2000). In order to avoid the confounding effect of PAP withdrawal (7 days prior to week 52 assessments), BP was not measured at week 52 but already at week 48, when study 2 participants could still use PAP. Blood pressure significantly decreased under tirzepatide treatment as compared to placebo. The net effect over placebo for SBP was -7.6 mmHg in study 1, and -3.7 mmHg in study 2. The inter-study difference may be explained by the difference in concomitant PAP use. Since PAP was shown to have antihypertensive effect in OSA (Javaheri et al. 2017), there may have been more space for improvement of hypertension in PAP non-users of study 1.

The reduction in body weight was significant. The net effect over placebo in terms of mean percent change in body weight from baseline to week 52 was -16.1% in study 1 and – 17.3% in study 2. Whereas subjects lost almost 20% of body weight over 1 year treatment with tirzepatide (-17.7% / -19.6%), the weight-reducing effect was low among placebo subjects (-1.6% / -2.3%). Diet counselling was given to all participants. The difference in weight loss between the arms may lead to partial unblinding, however, this appears inevitable.

Descriptive summary of PAP use in study 2

It appears there were no minimum requirements in terms of PAP adherence pre-specified in study 2. Instead, categories of PAP use (0 to <2 h; ≥2 to <4 h; ≥4 to <6 h; ≥6 h) were defined and changes in categories were described for both arms from baseline to week 52. It is evident that study 2 was not designed to show a (potentially decreasing) effect on PAP use under tirzepatide, and no such claim is made. Apart from study design aspects, however, no such trend or signal was observed. Across both the placebo and tirzepatide arm, the category of low PAP use (0 to <2 h) increased and the categories of intensive PAP use (≥ 4 to <6 h and ≥6 h) decreased over the 1-year treatment period. Factors in category shifts are similar across arms (Tab. GPI2.4.7). There is no signal that tirzepatide would potentially decrease PAP use as compared to placebo.

4.4.4. Conclusions on the clinical efficacy

Available efficacy data demonstrate beneficial effects of tirzepatide in the treatment of moderate to severe OSA patients with obesity (BMI ≥ 30 kg/m^2). Benefits were clearly shown for reduction of sleep-disordered breathing, as expressed by relevant reduction of AHI (defined as primary) and associated hypoxic burden during sleep, which also takes duration and degree of oxygen desaturation into account. The hypoxic burden during sleep is at the bottom of all (consequential) OSA symptomatology, however, formally, is a surrogate lab parameter. The crosslink to OSA symptoms was intended to be made by

introducing two PROs to reflect sleep-related impairment during daytime (PROMIS-SRI) and sleep disturbance overnight (PROMIS-SD), both reflecting a 7-day recall period. Although significant superiority over placebo could be shown for both 8-item questionnaires, there is uncertainty about the clinical relevance due to uncertain external validity of the questionnaires in an obese OSA population and the fact that net effects over placebo were clearly lower than MWPC.

In line with the outcome of previous clinical trials to support the use of tirzepatide in diabetes and weight management, benefits were shown across several metabolic CV risk factors, like e.g. hsCRP, SBP and body weight. No specific molecular mode of action is claimed for tirzepatide in OSA treatment. Given the association between obesity and OSA, the beneficial effects of tirzepatide on sleep and disordered breathing may well secondarily result from body weight reduction and associated effects.

Until today, no medication has been approved for OSA treatment. Only symptom-oriented medication for improvement of daytime sleepiness is available. First line therapy in OSA is (continuous) PAP, administered overnight via nasal or mouth appliances. Two pivotal phase 3 studies were conducted following an identical Protocol, however, distinct in terms of the population. In study 1, PAP refusing subjects were recruited, while study 2 allowed concomitant PAP use over the 52-week treatment period. Unfortunately, it appears, there were no minimum requirements as regards PAP adherence. Furthermore, the foremost clinical interest in study 2 would have been to see whether tirzepatide can bring an additional clinical benefit on top of PAP in adherent patients. However, the study design does not allow such conclusions since PAP had to be discontinued 7 days prior to endpoint assessment at week 52.

4.5. Clinical safety

Introduction

The safety of tirzepatide has been characterized in 14,512 clinical trial participants studied in Phase 3 development programs for T2DM (n=9,674) and weight management (n=4,838). Of these participants, 10,111 received at least 1 dose of tirzepatide (T2DM [n=6,523]; weight management [n=3,588]). The OSA studies include participants with OSA and obesity, and as such, represent a subset of the broad weight management population. The 2 OSA studies provide controlled data specific to this indication to allow systematic assessment of safety in this population.

The submission data cut-off date for the application is 24 April 2024.

Throughout the clinical trials in support of the existing indications, the most frequently reported adverse reactions were gastrointestinal disorders and these were mostly mild or moderate in severity. Nausea, diarrhoea, vomiting, abdominal pain, and constipation are listed as very common ARs. The incidence of nausea, diarrhoea and vomiting was higher during the dose escalation period and decreased over time. In the placebo-controlled phase 3 studies in patients with BMI > 27 kg/m^2 with or without T2DM, GI disorders were increased for tirzepatide 5 mg (51.3 %), 10 mg (55.2 %) and 15 mg (55.6 %) compared with placebo (28.5 %). Nausea occurred in 22.1 %, 28.8 % and 27.9 % versus 8.3 % and diarrhoea in 16.9 %, 19.3 % and 21.7 % versus 8.0 % for tirzepatide 5 mg, 10 mg and 15 mg respectively versus placebo.

Treatment with tirzepatide resulted in a maximum mean increase in heart rate of 3 to 5 beats per minute vs. 1 beat per minute in placebo-treated patients. In the placebo-controlled phase 3 studies in patients with BMI ≥ 27 kg/m2 with or without T2DM, treatment with tirzepatide resulted in mean increases from baseline in pancreatic amylase of 20 % to 24 % (placebo: 3.8%) and lipase of 29 % to 35 % (placebo: 5.3 %).

Patient exposure

Study I8F-MC-GPIF (SURMOUNT-OSA) is a master protocol that supported 2 pivotal independent studies. Each independent study was a multi-centre, randomized, parallel-arm, double-blind, placebo-controlled study with a 52-week treatment duration to investigate the effects of treatment with QW tirzepatide at the MTD (10 or 15 mg) compared with placebo in adult participants with moderate to severe OSA (AHI ≥15) and obesity (BMI ≥30 kg/m^2). Participants completed a safety follow-up visit 4 weeks after the last treatment visit.

Table 27 Phase 3 Studies Contributing to Safety Assessments in the Tirzepatide OSA Application

	Study 1		Study 2	
Participant Population	≥18 years with moderate-to severe OSA (AHI ≥15) and BMI ≥30 kg/m^2, with ≥1 unsuccessful dietary effort to lose body weight			
Background Therapy	Reduced-calorie diet and increased physical activity			
Design	Randomized, double-blind, placebo-controlled			
Study Duration	52 weeks + 4-week safety follow-up			
PAP Use	unable or unwilling to use PAP therapy		on PAP therapy for at least 3 consecutive months at screening and planned to continue PAP therapy during the study	
Participants in Safety Population	Placebo	120	Placebo	114
	Tirzepatide	114	Tirzepatide	119
	Total	234	Total	233

Abbreviations: AHI = apnea-hypopnea index; BMI = body mass index; OSA = obstructive sleep apnea; PAP = positive airway pressure.

- A total of 233 participants received at least 1 dose of tirzepatide, for a total of 218.6 participant-years exposure, and 234 received at least 1 dose of placebo.
- The mean exposure to tirzepatide was 49.0 weeks, and mean exposure to placebo was 43.7 weeks.
- In the tirzepatide group, 79.8% of participants were exposed for at least 52 weeks. In the placebo group, 67.1% of participants were exposed for at least 52 weeks.

In addition, the mean exposure to tirzepatide and placebo in Study 1 (tirzepatide 47.8 weeks; placebo 43.3 weeks) was similar to that in Study 2 (tirzepatide 50.0 weeks; placebo 44.1 weeks).

Table 28 Summary of Study Drug Duration. Safety Population. OSA Analysis Set

	Placebo (N=234)	Tirzepatide (N=233)
Mean (SD) weeks exposure	43.73 (15.9)	48.95 (11.0)
Total participant-years	196.11	218.58
Weeks of exposure, n (%)		
≥36	180 (76.9)	212 (91.0)
≥48	174 (74.4)	206 (88.4)
≥52	157 (67.1)	186 (79.8)

Abbreviations: n = number of participants in specified category N = number of participants in the analysis population; OSA = obstructive sleep apnea; SD = standard deviation.

Notes: Duration of exposure is calculated as date of last dose of study intervention – date of first dose of study intervention + 7. Duration of exposure in weeks is calculated as duration of exposure in days / 7. Total participant-year is calculated as the sum of duration of exposure in days for all participants/365.25.

Studies 1 and 2 used the same dose-escalation scheme approved for tirzepatide that started at a 2.5 mg dose for 4 weeks followed by dose-escalation increments of 2.5 mg every 4 weeks to reach a MTD of 10 or 15 mg. Participants who tolerated:

- 10 mg, but not 12.5 or 15 mg continued on 10 mg as their MTD
- 12.5 mg, but not 15 mg continued on 10 mg as their MTD, and
- 15 mg continued on 15 mg as their MTD.

Participants who did not tolerate at least 10 mg were discontinued from the study drug but were expected to remain in the study for continued follow-up. Throughout these documents, patients treated with tirzepatide MTD will be referred to as "tirzepatide" group, regardless of whether their MTD was the 10 or 15 mg dose.

Adverse events

The following Table provides a comparative summary of the numbers and percentages of participants who experienced a TEAE, SAE, death, or discontinued from study or permanently discontinued study drug due to an AE by treatment group between the OSA Analysis Set (N=467) and the Placebo-controlled Weight Management Analysis Set (N=4056).

No deaths were reported during OSA studies. The percentages of participants reporting SAEs and discontinuation from study drug due to an AE were similar between tirzepatide and placebo groups. The percentage of discontinuations from study due to an AE was lower in the tirzepatide group (0.4%) compared to placebo (3.0%). The percentage of participants reporting TEAEs was numerically higher in the tirzepatide group (81.5%) than the placebo group (74.8%).

The comparison between tirzepatide and placebo groups are generally consistent with the findings from the analysis of pooled data from SURMOUNT-1, -2, and -3, although fewer discontinuations from the study drug or study due to AEs in tirzepatide-treated participants were observed in the OSA Analysis Set.

Overall, the safety findings remain consistent with the known safety profile of tirzepatide for weight management.

Table 29 Overview of Adverse Events. Safety Population. OSA Analysis Set

Category[b]	OSA Analysis Set			Placebo-Controlled Weight Management Analysis Set (AS1-S)[a]		
	Placebo (N=234) n (%)	Tirzepatide (N=233) n (%)	Tirzepatide vs. Placebo p-Value[c]	Placebo (N=1250) n (%)	Tirzepatide_ALL (N=2806) n (%)	Tirzepatide_ALL vs. Placebo p-Value[c]
Deaths[d]	0	0	NA	5 (0.4)	10 (0.4)	0.759
SAEs	19 (8.1)	16 (6.9)	0.599	81 (6.5)	178 (6.3)	0.776
Discontinuation from study due to AE	7 (3.0)	1 (0.4)	0.030	25 (2.0)	68 (2.4)	0.701
Discontinuation from study treatment due to AE	10 (4.3)	9 (3.9)	0.801	39 (3.1)	183 (6.5)	<0.001
TEAEs	175 (74.8)	190 (81.5)	0.078	926 (74.1)	2241 (79.9)	<0.001

Abbreviations: AE = adverse event; n = number of participants with at least 1 AE per event type; N = number of participants in the treatment group; NA = not applicable; SAE = serious adverse event; OSA = obstructive sleep apnea; TEAE = treatment-emergent adverse event; vs. = versus.

a Pooled data from Studies SURMOUNT-1, SURMOUNT-2, and SURMOUNT-3 from first dose of treatment to end of safety follow-up visit or date of early withdrawal (SURMOUNT-1 includes the primary treatment period, and study withdrawal refers to withdrawal during the primary treatment period for SURMOUNT-1).

b Participants may be counted in more than 1 category.

c p-Values are from Cochran-Mantel-Haenszel test of general association stratified by study.

d Deaths are also included as SAEs and discontinuations due to AEs.

Frequently reported TEAEs

Except for Nasopharyngitis, COVID-19, and Upper respiratory tract infection, all other frequently reported TEAEs were reported by a higher percentage of participants in the tirzepatide group than placebo.

Table 30 Summary and Analysis of TEAEs Occurring in ⩾5% of Participants in Any Treatment Group. Safety Population. OSA Analysis Set

Preferred Term	Placebo (N=234) n (%)	Tirzepatide (N=233) n (%)	Tirzepatide vs. Placebo p-Value[a]
Diarrhoea	25 (10.7)	56 (24.0)	<0.001
Nausea	18 (7.7)	55 (23.6)	<0.001
Constipation	8 (3.4)	36 (15.5)	<0.001
Vomiting	6 (2.6)	31 (13.3)	<0.001
Eructation	1 (0.4)	19 (8.2)	<0.001
Nasopharyngitis	20 (8.5)	18 (7.7)	0.696
Dyspepsia	3 (1.3)	16 (6.9)	0.002
Gastrooesophageal reflux disease	1 (0.4)	15 (6.4)	<0.001
COVID-19	21 (9.0)	14 (6.0)	0.220
Injection site reaction	1 (0.4)	14 (6.0)	<0.001
Abdominal pain	6 (2.6)	12 (5.2)	0.141
Upper respiratory tract infection	18 (7.7)	12 (5.2)	0.271

Abbreviations: n = number of participants with at least 1 TEAE; N = number of participants in treatment group; OSA = obstructive sleep apnea; TEAE = treatment-emergent adverse event; vs. = versus.

a p-Values are from Cochran-Mantel-Haenszel test of general association stratified by study.

Treatment differences in less frequently reported TEAEs by SOC and PT

In addition to the most frequently reported TEAEs, treatment imbalances between tirzepatide and placebo (p-value <0.05 or odds ratio ≥2; tirzepatide count ≥4) were observed for the following TEAEs (individual PTs) reported by at least 1% before rounding in any treatment group (Table ISS.4.12):

- Gastrointestinal disorders
    - Abdominal pain upper (tirzepatide, 4.7%; placebo, 1.7%)
    - Abdominal distension (tirzepatide, 3.9%; placebo, 1.3%)
    - Flatulence (tirzepatide, 1.7%; placebo, 0.9%)
    - Haemorrhoids (tirzepatide, 1.7%; placebo, 0.4%)
- Infections and infestations
    - Gastroenteritis (tirzepatide, 4.7%; placebo, 2.1%)
    - Respiratory tract infection (tirzepatide, 1.7%; placebo, 0.4%)
- Skin and subcutaneous tissue disorders
    - Alopecia (tirzepatide, 4.3%; placebo, 0.9%)
- Metabolism and nutrition disorders
    - Decreased appetite (tirzepatide, 3.0%; placebo, 1.3%)
- Investigations
    - Lipase increased (tirzepatide, 3.0%; placebo, 0%)
    - Heart rate increased (tirzepatide, 2.6%; placebo, 0.9%)
- Renal and urinary disorders
    - Nephrolithiasis (tirzepatide, 3.0%; placebo, 0.9%)
- General disorders and administration site conditions
    - Fatigue (tirzepatide, 2.6%; placebo, 0.4%)
- Psychiatric disorders
    - Insomnia (tirzepatide, 2.1%; placebo, 0.9%)

Treatment-Emergent Adverse Events by Maximum Severity

Of the participants reporting TEAEs with a maximum severity rating, the majority reported TEAEs of mild or moderate severity (tirzepatide, 87.4%; placebo, 92.0%).

The frequency of participants reporting severe events for frequently reported TEAEs was as follows:

- Diarrhoea (tirzepatide, 1.3%; placebo, 0%)
- Nausea (tirzepatide, 1.3%; placebo, 0%)
- Gastrooesophageal reflux disease (tirzepatide, 0.4%; placebo, 0%)

No other frequently reported events were reported as severe in either treatment group.

Special Safety Topics Including Adverse Events of Interest

TEAEs of Gastrointestinal Disorders

GI events are the most common TEAEs associated with the use of tirzepatide (Mounjaro package insert, 2023; Zepbound package insert, 2024). These events are generally mild or moderate in severity, dose

dependent, and mostly occur early after treatment initiation during dose-escalation and resolve or stabilize over time.

The proportion of participants experiencing at least 1 TEAE in the Gastrointestinal disorders SOC was higher in the tirzepatide (54.9%) group than the placebo group (23.5%). The most frequently reported GI-related TEAEs were Diarrhoea, Nausea, Constipation, and Vomiting (see Table on Frequently reported TEAEs above).

A total of 8 (tirzepatide, 8 [3.4%]; placebo, 0) participants experienced at least 1 serious or severe GI event. Of the 8 tirzepatide-treated participants,

- 2 (0.9%) experienced 3 serious events
- 7 (3.0%) experienced 11 severe events, and
- the event in 1 participant was both serious and severe (Pancreatitis acute). Further details on Pancreatitis acute, see below.

Table 31 Summary of Severe or Serious Gastrointestinal Events. Safety Population. OSA Analysis Set

Preferred Term	Placebo N = 234 n (%)	Tirzepatide N = 233 n (%)	Tirzepatide vs. Placebo p-Value[a]
Participants with ≥1 severe/serious GI TEAE	0	8 (3.4)	0.004
Diarrhoea	0	5 (2.1)	0.025
Nausea	0	3 (1.3)	0.085
Gastrooesophageal reflux disease	0	1 (0.4)	0.305
Pancreatitis acute	0	1 (0.4)	0.328

Abbreviations: GI = gastrointestinal; n = number of participants with at least 1 TEAE; N = number of participants in the treatment group; OSA = obstructive sleep apnea; TEAE = treatment-emergent adverse event; vs. = versus.

[a] p-Values are from the Cochran-Mantel-Haenszel test of general association stratified by study.

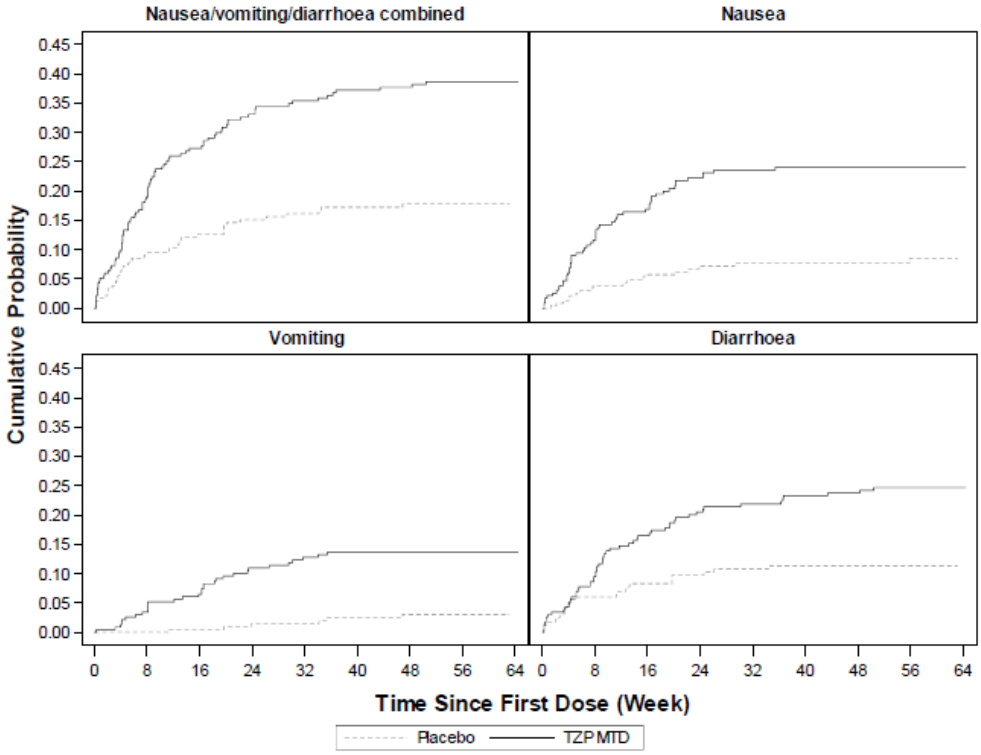
The SOC of GI disorders was the most common AE class leading to permanent discontinuation of the study drug. The number of participants that discontinued the study drug due to a GI event was numerically higher in the tirzepatide group than the placebo group (tirzepatide: 2.1%, and placebo: 0.4%).

The most frequently reported GI PTs leading to permanent discontinuation of study drug were Nausea (tirzepatide, 1.3%; placebo, 0.0%), and Diarrhoea (tirzepatide, 0.9%; placebo, 0.4%).

Consistent with the known safety profile of tirzepatide,

- the probability of onset of Diarrhoea, Nausea, and Vomiting was higher for the tirzepatide group than the placebo group, and
- the probability of onset of the diarrhoea, nausea and vomiting cluster was highest early in the trial. Onset of Nausea and Diarrhoea was most common during the dose-escalation period.

Figure 10 Plot of time to onset of nausea, vomiting, and diarrhoea for the Safety Population of the OSA Analysis Set.



Note: TZP MTD is tirzepatide up to 15 mg once weekly.

Consistent with the known safety profile of tirzepatide,

- the prevalence of Diarrhoea, Nausea, and Vomiting was higher for tirzepatide than the placebo group,
- the combined prevalence of Diarrhoea, Nausea, and Vomiting events in tirzepatide-treated participants peaked around Week 12. This trend was driven most by events of Nausea, and
- the combined prevalence of Diarrhoea, Nausea, and Vomiting ranged from 9.9% to 18.3% in the tirzepatide group at any period during the treatment period.

Dehydration Events

Dehydration events were reviewed because GI events, such as vomiting or diarrhoea, may lead to dehydration and volume depletion, which can cause a deterioration in renal function including acute renal failure.

One participant in the OSA Analysis Set (tirzepatide, 1 [0.4%]; placebo, 0%) experienced 1 TEAE of Dehydration. The event was moderate in severity, and not serious, but led to discontinuation of the study drug. The dehydration-related safety findings remain consistent with the known safety profile of tirzepatide.

Renal Safety

In patients with chronic kidney disease and end-stage renal disease, OSA is frequently present, and prevalence increases as kidney function declines (Nicholl et al. 2012; Abuyassin et al. 2015). Conversely, nocturnal hypoxia is associated with increased risk of kidney function loss (Ahmed et al. 2011; Sakaguchi et al. 2013; Lin et al. 2017; Voulgaris et al. 2019b). Thus, a bidirectional relationship is suspected, with

chronic kidney disease increasing risk for OSA, and OSA increasing risk of renal injury (Abuyassin et al. 2015).

There have been post-marketing reports of AKI and worsening of chronic renal failure in patients treated with tirzepatide and other incretins. A majority of the reported events occurred in patients who had experienced nausea, vomiting, or diarrhoea, leading to volume depletion.

In the Phase 3 OSA studies, participants were excluded if they had renal impairment measured as eGFR <30 mL/min/1.73 m^2.

TEAEs of Renal Disorders

One participant (tirzepatide, 1 [0.4%]; placebo, 0) experienced 1 treatment-emergent renal event, that is, Acute kidney injury. The event was severe and serious and led to discontinuation of the study drug. The narrative was provided. On study Day 33, i.e. 4 days after receiving the second tirzepatide dose (5 mg), the patient experienced the serious adverse event of hypokalaemia (severe) and moderate dehydration on the next day. On Study Day 35, the patient experienced SAEs of gastroenteritis (severe) and acute kidney injury (severe). On Study Day 36, the study participant recovered from the events of dehydration, gastroenteritis, hypokalaemia, and acute kidney injury. On Study Day 59 (when the third dose would have been due), the study drug was permanently discontinued. The Investigator's assessment for events of hypokalaemia, acute kidney injury, dehydration, and gastroenteritis was as follows: not related to the study drug.

Nephrolithiasis was reported by 7 (3.0%) tirzepatide-treated participants and 2 (0.9%) placebo-treated participants. Of these, 3 participants had a medical history of nephrolithiasis and 1 participant discontinued study treatment due to an SAE of acute kidney injury (see above).

Renal Function (Measured by eGFR and UACR)

Estimated glomerular filtration rate

Change from baseline

The Table below presents a summary and analysis of eGFR in participants in the OSA Analysis Set. Mean baseline eGFR values were similar across the treatment groups. At Week 52, mean reductions from baseline in eGFR were small and similar between the tirzepatide and placebo groups.

Table 32 Change from Baseline in eGFR (CKD-EPI) at Week 52 and the Safety Follow-Up. MMRM by Treatment and Visit. Safety Population. OSA Analysis Set

eGFR CKD-EPI (mL/min/1.73m^2)	Placebo (N = 234)	Tirzepatide (N = 233)
Baseline	n=217	n=229
Actual value, LS mean (SE)	95.0 (1.19)	93.7 (1.16)
52 weeks	n=174	n=211
CFB, LS mean (SE)	-1.9 (0.60)	-2.1 (0.55)
Change difference from placebo (95% CI)	-	-0.2 (-1.8, 1.4)
Safety follow-up	n=185	n=213
CFB, LS mean (SE)	-2.4 (0.66)	-0.6 (0.62)
Change difference from placebo (95% CI)	-	1.9 (0.1, 3.7)

Abbreviations: CFB = change from baseline; CI = confidence interval; CKD-EPI = Chronic Kidney Disease-Epidemiology Collaboration; eGFR = estimated glomerular filtration rate; LS = least squares; MMRM = mixed model repeated measures; n = number of participants in the population with baseline and postbaseline value at the specified time point; N = number of participants in the safety population in the specified treatment group; OSA = obstructive sleep apnea; SE = standard error.

Categorical shift

The Table below present a summary of shift from minimum baseline to minimum post-baseline in eGFR for participants the OSA Analysis Set.

Most participants had a minimum baseline eGFR of ≥60 mL/min/1.73 m^2 (tirzepatide, 94.4%; placebo, 94.9%).

For both tirzepatide and placebo groups, the majority of participants' eGFR remained in the same category. The percentage of participants shifting to a lower eGFR category was comparable in the tirzepatide group (24%) and placebo group (21%).

Table 33 Shift Table for Estimated Glomerular Filtration Rate from Minimum Baseline to Minimum Post-baseline. Safety Population. OSA Analysis Set

	Placebo (M = 224)	Tirzepatide (M = 232)
Remained in the same category, n (%)	168 (75.0)	168 (72.4)
Shifted to a lower eGFR category, n (%)	48 (21.4)	56 (24.1)
Shifted to a higher eGFR category, n (%)	8 (3.6)	8 (3.4)

Abbreviations: eGFR = estimated glomerular filtration rate; M = number of participants in the population with baseline and at least 1 postbaseline result in the specified treatment group; MTD = maximum tolerated dose; OSA = obstructive sleep apnea.

Urine albumin/creatinine ratio (UACR)

Change from baselAine

The Table below presents a summary and analysis of UACR in participants of the OSA Analysis Set. Mean baseline UACR values were similar across the treatment groups. A greater reduction in UACR with tirzepatide than placebo was observed when expressed as percent change from baseline at all post-baseline visits.

Table 34 Percent Change from Baseline in UACR at Week 52 and Safety Follow-Up. MMRM by Treatment and Visit Using Log Transformation. Safety Population. OSA Analysis Set

UACR (g/kg)	Placebo (N = 234)	Tirzepatide (N = 233)
Baseline	(n = 217)	(n = 229)
Actual value, estimate (SE)	9.8 (0.69)	9.7 (0.66)
Week 52	(n = 171)	(n = 210)
Percent CFB, estimate (SE)	-6.4 (5.21)	-29.6 (3.61)
Percent change difference from placebo (95% CI)		-24.8 (-35.2, -12.8)
Safety follow-up	(n = 184)	(n = 211)
Percent CFB, estimate (SE)	-4.7 (5.62)	-21.7 (4.34)
Percent change difference from placebo (95% CI)		-17.9 (-29.9, -3.7)

Abbreviations: CFB = change from baseline; CI = confidence interval; MMRM = mixed model repeated measures; n = number of participants in the population with baseline and postbaseline value at the specified time point; N = number of participants in the safety population in the specified treatment group; OSA = obstructive sleep apnea; SE = standard error; UACR = urine albumin/creatinine ratio.

Renal Safety Conclusions

Key conclusions regarding the assessment of renal safety with tirzepatide are:

- Overall, the percentage of tirzepatide-treated participants with TEAEs of renal disorders was low (0.4%). One participant reported one event-based on the SMQ search, which was a serious (also severe) event of Acute kidney injury, which led to discontinuation of the study drug.

- For both tirzepatide and placebo groups, the majority of participants' eGFR remained in the same category. The percentage of participants shifting to a lower eGFR category was comparable in the tirzepatide (24%) and placebo (21%) groups.
- For both tirzepatide and placebo groups, the majority of participants' UACR remained in the same category. Compared to placebo, a lower percentage of tirzepatide-treated participants shifted to a higher UACR category and a higher percentage shifted to a lower UACR category.

These data demonstrate that overall, treatment with tirzepatide does not negatively impact kidney function and lowers albuminuria compared to placebo. The overall renal safety findings remain consistent with the known safety profile of tirzepatide.

Hepatobiliary Disorders

OSA is associated with metabolic dysfunction-associated steatotic liver disease, a common condition affecting up to 75% of people with obesity, and 1 in 4 persons globally (Loomba and Sanyal 2013).

While the mechanism is unknown, chronic intermittent hypoxemia may drive a number of adverse events, such as increased oxidative stress, insulin resistance, disruption in hepatic lipid metabolism, atherosclerosis, and hepatic steatosis and fibrosis (Mesarwi et al. 2019; Parikh et al. 2019).

Participants with acute or chronic hepatitis, signs and symptoms of any liver disease other than MASLD, or ALT >3×ULN, ALP >1.5×ULN, or total bilirubin level >1.2×ULN (except for cases of known Gilbert's syndrome) were excluded from the Phase 3 OSA studies.

Hepatic Events

Treatment-emergent hepatic events were reported in 3 (1.3%) participants in the tirzepatide group and 6 (2.6%) participants in the placebo group.

Table 35 Summary of Treatment-Emergent Hepatic Events. MedDRA Preferred Term by Decreasing Frequency within SMQ. Safety Population. OSA Analysis Set

SMQ Preferred Term	Placebo (N=234) n (%)	Tirzepatide (N=233) n (%)
Participants with ≥1 TEAE	6 (2.6)	3 (1.3)
Hepatic failure, fibrosis, and cirrhosis and other liver damage-related conditions (Narrow)	3 (1.3)	3 (1.3)
Hepatic steatosis	3 (1.3)	3 (1.3)
Liver related investigations, signs and symptoms	4 (1.7)	0
Broad	1 (0.4)	0
Blood alkaline phosphatase increased	1 (0.4)	0
Narrow	3 (1.3)	0
Alanine aminotransferase increased	1 (0.4)	0
Gamma-glutamyltransferase increased	1 (0.4)	0
Hepatic function abnormal	1 (0.4)	0
Transaminases increased	1 (0.4)	0

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities; n = number of participants with at least 1 treatment-emergent adverse event; N = number of participants in the specified treatment group; OSA = obstructive sleep apnea; SMQ = Standardized MedDRA Query; TEAE = treatment-emergent adverse event.

No participants reported severe or serious hepatic events.

Hepatic Analytes

Shifts in Hepatic Analytes from Baseline to Post-baseline

Alanine aminotransferase (ALT)

- Overall, a lower percentage of participants in the tirzepatide group had post-baseline ALT ≥3× ULN compared with the placebo group (0.9% and 2.7%, respectively)
- No participants had post-baseline ALT ≥5×ULN.

Aspartate aminotransferase (AST)

- No participants in the tirzepatide group had post-baseline AST ≥3×ULN compared with 3 (1.3%) participants in the placebo group.
- No participants had post-baseline AST ≥5×ULN.

Total bilirubin

- No participants had total bilirubin values ≥2×ULN post-baseline.

Alkaline phosphatase (ALP)

- No participants had a post-baseline ALP value ≥2×ULN.

Decreases from baseline to Week 52 for all hepatic analytes (ALT, AST, and ALP) except bilirubin were observed for tirzepatide. At Week 52, the mean percent decrease in ALT, AST, and ALP was greater in the tirzepatide-treated group compared to the placebo-treated group.

No TEAEs of hepatic enzyme abnormalities were reported for tirzepatide-treated participants.

Evaluation of Drug-Induced Serious Hepatotoxicity

A hepatocellular drug-induced liver injury (DILI) screening plot was created for all participants from the safety population using:

- maximum post-baseline transaminases (ALT or AST) whichever was higher, regardless of the time between the two maximum values, divided by the ULN on the x-axis, and
- maximum post-baseline total bilirubin divided by the ULN on the y-axis

Two (0.9%) tirzepatide-treated participants and 6 (2.7%) placebo-treated participants had ALT/AST ≥3 ×ULN. No participants met the criteria for hyperbilirubinemia. No participants had serum ALT and total bilirubin levels of >3×ULN and >2×ULN, respectively (Hy's Law).

Overall, the hepatic safety findings remain consistent with the known safety profile of tirzepatide for weight management. Based on the results, tirzepatide is not associated with adverse hepatic events or drug-induced liver injury.

Gallbladder-Related Disorders

There is limited literature on the association of OSA with gallbladder-related disorders. A national observational study in Taiwan showed increased risk of gallstones in patients with OSA compared to those without (adjusted hazard ratio = 1.53, 95% CI = 1.16–2.03) after adjustment for age, sex, hyperlipidaemia, diabetes, hypertension, chronic obstructive pulmonary disease, stroke, and coronary artery disease (Chen et al. 2019).

In addition, many epidemiological studies have found increased risk of gallbladder disease with greater BMI. Studies report a 2- to 7-fold increase in risk among persons with obesity, depending on BMI category (Aune et al. 2015; Figueiredo et al. 2017). Approximately 25% of people with a BMI ≥40 kg/m^2 show evidence of gallbladder disease (Stinton and Shaffer 2012).

Treatment-emergent gallbladder disease was reported in 2 (0.9%) participants in the tirzepatide group and 2 (0.9%) participants in the placebo group. Each of the 4 participants reported Cholelithiasis.

No tirzepatide-treated participants and 2 (0.9%) placebo-treated participants reported serious or severe gallbladder-related events (PT of Cholelithiasis) in the OSA Analysis Set. Both placebo-treated participants experienced serious events.

The overall gallbladder-related safety findings are adequately described in product labeling and remain consistent with the known safety profile of tirzepatide.

Major Depressive Disorder/Suicidal Ideation or Behaviour

The systematic literature review revealed there are high rates of depression in people with OSA and increased prevalence of OSA in individuals with MDD. Undiagnosed and untreated OSA is associated with depression, and treatment of OSA is related to improvement in both OSA and psychiatric symptoms (Ohayon 2003; Gupta and Simpson 2015). Meta-analysis also supports a bidirectional relationship between overweight or obesity and depression (Luppino et al. 2010).

Sleep apnoea is associated with increased prevalence of suicidal ideation, planning, and attempts (Bishop et al. 2018). The association of obesity to suicidal ideation and behaviour is more complex, with conflicting findings and the potential of multiple contributing factors confounding the association (Dutton et al. 2013; Klinitzke et al. 2013; Wagner et al. 2013).

Participants were excluded from the Phase 3 OSA studies if any of the following applied:

- history of clinically relevant medical, behavioural, or psychiatric disorder, other than OSA, that is associated with insomnia or excessive sleepiness
- are, in the judgment of the investigator, actively suicidal and therefore deemed to be at significant risk for suicide (based on answers to C-SSRS)
- PHQ-9 score of 15 or more at Visit 1 or 2, prior to randomization.

Due to the increased risk of depression in patients with obesity and OSA, AEs of MDD or suicidal ideation or behaviour are a topic of interest in the tirzepatide Phase 3 OSA studies. At baseline, at least 1 pre-existing condition in the Psychiatric disorders SOC was reported by 22.9% of participants in the OSA Analysis Set and the most commonly reported PTs were Depression (9.6%), Anxiety (9.0%), and Insomnia (3.0%).

TEAEs of Major Depressive Disorder or Suicidal Ideation or Behaviour

A total of 9 (tirzepatide, 2.1%; placebo, 1.7%) participants reported at least 1 TEAE of MDD or suicidal ideation or behaviour events in the OSA Analysis Set.

Table 36 Summary of Treatment-Emergent Major Depressive Disorder/Suicidal Ideation Events. MedDRA Preferred Term by Decreasing Frequency within SMQ and Scope. Safety Population. OSA Analysis Set

SMQ Scope Preferred Term	Placebo (N=234) n (%)	Tirzepatide (N=233) n (%)
Participants with ≥1 TEAE	4 (1.7)	5 (2.1)
Depression (excl suicide and self-injury)	4 (1.7)	3 (1.3)
Narrow	4 (1.7)	3 (1.3)
Depression	4 (1.7)	3 (1.3)
Suicide/self-injury	0	2 (0.9)
Narrow	0	2 (0.9)
Suicide attempt	0	2 (0.9)

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities; n = number of participants with event; N = number of participants in population; OSA = obstructive sleep apnea; SMQ = Standardized MedDRA Query; TEAE = treatment-emergent adverse event.

A total of 2 (0.9%) tirzepatide-treated participants and 3 (1.3%) participants in the placebo group experienced at least 1 severe or serious TEAE of MDD or suicidal ideation or behaviour in the OSA Analysis Set.

Two (0.9%) tirzepatide-treated participants experienced 2 serious events of Suicide attempt.

The first case of SAE suicide attempt concerned a patient, who committed a suicide attempt on Day 297 of tirzepatide treatment. A history of depression including prior suicide attempts was reported. Tirzepatide dose was not changed. The subject completed the study on study drug.

The second case of SAE suicide attempt concerned a patient with medical history of anxiety and was rated as related to study drug (tirzepatide). Throughout the study duration, participant denied suicidal ideation or behaviour on C-SSRS assessments; PHQ score was 0 on Study Day 150 and 1 on Study Day 348.

Participant completed treatment and study participation. Following completion of the study, the patient reported experiencing serious and severe mood swings beginning on the first day of the study, and additionally, that patient made a suicide attempt and was hospitalized on Study Day 296, approximately 3 months prior to study completion. Sertraline and trazadone were added after the hospitalization and discontinued approximately 6 weeks later.

It is somehow noticeable that C-SSRS tests during the study did not point to any suicidal risk. Since the patient reported to have experienced severe mood swings from the first day of the study, the event had to be rated as related to study drug. In terms of treatment response, it is noted that the patient achieved BMI reduction by about 25% at week 52 as compared to baseline.

Columbia-Suicide Severity Rating Scale

The C-SSRS is a scale that captures the occurrence, severity, and frequency of suicidal ideation, behaviour, or both during the assessment period via questionnaire.

Table ISS.4.46 summarizes the percentage of participants that reported at least 1 "yes" answer on the C-SSRS in the OSA Analysis Set. One (0.5%) placebo-treated participant reported "wish to be dead" and 1 (0.4%) tirzepatide-treated participant reported "non-fatal suicide attempt" on the C-SSRS. The other tirzepatide-treated participant that reported a suicide attempt did not have any "yes" responses on the suicidal ideation or suicidal behaviour portions of the C-SSRS.

Patient Health Questionnaire-9

The PHQ-9 is a validated self-reported screening tool that assesses the presence and intensity of depressive symptoms in a primary care setting (Kroenke et al. 2001). Each of the 9 criteria is scored from 0 (or not at all) to 3 (or nearly every day). The individual scores from each PHQ-9 question are then totalled. Total scores for the PHQ-9 range from 0 to 27, with total scores categorized (0-4: none or not depressed; 5-9: mild; 10-14: moderate; 15-19: moderately severe; 20-27: severe).

For both the tirzepatide and placebo groups, the majority of participants' PHQ-9 score remained in the same category reported at baseline. The percentage of participants shifting to a lower PHQ-9 category (consistent with improvement in depressive symptoms) was numerically higher in the tirzepatide group than in the placebo group. The percentage of participants shifting to a higher category (consistent with worsening of depressive symptoms) was numerically lower in the tirzepatide group than in the placebo group.

Table 37 Shift Table Summary of PHQ-9 from Maximum Baseline to Maximum Post-baseline from Baseline to Safety Follow-up. Safety Population. OSA Analysis Set

Shift Category	Placebo (N=218) n (%)	Tirzepatide (N=230) n (%)
Remained in the same category	128 (58.7)	141 (61.3)
Moved to a higher category (consistent with worsening)	62 (28.4)	41 (17.8)
Moved to a lower category (consistent with improvement)	27 (12.4)	47 (20.4)

Abbreviations: n = number of participants in each shift category; N = number of participants in treatment group; OSA = obstructive sleep apnea; PHQ-9 = Patient Health Questionnaire-9.

Major Depressive Disorder/Suicidal Ideation or Behaviour Conclusions

Depression and depressive symptoms were common at baseline with 9.6% of participants in the OSA Analysis Set reporting pre-existing depression, and 37.7% of participants having at least mild depression by PHQ-9 total score prior to the first dose of study drug.

- The percentage of participants reporting TEAEs for the Depression SMQ was similar in the tirzepatide and placebo groups (tirzepatide, 1.3%; placebo, 1.7%), and 2 (0.9%) tirzepatide-treated participants reported events of Suicide attempt in the Suicide/self-injury SMQ.
- Based on the PHQ-9 total score, there was a higher percentage of placebo-treated participants compared with tirzepatide-treated participants who experienced a shift to higher categories of depression.
- The overall rate of severe or serious events of depression or suicidality was 0.9% in tirzepatide-treated participants compared to 1.3% in placebo-treated participants. In all cases, participants had either medical history of depression and/or anxiety, concomitant medications suggestive of psychiatric illness, or both.

Individuals with OSA are at an increased risk of depression and suicidality, and the obesity population and specifically the population experiencing weight reduction is known to be at risk for depression and suicidality. Based on the clinical trial results, the baseline risk of the population, and the known mechanisms of incretin-based therapies, the data from the OSA Analysis Set do not support an association between tirzepatide and MDD, or between tirzepatide and suicidal ideation or behaviour. This is consistent with the safety assessment previously conducted for tirzepatide.

Exocrine Pancreas Safety

Pancreatitis has been reported with the use of GLP-1 receptor agonists. The FDA and the EMA have explored multiple streams of data pertaining to a pancreatic safety signal associated with incretin-based

drugs and both agencies continue to monitor pancreatic AEs associated with the use of incretins (Egan et al. 2014). Accordingly, the current Mounjaro SmPC contains an explicit warning on acute pancreatitis in section 4.4.

Lilly implemented measures during the tirzepatide clinical development program, including the OSA studies, to minimize potential risks of pancreatitis. Specifically, participants with a history of chronic or acute pancreatitis were excluded from participation in tirzepatide clinical studies, and participants diagnosed with acute or chronic pancreatitis by investigators during the study were required to be permanently discontinued from the study drug.

Measures were implemented to identify actual and potential cases of pancreatitis based on clinical signs, symptoms, laboratory assessments, and expert evaluations utilizing:

- relevant AEs
- serial enzyme measurements, and
- independent adjudication of events.

The diagnosis of acute pancreatitis required at least 2 of the following 3 features:

- abdominal pain, characteristic of acute pancreatitis (generally located in the epigastrium and radiating to the back in approximately half the cases [Banks and Freeman 2006; Koizumi et al. 2006]; the pain is often associated with nausea and vomiting)
- serum amylase (total, pancreatic, or both), lipase ≥3×ULN, or both, and
- characteristic findings of acute pancreatitis on computed tomography scan or magnetic resonance imaging.

Criteria for sending cases for adjudication were intentionally broad to capture all potential cases of pancreatitis and included all suspected cases of acute or chronic pancreatitis and / or AEs of severe or serious abdominal pain of unknown aetiology.

Summary of investigator-reported and CEC-adjudicated cases

The Table below summarizes investigator-reported events and adjudicated pancreatic events for the OSA Analysis Set.

A total of 2 (0.9%) tirzepatide-treated participants with 2 events and no placebo-treated participants experienced events of suspected pancreatitis that were sent for CEC adjudication.

In total, 2 (0.9%) tirzepatide-treated participants and no placebo-treated participants were confirmed by adjudication to each have 1 event of acute pancreatitis. No cases of chronic pancreatitis or unknown (unable to determine) were reported, and no cases were assessed by the adjudicators as severe or critical.

In 1 of the 2 cases of adjudication-confirmed acute pancreatitis in tirzepatide-treated participants, imaging results were used in combination with symptoms and pancreatic enzymes for adjudication. The event experienced by the other participant was reported as Lipase increased by the investigator, and it was adjudicated based on independently reported events of abdominal pain and elevated lipase, without imaging results. Both patients discontinued tirzepatide, recovered and completed the study off drug.

The exposure-adjusted incidence rate per 100 patient-years of exposure for treatment-emergent adjudication-confirmed pancreatitis in the OSA Analysis Set was 0.84 per 100 patient-years for tirzepatide and 0 per 100 patient-years for placebo.

Table 38 Summary of Adjudicated Pancreatic Events. Safety Population. OSA Analysis Set

Events	Placebo (N = 234) n (%); Events	Tirzepatide (N = 233) n (%); Events
Investigator-reported events	0	2 (0.9); 2
Non investigator-reported triggered events	0	0
CEC pancreatitis assessment	0	2 (0.9); 2
No	0	0
Unknown (unable to determine)	0	0
Yes	0	2 (0.9); 2
Acute pancreatitis	0	2 (0.9); 2
Chronic pancreatitis	0	0
Diagnostic criteria used to confirm acute pancreatitis		
Symptoms and imaging	0	0
Symptoms and elevated enzymes	0	1 (0.4); 1
Imaging and asymptomatic elevated enzymes	0	0
Symptoms, imaging, and elevated enzymes	0	1 (0.4); 1

Abbreviations: CEC = clinical endpoint committee; n = number of participants with at least 1 pancreatic event; N = total number of participants in the specified treatment group; OSA = obstructive sleep apnea.

In addition to the events identified by investigators and sent for adjudication, treatment-emergent pancreatic AEs were identified using MedDRA PTs contained within Acute pancreatitis SMQ (narrow terms), and Pancreatitis chronic PT. No additional events of confirmed acute pancreatitis were identified through this MedDRA search strategy.

Pancreatic Enzymes

Categorical shifts

Serum p-amylase

The Table below presents a summary of shifts in p-amylase from maximum baseline to maximum post-baseline for participants with a maximum baseline ≤1×ULN and >1×ULN in the OSA Analysis Set.

During the post-baseline period, most participants in both the tirzepatide (87.1%) and placebo (88.0%) groups had p-amylase values in the normal range (≤1×ULN).

One (0.4%) tirzepatide-treated participant shifted from baseline p-amylase value of ≤1×ULN to post-baseline value >3×ULN. This participant did not have investigator-reported events submitted for adjudication. No placebo participants had post-baseline p-amylase values >3×ULN.

Table 39 Summary of Categorical Shifts in p-Amylase from Baseline to Safety Follow-up. Safety Population. OSA Analysis Set

Treatment	Maximum Baseline	Maximum Postbaseline, n (%)						
		≤1×ULN	>1×ULN to ≤3×ULN	>3×ULN to ≤5×ULN	>5×ULN to ≤10×ULN	>10×ULN	Missing	Total
Placebo (N = 234)	≤1×ULN	201 (85.9)	13 (5.6)	0	0	0	12 (5.1)	226 (96.6)
	>1×ULN	5 (2.1)	3 (1.3)	0	0	0	0	8 (3.4)
	Missing	0	0	0	0	0	0	0
	Total	206 (88.0)	16 (6.8)	0	0	0	12 (5.1)	234 (100.0)
Tirzepatide (N = 233)	≤1×ULN	200 (85.8)	28 (12.0)	1 (0.4)	0	0	1 (0.4)	230 (98.7)
	>1×ULN	2 (0.9)	0	0	0	0	0	2 (0.9)
	Missing	1 (0.4)	0	0	0	0	0	1 (0.4)
	Total	203 (87.1)	28 (12.0)	1 (0.4)	0	0	1 (0.4)	233 (100.0)

Abbreviations: n = number of participants in each shift category; N = number of participants in the population with postbaseline value; OSA = obstructive sleep apnea; ULN = upper limit of normal.

Serum lipase

The Table below presents a summary of shifts in serum lipase from maximum baseline to maximum post-baseline for participants with a maximum baseline ≤1×ULN and >1×ULN in the OSA Analysis Set.

During the post-baseline period, most participants in both the tirzepatide (63.1%) and placebo (83.8%) groups had lipase values in the normal range (≤1×ULN).

Of the 5 (2.1%) tirzepatide-treated participants who shifted from baseline lipase value of ≤1×ULN to post-baseline value >3×ULN, none had investigator-reported events submitted for adjudication.

One tirzepatide-treated participant with elevated lipase at screening and maximum post-baseline lipase >3 to ≤5×ULN at Week 24 had adjudication-confirmed acute pancreatitis. One placebo-treated participant (0.4%) shifted from baseline lipase of ≤1×ULN to post-baseline lipase >5 to ≤10×ULN at the safety follow-up visit. No cases of elevated lipase in the placebo group were submitted for adjudication.

Table 40 Summary of Categorical Shifts in Lipase from Baseline to Safety Follow-up. Safety Population. OSA Analysis Set

Treatment	Maximum Baseline	Maximum Postbaseline, n (%)						
		≤1×ULN	>1×ULN to ≤3×ULN	>3×ULN to ≤5×ULN	>5×ULN to ≤10×ULN	>10×ULN	Missing	Total
Placebo (N = 234)	≤1×ULN	188 (80.3)	18 (7.7)	0	1 (0.4)	0	12 (5.1)	219 (93.6)
	>1×ULN	7 (3.0)	4 (1.7)	3 (1.3)	0	0	0	14 (6.0)
	Missing	1 (0.4)	0	0	0	0	0	1 (0.4)
	Total	196 (83.8)	22 (9.4)	3 (1.3)	1 (0.4)	0	12 (5.1)	234 (100.0)
Tirzepatide (N = 233)	≤1×ULN	143 (61.4)	71 (30.5)	4 (1.7)	1 (0.4)	0	1 (0.4)	220 (94.4)
	>1×ULN	3 (1.3)	7 (3.0)	1 (0.4)	1 (0.4)	0	0	12 (5.2)
	Missing	1 (0.4)	0	0	0	0	0	1 (0.4)
	Total	147 (63.1)	78 (33.5)	5 (2.1)	2 (0.9)	0	1 (0.4)	233 (100.0)

Abbreviations: n = number of participants in each shift category; N = number of participants in the population with postbaseline value; OSA = obstructive sleep apnea; ULN = upper limit of normal.

Time course of pancreatic enzymes

The figure below presents a time profile for mean pancreatic amylase and lipase at planned time points for participants in the OSA Analysis Set.

Mean baseline serum p-amylase and lipase levels were similar among the treatment groups.

Compared to the placebo group, mean serum levels of p-amylase for participants in the tirzepatide group increased from Week 0 to Week 52; mean serum lipase values increased from Week 0 to Week 24 and plateaued through Week 52. All mean values remained within the normal range.

Mean p-amylase and lipase values had decreased at the time of the safety follow-up in the tirzepatide group but were still higher than baseline and higher than the placebo group.

Figure 11 Time profile for estimated geometric mean of pancreatic enzymes for participants in the OSA Analysis Set (p-amylase)

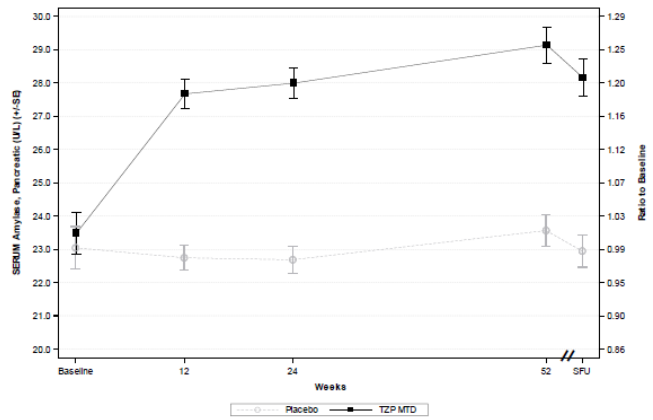
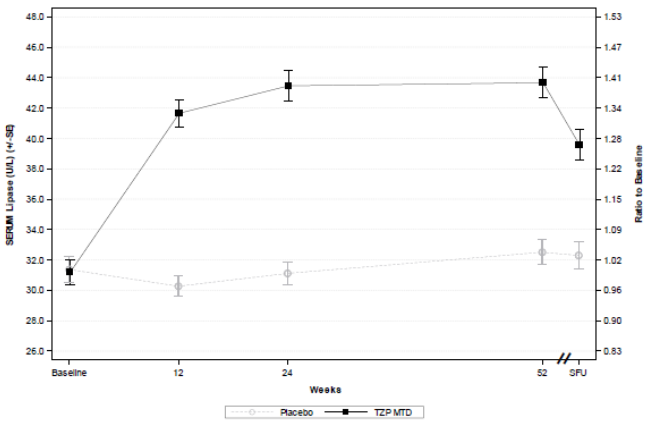


Figure 12 Time profile for estimated geometric mean of pancreatic enzymes for participants in the OSA Analysis Set (lipase).



Exocrine Pancreas Conclusions

Pancreatic events

- A total of 2 (0.9%) tirzepatide-treated participants had 2 events of suspected pancreatitis that were sent for CEC adjudication.
    - 2 (0.9%) tirzepatide-treated participants were confirmed to have 2 events of acute pancreatitis by adjudication. Both events of acute pancreatitis were mild in severity as assessed by the adjudicators.
    - 1 of the 2 events of acute pancreatitis was reported as an SAE.
- The exposure-adjusted incidence rate per 100 patient-years of exposure for treatment-emergent adjudication-confirmed pancreatitis was 0.84 per 100 patient-years for tirzepatide in the OSA studies. The rate for tirzepatide in the Phase 3 weight management studies was 0.13 per 100 patient-years.

Pancreatic enzymes

- Tirzepatide was associated with increases in p-amylase and lipase. More tirzepatide-treated participants had elevated pancreatic enzymes >3×ULN compared to placebo (0.4% vs. 0% p-amylase, and 3.0% vs. 1.7% lipase).
- After peaking around 24 weeks of treatment, pancreatic enzyme levels remained stable through 52 weeks, and decreased during the 4-week safety follow-up.
- Similar to observations in prior studies of tirzepatide, elevated pancreatic enzymes were not consistently associated with symptoms or events of pancreatitis.
- Elevations in pancreatic enzymes in tirzepatide-treated participants were consistent with observations in prior studies of tirzepatide in weight management.

The overall pancreatitis-related safety findings are adequately described in tirzepatide product labelling and remain consistent with the known safety profile of tirzepatide.

Cardiovascular Safety

Incretin class

One of the known effects of incretins is to increase heart rate (HR) (Lorenz et al. 2017). Changes in HR attenuate over time (Sun et al. 2015; Marso et al. 2016b; Holman et al. 2017; Lorenz et al. 2017), and in long-term CV outcomes studies, incretins have been associated with reduced risk for MACE in participants with T2DM (Drucker 2018) and those who have obesity or overweight without T2DM (Lincoff et al. 2023).

Analyses of Blood Pressure

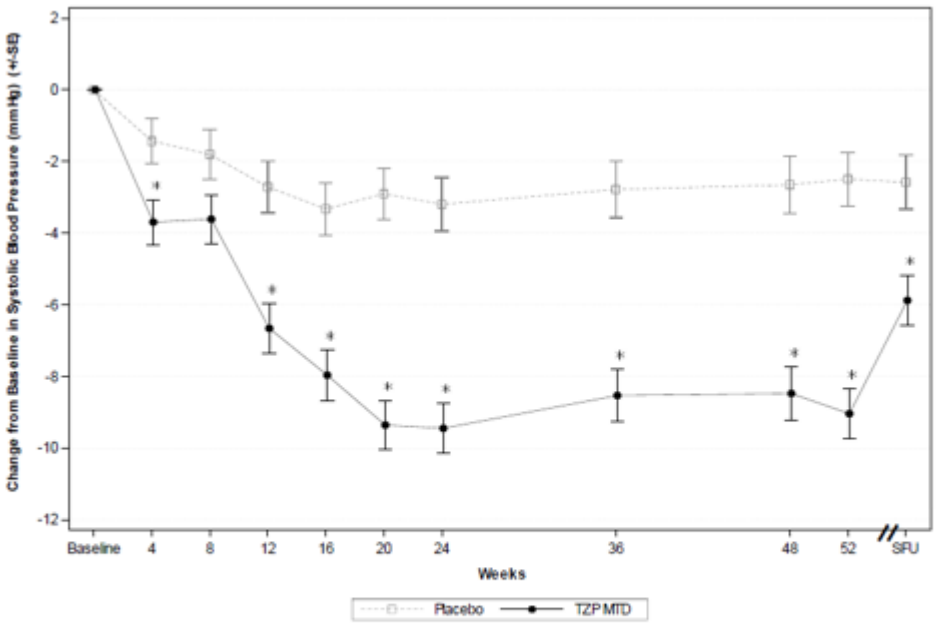
Change from baseline in SBP at Week 48 was a key secondary efficacy endpoint controlled for type 1 error and change in DBP at Week 48 was an additional secondary efficacy endpoint. BP was assessed at Weeks 48 as an efficacy endpoint because PAP suspension at Week 52 could potentially confound the assessment of BP.

Baseline mean sitting SBP values were similar between the tirzepatide and placebo groups in the OSA Analysis Set (tirzepatide: 129.5 mmHg, and placebo: 130.5 mmHg).

In the tirzepatide group, mean SBP decreased from Week 0 to Week 20 and plateaued through Week 52. In the placebo group, SBP slightly decreased from baseline through Week 16, and then plateaued. Reductions in SBP were greater in the tirzepatide group compared to the placebo group at all time points through Week 52 and the safety follow-up visit, except Week 8. The maximal decreases in SBP were for tirzepatide: -9.5 mmHg, and for placebo: -3.3 mmHg.

The reductions in SBP were consistent with those observed previously in the weight management populations.

Figure 13 Change from baseline in systolic blood pressure by treatment and visit for the OSA Analysis Set.



Abbreviations: LS mean = least squares mean; MMRM = mixed model repeated measures; MTD = maximum tolerated dose; OSA = obstructive sleep apnea; SE = standard error; SFU = safety follow-up; TZP = tirzepatide.
Note: Mean estimate (+/- error bar) are LSmean (+/- SE) calculated from MMRM model: Variable = Baseline + Substudy Identifier + Baseline OSA Severity Group 2 + Sex + Geographic Region 1 + Treatment + Time + Treatment*Time (Type III sum of squares).
Variance-Covariance structure (Change from Baseline) = Unstructured.
*p-Value for TZP versus Placebo comparison less than 0.05

Change in Diastolic Blood Pressure

Baseline mean sitting DBP values were similar between the tirzepatide and placebo groups in the OSA Analysis Set (tirzepatide: 83.5 mmHg, and placebo: 82.2 mmHg.

In the tirzepatide group, mean DBP decreased through Week 52, with the greatest reduction occurring at Week 24. In the placebo group, DBP slightly decreased from baseline through Week 24, and then plateaued. Reductions in DBP were greater in tirzepatide compared to the placebo group from Week 16 through Week 52. The maximal decreases in DBP through Week 52 were for tirzepatide: -4.3 mmHg, and for placebo: -2.0 mmHg.

The reductions in DBP were consistent with those observed previously in the weight management populations.

Treatment-Emergent Abnormal Blood Pressure

Lilly evaluated the number of participants who had treatment-emergent abnormal vital signs at any time during the OSA studies. The change from the minimum value during the baseline period to the minimum value during the post-baseline period was used to assess decreases.

Changes from the maximum value during the baseline period to the maximum value during the post-baseline period was used to assess increases.

The threshold criteria for identifying participants with treatment-emergent BP abnormalities are:

Parameter	Low	High
SBP (mmHg)	≤90 and decrease from baseline ≥20	≥129 and increase from baseline ≥20 ≥140 and increase from baseline ≥20
DBP (mmHg)	≤50 and decrease from baseline ≥10	≥90 and increase from baseline ≥10

For increases in SBP, fewer tirzepatide-treated participants met abnormal criteria compared to placebo, with no notable differences for increase in DBP. For decreases in SBP and DBP, no notable differences were observed in the number of participants who met abnormal criteria between tirzepatide and placebo.

Hypotension

While decreases in BP are expected to be beneficial in those with OSA and overweight or obesity, hypotension-related events have been observed with other incretin-based therapies for this population, and hypotension is an ADR for tirzepatide in those with obesity, or overweight with weight-related comorbidities.

Approximately 58% of participants reported hypertension at baseline, and 48.6% were taking antihypertensive medications.

In the broad cluster of hypotension, more tirzepatide-treated participants reported treatment-emergent hypotension-related events (6 participants, 2.6%) than placebo (2 participants, 0.9%). This treatment group difference was primarily driven by AEs reported under the PT of Hypotension.

Of the 6 tirzepatide-treated participants reporting 7 hypotension-related events, 1 reported an SAE of Hypotension, and all others were non-serious and mild or moderate in severity. No tirzepatide-treated participants had a documented SBP <90 mmHg during the treatment period in the studies. No events were associated with clinically significant outcomes.

Upon review of symptomatic terms, there was no clear temporal association of the AE with low BP. Thus, the Hypotension narrow cluster was used to inform the ADR assessment. Hypotension is listed in the current SmPC section 4.8 as common ADR. Reference to OSA patients is added in the footnote.

Pulse Rate

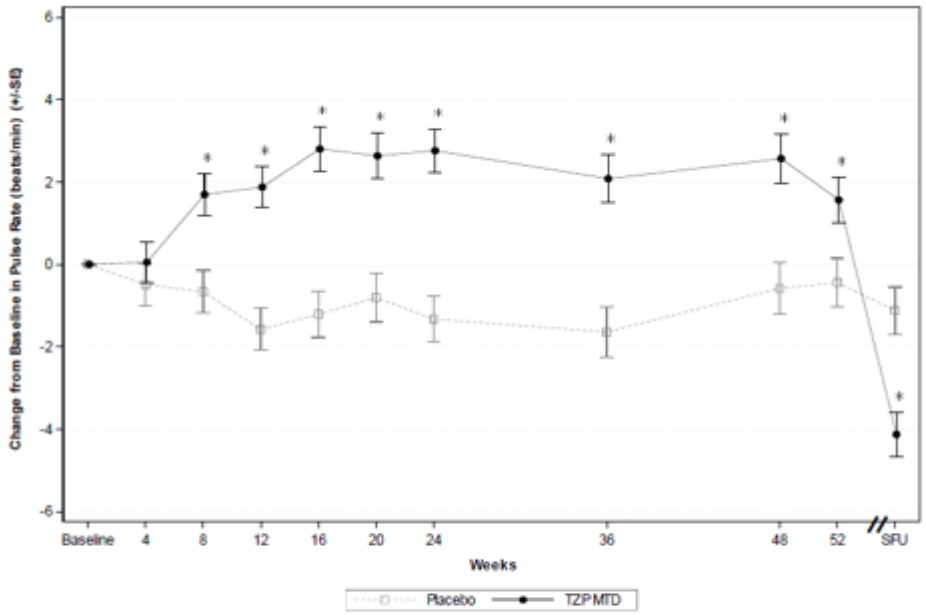
Change in Pulse Rate

Baseline mean sitting pulse rate values were similar between the tirzepatide and placebo groups in the OSA Analysis Set (tirzepatide: 74.2 bpm, and placebo: 74.1 bpm).

There were minimal mean changes from baseline over time for mean pulse rate in the placebo group. The mean pulse rate began to increase in the tirzepatide group at Week 8 and reached the maximum value during dose-escalation. The maximal mean increase in pulse rate was 2.8 bpm.

Mean pulse rate then gradually decreased throughout the treatment period with the mean change from baseline at 52 weeks being 1.6 bpm for tirzepatide. At the time of the safety follow-up assessment, mean pulse rate values for tirzepatide were 3.0 bpm lower than placebo and 4.1 bpm lower than the baseline values for the tirzepatide group.

Figure 14 Change from baseline in pulse rate by treatment and visit in the OSA Analysis Set.



Abbreviations: LS mean = least squares mean; MMRM = mixed model repeated measures; MTD = maximum tolerated dose; OSA = obstructive sleep apnea; SE = standard error; SFU = safety follow-up; TZP = tirzepatide.
Note: Mean estimate (+/- error bar) are LSmean (+/- SE) calculated from MMRM model: Variable = Baseline + Substudy Identifier + Baseline OSA Severity Group 2 + Sex + Geographic Region 1 + Treatment + Time + Treatment*Time (Type III sum of squares).
Variance-Covariance structure (Change from Baseline) = Unstructured.
*p-Value for TZP versus Placebo comparison less than 0.05

The changes in pulse rate were consistent with a known effect of incretins and the safety profile of tirzepatide for weight management. Adequate wording on changes in HR is included in the current SmPC section 4.8.

Treatment-Emergent Abnormal Pulse Rate

Lilly evaluated the number of participants who had treatment-emergent abnormal pulse rate at any time during the OSA studies.

More tirzepatide-treated participants experienced pulse rate of more than 100 bpm at any visit than placebo, but the percentage of participants meeting this threshold at 2 or more consecutive visits, or 3 or more visits was low and similar between groups. No participants reached the threshold of greater than 130 bpm.

Similar percentages of tirzepatide-treated participants met the criterion of change from baseline greater than 20 bpm at any visit, at 2 or more consecutive visits, and at 3 or more visits compared to placebo. The percentage of participants meeting this threshold at 2 or more consecutive visits, or 3 or more visits was low in both treatment groups.

Table 41 Summary of Participants Meeting Threshold Criteria for Abnormal Pulse Rate Post-baseline. Safety Population. OSA Analysis Set

Threshold Criteria for Pulse Rate (bpm)	Placebo (N = 234) n (%)	Tirzepatide (N = 233) n (%)	Tirzepatide vs. Placebo p-Value[a]
N1	229	232	
>100 at any visit	11 (4.8)	18 (7.8)	0.166
>100 for ≥2 consecutive visits	4 (1.7)	5 (2.2)	0.726
>100 for ≥3 visits	4 (1.7)	3 (1.3)	0.707
>130 at any visit	0	0	NA
N2	229	232	
CFB >20 at any visit	10 (4.4)	15 (6.5)	0.306
CFB >20 for ≥2 consecutive visits	1 (0.4)	2 (0.9)	0.563
CFB >20 for ≥3 visits	1 (0.4)	2 (0.9)	0.563
>100 and CFB ≥15 at any visit	3 (1.3)	8 (3.4)	0.121
<50 and CFB ≤-15 at any visit	2 (0.9)	0	0.146

Abbreviations: CFB = change from baseline; n = number of participants meeting threshold criteria; N = number of participants in the population; NA = not applicable; N1 = total number of participants in specified time point; N2 = total number of participants with both baseline and postbaseline results in specified category; OSA = obstructive sleep apnea; vs. = versus.

[a] p-Values are from Cochran-Mantel-Haenszel test of general association stratified by study.

Treatment-Emergent Arrhythmias and Cardiac Conduction Disorders

Similar percentages of participants in the tirzepatide group (5.6%) and the placebo group (4.7%) experienced at least 1 TEAE of arrhythmia and cardiac conduction disorders. Most events in the tirzepatide group occurred in the Arrhythmia related investigations, signs and symptoms SMQ (tirzepatide, 3.9%; placebo, 2.1%), with Heart rate increased (tirzepatide 2.6%; placebo 0.9%) and Tachycardia (tirzepatide 0.9%; placebo 0.4%) comprising the majority of events. Supraventricular tachyarrythmias (narrow SMQ) were observed more often across placebo patients (2.1%) as compared to tirzepatide (0.9%).

Cardiovascular Safety Conclusions

Key CV safety conclusions for the OSA Analysis Set are:

- There were no CEC-confirmed MACE events in tirzepatide-treated participants, and 2 events in 1 placebo-treated participant.
- Mean reductions in SBP and DBP were greater with tirzepatide compared to placebo.
- Numerically more hypotension-related TEAEs, driven by the PT Hypotension were observed with tirzepatide than placebo. These TEAEs were infrequent and generally mild and moderate in severity for participants.
- Pulse rate increased from baseline through dose-escalation to a maximum value (tirzepatide, 2.8 bpm) then gradually decreased toward baseline at 52 weeks (tirzepatide, 1.6 bpm). More tirzepatide-treated participants met abnormally high criteria compared with placebo. However, the percentage of participants meeting abnormally high pulse rate categories for 2 or more consecutive or 3 or more visits was low.
- Similar frequencies of participants in tirzepatide and placebo groups experienced at least 1 TEAE, or serious or severe AE, of arrhythmia or cardiac conduction disorders.

Based on these results, the CV safety profile observed in the OSA studies appears consistent with that of the known safety profile of tirzepatide and is adequately described in product labelling.

Malignancy

Treatment-Emergent Malignant Neoplasm Events

The Table below presents a summary of the incidence of malignancy events by anatomical location of malignancy for participants in the tirzepatide Phase 3 OSA studies. One tirzepatide treated participant reported treatment-emergent malignancy of clear cell renal carcinoma.

Table 42 Treatment-Emergent Malignancies. OSA Analysis Set

Location of Cancer Preferred Term	Placebo (N=234) n (%)	Tirzepatide (N=233) n (%)
Participants with ≥1 TEAE of Malignancy	7 (3.0)	1 (0.4)
Malignant tumors	6 (2.6)	1 (0.4)
Narrow	6 (2.6)	1 (0.4)
Clear cell renal carcinoma	0	1 (0.4)
Gastric cancer	1 (0.4)	0
Malignant melanoma	1 (0.4)	0
Metastasis	1 (0.4)	0
Plasma cell myeloma	1 (0.4)	0
Prostate cancer metastatic[a]	1 (0.6)	0
Squamous cell carcinoma of skin	1 (0.4)	0
Tonsil cancer metastatic	1 (0.4)	0
Tumors of unspecified malignancy	1 (0.4)	0
Narrow	1 (0.4)	0
Neoplasm skin	1 (0.4)	0

Abbreviations: n = number of participants with event; N = number of participants in the population; OSA = obstructive sleep apnea; TEAE = treatment-emergent adverse event.

[a] Denominator adjusted because of gender-specific event for males: N = 165 (tirzepatide); N = 161 (placebo).

No cases of MTC or C-cell hyperplasia were reported. No cases of pancreatic cancer were reported. These results do not suggest an increased incidence of thyroid, pancreatic, or any other malignancy with tirzepatide treatment, and are consistent with the findings from other tirzepatide studies supporting T2DM and weight management. Lilly will continue to carefully assess the risk for malignancies in ongoing studies and through post-marketing cases.

Thyroid Safety

Thyroid C-cell tumors, also known as MTC, are a rare carcinoma and account for 1% to 2% of thyroid cancers (Wells et al. 2015). Preclinical rodent studies have suggested that GLP-1 receptor agonists may be associated with an increased risk of thyroid C-cell tumors (Trujillo 2020). However, human data to date do not support the association of GLP-1 receptor agonists with thyroid C-cell tumors in humans (Hegedüs et al. 2018; Bethel et al. 2019; Liang et al. 2019). Although clinical trial data show no association between thyroid cancer and incretin-based therapies to date, a recent publication has triggered more discussion about thyroid cancer risk and GLP-1 receptor agonists treatment (Bezin et al. 2023; Endo et al. 2023; Goldenberg and Jain 2023; Mañas-Martinez and Gimeno-Orna 2023; Smits and van Raalte 2023). Thyroid safety continues to be evaluated with incretin-based therapies.

Lilly implemented measures during the tirzepatide OSA studies to monitor, identify and minimize potential thyroid safety risks:

- exclusion criteria: family or personal history of MTC or multiple endocrine neoplasia type 2, and participants who met the following specific screening serum calcitonin values:

  o ≥20 ng/L at screening, if eGFR ≥60 mL/min/1.73 m^2,
  o ≥35 ng/L at screening, if eGFR <60 mL/min/1.73 m^2

- reporting of any case of thyroid malignancy, including C-cell hyperplasia, MTC, or MEN Syndrome type 2, and
- monitoring of calcitonin. Participants with significant elevation of calcitonin may have been discontinued from study drug.

No events of MTC were reported.

Calcitonin

The purpose of calcitonin measurements was to assess the potential of tirzepatide to affect thyroid C-cell function, which may have indicated development of C-cell hyperplasia or neoplasms.

Categorical shifts in calcitonin, baseline to post-baseline

Maximum baseline to maximum post-baseline categorical shifts in calcitonin in the OSA Analysis Set were summarized.

Nearly all participants had baseline calcitonin values ≤20 ng/L; a total of 6 participants had missing values. During the study period, most participants remained in the same category as at baseline. None of the participants discontinued the study treatment due the increased blood calcitonin levels. No meaningful difference in the percentage of participants who shifted to a higher calcitonin category post-baseline between tirzepatide and placebo groups was observed.

Key conclusions related to thyroid safety with tirzepatide in the OSA studies are:

- no cases of MTC or C-cell hyperplasia were identified, and
- the percentage of participants who shifted to a higher calcitonin category post-baseline was low.

In summary, these results showed no evidence for increased risk of MTC, C-cell hyperplasia, or clinically relevant elevation of calcitonin levels with tirzepatide treatment. These results are consistent with the results seen in the weight management applications. The overall thyroid safety findings are adequately described in product labeling and remain consistent with the know safety profile of tirzepatide. *Blood calcitonin increase* is listed in section 4.8 of the current SmPC as uncommon adverse reaction.

Hypoglycaemia

People with diabetes at screening/randomization were excluded from Studies 1 and 2. Compared to studies in participants with T2DM in which glucometers were provided to all participants, OSA Studies 1 and 2 did not include the routine use of glucometers to systematically capture and report hypoglycaemia. Glucometers were provided to those participants who developed diabetes during the study, or to those who reported symptoms suggestive of hypoglycaemia requiring BG confirmation. Participants who were given glucometers were also provided diaries to record relevant information (for example, glucose values, symptoms). However, most participants in Studies 1 and 2 did not have glucometers.

No episodes of severe hypoglycaemia were reported. A single episode of hypoglycaemia with BG <54 mg/dL was reported post-baseline across Studies 1 and 2. It was reported by a placebo-treated participant in Study 1.

Hypersensitivity Reactions

- Immediate hypersensitivity (/ anaphylaxis) included all TEAEs that occurred within 24 hours of study drug administration, and
- non-immediate hypersensitivity included all TEAEs that occurred more than 24 hours after study drug administration, but prior to the next administration of the study drug.

Immediate hypersensitivity reactions

The percentage of participants reporting immediate hypersensitivity reactions was the same in tirzepatide- and placebo-treated participants (tirzepatide, 0.4%; placebo, 0.4%).

No events were serious, and all were mild or moderate in severity.

No discontinuations of the study drug due to immediate hypersensitivity reactions were reported.

Table 43 Summary of Treatment-Emergent Immediate Hypersensitivity Reactions. Safety Population. OSA Analysis Set

Event Category (Scope) Preferred Term	Placebo (N=234) n (%)	Tirzepatide (N=233) n (%)	Tirzepatide vs. Placebo[a] p-value
Participants with ≥1 TEAE	1 (0.4)	1 (0.4)	0.971
Hypersensitivity (Narrow)			
Injection site rash	0	1 (0.4)	0.305
Angioedema	1 (0.4)	0	0.330

Abbreviations: N = number of participants in the specified treatment group; n = number of participants with at least 1 TEAE; TEAE = treatment-emergent adverse event; vs. = versus.

[a] p-values are from Cochran-Mantel-Haenszel test of general association stratified by study.

Non-immediate hypersensitivity reactions

The percentage of participants reporting non-immediate hypersensitivity reactions was similar in tirzepatide-treated participants compared to placebo (tirzepatide, 2.6%; placebo, 2.1%).

No events were serious. Two events in 2 tirzepatide-treated participants were considered severe (1 severe event of Anaphylactic reaction and Urticaria, each).

The severe anaphylactic reaction occurred in a patient (with pre-existing anaphylactic reactions to food) three days after administration of 7.5 mg tirzepatide on Study Day 67. The patient recovered on the same day and completed the study on tirzepatide. A severe non-immediate event of urticaria was observed in a patient on Study Day 353, i.e. very shortly before study termination. She presented with a history of drug intolerance and neurodermitis. The event occurred 2 days after administration of a 15 mg tirzepatide dose and recovered within 3 days.

One placebo participant discontinued the study drug and study due to the non-immediate hypersensitivity reaction of Injection site urticarial.

Table 44 Summary of Treatment-Emergent Non-Immediate Hypersensitivity Reactions. Safety Population. OSA Analysis Set

Event Category (Scope) Preferred Term	Placebo (N=234) n (%)	Tirzepatide (N=233) n (%)	Tirzepatide vs. Placebo p-value
Participants with ≥1 TEAE	5 (2.1)	6 (2.6)	0.728
Anaphylactic reaction (Narrow)	0	1 (0.4)	0.305
Anaphylactic reaction	0	1 (0.4)	0.305
Hypersensitivity (Narrow)	5 (2.1)	6 (2.6)	0.728
Urticaria	0	3 (1.3)	0.080
Anaphylactic reaction	0	1 (0.4)	0.305
Drug hypersensitivity	0	1 (0.4)	0.328
Injection related reaction	0	1 (0.4)	0.328
Dermatitis allergic	1 (0.4)	1 (0.4)	0.971
Hand dermatitis	1 (0.4)	0	0.330
Injection site urticaria	1 (0.4)	0	0.330
Rash pruritic	1 (0.4)	0	0.330
Rhinitis allergic	1 (0.4)	0	0.307

Abbreviations: n = number of participants with at least 1 TEAE; N = number of participants in the specified treatment group; OSA = obstructive sleep apnea; TEAE = treatment-emergent adverse event; vs. = versus.

[a] p-Values are from Cochran-Mantel-Haenszel test of general association stratified by study.

Key hypersensitivity reaction safety conclusions are:

- No tirzepatide-treated participants discontinued the study drug due to hypersensitivity reactions.
- One anaphylactic reaction (tirzepatide) was observed. The event was not considered to be related to the study drug and did not lead to discontinuation.
- Overall, the percentage of participants reporting immediate and non-immediate hypersensitivity reactions was low. The frequency of immediate (tirzepatide, 0.4%; placebo, 0.4%) and non-immediate (tirzepatide, 2.6%; placebo, 2.1%) hypersensitivity reactions was similar in tirzepatide- and placebo-treated participants.
- Most hypersensitivity reactions were mild or moderate in severity. A total of 2 (0.9%) tirzepatide-treated participants in the OSA Analysis Set reported severe non-immediate hypersensitivity events. No serious events were reported.

Injection Site Reactions

In the OSA studies, study drug was self-administered once weekly as an SC injection in the abdomen or thigh; a caregiver may have administered the injection in the participant's upper arm. Participants were provided with single-dose pens for ease of administration of study drug.

The percentage of participants reporting at least 1 injection site reaction was higher in tirzepatide-treated participants compared to placebo (tirzepatide, 8.6%; placebo, 2.6%). No events were serious, and all were mild or moderate in severity. One participant (placebo) discontinued the study drug and study due to Injection site urticaria.

Table 45 Summary of Treatment-Emergent Injection Site Reactions. MedDRA Preferred Term by Decreasing Frequency within HLT. Safety Population. OSA Analysis Set

High-Level Term Preferred Term	Placebo (N=234) n (%)	Tirzepatide (N=233) n (%)	Tirzepatide vs. Placebo p-Value
Participants with ≥1 TEAE	6 (2.6)	20 (8.6)	0.004
Injection site reactions	6 (2.6)	19 (8.2)	0.007
Injection site reaction	1 (0.4)	14 (6.0)	<0.001
Injection site bruising	4 (1.7)	3 (1.3)	0.688
Injection site pruritus	0	3 (1.3)	0.085
Injection site erythema	0	2 (0.9)	0.165
Injection site rash	0	1 (0.4)	0.305
Injection site pain	1 (0.4)	0	0.330
Injection site urticaria	1 (0.4)	0	0.330
Administration site reactions NEC	0	1 (0.4)	0.305
Administration site reaction	0	1 (0.4)	0.305

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities; n = number of participants with at least 1 treatment-emergent adverse event; N = number of participants in the specified treatment group; OSA = obstructive sleep apnea; NEC = not elsewhere classified; TEAE = treatment-emergent adverse event; vs. = versus.

[a] p-Values are from Cochran-Mantel-Haenszel test of general association stratified by study.

Most events (133 of 164 [81.1%]) in the tirzepatide group occurred more than 6 hours after study drug administration, with 40.2% of events (66 of 164 events) occurring from 24 hours to 14 days after study drug administration.

Table 46 Summary of Injection Site Reaction Timing, Based on eCRF. Safety Population. OSA Analysis Set

Reaction Timing Following Study Drug Administration	Placebo (N=234) n (%)	Tirzepatide (N=233) n (%)
Number of events reported on eCRF[a]	6	164
During drug administration	0	5 (3.0)
Within 30 minutes of administration	1 (16.7)	1 (0.6)
>30 minutes to 6 hours from administration	0	21 (12.8)
>6 hours to 24 hours from administration	0	67 (40.9)
>24 hours to 14 days from administration	5 (83.3)	66 (40.2)
>14 days from administration	0	0
Unknown	0	4 (2.4)

Abbreviations: eCRF = electronic case report form; n = number of events; N = number of participants in the population; OSA = obstructive sleep apnea.

[a] Included events with at least 1 sign and symptom.

Note: The percentage is calculated based on the total number of events.

Immunogenicity

A participant was evaluable for TE ADA if the participant had a baseline ADA result, and at least 1 non-missing post-baseline ADA result.

A Participant was TE ADA+ if an evaluable participant who had a

- baseline status of ADA Not Present and at least 1 post-baseline status of ADA Present with titer ≥2×MRD of the ADA assay, or

- baseline and post-baseline status of ADA Present, with the post-baseline titer being 2 dilutions (4-fold) greater than the baseline titer.

in the OSA Analysis Set, 6.6% of evaluable tirzepatide-treated participants had detectable tirzepatide ADA at baseline. The percentage of TE ADA+ participants was 60.6%.

Table 47 Summary of Treatment-Emergent Tirzepatide ADA Status During Treatment Period. Safety Population. OSA Analysis Set

Category	Tirzepatide (N=233) n (%)
Participants evaluable for TE ADA	226 (97.0)
Baseline ADA present	15 (6.6)
Postbaseline TE ADA+ (during planned treatment period)	137 (60.6)
Postbaseline TE ADA inconclusive	0
Postbaseline TE ADA-	89 (39.4)

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

Note: The denominator for percent is the number of participants who were TE ADA evaluable in the tirzepatide treatment group, except for participants evaluable for TE ADA, for which the denominator is the number of participants in the safety population.

Hypersensitivity reactions by TE ADA status

A higher percentage of tirzepatide-treated TE ADA+ participants (4.4%) experienced hypersensitivity reactions compared to TE ADA- participants (1.1%).

Table 48 Summary of Hypersensitivity Reactions by TE ADA Status During the Planned Treatment Period. OSA Analysis Set

TE ADA status	Tirzepatide (N=233)	
	M	m (%)
TE ADA+	137	6 (4.4)
TE ADA-	89	1 (1.1)
Not evaluable	7	0

Abbreviations: ADA = anti-drug antibody; M = total number of participants in specified TE ADA status; m = number of participants in specified category (TE ADA+, TE ADA-, or not evaluable with hypersensitivity reaction); N = total number of participants in specified treatment group; OSA = obstructive sleep apnea; TE = treatment-emergent.

- The events reported in TE ADA+ participants were mostly mild to moderate in severity.
- Of the 2 participants identified as having a severe hypersensitivity reaction (see above), both were TE ADA+.
- Of the 6 TE ADA+ participants that experienced 1 or more hypersensitivity reactions, the ADA titer range was 1:40 to 1:5120 during the treatment period.
- 7 of the 137 TE ADA+ participants had a maximum ADA titer of 1:5120. Of these 7, 1 participant experienced severe Anaphylactic reaction, while no hypersensitivity events were reported for the other 6 TE ADA+ participants with titers of 1:5120.
- No apparent pattern of a temporal relationship was observed between TE ADA status or titer and the emergence or resolution of individual hypersensitivity reactions.

Injection site reactions by TE ADA status

A higher percentage of tirzepatide-treated TE ADA+ participants (13.9%) experienced injection site reactions compared to TE ADA- participants (1.1%).

Table 49 Summary of Injection Site Reactions by TE ADA Status During the Planned Treatment Period. OSA Analysis Set

	Tirzepatide (N=233)	
TE ADA status	M	m (%)
TE ADA+	137	19 (13.9)
TE ADA-	89	1 (1.1)
Not evaluable	7	0

Abbreviations: ADA = anti-drug antibodies; m = number of participants in specified category (TE ADA+, TE ADA, or not evaluable with injection site reaction); M = total number of participants in specified TE ADA status; N = total number of participants in specified treatment group; OSA = obstructive sleep apnea; TE = treatment-emergent.

- Of the 19 TE ADA+ participants that experienced 1 or more injection site reaction(s) per the pre-specified MedDRA search strategy, the ADA titer range was 1:10 to 1:5120 during the treatment period.
- 7 of the 137 TE ADA+ participants had a maximum ADA titer of 1:5120. Of these 7, 2 participants experienced mild injection site reactions while no injection site reactions were reported for the other 5 TE ADA+ participants with titers of 1:5120.
- No apparent pattern of a temporal relationship was observed between TE ADA status or titer and the emergence or resolution of individual injection site reactions.

Participants with TE ADA and Severe/Serious Hypersensitivity or Injection Site Reaction (AESIs)

Both tirzepatide-treated participants with severe hypersensitivity reactions were TE ADA.

The first participant did not have ADA present at baseline. The participant reported TEAEs of severe Anaphylactic reaction (Study Day 67) and mild Injection site reaction (Study Day 242). The participant was TE ADA+ on Study Day 85 (titer of 1:160), with peak titer (1:5120) at Study Day 275. The participant completed the study on study drug.

The other participant did not have ADA present at baseline. The participant reported a TEAE of severe Urticaria on Study Day 353. The participant was TE ADA+ on Study Day 85 (titer of 1:160), with a peak titer of 1:320 on Study Day 366. The participant completed the study on the study drug.

Key immunogenicity conclusions with regard to safety are as follows:

- A higher percentage of TE ADA+ participants than TE ADA- participants reported hypersensitivity reactions. Of the 6 TE ADA+ participants reporting hypersensitivity events, 4 reported events that were mild or moderate in severity.
- A higher percentage of TE ADA+ participants than TE ADA- participants reported injection site reactions based on the predefined MedDRA search strategy. All of these events were non-serious and non-severe.

The percentage of participants who are TE ADA+ and the relationship between TE ADA+/- status and hypersensitivity and injection site is consistent with the known safety profile for tirzepatide for weight management.

Of the 60.6% of participants that were TE ADA+, 16.8% experienced a hypersensitivity or injection-site reaction and the majority were mild or moderate in severity. No apparent pattern of a temporal relationship was observed between TE ADA status or titer and the emergence or resolution of individual hypersensitivity reactions or injection-site reactions. Overall, these conclusions are consistent with the known safety profile of tirzepatide for weight management.

Serious adverse event/deaths/other significant events

A summary of SAEs reported by at least 1 participant in the tirzepatide group of the OSA Analysis Set has been provided by the applicant.

Overall, the percentage of participants reporting at least 1 SAE was similar in the tirzepatide and placebo groups. An excerpt of SAEs per SOC (of special interest or with higher frequency than placebo) is provided below.

Table 50 Summary and Analysis of Serious Adverse Events Reported by ⩾1 Tirzepatide-Treated Participant (Excerpt). Safety Population. OSA Analysis Set

System Organ Class Preferred Term	Placebo (N=234) n (%)	Tirzepatide (N=233) n (%)	Tirzepatide vs. Placebo p-Value[a]
Participants with ≥1 SAE	19 (8.1)	16 (6.9)	0.599
Renal and urinary disorders	0	4 (1.7)	0.047
Nephrolithiasis	0	2 (0.9)	0.156
Acute kidney injury	0	1 (0.4)	0.328
Hydronephrosis	0	1 (0.4)	0.328
Psychiatric disorders	1 (0.4)	2 (0.9)	0.551
Suicide attempt	0	2 (0.9)	0.146
Mood swings	0	1 (0.4)	0.305
Gastrointestinal disorders	0	2 (0.9)	0.156
Diarrhoea	0	2 (0.9)	0.156
Pancreatitis acute	0	1 (0.4)	0.328
Cardiac disorders	3 (1.3)	1 (0.4)	0.318
Atrial fibrillation	2 (0.9)	1 (0.4)	0.575
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	5 (2.1)	1 (0.4)	0.098
Clear cell renal cell carcinoma	0	1 (0.4)	0.305

Abbreviations: n = number of participants with at least 1 SAE; N = number of participants in the treatment group; OSA = obstructive sleep apnea; SAE = serious adverse event; vs. = versus.

[a] p-Values are from Cochran-Mantel-Haenszel test of general association stratified by study.

No deaths were reported in the OSA Analysis Set.

Discontinuation due to adverse events

In the OSA studies, participants were to remain in the study after permanent discontinuation of study drug so that additional information could be collected. The discussion in this section will focus on AEs that led participants to permanently discontinue the administration of study drug.

The percentage of participants discontinuing study drug due to an AE was similar in the tirzepatide (3.9%) and placebo (4.3%) groups. The most frequently reported AEs leading to discontinuation of

tirzepatide were in the Gastrointestinal disorders SOC (2.1%). These results are generally consistent with the known safety profile of tirzepatide.

Table 51 Summary of Adverse Events Reported by ⩾1 Tirzepatide-Treated Participant as Primary Reason for Treatment Discontinuation. Safety Population. OSA Analysis Set

System Organ Class Preferred Term	Placebo (N=234) n (%)	Tirzepatide (N=233) n (%)	Tirzepatide vs. Placebo p-Value[a]
Participants with ≥1 DCAE	10 (4.3)	9 (3.9)	0.801
Gastrointestinal disorders	1 (0.4)	5 (2.1)	0.096
Nausea	0	3 (1.3)	0.074
Diarrhoea	1 (0.4)	2 (0.9)	0.551
Abdominal pain	1 (0.4)	1 (0.4)	0.998
Inguinal hernia	0	1 (0.4)	0.328
Vomiting	0	1 (0.4)	0.305
Infections and infestations	0	1 (0.4)	0.328
Gastroenteritis	0	1 (0.4)	0.328
Injury, poisoning and procedural complications	0	1 (0.4)	0.328
Road traffic accident	0	1 (0.4)	0.328
Investigations	0	1 (0.4)	0.328
Lipase increased	0	1 (0.4)	0.328
Metabolism and nutrition disorders	0	1 (0.4)	0.328
Dehydration	0	1 (0.4)	0.328
Hypokalaemia	0	1 (0.4)	0.328
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	5 (2.1)	1 (0.4)	0.098
Clear cell renal cell carcinoma	0	1 (0.4)	0.305
Nervous system disorders	0	1 (0.4)	0.328
Cerebral haemorrhage	0	1 (0.4)	0.328
Coma	0	1 (0.4)	0.328
Renal and urinary disorders	0	1 (0.4)	0.328
Acute kidney injury	0	1 (0.4)	0.328

Abbreviations: AE = adverse event; DCAE = discontinuation of study drug due to AE; n = number of participants with at least 1 event; N = number of participants in the treatment group; OSA = obstructive sleep apnea; vs. = versus.

[a] p-Values are from Cochran-Mantel-Haenszel test of general association stratified by study.

Post marketing experience

Worldwide sales of tirzepatide following first approval (June 2022) have been collected for the cumulative period ending on 31 March 2024. An estimated 4,450,200 patients have been exposed to tirzepatide (any dose) with 1,925,200 patient-years of exposure.

Cumulatively through 10 April 2024, there have been 82,329 AEs reported from 41,049 post-marketing cases. Amongst these, 4,376 were SAEs reported from 2,881 post-marketing cases. The most frequently reported SAEs in the post-marketing setting by individual MedDRA PT were

- Pancreatitis (n = 371; reporting rate: 0.008%)
- Vomiting (n = 223; reporting rate: 0.005%)
- Dehydration (n = 150; reporting rate: 0.003%)
- Diarrhoea (n = 144; reporting rate: 0.003%)
- Nausea (n = 131; reporting rate: 0.003%), and
- Acute kidney injury (n = 79; reporting rate: 0.002%).

Deaths

Cumulatively through 10 April 2024, there were 114 cases reporting 138 events with a fatal outcome. Of these 138 events, 65 events were confounded by underlying conditions/diseases such as recent surgery, decreased appetite, cardiac disorders, renal failure, terminal pancreatic cancer, uncontrolled T2DM, tobacco use, obesity, depression, COVID-19, clostridium difficile infection, extensive comorbidity including autonomic nervous system imbalance. 73 events also had limited information relating to time to onset, cause of death, medical history, concomitant medications, autopsy details for an adequate medical assessment. No pattern in the cause of death was observed, and no new safety signals were detected related to this topic.

Important potential risks

Cumulatively through 10 April 2024, SAEs for the following important potential risks were reported with the use of tirzepatide (Table below). In context of the overall exposure of 4,450,200 patients, the reporting rates of these important potential risks are low and do not suggest a new safety finding.

Table 52 Reporting of Post-marketing Important Potential Risks through 10 April 2024

Important Potential Risk	MedDRA Search Strategy	Number of SAEs (Reporting Rate)
Medullary thyroid cancer	HLT: *Thyroid neoplasms malignant* PT: *Thyroid C-cell hyperplasia*	32 (0.0007%)
Pancreatic malignancy	PTs: *Pancreatic carcinoma; Pancreatic carcinoma metastatic; Pancreatic carcinoma recurrent; Adenocarcinoma pancreas; Pancreatic sarcoma; Pancreatic cystadenoma; Pancreatic carcinoma stage 0; Pancreatic carcinoma stage I; Pancreatic carcinoma stage II; Pancreatic carcinoma stage III;; Pancreatic carcinoma stage IV; Cystadenocarcinoma pancreas; Solid pseudopapillary tumors of the pancreas; Acinar cell carcinoma of pancreas; Ductal adenocarcinoma of pancreas; Intraductal papillarymucinous carcinoma of pancreas; Pancreatoblastoma*	24 (0.0005%)

Important Potential Risk	MedDRA Search Strategy	Number of SAEs (Reporting Rate)
Diabetic retinopathy complications[a]	PTs: *Arteriosclerotic retinopathy; Blindness; Choroidal neovascularisation; Cystoid macular oedema; Detachment of macular retinal pigment epithelium; Detachment of retinal pigment epithelium; Diabetic blindness; Diabetic eye disease; Diabetic retinal oedema; Diabetic retinopathy; Diabetic uveitis; Exudative retinopathy; Eye laser surgery; Fundoscopy; Fundoscopy abnormal; Intra-ocular injection; Macular detachment; Macular oedema; Maculopathy; Noninfective chorioretinitis; Noninfective retinitis; Phacotrabeculectomy; Retinal aneurysm; Retinal arteriovenous malformation; Retinal artery embolism; Retinal artery occlusion; Retinal artery stenosis; Retinal collateral vessels; Retinal cryoablation; Retinal detachment; Retinal exudates; Retinal haemorrhage; Retinal laser coagulation; Retinal neovascularisation; Retinal oedema; Retinal operation; Retinal thickening; Retinal vascular disorder; Retinal vascular occlusion; Retinal vein occlusion; Retinitis; Retinopathy; Retinopathy haemorrhagic; Retinopathy hypertensive; Retinopathy hyperviscosity; Retinopathy proliferative; Venous stasis retinopathy; Vitrectomy; Scintillating scotoma; Vision blurred; Visual impairment; Blindness transient; Blindness unilateral; Sudden visual loss; Visual acuity reduced; Visual acuity reduced transiently; Diplopia; Triplopia; Amaurosis; Amaurosis fugax*	42 (0.0009%)

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; SAE = serious adverse event.

[a] Important Potential Risk for the EU.

Overall, the post-marketing safety data continue to support the safety profile of tirzepatide for weight management established with clinical trials.

4.5.1. Discussion on clinical safety

A thorough and comprehensive analysis of safety results in the obese OSA population was provided. Eligible subjects in the OSA Analysis Set had to present with moderate to severe OSA (AHI $\geq$ 15) and

obesity (BMI $\geq$ 30 kg/m^2). Hence, with regard to body weight there is complete overlap with the target population specified for the existing weight management indication of Mounjaro. Overall, the safety profile observed in obese OSA patients was consistent with that of the known safety profile of tirzepatide and was adequately reflected in the product labelling.

The SURMOUNT-OSA safety population comprises N=233 patients receiving tirzepatide and N=234 placebo patients. For the majority of subjects (tirzepatide: 79.8%; placebo: 67.1%) exposure to study drug extended over the entire 52-week treatment period. Subsequent to the initial titration period (2.5 mg dose increments every 4 weeks) tirzepatide patients were maintained on the maximum tolerated dose (MTD) of either 10 mg or 15 mg tirzepatide (once weekly injection) for the remainder of the study. The maximum weekly dose of 15 mg is identical across existing T2DM, weight management and newly proposed OSA indications.

Like already known for the existing indications, most frequently occurring TEAEs were gastrointestinal (diarrhoea: tirzepatide 24.0%, placebo 10.7%; nausea: tirzepatide 23.6%, placebo 7.7%; constipation: tirzepatide 15.5%, placebo 3.4%; vomiting: tirzepatide 13.3%, placebo 2.6%). GI adverse events typically occur during dose escalation and reach a plateau over the remaining treatment period. The combined prevalence of diarrhoea, nausea, and vomiting ranged from 9.9% to 18.3% in the tirzepatide group at any period during the treatment period. Severity was mild (59.4%) or moderate (35.2%) in most cases.

Based on the vast clinical dataset from previous trials, an elaborate analysis of AEs of special interest was provided. Apart from GI-related TEAEs, these relate to renal / hepatic safety, hepatobiliary / gallbladder disorders, major depressive disorder / suicidal ideation, pancreas- and CV-related safety, malignancy / thyroid safety, hypersensitivity / injection site reactions, and immunogenicity.

Pancreatitis has been reported with the use of GLP-1 receptor agonists. Accordingly, the current Mounjaro SmPC contains an explicit warning on acute pancreatitis in section 4.4. A total of 2 (0.9%) tirzepatide-treated participants with 2 events and no placebo-treated participants experienced events of suspected pancreatitis that were sent for CEC adjudication. Both were confirmed by adjudication as events of acute pancreatitis (either based on symptoms plus imaging or symptoms plus elevated enzymes). However, no cases were assessed by the adjudicators as severe or critical. Along the same lines, tirzepatide was associated with increases in p-amylase and lipase. More tirzepatide-treated participants had elevated pancreatic enzymes >3×ULN compared to placebo (0.4% vs. 0% for p-amylase, and 2.1% vs. 1.3% for lipase). After peaking around 24 weeks of treatment, pancreatic enzyme levels remained stable through 52 weeks, and decreased during the 4-week safety follow-up. Similar to observations in prior studies of tirzepatide, elevated pancreatic enzymes were not consistently associated with symptoms or events of pancreatitis. Elevations in pancreatic enzymes in tirzepatide-treated participants were consistent with observations in prior studies of tirzepatide in weight management. The overall pancreatitis-related safety findings are adequately described in tirzepatide product labelling and remain consistent with the known safety profile of tirzepatide

In terms of CV safety, one of the known effects of incretins is to increase HR. Baseline mean sitting pulse rate values were similar between the tirzepatide and placebo groups (around 74 bpm). While there were minimal mean changes from baseline over time in the placebo group, the mean pulse rate began to increase in the tirzepatide group at Week 8 and reached the maximum value during dose-escalation (max. mean increase in pulse rate was 2.8 bpm). Thereafter, mean PR gradually decreased throughout the treatment period with the mean change of 1.6 bpm for tirzepatide from baseline at week 52. The changes in pulse rate were consistent with a known effect of incretins and the safety profile of tirzepatide for weight management. Adequate wording on changes in HR is included in the current SmPC section 4.8.

The change from baseline in SBP at Week 48 was a key secondary efficacy endpoint controlled for type 1 error. Baseline mean sitting SBP values were similar between the tirzepatide and placebo groups (tirzepatide: 129.5 mmHg, and placebo: 130.5 mmHg). In the tirzepatide group, mean SBP decreased from Week 0 to Week 20 and plateaued through Week 52. Reductions in SBP were greater in the tirzepatide group compared to the placebo group at all time points through Week 52 and the safety follow-up visit, except Week 8. The maximal decreases in SBP were for tirzepatide: -9.5 mmHg, and for placebo: -3.3 mmHg.

Approximately 58% of participants reported hypertension at baseline as pre-existing condition, and 48.6% were taking antihypertensive medications. Accordingly, decreases in BP are expected to be beneficial in those with OSA and overweight or obesity. On the other side, hypotension-related events have been observed with other incretin-based therapies for this population, and hypotension is an ADR for tirzepatide in those with obesity, or overweight with weight-related comorbidities (labelled as common ADR). However, the decrease in BP did not translate into high numbers of hypotension reported as TEAE during the OSA trials. Treatment-emergent hypotension-related events were reported in more tirzepatide-treated participants (n=6, 2.6%) as compared to placebo (2 participants, 0.9%). No tirzepatide-treated participants had a documented SBP <90 mmHg during the treatment period in the studies. No events were associated with clinically significant outcomes. The reductions in SBP were consistent with those observed previously in the weight management populations.

Preclinical rodent studies have suggested that GLP-1 receptor agonists may be associated with an increased risk of thyroid C-cell tumors. Lilly implemented measures during the tirzepatide OSA studies to monitor, identify and minimize potential thyroid safety risks, like e.g. exclusion of those with a family or personal history of MTC, or presenting with serum calcitonin values of ≥20 ng/L at screening (if eGFR ≥60 mL/min/1.73 m^2). Calcitonin levels were monitored. In terms of malignancy, no cases of MTC or C-cell hyperplasia and no cases of pancreatic cancer were reported.

Hypersensitivity reactions are listed in the current SmPC section 4.8 as known adverse reactions of Mounjaro therapy. Hypersensitivity reactions, either immediate (occurring within 24 hours of study drug administration) or non-immediate (occurring after > 24 hours) and sometimes severe, have also been reported in 3.0 % of tirzepatide-treated patients and 2.1 % of placebo-treated patients across the two OSA trials. Hence, incidence rates of hypersensitivity among OSA patients fully align with those observed across the established indications.

In the OSA studies, study drug was self-administered once weekly as an SC injection in the abdomen or thigh; a caregiver may have administered the injection in the participant's upper arm. Participants were provided with single-dose pens for ease of administration of study drug. The percentage of participants reporting at least 1 injection site reaction was higher in tirzepatide-treated participants compared to placebo (tirzepatide, 8.6%; placebo, 2.6%). No events were serious, and all were mild or moderate in severity. One participant (placebo) discontinued the study drug and study due to Injection site urticaria. Injection site reactions are labelled as common ADR in the current SmPC.

in the OSA Analysis Set, the percentage of TE ADA+ participants was 60.6% during the planned treatment period, while 6.6% of evaluable tirzepatide-treated participants had detectable tirzepatide ADA at baseline. A higher percentage of tirzepatide-treated TE ADA+ participants (4.4%) experienced hypersensitivity reactions compared to TE ADA- participants (1.1%). Equally, a higher percentage of tirzepatide-treated TE ADA+ participants (13.9%) experienced injection site reactions compared to TE ADA- participants (1.1%). The rate of OSA patients developing ADA during the on-treatment period (60.6%) is in the same order of magnitude as already observed among patients with BMI $\geq$ 27 kg/m^2 with or without T2DM (56.1%). Immunogenicity-related safety findings are adequately reflected in SmPC section 4.8.

4.5.2. Conclusions on clinical safety

A vast dataset of safety findings for the use of tirzepatide in T2DM and weight management has already been generated within the scope of the previous SURPASS and SURMOUNT clinical development programme. For the present SURMOUNT-OSA studies, subjects were eligible if presenting with moderate to severe OSA (AHI $\geq$ 15) and obesity (BMI $\geq$ 30 kg/m^2). Hence, there is considerable overlap in the target population between the newly proposed OSA population and the established weight management population (BMI $\geq$ 30 kg/m^2 **or** BMI $\geq$ 27 kg/m^2 to < 30 kg/m^2 plus at least one weight-related comorbid condition, **e.g. obstructive sleep apnoea**).) As could be expected, the safety profile of tirzepatide in the obese OSA population largely aligns with the one already established for the existing indications. The most common TEAEs were gastrointestinal. Adverse events of special interest were comprehensively monitored. In terms of most frequently occurring TEAEs and AESI (e.g. pancreatitis, CV, thyroid malignancy, hypersensitivity) the safety profile of tirzepatide in the obese OSA population was consistent with the one for the established clinical use of tirzepatide.

4.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

5. Risk management plan

The MAH submitted an updated RMP version with this application (EU Risk Management Plan (Version 3.1). Rationale for submitting an updated RMP was to include the proposed new indication of obstructive sleep apnoea (OSA). The (main) proposed RMP changes were the following:

- A proposed new indication of OSA is included along with relevant information on incidence, prevalence, demography, main existing treatment options, natural history of the indicated condition, and important comorbidities.
- Updated overall cumulative exposure in tirzepatide clinical trial program, exposure in special populations, and post-authorisation experience.
- Updated information on important potential risks considering the proposed new indication of OSA.

The proposed updates in the RMP mainly concerned the background information on the new applied indication for tirzepatide (Mounjaro) regarding obstructive sleep apnoea (OSA).

The relevant sections of the RMP were proposed to be updated with information on epidemiology of OSA, clinical trials data from SURMOUNT-OSA and Post-authorisation Experience (module SV, DLP April 30th 2024). In addition, some minor changes have been made (mainly textual in nature) to the existing data of the RMP. These were acceptable; they also included updated information on paediatric studies which are now ongoing and update information on the protocol of both study 18F-MC-B014 and study 18F-MC-B011 that have been submitted in a separate procedure.

There is considerable overlap in the populations studied for weight management and for OSA. Therefore, the safety profile of tirzepatide in the obese OSA population for the most part is similar to the already established safety profile in the TD2M and Weight management indication. No new safety concerns were identified. The list of the safety specifications remains unchanged.

The MAH proposed no changes to the pharmacovigilance plan. There are additional pharmacovigilance activities included in the RMP of Mounjaro in relation to Medullary thyroid cancer (MTC), pancreatic

malignancy and diabetic retinopathy complications. However, as no new safety concerns have been identified, the established routine and additional pharmacovigilance activities are considered sufficient to also monitor the risks of Mounjaro in the new indication.

The MAH proposed no changes to the risk minimisation measures. Routine risk minimisation measures are in place for Mounjaro. Based on the new indication no changes are considered warranted.

Taking into account the negative position on the proposed use of tirzepatide in moderate to severe obese OSA patients as a new indication in SmPC section 4.1, changes to the RMP related to this new indication were not acceptable. See overall conclusions on the RMP.

Given the removal of OSA from the proposed indication in the response to the RSI, the withdrawal of version 3.1 of the RMP was considered acceptable. The MAH re-instates the approved version of the RMP, version 2.1. This is acceptable.

5.1. Overall conclusion on the RMP

Given the removal of OSA from the proposed indication, the withdrawal of version 3.1 of the RMP is acceptable. The MAH re-instates the approved version of the RMP, version 2.1. This is acceptable.

6. Changes to the Product Information

As a result of this variation, sections 4.1, 4.8, and 5.1 of the SmPC are proposed to be updated. The Package Leaflet (PL) is updated accordingly.

6.1.1. User consultation

The package leaflet is now being updated due to the addition of the new indication obstructive sleep apnoea in adults with obesity, the subject of this type II variation. The proposed text modifications to the package leaflet resulting from the addition of these data are minor and do not include text that is significantly different from that already user tested. Overall, the structure and design of the revised package leaflet has not changed due to the new information and the revisions do not significantly affect the overall readability. Therefore, the applicant does not consider it necessary to conduct further consultation with target patient groups further to that performed for the initial MAA. This is agreed.

6.1.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Mounjaro (tirzepatide) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

7. Benefit-Risk Balance

7.1. Therapeutic Context

7.1.1. Disease or condition

According to ICSD-3, obstructive sleep apnoea (OSA) is a sleep-related breathing disorder which is characterized by repetitive episodes of complete (apnoea) or partial (hypopnoea) upper airway obstruction occurring during sleep. These events (usually measured via polysomnography and indicated as event rate per hour sleep as the AHI Index) often result in reductions in blood oxygen saturation and are usually terminated by brief arousals from sleep. By definition, apnoeic and hypopnoeic events last a minimum of 10 seconds. Most events are 10 to 30 seconds in duration but occasionally persist for one minute or longer. Most patients awaken in the morning feeling tired and unrefreshed regardless of the duration of their time in bed. Excessive daytime sleepiness (EDS) is a major presenting complaint in many but not all cases. Secondary hypertension / sympathetic activity due to repetitive arousals during sleep, are discussed as possible reasons why EDS is not encountered in every OSA patient. With extreme sleepiness, sleep may occur while actively conversing, eating, walking, or driving. The likelihood to fall asleep during typical everyday activities is measured by the patient-recorded ESS questionnaire.

In simplified terms, ICSD criteria for OSA diagnosis require that the subject presents with AHI $\geq$ 5-14 events /h plus complaints of sleepiness or comorbid conditions, like e.g. hypertension, T2DM, CAD, AF or cognitive dysfunction. Alternatively, the OSA diagnosis is established in case of AHI $\geq$ 15 without any further conditions.

OSA is a common condition among patients with CV disease, affecting 40 to 60% of such patients (McEvoy et al. 2016). Inversely, population-based epidemiology studies have consistently shown the prevalence of hypertension, T2DM, CV disease, and stroke to be higher in people with OSA (Somers et al. 2008).

Furthermore, the prevalence of OSA is closely associated with obesity and obesity-related metabolic disorders. Some 60-90% of adults with OSA are overweight, and the relative risk of OSA in obesity (BMI > 29 kg/m^2) is $\geq$10 (Pillar & Shedhadeh 2008).

7.1.2. Available therapies and unmet medical need

Effective treatments for OSA include behavioural measures, medical devices, and surgery. Behavioural measures include abstinence from alcohol, avoiding supine sleep position, regular aerobic exercise, and weight loss. Exercise may improve OSA independently of weight loss (Gottlieb & Punjabi 2020).

Prospective cohort studies have shown the association between excess body weight and SDB. Relative to stable weight, a 10% weight gain predicted an approx. 32% (95% CI, 20%-45%) increase in the AHI, while a 10% weight loss predicted a 26% (95% CI, 18%-34%) AHI decrease (Peppard et al. 2000).

Positive airway pressure (PAP) is the primary therapy for individuals with symptomatic OSA of any severity. PAP devices deliver pressure to the airway through a mask worn over the nose or nose and mouth. This pressure acts as splint to prevent airway collapse during inspiration. PAP normalizes AHI in more than 90% of patients while wearing the device. Benefit depends on adherence to therapy, with more hours of use per night associated with greater symptom improvement and greater blood pressure reduction. Although arbitrary, adequate adherence is commonly defined as use for at least 4 hours per night for at least 5 nights per week (Gottlieb & Punjabi 2020).

Until today, no specific pharmacological OSA treatment is available. Following a symptomatic approach, medication has been licensed for improvement of excessive daytime sleepiness in patients with OSA or narcolepsy (e.g. solriamfetol, pitolisant). A novel pharmacological treatment to improve the hypoxic burden in OSA would create an additional treatment option, in particular for those patients refusing or not sufficiently adherent to primary PAP therapy.

7.1.3. Main clinical studies

The use of tirzepatide in patients with moderate to severe OSA (AHI $\geq$ 15) and obesity (BMI $\geq$ 30 kg/m^2) was examined in two phase 3 studies which shared the general design features in terms of duration and endpoints (the identical Master Protocol), however, differed as regards the study population. Study 1 (I8F-MC-GPI1) recruited subjects who were unable or unwilling to use PAP therapy and must not have used PAP for at least 4 weeks prior to Visit 1, while study 2 (I8F-MC-GPI2) included participants that had been on PAP therapy for at least 3 consecutive months prior to Visit 1 and planned to continue PAP therapy during the study.

Since PAP constitutes first-line therapy in OSA, the general concept of testing tirzepatide in both PAP and non-PAP OSA patient populations is endorsed. However, the primary interest would be to see whether tirzepatide can bring added benefit in PAP-compliant OSA patients. Unfortunately, however, study 2 was not designed to answer this question. Participants in study 2 were instructed to suspend PAP therapy for 7 days before polysomnographic and patient-reported outcome assessments at baseline, week 20, and week 52 to minimize the confounding effect of PAP therapy on SDB and PRO assessments. All endpoints were assessed from baseline to week 52 except for BP, which was measured at week 48 to prevent confounding the assessment due to PAP withdrawal.

In both parallel-arm pivotal studies (Study 1: N=234; Study 2: N=235), eligible subjects were randomized 1:1 to receive either individually titrated tirzepatide up to MTD (10 mg or 15 mg) per once weekly subcutaneous injection or placebo for an overall double-blind treatment duration of 52 weeks.

Clinical sites were globally distributed with about 10-18% European (CZ, DE) and 30-33% US portions. About two thirds of the study population were male (67.1 – 72.3%), which is in line with a higher prevalence of OSA in men reported in the literature (Punjabi 2008). Mean body weight at baseline was around 115 kg (mean around BMI 39 kg/m^2, with about 35% included subjects qualifying for class 3 obesity [BMI > 40 mg/m^2]).

Obesity was a requirement for participation as reflected by the proposed indication, however, that does not mean that the population is somehow artificial, given the dramatic increases in the number of overweight and obese adults over the last 10-15 years and population-based studies confirming that excess body weight is uniformly associated with a graded increase in OSA prevalence (Punjabi 2008). On the other hand, it is evident that restriction to obese OSA patients does not allow extrapolation of study results to the entire range of OSA patients, i.e. it is fully unclear whether tirzepatide would be of any benefit in the non-overweight OSA patient.

The primary efficacy endpoint was the change in AHI from baseline to week 52, collected via polysomnography (PSG). PSG assessments (including AHI, blood oxygen saturation parameters, PR, sleep parameters) were performed during 1-night, overnight clinic stays. In line with the chosen primary endpoint, included subjects had high AHI event rates (49.5-51.5) at baseline. Somehow surprising, given the high hypoxic burden of included subjects, the degree of daytime sleepiness, however, was not excessive, but only in the upper normal range at baseline (ESS 10.2-10.6). Improvement in EDS was only indirectly reflected by the pre-specified endpoint of combined achievement of AHI 5-14 with ESS $\leq$10 at week 52. It is acknowledged that there is no linear relation between AHI and symptoms (incl. EDS) in OSA and that there may be compensatory factors like comorbid hypertension that reduce

daytime sleepiness. However, it is noted that there may have been some enrichment regarding subjects' predominant baseline conditions in relation to the chosen efficacy endpoints.

The focus of the pivotal studies was set on patients' improvement in terms of apnoeic / hypopnoeic events during sleep, as reflected by the primary and a number of secondary endpoints (percent change in AHI, rate of participants with $\geq$ 50% AHI reduction, and hypoxic burden). It is acknowledged that periods of oxygen desaturation are at the bottom of all health risks associated with OSA. On the other side, the relation between AHI and improvement of clinical symptoms is unclear. In order to associate reduction of AHI scores from baseline with clinical improvement, the Applicant introduced two key-secondary PRO endpoints, i.e. PROMIS-SRI for sleep-related impairment at daytime and PROMIS-SD for sleep disturbance during the night. The array of endpoints is rounded up by endpoints reflecting improvement in OSA-related CV risks, like e.g. changes in hsCRP, SDB, DBP, body weight, lipids and fasting insulin levels. Essentially, the benefits of tirzepatide in terms of these CV risks has already previously been shown in the target populations of the existing T2DM and weight management indications.

7.2. Favourable effects

The favourable effect of tirzepatide in obese OSA patients was shown along three domains of efficacy endpoints, i.e. those related to improvement of sleep-disordered breathing (SDB), patient-reported outcomes (PRO), and OSA-related CV risk factors.

Tirzepatide demonstrated substantial AHI reduction. Mean AHI scores of about 50 at baseline were reduced by -50.7% in study 1 (placebo: -3.0%) and -58.7% in study 2 (placebo: -2.5%) after a 52-week treatment, thereby achieving highly significant placebo superiority. AHI reduction also translates into reduction of hypoxic burden. Mean SASHB values, which reflect the degree and duration of oxygen desaturation during sleep (apart from event frequency), were reduced by -65.5% in study 1 (placebo: -17.3%) and by -75.2% in study 2 (placebo: -30.4%). In accordance with the reduction of hypoxic events and hypoxic burden, tirzepatide significantly increased the likelihood for participants to reach AHI < 5 or AHI < 15 without EDS (ESS $\leq$ 10) representing those who achieved a wider definition of OSA remission and are not typically indicated for further treatment (Study 1: OR 7.3 [3.2, 17.0]; Study 2: OR 6.6 [3.1, 14.0]). Overall, impaired breathing leading to hypoxic events during sleep is the underlying cause of OSA and related health risks / symptomatology. The beneficial effect of tirzepatide has consistently been shown across all sleep-disordered breathing related endpoints, including reduction of the AHI from baseline to week 52 of treatment, which was measured as primary.

As concerns PRO results, two 8-item questionnaires were introduced as key secondaries to reflect improvement in terms of sleep-related impairment during daytime (PROMIS-SRI) and sleep disturbance during night (PROMIS-SD). Only the pooled analysis was pre-specified as confirmatory. Using both the treatment-regimen and efficacy estimands, pooled tirzepatide demonstrated superiority compared with placebo for mean PROMIS-SRI and PROMIS-SD scores (improvement) from baseline to Week 52 ($p<0.001$) in the pooled analyses. For the treatment-regimen estimand, the mean change difference from placebo at week 52 in T-scores was -3.9 (95% CI: -5.7, -2.2; $p<0.001$) for PROMIS-SRI and -3.0 (95% CI: -4.5, -1.5; $p<0.001$) for PROMIS-SD.

Meaningful Within-Patient Change (MWPC) thresholds for improvement in PROMIS SRI and PROMIS SD T-scores were derived empirically based on data from participants in Studies 1 and 2. Using the anchor-based methodology, the estimated MWPC thresholds were $\leq$-8.0 change in PROMIS SRI for Study 1, $\leq$-10.0 change in PROMIS SRI for Study 2, and $\leq$-7.5 change in PROMIS SD for Studies 1 and 2. Using the efficacy estimand, the proportion of participants in Studies 1 and 2 tirzepatide groups that met or surpassed the MWPC thresholds for improvement in sleep-related impairment (PROMIS SRI) and sleep

disturbance (PROMIS SD) from baseline to Week 52 was significantly greater than the proportion of participants that met the thresholds in the placebo groups. For both PROMIS questionnaires, high scores indicate high degree of sleep-related impairment / sleep disturbance.

In line with the outcome of clinical studies in support of the established tirzepatide indications like diabetes or weight management, considerable benefit in terms of CV risk factors could also be shown in OSA patients with obesity.

In terms of chronic low-grade inflammation, hs-CRP levels at baseline were in the range of 2.7 – 3.6 mg/L, thereby at the interface between predicting moderate (1.0 – 3.0 mg/L) to high (3.0 – 10.0) risk of heart disease. Across both studies, hsCRP values were reduced by > 40% achieving statistical significance over placebo for both estimands, the effect was slightly more pronounced in PAP patients of study 2 (-48.2%) as compared to PAP refusing patients of study 1 (-40.1%).

Blood pressure significantly decreased under tirzepatide treatment as compared to placebo. The net effect over placebo for SBP was -7.6 mmHg in study 1, and -3.7 mmHg in study 2 from baseline to week 48. The inter-study difference may be explained by the difference in concomitant PAP use. Since PAP was shown to have antihypertensive effect in OSA (Javaheri et al. 2017), there may have been more space for improvement of hypertension in PAP non-users of study 1.

The reduction in body weight was significant. The net effect over placebo in terms of mean percent change in body weight from baseline to week 52 was -16.1% in study 1 and – 17.3% in study 2. Whereas subjects lost almost 20% of body weight over 1 year treatment with tirzepatide (-17.7% / -19.6%), the weight-reducing effect was low among placebo subjects (-1.6% / -2.3%). Diet counselling was given to all participants.

7.3. Uncertainties and limitations about favourable effects

Although the overall effects of tirzepatide in obese OSA patients are considered favourable, remaining uncertainties can be summed up as follows.

At screening, subjects were not recruited applying ICSD-3 diagnostic criteria in its entirety. In simplified terms, ICSD criteria for OSA diagnosis require that the subject presents with AHI $\geq$ 5-14 events /h plus complaints of sleepiness or comorbid conditions, like e.g. hypertension, T2DM, CAD, AF or cognitive dysfunction. Alternatively, the OSA diagnosis is established in case of AHI $\geq$ 15 without any further conditions. ICSD criteria do not differentiate between mild, moderate and severe OSA. The distinction in severity of Sleep Related Obstructive Breathing Events as Mild (5 to 15), Moderate (15 to 30) and Severe (greater than 30 events per hour) is based on expert consensus only (Gottlieb & Punjabi 2020). For pivotal studies 1 and 2, however, subjects exclusively qualified on the AHI $\geq$ 15 criterion. This is in line with the chosen primary endpoint (AHI reduction), however, is considered not to represent the full spectrum of OSA patients. The benefit in OSA patients with 5-14 AHI events/h plus accompanying symptoms, like e.g. sleepiness is unclear.

In a similar way, baseline conditions of recruited subjects are well matched to the array of pre-specified endpoints. The emphasis was set on reduction of hypoxic burden (AHI), and less so on improvement of EDS, which usually is considered a key symptom in OSA. Subjects had considerably high AHI scores at baseline (around 50), however, this did not translate into excessive daytime sleepiness. ESS scores at baseline indicated daytime sleepiness not to be excessive, but to be in the upper normal range (ESS 10.2 – 10.6). To contextualize, ESS scores at baseline in the pivotal OSA study of approved solriamfetol (symptom-oriented approach) were 15-16, i.e. at the interface between moderate to severe excessive daytime sleepiness (Sunosi SmPC).

The use of tirzepatide is proposed for patients with moderate to severe OSA with concomitant obesity (BMI $\geq$ 30 kg/m^2). The beneficial effect of tirzepatide on hypoxic burden parameters is assumed to largely result from the weight reduction that could be achieved in the target population. OSA is highly associated with obesity. The favourable/unfavourable effect of weight reduction/weight gain on AHI event rates has independently been shown (Peppard et al. 2000). However, not every OSA patient is overweight. Obtained study results cannot be extrapolated to non-overweight OSA patients.

The clearest benefit of tirzepatide in obese OSA patients was shown for reduction of hypoxic burden and improvement in physical parameters like reduction of body weight, SDB, and inflammation (hsCRP). As opposed to sleep-disordered breathing or CV-related risks, the beneficial effect of tirzepatide on OSA symptoms, as expressed by PROs, is less clear.

Two 8-item questionnaires were introduced as key secondaries to reflect improvement in terms of sleep-related impairment during daytime (PROMIS-SRI) and sleep disturbance during night (PROMIS-SD). Validity and psychometric properties of the PROMIS SRI and PROMIS SD for the intended context of use, i.e. individuals with moderate-to-severe OSA and obesity, is unclear. In addition, a MWPC threshold was not established before its use in therapeutic confirmatory trials. Instead, establishment of MWPC was based on the SURMOUNT-OSA study. Although the pooled analysis of studies 1 and 2 yielded significant superiority over placebo for PROMIS-SRI and PROMIS-SD, the clinical significance of these findings is unclear. For both PROs, the net reduction of T scores was lower than half of the threshold, defined as meaningful change within a patient.

It is unclear whether tirzepatide can be recommended to obese OSA patients that are adherent to CPAP. CPAP is generally acknowledged as first-line therapy option. In study 2, patients were instructed to suspend PAP use 7 days prior to endpoint assessment. It is therefore unclear whether tirzepatide treatment brings additional benefit on top of adherent PAP use.

7.4. Unfavourable effects

A thorough and comprehensive analysis of safety results in the obese OSA population was provided. Eligible subjects in the OSA Analysis Set had to present with OSA (AHI $\geq$15) and obesity (BMI $\geq$ 30 kg/m^2). Hence, with regard to body weight there is overlap with the target population specified for the existing weight management indication of Mounjaro. Overall, the safety profile observed in obese OSA patients was consistent with that of the known safety profile of tirzepatide and was adequately reflected in the product labelling.

In terms of exposure, SURMOUNT-OSA safety population comprised N=233 patients receiving tirzepatide and N=234 placebo patients. For the majority of subjects (tirzepatide: 79.8%; placebo: 67.1%) exposure to study drug extended over the entire 52-week treatment period. The maximum weekly dose of 15 mg is identical across existing T2DM, weight management and newly proposed OSA indications.

Like already known for the existing indications, most frequently occurring TEAEs were gastrointestinal (diarrhoea: tirzepatide 24.0%, placebo 10.7%; nausea: tirzepatide 23.6%, placebo 7.7%; constipation: tirzepatide 15.5%, placebo 3.4%; vomiting: tirzepatide 13.3%, placebo 2.6%). GI adverse events typically occur during dose escalation and reach a plateau over the remaining treatment period. The combined prevalence of diarrhoea, nausea, and vomiting ranged from 9.9% to 18.3% in the tirzepatide group at any period during the treatment period.

Based on the vast clinical dataset from previous trials, an elaborate analysis of AEs of special interest was provided. Apart from GI-related TEAEs, these relate to renal / hepatic safety, hepatobiliary / gallbladder disorders, major depressive disorder / suicidal ideation, pancreas- and CV-related safety, malignancy / thyroid safety, hypersensitivity / injection site reactions, and immunogenicity.

Pancreatitis has been reported with the use of GLP-1 receptor agonists and constitutes a crucial safety concern in incretin therapy. Accordingly, the current Mounjaro SmPC contains an explicit warning on acute pancreatitis in section 4.4. A total of 2 (0.9%) tirzepatide-treated participants with 2 events and no placebo-treated participants experienced events of suspected pancreatitis that were sent for CEC adjudication. Both were confirmed by adjudication as events of acute pancreatitis (either based on symptoms plus imaging or symptoms plus elevated enzymes). However, no cases were assessed by the adjudicators as severe or critical. Along the same lines, tirzepatide was associated with increases in p-amylase and lipase. Similar to observations in prior studies of tirzepatide, elevated pancreatic enzymes were not consistently associated with symptoms or events of pancreatitis. Elevations in pancreatic enzymes in tirzepatide-treated participants were consistent with observations in prior studies of tirzepatide in weight management. The overall pancreatitis-related safety findings are adequately described in tirzepatide product labelling. If pancreatitis is suspected, tirzepatide should be discontinued.

As concerns CV safety, one of the known effects of incretins is to increase HR. The changes in pulse rate were consistent with a known effect of incretins and the safety profile of tirzepatide for weight management. The mean change from baseline was 1.6 bpm for tirzepatide at week 52. Adequate wording on changes in HR is included in the current SmPC section 4.8.

A beneficial effect of tirzepatide was observed on SDB of included subjects. Approximately 58% of participants reported hypertension at baseline as pre-existing condition, and 48.6% were taking antihypertensive medications. Baseline mean sitting SBP values were similar between the tirzepatide and placebo groups (tirzepatide: 129.5 mmHg, and placebo: 130.5 mmHg). Reductions in SBP were greater in the tirzepatide group compared to the placebo group at all time points through Week 52 and the safety follow-up visit, except Week 8. The maximal decreases in SBP were for tirzepatide: -9.5 mmHg, and for placebo: -3.3 mmHg.

No cases of medullary thyroid carcinoma or C-cell hyperplasia and no cases of pancreatic cancer were reported.

Hypersensitivity reactions are listed in the current SmPC section 4.8 as known adverse reactions of Mounjaro therapy. Hypersensitivity reactions, either immediate (occurring within 24 hours of study drug administration) or non-immediate (occurring after > 24 hours) and sometimes severe, have also been reported in 3.0 % of tirzepatide-treated patients and 2.1 % of placebo-treated patients across the two OSA trials. Hence, incidence rates of hypersensitivity among OSA patients fully align with those observed across the established indications. As specified in SmPC section 4.8, hypersensitivity reactions have been reported in the pool of T2DM placebo-controlled trials in 3.2% of tirzepatide-treated patients compared to 1.7% of placebo patients.

There are no safety-related concerns that arise from characterization of tirzepatide use in obese OSA patients in relation to the established safety profile of tirzepatide in the existing T2DM and weight management indications.

7.5. Uncertainties and limitations about unfavourable effects

The degree of uncertainty about unfavourable effects is low in view of

- the large dataset obtained from previous clinical development programmes (SURPASS and SURMOUNT) / post-marketing experience,
- the overlap between previous and newly examined SURMOUNT-OSA population (e.g. obesity [BMI $\geq$ 30 kg/m^2] or OSA as one weight-related comorbid conditions in subjects with BMI $\geq$ 27 kg/m^2),

- the overlap in posology / maximum weekly dose (15 mg),
- and the safety profile obtained for the use of tirzepatide in OSA, which largely aligns with the established safety profile of tirzepatide.

7.6. Effects Table

Table 53 Effects Table for Tirzepatide in the Treatment of Adults with OSA and Obesity (Data Cut Off: 10 April 2024 for the Primary Outcome DBL)

Effect	Tirzepatide Study 1 N=114	Placebo Study 1 N=120	Tirzepatide Study 2 N=119	Placebo Study 2 N=114	Uncertainties / Strength of evidence
Favourable Effects					
Change in AHI[a]					
Mean AHI at baseline (events/h)	52.9	50.1	46.1	53.1	• Improvement of sleep-related breathing disturbance is clinically important. Hypoxic burden is at the bottom of all OSA-related health risks. • A major drawback in the design of Study 2 is that it does not allow any conclusion about the (potentially added) benefit of tirzepatide in OSA patients with minimum PAP adherence. • The benefit of tirzepatide in terms of CV risk factors (inflammation marker hsCRP, weight reduction, decrease in SDB) was shown in obese OSA patients like already shown for existing indications.
Mean CFB to Week 52 (events/h)	-25.3	-5.3	-29.3	-5.5	
Mean difference vs placebo (95% CI)	-20.0*** (-25.8, -14.2)	N/A	-23.8*** (-29.6, -17.9)	N/A	
Hypoxic Burden[a]					
Baseline geometric mean (%min/h)	153.6	137.8	132.2	142.1	
Mean percent CFB to Week 52 (%)	-65.5	-17.3	-75.2	-30.4	
Mean difference vs placebo (%) (95% CI)	-58.3*** (-66.8, -47.7)	N/A	-64.3*** (-74.1, -50.9)	N/A	
Effect	**Pooled Study 1 and Study 2**				
	Tirzepatide N=233		**Placebo N=234**		
PROMIS-SRI[a]					
Baseline T-scores	54.5		54.9		• The external validity of PROMIS Questionnaires in the obese OSA population is unclear.
Mean CFB in T-scores to Week 52	-7.5		-3.6		

Effect	Tirzepatide Study 1 N=114	Placebo Study 1 N=120	Tirzepatide Study 2 N=119	Placebo Study 2 N=114	Uncertainties / Strength of evidence
Mean change difference from placebo at Week 52 (95% CI)	-3.9*** (-5.7, -2.2)		N/A		• Although significant superiority over placebo is shown for PROMIS-SRI and PROMIS–SD, the net effect over placebo is only half as large as the minimal clinically meaningful change within a patient.
PROMIS-SD[a]					
Baseline T-scores	55.0		54.9		
Mean CFB in T-scores to Week 52	-5.7		-2.7		
Mean change difference from placebo at Week 52 (95% CI)	-3.0*** (-4.5, -1.5)		N/A		
Unfavourable Effects					
Acute pancreatitis (adjudication confirmed)					
Number and percent of participants during the study (n [%]) OSA Analysis Set	2 (0.9)		0		• A comprehensive review was completed for safety topics including, GI AE, gallbladder disorders, major depressive disorders/suicidality, exocrine pancreas safety, CV safety, thyroid C-cell safety, and hypersensitivity. Overall, the safety profile demonstrated in the OSA clinical programme is generally consistent with the established safety profile of tirzepatide. • Although a smaller dataset, the frequency of adjudication-confirmed acute pancreatitis (uncommon) in the OSA Analysis Set is consistent with the frequency in the larger weight management analysis set currently presented in the SmPC.

Abbreviations: AHI Apnoea-Hypopnoea Index, ANCOVA Analysis of covariance, CFB Change from baseline, CI Confidence interval, PROMIS Patient-Reported Outcomes Measurement Information System, SD Sleep disturbance, SRI Sleep-related impairment

Notes:

[a] Treatment-regimen estimand, ANCOVA with multiple imputation by treatment for missing data at Week 52

*** p-value <0.001 versus placebo, controlled for submission-wise type I error

7.7. Benefit-risk assessment and discussion

7.7.1. Importance of favourable and unfavourable effects

Overall, favourable effects could be demonstrated for the use of tirzepatide in obese OSA patients. One prominent favourable aspect is that with tirzepatide treatment a considerable reduction in hypoxic burden overnight could be shown. The AHI event rate of apnoeic or hypopnoeic periods during sleep and the SASHB-hypoxic burden endpoint, which also takes the duration and severity of oxygen desaturation into account, were reduced by around 50% from baseline net effect over placebo. Importance is assigned to these effects, since disturbed breathing and resulting oxygen desaturation is considered at the bottom of all OSA-related CV risks.

The newly proposed use of tirzepatide in obese OSA patients is included in the established tirzepatide indications. No specific molecular mode of action is claimed for tirzepatide in the treatment of OSA. The doses and dosing intervals tested in obese OSA patients were the same as already approved for the T2DM and weight management indication. The association between obesity and OSA is widely acknowledged. The beneficial effect of tirzepatide in the obese OSA population is assumed to secondarily result from the reduction in body weight that was achieved (and that was analogously shown in previous clinical trials with tirzepatide in the approved target populations).

It is noted that the MAH does not claim an indication across the full spectrum of OSA patients. Subjects with moderate to severe OSA were eligible to the clinical trials, if also presenting with obesity (BMI $\geq$ 30 kg/m^2). Obtained efficacy results cannot be extrapolated to non-overweight OSA patients. Therefore, benefit of tirzepatide in non-overweight OSA patients is unclear.

CPAP treatment constitutes the first line treatment option in OSA. Despite its uncontested clinical benefit, wearing a CPAP mask is not tolerable to every OSA patient. Poor adherence or complete refusal of CPAP in a portion of OSA patients has been reported. It would have been of particular interest to examine whether tirzepatide can bring added benefit in PAP-adherent patients. Unfortunately, study 2 was not designed to address this question. Although conducted in CPAP patients, subjects were instructed to suspend CPAP use 7 days prior to endpoint assessment in order not to confound study results by concomitant CPAP use. It is therefore unclear if tirzepatide is of any (added) benefit in PAP adherent OSA patients. This is considered an important drawback in the overall clinical significance of results obtained from Study 2.

From the safety perspective, results from the SURMOUNT-OSA dataset correspond to the safety profile as already established across the broad database in the T2DM and weight management population. This applies both to most frequently observed gastrointestinal TEAEs and the elaborate analysis of AEs of special interest, like pancreatitis, CV safety, malignancy, hypersensitivity and others.

7.7.2. Balance of benefits and risks

Balancing favourable and unfavourable effects, it is concluded that listing the proposed use of tirzepatide in moderate to severe obese OSA patients as a new indication in SmPC section 4.1 is not endorsed by CHMP. Nonetheless, the beneficial effects of tirzepatide in this patient subgroup are acknowledged. Hence, there is no objection to adding a statement in section 4.1 that refers to the newly conducted clinical studies. This conclusion is based on the following considerations.

a) The newly proposed use of tirzepatide for the treatment of moderate to severe OSA in patients with obesity (BMI $\geq$ 30 kg/m^2) is considered as already covered by the existing indications of

Mounjaro. Obesity (BMI $\geq$ 30 kg/m^2) as such already qualifies for the approved weight management indication. Therefore, it is concluded that the use of tirzepatide in patients with moderate to severe OSA and obesity is already covered by the weight management indication in the current label. Additonally, patients are eligible for the weight management indication, if presenting with a BMI of $\geq$ 27 kg/m^2 in the presence of at least one weight-related comorbid condition, e.g. OSA.

b) The association between overweight and OSA is uncontested. OSA is already labelled as weight-related comorbid condition. No specific mode of action is claimed for tirzepatide in OSA. The beneficial effect is assumed to secondarily result from the weight reduction that could be achieved under 1-year tirzepatide treatment during the OSA trials. The benefit observed in obese OSA patients cannot be extrapolated to non-obese subjects. The effect of tirzepatide in non-overweight OSA patients is unclear. Numerous deleterious effects of overweight as causal (or contributory) risk factor are established for many conditions, e.g. CV events, diabetes, need for hip/ knee replacement etc. The beneficial secondary effect in these conditions is considered as already largely covered by the existing weight management indication.

c) On the other hand, the beneficial outcome of tirzepatide treatment in obese OSA patients is acknowledged, while no additional safety issues were observed as compared to the established safety profile. Importance is primarily assigned to the reduction of hypoxic events / hypoxic burden, which is considered at the bottom of all health risks associated with OSA. Therefore, no objection is raised against presenting essential study results in SmPC section 5.1 and referring to these data in section 4.1. However, presentation of data should explicitly inform that study 2 does not allow any recommendation for tirzepatide use in PAP adherent patients. The fact that study 2 does not answer the question whether tirzepatide is of any added benefit in OSA patients with a minimum degree of PAP adherence is a major limitation.

7.7.3. Additional considerations on the benefit-risk balance

The MAH initially submitted a variation application under category C.I.6.a of the variation classification Guideline with the scope to include:

"*Extension of indication to include, as an adjunct to diet and exercise, the treatment of moderate to severe obstructive sleep apnoea (OSA) in adults with obesity for MOUNJARO based on final results from studies I8F-MC-GPI1 and I8F-MC-GPI2. These are multicentre, randomized, parallel-arm, double-blind, placebo-controlled studies investigating the effects of tirzepatide compared with placebo in adult participants with moderate-to-severe OSA and obesity. As a consequence, sections 4.1, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 3.1 of the RMP has also been submitted.*"

Based on the assessment of the data contained in the application, and the additional information provided during the procedure, the CHMP is of the view that the following changes to the MA should be introduced:

"*Update of sections 4.1, 4.8 and 5.1 of the SmPC based on final results from studies I8F-MC-GPI1 and I8F-MC-GPI2. These are multicentre, randomized, parallel-arm, double-blind, placebo-controlled studies investigating the effects of tirzepatide compared with placebo in adult participants with moderate-to-severe OSA and obesity. The Package Leaflet is updated accordingly.*"

These changes fall under category C.1.4 of the variation classification Guideline.

In reply to a Request for Supplementary Information during the procedure, the MAH updated the product information accordingly.

As requested, with the responses the MAH has made an amendment in SmPC section 4.1 to include a cross reference to the trial results with respect to OSA in SmPC section 5.1. It is considered acceptable to add the trial results with respect to OSA to section 5.1 of the SmPC, and to add to the wording of the current indication a reference to SmPC section 5.1, where the effects on OSA are described.

7.8. Conclusions

The present EoI Variation was intended to support the newly proposed use of tirzepatide in moderate to severe OSA patients with obesity. To support the newly proposed indication, the Applicant proposed changes to sections 4.1, 4.8, and 5.1. There were major objections to the introduction of a new indication in SmPC section 4.1.

During the procedure, the MAH accepted not to list the use of tirzepatide in obese moderate to severe OSA patients as a separate indication in SmPC section 4.1, but to include a statement that refers to the newly conducted clinical studies, which are presented in detail in section 5.1.

The overall B/R of Mounjaro remains positive.