Medicines & Healthcare products Regulatory Agency

MHRA

Public Assessment Report

National Procedure

Mounjaro 2.5 mg solution for injection in pre-filled pen
Mounjaro 5 mg solution for injection in pre-filled pen
Mounjaro 10 mg solution for injection in pre-filled pen
Mounjaro 7.5 mg solution for injection in pre-filled pen
Mounjaro 12.5 mg solution for injection in pre-filled pen
Mounjaro 15 mg solution for injection in pre-filled pen

tirzepatide

PLGB 14895/0317-0318-0320-0321-0322-0323

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LAY SUMMARY

Mounjaro 2.5, 5, 7.5 10, 12.5, and 15 mg solution for injection in pre-filled pen tirzepatide

This is a summary of the Public Assessment Report (PAR) for Mounjaro 2.5, 5, 7.5 10, 12.5, and 15 mg solution for injection in pre-filled pen. It explains how these products were assessed and their authorisation recommended, as well as their conditions of use. It is not intended to provide practical advice on how to use these products.

These products will be referred to as Mounjaro in this lay summary for ease of reading.

For practical information about using Mounjaro, patients should read the Patient Information Leaflet (PIL) or contact their doctor or pharmacist.

What are Mounjaro and what are they used for?

These products have been authorised by MHRA for Great Britain (consisting of England, Scotland and Wales). In coming to its decision, MHRA has relied on a European Commission (EC) decision on 15 September 2022 (EMEA/H/C/005620), in accordance with the advice from the Committee for Medicinal Products for Human Use (CHMP). This is known as the EC Decision Reliance Procedure.

Mounjaro is used to treat adults with type 2 diabetes mellitus:

- on its own when a patient is unable to take metformin (another diabetes medicine).
- with other medicines for diabetes when they are not enough to control the patient's blood sugar levels. These other medicines may be medicines taken by mouth and/or insulin given by injection.

It is important that the patient continues to follow the advice on diet and exercise given to them by their doctor, pharmacist or nurse.

Mounjaro is also used together with reduced-calorie diet and increased physical activity for weight loss and to help keep the weight under control in adults, who have:

- a BMI of 30 kg/m² or greater (obesity) or
- a BMI of at least 27 kg/m² but less than 30 kg/m² (overweight) and weight-related health problems (such as prediabetes, type 2 diabetes, high blood pressure, abnormal levels of fats in the blood, breathing problems during sleep called 'obstructive sleep apnoea' or a history of heart attack, stroke or blood vessel problems).

BMI (Body Mass Index) is a measure of weight in relation to height.

How do Mounjaro work?

Mounjaro contains an active substance called tirzepatide. Mounjaro is used to treat adults with type 2 diabetes mellitus by reducing the level of sugar in the body only when the levels of sugar are high. When used for weight loss and weight maintenance in adults, Mounjaro primarily works by regulating the patient's appetite, giving the patient a sense of satiety

('fullness'), making the patient feel less hungry and experience less food cravings. This will help the patient to eat less food and reduce their body weight.

How are Mounjaro used?
The pharmaceutical form of these medicines is solution for injection, and the route of administration is subcutaneous use (injection under the skin).

- The starting dose is 2.5 mg once a week for four weeks. After four weeks the patient's doctor will increase the dose to 5 mg once a week.
- The patient's doctor may increase the patient's dose by 2.5 mg increments to 7.5 mg, 10 mg, 12.5 mg or 15 mg once a week if needed. In each case the patient's doctor will tell the patient to stay on a particular dose for at least 4 weeks before going to a higher dose.

The dose should not be changed unless the patient's doctor tells them to.

For further information on how Mounjaro are used, refer to the PIL and Summaries of Product Characteristics (SmPCs) available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

These medicines can only be obtained with a prescription.

The patient should always take the medicine exactly as their doctor/pharmacist has told them. The patient should check with their doctor or pharmacist if they are not sure.

What benefits of Mounjaro have been shown in studies?
Mounjaro was effective at controlling blood glucose in five main studies involving more than 6,000 adults with type 2 diabetes. In these studies, the main measure of effectiveness was the reduction in the proportion of haemoglobin in the blood that has glucose attached (HbA1c). This indicates how well blood glucose is controlled.

In two studies, Mounjaro lowered HbA1c by up to 2.1 and 2.6 percentage points after 40 weeks when added to existing treatment consisting of lifestyle changes only or insulin glargine with or without metformin, respectively. These results compared with no decrease or a decrease of 0.9 percentage points, respectively, in patients who received placebo (dummy treatment).

In a third study, Mounjaro lowered HbA1c by up to 2.5 percentage points after 40 weeks when added to metformin treatment, compared with a decrease of 1.9 percentage points in patients who received semaglutide.

In a fourth study, Mounjaro lowered HbA1c by up to 2.4 percentage points after 52 weeks, when added to treatment with metformin with or without an SGLT2i, compared with a decrease of 1.3 percentage points in patients who received insulin degludec.

Finally, in a fifth study, Mounjaro lowered HbA1c by up to 2.6 percentage points after 52 weeks, when added to treatment with up to 3 oral medicines (metformin, SGLT2is and sulphonylureas), compared with a decrease of 1.4 percentage points in patients who received insulin glargine.

The new weight management indication is based on the results of two international, randomised, double-blind, placebo-controlled clinical trials, in overweight and obese adult patients with and without diabetes.

The studies showed that patients who were treated with Mounjaro had a significant weight loss over time compared to patients who took a placebo.

In the first study, 2,539 obese or overweight adults with at least one weight-related complication (that was not diabetes) were given either 5 mg, 10 mg or 15 mg Mounjaro, or a placebo, weekly over a 72-week period. The average percentage change in weight over the trial period was -16.0% for the 5 mg dose, -21.4% for the 10 mg dose, -22.5% for the 15 mg dose and -2.4% for the placebo. In addition, 89.4% (5 mg), 96.2% (10 mg) and 96.3% (15 mg) of patients taking Mounjaro lost at least 5% of their body weight compared to 27.9% of those taking the placebo.

In the second study, 938 obese or overweight adults with Type-2 diabetes were given either 10 mg or 15 mg Mounjaro or a placebo, weekly over a 72-week period. Mean percentage change in weight over the trial period was -13.4% for the 10 mg dose, -15.7% for the 15 mg dose and -3.3% for the placebo. In addition, 81.6% (10 mg) and 86.4% (15 mg) of patients taking Mounjaro lost at least 5% of their body weight compared to 30.6% of those taking the placebo.

What are the possible side effects of Mounjaro?
For the full list of all side effects reported with these medicines, see Section 4 of the PIL or the SmPCs available on the MHRA website.

If a patient gets any side effects, they should talk to their doctor, pharmacist or nurse. This includes any possible side effects not listed in the product information or the PIL that comes with the medicine. Patients can also report suspected side effects themselves, or a report can be made on their behalf by someone else who cares for them, directly via the Yellow Card scheme at https://yellowcard.mhra.gov.uk or search for 'MHRA Yellow Card' online. By reporting side effects, patients can help provide more information on the safety of this medicine.

The most common side effects with Mounjaro (which may affect more than 1 in 10 people) are:

- Low blood sugar (hypoglycaemia) is very common when tirzepatide is used with medicines that contain a sulphonylurea and/or insulin. If the patient is using a sulphonylurea or insulin, the dose may need to be lowered while they use tirzepatide (see section 2 of the PIL, 'Warnings and precautions'). Symptoms of low blood sugar may include headache, drowsiness, weakness, dizziness, feeling hungry, confusion, irritability, fast heartbeat and sweating.
- Feeling sick (nausea)*
- Diarrhoea*
- Being sick (vomiting) – this usually goes away over time**
- Constipation**

*These side effects are usually not severe. They are most common when first starting tirzepatide but decrease over time in most patients.

** Constipation and vomiting are very common when used for weight management, but common (may affect up to 1 in 10 people) when used for type 2 diabetes.

Why were Mounjaro approved?
MHRA decided that the benefits are greater than the risks and recommended that these medicines can be approved for use.

Mounjaro has been authorised with the condition to perform further studies regarding pharmacovigilance activities. See section below "What measures are being taken to ensure the safe and effective use of Mounjaro?"

What measures are being taken to ensure the safe and effective use of Mounjaro?
As for all newly-authorised medicines, a Risk Management Plan (RMP) has been developed for Mounjaro The RMP details the important risks of Mounjaro, how these risks can be minimised, any uncertainties (missing information) about Mounjaro, and how more information will be obtained about the important risks and uncertainties.

The following safety concerns have been recognised for Mounjaro:

Important identified risks:
- None

Important potential risks:
- Medullary thyroid cancer
- Pancreatic malignancy
- Diabetic retinopathy complications

Missing information
- Use in pregnancy and lactation
- Medication errors related to vial presentation
- Significant active or unstable major depressive disorder or other sever psychiatric disorder
- Off-label use in patients who do not meet the criteria for treatment (weight management)

Additional pharmacovigilance activities are planned to evaluate the potential risks of medullary thyroid cancer, pancreatic cancer and diabetic retinopathy.

Additional pharmacovigilance activities are also planned to evaluate the use of Mounjaro in pregnancuy and during breastfeeding. This includes a patient registry to collect data on pregnant patients and pregnancy related outcomes, an observational study of exposure during pregnancy and a study of the levels of Mounjaro found in breast milk of post-partum lactating females.

The information included in the SmPCs and the PIL is compiled based on the available quality, non-clinical and clinical data, and includes appropriate precautions to be followed by healthcare professionals and patients. Side effects of Mounjaro are continuously monitored and reviewed including all reports of suspected side-effects from patients, their carers, and healthcare professionals.

An RMP and a summary of the pharmacovigilance system have been provided with these applications and are satisfactory.

Other information about Mounjaro
Marketing authorisations were granted in Great Britain on 26 September 2022.

The full PAR for Mounjaro follows this summary.

This summary was last updated in January 2024.

TABLE OF CONTENTS

Please note, the below scientific discussion consists of the original assessment of this Marketing Authorisation. The original assessment is followed by a table of key post approval changes and relevant (non-safety related variation) annexes. The PAR is configured in this manner to improve the accuracy of this Public Assessment Report and to provide a better understanding of authorisation's lifecycle.

I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) considered that the applications for Mounjaro 2.5, 5, 7.5 10, 12.5, and 15mg solution for injection in pre filled pen (PLGB 14895/0317-0318-0320-0321-0322-0323) could be approved.

The products are approved for the following indications:
Mounjaro is indicated for the treatment of adults with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise

- as monotherapy when metformin is considered inappropriate due to intolerance or contraindications
- in addition to other medicinal products for the treatment of diabetes.

For study results with respect to combinations, effects on glycaemic control and the populations studied, refer to the SmPC available on the MHRA products website.

Mechanism of action

Tirzepatide is a long acting dual GIP and GLP-1 receptor agonist. Both receptors are present on the pancreatic α and β endocrine cells, brain, heart, vasculature, immune cells (leukocytes), gut and kidney. GIP receptors are also present on adipocytes.

Tirzepatide is highly selective to human GIP and GLP-1 receptors. Tirzepatide has high affinity to both the GIP and GLP-1 receptors. The activity of tirzepatide on the GIP receptor is similar to native GIP hormone. The activity of tirzepatide on the GLP-1 receptor is lower compared to native GLP-1 hormone.

These products have been authorised by MHRA for Great Britain (consisting of England, Scotland and Wales). In coming to its decision, MHRA has relied on a European Commission (EC) decision on 15 September 2022 (EMEA/H/C/005620), in accordance with the advice from the Committee for Medicinal Products for Human Use (CHMP). For the scientific discussion of the quality, non-clinical and clinical assessment conducted by the European Medicines Agency (EMA), please refer to the European Public Assessment Report, available on the EMA website.

These applications were approved under Regulation 50 of the Human Medicines Regulation 2012, as amended (previously Article 8.3 of Directive 2001/83/EC, as amended).

In line with the legal requirements for children's medicines, the applications included a licensing authority decision on the agreement of a paediatric investigation plan (PIP) (MHRA-100447-PIP01-22-M01). At the time of the submission of the applications the PIP was not yet completed as some measures were deferred.

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for these products at all sites responsible for the manufacture, assembly and batch release of these products.

A Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided with these applications and are satisfactory.

Marketing authorisations were granted on 26 September 2022.

II. PRODUCT INFORMATION

SUMMARY OF PRODUCT CHARACTERITICS (SmPC)

The SmPCs are in line with current guidelines and are satisfactory.

PATIENT INFORMATION LEAFLET

The PIL is in line with current guidelines and is satisfactory.

LABEL

The labelling is in line with current guidelines and is satisfactory.

III. QUALITY ASPECTS

MHRA considered that the quality data submitted for these applications is satisfactory.

The grant of marketing authorisations is recommended.

IV. NON-CLINICAL ASPECTS

MHRA considered that the non-clinical data submitted for these applications is satisfactory.

The grant of marketing authorisations is recommended.

V. CLINICAL ASPECTS

MHRA considered that the clinical data submitted for these applications is satisfactory.

The grant of marketing authorisations is recommended.

VI. RISK MANAGEMENT PLAN (RMP)

The applicant has submitted an RMP, in accordance with the requirements of Regulation 182 of The Human Medicines Regulation 2012, as amended. In addition to routine pharmacovigilance and risk minimisation measures, the following additional pharmacovigilance measures have been proposed:

Important potential risk: Medullary thyroid cancer	
Evidence for linking the risk to the medicine	In nonclinical studies, treatment-related increases in thyroid C-cell hyperplasia and neoplasia were observed with tirzepatide, at all doses, in a 2-year rat carcinogenicity study. The relevance of rodent thyroid tumours to humans is not known. The evidence for this potential risk comes from rodents with near-lifetime exposure. This effect on rodent thyroids has been observed consistently with other long-acting GLP-1 RAs, including liraglutide, exenatide once weekly, dulaglutide, and semaglutide, in near-lifetime exposure carcinogenicity studies. The relevance to humans cannot be determined from clinical and nonclinical studies. At this time, there is insufficient evidence to attribute thyroid C-cell disease to tirzepatide. Given the latency for cancer, the database for tirzepatide is of insufficient size and exposure duration to assess definitively for any particular type of cancer. Nonclinical data suggest that there is a risk for MTC with tirzepatide, and this has been determined to be a key safety finding from the nonclinical development programme.
Risk factors and risk groups	Medullary thyroid carcinoma develops from the C (parafollicular) cells and accounts for 5% to 10% of all thyroid cancers (Brady 2018), and up to 25% of MTC cases develop under multiple endocrine neoplasia-2A (IARC 2018). Compared to the general population (6.6%), patients with diabetes have a higher prevalence of thyroid disorders (10.8%) (Shih et al. 2012). However, the link between T2DM and thyroid cancer is arguable. Some studies did not show an association between diabetes, including T2DM and thyroid cancer risk (Kitahara et al. 2012; Shih et al. 2012; Seo et al. 2017). Other studies showed that patients with diabetes are 20% to 34% more likely to develop thyroid cancer compared to those without diabetes (Yeo et al. 2014; Li and Qian 2017).
Risk minimisation measures	**Routine risk minimisation measures:** • SmPC Section 5.3 **Additional risk minimisation measures:** • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • I8F-MC-B010: Medullary Thyroid Carcinoma Surveillance Study See Section Post-Authorisation Development Plan of this summary for an overview of the post-authorisation development plan.
Important potential risk: Pancreatic malignancy	

Evidence for linking the risk to the medicine	There is no evidence from clinical trials that GLP-1-based therapies increase the risk of pancreatic cancer. Some reports indicate a causal association with these agents, while others have failed to show such an association. A joint FDA and EMA publication states that, data demonstrate conflicting opinions about the strength of the association (Egan et al. 2014). To date, no causal relationship between tirzepatide and pancreatic malignancy has been established. From the Phase 2 and 3 clinical trial programmes for tirzepatide, a few cases of pancreatic malignancy were reported.
Risk factors and risk groups	Patients with long-standing T2DM are twice more likely to have pancreatic cancer than patients without T2DM (Yadav and Lowenfels 2013). About 0.5% of patients newly diagnosed with T2DM develop pancreatic cancer within 6 years of follow-up. Being the fourth leading cause of cancer mortality, pancreatic cancer is a highly mortal malignancy, with 75% of patients dying within the first year of diagnosis (Bracci 2012). The 5-year survival rate among patients with pancreatic malignancy is about 6% (Yadav and Lowenfels 2013).
Risk minimisation measures	**Routine risk minimisation measures:** • None **Additional risk minimisation measures:** • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • I8F-MC-B011: Tirzepatide Pancreatic Malignancy Study See Section II.C Post-Authorisation Development Plan of this summary for an overview of the post-authorisation development plan.
Important potential risk: Diabetic retinopathy complications	
Evidence for linking the risk to the medicine	Worldwide, the prevalence of DR ranges between 10% and 61% (median 28%) among patients with T2DM and between 1.5% and 31% (median 11%) among those newly diagnosed with T2DM (Ruta et al. 2013). The incidence rates of DR among adults aged 30 years and older with T2DM in the UK and Spain were 11.6 and 81.3 per 1000 people, respectively (Thomas et al. 2012; Romero-Aroca et al. 2017). Deterioration of DR among patients with improved glycaemic control is well documented with limited information for patients with T2DM specifically (Hooymans et al. 1982; Yau et al. 2012; Bain et al. 2019). A study conducted by Oslo Study Group-Brinchmann-Hansen et al. reported worsening of DR after introduction of stringent diabetes management within 3 months of

	treatment; approximately 50% of treated patients were affected compared with none of the patients treated conventionally (Oslo Study Group et al. 1985). A study conducted among patients with type 2 diabetes reported the risk of progression of DR after 3 and 9 years was 15.8% and 23%, respectively, for patients treated with intensive therapy compared with 15.3% and 27.8%, respectively, for patients undergoing treatment with either insulin or a sulphonylurea (Bain et al 2019). A meta-analysis of 4 randomised controlled trials reported that after 5 years of follow-up, more intensive glucose control was associated with a 13% reduction of eye events (risk ratio: 0.87; 95% confidence interval: 0.76, 1.00; p = 0.04; Feldman-Billard et al. 2018). Patients with a history of proliferative DR, diabetic maculopathy, or non-proliferative DR that required acute treatment were excluded from the tirzepatide clinical trial development programme. A dedicated retinopathy addendum to SURPASS-CVOT I8F-MC-GPGN (GPGN) is ongoing, which will further investigate the risk of disease progression for DR among patients treated with tirzepatide. The comparative analysis of the worsening of an existing DR with other diabetic treatment to tirzepatide treatment will be conducted after the addendum GPGN sub-study results are available. Therefore, there was limited experience to determine whether the safety profile in this patient population is different from that expected in the population without DR. In Phase 3 clinical trials, a dilated fundoscopic examination was performed when clinically indicated by any suspected adverse event of worsening retinopathy or clinically recommended during the course of the study. Worsening of fundoscopic examination result was observed in 18 tirzepatide-treated patients (0.35%).
Risk factors and risk groups	Patients with T2DM are at risk of developing microvascular complications including DR, nephropathy, and neuropathy. Modifiable risk factors for DR include high blood glucose, high blood pressure, high serum lipids, and smoking. Non-modifiable risk factors include diabetes duration, age, race, and genetic predisposition (Ding and Wong 2012; Scanlon et al. 2013).
Risk minimisation measures	**Routine risk minimisation measures:** • SmPC Section 4.4 **Additional risk minimisation measures:** • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Retinopathy addendum to SURPASS-CVOT (I8F-MC-GPGN) See Section II.C of this summary for an overview of the post-

	authorisation development plan.
Missing Information: Use in pregnant and/or breastfeeding women	
Risk minimisation measures	**Routine risk minimisation measures:** • SmPC Section 4.6 • PL Section 2 **Additional risk minimisation measures:** • None

Abbreviations: DR = diabetic retinopathy; EMA = European Medicines Agency; FDA = United States Food and Drug Administration; GLP-1 = glucagon-like peptide 1; MTC: medullary thyroid cancer; PL = package leaflet; RA = receptor agonist; SmPC = Summary of Product Characteristics; T2DM = type 2 diabetes mellitus.

This is acceptable.

VII. USER CONSULTATION

A full colour mock-up of the Patient Information Leaflet (PIL) has been provided with the applications, in accordance with legal requirements.

The PIL has been evaluated via a user consultation study in accordance with legal requirements. The results show that the PIL meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VIII. OVERALL CONCLUSION, BENEFIT/RISK AND RECOMMENDATION

The quality of the products is acceptable. The non-clinical and clinical data submitted have shown the positive benefit/risk of this/these products in the treatment adults with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise

- as monotherapy when metformin is considered inappropriate due to intolerance or contraindications
- in addition to other medicinal products for the treatment of diabetes.

The Summaries of Product Characteristics (SmPCs), Patient Information Leaflet (PIL) and labelling are satisfactory.

In accordance with legal requirements, the current approved GB versions of the SmPCs and PIL for these products are available on the MHRA website.

TABLE OF CONTENT OF THE PAR UPDATE

Steps taken after the initial procedure with an influence on the Public Assessment Report (non-safety variations of clinical significance).

Please note that only non-safety variations of clinical significance are recorded below and in the annexes to this PAR. The assessment of safety variations, where significant changes are made, are recorded on the MHRA website or European Medicines Agency (EMA) website. Minor changes to the marketing authorisation are recorded in the current SmPCs and/or PIL available on the MHRA website.

Application type	**Scope**	**Product information affected**	**Date of grant**	**Outcome**	**Assessment report attached Y/N**
II	To add a new indication for Mounjaro (tirzepatide) in Weight Management (WM). Also, the RMP has been updated.	SmPC and PIL	08 November 2023	Granted	Y (annex 1)

Annex 1

Reference: **PLGB 14895/0317-0318-0320-0321-0322-0323 - 0007**

Product: **Mounjaro 2.5, 5, 7.5 10, 12.5, and 15 mg solution for injection in pre-filled pen**

Type of Procedure: National

Submission category: Type II Variation

Reason
To add a new indication for Mounjaro (tirzepatide) for Weight Management (WM). Also, the RMP has been updated.

Supporting evidence
The MAH has submitted an updated Summaries of Product Characteristics (SmPCs), Patient information leaflet (PIL) and Risk Management Plan (RMP).

The application is based on pivotal and supporting evidence from a total 26 clinical studies:
- 2 global, pivotal Phase 3 WM studies (SURMOUNT-1 and SURMOUNT-2)
- the 36-week tirzepatide open-label lead-in for 1 ongoing global Phase 3 study (SURMOUNT-4)
- 8 supportive Phase 3 studies in participants with T2DM, including
    - 5 global studies (SURPASS-1 to -5)
    - 3 regional studies (SURPASS-J mono, SURPASS-J combo, SURPASS AP-Combo)
- 2 Phase 2 studies
- 3 biopharmaceutic studies, and
- 10 clinical pharmacology studies, including 2 mechanism of action studies.

In support of this variation, the Applicant has also submitted one new non-clinical study (Study 8485844), to further qualify impurities.

Evaluation
1. Non-clinical
Study 8485844 was an impurity qualification study in rats administered tirzepatide twice weekly by subcutaneous injection for 2 weeks.

Male and female Crl:CD (SD) rats were assigned to three groups (10/sex/group). One group was administered 3 mg/kg of tirzepatide without spiked levels of impurities (referred to as Lot A), one group was administered 3 mg/kg of tirzepatide with spiked levels of impurities (referred to as Lot B), and one group was administered the vehicle control (5 mM sodium phosphate and 140 mM sodium chloride, pH 7.0 ± 0.2). Rats were dosed by subcutaneous (SC) injection at a volume of 1.5 mL/kg on Days 1, 5, 8, 12, and 15 of the dosing phase, as in the previous toxicological studies.

The assessment of toxicity was based on mortality, clinical observations, body weights, food consumption, ophthalmic observations, and clinical and anatomic pathology.

All rats survived to their scheduled sacrifice. Tirzepatide-related body weight loss was slightly greater for rats administered 3 mg/kg tirzepatide Lot B, compared to Lot A, which correlated with differences in mean food consumption. Mean body weights at the end of the dosing phase were 13% to 19% lower for rats administered 3 mg/kg tirzepatide Lot A or Lot B, consistent with effects observed following administration of tirzepatide without impurities.

Tirzepatide-related clinical pathology effects were minor and generally similar in magnitude among rats administered tirzepatide from Lot A or Lot B. These findings consisted of minimally higher urea nitrogen concentration in males administered tirzepatide from Lot B and females administered tirzepatide from Lot A or B, mildly lower albumin concentration resulting in lower total protein concentration and albumin:globulin ratio and calcium (also for males administered Lot B) concentration for females administered tirzepatide from Lot A or B, and minimally lower triglyceride and cholesterol concentrations in both sexes administered tirzepatide from Lot A or B. The Applicant concluded that these findings were likely secondary to decreased food consumption and body weight, noted clinically, related to the pharmacologic activity of tirzepatide.

Tirzepatide-related increased thyroid/parathyroid weights were noted for males administered 3 mg/kg tirzepatide (Lot A or Lot B). No microscopic correlates were noted in the thyroid or parathyroid. No tirzepatide-related macroscopic observations were observed. Tirzepatide-related microscopic findings were limited to minimally decreased zymogen granules in the pancreas, which generally occurred at a low incidence and at a similar severity in rats administered 3 mg/kg tirzepatide Lot A or Lot B and were considered secondary to statistically significant decreased terminal body weights.

The applicant concluded that all effects observed in this study were non-adverse and consistent with tirzepatide pharmacology and with findings in repeat-dose toxicology studies conducted with tirzepatide. No differences between Lots A and B were observed with twice-weekly subcutaneous injection of 3 mg/kg tirzepatide to Cr1:CD (SD) rats for 2 weeks; therefore, it is concluded that no novel or exacerbated toxicities were associated with the impurities.

The impurity studies give no indication for novel or exacerbated toxicities associated with the impurities. The submitted study supplements the existing dossier with additional data with regards to qualification of impurities and supports the proposed variation.

An updated ERA to account for the increased population penetration of the product is not expected given the chemical nature of the product, i.e., a polypeptide that is completely degraded by peptidases following administration.

2. Clinical Pharmacology

2.1 Pharmacokinetics

Introduction

Since the dossier for the Type 2 diabetes mellitus (T2DM) application, 3 additional clinical pharmacology studies have been completed to

- characterize GE in participants with obesity (Study I8F-MC-GPHU)
- support registration of tirzepatide for T2DM in China (Study I8F-MC-GPHT)
- assess hypoglycaemia counter-regulation in T2DM.

The tirzepatide clinical pharmacology program characterizes the pharmacokinetics (PK),

pharmacodynamics (PD), and exposure-efficacy/safety relationships of tirzepatide doses ranging from 0.25 to 15 mg. Tirzepatide doses across a 60-fold range of 0.25 to 15 mg were evaluated over the course of multiple clinical pharmacology studies. Single doses of tirzepatide over a range of 0.25 to 8 mg were evaluated. A dose of 5 mg tirzepatide was identified as the maximum tolerated dose when given as a single dose in healthy participants. Hence, doses greater than 5 mg were attained by stepwise dose-escalation schemes in subsequent multiple dose evaluations. The terminal t1/2 was approximately 5 days, thereby supporting a once-weekly (QW) dosing regimen. QW multiple doses over a range of 0.5 to 15 mg were also studied. Multiple doses were studied for a duration of 4 weeks to up to 28 weeks. Study populations included 672 participants, of which 293 participants had T2DM.

The population PK/PD model established based on data submitted in the original T2DM application served as the base model for the population PK/PD analysis for chronic weight management (CWM). An additional study, Study I8F-MC-GPHK (SURMOUNT-1), is included in the population PK/PD analyses for CWM.

The mechanistic PD assessments of pancreatic α- and β-cell function and insulin sensitivity from Study I8F-MC-GPGT were provided in the original T2DM application. To support the CWM indication, mechanistic PD assessments of body weight and composition, appetite, food and caloric intake, and lipid metabolism from Study GPGT are also provided in the current application.

Analytical methods
The PK samples collected were analyzed to measure concentrations of tirzepatide. Samples were analyzed for tirzepatide using the same method over the course of clinical development The method was a validated liquid chromatography with mass spectrometry (LC/MS) assay, which detected tirzepatide intact mass, comprising the full-length peptide plus the linker and acyl side chain.

Absorption
The time to reach maximum tirzepatide concentration (tmax) was reported as 24 hours, with a range of 8 to 72 hours.

Bioavailability
The absolute bioavailability of a 5 mg subcutaneous (SC) dose of tirzepatide in healthy participants was approximately 80%, indicating a high level of drug absorption. The lyophilized formulation of tirzepatide was found to have comparable PK, safety, and tolerability to the solution formulation. The location of injection site did not have an impact on tirzepatide exposure, meaning that the drug can be administered to the abdomen, upper arm, or thigh without affecting its effectiveness. The PK of tirzepatide was found to be comparable when administered using either a prefilled syringe or a drug delivery device called a self-injection device (SDP).

Distribution
Tirzepatide was highly bound in human plasma with a mean percentage bound of 99.1%.
Mean (%CV) apparent volume of distribution (Vd/F) in
- participants with T2DM = 10.3 L, and
- participants with obesity or overweight = 9.7 L.

Tirzepatide is highly bound to plasma proteins and has a low volume of distribution.

Elimination
Mean (%CV) t1/2 = 5.4 days (18%) in participants with T2DM
Mean (%CV) t1/2 = 5.7 days (21%) in participants with obesity or overweight
Mean (%CV) CL/F = 0.0606 L/hr (23%) in participants with T2DM
Mean (%CV) CL/F = 0.0564 L/hr (21%) in participants with obesity or overweight

Excretion
Renal excretion was the primary route of elimination for tirzepatide. From the human 14C study, approximately 70% of the administered dose recovered, approximately 50% of the administered radioactivity was excreted in the urine, and approximately 21% was excreted in faeces. Tirzepatide was eliminated through metabolism with no intact tirzepatide observed in urine or faeces.

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. 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.

Dose proportionality and time dependency

- **Dose proportionality**

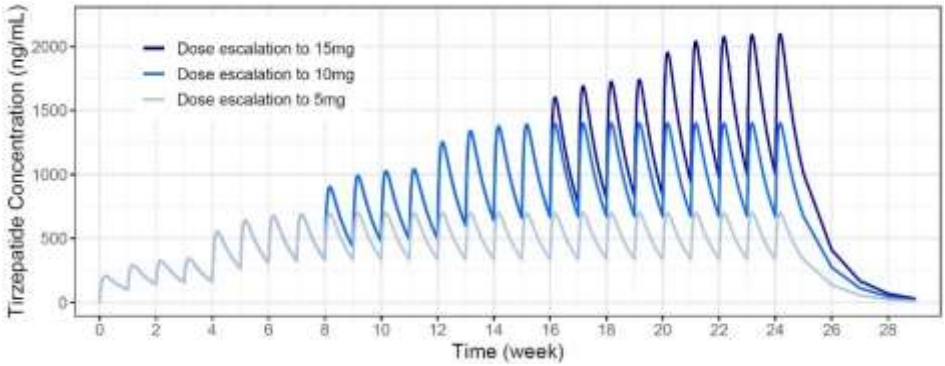
Over the single-dose range of 0.25 to 8 mg in healthy participants, ratios of dose-normalized geometric means and associated 90% CIs for Cmax and AUC(0-∞) were 0.851 (0.68, 1.06) and 0.826 (0.706, 0.966), respectively, suggesting that increases in exposure were in an approximately dose-proportional manner.

Exposure to tirzepatide also appeared to increase proportionally across the dose range of 0.25 to 15 mg. The average maximum plasma concentration (Cmax) 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·hr/mL, respectively (20.2% to 22.0% CV).

- **Time dependency**

Tirzepatide t1/2 was 5.7 days with tirzepatide concentrations reaching the limit of quantitation (2 ng/mL) by 4 weeks after a steady-state dose. Steady-state exposures were attained following 4 QW SC injections. Accumulation following multiple dose administration was about 1.7-fold.
PK profiles (based on PK model) following Phase 3 dosing regimen to attain maintenance dose levels of 5, 10, and 15 mg are shown in Figure 1.

Figure 1. Model predicted tirzepatide concentrations over time following tirzepatide once-weekly dose administration with dose escalation in participants with obesity or overweight.



Note: Tirzepatide concentrations following tirzepatide QW administration up to 24 weeks in a 105-kg individual were simulated using the tirzepatide population PK model. The solid lines denote concentrations following dose escalation up to 5, 10, or 15 mg. 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. Tirzepatide lower limit of quantification (LLOQ) is 2 ng/mL.

Tirzepatide shows dose proportional pharmacokinetics and the time dependency is consistent with the half-life.

Intra- and inter-individual variability
Tirzepatide shows moderate variability with CV of 23.8% on Cl from the PopPK and residual variability of 20.6 %

Pharmacokinetics in target population
Population Pharmacokinetic Analysis of Tirzepatide for Chronic Weight Management
Table 1 outlines the available number of observations and participants contributing to the key PK and exposure-response analyses from Phase 3 Study I8F-MC-GPHK (SURMOUNT-1, primary study period) for CWM in participants with obesity, or overweight with comorbidities. SURMOUNT-1 had 3 maintenance doses of tirzepatide (5, 10, and 15 mg) each with a starting dose of 2.5 mg with dose-escalation of 2.5 mg increments every 4 weeks until reaching the maintenance dose.

Table 1. Summary of the Number of Observations and Participants Included in the Tirzepatide Population Pharmacokinetic and Exposure Response Analyses

Analyses/Model	Number of observations (number of participants)
Population Pharmacokinetic	14317 (1880)
Body weight	54804 (2523)
Nausea, vomiting, and diarrhea	~1,194,000[a](2523)

[a] Nausea, vomiting, and diarrhea were each daily observations.

Measurements of tirzepatide concentration and body weight following treatment with tirzepatide were analyzed using nonlinear mixed effects modeling methodology.

A robust tirzepatide PK model supporting development of tirzepatide as a treatment for T2DM was previously developed from extensive data collected from clinical pharmacology, Phase 2, and Phase 3 studies. The model structure and parameter estimates from the previously developed model were used to inform the base model for the population PK analysis of data from SURMOUNT-1.

Overall, the population estimates from the SURMOUNT-1 population PK model are similar to the model estimates from the population PK model developed with data from patients with

T2DM (Table 2). A summary of the post hoc PK parameters from SURMOUNT-1 are provided in Table 3.

Table 2. Pharmacokinetic and Covariate Parameters in Population Model

Parameter	T2DM PK Model Population Estimate Bootstrap Median (95% CI)[a]	SURMOUNT-1 PK Model Population Estimate Bootstrap Median (95% CI)[a]
Bioavailability (F, fraction)	0.8 fixed	0.8 fixed
Absorption rate (ka, 1/h)	0.0373 0.0370 (0.0289, 0.0460)	0.0318 0.0321 (0.0280, 0.0395)
Clearance (CL, L/h/70kg)	0.0329 0.0329 (0.0313, 0.0342)	0.0371 0.0371 (0.0359, 0.0382)
Intercompartmental clearance (Q, L/h/70kg)	0.126 0.125 (0.101, 0.144)	0.0934 0.0930 (0.0851, 0.101)
Central volume of distribution (Vc, L/70kg)	2.47 2.46 (2.05, 2.92)	2.88 2.90 (2.45, 3.74)
Peripheral volume of distribution (Vp, L/70kg)	3.98 3.98 (3.56, 4.21)	4.05 4.03 (3.62, 4.31)
Covariate Effects		
*Covariate effect on F*b Relative study effect	-0.181 -0.181 (-0.220, -0.147)	NA[f]
Covariate effect on CL and Q[c] Body weight (kg) Fraction of fat mass	0.8 fixed 1 fixed	0.8 fixed 0.711 0.712 (0.638, 0.800)
*Covariate effect on Vc and Vp*d Body weight (kg) Fraction of fat mass	1 fixed 0.482 0.483 (0.447, 0.524)	1 fixed 0.417 0.416 (0.315, 0.526)
Covariate effect on ka[e] Lyophilized formulation	-0.161 -0.161 (-0.207, -0.107)	NA[g]
Interindividual variability CV%		
ka	22.5% 22.1 (14.9, 28.7)	15.2% 15.2 (14.4, 16.3)
CL	14.2% 14.2 (13.7, 14.7)	12.3% 12.3 (11.6, 13.0)
Vc	49.0% 49.5 (38.3, 62.3)	61.5% 61.1 (47.5, 71.2)
Proportional residual	58.1% 58.0 (56.1, 60.0)	65.2% 65.1 (62.0, 68.3)
Residual variability		
Proportional (%)	20.6% 20.6 (20.3, 21.0)	20.6% 20.6 (20.0, 21.3)

Abbreviations: BW = body weight; CI = bootstrap-derived confidence interval; CL = clearance; CV = coefficient of variation; F = bioavailability; FFM = fat-free mass (kg); ka = absorption rate constant; Q = intercompartmental clearance; T2DM = type 2 diabetes mellitus; Vc = central volume of distribution; Vd =

volume of distribution; Vp = peripheral volume of distribution; NA = not applicable.

[a] Median and 95% CI derived from bootstrap analysis.
[b] $F = \Theta_1 * (1 + \Theta_{10})$ where Θ_1 is the bioavailability value from Study GPGE and Θ_{10} is the relative fraction.
[C] iCL = pCL * [(FFM + fat mass* Θ_8)/70)]^0.8 where iCL is an individual's CL, pCL is the population CL, FFM is an individual's FFM, and Θ_8 is a fraction. The described structure was applied to CL and Q.
[d] iVd = pVd * [(FFM + fat mass* Θ_9)/70]^1 where iVd is an individual's Vd, pVd is the population Vd, FFM is an individual's FFM, and Θ_9 is a fraction. The described structure was applied to Vc and Vp. [e] ika = pka * (1 + Θ_{11}) where ika is an individual's ka, pka is the population ka, and Θ_{11} is a fraction. [f] A scalar for F in SURMOUNT-1 relative to 0.8 was tested and did not have an impact on the objective function.
[g] The solution formulation of tirzepatide was administered in SURMOUNT-1.

Table 3. Summary of Tirzepatide Population PK Post Hoc Parameters from Participants with or without T2DM

	Geometric mean (CV%)			
PK Parameter	**Non-T2DM in T2DM Program (n=307)**	**T2DM in T2DM Program (n=5495)**	**T2DM w/ BMI ≥27 kg/m² sub-population in SURPASS (n=1422)[a]**	**Non-T2DM GPHK (SURMOUNT-1) (n= 1880)**
Baseline Body Weight (kg) Arithmetic mean (SD)	79.8 (15.9)	90.0 (20.5)	94.5 (18.4)	105 (22.4)
Absorption rate (ka, 1/h)	0.0378 (23.7)	0.0366 (9.51)	0.0374 (10.4)	0.0319 (4.83)
Apparent clearance (CL/F, L/h)	0.0489 (22.3)	0.0606 (23.1)	0.0636 (20.6)	0.0564 (20.9)
Apparent volume of distribution (Vd/F, L)	7.94 (21.3)	10.3 (23.8)	10.7 (23.6)	9.66 (28.5)
Half-life (t1/2, days)	5.28 (12.7)	5.41 (18.1)	5.39 (19.0)	5.69 (20.9)
Accumulation ratio	1.67 (7.8)	1.70 (11.5)	1.69 (12.3)	1.75 (14.2)
5 mg average steady-state concentration (Css, ng/mL)	609 (22.3)	491 (23.1)	468 (20.6)	528 (20.9)
10 mg average steady-state concentration (Css, ng/mL)	1220 (22.3)	983 (23.1)	936 (20.6)	1060 (20.9)
15 mg average steady-state concentration (Css, ng/mL)	1830 (22.3)	1470 (23.1)	1400 (20.6)	1580 (20.9)

Abbreviations: BMI = body mass index; CV = geometric coefficient of variation; n = number of participants; Non-T2DM = without T2DM; PK = pharmacokinetics; SD = standard deviation; T2DM = type 2 diabetes mellitus.
[a] Participants with T2DM and with baseline BMI ≥27 kg/m² in T2DM program Phase 3 studies with PK objectives: Study GPGK (SURPASS-1), Study GPGM (SURPASS-4), and Study GPGI (SURPASS-5).

The updated PopPK model appears adequate to describe the pharmacokinetics in the whole population. Population parameters are similar following the inclusion of the subjects from Surmount 1. The effect of covariates is also similar with only weight being significant.

Special populations

- **Impaired renal function**

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 was no relationship identified between aspartate aminotransferase, alanine aminotransferase, bilirubin, albumin, and estimated glomerular filtration rate on tirzepatide PK.

- **Impaired hepatic function**

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. There was no relationship identified between aspartate aminotransferase, alanine aminotransferase, bilirubin, albumin, and estimated glomerular filtration rate on tirzepatide PK.

- **Gender**

Sex was investigated as a covariate on tirzepatide PK. However, it was not found to be of significance after accounting for the influence of body weight.

- **Race**

No significant difference in PK was detected based on race (Asian, black, or white) after accounting for body weight. No significant difference in PK was detected between Hispanic and non-Hispanic participants after accounting for body weight.

Study, I8F-MC-GPHT (GPHT), investigated the safety, tolerability, PK, PD, and efficacy of tirzepatide administered QW for either 16 or 24 weeks as SC injections to Chinese patients with T2DM. Cohort 1: QW SC doses of tirzepatide with dose escalation every 4 weeks. 2.5, 5, 7.5, and 10 mg, up to 16 weeks in total. Cohort 2: QW SC doses of tirzepatide with dose escalation every 4 weeks. 2.5, 5, 7.5, 10, 12.5, and 15 mg, up to 24 weeks in total.

Table 4. Pharmacokinetic Results:

Cohort 1			
	Week 0 2.5 mg tirzepatide QW SC (N=10)	**Week 7 5 mg tirzepatide QW SC (N=9)**	**Week 15 10 mg tirzepatide QW SC (N=9)**
	Geometric mean (geometric CV%)		
AUC(0-168) (ng.h/mL)	35100 (14%)	125000 (16%)	263000 (17%)
C_{max} (ng/mL)	306 (28%)	1030 (13%)	2200 (16%)
	Median (minimum-maximum)		
t_{max} (h)	24.00 (8.00-72.05)	24.00 (8.00-24.03)	24.00 (8.00-48.00)

	Geometric mean (minimum-maximum)		
$t_1/2$ (h)	133 (104-164)[a]	139 (113-226)	132 (113-153)
Cohort 2			
	Week 0 2.5 mg tirzepatide QW SC (N=10)	**Week 7 5 mg tirzepatide QW SC (N=10)**	**Week 23 15 mg tirzepatide QWSC (N=10)**
	Geometric mean (geometric CV%)		
AUC(0-168) (ng.h/mL)	30900 (14%)	110000 (16%)	357000 (16%)
C_{max} (ng/mL)	257 (17%)	915 (18%)	2930 (20%)
	Median (minimum-maximum)		
t_{max} (h)	23.12 (7.98-47.08)	24.00 (8.00-48.02)	23.95 (23.93-24.08)
	Geometric mean (minimum-maximum)		
$t_1/2$ (h)	145 (121-173)b	124 (90.8-170)c	126 (114-156)

Abbreviations: AUC(0-168) = area under the concentration versus time curve from time zero to 168 hours postdose; C_{max} = maximum observed drug concentration; CV = coefficient of variation; N = number of patients; QW = once weekly; SC = subcutaneous; t_{max} = time of maximum observed drug concentration.
a N = 7. b N =9. c N = 8.
Week 0: After 1st dose of 2.5 mg tirzepatide QW.
Week 7: After 4th dose of 5 mg tirzepatide QW.
Week 15: After 4th dose of 10 mg tirzepatide QW. Week 23: After 4th dose 15 mg tirzepatide QW.

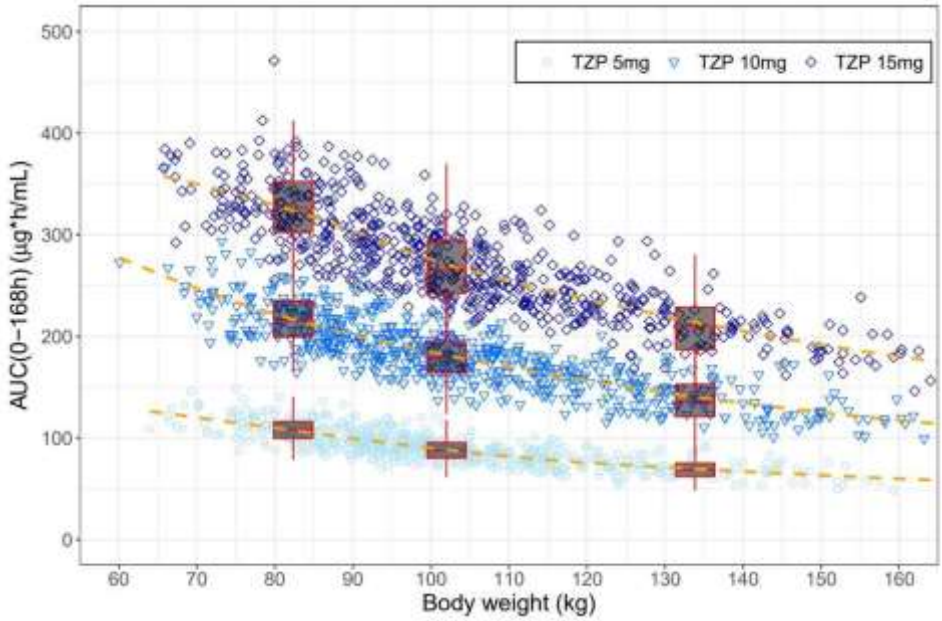
Median tmax for tirzepatide was approximately 24 hours postdose and geometric mean t1/2 was 5 to 6 days. PK parameters of tirzepatide in native Chinese patients with T2DM were consistent with those observed in previous studies in other populations.

- **Weight**

Body weight was identified to have a significant influence on tirzepatide PK (Figure 3). As tirzepatide treatment is associated with significant reduction in weight over time, body weight was evaluated as a time-varying as well as a baseline covariate. Approximately, every kilogram increase in weight was associated with a 1.1% decrease in tirzepatide exposure (AUC(0-168).

Body weight was the only statistically significant covariate on CL/F, and Vd/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.

Figure 2. Relationship between tirzepatide exposure and body weight for tirzepatide 5, 10, and 15 mg QW.



Abbreviations: $AUC_{(0}$-168) = area under the concentration versus time curve from time 0 to 168 hr after dose at steady state; QW = once weekly; TZP = tirzepatide. Note: Symbols denote individual values. The dashed lines are the loess smoothing fit for each treatment arm. The top and bottom margins of the boxplot represent the 75th and 25th percentiles and the whiskers extend to ±1.5 times interquartile range, respectively. The boxplots summarize data ≤90kg, between 90 and 120 kg, and >120 kg for each treatment arm. The x-axis positions of the boxplot are the median body weight for the aforementioned intervals (82, 102, and 134 kg).

- **Elderly**

Age was not found to influence tirzepatide PK. Approximately 112 (6%) participants were aged between 65 and 75 years, and 5 (<1%) participants were at least 75 years old in Study GPHK.

- **Children**

Tirzepatide has not been studied in paediatric participants.

Interactions

Drug-Drug Interactions due to the Impact of Tirzepatide on Gastric Emptying

Delay in gastric emptying (GE) caused by GLP-1 analogs has been shown to alter the absorption of some orally administered concomitant medications, leading to potential alterations in PK parameters related to rate of absorption (peak plasma concentration [Cmax] and extending time to peak concentration [tmax]), while minimally impacting the overall exposure (AUC). This is not unique to tirzepatide and is a known effect for the GLP-1 receptor agonist pharmacological class.

Impact of tirzepatide on GED in healthy participants and participants with T2DM using acetaminophen as a probe was studied within Phase 1 Study GPGA. The effect of GED was well characterized in participants with T2DM and a semi-mechanistic integrated acetaminophen PK/PBPK modelling approach was summarized in the original T2DM application. One drug-drug interaction study (Study I8F-MC-GPGR) was conducted to evaluate the effect of tirzepatide on combination oral contraceptive PK in healthy female participants.

Impact of tirzepatide on GED in participants with obesity or overweight was further studied in a Phase 1 study. Briefly, SC tirzepatide 5 mg was administered on Days 1 and 8; 10 mg on Days 15, 22, and 29; and 15 mg on Day 36 to participants with obesity or overweight and both with T2DM and without T2DM. Acetaminophen 1 g was administered before the first dose of tirzepatide (that is, acetaminophen alone, Day -1), and on Days 2 and 37 coinciding with time of peak tirzepatide exposure for the first and sixth doses of tirzepatide.

Consistent with the findings in participants with T2DM in Study GPGA, tirzepatide was observed to cause GED in participants with obesity or overweight with and without T2DM as evidenced by a delay in acetaminophen tmax and a decrease in Cmax (with no clinically meaningful impact on AUC). This GED was greatest following the first 5-mg tirzepatide dose (approximately 55% decrease in Cmax and a 1-hour delay in tmax compared to when acetaminophen was administered alone) and showed tachyphylaxis. That is, the impact on GED was less evident following repeated tirzepatide doses compared to when acetaminophen was administered alone as measured by impact on Cmax (approximately 32% reduction) and tmax (0.5 hour delay) on Day 37. In addition, acetaminophen Cmax reduced by a similar extent between participants with obesity or overweight without T2DM (55%) and with T2DM (56%) when acetaminophen was administered in the presence of 5 mg tirzepatide on Day 2 compared to when administered alone. However, the reduction in Cmax was greater for participants with T2DM (43%) compared to participants without T2DM (20%) when acetaminophen was administered in the presence of 15 mg tirzepatide on Day 37 compared to when administered alone.

Overall, Study GPHU provided additional evidence of GED effect in participants with obesity or overweight and together with the evaluation from the original T2DM application, supports the following conclusions:

- The maximum effect of tirzepatide on GED at 5-mg dose (maximum dose that can be administered without dose escalation) represented conservative clinical conditions, that is, a worst-case scenario. The recommended starting dose of tirzepatide is 2.5 mg.
- The slow titration to maintenance dose in clinical practice will allow for tachyphylaxis of the GE effect.
- Based on PBPK model prediction, it is not anticipated that tirzepatide treatment will result in clinically meaningful impact on orally administered drugs.
- Impact on GED is of similar magnitude in participants with obesity or overweight without T2DM as in those with T2DM after the first dose of tirzepatide with faster tachyphylaxis of the GED effect in those without T2DM (that is, the GED effect diminishes faster).
- Oral contraceptive (OC) PK would not 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 the GED effect diminishes with time and the tachyphylaxis is faster in participants with obesity or overweight without T2DM.

Peak exposure to the OC as measured by Cmax 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 tmax of 2.5 to 4.5 hr were observed when the OC was administered in the presence of 5 mg tirzepatide.

Overall exposure to OC as measured by 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.

However, exposure to OCs are known to be related to body weight, thus individuals would be expected to already have lower exposure.

The SmPC reflects that obese or overweight female patients using oral contraceptives should consider also using a barrier method of contraception or switching to a non-oral contraceptive method for 4 weeks after starting Mounjaro and for 4 weeks after each increase in dose as Mounjaro may affect how well the contraceptive pill works in these patients.

Exposure relevant for safety evaluation

Table 5. Tirzepatide Exposure Indices Based on SURMOUNT-1 Population PK

	Geometric mean (CV%)		
Exposure Parameter	**Tirzepatide 5 mg QW (n = 626)**	**Tirzepatide 10 mg QW (n=629)**	**Tirzepatide 15 mg QW (n=625)**
C_{max} (ng/mL)	710 (19.5)	1410 (21.2)	2120 (19.7)
AUC (ng*h/mL)	88900 (20.2)	177000 (22.0)	266000 (20.4)

Abbreviations: AUC = area under the concentration versus time curve at steady state; CV = geometric coefficient of variation; C_{max} = maximum observed drug concentration; n = number of participants; PK = pharmacokinetics;
QW = once weekly.
Note: The arithmetic mean baseline body weight was 103 kg, 106 kg, and 106 kg for tirzepatide 5 mg, 10mg, and 15mg QW groups, respectively.

2.2 Pharmacodynamics

Introduction

Tirzepatide decreases food intake and reduces body weight through decreased calorie intake. Tirzepatide delays GE. The delay is largest after the first dose and shows tachyphylaxis after repeated doses.

Mechanism of action

Study I8F-MC-GPGT: The Effect of Tirzepatide on α and β Cell Function and Insulin

A Phase 1, multicentre, randomised, sponsor, investigator- and participant-blind, parallel-arm study was conducted in 117 participants with T2DM treated with diet and exercise and stable dose(s) of metformin with the primary objective to compare the effect of tirzepatide and placebo on total clamp disposition index after 28 weeks of treatment, with the 15 mg tirzepatide dose being attained via the same stepwise escalation used in Phase 3 studies. This study also compared the effects of tirzepatide relative to placebo and a selective GLP-1 receptor agonist semaglutide 1 mg on body weight and composition, food and caloric intake, appetite, and lipid metabolism.

A total of 117 participants with T2DM, 86 males and 31 females, aged between 38 and 74 years were enrolled and received at least 1 dose of tirzepatide. This study has previously been reported, therefore a summary only is included below.

Body weight, waist circumference, and body composition

Both tirzepatide and semaglutide led to statistically significant reductions in body weight compared to baseline at all postbaseline measurements. Starting from Week 5 and continuing until Week 28, participants treated with tirzepatide experienced a significantly greater reduction in body weight compared to both placebo and semaglutide. At Week 28,

participants treated with tirzepatide achieved approximately 11 kg of weight loss, while those treated with semaglutide achieved approximately 7 kg of weight loss. Tirzepatide resulted in a significantly larger reduction in waist circumference compared to both placebo and semaglutide at Week 28. The reduction in waist circumference for tirzepatide was approximately twice as large as that for semaglutide. The baseline characteristics of fat mass and fat-free mass were similar across the three treatment groups. At Week 28, participants treated with tirzepatide and semaglutide experienced statistically significant reductions in both fat mass and fat-free mass compared to baseline. Tirzepatide led to a greater reduction in fat-free mass compared to both placebo and semaglutide at Week 28. Tirzepatide also resulted in a significantly greater reduction in fat mass compared to both placebo and semaglutide at Week 28. At Week 28, participants treated with tirzepatide experienced a 7% loss in fat mass as a percentage of total body mass compared to baseline, while participants treated with semaglutide experienced a 4% loss. The reduction in fat mass as a percentage of total body mass was significantly greater in participants treated with tirzepatide compared to semaglutide.

Overall, these findings suggest that both tirzepatide and semaglutide are effective in reducing body weight, but tirzepatide appears to be more effective in achieving greater weight loss, reducing waist circumference, and improving fat mass and fat-free mass compared to both placebo and semaglutide.

Food and caloric intake

Ad libitum food intake, assessed through total energy intake (kcal) during a 45-minute buffet meal at noon, was measured at baseline, Week 8, Week 16, and Week 28.
At baseline, participants in the placebo, semaglutide, and tirzepatide treatment groups consumed similar calories.

At Week 8, all three treatment groups consumed significantly fewer calories compared to baseline. Participants treated with tirzepatide and semaglutide showed a larger reduction in energy intake compared to the placebo group. The reduction in energy intake was statistically significant for tirzepatide versus placebo and semaglutide versus placebo.
The reduction in energy intake from baseline was numerically larger in participants treated with tirzepatide compared to semaglutide at Week 8, but the difference was not statistically significant.

At Week 16, all three treatment groups consumed significantly fewer calories compared to baseline. Participants treated with tirzepatide showed a trend in decreasing energy intake compared to placebo, while participants treated with semaglutide had a statistically significant reduction in energy intake compared to placebo.

At Week 28, the placebo group consumed similar calories to baseline, whereas participants treated with tirzepatide or semaglutide showed a statistically significant reduction in energy intake from baseline. Both tirzepatide and semaglutide led to a significantly larger reduction in energy intake compared to the placebo group.

The reduction in energy intake from baseline was numerically larger in participants treated with tirzepatide compared to semaglutide at Week 28, but the difference was not statistically significant.

Overall, these findings indicate that both tirzepatide and semaglutide resulted in reduced energy intake during ad libitum food intake compared to baseline. The reductions were statistically significant and more pronounced in participants treated with tirzepatide and semaglutide compared to the placebo group. There was a trend towards greater reduction in energy intake with tirzepatide compared to semaglutide, although the difference was not statistically significant in all cases.

Both tirzepatide and semaglutide led to a significant reduction in fasting appetite compared to baseline. At Week 28, tirzepatide showed a greater reduction in fasting appetite compared to placebo, while semaglutide did not demonstrate a significant difference.

Overall, findings indicate that at 28 weeks, tirzepatide exhibited beneficial effects on lipid metabolism compared to both placebo and semaglutide. The improvements were observed during the hyperglycemic clamp, post-meal in the sMMTT, and in the fasting state. These results suggest that tirzepatide has a positive impact on various lipid-related markers and may be effective in improving lipid metabolism.

Study I8F-MC-GPHG: A Randomised, Placebo-Controlled, Crossover Study to Investigate the Effect of Once-Weekly Tirzepatide on the Counter-Regulatory Response to Hypoglycemia in Patients with Type 2 Diabetes Mellitus

GPHG was a Phase 1, single-centre, 2-period, crossover, randomised, participant- and investigator-blind study in participants with T2DM. This study was designed to compare tirzepatide 15 mg QW and placebo with respect to secretion of counter-regulatory hormones in response to a hypoglycemic stimulus and parameters of recovery from hypoglycemia.

A total of 42 participants with T2DM between the ages of 40 and 67 years, inclusive, with a body mass index from 24.4 to 41.7 kg/m2, inclusive, received at least 1 dose of study drug. Thirty-three participants completed the study.

Results

Hypoglycaemic clamp procedure

During the hypoglycaemic clamp procedure, mean nadir plasma glucose (PG) concentrations were 47.5 mg/dL (2.63 mmol/L) in the placebo treatment group and 44.5 mg/dL (2.47 mmol/L) in the tirzepatide treatment group. Thus, both treatment groups approximated the target PG of 45 mg/dL (2.5 mmol/L). In the placebo treatment group, 73% of participants achieved the target nadir PG concentration of 45 mg/dL (2.5 mmol/L) or lower compared to 91% in the tirzepatide treatment group.

The primary analysis of glucagon response showed no statistically significant difference in the change in glucagon concentration from the target PG plateau of 100 mg/dL (5.5 mmol/L) to the target PG nadir plateau of 45 mg/dL (2.5 mmol/L) when receiving tirzepatide 15 mg QW compared to placebo. The sensitivity analysis, including only participants who reached the target nadir PG of 45 mg/dL (2.5 mmol/L), showed similar results.

The secondary analyses of counter-regulatory hormone response during induced hypoglycaemia showed:

- no statistically significant difference in the change in glucagon concentration from the target PG plateau of 100 mg/dL (5.5 mmol/L) to the target PG plateau of 63 mg/dL (3.5 mmol/L) and recovery to 72 mg/dL (4.0 mmol/L) when receiving tirzepatide compared to placebo supporting the findings of the primary analysis

- no statistically significant difference in the change in growth hormone concentrations from the target PG plateau of 100 mg/dL (5.5 mmol/L) in response to induced hypoglycaemia and recovery when receiving tirzepatide compared to placebo
- statistically significantly smaller increases in cortisol, adrenaline, and noradrenaline concentrations occurring later in response to induction of hypoglycaemia when receiving tirzepatide compared to placebo. There was no difference in the response between the treatment groups following recovery of PG to 72 mg/dL (4.0 mmol/L), and
- cortisol, adrenaline, and noradrenaline secreted earlier in placebo-treated participants compared to tirzepatide-treated participants may indicate a higher glycaemic threshold for these stress hormones in the placebo treatment group

The secondary analysis of insulin and C-peptide responses during induced hypoglycaemia showed significantly greater decreases in insulin and C-peptide concentrations from the target PG plateau of 100 mg/dL (5.5 mmol/L) in response to induced hypoglycaemia when receiving tirzepatide compared to placebo.

The secondary analyses of clinical hypoglycaemia showed:
- statistically significantly lower overall hypoglycaemia symptom scores at the target PG plateaus of 63 and 45 mg/dL (3.5 and 2.5 mmol/L) when receiving tirzepatide compared to placebo. There was no difference in the overall hypoglycaemia symptom score between the treatment groups following recovery of PG to 72 mg/dL (4.0 mmol/L), and
- no statistically significant difference in the proportions of participants who were aware of hypoglycaemia during induced hypoglycaemia and recovery when receiving tirzepatide compared to placebo.

The secondary analysis of time to recovery to PG 72 mg/dl showed that time to recovery from the nadir PG of 45 mg/dL (2.5 mmol/L) to PG of 72 mg/dL (4.0 mmol/L) was statistically significantly increased by 4 minutes with a p-value of 0.0023, in the tirzepatide treatment group compared to placebo. This finding may reflect imbalances between the treatment groups in PG concentrations achieved at nadir, insulin and glucose infusion rates, and probably insulin sensitivity. The inclusion of PG achieved at nadir in the model used for the analysis reduced the difference between the groups. However, the difference remained significant with a p-value of 0.0488. Other confounders mentioned earlier could not be corrected for in the analysis of time to recovery from the nadir PG of 45 mg/dL (2.5 mmol/L) to PG of 72 mg/dL (4.0 mmol/L). Future studies may be performed to investigate their effect on PG recovery. The recovery from hypoglycaemic symptoms was similar in the 2 groups as indicated by the similar frequency of hypoglycaemia symptoms during the recovery period.

Relationship between plasma concentration and effect
The PK/PD exposure-response relationships for the time course of body weight and tolerability (N/V/D) endpoints from the Phase 3 Study GPHK were evaluated based on semi-mechanistic models.

The PK/PD exposure-response relationships for the time course of body weight was characterized using the data from the Phase 3 Study SURMOUNT-1 and informed by a previously developed model structure for T2DM. A sequential PK/PD modelling approach was used to characterise the effect of tirzepatide on body weight reduction in participants with obesity or overweight. An indirect response model was used to account for a delay in

the effect of tirzepatide in reducing body weight and a maximum effect model best described the concentration-effect relationship. To best elucidate the effect of tirzepatide in reducing body weight, the dependent variables used for the modelling were fat-free mass (FFM) and fat mass. Individual FFM and fat mass were calculated for each participant according to their total body weight, height, and sex. Although the model was developed using the subcomponents only, the sum of the predicted FFM and fat mass gave the model-predicted total body weight, which was compared against the observed body weight.

Measurements of tirzepatide concentration and body weight following treatment with tirzepatide were analysed using nonlinear mixed effects modelling methodology. Exploratory graphical analyses were used to identify trends, patterns, and outliers in the data prior to initiation of modeling. The models were evaluated using standard methods, including bootstrap analysis and visual predictive checks (VPCs), to verify that the model predictions matched the observed data with acceptable precision and accuracy.

For the analysis of the occurrence of nausea, vomiting, and diarrhoea, a discrete-time Markov model structure was used to estimate transition probabilities between adverse event states and assess the impact of drug effects and covariates on these probabilities. The models were evaluated using bootstrap analysis and VPCs to verify the precision of parameter estimates and to check that models maintained fidelity with the observed data.

A maximum effect model best described the concentration-effect relationship for body weight. The typical ‘half-life’ for weight reduction was estimated to be about 22 weeks. This means that it would take about 2 years on a stable dose to get to a new steady state of body weight. A time-varying placebo effect was also included in the model. The placebo effect waned over time, with a half-life of about 40 weeks. Tirzepatide had a significant effect in lowering body weight. According to the drug effect in the model, the reduction in body weight was predominantly due to tirzepatide decreasing fat mass about 3 times more than decreasing FFM. The drug effect was dose dependent, with higher doses resulting in greater reduction in body weight.

Table 6. Parameter estimates of tirzepatide with reduction model

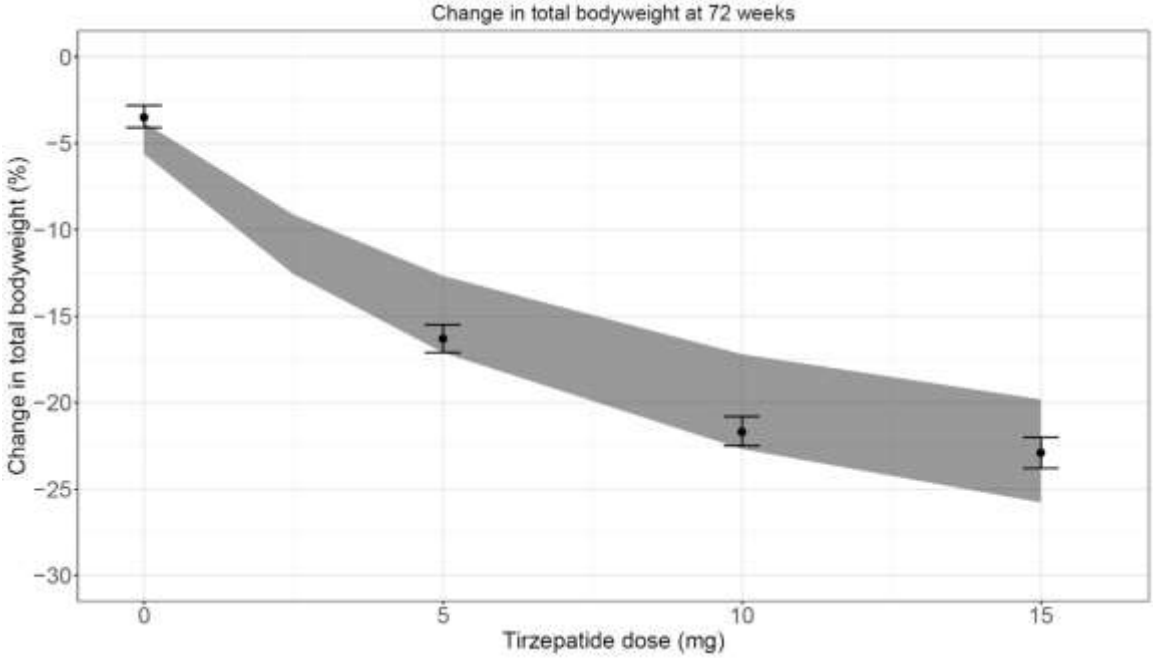
Population Parameter	Estimate (95% CI)[a]
Baseline fat-free mass (kg)	73.5 (72.6, 74.3)
Baseline fat mass (kg)	45.0 (43.4, 46.3)
First-order elimination rate constant, Kout (week^{-1})	0.0314 (0.0295, 0.0348)
Maximum effect for drug inhibiting formation of fat free mass	0.144 (0.119, 0.176)
Maximum effect for drug inhibiting formation of fat mass	0.319 (0.266, 0.385)
IC50 for drug inhibiting formation of fat free mass (ng/mL)	1760 (1490, 2030)
IC50 for drug inhibiting formation of fat mass (ng/mL)	518 (390, 678)
Placebo fractional reduction in fat-free mass Kin	0.0658 (0.0594, 0.0698)
Placebo fractional reduction in fat mass Kin	0.213 (0.192, 0.228)
Half life of waning placebo effect (weeks)	40.3 (34.6, 54.4)
Covariate Effects	
Fractional change in baseline fat-free mass in females	-0.312 (-0.322, -0.302)
Fractional change in fat mass in females	0.0539 (0.0170, 0.0994)
Fractional change in drug maximum effect for fat-free mass in females	1.78 (1.37, 2.33)
Fractional change in drug maximum effect for fat mass in females	0.809 (0.528, 1.12)
Fractional change in drug IC50 effect for fat-free mass in females	1.14 (0.836, 1.55)
Fractional change in drug IC50 effect for fat mass in females	2.05 (1.31, 3.19)
Fractional change in baseline fat-free mass in Asians	-0.110 (-0.128, -0.0905)
Fractional change in baseline fat mass in Asians	-0.254 (-0.291, -0.214)
Interindividual variability (CV%)	
Baseline fat-free mass	11.0 (10.5, 11.5)
Baseline fat mass	29.3 (28.1, 30.4)
Correlation between the random effects for baseline fat and fat-free mass	0.851 (0.835, 0.864)
Correlation between the random effects for baseline fat-free mass and Kout	-0.140 (-0.212, -0.0667)
Correlation between the random effects for baseline fat mass and Kout	-0.172 (-0.246, -0.0936)
First-order elimination rate constant, Kout	124 (110, 140)
Maximum drug effect on fat-free mass	84.5 (68.4, 102)
Maximum drug effect on fat mass	69.6 (54.4, 85.1)
Correlation between the random effects for maximum effect (IMAX)	0.993 (0.988, 0.994)
IC50 for drug inhibiting formation of fat free mass	25.7 (19.4, 34.7)
IC50 for drug inhibiting formation of fat mass	47.4 (35.3, 66.1)
Correlation between the random effects for IC50	0.9994 (0.9986, 0.9998)
Placebo effect for fat-free mass	96.6 (87.5, 107)
Placebo effect on fat mass	94.7 (86.3, 106)
Correlation between the random effects for placebo	0.977 (0.972, 0.985)
Residual error	
Proportional for fat-free mass (%)	0.985 (0.910, 1.04)
Proportional for fat mass (%)	3.35 (3.08, 3.54)
Correlation between residual error (%)	98.4 (98.4, 98.6)

Abbreviations: CI = confidence interval; CV = coefficient of variation; IC50 = drug concentration that produces 50% of IMAX; Kin = formation rate; Kout = first-order elimination rate constant. a Confidence interval obtained from a bootstrap analysis.

The population PK/PD model was used to predict the dose/exposure-response relationship after 72 weeks of treatment. Model predictions of body weight showed a clear dose-related response (Figure 3, Figure 4, and Figure 5) for reduction in weight across the tirzepatide QW doses of 5, 10, and 15 mg.

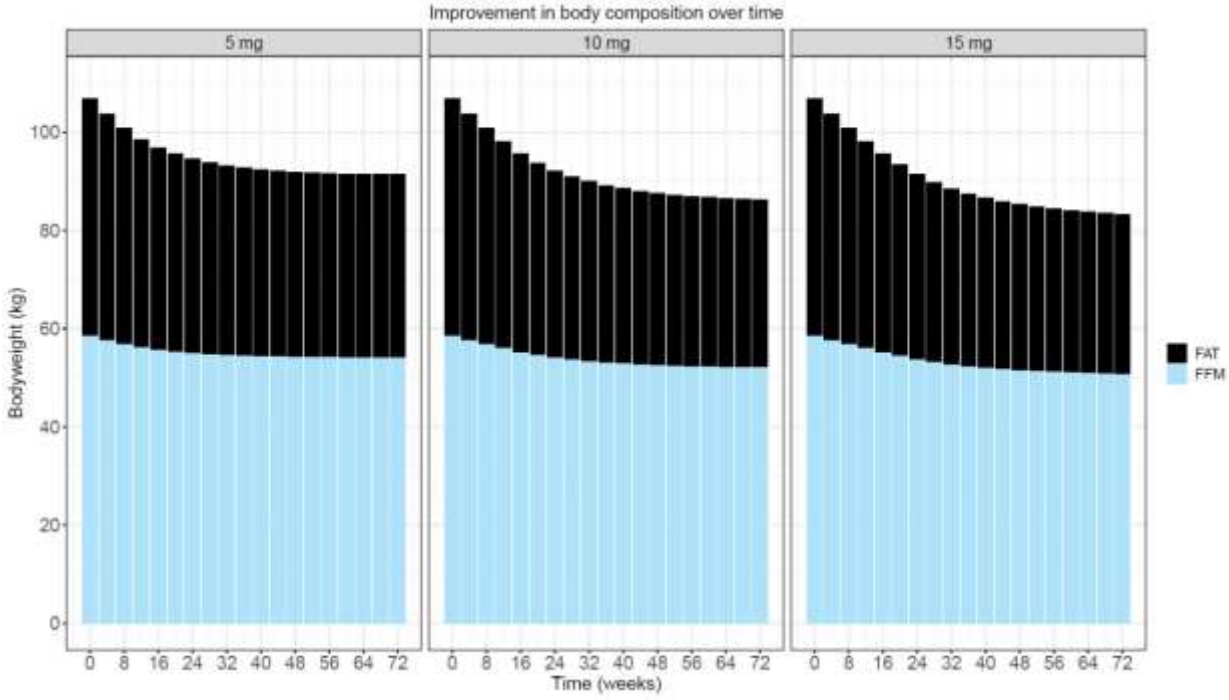
The predicted dose-dependent changes in the weight and body composition metrics after 72 weeks of treatment are shown in Figure 6.

Figure 3. Dose/exposure-response relationship of tirzepatide after 72 weeks of treatment.



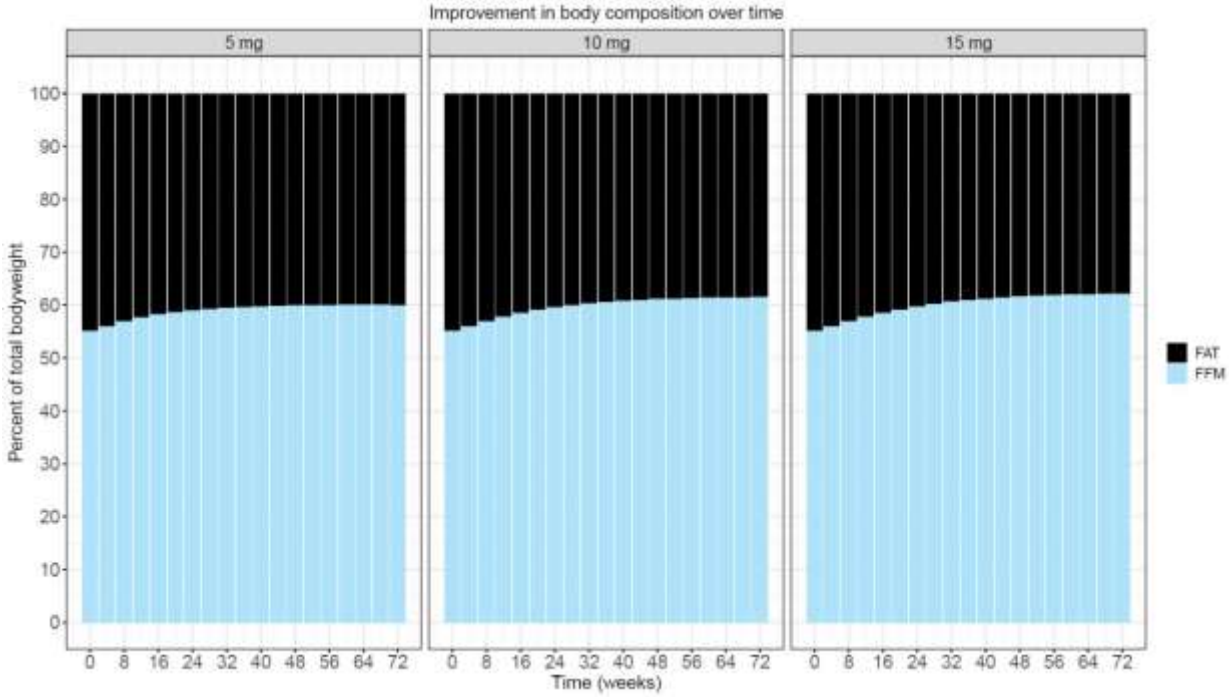
Note: The shaded area is the 95% confidence interval of model predictions. The points and error bars are the observed mean and 95% confidence interval, respectively.

Figure 4. Typical decrease in body weight as a sum of fat mass and fat-free mass over time following tirzepatide doses of 5, 10, or 15 mg.



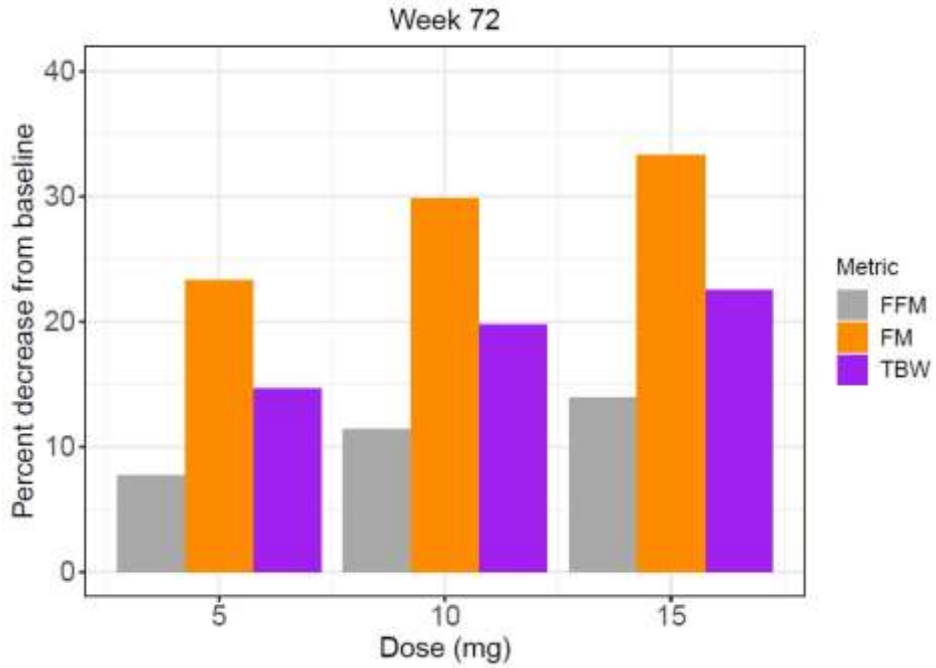
Abbreviation: FFM = fat-free mass.

Figure 5. Typical change in body composition over time following tirzepatide doses of 5, 10, or 15 mg.



Abbreviation: FFM = fat-free mass.

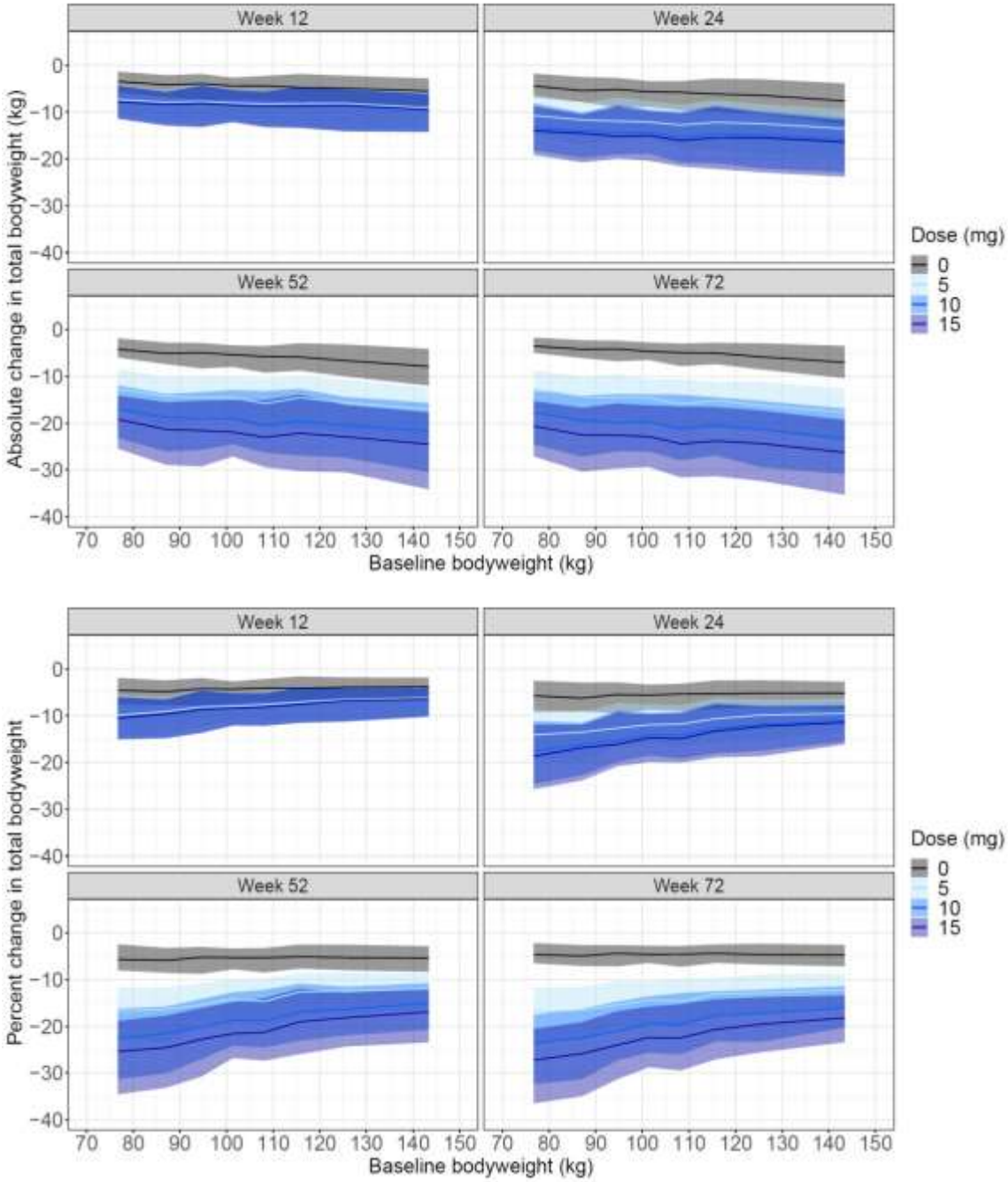
Figure 6. Model-predicted median decrease in weight, fat-free mass, and fat mass after 72 weeks of treatment.



Abbreviations: FFM = fat-free mass; FM = fat mass; TBW = total body weight.

Simulations were conducted to evaluate the impact of baseline body weight on subsequent weight reduction. The results showed that participants with higher baseline body weight will lose more weight in absolute terms, while participants with lower baseline body weight will have a greater percent decrease in weight relative to baseline (Figure 7). This indicates that individuals with higher baseline body weight will still lose a substantial amount of weight relative to their baseline.

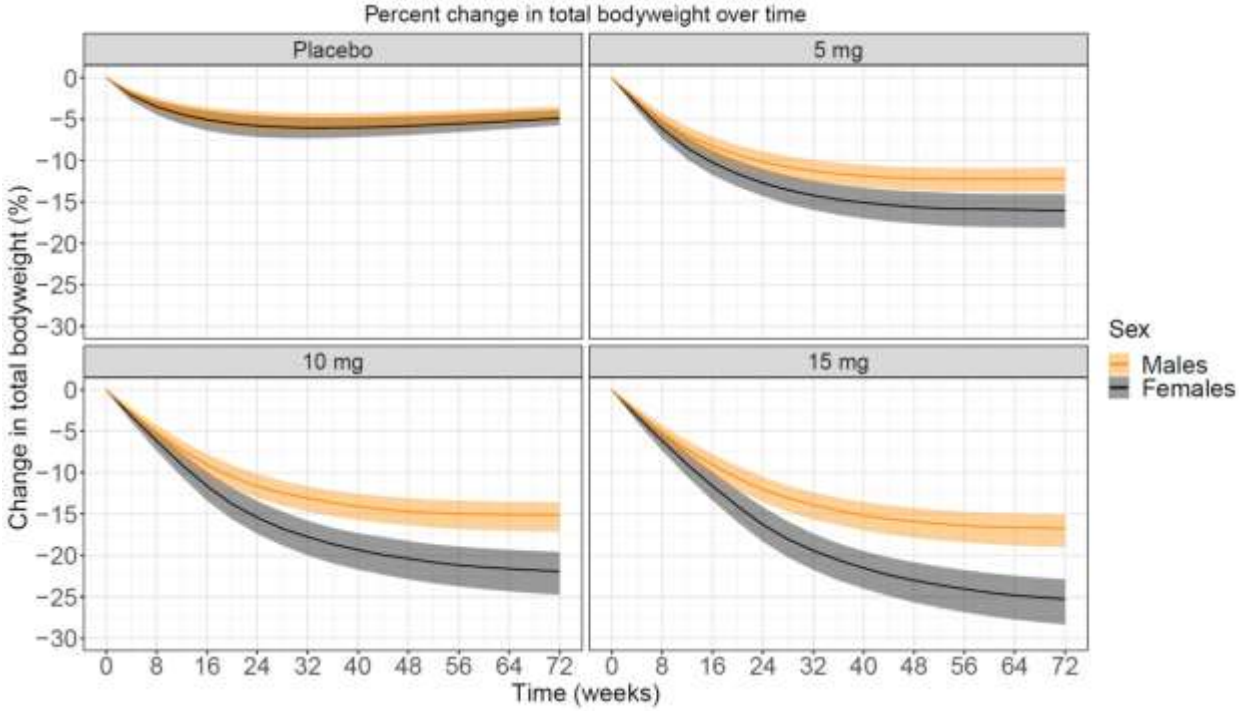
Figure 7. Change in body weight at various time points in relation to body weight at baseline. Top 4 panels: absolute change in body weight. Bottom 4 panels: percent change from baseline.



Note: The continuous line is the mean prediction. The shaded area is the 95% confidence interval. Mean baseline weight in the simulation was 107 kg.

Additionally, sex was a significant covariate on baseline and was included in the final model. Females had a 31% lower baseline FFM than males. Females also had a 5% higher baseline fat mass than males. There were also significant differences in drug effect parameters between males and females. Females had a higher Imax and a higher concentration to achieve 50% of Imax (IC50) relative to males. A simulation was performed to obtain a clearer understanding of the difference. Figure 8 shows that females have greater weight reduction compared to males.

Figure 8. Model-predicted differences between males and females in response to tirzepatide.



Note: The continuous line is the mean prediction. The shaded area is the 95% confidence interval.

Asian race was also a statistically significant covariate in the model, with Asian participants being estimated to have 11% and 25% lower FFM and fat mass at baseline compared to non-Asians, respectively. However, race was not shown as a significant covariate on drug effect.

There is a clear exposure response relationship for decrease in bodyweight versus dose. A number of factors have been identified that effect the response. Given that, in the overall population, there is a relationship between exposure and response, any factors that affect exposure (decrease) will impact on efficacy but generally not enough to warrant a dose adjustment. Although exposure will be lower in over-weight subjects, there is a greater effect seen with higher baseline body weight. Males have a lower effect than females as do subjects of Asian race.

Exposure-Response Relationships for Gastrointestinal (GI) tolerability

The previously established model derived from the tirzepatide Phase 3 studies in participants with T2DM was used to assess the prevalence of N/V/D events in SURMOUNT-1. Similarly, a sequential modelling approach was taken to fit an individual participant's PK time course with the occurrence of N/V/D AEs in participants with obesity or overweight in SURMOUNT-1. The time-varying impact of weight reduction on PK concentration was accounted for in the models at each dosing record in the N/V/D dataset. Discrete-time Markov models were used to estimate transition probabilities between AE states and the impact of drug effects and covariates on these probabilities. Nausea and vomiting event data were analysed using a single integrated model, while the diarrhoea data were analysed separately with the same model structure. Tolerance compartment model structures were included to describe tachyphylaxis that develops with sustained drug exposure.

Differences in AEs between sexes were included in the model. Females have a decrease in the nausea and vomiting tolerance rate constant (KTOL) relative to males. Therefore, females will develop tolerance slower than males resulting in a higher and more persistent probability

of nausea and vomiting.

The implementation of stepwise dose-escalation scheme based on the model, starting at 2.5-mg dose for 4 weeks, followed by increases in doses by 2.5-mg increments every 4 weeks to attain maintenance dose levels of 5, 10, and 15 mg, was confirmed to have mitigated GI AEs in the SURMOUNT-1 study. A majority of the events of N/V/D at the 5, 10, and 15 mg dose levels were reported during the dose-escalation phase. The incidence of GI events decreased over time and were less than 10% for nausea and less than 2% for vomiting and diarrhoea at steady state.

Dosing rationale

Tirzepatide doses of 5, 10, and 15 mg administered SC QW were studied in the Phase 3 program.

- These doses and associated escalation scheme were selected based on the assessment of safety, efficacy (weight reduction benefit), and GI tolerability data followed by exposure-response modeling of data in participants with T2DM, of which the major also are with obesity or overweight, in Phase 1 and 2 studies.
- Dosing algorithm consisted of a starting dose of 2.5 mg accompanied by escalation by 2.5 mg increments every 4 weeks to attain maintenance dose levels of 5, 10, and 15 mg.
- This stepwise escalation scheme was expected to allow time for development of tolerance to GI events and thereby improve GI tolerability.
  The selected dose and escalation scheme permitted the evaluation of benefit-risk considerations for 5, 10, and 15 mg doses of tirzepatide to enable the selection of doses for commercialization.
- Efficacy: Exposure-response models estimated robust weight reduction from baseline at 72 weeks following the 5, 10, and 15 mg tirzepatide doses in participants with obesity or overweight (Figure 5 above), with predicted mean (95% CI):
- 5 mg: -14.6% (-17.1, -12.7)
- 10 mg: -19.7%, (-22.7, -17.2)
- 15 mg: -22.5%. (-25.8, -19.8)
- GI tolerability: The implementation of stepwise dose-escalation scheme based on the exposure-response model was confirmed to have mitigated GI AEs in SURMOUNT-1. A majority of the events of N/V/D at the 5-, 10-, and 15-mg dose levels were reported during the dose-escalation phase.
- No dose adjustment was warranted based on any participant factors in the covariate analyses.

In summary, all three Phase 3 maintenance dose levels of tirzepatide, that is, 5, 10, and 15 mg, offer robust weight reduction efficacy without dose-limiting tolerability or safety concerns. Additionally, the GI AE data support the stepwise dose-escalation approach starting at 2.5 mg QW for 4 weeks with 2.5-mg increments every 4 weeks to attain dose levels of 5, 10, and 15 mg tirzepatide. The totality of clinical safety and efficacy data and the exposure-response model-based analyses support the QW administration of tirzepatide up to the maximum dose of 15 mg as efficacious doses with an acceptable safety profile.

Immunogenicity

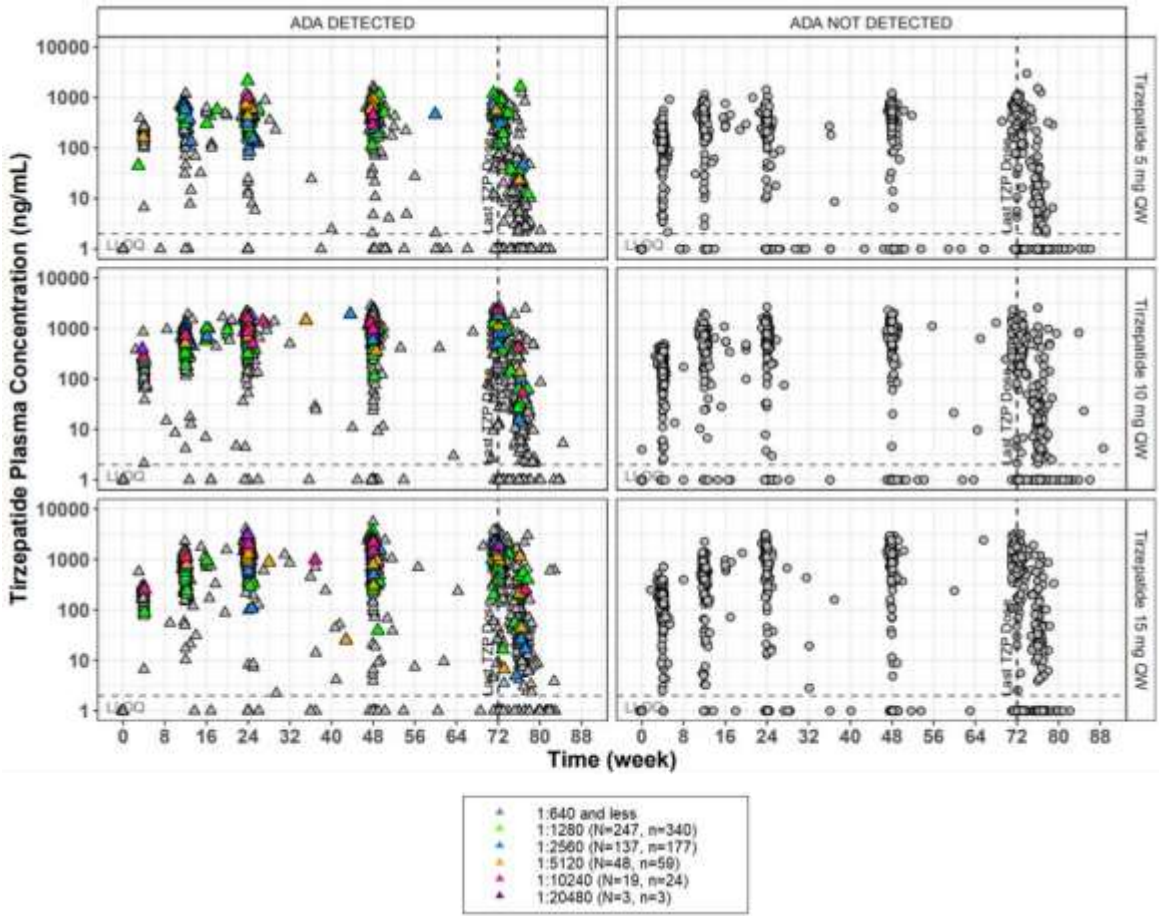
The Integrated Summary of Immunogenicity provides a comprehensive summary of the entire immunogenicity investigation for the tirzepatide program, including details of

immunogenicity assays; data from clinical studies across the clinical program; and the relationship of immunogenicity to exposure, efficacy, and safety of tirzepatide.

Briefly, the potential impact of immunogenicity and ADAs on tirzepatide PK was investigated as follows:

- No overt pattern or trend was evident in the graphical comparison of tirzepatide concentrations in participants with ADA compared with participants without ADA. The range of observed tirzepatide concentrations was comparable in participants with and without ADA and there were no overt time-dependent trends (Figure 9).
- No relationship between ADA and CL was detected when ADA status or ADA titer was tested as a covariate. No statistically significant difference was observed in tirzepatide CL/F across the range of observed ADA titer values (Figure 10).
- No relationship between neutralizing antibody and tirzepatide CL was detected (Figure 11).

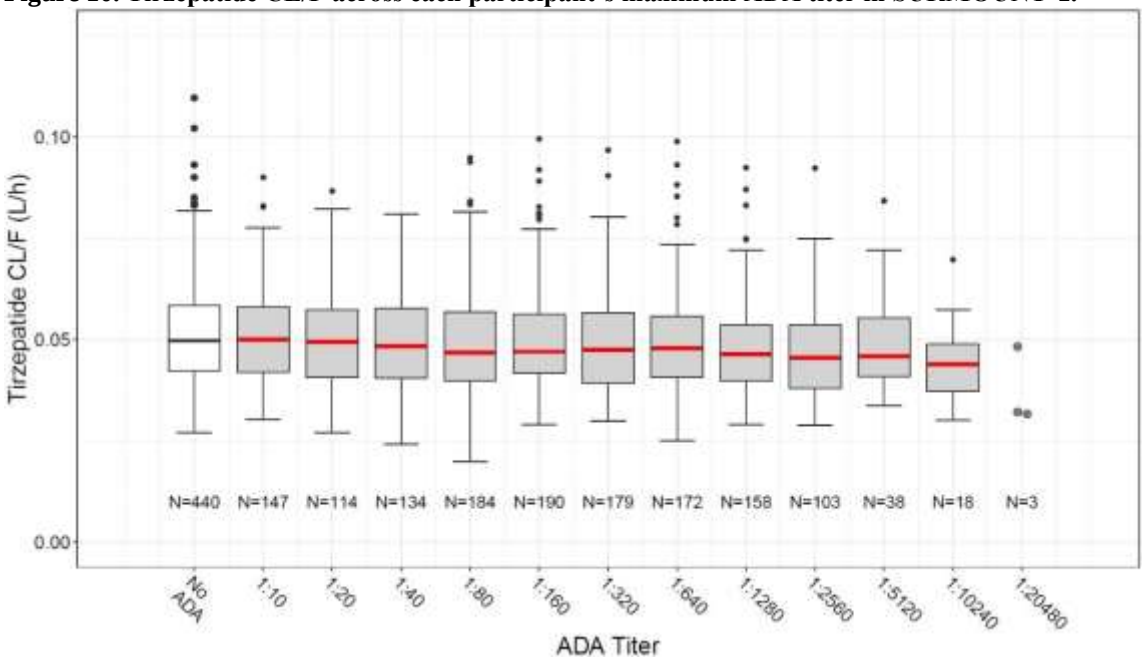
Figure 9. Comparison of observed tirzepatide concentrations from participants with detected (left panel) and undetected (right panel) tirzepatide ADA in SURMOUNT-1.



Abbreviations: ADA = antidrug antibody; LLOQ = lower limit of quantitation (2 ng/mL); N = number of participants; n = number of observations; QW = once weekly; SURMOUNT-1 = Phase 3 study name for obesity.

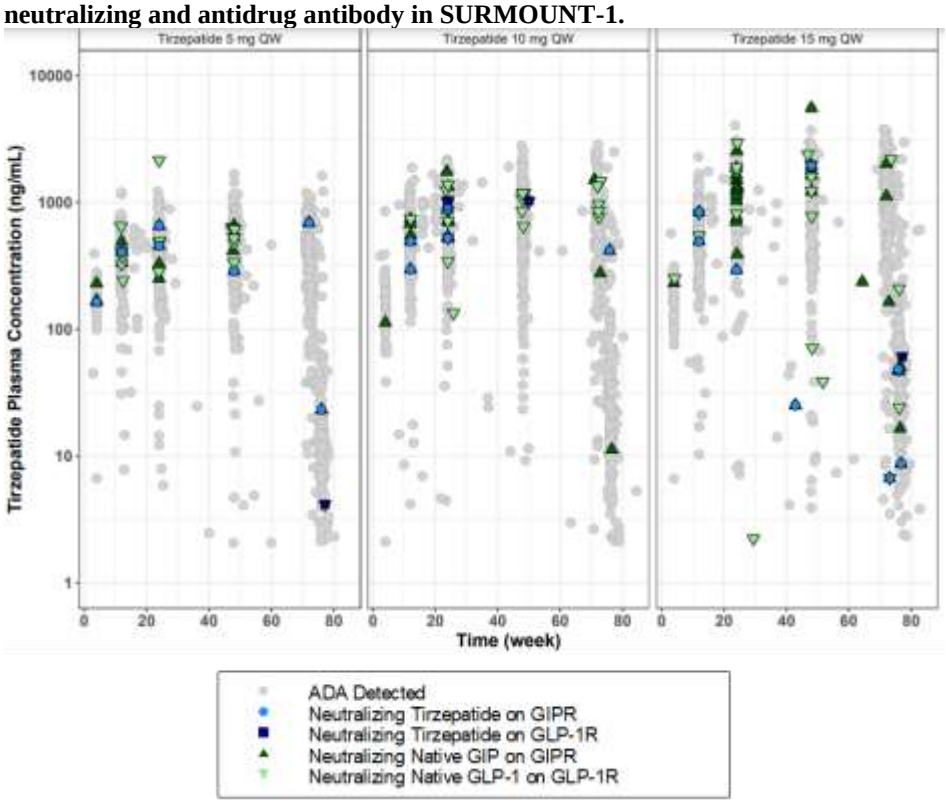
Note: Results below LLOQ were included in the plot with an assigned value of 1 ng/mL.

Figure 10. Tirzepatide CL/F across each participant's maximum ADA titer in SURMOUNT-1.



Abbreviations: ADA = antidrug antibody; CL/F = apparent clearance; N = number of participants; SURMOUNT-1 = Phase 3 study name for obesity.
Note: Solid circles denote individual values. The top and bottom margins of the boxplot represent the 75th and 25th percentiles, and the middle line of the boxplot represent the median. The whiskers extend to ±1.5 times interquartile range.

Figure 11. Comparison of observed tirzepatide concentrations from participants with detected tirzepatide neutralizing and antidrug antibody in SURMOUNT-1.



Abbreviations: ADA = antidrug antibody; GIP = glucose-dependent insulinotropic polypeptide; GIPR = glucose-dependent insulinotropic polypeptide receptor; GLP1 = glucagon-like peptide-1; GLP-1R = glucagon-like peptide-1 receptor;
LLOQ = lower limit of quantitation; QW = once weekly; SURMOUNT-1 = Phase 3 study name for obesity.
Note: LLOQ = 2 ng/mL.

Antidrug antibody (ADA) status and ADA titer do not appear to affect the exposure of tirzepatide.

Overall conclusions on pharmacodynamics

Tirzepatide PK and its relationships to efficacy, tolerability, and safety following administration of QW SC tirzepatide in patients with obesity or overweight were described by robust population PK and exposure-response models, which enabled prediction of tirzepatide concentrations and accompanying effects across dose amounts and time with adequate accuracy and precision.

Based on the evaluation of the influence of intrinsic and extrinsic factors on tirzepatide PK concentrations and body weight reduction across time, dose adjustments are not required for SC QW dose of tirzepatide based on body weight, sex, age, race, renal impairment, or hepatic impairment in participants with obesity or overweight.

Based on the evaluation of the relationship between tirzepatide concentrations and tolerability, dose-escalation with a starting dose of tirzepatide 2.5 mg QW for 1 month followed by 2.5 mg monthly dose increases up to the maximum SC dose of 15 mg QW was adequately tolerated in participants with obesity or overweight. Changes to dose escalation scheme are not required.

3. Clinical Efficacy

Introduction

SURMOUNT-1 (in a non-diabetic overweight/obese population) and SURMOUNT-2 (in a T2DM overweight/obese population) provide the pivotal evaluation of efficacy, safety, and tolerability of QW treatment with subcutaneous (sc) tirzepatide at maintenance doses of 5, 10, and 15 mg in SURMOUNT-1 and of 10 and 15 mg in SURMOUNT-2 compared with placebo in a population of participants with obesity or overweight, representing a broad range of patients who may be treated in clinical practice.Key design elements of the pivotal, Phase 3 studies are provided in Table 7.

Table 7. Study Design Features for SURMOUNT-1 and SURMOUNT-2

Design Elements	I8F-MC-GPHK SURMOUNT-1	I8F-MC-GPHL SURMOUNT-2
Participant Population	Participants with obesity, or overweight with at least 1 weight-related comorbid condition, without diabetes	Participants with obesity or overweight and T2DM
Comparator	Placebo	
Randomization	1:1:1:1 (TZP 5 mg: TZP 10 mg: TZP 15 mg: PBO)	1:1:1 (TZP 10 mg: TZP 15 mg: PBO)
Treatment Duration	72 weeks[a]	72 weeks
Primary Endpoint	• Mean percent change in body weight • Proportion of participants who achieved ≥5% body weight reduction	
Blinding	Double-blind	
Trial Size (N)	2539[a]	938
Countries that Enrolled Participants	Argentina, Brazil, China, India, Japan, Mexico, Russian Federation, Taiwan, and United States	Argentina, Brazil, India, Japan, Russian Federation, Taiwan, and United States

Abbreviations: N = number of participants in category; PBO = placebo; T2DM = type 2 diabetes mellitus; TZP = tirzepatide.

[a] Information in this table for SURMOUNT-1 is for the completed primary study period.

SURMOUNT-1 also included two sub studies (presented as ABPM and DXA addenda). The DXA addendum was conducted in a subset of study participants to evaluate changes in body composition associated with weight loss. The ABPM addendum was conducted in a subset of study participants to evaluate the impact of tirzepatide on blood pressure and heart rate.

Data from the 36-week open-label tirzepatide lead-in period of SURMOUNT-4, which did not include a placebo or active comparator, provide additional support for clinically meaningful reductions in body weight, improvements in cardiometabolic parameters, and improvements in patient-reported physical functioning with tirzepatide treatment, in participants with obesity or overweight, without T2DM.

Dose-response studies and main clinical studies

Dose response studies

No specific new dose-response studies were carried out as part of the CWM clinical development.

The doses and dose-escalation scheme used in SURMOUNT-1 and SURMOUNT-2 were selected based on assessment of safety, efficacy (weight reduction and glycaemic control) and GI tolerability data from the Phase 2 studies, exposure-response modelling of data from T2DM in Phase 1 and 2 studies, and the model prediction for participants without T2DM with obesity. The dosing algorithm starting at a dose of 2.5 mg with dose escalation of 2.5-mg increments every 4 weeks up to target dose was expected to permit time for development of tolerance to GI events and was predicted to minimise GI tolerability concerns.

The maximum proposed dose of 15 mg was selected to maintain an exposure multiple of 1.6 to 2.4 to the no-observed-adverse-effect level doses in 6-month monkey and rat toxicology studies, respectively. The selected doses and dose-escalation scheme are consistent with those approved for tirzepatide in adults with T2DM and is the proposed dosing recommendation in product labelling for the CWM indication.

Main studies

As indicated above, the pivotal data come from the SURMOUNT-1 and SURMOUNT-2 trials in non-diabetic and diabetic overweight/obese patients, respectively. The trials share many methodological aspects which are presented together below (while differences are highlighted and discussed).

SURMOUNT-1 (I8F-MC-GPHK)

Study Title

Efficacy and Safety of Tirzepatide Once Weekly in Participants without Type 2 Diabetes Who Have Obesity or Are Overweight with Weight- Related Comorbidities: A Randomised, Double-Blind, Placebo-Controlled Trial (SURMOUNT-1).

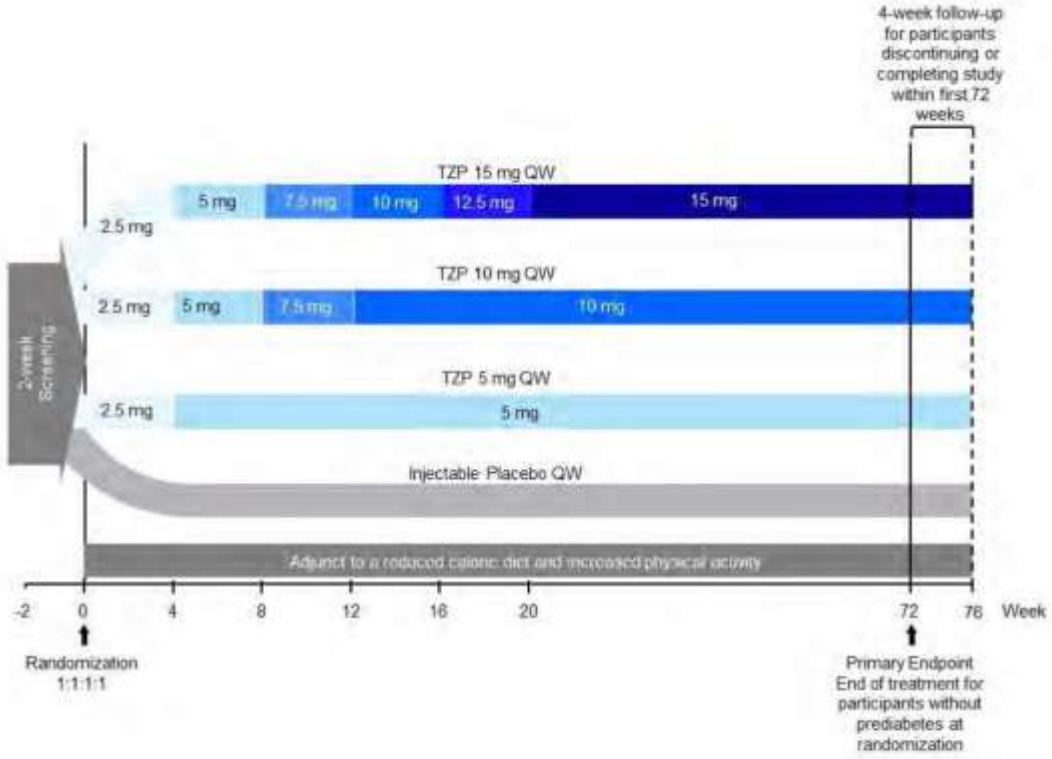
Study design

SURMOUNT-1 was a Phase 3, multicentre, double-blind study that randomly assigned participants (1:1:1:1) to receive once-weekly, injectable placebo or tirzepatide 5, 10, or 15 mg. The study investigated the efficacy and safety of once-weekly doses of tirzepatide 5, 10, and 15 mg compared with placebo on weight reduction.

The primary study period of SURMOUNT-1 included a 2-week screening period, 72-week primary treatment period, and 4-week study follow up (SFU) period for all participants

except for those with prediabetes at randomisation continuing into the additional 2-year treatment period. In addition, the study includes an additional 2-year treatment period followed by a 17-week SFU for participants with prediabetes at randomisation. The 2-year treatment period for participants with prediabetes at randomisation is ongoing and is not in scope of this document. In this document, only data from the 72-week treatment period (the primary study period) in all study participants are reported. An outline of the study design is shown below:

Figure 12. Study scheme.



Abbreviations: QW = once weekly; TZP = tirzepatide.
Note: All participants will be randomized to at least 72 weeks of treatment to study the effects on body weight reduction. Participants who have prediabetes will be studied for a total of 176 weeks of treatment to provide sufficient follow-up time to detect potential differences in progression to T2DM.

SURMOUNT-2 (I8F-MC-GPHL)

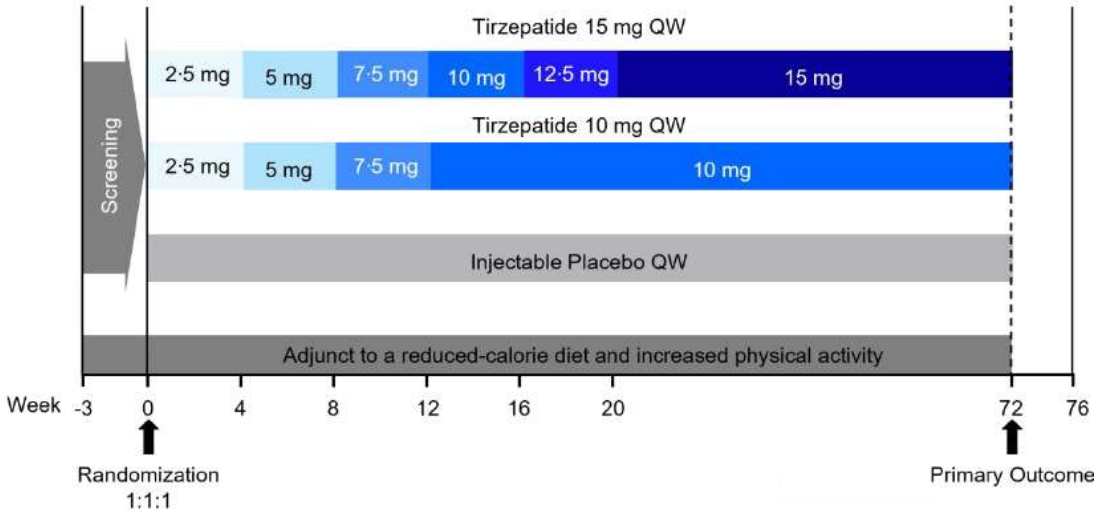
Study Title

Efficacy and Safety of Tirzepatide Once Weekly in Participants with Type 2 Diabetes Who Have Obesity or Are Overweight: A Randomised, Double-Blind, Placebo-Controlled Trial (SURMOUNT-2)

Study design

SURMOUNT-2 was a Phase 3, multicentre, randomised, parallel-arm, placebo-controlled, double-blinded, 72-week study that investigated the safety and efficacy of treatment with tirzepatide in participants with type 2 diabetes mellitus (T2DM) who have obesity (body mass index [BMI] ≥30 kg/m2) or are overweight (BMI ≥27 kg/m2) and were randomised in a 1:1:1 ratio (tirzepatide 10 mg QW, tirzepatide 15 mg QW, and placebo), in conjunction with a reduced-calorie diet and increased physical activity. SURMOUNT-2 included a 3-week screening period, a 72-week double-blind treatment period, and a 4-week safety follow-up period. An outline of the study design is shown below:

Figure 13. SURMOUNT-2 study scheme



Abbreviations: QW = once weekly.

The follow-up period for both studies was only 4 weeks. A SURMOUNT-1 extension is ongoing, as is also SURMOUNT-4 which is expected to provide data on the maintenance of the effect on weight, and the possible impact of tirzepatide withdrawal.

It is noted that both studies were conducted in US and different countries across the world. However, there were no participating sites from the UK or other European countries. This raises concerns about the relevance of the study population and consequentially the findings to the UK population. The Applicant has provided further information and a discussion to address this point. The SURMOUNT studies included a diverse population in terms of race, other demographics, regions and countries and the results were generally consistent across subgroups. A considerable percentage of the study population in both trials were from US which has many similarities, including sharing the same clinical guidelines, with the UK. In the previous SURPASS program, where representation of European and UK patients was much greater and in which again the majority of patients were overweight or obese, no major concerns about regional differences (particularly compared to US) were raised.

It is unlikely that including UK and other European patients would have had a major impact on the overall findings but the possibility of a different, potentially smaller, effect size on weight loss and other parameters cannot be excluded. This is a limitation of the current program and is considered in the overall benefit:risk evaluation.

Methods

- **Study Participants**

The key inclusion/exclusion criteria are summarised below.

Main inclusion criteria

In SURMOUNT-1, to be eligible for the study, participants
- had to be 18 years or older
- have either
  - obesity, defined as having a BMI of 30 kg/m2 or more, or
  - overweight, defined as having a BMI of 27 kg/m2 or more, with at least 1 weight-related comorbid condition, including
    - hypertension

  - dyslipidaemia,
  - obstructive sleep apnoea (OSA) or
  - CV disease, and

- have a history of 1 self-reported unsuccessful dietary effort to lose weight.

In SURMOUNT-2, to be eligible for the study participants had to be again ≥18 years and have a history of ≥1 self-reported unsuccessful dietary effort to lose weight. In this case however, they only needed to have BMI ≥27 kg/m2 screening, and have a diagnosis of T2DM with HbA1c ≥7% (≥53 mmol/mol) to ≤10% (86 mmol/mol) at screening, on stable therapy for the last 3 months prior to screening (diet or exercise alone or any oral antihyperglycemic medications except DPP-4 inhibitors and GLP-1 RA)

Main exclusion criteria

In SURMOUNT-1, participants were not eligible for the study if they had

- type 1 diabetes mellitus or T2DM
- received treatment with medications that may cause weight gain within 3 months prior to randomisation
- taken medications or remedies intended for weight loss within 3 months prior to randomisation
- reported a change in body weight greater than 5 kg within 3 months prior to screening
- obesity induced by other endocrinologic disorders, or diagnosed monogenetic or syndromic forms of obesity
- renal impairment measured as estimated (eGFR <30 mL/min/1.73 m2)
- acute or chronic hepatitis, signs and symptoms of any other liver disease other than nonalcoholic fatty liver disease.
- a history of chronic or acute pancreatitis
- a family history or personal history of MTC or multiple endocrine neoplasia syndrome type 2
- a history of significant active or unstable MDD or other severe psychiatric disorders within the last 2 years, or
- any lifetime history of a suicide attempt.

In SURMOUNT-2, participants were not eligible for the study if they had

- type 1 diabetes mellitus
- a history of proliferative diabetic retinopathy; diabetic macular oedema, or nonproliferative diabetic retinopathy that requires acute treatment
- a history of severe hypoglycaemia and/or hypoglycaemia unawareness within the 6 months prior to Visit 1
- ≥2 confirmed fasting SMBG values >270 mg/dL (15.0 mmol/L) (on 2 nonconsecutive days) prior to Visit 3
- current or prior treatment (within 3 months prior to Visit 1) with DPP-4 inhibitors, oral GLP-1 RA, or any injectable therapy for T2DM

Otherwise, the criteria for other conditions were similar to SURMOUNT-1

Treatments

The starting dose of tirzepatide in SURMOUNT-1 and -2 was 2.5 mg once weekly, with subsequent dose-escalation increments of 2.5 mg every 4 weeks. In SURMOUNT-1, participants in the tirzepatide groups were randomly assigned to reach 1 of 3 once-weekly

maintenance doses of tirzepatide (5, 10, or 15 mg), and in SURMOUNT-2, participants in the tirzepatide groups were randomly assigned to reach a once-weekly maintenance dose of tirzepatide 10 or 15 mg (Table 8).

Table 8. Tirzepatide Dose-Escalation Scheme in the Phase 3 Studies

Treatment Group	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 5 mg	2.5 mg	5 mg	5 mg	5 mg	5 mg	5 mg
Tirzepatide 10 mg	2.5 mg	5 mg	7.5 mg	10 mg	10 mg	10 mg
Tirzepatide 15 mg	2.5 mg	5 mg	7.5 mg	10 mg	12.5 mg	15 mg

5 mg was a maintenance dose in SURMOUNT-1 but was not a maintenance dose in SURMOUNT-2.
Note 1: Blue text indicates participants were taking their final assigned dose.
Note 2: SURMOUNT-4 used a similar dose-escalation scheme, but to participants continued dose-escalation to their maximum tolerated dose of tirzepatide (10 or 15 mg) rather than being randomly assigned to a fixed dose.

Treatment duration

The treatment duration for the primary study period of SURMOUNT-1 was 72 weeks. As shown in the Table above, the longest dose-escalation period was 20 weeks. Therefore, the 72-week treatment duration allowed the evaluation of tirzepatide maintenance doses for 68 weeks for 5 mg, 60 weeks for 10 mg, and 52 weeks for 15 mg. In SURMOUNT-2 the primary endpoint of 72 weeks allowed for 52 (tirzepatide 15 mg) or 60 (tirzepatide 10 mg) weeks on the assigned maintenance doses of tirzepatide.

Background interventions

Participants received lifestyle counselling sessions with a dietitian or equivalent qualified professional, focused on calculating energy needs and recommending healthy balanced meals, a caloric deficit of 500 kcal/day, and 150 minutes/week of physical activity.

Concomitant Therapy

Participants were permitted to use concomitant medications, except certain medications (for example; other medications for weight management) that may interfere with the assessment of efficacy and safety characteristics of the study treatments. In SURMOUNT-1 participants who developed diabetes during the study could initiate medication for glucose control, with the exception of DPP-4 inhibitors or GLP-1R agonists.

In SURMOUNT-2 use of concomitant glucose-lowering medications was permitted, with the exception of GLP-1 RA, DPP-4 inhibitors, or other injectable therapies. To minimise the risk of hypoglycaemia, participants taking insulin secretagogues (for example, sulfonylureas) had their dose halved (or stopped if already on the lowest dose) at randomisation. All other AHMs were continued at their current dose at randomisation. Participants who developed persistent hyperglycaemia during the treatment period could initiate rescue therapy.

As noted above, the dose escalation and doses administered are the same as the currently approved tirzepatide posology in the T2DM indication. Dose escalation is well established for GLP-1 receptor agonists, predominately to mitigate side effects. For the current tirzepatide T2DM indication, titration steps to the maintenance doses (5, 10, and 15 mg) are recommended every 4 weeks and the same approach was used here. No different regimen was tested (for example a longer dose-escalation period or lower than 5 mg or higher than 15 mg dose).

Three dose levels were tested in SURMOUNT-1 and sufficient data have been generated to permit their individual evaluation to support relevant posology recommendation.

In contrast to SURMOUNT-1, only the two highest maintenance doses 10 and 15 mg were investigated in SURMOUNT-2. The rationale provided in the protocol is that: tirzepatide 5 mg dose was not selected as a maintenance dose since it was considered unlikely to help address the unmet need of achieving greater than 10% weight loss. This is based on data from the T2DM Phase 2 Study GPGB showing that only 16.7% of participants on 5 mg achieved >10% weight loss compared to 45.5% and 54.3% of participants on 10 mg and 15 mg, respectively, in the 26-week on treatment analysis; also patients treated with tirzepatide 5 mg demonstrated a placebo-corrected mean body weight loss of 4.4 kg and mean percentage weight loss of 4.7%. Lack of efficacy and safety data with the 5 mg dose in this population is a limitation of the study.

In relation to other measures, participants received the study medication in a background of dietary/lifestyle measures and exercise (details are included in the study protocol). This is in line with regulatory guidance.

- **Objectives and endpoints**

The co-primary endpoints for assessment of efficacy in both SURMOUNT-1 & -2 were percent change in body weight and percentage of participants reaching ≥5% body weight reduction, measured from randomisation to Week 72.

The primary endpoints are in accordance with relevant regulatory guidance. Similarly, the key secondary endpoints including body weight outcomes, cardiovascular/metabolic parameters and patient reported outcomes are also mostly in line with the regulatory guideline and offer a broader perspective of the effects of tirzepatide in this population. Individual endpoints are further discussed in the relevant sections below.

- **Sample size**

SURMOUNT-1 (I8F-MC-GPHK, non-diabetic patients)

Approximately 3429 participants were screened to achieve 2400 randomly assigned to study intervention (600 participants per intervention group).

A total of 2400 participants were planned to be randomised in a 1:1:1:1 ratio to tirzepatide 5 mg (n=600), tirzepatide 10 mg (n=600), tirzepatide 15 mg (n=600), and placebo (n=600). The sample size determination assumed that evaluation of superiority of 10 mg tirzepatide and tirzepatide 15 mg to placebo was to be conducted in parallel, each at a 2-sided significance level of 0.025 using a 2-sample t-test.

The sample size was based on the following assumptions: a difference of at least 11% mean body weight percentage reduction from randomisation at 72 weeks for 10-mg tirzepatide and/or tirzepatide 15 mg compared with placebo, a common SD of 10%, 90% power to demonstrate superiority of tirzepatide 10 mg and/or 15 mg to placebo, and a dropout rate of 25%.

The chosen sample size and randomisation ratio also provides >90% power to establish superiority of 10 mg tirzepatide and 15 mg tirzepatide doses to placebo in term of percentage of participants achieving at least 5% body weight reduction at 72 weeks, conducted in

parallel using a Fisher's exact test, each at a 2-sided significance level of 0.025, assuming 25% placebo-treated participants and 90% tirzepatide-treated participants achieving the goal and a dropout rate of 25%.

In addition, assuming that approximately 60% of the randomised population will have prediabetes, the study sample size was planned to also provide more than 90% power to demonstrate superiority of tirzepatide (all doses combined) over placebo in terms of delaying the onset of diabetes for participants with prediabetes at study entry. The sample size calculation were derived based on the following assumptions: 1.6% (corresponding to annual hazard rate of 0.54%) of participants randomised to tirzepatide and 6% of participants randomised to placebo (corresponding to annual hazard rate of 2.1%) will progress to diabetes during the 3-year period; 49% drop out rate (corresponding to annual drop-out rate of 22%) during the same period; and a 2-sided significance level of 0.05.

SURMOUNT-2 (I8F-MC-GPHL, diabetic patients)
Approximately 1300 participants were screened to achieve 900 randomly assigned to study intervention (300 participants per intervention group).

A total of 900 participants were planned to be randomised in a 1:1:1 ratio to tirzepatide 10 mg (n=300), tirzepatide 15 mg (n=300), and placebo (n=300). The sample size determination assumed that evaluation of superiority of tirzepatide 10 mg and tirzepatide 15 mg to placebo was to be conducted in parallel, each at a 2-sided significance level of 0.025 using a 2-sample t-test.

The sample size was based on the following assumptions: a difference of at least 11% mean body weight percentage reduction from randomisation at 72 weeks for tirzepatide 10 mg and/or tirzepatide 15 mg compared to placebo, a common SD of 10%, 90% power, and a dropout rate of 25%.

The chosen sample size and randomisation ratio also provides >90% power to establish superiority of 10 mg tirzepatide and 15 mg tirzepatide dose to placebo in terms of proportion of participants achieving at least 5% body weight reduction at 72 weeks, conducted in parallel using a Chi-square test, each at a 2-sided significance level of 0.025, assuming 25% placebo treated participants and 90% tirzepatide-treated participants achieving the goal and a dropout rate of 25%.

Randomisation
SURMOUNT-1 (I8F-MC-GPHK, non-diabetic patients)
Participants were randomised in a 1:1:1:1 to once-weekly tirzepatide 5 mg, 10 mg, 15 mg, or placebo. Randomisation was stratified by prediabetes status, country, and sex. Countries with fewer than 10 randomised participants were pooled into 1 category (pooled country).

SURMOUNT-2 (I8F-MC-GPHL, diabetic patients)
Participants were randomised in a 1:1:1 ratio to receive tirzepatide 10 mg, tirzepatide 15 mg, or placebo. The randomisation was stratified by country, sex (female, male), and type of antihyperglycemic medications (AHM) used at randomisation (classified according to its potential effect on body weight). Countries with fewer than 10 randomised participants were pooled into 1 category (pooled country).

An upper limit of 70% enrolment of women will be used to ensure a sufficiently large sample

of men. In addition, an upper limit of 30% enrolment of participants treated with SU will be used to allow sufficient enrolment of participants treated with other antihyperglycemic medications.

- **Blinding (masking)**

SURMOUNT-1 (I8F-MC-GPHK, non-diabetic patients)
This study was double-blind, randomised study. Treatment assignments remained blinded for the sponsor, investigators, site staff, clinical monitors, and participants. After the primary endpoint database lock at Week 72, all individuals from the sponsor with study conduct responsibilities remained blinded to treatment assignments. Study drug dose escalation was also double-blind. The identity of tirzepatide and placebo was masked because both study drugs were provided in SDP with the same appearance.

SURMOUNT-2 (I8F-MC-GPHL, diabetic patients)
This was a double-blind, randomised study. Investigators, site staff, clinical monitors, and participants remained blinded to the treatment assignments.

Emergency unblinding may be performed. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's treatment assignment is warranted for medical management of the event. The participant's safety must always be the first consideration in making such a determination.

If an investigator, site personnel performing assessments or participant is unblinded, the participant is discontinued from the study. In cases where there are ethical reasons to have the participant remain on study drug, the investigator must obtain specific approval for the participant to continue in the study.

The blinding procedure as described in SURMOUNT-1 and SURMOUNT-2 studies is considered acceptable.

Analysis sets
SURMOUNT-1 (I8F-MC-GPHK, non-diabetic patients)
The following analysis sets were defined:

Analysis Set	Description
Entered Participants	All participants who sign informed consent
Randomized Participants	All participants who are randomly assigned a study treatment
Modified Intent-to-Treat (mITT)	All randomly assigned participants who are exposed to at least 1 dose of study drug. Participants will be included in the treatment group they were randomized to.
Efficacy Analysis Set (EAS)	Data obtained during treatment period from mITT, excluding data after discontinuation of study drug (last dose date + 7 days).
Full Analysis Set (FAS)	Data obtained during treatment period from mITT, regardless of adherence to study drug.
Safety Analysis Set (SS)	Data obtained during the treatment period plus safety follow-up period from mITT, regardless of adherence to study drug.

SURMOUNT-2 (I8F-MC-GPHL, diabetic patients)
The following analysis sets were defined:

Population	Description
Entered	All participants who sign informed consent
Randomized	All participants who are randomly assigned a study drug.
Modified Intent-to-Treat (mITT)	All randomly assigned participants who are exposed to at least 1 dose of study drug. Participants will be included in the treatment group to which they were randomized.
Efficacy Analysis Set (EAS)	For glycemic control related endpoints: Data obtained during treatment period from mITT, excluding data after initiation of rescue antihyperglycemic medication or premature discontinuation of study drug (last dose date + 7 days). For other endpoints: Data obtained during treatment period from mITT, excluding data after premature discontinuation of study drug (last dose date + 7 days).
Full Analysis Set (FAS)	Data obtained during treatment period from mITT, regardless of adherence to study drug or initiation of rescue antihyperglycemic medication.
Safety Analysis Set (SS)	Data obtained during the treatment period plus safety follow-up period from mITT, regardless of adherence to study drug or initiation of rescue antihyperglycemic medication.

The definition of the analysis populations in both studies is considered acceptable. The inclusion of participants who took at least one dose of study drug in the mITT is supported and is in line with the intention-to-treat principle, as the decision of whether or not to take the study drug is not likely to have been influenced by knowledge of treatment assignment in a double-blind trial.

Statistical methods/Estimands
The co-primary endpoints for assessment of efficacy in SURMOUNT-1 and SURMOUNT-2 studies were percent change in body weight and percentage of participants reaching ≥5% body weight reduction, measured from randomisation to Week 72.
The alternative hypotheses in SURMOUNT-1 and SURMOUNT-2 for the primary objective are the following:

- H10,1: QW tirzepatide 10 mg is superior to placebo for percent change in body weight from randomisation AND percentage of participants who achieve ≥5% body weight reduction at 72 weeks.
- H15,1: QW tirzepatide 15 mg is superior to placebo for percent change in body weight from randomisation AND percentage of participants who achieve ≥5% body weight reduction at 72 weeks.

The above two hypotheses in each study were tested in parallel, each at a 2-sided significance level of 0.025.
Additional clinical endpoints for SURMOUNT-1 and SURMOUNT-2 studies included:

- percentage of participants reaching ≥10%, ≥15%, and ≥20% body weight reduction
- change in waist circumference
- change in triglycerides, non-HDL cholesterol, and HDL cholesterol
- change in systolic and diastolic BP
- change in fasting insulin, and
- change in HbA1c.

Additional endpoints relating to glycaemic control, including percentage of participants who

achieve HbA1c <7%, ≤6.5%, and <5.7% and change in FSG, were evaluated in SURMOUNT-2 study.

In SURMOUNT-1 and SURMOUNT-2, two patient reported outcome (PRO) measures, SF-36v2 acute form and IWQOLLite-CT, were implemented to assess HRQoL.

Summary descriptive statistics for continuous measures were include sample size, mean, SD, median, minimum, and maximum. Summary statistics for categorical measures (including categorized continuous measures) included sample size, frequency, and percentages. Kaplan-Meier method will be used for estimation of cumulative event-free survival rates over time, and Cox proportional hazards regression analysis will be used to compare hazards rates among treatments.

Tests of treatment effects were conducted at a 2-sided alpha level of 0.05, and the CI were calculated at 95% 2-sided.

The definition of treatment effect in the tirzepatide clinical studies was prespecified with estimands.

Estimands definition - SURMOUNT-1 (I8F-MC-GPHK, non-diabetic patients)

Estimand	Definition
Treatment Regimen	The average treatment effect of tirzepatide relative to placebo at 72 weeks, as an adjunct to a reduced-calorie diet and increased physical activity, for the randomized participants regardless of the adherence to study drug
Efficacy	The average treatment effect of tirzepatide relative to placebo at 72 weeks, as an adjunct to a reduced-calorie diet and increased physical activity, in the randomized participants had they remained on their randomized treatment for the entire planned 72-week treatment duration

Estimands definition - SURMOUNT-2 (I8F-MC-GPHK, diabetic patients)

Estimand	Definition
Treatment Regimen	The average treatment effect of tirzepatide relative to placebo at 72 weeks, as an adjunct to a reduced-calorie diet and increased physical activity, for the randomly assigned participants[a] regardless of the adherence to study drug or initiation of rescue medication for hyperglycemia.
Efficacy	The average treatment effect of tirzepatide relative to placebo at 72 weeks, as an adjunct to a reduced-calorie diet and increased physical activity, for the randomly assigned participants[a] had they remained on their randomized treatment for the entire planned 72-week treatment duration (glycemic and nonglycemic endpoints) and without using rescue medication for hyperglycemia (glycemic endpoints only).

Treatment-regimen estimand analyses

The primary efficacy analyses for the body weight, cardiometabolic, and physical function endpoints for the treatment-regimen estimand were conducted using the FAS, which included data from participants in the mITT, regardless of treatment adherence (and use of rescue medication for glycaemic control related endpoints).

Primary analysis

Analysis of continuous data at the primary endpoint visit used an analysis of covariance model adjusted for baseline value and stratification factors, unless specified otherwise. Analysis of proportion of participants achieving target thresholds at the primary endpoint was performed by dichotomizing the continuous outcome followed by a logistic regression that

was adjusted for baseline value and stratification factors.

Secondary analyses
Same as primary analysis. Assessment of the key secondary objectives was conducted with hybrid imputation of missing.

Missing data
Missing data at the primary endpoint visit were imputed using hybrid imputation. Hybrid imputation approach is dependent on the nature of intercurrent events that resulted in missing data, as described below.

Missing data solely due to exceptional circumstances (Category 1), were consider missing at random and were imputed using all non-missing data of the primary outcome measurement from the same treatment arm. Missing data due to other ICEs (Category 2), were imputed based on retrieved dropouts in the same treatment arm, defined as observed primary outcome measurements from participants in the same treatment group, who had their efficacy assessed after early discontinuation of the study drug. In cases where there are not enough retrieved dropouts to provide a reliable imputation model (e.g., the model implemented by the SAS program does not converge), an alternative multiple imputation method with reference to the placebo group (that is, placebo multiple imputation) was used. In cases where placebo multiple imputation method is used for missing data imputation in Category 2 due to not enough retrieved dropouts, the missing data in Category 1 was also imputed using all non-missing data of the primary outcome measurement from the placebo group.
Missing body weight data at 72 weeks were imputed first based on imputation method as described above, then the continuous measurements was categorized into status of achieving at least 5% body weight reduction (Yes or No).

Sensitivity analyses
The following sensitivity analyses were performed to assess the robustness of the primary efficacy results using different missing data imputation methods:

- Placebo multiple imputation: Missing values of change in body weight at the 72-week visit were imputed based on observed body weight change from baseline values at the visit from participants in the placebo treatment group.
- Return to baseline imputation: Missing values of body weight at the 72-week visit were imputed using the return-to-baseline multiple imputation method to account for within subject variability.

Efficacy estimand analyses
The efficacy analyses for the primary and key secondary efficacy endpoints for the efficacy estimand were conducted using the EAS, which excludes data from participants in the mITT after taking rescue medication (SURMOUNT-2) or premature discontinuation of treatment (SURMOUNT-1 and SURMOUNT-2).

Primary analysis
The efficacy estimand analysis for a longitudinal continuous variable used an MMRM using restricted maximum likelihood estimation under missing at random. The MMRM model included terms for treatment group, visit, treatment-by visit interaction, stratification factors (type of AHM used at randomisation, sex, and country/pooled country) as fixed effects, and baseline body weight as a covariate. An unstructured covariance structure will model relationship of within-patient errors. If this model fails to converge, alternative variance

covariance structures were considered. Two-sided 95% CIs for mean percent change in body weight from randomisation to the 72-week visit for tirzepatide 10 mg and 15 mg compared to placebo were derived and summarized.

Analysis of proportion of participants achieving target thresholds at the primary endpoint visit used a logistic regression model. Two-sided 95% CI and odds ratio for percentage of participants achieving at least 5% body weight reduction from baseline to the 72-week visit between tirzepatide 10 mg and placebo, as well as tirzepatide 15 mg and placebo were derived.

Missing data

Missing values were imputed using the predicted values from MMRM analysis for respective endpoints. The imputed values were further dichotomized for analysis of proportion of participants achieving target thresholds, if applicable. For continuous outcomes collected only once postbaseline, the last observation carried forward approach was applied to impute the missing endpoint, unless specified otherwise.

Objective, endpoint, and statistical methods

SURMOUNT-1 (I8F-MC-GPHK, non-diabetic patients)

Objectives	Endpoint	Statistical Methods[a]
Primary		
To demonstrate superiority of once-weekly TZP 10 mg and/or TZP 15 mg to placebo for percent change in body weight	Mean percent change in body weight from baseline	**Treatment-regimen estimand**: ANCOVA at Week 72 with hybrid imputation[b] for missing values **Efficacy estimand**: MMRM
To demonstrate superiority of once-weekly TZP 10 mg and/or TZP 15 mg to placebo for the percentage of participants achieving at least 5% body weight reduction	Percentage of participants achieving at least 5% body weight reduction from baseline	**Treatment-regimen estimand**: Logistic regression at Week 72 with hybrid imputation[b] for missing values **Efficacy estimand**: Logistic regression at Week 72 with imputation of missing values using MMRM

SURMOUNT-1 (I8F-MC-GPHK, non-diabetic patients)

Key Secondary		
To demonstrate superiority of once-weekly pooled TZP 10 mg and 15 mg to placebo for change in body weight at 20 weeks	Mean change in body weight from baseline	**Treatment-regimen estimand**: ANCOVA at 20 weeks with hybrid imputation[b] for missing values **Efficacy estimand**: MMRM
To demonstrate superiority of once-weekly TZP 5 mg to placebo for percent change in body weight	Mean percent change in body weight from baseline	**Treatment-regimen estimand**: ANCOVA at Week 72 with hybrid imputation[b] for missing values **Efficacy estimand**: MMRM
To demonstrate superiority of once-weekly TZP 5 mg to placebo for percentage of participants achieving at least 5% body weight reduction	Percentage of participants achieving at least 5% body weight reduction from baseline	**Treatment-regimen estimand**: Logistic regression at Week 72 with hybrid imputation[b] for missing values

To demonstrate superiority of once-weekly TZP 10 mg and/or TZP 15 mg to placebo for percentage of participants achieving at least 10%, 15%, and 20% body weight reduction	Percentage of participants achieving at least 10%, 15%, and 20% body weight reduction from baseline	**Treatment-regimen estimand**: Logistic regression at Week 72 with hybrid imputation[b] for missing values **Efficacy estimand**: Logistic regression at Week 72 with imputation of missing values using MMRM
To demonstrate superiority of once-weekly TZP 10 mg and/or 15 mg, to placebo for mean change in waist circumference	Mean change in waist circumference from baseline	**Treatment-regimen estimand**: ANCOVA at Week 72 with hybrid imputation[b] for missing values **Efficacy estimand**: MMRM
To demonstrate superiority of once-weekly pooled TZP 5 mg, 10 mg, and 15 mg to placebo for lipid parameters	Mean change in triglycerides, high-density lipoprotein cholesterol, and non-high-density lipoprotein cholesterol from baseline	**Treatment-regimen estimand**: ANCOVA at Week 72 with hybrid imputation[b] for missing values **Efficacy estimand**: MMRM
To demonstrate superiority of once-weekly pooled TZP 5 mg, 10 mg, and 15 mg to placebo for systolic blood pressure	Mean change in systolic blood pressure from baseline	**Treatment-regimen estimand**: ANCOVA at Week 72 with hybrid imputation[b] for missing values **Efficacy estimand**: MMRM
To demonstrate superiority of once-weekly pooled TZP 5 mg, 10 mg, and 15 mg to placebo for fasting insulin	Mean change in fasting insulin from baseline	**Treatment-regimen estimand**: ANCOVA at Week 72 with hybrid imputation[b] for missing values **Efficacy estimand**: MMRM
To demonstrate superiority of once-weekly pooled TZP 10 mg and 15 mg to placebo for Short-Form 36, Version 2, acute form Physical Functioning domain score	Mean change in Short-Form 36, Version 2, acute form Physical Functioning domain score from baseline	**Treatment-regimen estimand:** ANCOVA at Week 72 with hybrid imputation[b] for missing values **Efficacy estimand**: ANCOVA with LOCF for missing values
Additional secondary		
To demonstrate the mean change of once-weekly pooled TZP 5 mg, 10 mg, and 15 mg to placebo for HbA1c	Mean change in HbA1c from baseline	**Treatment-regimen estimand:** ANCOVA at Week 72 with hybrid imputation[b] for missing values **Efficacy estimand:** MMRM

Abbreviations: ANCOVA = analysis of covariance; COVID-19 = coronavirus disease 2019; HbA1c = hemoglobin
A1c; LOCF = last observation carried forward; MMRM = mixed model repeated measures; TZP = tirzepatide.
a Estimands are defined in the next table.
b Hybrid imputation: for missing values solely due to COVID-19, missing at random assumption was used for imputation; for missing values due to other intercurrent events, multiple imputation with retrieved dropouts was used.

SURMOUNT-2 (I8F-MC-GPHL, non-diabetic patients)

Objectives	Endpoint	Statistical Methods[a]
Primary		
To demonstrate that tirzepatide 10 and/or 15 mg QW is superior to placebo at 72 weeks for percent change in body weight	Mean percent change in body weight from randomization	**Treatment-regimen estimand**: ANCOVA at Week 72 with hybrid imputation[b] for missing values **Efficacy estimand**: MMRM
To demonstrate that tirzepatide 10 and/or 15 mg QW is superior to placebo at 72 weeks for the proportion of participants with ≥5% body weight reduction	Percentage of participants who achieve ≥5% body weight reduction from randomization	**Treatment-regimen estimand**: Logistic regression at Week 72 with hybrid imputation[b] for missing values **Efficacy estimand**: Logistic regression at Week 72 with imputation of missing values using MMRM

Secondary analyses (objective, endpoint, and statistical methods)

Key Secondary, by Dose Analysis		
For QW tirzepatide 10- and/or 15-mg doses, to demonstrate superiority to placebo in change from randomization for weight reduction targets (measured at 72 weeks)	Percentage of participants who achieve ≥10%, ≥15%, and ≥20% body weight reduction	**Treatment-regimen estimand**: Logistic regression at Week 72 with hybrid imputation[b] for missing values **Efficacy estimand**: Logistic regression at Week 72 with imputation of missing values using MMRM
For QW tirzepatide 10- and/or 15-mg doses, to demonstrate superiority to placebo in change from randomization for glycemic endpoints measured at 72 weeks	Mean change in HbA1c (%)	**Treatment-regimen estimand**: ANCOVA at Week 72 with hybrid imputation[b] for missing values **Efficacy estimand**: MMRM
For QW tirzepatide 10- and/or 15-mg doses, to demonstrate superiority to placebo in change from randomization for glycemic endpoints measured at 72 weeks	Percentage of participants who achieve HbA1c <7%, ≤6.5%, and <5.7%	**Treatment-regimen estimand**: Logistic regression at Week 72 with hybrid imputation[b] for missing values **Efficacy estimand**: Logistic regression at Week 72 with imputation of missing values using MMRM
For QW tirzepatide 10- and/or 15-mg doses, to demonstrate superiority to placebo in change from randomization for glycemic endpoints measured at 72 weeks	Mean change in fasting glucose (mg/dL)	**Treatment-regimen estimand**: ANCOVA at Week 72 with hybrid imputation[b] for missing values **Efficacy estimand**: MMRM
For QW tirzepatide 10- and/or 15-mg doses, to demonstrate superiority to placebo in change from randomization for waist circumference measured at 72 weeks	Mean change in waist circumference (cm)	**Treatment-regimen estimand**: ANCOVA at Week 72 with hybrid imputation[b] for missing values **Efficacy estimand**: MMRM
Key secondary, pooled dose analysis		
For QW tirzepatide (all doses combined) to demonstrate superiority to placebo in change from randomization for lipid parameters measured at 72 weeks	Mean change in fasting Triglycerides, HDL cholesterol, and non-HDL cholesterol	**Treatment-regimen estimand**: ANCOVA at Week 72 with hybrid imputation[b] for missing values **Efficacy estimand**: MMRM
For QW tirzepatide (all doses combined) to demonstrate superiority to placebo in change from randomization for SBP measured at 72 weeks	Mean change in SBP (mm Hg)	**Treatment-regimen estimand**: ANCOVA at Week 72 with hybrid imputation[b] for missing values **Efficacy estimand**: MMRM

Abbreviations: ANCOVA = analysis of covariance; BMI = body mass index; COVID-19 = coronavirus disease 2019; HbA1c = glycosylated hemoglobin A1c; HDL = high-density lipoprotein; MMRM = mixed model repeated measures; QW = once weekly; SBP = systolic blood pressure.
a Estimands are defined in the next table.
b Hybrid imputation: for missing values solely due to COVID-19, missing at random assumption was used for imputation; for missing values due to other intercurrent events, multiple imputation with retrieved dropouts was used.

- **Multiplicity adjustment**

SURMOUNT-1 and SURMOUNT-2 support the use of tirzepatide for CWM in adults and were adequately powered to assess coprimary and key secondary efficacy objectives.

Results

- **Participant flow**

In SURMOUNT-1, a total of 2539 participants were randomised. All participants randomly assigned to treatment received at least 1 dose of study drug. More participants randomised to tirzepatide completed the primary period of the study (88.4% to 89.8%) and study treatment (83.6% to 85.7%) than participants randomised to placebo (77% for study, 73.6% for study treatment). The most common reason for study discontinuation and study drug discontinuation was withdrawal by subject.

Table 9. Summary of SURMOUNT-1 Disposition

	Placebo (N = 643)	TZP 5 mg (N = 630)	TZP 10 mg (N = 636)	TZP 15 mg (N = 630)
	n (%)			
Completed primary study period on study drug	473 (73.6)	540 (85.7)	532 (83.6)	535 (84.9)
Completed primary study period	495 (77.0)	561 (89.0)	562 (88.4)	566 (89.8)

Abbreviations: n = number of participants within category; N = number of participants randomized; TZP = tirzepatide
Source: GPHK CSR, Table GPHK.8.1.

SURMOUNT-1 consisted of 4 periods. At the time the study report was compiled, the primary study period of the study, which includes screening, 72-week treatment period, and 4-week SFU, was complete. The additional 2-year treatment period for participants with prediabetes at randomisation is ongoing.

In SURMOUNT-2 all 938 participants randomly assigned to treatment received at least 1 dose of study drug and were included in the mITT population. In total, 94.9% and 90.7% of participants assigned to tirzepatide 10 or 15 mg, respectively, completed the study compared with 89.2% receiving placebo. In addition, 90.7% and 86.2% of participants randomly assigned to tirzepatide 10 or 15 mg, respectively, completed the study drug compared with 85.1% of participants randomly assigned to placebo.

The primary reason for discontinuation from study was withdrawal by subject. It was the primary reason for discontinuation in the placebo and tirzepatide 10-mg groups (5.1% and 2.2%, respectively). In the tirzepatide 15-mg group, equal numbers of participants discontinued due to withdrawal by subject and lost to follow-up (n=10 [3.2%] for each). The primary reason for discontinuation from study drug across the tirzepatide 10- and 15-mg groups was AEs (3.8% and 7.4%, respectively) followed by withdrawal by subject.

- **Conduct of the study**

Concomitant medication

In SURMOUNT-1 concomitant medications needed to *manage BP* were allowed during the study. At least 1 antihypertensive therapy was used by 757 (29.8%) participants at baseline. The most frequently used antihypertensive therapy classes were angiotensin II receptor blockers, angiotensin-converting enzyme inhibitors, and thiazides. Concomitant medications needed to *manage lipids* were allowed during the study. At least 1 lipid-lowering therapy was used by 429 (16.9%) participants at baseline. The most common were statins. In terms of *antihyperglycemic* medications during the study, there were 20 (0.8%) participants who initiated use of antihyperglycemic medications after randomisation. From those patients there were 5 participants who were diagnosed with T2DM and received either metformin (n = 4) or semaglutide (n = 1). Of these participants, 3 had prediabetes and 2 did not have prediabetes at

randomisation. Four of the participants were in the placebo group, and 1 participant was in tirzepatide 10-mg group. Important protocol deviations were captured for 12 of these 20 participants. Overall, antihyperglycemic medications were predominately used in the placebo group compared with the tirzepatide groups, irrespective of a reason to initiate the therapy.

In SURMOUNT-2 598 (63.8%) participants used ≥1 *antihypertensive* medication. There were numerically more participants randomly assigned to tirzepatide than to placebo who experienced decreased antihypertensive therapy use during the trial. At baseline, 486 (51.8%) participants used ≥1 *lipid-lowering* medication, most commonly statins. Metformin was the most common antihyperglycemic medication (AHM) used by 88.7% of participants at baseline (Visit 3). At baseline (Visit 3), 26.7% of participants were on SU. A total of 118 (12.6%) participants initiated rescue therapy for persistent hyperglycaemia: placebo: 101 (32.1%), tirzepatide 10 mg: 9 (2.9%) participants, and tirzepatide 15 mg: 8 (2.6%) participants.

Protocol Deviations

In SURMOUNT-1 a total of 360 participants (14.2%) had at least 1 *important* protocol deviation. The most common important protocol deviations were related to the investigational product, study procedures, and eligibility. In SURMOUNT-2 a total of 165 participants (17.6%) had ≥1 important protocol deviation with comparable percentages across the 3 treatment groups. The most common important protocol deviations were related to study procedure compliance (4.6%), treatment assignment or randomisation (related to stratification) (4.6%), and informed consent (3.7%). These important protocol deviations were not likely to have a significant impact on the analyses or conclusions of the trials.

- **Baseline data**

SURMOUNT-1

Table 10. Summary of Baseline Demographics and Clinical Characteristics in SURMOUNT-1. All Randomised Population

Attribute	Placebo (N=643)	TZP 5 mg (N=630)	TZP 10 mg (N=636)	TZP 15 mg (N=630)	Total (N=2539)
Age (years), mean ± SD	44.4 ± 12.5	45.6 ± 12.7	44.7 ± 12.4	44.9 ± 12.3	44.9 ± 12.5
Age Category 1 (years), n (%)					
<65	609 (94.7)	578 (91.7)	605 (95.1)	595 (94.4)	2387 (94.0)
≥65	34 (5.3)	52 (8.3)	31 (4.9)	35 (5.6)	152 (6.0)
Age Category 2 (years), n (%)					
<75	640 (99.5)	629 (99.8)	635 (99.8)	627 (99.5)	2531 (99.7)
≥75	3 (0.5)	1 (0.2)	1 (0.2)	3 (0.5)	8 (0.3)
Female, n (%)	436 (67.8)	426 (67.6)	427 (67.1)	425 (67.5)	1714 (67.5)
Male, n (%)	207 (32.2)	204 (32.4)	209 (32.9)	205 (32.5)	825 (32.5)
Weight (kg), mean ± SD	104.8 ± 21.4	102.9 ± 20.7	105.8 ± 23.3	105.6 ± 22.9	104.8 ± 22.1
Height (cm), mean ± SD	165.6 ± 9.3	165.7 ± 9.0	166.1 ± 9.3	166.1 ± 9.7	165.9 ± 9.3
BMI (kg/m^2), mean ± SD	38.2 ± 6.9	37.4 ± 6.6	38.2 ± 7.0	38.1 ± 6.7	38.0 ± 6.8
BMI Categories (kg/m^2), n (%)					
<30	24 (3.7)	38 (6.0)	38 (6.0)	40 (6.3)	140 (5.5)
≥30 to <35	227 (35.3)	241 (38.3)	209 (32.9)	199 (31.6)	876 (34.5)
≥35 to <40	180 (28.0)	174 (27.6)	187 (29.4)	179 (28.4)	720 (28.4)
≥40	212 (33.0)	177 (28.1)	202 (31.8)	212 (33.7)	803 (31.6)

Waist circumference (cm), mean ± SD	114.0 ± 14.9	113.2 ± 14.3	114.8 ± 15.8	114.4 ± 15.6	114.1 ± 15.2
Prediabetes, n (%)	270 (42.0)	247 (39.2)	262 (41.2)	253 (40.2)	1032 (40.6)
Duration of obesity (years), mean ± SD	14.0 ± 10.7	14.0 ± 10.8	14.7 ± 11.1	14.8 ± 10.8	14.4 ± 10.8
Systolic blood pressure (mmHg), mean ± SD	122.9 ± 12.8	123.6 ± 12.5	123.8 ± 12.8	123.0 ± 12.9	123.3 ± 12.7
Diastolic blood pressure (mmHg), mean ± SD	79.6 ± 8.0	79.3 ± 8.1	79.9 ± 8.3	79.3 ± 8.2	79.5 ± 8.2
Pulse rate (bpm), mean ± SD	72.9 ± 9.3	72.3 ± 9.6	71.8 ± 9.6	72.5 ± 10.0	72.4 ± 9.6
Lipid levels, geometric mean (% CV)					
Total cholesterol (mg/dL)	187.5 (20.5)	187.1 (21.0)	190.6 (19.9)	187.5 (19.9)	188.2 (20.4)
HDL-C (mg/dL)	46.6 (27.0)	47.6 (26.3)	47.6 (26.1)	47.6 (25.8)	47.3 (26.3)
LDL-C (mg/dL)	109.4 (30.7)	108.7 (30.1)	112.3 (30.3)	109.3 (29.8)	109.9 (30.2)
Triglycerides (mg/dL)	130.8 (49.2)	128.7 (51.7)	125.7 (51.1)	128.1 (47.3)	128.3 (49.8)
Non-HDL-C (mg/dL)	138.3 (26.9)	137.0 (27.1)	140.4 (26.6)	137.5 (26.1)	138.3 (26.7)
VLDL-C (mg/dL)	59.3 (46.5)	57.7 (46.2)	56.9 (48.0)	58.1 (45.1)	58.0 (46.5)
Free fatty acids (mEq/L)	0.47 (44.0)	0.46 (49.0)	0.48 (42.3)	0.46 (47.4)	0.47 (45.7)
eGFR (CKD-EPI), (mL/min/1.73 m^2), mean ± SD	98.1 ± 18.3	97.6 ± 17.9	98.3 ± 18.3	98.2 ± 17.7	98.1 ± 18.0

Abbreviations: BMI = body mass index; CKD-EPI = chronic kidney disease-epidemiology; CSR = clinical study report; CV = coefficient of variation; eGFR = estimated glomerular filtration rate; HDL-C = high-density lipoprotein-cholesterol; LDL-C = low-density lipoprotein-cholesterol; N = number of participants in population; n = number of participants in the specified category; SD = standard deviation; TZP = tirzepatide; VLDL-C =very low-density lipoprotein-cholesterol.

At baseline, nearly two thirds of participants in SURMOUNT-1 had 1 or more weight-related comorbidities, including 32.3% with hypertension, 29.8% with dyslipidaemia, 7.8% with obstructive sleep apnoea, and 3.1% with atherosclerotic cardiovascular disease. Additionally, 40.6% of participants had prediabetes as determined by baseline FSG, HbA1c, and oral glucose tolerance test.

SURMOUNT-2

Table 11. Summary of Baseline Demographics and Clinical Characteristics in SURMOUNT-2 All Randomised Population

Attribute	Placebo (N=315)	TZP 10 mg (N=312)	TZP 15 mg (N=311)	Total (N=938)
Age (years), mean ± SD	54.7 ± 10.5	54.3 ± 10.7	53.6 ± 10.6	54.2 ± 10.6
Age Category 1 (years), n (%)				
<65	258 (81.9)	258 (82.7)	257 (82.6)	773 (82.4)
≥65	57 (18.1)	54 (17.3)	54 (17.4)	165 (17.6)
Age Category 2 (years), n (%)				
<75	310 (98.4)	306 (98.1)	309 (99.4)	925 (98.6)
≥75	5 (1.6)	6 (1.9)	2 (0.6)	13 (1.4)

Female, n (%)	159 (50.5)	158 (50.6)	159 (51.1)	476 (50.7)
Male, n (%)	156 (49.5)	154 (49.4)	152 (48.9)	462 (49.3)
Weight (kg), mean ± SD	101.7 ± 22.3	100.9 ± 20.9	99.6 ± 20.1	100.7 ± 21.1
Height (cm), mean ± SD	166.5 ± 9.9	167.3 ± 9.1	166.9 ± 10.4	166.9 ± 9.8
BMI (kg/m^2), mean ± SD	36.6 ± 7.3	36.0 ± 6.4	35.7 ± 6.1	36.1 ± 6.6
BMI Categories (kg/m^2), n (%)				
<30	52 (16.5)	60 (19.2)	51 (16.4)	163 (17.4)
≥30 to <35	105 (33.3)	92 (29.5)	114 (36.7)	311 (33.2)
≥35 to <40	71 (22.5)	94 (30.1)	85 (27.3)	250 (26.7)
≥40	87 (27.6)	66 (21.2)	61 (19.6)	214 (22.8)
Waist circumference (cm), mean ± SD	116.0 ± 15.7	114.2 ± 14.1	114.6 ± 13.1	114.9 ± 14.4
Duration of obesity (years), mean ± SD	18.1 ± 11.7	17.6 ± 12.0	17.5 ± 11.0	17.7 ± 11.5
Duration of T2DM (years), mean ± SD	8.8 ± 6.2	8.8 ± 6.9	8.0 ± 6.4	8.5 ± 6.5
HbA1c (%), mean ± SD	8.0 ± 0.8	8.0 ± 0.8	8.1 ± 1.0	8.0 ± 0.9
Participants with ≥1 antihyperglycemic medication, n (%)	291 (92.4)	296 (94.9)	288 (92.6)	875 (93.3)
Metformin	274 (87.0)	282 (90.4)	276 (88.7)	832 (88.7)
SGLT2 inhibitors	66 (21.0)	63 (20.2)	62 (19.9)	191 (20.4)
Sulfonylureas	94 (29.8)	78 (25.0)	78 (25.1)	250 (26.7)
Systolic blood pressure (mmHg), mean ± SD	131.0 ± 11.9	130.6 ± 12.2	130.0 ± 12.3	130.5 ± 12.1
Diastolic blood pressure (mmHg), mean ± SD	79.4 ± 8.4	80.2 ± 8.1	79.7 ± 8.7	79.8 ± 8.4
Pulse rate (bpm), mean ± SD	74.8 ± 9.9	75.9 ± 10.4	75.6 ± 9.4	75.4 ± 9.9
Lipid levels, mean ± SD				
Total cholesterol (mg/dL)	179.5 ± 41.1	178.8 ± 42.5	172.0 ± 42.0	176.8 ± 42.0
HDL-C (mg.dL)	44.1 ± 11.3	45.3 ± 12.3	43.5 ± 10.8	44.3 ± 11.5
LDL-C (mg/dL)	98.5 ± 33.3	97.5 ± 34.9	93.5 ± 35.6	96.5 ± 34.6
Triglycerides (mg/dL)	189.0 ± 116.4	184.9 ± 139.3	179.2 ± 127.4	184.4 ± 127.9
Non-HDL-C (mg/dL)	135.4 ± 40.0	133.5 ± 41.4	128.5 ± 40.9	132.5 ± 40.8
VLDL-C (mg/dL)	79.3 ± 34.0	76.2 ± 34.2	77.6 ± 32.6	77.7 ± 33.6
Free fatty acids (mEq/L)	0.6 ± 0.2	0.6 ± 0.2	0.6 ± 0.2	0.6 ± 0.2
eGFR (CKD-EPI), (mL/min/1.73 m^2), mean ± SD	93.5 ± 19.1	95.9 ± 17.8	96.2 ± 17.5	95.2 ± 18.2

Abbreviations: BMI = body mass index; CKD-EPI = chronic kidney disease-epidemiology; CSR = clinical study report; CV = coefficient of variation; eGFR = estimated glomerular filtration rate; HbA1c = glycosylated hemoglobin A1c; HDL-C = high-density lipoprotein-cholesterol; LDL-C = low-density lipoprotein-cholesterol; N = number of participants in population; n = number of participants in the specified category; SD = standard deviation; SGLT2 = sodium-glucose co-transporter-2; T2DM = type 2 diabetes in word docs; TZP = tirzepatide; VLDL-C = very low-density lipoprotein-cholesterol.

All participants in SURMOUNT-2 had T2DM at baseline. The mean duration of T2DM was 8.5 years and 93.4% of participants were receiving ≥1 antihyperglycemic medication at baseline. Mean HbA1c at baseline was 8.0%. Also 87.4% of participants in SURMOUNT-2 had 1 or more weight-related comorbidities in addition to T2DM, including 66.1% with hypertension, 61.1% with dyslipidaemia, 8.3% with obstructive sleep apnoea, and 10.3% with atherosclerotic cardiovascular disease.

The majority of subjects in both trials were female and middle age. The vast majority were younger than 65 years with few participants over 75 years. In SURMOUNT-2 however, the percentage of males was larger and the population was generally older. Most were recruited in the US.

In SURMOUNT-1 the mean baseline BMI was 38.0 kg/m2 with around 32% of the participants having a BMI at least 40 kg/m2, (Class 3 obesity). In terms of comorbidities, a large percentage had history of hypertension and dyslipidaemia (although both apparently relatively well controlled) and other conditions, and around 40% met the criteria for pre-diabetes. In the diabetic population of SURMOUNT-2, mean BMI was slightly lower, and patients were more equally distributed across BMI classes. Again, a large proportion of patients had also other comorbidities.

Overall, the studies included a fairly diverse population, and the key demographic and disease characteristics look similar to those seen in previous trials in this field; the treatment groups appear also generally well balanced in both studies. Of importance there were very small differences in baseline weight and BMI (including BMI categories) between the treatment arms.

- **Numbers analysed**

The tables provide the number of participants included in each analysis population in SURMOUNT-1 and -2.

Table 12. Number of Participants in Each Analysis Population or Data Set, SURMOUNT-1

Analysis Population or Data Sets	Number of Participants
Entered Participants	3238
Randomized Participants	2539
Modified intent-to-treat	2539
Efficacy Analysis Set (EAS)[a]	2539
Full Analysis Set (FAS)	2539
Safety Analysis Set	2539

[a] The number of participants in the EAS may differ slightly for different measures when the analysis requires baseline value and at least 1 postbaseline value. For this reason, the baseline mean values from EAS and FAS may sometimes be slightly different.

Sources: Table GPHK.8.1 and Table GPHK.8.3

Table 13. Number of Participants in Each Analysis Population or Dataset, SURMOUNT-2

Analysis Population or Datasets	Number of Participants
Entered participants	1514
Randomized participants	938
Modified intent-to-treat	938
Efficacy analysis set (EAS)[a]	938
Full analysis set (FAS)	938
Safety analysis set	938

[a] The number of participants in the EAS may differ slightly for different measures when the analysis requires baseline value and ≥1 postbaseline value. For this reason, the baseline mean values from EAS and FAS may sometimes be slightly different.

- **Outcomes and estimation**

Primary Efficacy Endpoints for Primary Study Period

The results for the co-primary efficacy endpoints (percent change in body weight and percentage of participants reaching ≥5% body weight reduction at week 72) are shown below.

SURMOUNT-1

Percent change in body weight at Week 72

Using both the treatment-regimen and efficacy estimands, tirzepatide 10 and 15 mg each achieved superiority compared with placebo for mean percent change in body weight reduction from baseline to 72 weeks (Table 14 and Figure 14). Tirzepatide 5 mg also achieved superiority compared with placebo for mean percent change in body weight reduction from baseline to 72 weeks, which is discussed below as a key secondary endpoint.

Table 14. Mean Percent Change from Baseline in Body Weight at Week 72 mITT Population – Full Analysis Set; Efficacy Analysis Set

Parameters	Placebo (N = 643)	TZP 5 mg[a] (N = 630)	TZP 10 mg (N = 636)	TZP 15 mg (N = 630)
Treatment-regimen Estimand[b]				
Baseline (kg)	104.8	102.9	105.8	105.6
Percent change from baseline at 72 weeks (%)	-3.1†††	-15.0†††	-19.5†††	-20.9†††
Percent change difference from placebo at 72 weeks (%) (95% CI)	N/A	-11.9*** (-13.4, -10.4)	-16.4*** (-17.9, -14.8)	-17.8*** (-19.3, -16.3)
Efficacy Estimand[c]				
Baseline (kg)	104.8	102.9	105.9	105.5
Percent change from baseline at 72 weeks (%)	-2.4†††	-16.0†††	-21.4†††	-22.5†††
Percent change difference from placebo at 72 weeks (%) (95% CI)	N/A	-13.5*** (-14.6, -12.5)	-18.9*** (-20.0, -17.8)	-20.1*** (-21.2, -19.0)

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; mITT population = modified intent-to-treat population; MMRM = mixed model for repeated measures; N = number of participants who were randomly assigned and received at least 1 dose of study drug; N/A = not applicable; TZP = tirzepatide.

[a] For the tirzepatide 5-mg group, percent change in body weight at Week 72 is a key secondary objective. Section 5.1.3.1 discusses the results for the tirzepatide 5-mg group.

[b] ANCOVA with hybrid imputations for missing body weight at 72 weeks. Section 3.7.1 defines hybrid imputation.

[c] MMRM analysis.

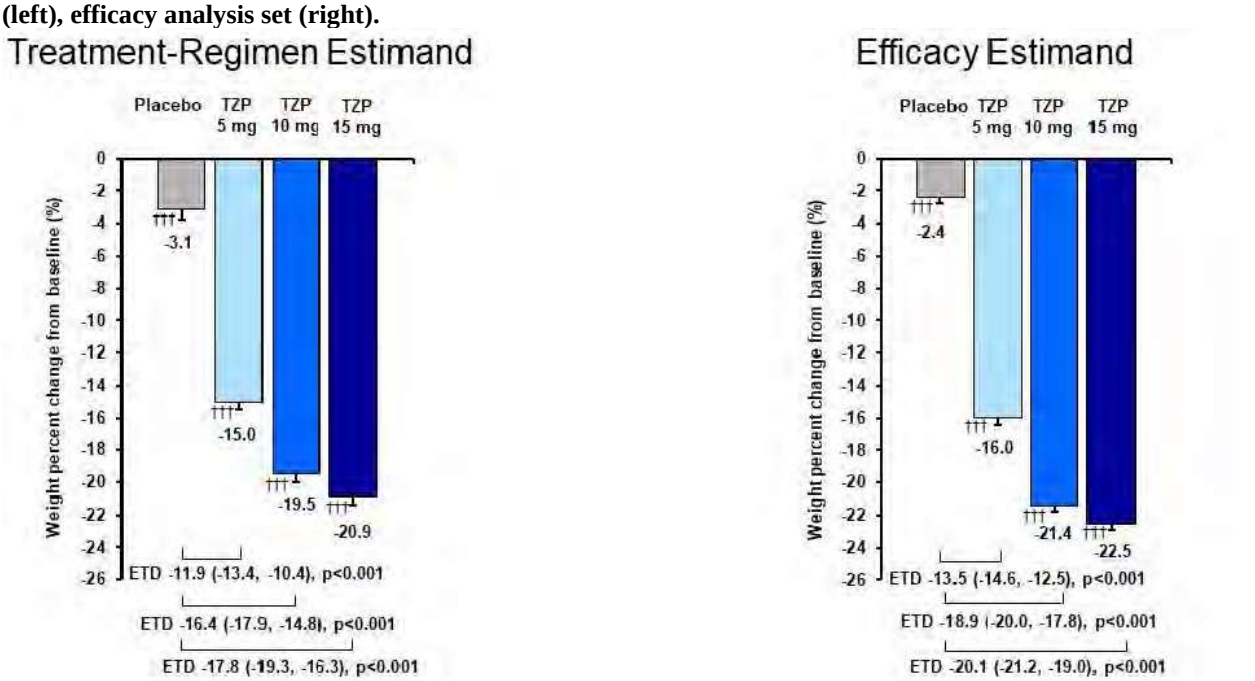
Note: Shown are least squares means.

***p-Value <0.001 versus placebo for superiority.

†††p-Value <0.001 versus baseline.

Sources: Table GPHK.8.17 and Table GPHK.8.18

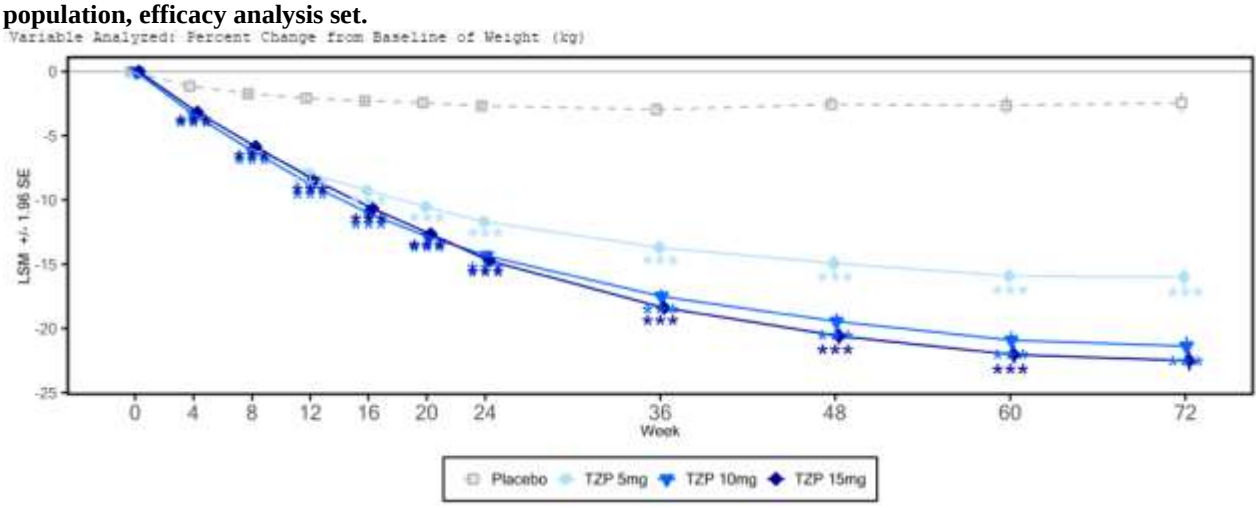
Figure 14. Percent change from baseline in body weight at 72 weeks: mITT population, full analysis set (left), efficacy analysis set (right).



Abbreviations: ANCOVA = analysis of covariance; ETD = estimated treatment difference; mITT = modified intent-to-treat; MMRM = mixed model for repeated measures; TZP = tirzepatide.
Note 1: ANCOVA analysis for treatment-regimen estimand; MMRM analysis for efficacy estimand
Note 2: Least squares means are shown.
†††p-Value <0.001 versus baseline.
Source: Table GPHK.8.17 and Table GPHK.8.18

Figure 15 shows the percent change in body weight over time. Using the efficacy estimand, participants treated with tirzepatide 5, 10, and 15 mg had significant reductions in body weight from baseline compared with placebo starting at Week 4 until Week 72. At Week 16, the tirzepatide 10 and 15-mg groups diverged from the tirzepatide 5-mg group.

Figure 15. Plot of estimated mean for percent change in body weight from baseline to Week 72: mITT population, efficacy analysis set.



p-value vs. Placebo: ***p<0.001; **p<0.01; *p<0.05

Percentage of Participants with ≥5% Body Weight Reduction

Using both the treatment-regimen and efficacy estimands, tirzepatide 10 and 15 mg each achieved superiority compared with placebo for the percentage of participants achieving ≥5% body weight reduction from baseline to 72 weeks (Table 15; Figure 16). Tirzepatide 5 mg also achieved superiority compared with placebo for the percentage of participants achieving ≥5% body weight reduction from baseline to 72 weeks.

Table 15. Percentage of participants achieving at least 5% body weight reduction at 72 weeks

	Placebo (N = 643)	TZP 5 mg[a] (N = 630)	TZP 10 mg (N = 636)	TZP 15 mg (N = 630)
Treatment-regimen estimand[b]	34.5	85.1***	88.9***	90.9***
Efficacy estimand[c]	27.9	89.4***	96.2***	96.3***

Abbreviation: N = number of participants who were randomly assigned and received 1 dose of study drug; TZP = tirzepatide.

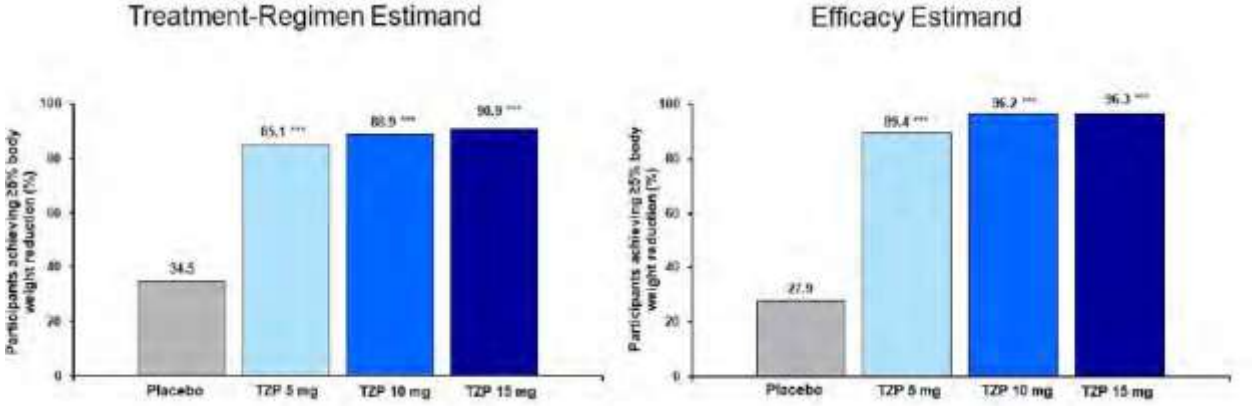
a For the tirzepatide 5-mg group, the percentage of participants achieving at least 5% or more body weight reduction at Week 72 is a key secondary objective.

b Logistic regression with hybrid imputation analysis for treatment-regimen estimand.

c Logistic regression with missing value imputed by MMRM analysis for efficacy estimand.

*** p-Value <0.001 versus placebo for superiority.

Figure 16. Percentage of participants from randomisation achieving body weight reduction targets ≥5% at Week 72: mITT population, full analysis set (left), efficacy analysis set (right).



Abbreviations: mITT = modified intent-to-treat; MMRM = mixed model for repeated measures; TZP = tirzepatide.
Note 1: Logistic regression with missing value imputed by MMRM analysis for efficacy estimand; logistic regression with hybrid imputation analysis for treatment-regimen estimand. Section 3.7.1 defines hybrid imputation.
Note 2: For the tirzepatide 5-mg group, the percentage of participants achieving ≥5% or more body weight reduction at Week 72 is a key secondary objective. Section 5.1.3.3 discusses the results for the tirzepatide 5-mg group.
***p-Value <0.001 versus placebo for superiority.
Sources: Table GPHK.8.20 and Table GPHK.8.21

SURMOUNT-2

Percent change in body weight at Week 72

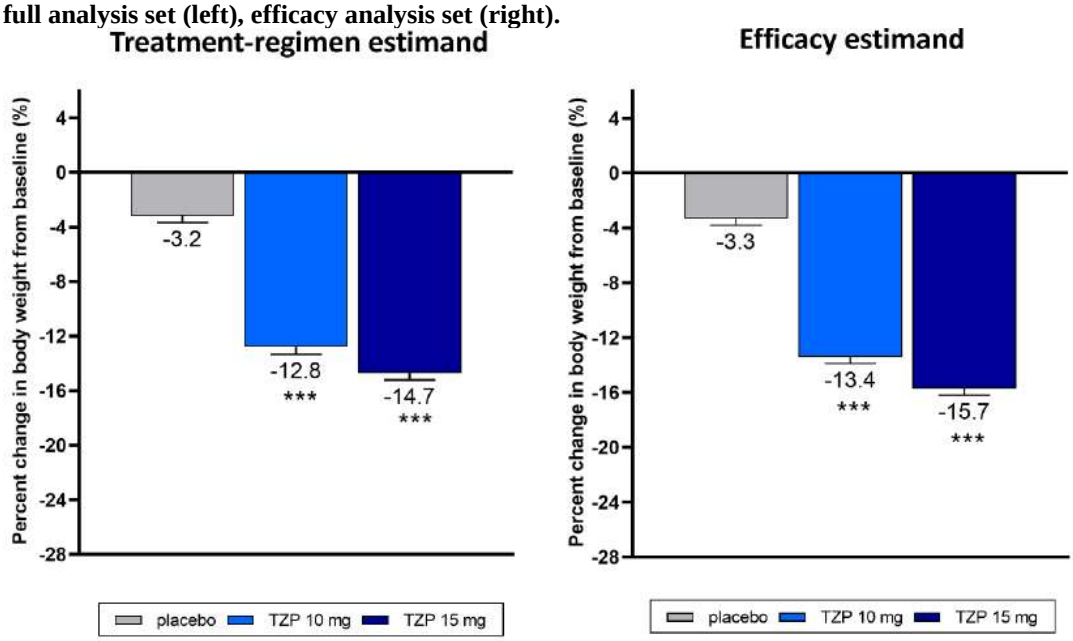
Using both the treatment-regimen and efficacy estimands, tirzepatide 10 and 15 mg each achieved superiority compared with placebo for mean percent change in body weight reduction from baseline to 72 weeks.

Table 16. Mean Percent Change from Baseline in Body Weight at Week 72 in SURMOUNT-2 mITT Population – Full Analysis Set; Efficacy Analysis Set

Parameters	Placebo (N=315)	TZP 10 mg (N=312)	TZP 15 mg (N=311)
Treatment-regimen estimand[a]			
Baseline (kg)	101.7	100.9	99.6
Mean percent change from baseline at 72 weeks (%)	-3.2†††	-12.8†††	-14.7†††
Mean percent change difference from placebo at 72 weeks (%) (95% CI)	-	-9.6 (-11.1, -8.1)***	-11.6 (-13.0, -10.1)***
Efficacy estimand[b]			
Baseline (kg)	101.8	101.1	99.5
Mean percent change from baseline at 72 weeks (%)	-3.3†††	-13.4†††	-15.7†††
Mean percent change difference from placebo at 72 weeks (%) (95% CI)	-	-10.14 (-11.5, -8.8)***	-12.4 (-13.7, -11.0)***

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; MMRM = mixed model for repeated measures; N = number of participants who were randomly assigned and received 1 dose of study drug; TZP = tirzepatide.
a ANCOVA with hybrid imputations for missing body weight at 72 weeks. Section 3.7.1 defines hybrid imputation.
b MMRM analysis.
Note: Shown are the least-squares means.
***p-Value <.001 versus placebo for superiority; †††p-value <.001 versus baseline.

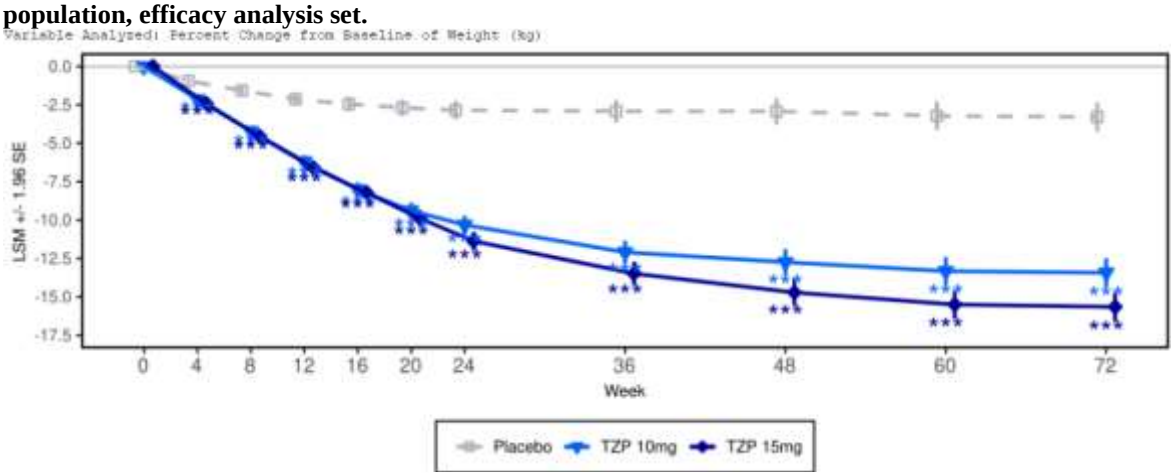
Figure 17. Percent change from baseline in body weight at Week 72 in SURMOUNT-2: mITT population, full analysis set (left), efficacy analysis set (right).



Abbreviations: ANCOVA = analysis of covariance; CSR = clinical study report; mITT = modified intent-to-treat; MMRM = mixed model for repeated measures; TZP = tirzepatide.
Note 1: ANCOVA analysis for treatment-regimen estimand; MMRM analysis for efficacy estimand.
Note 2: Shown are the least squares means ± standard errors.
***p-Value <.001 versus placebo for objectives controlled for type 1 error.

Figure 18 shows the percent change in body weight over time. Using the efficacy estimand, participants treated with tirzepatide 10 and 15 mg had significant reductions in body weight from baseline compared with placebo starting at Week 4 until Week 72. The reductions in body weight from baseline were numerically greater in the tirzepatide 15-mg group compared to the tirzepatide 10-mg group.

Figure 18. Plot of estimated mean for percent change in body weight from baseline to Week 72: mITT population, efficacy analysis set.



p-value vs. Placebo: ***p<0.001; **p<0.01; *p<0.05

Percentage of Participants with ≥5% Body Weight Reduction

Using both the treatment-regimen and efficacy estimands, tirzepatide 10 and 15 mg each achieved superiority compared with placebo for the percentage of participants achieving ≥5% body weight reduction from baseline to 72 weeks (Table 17; Figure 19).

Table 17. Percentage of participants achieving ≥5% body weight reduction at 72 weeks

	Placebo (N=315)	TZP 10 mg (N=312)	TZP 15 mg (N=311)
Treatment-regimen estimand[a]	32.5	79.2***	82.8***
Efficacy estimand[b]	30.6	81.6***	86.4***

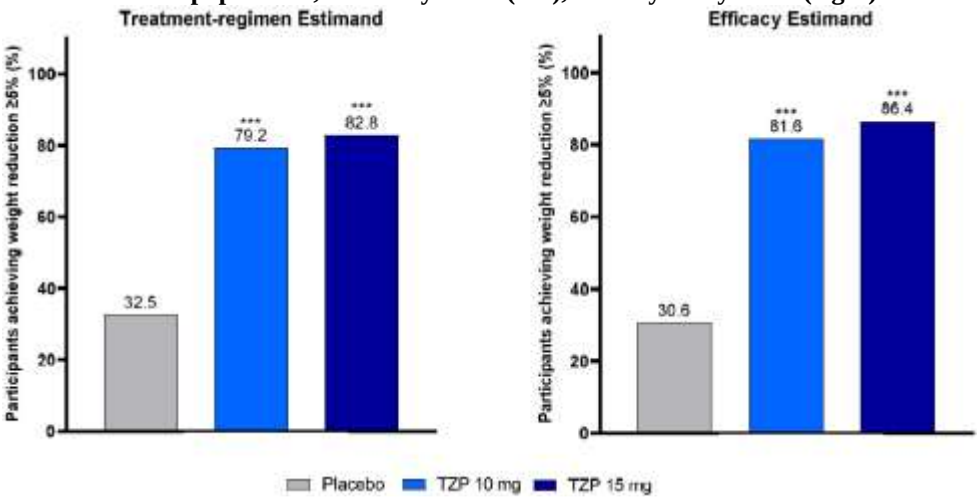
Abbreviations: MMRM = mixed model for repeated measures; N = number of participants who were randomly assigned and received 1 dose of study drug; TZP = tirzepatide.

a Logistic regression with hybrid imputation analysis for treatment-regimen estimand.

b Logistic regression with missing value imputed by MMRM analysis for efficacy estimand.

*** p-Value <.001 versus placebo for superiority.

Figure 19. Percentage of participants from randomisation achieving body weight reduction target ≥5% at Week 72: mITT population, full analysis set (left), efficacy analysis set (right).



Abbreviations: mITT = modified intent-to-treat; MMRM = mixed model for repeated measures; TZP = tirzepatide.

Note 1: Logistic regression with hybrid imputation analysis for the treatment-regimen estimand; logistic regression with missing value imputed by MMRM analysis for the efficacy estimand. Section 3.7.1 defines hybrid imputation.

***p-Value <.001 versus placebo for superiority.

The primary analyses in both SURMOUNT-1 and -2 showed (for both estimands) a highly significant and clinically relevant positive effect of tirzepatide on the co-primary endpoints, although the effect size was slightly less pronounced in the diabetic patients of SURMOUNT-2. Similar differences between diabetic and non-diabetic populations were observed also in previous studies with other GLP-1 RAs. It has been suggested that this may be related to the varying effects of other background anti-diabetic therapies on body weight.

Of note, in SURMOUNT-1 more than 85% of participants achieved a weight reduction of 5% or more, even with the lowest dose, a threshold that is considered clinically meaningful and likely to result in health benefits. In SURMOUNT-2 a 5 mg maintenance dose was not examined but it is likely that again a significant proportion of patients might be able to achieve a clinically relevant weight loss, even with that dose.

Table 18 and 19 below summarise the treatment effects and corresponding 95% CI for the co-primary endpoints expressed in absolute terms.

Table 18. Mean change from baseline in body weight (kg) at week 72.

	Treatment-regimen Estimand	Efficacy Estimand
SURMOUNT-1	Difference estimate (95% CI)	Difference estimate (95% CI)
TZP 5mg vs Placebo	-1.91 (-4.34, 0.52)	-1.9 (-4.3, 0.6)
TZP 10mg vs Placebo	1.05 (-1.37, 3.48)	1.1 (-1.4, 3.5)
TZP 15mg vs Placebo	0.80 (-1.63, 3.23)	0.7 (-1.7, 3.2)
SURMOUNT-2		
TZP 10mg vs Placebo	-0.79 (-4.10, 2.52)	-0.7 (-4.0, 2.7)
TZP 15mg vs Placebo	-2.05 (-5.36, 1.26)	-2.2 (-5.5, 1.1)

Table 19. Proportion of participants achieving ≥5% body weight reduction

	Treatment-regimen Estimand	Efficacy Estimand
SURMOUNT-1	Difference estimate (95% CI)	Difference estimate (95% CI)
TZP 5mg vs Placebo	50.26 (44.31, 56.21)	61.28 (57.03, 65.54)
TZP 10mg vs Placebo	54.55 (49.11, 59.99)	68.18 (64.40, 71.97)
TZP 15mg vs Placebo	56.43 (50.91, 61.96)	68.62 (64.86, 72.37)
SURMOUNT-2		
TZP 10mg vs Placebo	46.81 (39.49, 54.13)	50.96 (44.25, 57.66)
TZP 15mg vs Placebo	50.42 (43.05, 57.78)	55.75 (49.34, 62.15)

Key Secondary Efficacy Endpoints for Primary Study Period

SURMOUNT-1

Tirzepatide 5 mg Body Weight Endpoints

Using both the treatment-regimen and efficacy estimands, tirzepatide 5 mg achieved superiority compared with placebo for percent change in body weight reduction from baseline to 72 weeks and for the percentage of participants achieving ≥5% body weight reduction from baseline to 72 weeks.

Pooled tirzepatide 10 and 15 mg; Mean Change in Body Weight at Week 20

Using the treatment-regimen and efficacy estimands, pooled tirzepatide 10 and 15 mg achieved superiority compared with placebo for mean change reduction in body weight (kg) at 20 weeks.

Table 20. Mean Change from Baseline in Body Weight (kg) at Week 20 mITT Population – Full Analysis Set; Efficacy Analysis Set

Parameters (kg)	Placebo (N = 643)	TZP 10/15 mg (N = 1266)
Treatment-regimen estimand[a]		
Baseline	104.8	105.7
Change from baseline at 20 weeks	-2.7†††	-12.8†††
Change difference from placebo at 20 weeks (95% CI)	N/A	-10.1*** (-10.7, -9.6)
Efficacy Estimand[b]		
Baseline	104.8	105.7
Change from baseline at 20 weeks	-2.5†††	-13.2†††
Change difference from placebo at 20 weeks (95% CI)	N/A	-10.7*** (-11.2, -10.1)

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; mITT = modified intent-to-treat; MMRM = mixed model for repeated measures; N = number of participants who were randomly assigned and received at least 1 dose of study drug; N/A = not applicable; TZP = tirzepatide.

[a] ANCOVA with hybrid imputations for missing body weight at 20 weeks. Section 3.7.1 defines hybrid imputation.

[b] MMRM analysis.

Note: Shown are the least squares means.

***p-Value <0.001 versus placebo for superiority.

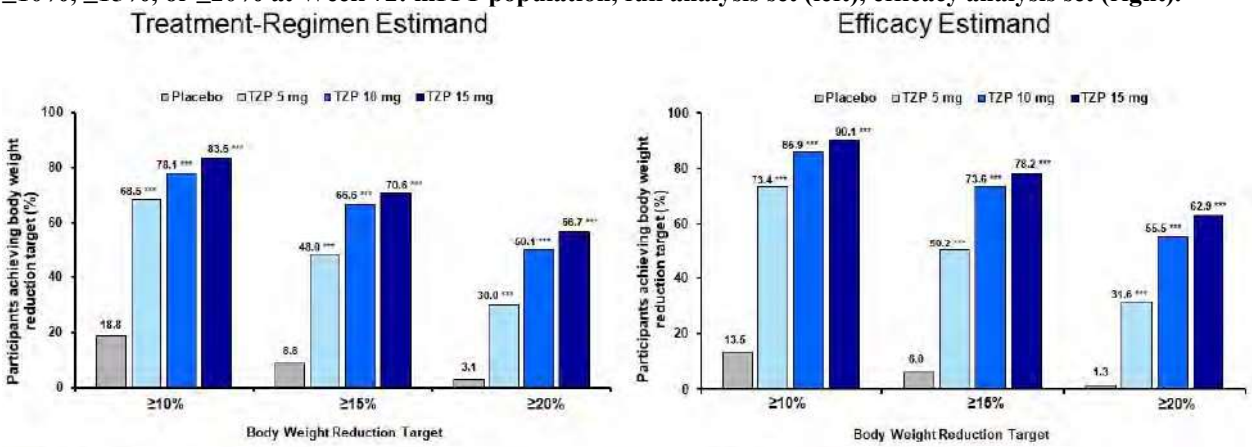
†††p-Value <0.001 versus baseline.

Sources: Table GPHK.8.24 and Table GPHK.8.25

Percentage of Participants with ≥10%, ≥15%, or ≥20% Body Weight Reduction at Week 72

Using both the treatment-regimen and efficacy estimands, tirzepatide 10 and 15 mg each achieved superiority compared with placebo for the percentage of participants achieving ≥10%, ≥15%, and ≥20% body weight reduction from baseline to 72 weeks (Figure 20). The tirzepatide 5-mg group also had significantly greater percentage of participants achieving ≥10%, ≥15%, and ≥20% body weight reduction from baseline to 72 weeks compared with placebo.

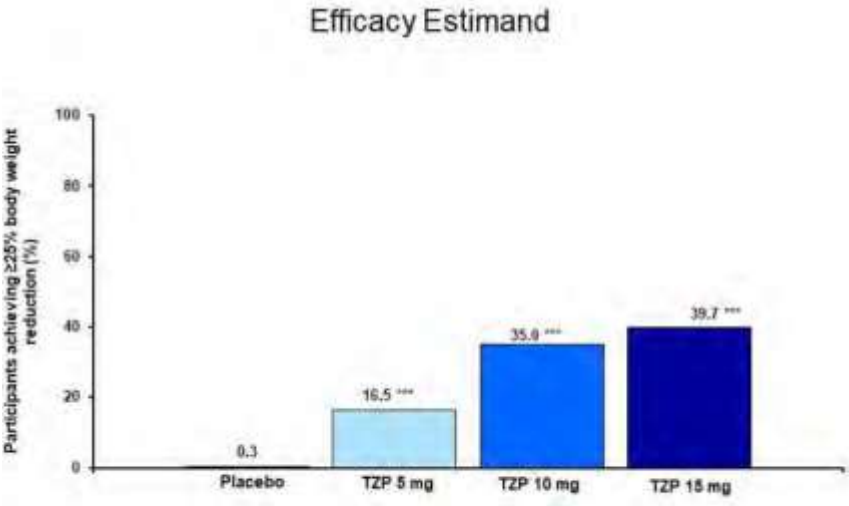
Figure 20. Percentage of participants from randomisation achieving body weight reduction targets of ≥10%, ≥15%, or ≥20% at Week 72: mITT population, full analysis set (left), efficacy analysis set (right).



Abbreviations: mITT = modified intent-to-treat; MMRM = mixed model for repeated measures; TZP = tirzepatide.
Note 1: Logistic regression with missing value imputed by MMRM analysis for efficacy estimand; logistic regression with hybrid imputation analysis for treatment-regimen estimand. Section 3.7.1 defines hybrid imputation.
Note 2: For the tirzepatide 5-mg group, the percentage of participants achieving ≥10% or ≥15% body weight reductions at Week 72 is an additional secondary objective and is not controlled for type 1 error. Additionally, ≥20% body weight reduction at Week 72 is an exploratory objective for the tirzepatide 5-mg group. Section 5.1.4.1 discusses the results for the tirzepatide 5-mg group.
***p-Value <0.001 versus placebo for superiority.
Sources: Table GPHK.8.20 and Table GPHK.8.21

As part of the *exploratory* endpoints, the percentage of participants with ≥25% body weight reduction at Week 72 was assessed, showing again a greater effect for tirzepatide 5, 10, and 15 mg compared with placebo (Figure 21).

Figure 21. Percentage of participants with ≥25% body weight reduction from baseline to Week 72: mITTpopulation, efficacy analysis set.



Abbreviations: mITT = modified intent-to-treat; TZP = tirzepatide.
Note: Logistic regression.
***p-Value <0.001 versus placebo.
Source: Table GPHK.8.20

Mean change in waist circumference from baseline to Week 72

Using both the treatment-regimen and efficacy estimands, tirzepatide 10 and 15 mg each achieved superiority compared with placebo for mean change reduction in waist circumference at 72 weeks (Table 21). Tirzepatide 5 mg also achieved a significantly greater mean change reduction in waist circumference at 72 weeks compared with placebo.

Table 21. Mean Change from Baseline in Waist Circumference at Week 72 mITT Population – Full Analysis Set; Efficacy Analysis Set

Parameters (cm)	Placebo (N = 643)	TZP 5 mg[a] (N = 630)	TZP 10 mg (N = 636)	TZP 15 mg (N = 630)
Treatment-regimen Estimand[b]				
Baseline	114.0	113.2	114.8	114.4
Change from baseline at 72 weeks	-4.0†††	-14.0†††	-17.7†††	-18.5†††
Change difference from placebo at 72 weeks (95% CI)	N/A	-10.1*** (-11.6, -8.6)	-13.8*** (-15.2, -12.3)	-14.5*** (-15.9, -13.0)
Efficacy Estimand[c]				
Baseline	114.0	113.2	114.9	114.4
Change from baseline at 72 weeks	-3.4†††	-14.6†††	-19.4†††	-19.9†††
Change difference from placebo at 72 weeks (95% CI)	N/A	-11.2*** (-12.3, -10.0)	-16.0*** (-17.2, -14.9)	-16.5*** (-17.7, -15.4)

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; mITT = modified intent-to-treat; MMRM = mixed model for repeated measures; N = number of participants who were randomly assigned and received at least 1 dose of study drug; N/A = not applicable; TZP = tirzepatide.

[a] For the tirzepatide 5-mg group, mean change in waist circumference at Week 72 is an additional secondary objective. Section 5.1.4.2 discusses the results for the tirzepatide 5-mg group.

[b] ANCOVA with hybrid imputations for values at 72 weeks. Section 3.7.1 defines hybrid imputation.

[c] MMRM analysis

Note: Shown are least-squares means.

***p-Value <0.001 versus placebo for superiority.

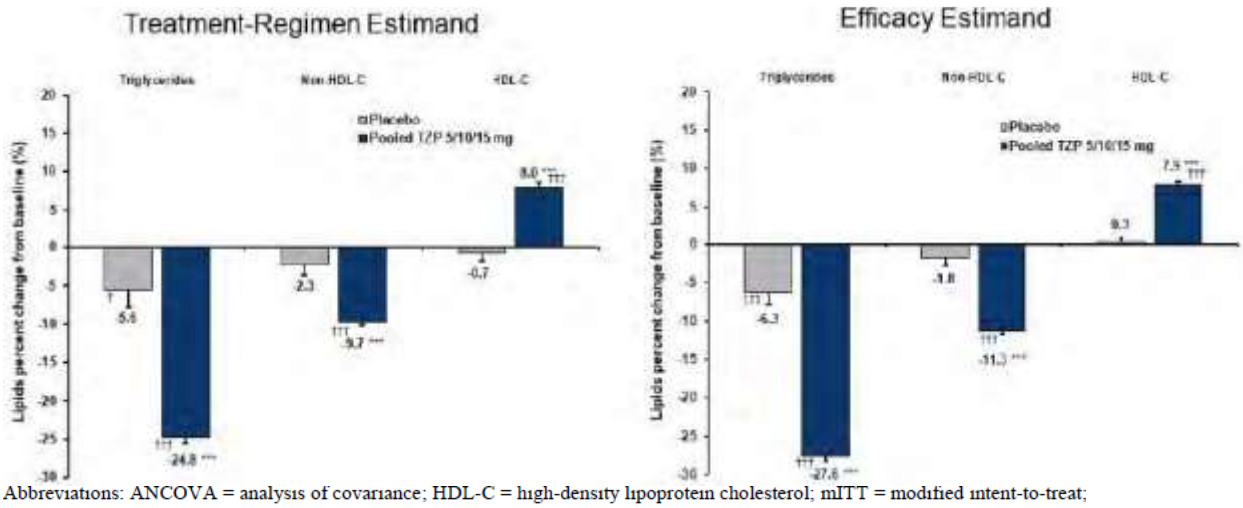
†††p-Value <0.001 versus baseline.

Sources: Table GPHK.8.26 and Table GPHK.8.27

Change in triglycerides, non-HDL cholesterol, and HDL cholesterol from baseline to Week 72

Using both the treatment-regimen and efficacy estimands, pooled tirzepatide 5, 10, and 15 mg achieved superiority compared with placebo for mean percent change (Figure 22) showing a reduction in triglycerides and non-HDL cholesterol, and increase in HDL cholesterol.

Figure 22. Percent change from baseline in triglycerides, HDL-C, and non-HDL-C at 72 weeks: mITT population, full analysis set (left), efficacy analysis set (right).



Abbreviations: ANCOVA = analysis of covariance; HDL-C = high-density lipoprotein cholesterol; mITT = modified intent-to-treat; MMRM = mixed model for repeated measures; TZP = tirzepatide.

Note 1: MMRM analysis for efficacy estimand; ANCOVA analysis for treatment-regimen estimand.

Note 2: Data presented are the estimated means ± standard errors.

Note 3: Log transformations were applied to raw data for lipid parameters.

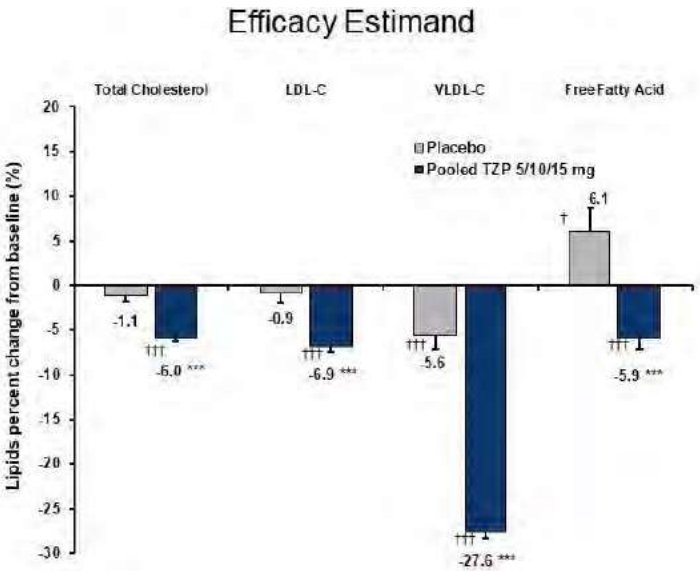
***p-Value <0.001 versus placebo for superiority.

†p-Value <0.05, †††p-value<0.001 versus baseline.

Sources: Table GPHK.8.28. Table GPHK.8.29. Table GPHK.8.30. and Table GPHK.8.31

Changes in LDL-cholesterol, VLDL-cholesterol, total cholesterol, and FFAs from baseline to 72 weeks were assessed as part of the *additional* secondary endpoints. Using the efficacy estimand, pooled tirzepatide 5, 10, and 15 mg was statistically significant compared with placebo for mean percent change in VLDL-C, LDL-C, total cholesterol, and FFAs at 72 weeks (Figure 23).

Figure 23. Percent change from baseline in total cholesterol, LDL-C, VLDL-C, and FFAs at 72 weeks: mITT population, efficacy analysis set.



Abbreviations: FFA = free fatty acid; mITT = modified intent-to-treat; MMRM = mixed model for repeated measures; LDL-C = low-density lipoprotein cholesterol; TZP = tirzepatide; VLDL-C = very low-density lipoprotein cholesterol.
Note 1: MMRM analysis for efficacy estimand.
Note 2: Data are presented are the estimated means ± standard errors.
Note 3: Log transformations were applied to raw data for lipid parameters.
***p-value <0.001 versus placebo.
†p-value <0.05, †††p-value<0.001 versus baseline.
Sources: Table GPHK.8.28 and Table GPHK.8.29

Mean change in systolic blood pressure (SBP) from baseline to Week 72

Using both the treatment-regimen and efficacy estimands, pooled doses of tirzepatide 5, 10, and 15 mg achieved superiority compared with placebo in mean change reduction in SBP at 72 weeks (Table 22). Pooled data for tirzepatide 5, 10, and 15 mg showed significant reductions in SBP compared with placebo starting at Week 4 through Week 72. By Week 24, SBP reductions plateaued for the pooled tirzepatide group (Figure 24).

Table 22. Mean Changes in Systolic Blood Pressure at 72 Weeks mITT Population – Full Analysis Set; Efficacy Analysis Set

Parameter (mmHg)	Placebo (N = 643)	Pooled TZP 5/10/15 mg (N = 1896)
Treatment-regimen estimand[a]		
Baseline	122.9	123.5
Change from baseline	-1.0	-7.2†††
Change difference from placebo at 72 weeks (95% CI)	N/A	-6.2*** (-7.7, -4.8)
Efficacy Estimand[b]		
Baseline	122.8	123.4
Change from baseline at 72 weeks	-1.3††	-8.1†††
Change difference from placebo at 72 weeks (95% CI)	N/A	-6.8*** (-7.9, -5.7)

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; mITT = modified intent-to-treat; MMRM = mixed model for repeated measures; N = number of participants who were randomly assigned and received at least 1 dose of study drug; N/A = not applicable; SBP = systolic blood pressure; TZP = tirzepatide.

[a] ANCOVA with hybrid imputations for missing SBP at 72 weeks. Section 3.7.1 defines hybrid imputation.

[b] MMRM analysis

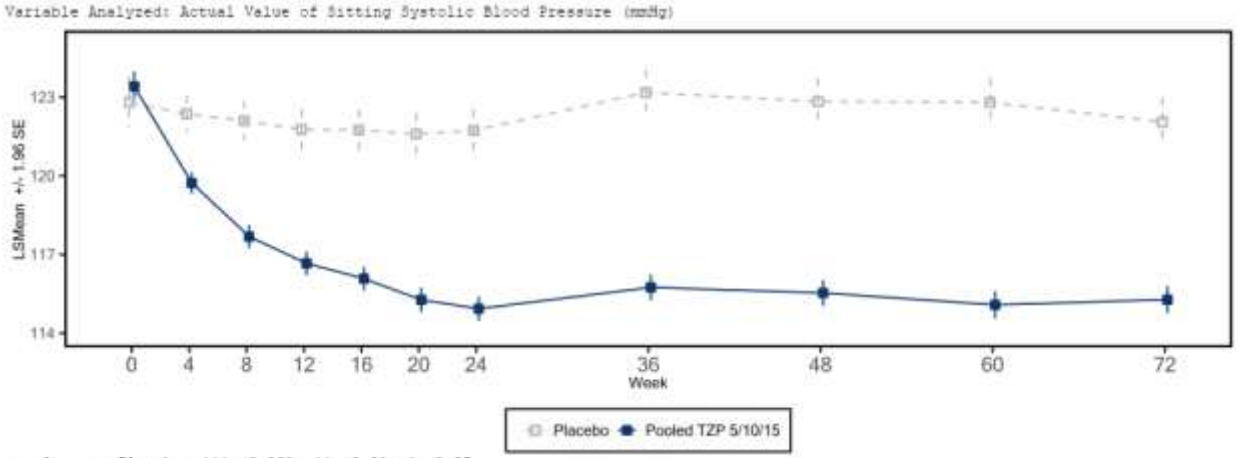
Note: Shown are least-squares means.

***p-Value <0.001 versus placebo for superiority.

††p-value <0.01, †††p-value <0.001 versus baseline.

Sources: Table GPHK.8.34 and Table GPHK.8.35

Figure 24. Actual SBP over time.



p-value vs. Placebo: ***p<0.001; **p<0.01; *p<0.05
Abbreviations: ANOVA = analysis of variance; DBP = diastolic blood pressure; LSMean = least squares mean; MMRM = mixed model repeated measures; SBP = systolic blood pressure; SE = standard error.
Note 1: Only subjects with non-missing baseline value and at least one non-missing post-baseline value of the response variable were included in analysis.
MMRM model for post-baseline measures: Variable = Baseline + Analysis Country + Sex + Prediabetes Status at Randomization + Treatment + Time + Treatment*Time (Type III sum of squares).
ANOVA model for baseline measures: Variable = Treatment (Type III sum of squares).

Diastolic blood pressure (DBP) at Week 72 was assessed as part of the *additional* secondary endpoints. Using the efficacy estimand, pooled data for tirzepatide 5, 10, and 15 mg showed also statistically significant mean decrease in DBP at 72 weeks compared to placebo.

Mean Change from Baseline in Fasting Insulin at Week 72

Using both the treatment-regimen and efficacy estimands, pooled doses of tirzepatide 5, 10, and 15 mg achieved superiority compared with placebo in mean reduction change in fasting insulin at Week 72.

Table 23. Mean Changes in Fasting Insulin from Baseline to Week 72 mITT Population – Full Analysis Set; Efficacy Analysis Set

Parameters	Placebo (N = 643)	Pooled TZP 5/10/15 mg (N = 1896)
Treatment-regimen estimand[a]		
Baseline (mIU/L)	12.0	11.7
Change from baseline at 72 weeks (mIU/L)	-0.8	-5.1
Percent change from baseline (%)	-6.6	-42.9†††
Percent change difference from placebo at 72 weeks (%) (95% CI)	N/A	-38.9*** (-44.8, -32.4)
Efficacy Estimand[b]		
Baseline (mIU/L)	12.0	11.7
Change from baseline at 72 weeks (mIU/L)	-1.1	-5.5
Percent change from baseline at 72 weeks (%)	-9.7†††	-46.9†††
Percent change difference from placebo at 72 weeks (%) (95% CI)	N/A	-41.2*** (-44.9, -37.3)

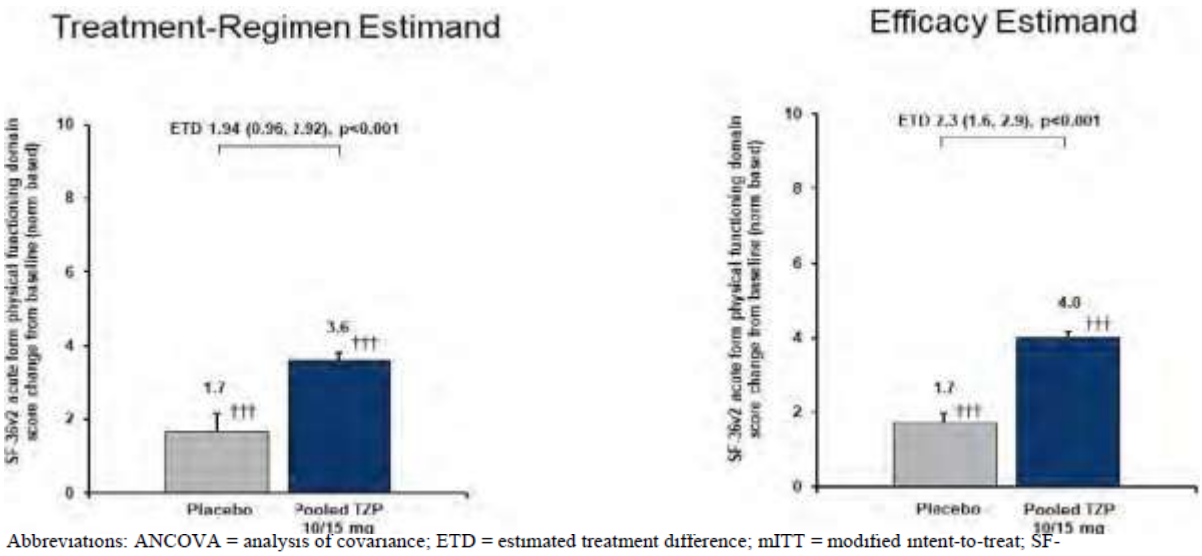
Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; mITT = modified intent-to-treat; MMRM = mixed model for repeated measures; N = number of participants who were randomly assigned and received at least 1 dose of study drug; N/A = not applicable; TZP = tirzepatide.
A ANCOVA with hybrid imputation for missing values. Section 3.7.1 defines hybrid imputation.
B MMRM analysis
Note 1: Shown are estimated means.
Note 2: Log transformations were applied to raw data.
***p-Value <0.001 versus placebo for superiority.
†††p-Value <0.001 versus baseline.
Sources: Table GPHK.8.38 and Table GPHK.8.39

Patient reported Outcomes

In general, in the tirzepatide CWM development program, 2 PROs, SF-36v2 and IWQOL-Lite-CT were implemented. SF-36v2 was the main measure and was presented as part of the key secondary endpoints while IWQOL-Lite-CT was assessed as part of the *additional* secondary endpoints.

The SF-36v2 acute form (1-week recall period) is a 36-item, generic, patient-administered measure designed to assess different domains (8) of health-related quality of life. The *Physical Functioning* domain assesses health functioning at the time of assessment, whereas the other 7 domains assess health functioning from the past week. Using both the treatment-regimen and efficacy estimands, pooled tirzepatide 10 and 15 mg achieved superior improvements compared with placebo in change of SF-36v2 acute form Physical Functioning domain at Week 72 (Figure 25). Tirzepatide 5 mg also achieved a significantly greater improvement in the score.

Figure 25. Change from baseline in SF-36v2 Acute Form Physical Functioning Domain at 72 weeks: mITT population, full analysis set (left), efficacy analysis set (right).



Abbreviations: ANCOVA = analysis of covariance; ETD = estimated treatment difference; mITT = modified intent-to-treat; SF-36v2 = Short-Form-36 Health Survey, Version 2; TZP =tirzepatide.
Note 1: ANCOVA analysis
Note 2: Data are norm-based least squares means
Note 3: Scores above 0 indicate functional improvement.
†††p-Value <0.001 versus baseline.
Sources: Table GPHK.8.40 and Table GPHK.8.41

As part of the *additional* secondary endpoints the norm-based change from baseline in SF-36v2 component summary scores and domains at Week 72 (LOCF) were presented and it is reported that at Week 72, all tirzepatide groups showed significant improvements from baseline, with the exception of the tirzepatide 10-mg group for the Mental Component Summary Score. All tirzepatide groups showed significant improvements compared with

placebo for all domain and component scores.

The IWQOL-Lite-CT is a 20-item, obesity-specific patient-reported outcome instrument developed for use in obesity clinical trials. It assesses 2 primary domains of obesity-related health-related quality of life physical composite and a psychosocial composite. As part of the *additional* secondary endpoints, results on the change in IWQOL-Lite-CT results from baseline to 72 weeks showed that participants randomly assigned tirzepatide 5, 10, and 15 mg had significantly improved scores compared with placebo for all 3 IWQOL-Lite CT composites and the total score assessed.

Additional assessments using EQ-5D-5L (as part of the *exploratory* endpoints) showed also positive effects in favour of tirzepatide.

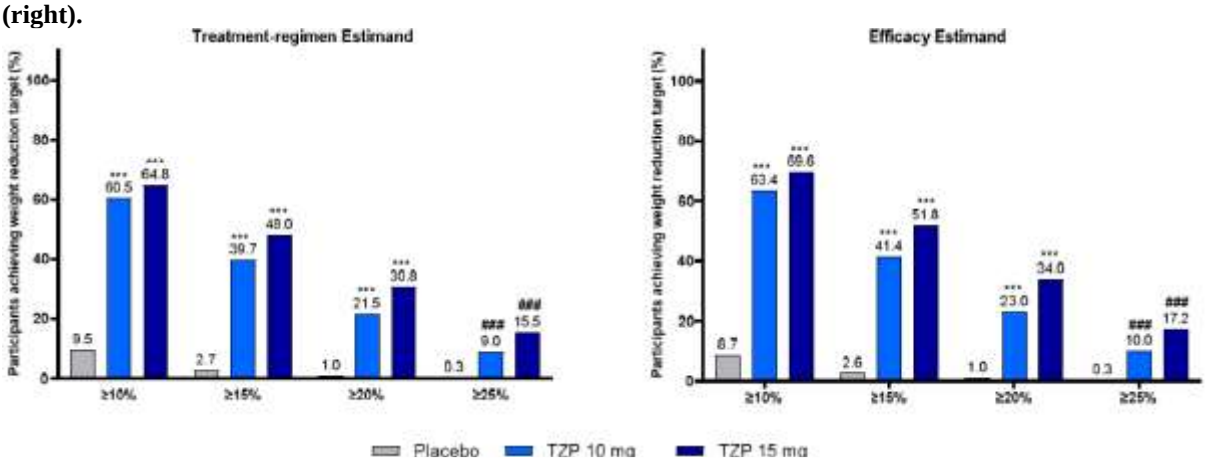
Consistent results were seen across all key secondary endpoints in favour of tirzepatide. Significantly more tirzepatide treated participants achieved considerable reductions in body weight of 10%, 15% or 20% or more and a substantial percentage (almost 40% of those who received the highest dose; efficacy estimand) had a ≥25% body weight reduction.
Greater improvements with significant differences compared to placebo were also seen with tirzepatide in all measured cardiovascular and metabolic parameters, including waist circumference, systolic and diastolic blood pressure, fasting insulin and lipids.
Obesity and associated co-morbidities can negatively impact physical function and activities and quality of life. The PRO results showed again significant improvements in most measured parameters with tirzepatide.

SURMOUNT-2

Percentage of Participants with ≥10%, ≥15%, or ≥20% Body Weight Reduction at Week 72

Using both the treatment-regimen and efficacy estimands, tirzepatide 10 and 15 mg each achieved superiority compared with placebo for the percentage of participants achieving ≥10%, ≥15%, and ≥20% body weight reduction from baseline to 72 weeks (Figure 26). The body weight reduction >25% at Week 72 was an *exploratory* endpoint, showing again a greater effect for tirzepatide 10 and 15 mg compared with placebo.

Figure 26. Percentage of participants from randomisation achieving body weight reduction targets of ≥10%, ≥15%, ≥20%, and >25% at Week 72: mITT population, full analysis set (left), efficacy analysis set (right).

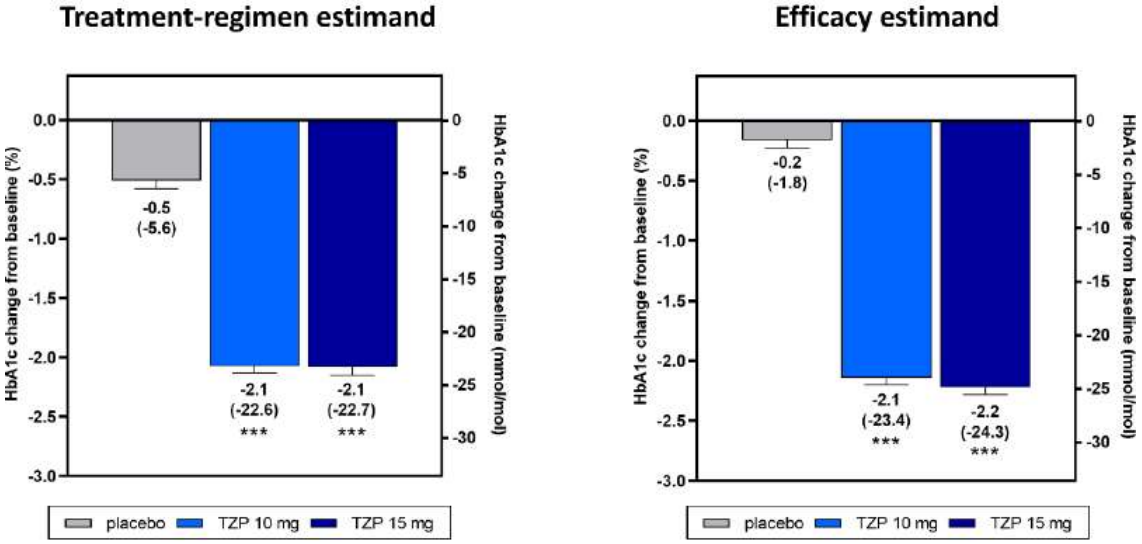


Abbreviations: mITT = modified intent-to-treat; MMRM = mixed model for repeated measures; TZP = tirzepatide. Note 1: Logistic regression with hybrid imputation analysis for the treatment-regimen estimand; logistic regression with missing value imputed by MMRM analysis for the efficacy estimand. Section 3.7.1 defines hybrid imputation. ***p-Value <.001 versus placebo for superiority. ### p-Value <.001 versus placebo for objectives not controlled for type 1 error.

Change in HbA1c and percentage of participants achieving HbA1c targets of <7%, ≤6.5%, and <5.7% at 72 weeks

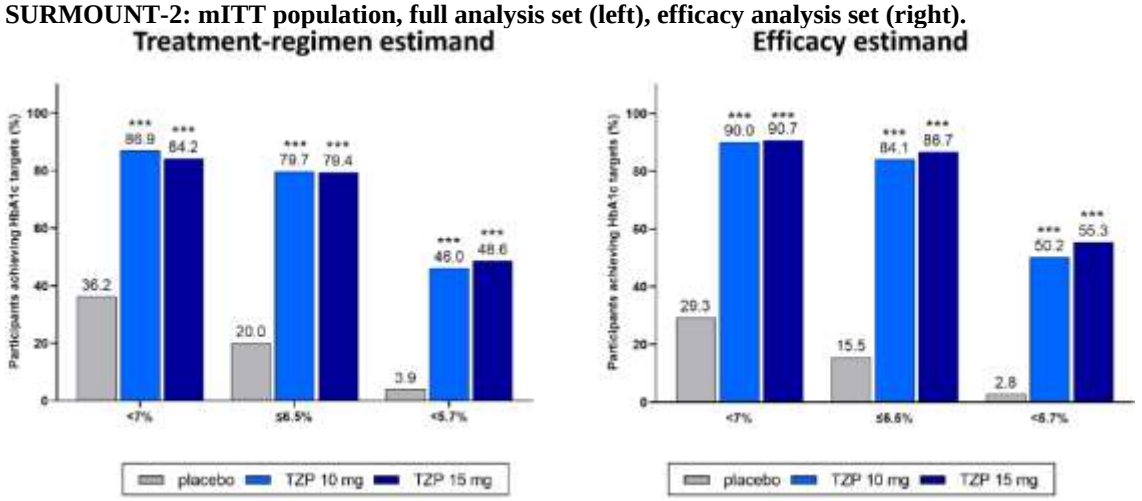
Tirzepatide 10 and 15 mg achieved superiority on the endpoint of mean change in HbA1c (reduction) compared with placebo at 72 weeks, using both the treatment-regimen and efficacy estimands (Figure 27). This analysis was a key secondary endpoint controlled for type 1 error. Significantly higher percentages of participants treated with tirzepatide 10 or 15 mg compared with placebo achieved HbA1c <7%, ≤6.5%, and <5.7% at 72 weeks, using both the treatment-regimen and efficacy estimands (Figure 28). These analyses were key secondary endpoints controlled for type 1 error.

Figure 27. Mean change from baseline in HbA1c (%) at Week 72 in SURMOUNT-2: mITT population, full analysis set (left), efficacy analysis set (right).



Abbreviations: CSR = clinical study report; HbA1c = glycosylated hemoglobin A1c; mITT = modified intent-to-treat; TZP = tirzepatide.
Note 1: Shown are the least squares means ± standard errors.
Note 2: mmol/mol values are shown in parentheses.
***p-Value <.001 versus placebo-controlled for type 1 error.

Figure 28. Percentage of participants achieving HbA1c <7%, ≤6.5%, and <5.7% at Week 72 in SURMOUNT-2: mITT population, full analysis set (left), efficacy analysis set (right).



Abbreviations: CSR = clinical study report; HbA1c = glycosylated hemoglobin A1c; mITT = modified intent-to-treat;
TZP = tirzepatide.
***p-Value <.001 versus placebo-controlled for type 1 error.

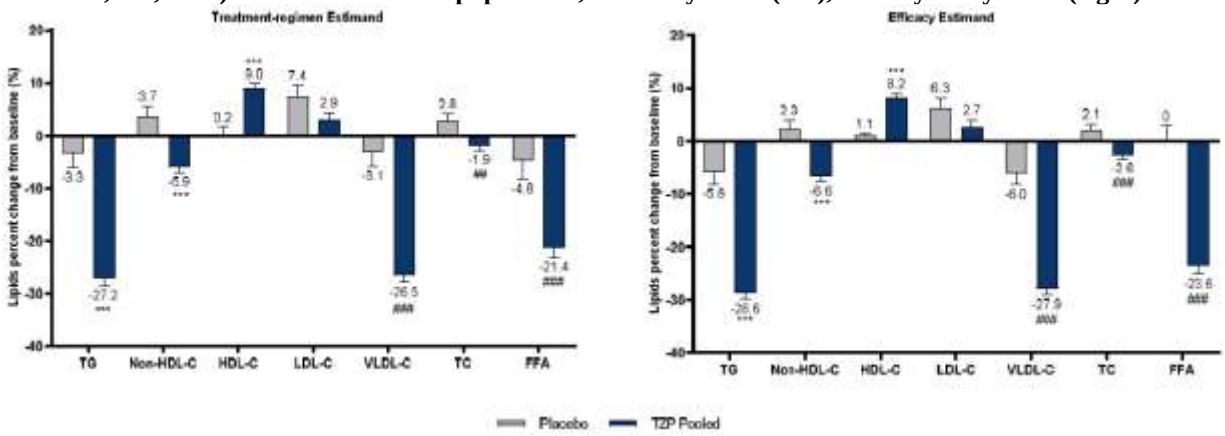
Fasting serum glucose (FSG)

Tirzepatide 10 and 15 mg each achieved superiority for mean change (reduction) in FSG at 72 weeks compared with placebo, using the treatment-regimen and efficacy estimands. This analysis was a key secondary endpoint controlled for type 1 error. Mean change of fasting glucose as measured in 7-point self-monitored blood glucose was an additional secondary endpoint not controlled for type 1 error. Tirzepatide 10 and 15 mg each had significant reduction compared with placebo.

Mean Change from Baseline in Lipid Parameters at Week 72

Figure 29 presents mean changes (for pooled tirzepatide) from baseline at 72 weeks for lipid parameters (triglycerides, non-HDL-C, HDL-C, LDL-C, VLDL-C, total cholesterol, and FFA) in conventional units. Analyses of LDL-C, VLDL-C, total cholesterol, and FFA is part of additional secondary objectives, but have been presented along with results for triglycerides, non-HDL-C, and HDL-C. Using both the treatment-regimen and efficacy estimands, pooled tirzepatide 10 and 15 mg achieved superiority compared with placebo for mean percent reduction in triglycerides, reduction in non-HDL-C, and increase in HDL-C.

Figure 29. Mean change from baseline in lipid parameters (triglycerides, non-HDL-C, HDL-C, LDL-C, VLDL-C, TC, FFA) at 72 weeks: mITT population, full analysis set (left), efficacy analysis set (right).



Abbreviations: ANCOVA = analysis of covariance; FFA = free fatty acid; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; mITT = modified intent-to-treat; MMRM = mixed model for repeated measures; TC = total cholesterol; TZP = tirzepatide; VLDL-C = very low-density lipoprotein cholesterol.
Note 1: MMRM analysis for the efficacy estimand; ANCOVA analysis for the treatment-regimen estimand.
Note 2: Data presented are the estimated means ± standard errors.
Note 3: Log transformations were applied to raw data for lipid parameters.
***p-Value <.001 versus placebo for superiority. ##p-Value <.01, ###p-value <.001 versus placebo for superiority.

Mean change in SBP from baseline to Week 72

Using both the treatment-regimen and efficacy estimands, pooled doses of tirzepatide 10 and 15 mg achieved superiority compared with placebo in mean reduction in SBP at 72 weeks (-5.16 [-7.23, -3.08] mmHg compared to placebo).

Using the efficacy estimand, pooled doses of tirzepatide 10 and 15 mg were also statistically significant compared with placebo for mean decrease in DBP at 72 weeks (-2.38 [-3.46, -1.3] mmHg compared to placebo; assessed as an *additional* secondary endpoint).

In consistence with the results of the primary analysis as well as the findings of SURMOUNT-1 most key secondary endpoints in SURMOUNT-2 were in favour of tirzepatide.

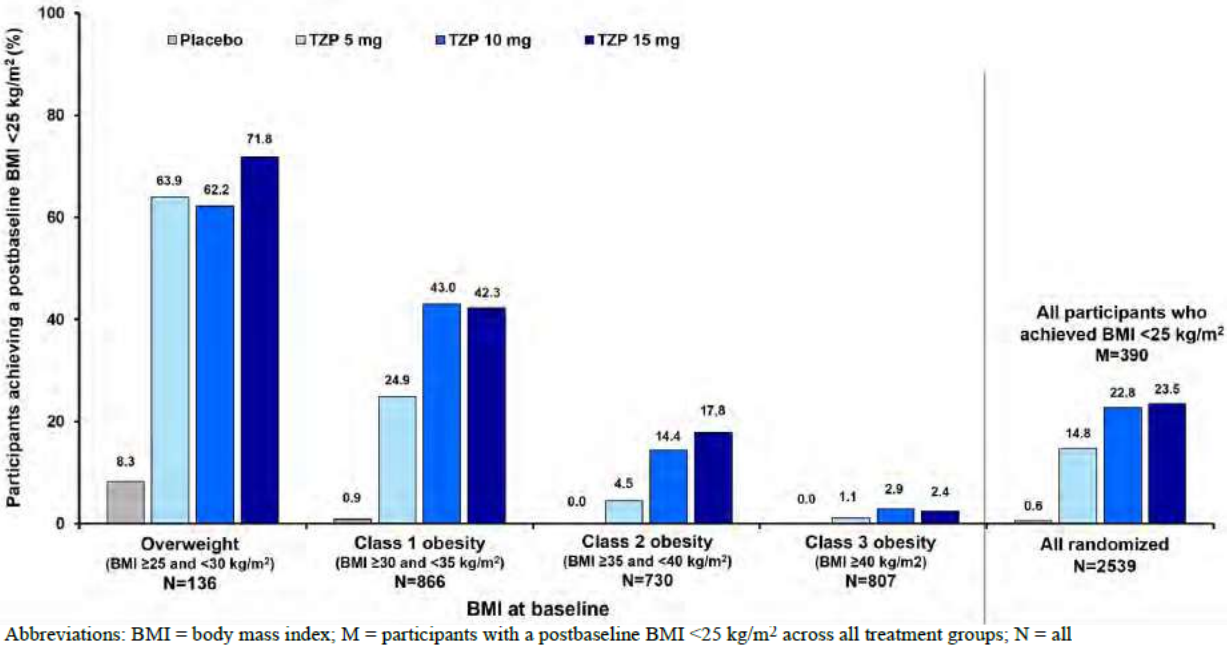
Again significantly more tirzepatide treated participants achieved considerable reductions in body weight of 10%, 15% or 20% or more, and a up to 15-17% of those who received the highest dose had a ≥25% body weight reduction. Overall, however, the effect appears less pronounced than SURMOUNT-1.

Significant differences compared to placebo were also seen with tirzepatide in waist circumference diabetic parameters (as rather expected in this T2DM population), lipids and blood pressure. It is noted that in contrast to the non-diabetic patients of SURMOUNT-1, a neutral (if not slightly negative effect) was seen in LDL-C. The importance of this finding is uncertain as a positive effect on LDL-C was seen in previous tirzepatide studies.

Other secondary and exploratory efficacy endpoints
SURMOUNT-1
A number of additional secondary and exploratory endpoints were examined, including further analyses of the effect of therapy on weight, BMI, lipids and diastolic blood pressure (see above), HbA1c and fasting glucose, and PROs. The results were generally consistent with the primary and key secondary analyses showing significant positive effects in favour or tirzepatide compared to placebo. Of interest are the results showing shifts in BMI class and glycaemic parameters, these are briefly shown below.

BMI class
In terms of shifts in BMI class, a significant greater number of patients in the active groups achieved a postbaseline BMI <25 kg/m2, as shown below.

Figure 30. Percentage of participants achieving a postbaseline BMI <25 kg/m2: mITT population, efficacy analysis set.



Abbreviations: BMI = body mass index; M = participants with a postbaseline BMI <25 kg/m² across all treatment groups; N = all randomized participants in the specified category; TZP = tirzepatide.
Source: Table GPHK.5.22

Diabetes status

More patients in the active groups showed favourable shifts in glycaemic category during the study:

Prediabetes at baseline to normoglycemia at Week 72

Of 1032 participants with prediabetes at baseline, 893 reverted to normoglycemia at Week 72:

- placebo: 167 (61.9% of 270) participants, and
- pooled tirzepatide 5, 10, and 15 mg: 726 (95.3% of 762) participants.

Prediabetes at baseline to suspected T2DM at Week 72

Of 1032 participants with prediabetes at baseline, 5 converted to suspected T2DM at Week 72:

- placebo: 4 (1.5% of 270) participants, and
- pooled tirzepatide 5, 10, and 15 mg: 1 (0.1% of 762) participant.

Normoglycemia at baseline to prediabetes at Week 72

Of 1507 participants with normoglycemia at baseline, 32 converted to prediabetes at Week 72:

- placebo: 25 (6.7% of 373) participants, and
- pooled tirzepatide 5, 10, and 15 mg: 7 (0.6% of 1134) participants.

There were also statistically significant reductions in HbA1c (up to 0.4%) and FSG (up to 0.6 mmol/l) from baseline to week 72) compared to placebo.

Two-hour oral-glucose tolerance tests (OGTT) were carried out at Visit 2 (Week -1) and Visit 21 (Week 72). During the test study sites collected samples of plasma glucose, C-peptide, and plasma insulin at 0, 30, 60, 90, and 120 minutes. Compared with placebo, all 3 tirzepatide groups had significant reductions in plasma glucose, C-peptide, and plasma insulin AUC at Week 72.

Baseline and postbaseline glycaemic response categories were analysed to determine the percentage of participants with shifts in glycaemic classification. Table 24 shows the categorical shifts in glycaemic responses during OGTT.

Table 24. Shift Table Summary of Glycaemic Response Categories in OGTT from Baseline to 72 Weeks, mITT Population – Efficacy Analysis Set

Variable Analysed: Glycemic Response Categories During OGTT

		Post-baseline result			
Treatment	Baseline result	Normal	Moderate Impairment	Severe Abnormality	Missing
Placebo (N=643)	Normal	88 (13.7)	37 (5.8)	22 (3.4)	89 (13.8)
	Moderate Impairment	41 (6.4)	35 (5.4)	25 (3.9)	74 (11.5)
	Severe Abnormality	30 (4.7)	43 (6.7)	77 (12.0)	78 (12.1)
	Missing	2 (0.3)	1 (0.2)	1 (0.2)	0
TZP 5mg (N=630)	Normal	156 (24.8)	5 (0.8)	5 (0.8)	72 (11.4)
	Moderate Impairment	84 (13.3)	14 (2.2)	11 (1.7)	39 (6.2)
	Severe Abnormality	102 (16.2)	50 (7.9)	25 (4.0)	62 (9.8)
	Missing	2 (0.3)	1 (0.2)	0	2 (0.3)
TZP 10mg (N=636)	Normal	145 (22.8)	12 (1.9)	1 (0.2)	85 (13.4)
	Moderate Impairment	115 (18.1)	14 (2.2)	8 (1.3)	39 (6.1)
	Severe Abnormality	121 (19.0)	22 (3.5)	13 (2.0)	56 (8.8)
	Missing	2 (0.3)	0	1 (0.2)	2 (0.3)
TZP 15mg (N=630)	Normal	135 (21.4)	8 (1.3)	5 (0.8)	76 (12.1)
	Moderate Impairment	99 (15.7)	11 (1.7)	6 (1.0)	43 (6.8)
	Severe Abnormality	140 (22.2)	29 (4.6)	9 (1.4)	63 (10.0)
	Missing	3 (0.5)	0	0	3 (0.5)

Abbreviations: BF = before; LOCF = last observation carried forward; N = number of participants in the population in the specified treatment group; n = number of participants in the specified category; OGTT = oral glucose tolerance test; TRT = treatment; TZP = tirzepatide.

Note: The post-baseline result is based on LOCF (Week 72 BF OFF TRT).

Consistent results in favour of tirzepatide were again recorded across most additional secondary and exploratory endpoints.

Among the findings of SURMOUNT 1, it is of note that a considerable percentage of participants, even from higher BMI classes, achieved a normal postbaseline BMI (<25 kg/m2). A significant effect was also seen in glycaemic parameters; almost 95% of the tirzepatide treated participants initially diagnosed with prediabetes reverted to normoglycemia by the end of the trial, compared to 61.9% of those who received placebo. At the same time very few patients progressed to (pre-) diabetes.

SURMOUNT-2
A number of additional secondary and exploratory endpoints were also examined in SURMOUNT-2 mostly showing positive effects in favour of the active. Among those it is worth mentioning the results of PROs.

Tirzepatide 10 and 15 mg achieved significantly greater improvement on the change from baseline (increase) in mean SF-36v2 acute form Physical Functioning domain score compared with placebo at 72 weeks, using the efficacy estimand. This analysis was not controlled for type 1 error. The placebo-adjusted value for mean change from baseline in SF-36v2 acute form Physical Functioning domain was 4.2 and 3.8 for the tirzepatide 10- and 15-mg treatment groups, respectively, using the efficacy estimand.

A meaningful within-patient change threshold was also evaluated quantitatively for the SF-36v2 acute form Physical Functioning domain (norm-based score), using anchor-based and distribution-based approaches. The meaningful within-patient change threshold for improvement was 5.76 for the Physical Functioning domain norm-based score (with an associated range from 3.84 to 7.72). When applied to individual patient change scores from baseline to Week 72, 34.2% and 35.6% of participants receiving tirzepatide 10 and 15 mg, respectively, achieved clinically meaningful improvements in physical functioning as assessed by the SF-36v2 Physical Functioning domain (that is, change from baseline ≥5.76) compared with 24.1% in the placebo group.

In addition to the Physical Functioning domain, at Week 72 (LOCF), both tirzepatide groups showed significant improvements compared with placebo for the General Health domain and the Physical Component Summary scores. The tirzepatide 15-mg group also showed significant improvement compared with placebo for the Bodily Pain, Vitality, and Social Functioning domains scores.

For IWQOL-Lite-CT, at Week 72 (LOCF), tirzepatide 10- and 15-mg groups each showed significantly greater improvements compared with placebo in IWQOL-Lite-CT Physical Function composite, Physical composite, Psychosocial composite, and total scores. Also EQ-5D-5L VAS scores for both tirzepatide groups and the placebo group significantly improved from baseline to 72 weeks (LOCF), indicating better overall health status. Compared with placebo, both tirzepatide groups had significantly improved EQ-5D-5L VAS scores. These analyses were not controlled for type 1 error.

- **Ancillary analyses**

Subgroup Analyses for Primary Study Period
Subgroup analyses were conducted to assess treatment interaction with important factors potentially affecting the change from baseline in body weight for the mITT population for the efficacy estimand.

Subgroup analyses included the participant characteristics of

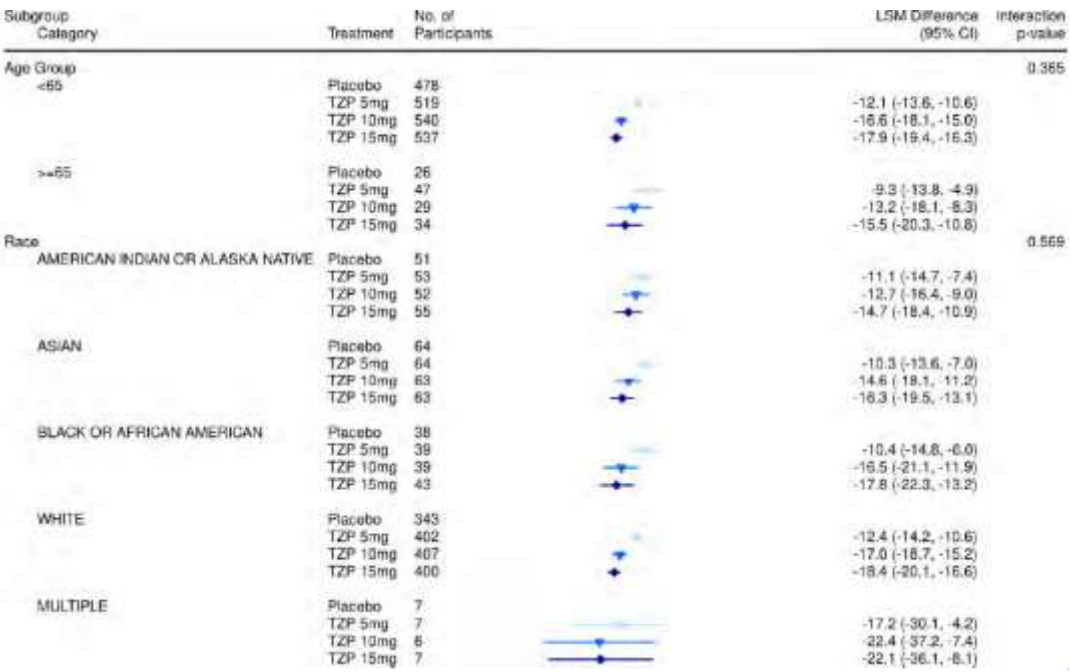
- age group (<65, ≥65 years)
- race
- sex
- ethnicity
- region of enrollment (US, outside the US)
- baseline BMI group (<30, ≥30 and <35, ≥35 and <40, ≥40 kg/m2), and
- glycaemic status at randomisation (normoglycemia versus prediabetes; applicable to SURMOUNT-1 only)
- baseline HbA1c category (≤8.5%, >8.5%; applicable to SURMOUNT-2 only), and
- type of AHM used at randomisation (weight loss, weight gain, or weight neutral; applicable to SURMOUNT-2 only).

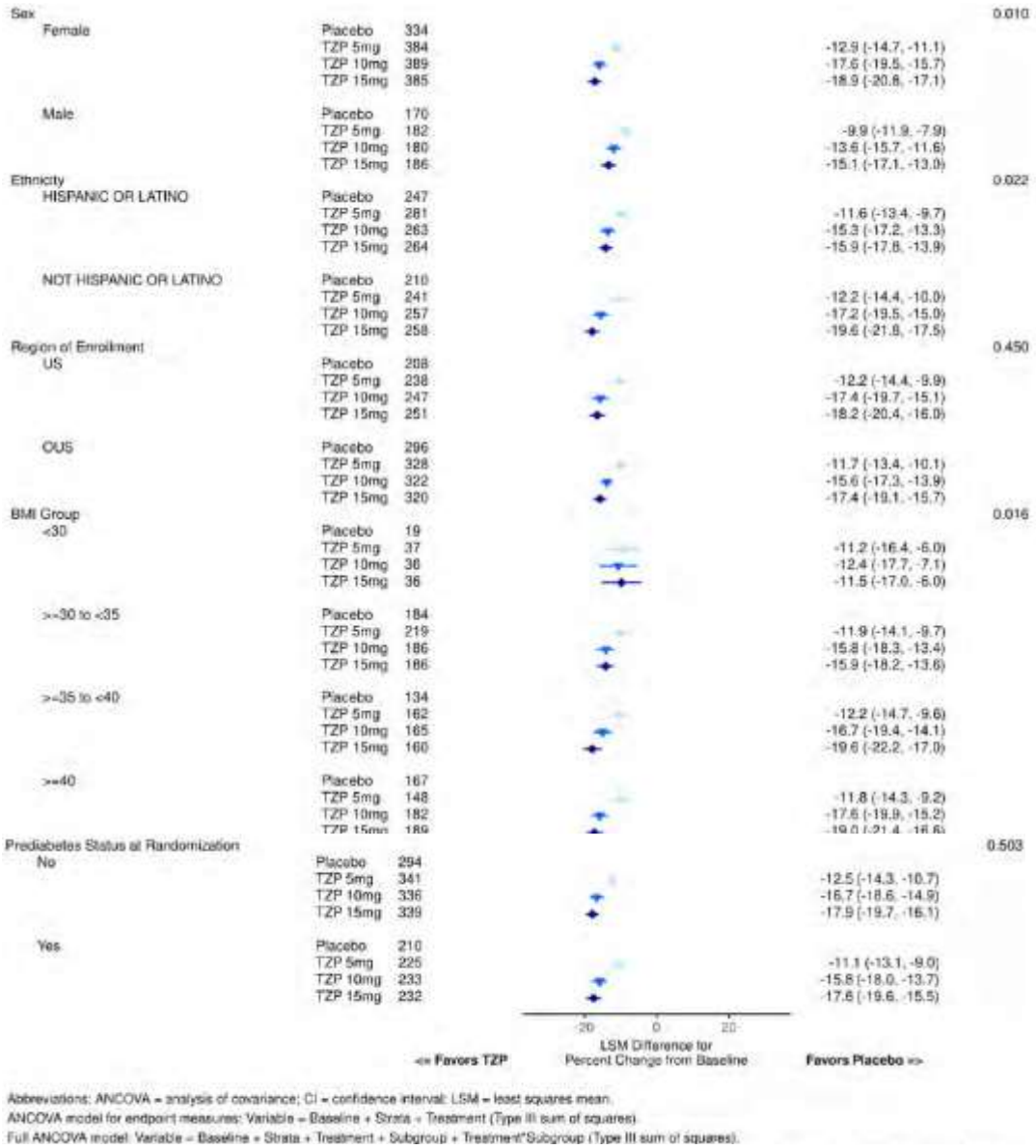
SURMOUNT-1

Percent Change in Body Weight

For the treatment-regimen estimand, all subgroups showed significantly better weight reduction in the tirzepatide groups compared with the placebo group. The treatment-by-subgroup interactions were statistically significant for sex, ethnicity, and BMI group. Similarly, for the efficacy estimand all subgroups showed significantly better weight reduction in the tirzepatide groups compared with the placebo group. The treatment-by-subgroup interactions were statistically significant for, race, sex, ethnicity, region of enrolment, and BMI group. Figure 31 below shows the subgroup analyses results for the treatment-regimen estimand.

Figure 31. Summary and analysis of percent change in body weight (%) by subgroup: mITT population, full analysis set.





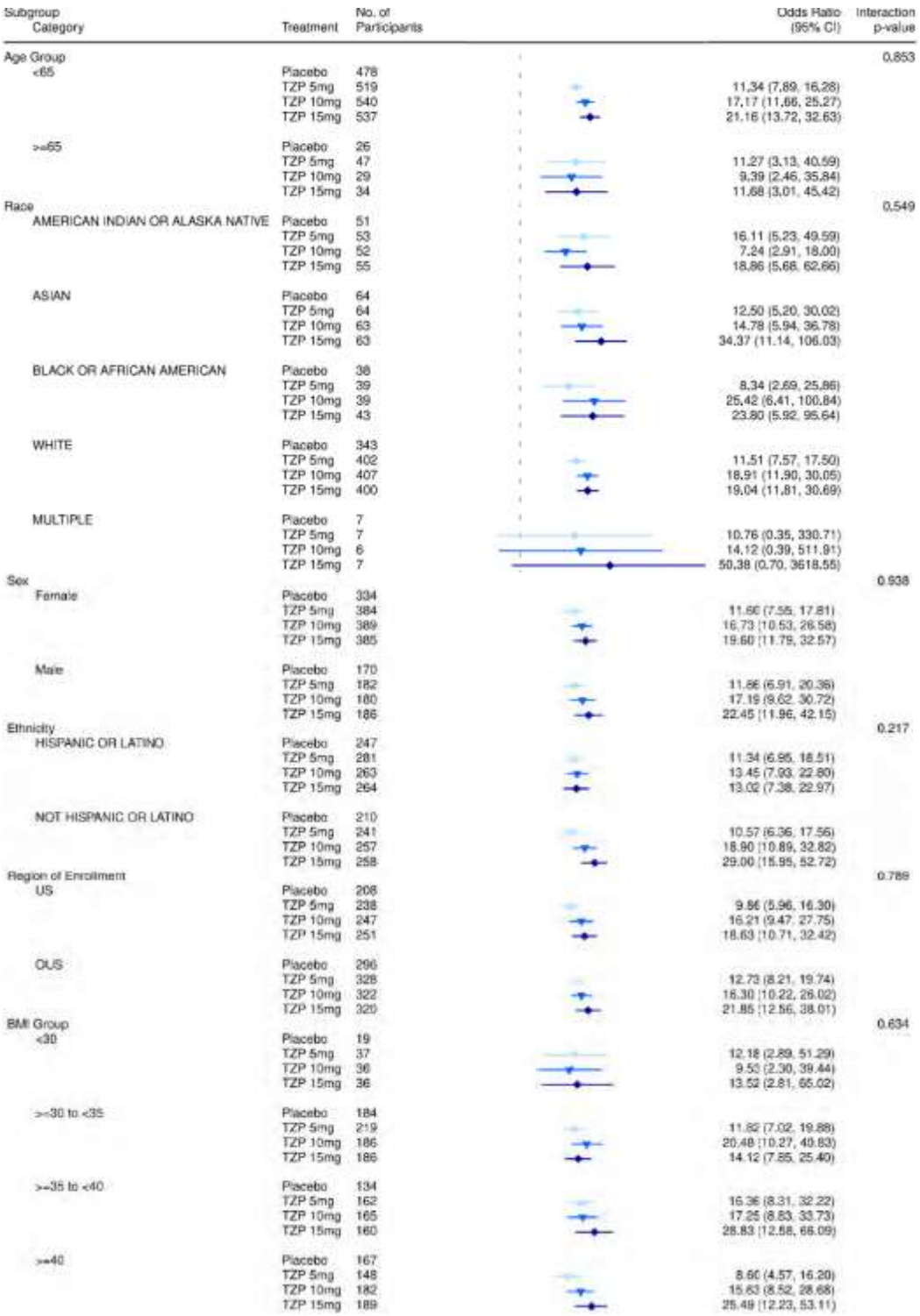
Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; LSM = least squares mean.
ANCOVA model for endpoint measures: Variable = Baseline + Strata + Treatment (Type III sum of squares).
Full ANCOVA model: Variable = Baseline + Strata + Treatment + Subgroup + Treatment*Subgroup (Type III sum of squares).

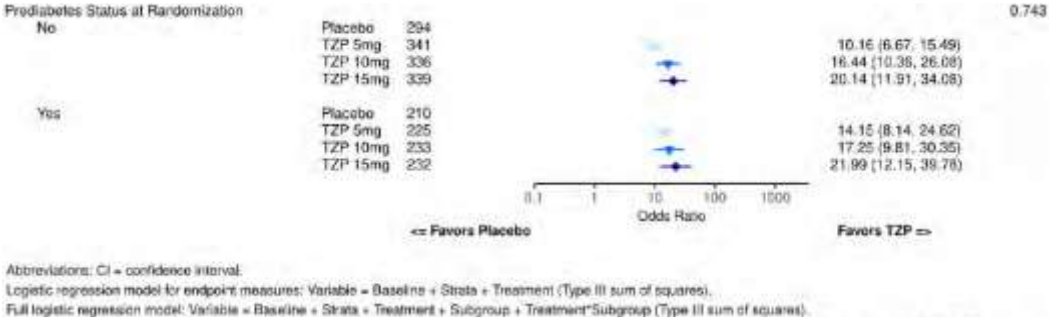
Percentage of Participants Achieving ≥5% Body Weight Reduction

For the treatment-regimen estimand, all subgroups showed significantly better weight reduction in the tirzepatide groups compared with the placebo group, except when Race = "Multiple" but the small sample size in this subcategory limited the interpretation. There were no statistically significant treatment-by-subgroup interactions for any of the subgroups.

Similarly, for the efficacy estimand all subgroups showed significantly better weight reduction in the tirzepatide groups compared with the placebo group, except when Race = "Multiple", but the small sample size in this subcategory limited the interpretation. The treatment-by-subgroup interactions were statistically significant for ethnicity and BMI group; however, the finding does not seem to be clinically relevant. It may be driven by the relative, similar efficacy of the tirzepatide 5-mg dose compared with tirzepatide 10- and 15-mg doses being different within subgroups. Figure 32 below shows the subgroup analyses results for the treatment-regimen estimand.

Figure 32. Summary and analysis of percentage of participants Achieving ≥5% Body Weight Reduction by subgroup: mITT population, full analysis set.





Abbreviations: CI = confidence interval.
Logistic regression model for endpoint measures: Variable = Baseline + Strata + Treatment (Type III sum of squares).
Full logistic regression model: Variable = Baseline + Strata + Treatment + Subgroup + Treatment*Subgroup (Type III sum of squares).

Overall, there were consistent results in co-primary endpoints in favour of tirzepatide across most subgroups. It should be noted though that tests for interaction lack power and the results should be interpreted with caution.

There was a statistically significant interaction between treatment and sex for the % change in body weight reduction with the effect of treatment being greater in females than males. It is argued that this may be due to the greater weight reduction observed for female participants and the relatively smaller mean weight at baseline in the placebo group and tirzepatide 5-mg treatment groups for male participants. Nevertheless, in both female and male subgroups there were significantly greater weight reductions with tirzepatide compared with placebo. No significant interaction with sex was seen in the co-primary analysis for % achieving ≥5% weight reduction.

A statistically significant interaction was also found also between treatment and BMI Group for the % change in body weight reduction at 72 weeks; the effect of treatment was greater in higher baseline BMI groups. It is argued that this interaction may be caused by the similar weight reduction observed for all 3 tirzepatide treatment groups in the subset of BMI <30 kg/m2, and the larger but similar weight reduction observed in the tirzepatide 10- and 15-mg treatment groups from the subset of BMI ≥30 kg/m2 to <35 kg/m2. Still all BMI subgroups showed significantly better weight reduction with tirzepatide compared with placebo.

In the subgroup of overweight patients (BMI <30 kg/m2), all three doses had very similar effects on both primary endpoints. Although it appears that most overweight patients would be able to achieve a considerable and clinically relevant weight loss on the lower 5 mg dose, others may require a higher dose to reach their weight reduction targets. In such cases it would be important to have the flexibility of different doses to meet the patient needs. Up titration to higher doses should be based on the individual response and targets and this is reflected in the SmPC.

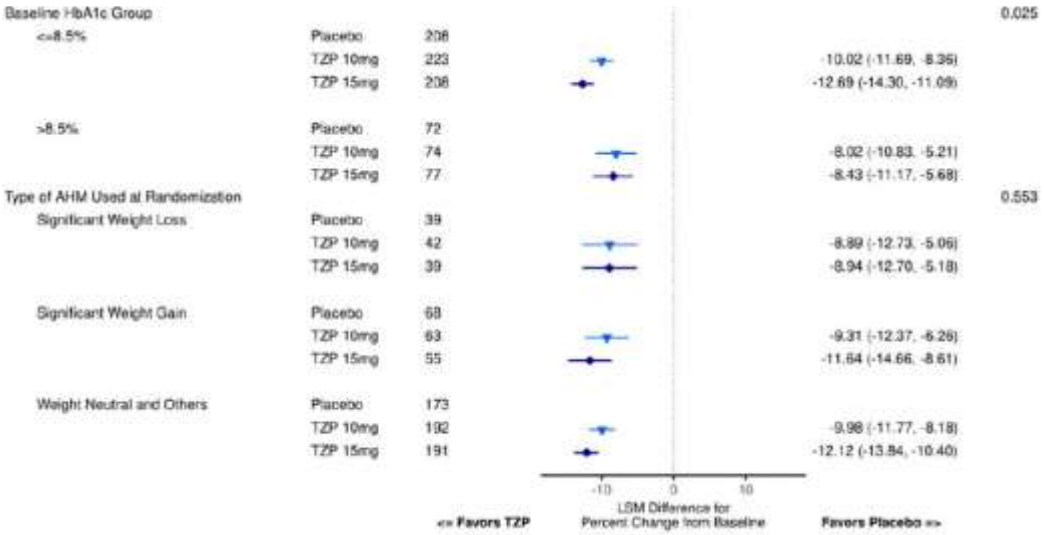
SURMOUNT-2

Percent Change in Body Weight

For the treatment-regimen estimand, all subgroups showed a significantly greater percentage of weight reduction in the tirzepatide groups than in the placebo group, except when Race was “Multiple” but the small sample size in this subcategory limited the interpretation. The treatment-by-subgroup interactions were statistically significant for baseline HbA1c group. Figure 33 below shows the subgroup analyses results for the treatment-regimen estimand.

Figure 33. Plot of estimated mean for percent change in body weight (%) by subgroup: mITT population, full analysis set.

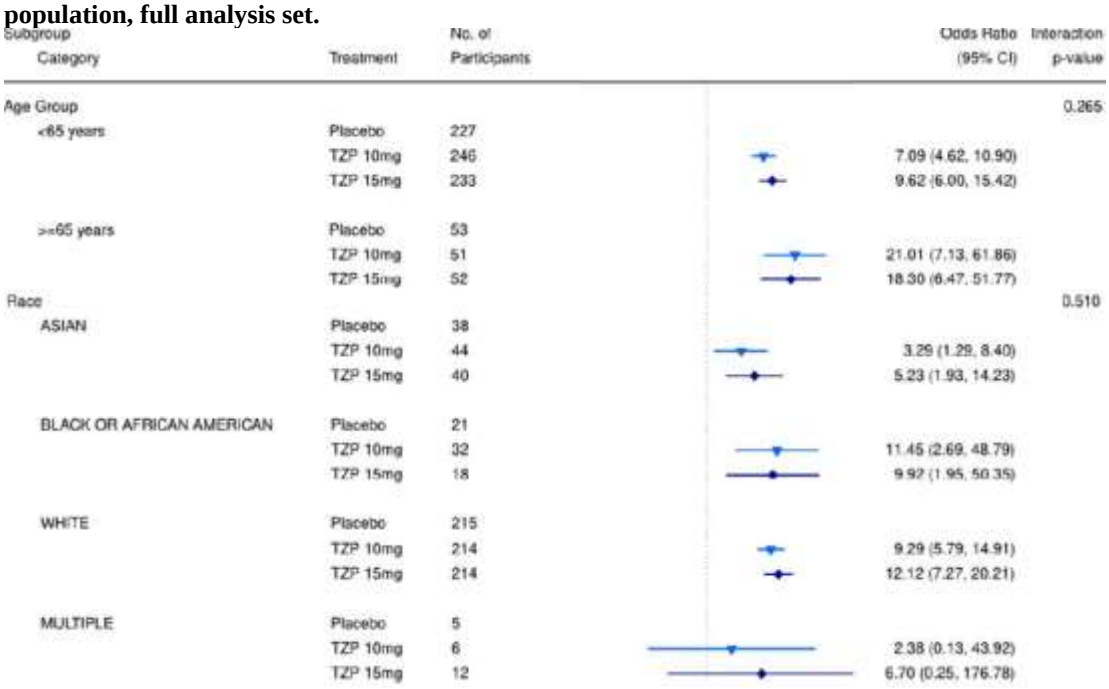
Subgroup Category	Treatment	No. of Participants	LSM Difference (95% CI)	Interaction p-value
Age Group				0.375
<65 years	Placebo	227		
	TZP 10mg	246	-9.44 (-11.06, -7.82)	
	TZP 15mg	233	-11.49 (-13.07, -9.91)	
>=65 years	Placebo	53		
	TZP 10mg	51	-10.53 (-13.74, -7.32)	
	TZP 15mg	52	-12.49 (-15.56, -9.41)	
Race				0.409
ASIAN	Placebo	38		
	TZP 10mg	44	-6.50 (-9.70, -3.30)	
	TZP 15mg	40	-8.28 (-11.55, -5.01)	
BLACK OR AFRICAN AMERICAN	Placebo	21		
	TZP 10mg	32	-9.48 (-14.63, -4.34)	
	TZP 15mg	18	-12.79 (-18.45, -7.12)	
WHITE	Placebo	215		
	TZP 10mg	214	-10.14 (-11.88, -8.39)	
	TZP 15mg	214	-11.90 (-13.55, -10.26)	
MULTIPLE	Placebo	5		
	TZP 10mg	6	-5.23 (NA, NA)	
	TZP 15mg	12	-18.30 (NA, NA)	
Sex				0.104
Female	Placebo	141		
	TZP 10mg	148	-10.77 (-12.94, -8.59)	
	TZP 15mg	144	-12.89 (-14.99, -10.80)	
Male	Placebo	139		
	TZP 10mg	149	-8.40 (-10.24, -6.55)	
	TZP 15mg	141	-10.09 (-11.92, -8.26)	
Ethnicity				0.212
HISPANIC OR LATINO	Placebo	163		
	TZP 10mg	175	-10.62 (-12.50, -8.75)	
	TZP 15mg	170	-11.70 (-13.55, -9.86)	
NOT HISPANIC OR LATINO	Placebo	112		
	TZP 10mg	119	-8.12 (-10.33, -5.92)	
	TZP 15mg	105	-11.04 (-13.24, -8.84)	
Region of Enrollment				0.222
US	Placebo	93		
	TZP 10mg	106	-9.16 (-11.68, -6.64)	
	TZP 15mg	97	-11.91 (-14.36, -9.45)	
OUS	Placebo	187		
	TZP 10mg	191	-9.86 (-11.58, -8.14)	
	TZP 15mg	188	-11.38 (-13.06, -9.69)	
BMI Group				0.283
<30	Placebo	47		
	TZP 10mg	55	-7.24 (-10.75, -3.74)	
	TZP 15mg	44	-9.94 (-13.50, -6.37)	
>=30 to <35	Placebo	97		
	TZP 10mg	88	-9.68 (-12.22, -7.13)	
	TZP 15mg	105	-10.88 (-13.23, -8.53)	
>=35 to <40	Placebo	62		
	TZP 10mg	91	-9.31 (-12.25, -6.37)	
	TZP 15mg	79	-13.18 (-16.16, -10.20)	
>=40	Placebo	74		
	TZP 10mg	63	-12.13 (-14.94, -9.32)	
	TZP 15mg	57	-12.45 (-15.23, -9.68)	

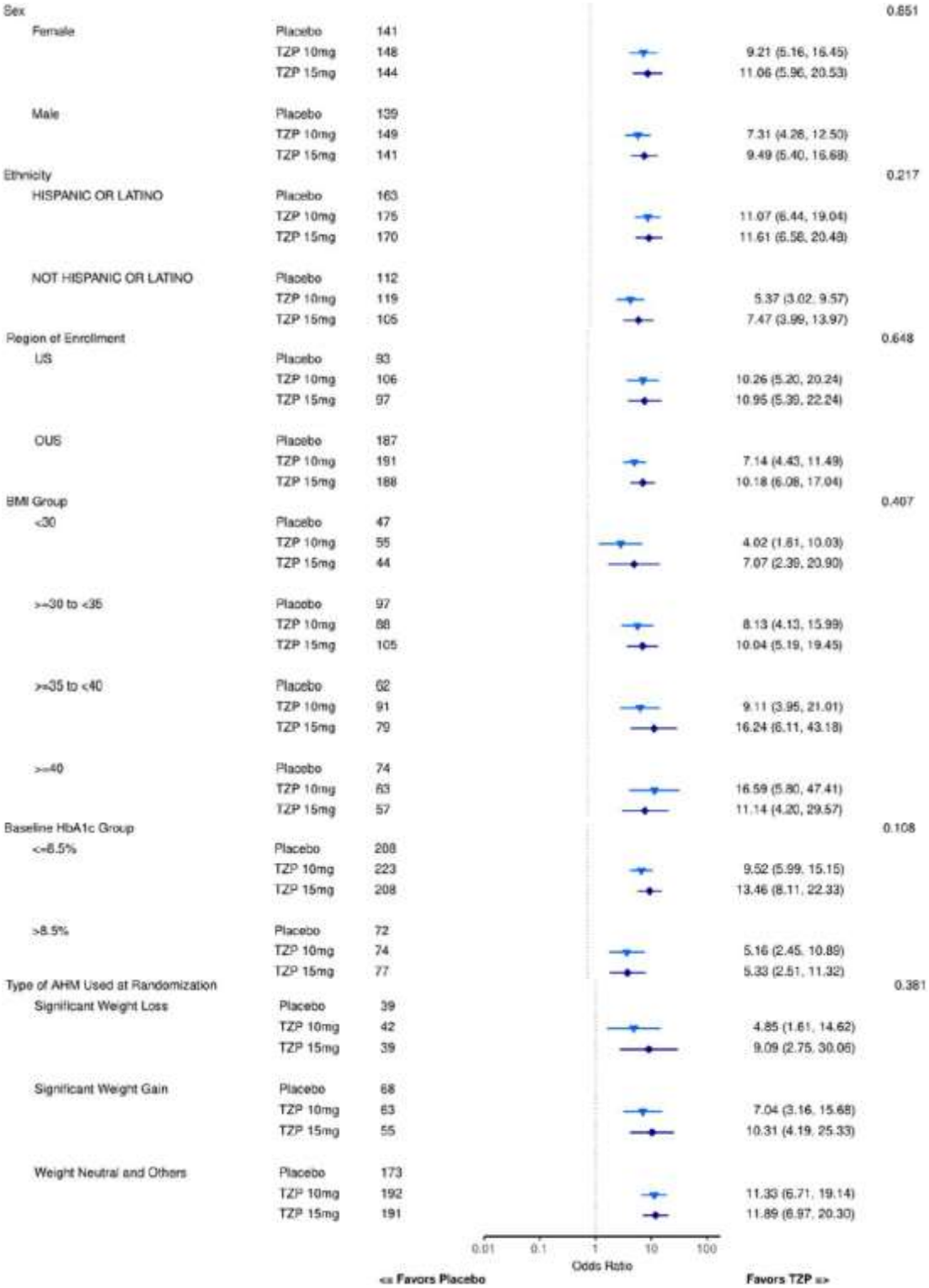


Percentage of Participants Achieving ≥5% Body Weight Reduction

For the treatment-regimen estimand, all subgroups showed a significantly greater percentage of participants achieving ≥5% body weight reduction in the tirzepatide groups than in the placebo group, except when race was "Multiple" but the small sample size in this subcategory limited the interpretation. There were no statistically significant treatment-by-subgroup interactions for any of the subgroups.

Figure 34. Plot of proportion of participants achieving ≥5% body weight reduction by subgroup: mITT population, full analysis set.





As in SURMOUNT-1, in SURMOUNT-2 there were generally consistent results in the co-primary endpoints in favour of tirzepatide across most subgroups. Although no significant interactions were detected in key subgroups some similar patterns were seen, for example, the effect of treatment being somewhat greater in females than males.

Summary of main efficacy results

Title: Efficacy and Safety of Tirzepatide Once Weekly in Participants without Type 2 Diabetes Who Have Obesity or Are Overweight with Weight- Related Comorbidities: A Randomised, Double-Blind, Placebo-Controlled Trial (SURMOUNT-1)					
Study identifier	I8F-MC-GPHK				
Design	Study I8F-MC-GPHK is a Phase 3, multicenter, randomised, placebo controlled, double-blinded study of the safety and efficacy of 5, 10, and 15 mg tirzepatide (TZP) once weekly compared with placebo for weight management when used in conjunction with a reduced-calorie diet and increased physical activity, in participants with obesity (BMI ≥30 kg/m2) or overweight (BMI ≥27 kg/m2) with weight-related comorbidities (excluding T2DM).				
	Duration of main phase: Duration of Run-in phase: Duration of follow-up: Duration of Extension phase:	72 weeks 3 weeks screening period 4 weeks 2 years treatment period for participants with prediabetes at randomisation			
Hypothesis	<u>Co-primary objectives</u> • To demonstrate superiority of once weekly TZP 10 mg and/or TZP 15 mg to placebo for percent change in body weight • To demonstrate superiority of once weekly TZP 10 mg and/or TZP 15 mg to placebo for the percentage of participants achieving at least 5% body weight reduction				
Treatments groups	TZP 5 mg	N = 630			
	TZP 10 mg	N = 636			
	TZP 15 mg	N = 630			
	Placebo	N = 643			
Endpoints and definitions	Co-Primary endpoints	• Mean percent change from baseline in body weight at 72 weeks • Percentage of participants achieving at least 5% body weight reduction at 72 weeks			
	Key Secondary endpoints	• Mean Change in Body Weight at Week 20 • Mean percent change in body weight with TZP 5mg at Week 72 • Percentage of study participants who achieve ≥5% body weight reduction with TZP 5mg at Week 72 • Percentage of participants who achieve, ≥10%, ≥15%, ≥20% body weight reduction at Week 72 • Mean change in waist circumference (cm) at Week 72 • Mean change in SF-36v2 acute form Physical Functioning domain score at Week 72 • Mean change from randomisation in triglycerides (mg/dL), non-HDL cholesterol (mg/dL) HDL cholesterol (mg/dL) at Week 72 • Mean change in SBP (mmHg) at Week 72 • Mean change in fasting insulin (pmol/L) at Week 72			
Database lock	10 June 2022				
<u>Results</u>					
Analysis description	Primary Analysis				
Analysis population and time point description	The results for the **Treatment-regimen estimand** are presented here: Full analysis set (all randomised patients; N=2539); 72 weeks				
Results	Treatment group	Placebo	TZP 5 mg	TZP 10 mg	TZP 15 mg
	Number of subject	643	630	636	630
	Percent change from baseline at 72 weeks (%)	-3.1†††	-15.0†††	-19.5†††	-20.9†††

	Percent change difference from placebo at 72 weeks (%)	N/A	-11.9 ***	-16.4 ***	-17.8 ***
	95% CI	N/A	(-13.4,-10.4)	(-17.9,-14.8)	(-19.3,-16.3)
	p-value	††† <0.001 versus baseline *** <0.001 versus placebo for superiority			
	Percentage of Participants with ≥5% Body Weight Reduction (%)	34.5	85.06	88.94	90.87
	Odds ratio (95% CI)	N/A	11.47 *** (8.03, 16.38)	16.72 *** (11.51,24.28)	20.63 *** (13.58,31.33)
	p-value	*** <0.001 versus placebo for superiority			
Analysis description	Secondary analysis [See tables and results above]				

Title: Efficacy and Safety of Tirzepatide Once Weekly in Participants with Type 2 Diabetes Who Have Obesity or Are Overweight: A Randomised, Double-Blind, Placebo-Controlled Trial (SURMOUNT-2)		
Study identifier	I8F-MC-GPHL	
Design	Study I8F-MC-GPHL was a Phase 3, multicenter, randomised, parallel-arm, placebo-controlled, double-blinded, 72-week study that investigated the safety and efficacy of treatment with tirzepatide 10 and 15 mg QW SC compared with placebo QW, in conjunction with a reduced-calorie diet and increased physical activity, on weight management in participants with T2DM who have obesity (BMI ≥30 kg/m2) or are overweight (BMI ≥27 kg/m2).	
	Duration of main phase: Duration of Run-in phase: Duration of follow-up:	72 weeks 3 weeks screening period 4 weeks
Hypothesis	<u>Co-primary objectives</u> • To demonstrate superiority of once weekly TZP 10 mg and/or TZP 15 mg to placebo for percent change in body weight • To demonstrate superiority of once weekly TZP 10 mg and/or TZP 15 mg to placebo for the percentage of participants achieving at least 5% body weight reduction	
	TZP 10 mg	N = 312
	TZP 15 mg	N = 311
	Placebo	N = 315
Endpoints and definitions	Co-Primary endpoints	• Mean percent change from baseline in body weight at 72 weeks • Percentage of participants achieving at least 5% body weight reduction at 72 weeks
	Key Secondary endpoints	• Percentage of participants who achieve, ≥10%, ≥15%, ≥20% body weight reduction at Week 72 • Mean change in HbA1c (%) at Week 72 • Percentage of participants who achieve HbA1c <7%, ≤6.5%, and <5.7% at Week 72 • Mean change in fasting glucose (mg/dL) at Week 72 • Mean change in waist circumference (cm) at Week 72 • Mean change from randomisation in triglycerides (mg/dL), non-HDL cholesterol (mg/dL) HDL cholesterol (mg/dL) at Week 72 • Mean change in SBP (mmHg) at Week 72
Database lock	19 April 2023	
<u>Results</u>		

Analysis description	Primary Analysis			
Analysis population and time point description	The results for the **Treatment-regimen estimand** are presented here: Full analysis set (all randomised patients; N= 938); 72 weeks			
Results	Treatment group	Placebo	TZP 10 mg	TZP 15 mg
	Number of subject	315	312	630
	Percent change from baseline at 72 weeks (%)	-3.2†††	-12.8†††	-14.7†††
	Percent change difference from placebo at 72 weeks (%)	N/A	-9.6 ***	-11.6 ***
	95% CI	N/A	(-11.1,-8.1)	(-13.0,-10.1)
	p-value	††† <0.001 versus baseline *** <0.001 versus placebo for superiority		
	Percentage of Participants with ≥5% Body Weight Reduction (%)	32.5	79.2	82.8
	Odds ratio (95% CI)	N/A	8.30 *** (5.59, 12.32)	10.50*** (6.84, 16.11)
	p-value	*** <0.001 versus placebo for superiority		
Analysis description	Secondary analysis [See tables and results above]			

Clinical studies in special populations

In relation to the effect of tirzepatide in older patients it is noted that the SURMOUNT 1- &-2 studies included a relatively small number of patients ≥65 years and very few older than 75 years. The results in older patients ≥65 years suggest a generally consistent effect with their younger counterparts while in those ≥75 years the pooled findings from the SURMOUNT and SURPASS studies still indicate a significant effect on weight loss endpoints. Overall, the data do not raise concerns about diminished efficacy in older patients.

In patients with renal and hepatic impairment the information is limited as participants with severe disease were excluded. In the small number of patients with moderate renal impairment the results suggest similar efficacy to the overall study population, although the numbers are very small to draw firm conclusions. At present no dose adjustment is recommended for patients with renal or hepatic impairment; caution is however advised for patients with severe renal impairment and ESRD as well as those with hepatic impairment due to the limited experience in these groups.

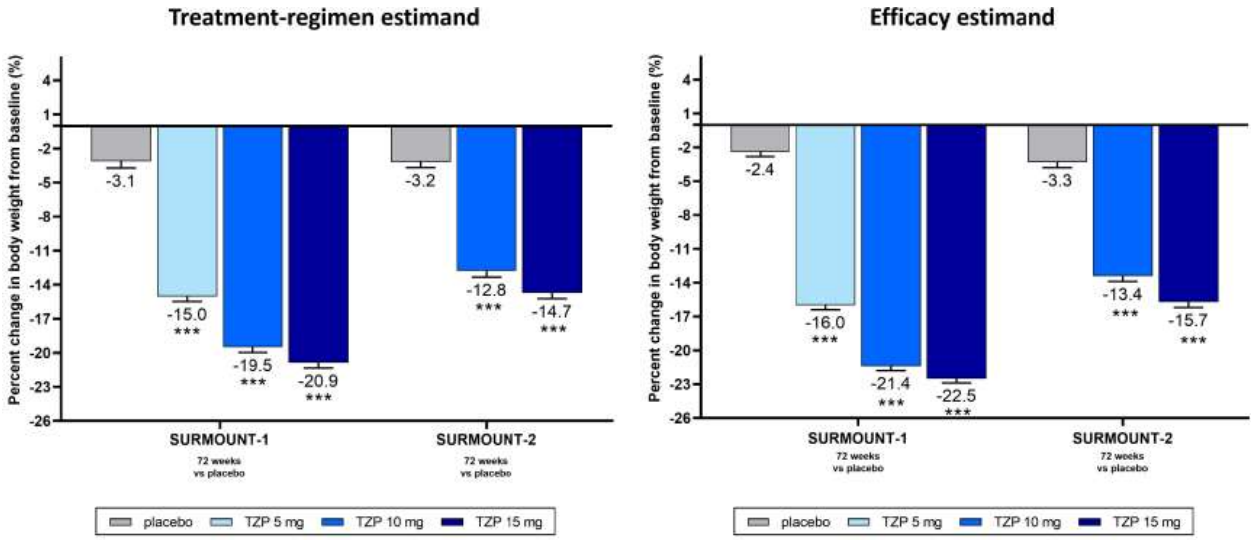
No efficacy data are currently available in other special groups such as pregnant women (use not recommended) and paediatric patients.

Analysis performed across trials (pooled analyses AND meta-analysis)

The Clinical Efficacy Summary includes a section summarising and comparing the SURMOUNT-1 results with those of SURMOUNT-2, which however, does not provide any additional information over the separate reports. Otherwise, no pooled or other similar analyses have been provided.

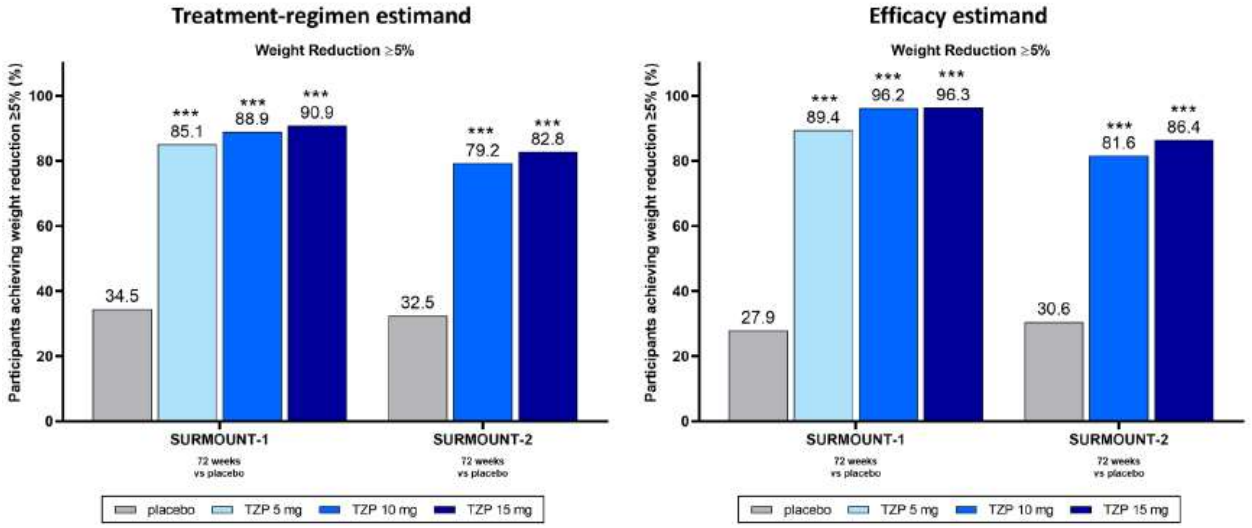
Nevertheless, it is helpful to include here some graphs showing together the co-primary endpoints in the two SURMOUNT trials.

Figure 35. Percent change from baseline in weight at primary endpoint in Phase 3 studies of obesity or overweight without T2DM (SURMOUNT-1) and with T2DM (SURMOUNT-2): mITT population, full analysis set (left panel), efficacy analysis set (right panel).



Abbreviations: CSR = clinical study report; mITT = modified intent-to-treat; T2DM = type 2 diabetes mellitus; TZP = tirzepatide;
vs = versus. Note: Shown are the least squares means ± standard errors.
***p-Value <.001 versus placebo, controlled for type 1 error.

Figure 36. Overview of participants achieving weight reduction of ≥5% in Phase 3 studies of obesity or overweight without T2DM (SURMOUNT-1) and with T2DM (SURMOUNT-2): mITT population, full analysis set (left), efficacy analysis set (right).



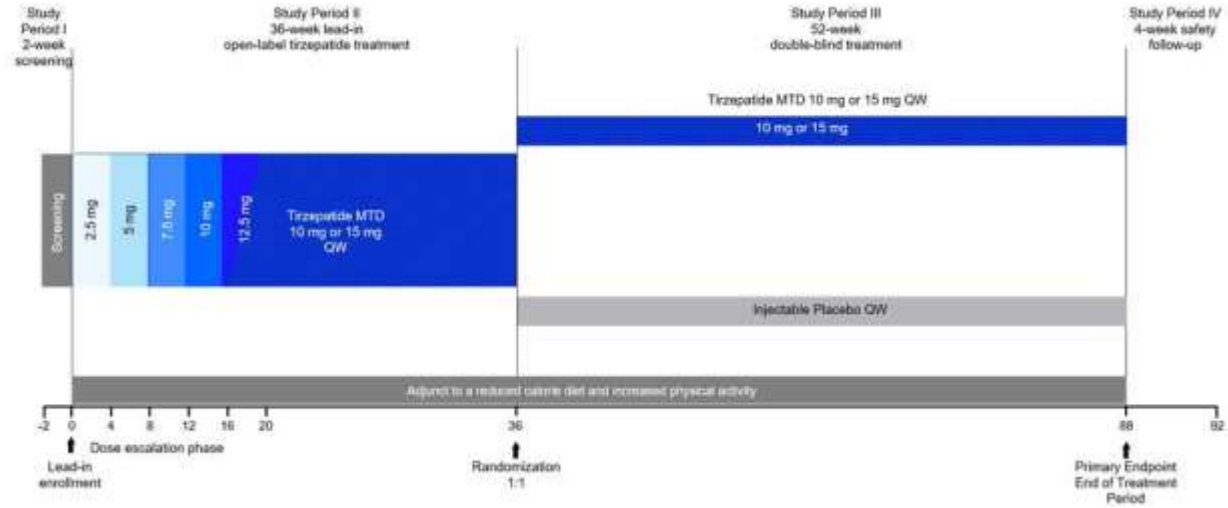
Abbreviations: CSR = clinical study report; mITT = modified intent-to-treat; T2DM = type 2 diabetes mellitus; TZP = tirzepatide;
vs = versus. Note: p-Value is from logistic regression analysis.
***p-Value <.001 versus placebo, controlled for type 1 error

Supportive studies

SURMOUNT-4

Some preliminary results from the ongoing Phase 3 SURMOUNT-4 have been provided. This is a multicentre, double-blind, placebo-controlled study that was designed to assess the efficacy and safety of once-weekly tirzepatide 10 or 15 mg compared with once-weekly placebo for maintenance of weight reduction in participants with obesity or overweight without T2DM. During an initial 36-week, open-label, tirzepatide lead-in treatment period, all participants received tirzepatide (10 or 15 mg MTD). At the end of the lead-in period, participants were randomly assigned to switch to either once-weekly placebo or to continue on the tirzepatide MTD.

Figure 37 Surmount 4 study design, including the dose-escalation scheme.



The *open-label tirzepatide lead-in period* and protocol-specified interim database lock at 36 weeks are complete and the findings are summarised below.

A total of 782 participants enrolled received at least 1 dose of tirzepatide in the 36-week open-label tirzepatide lead-in period of SURMOUNT-4 and were included in the enrolled population. The baseline demographic and clinical characteristics of participants in the 36-week open-label tirzepatide treatment period were similar with those in SURMOUNT-1
The weight reduction profile of tirzepatide during the open-label lead-in phase of SURMOUNT-4 is consistent with that observed in SURMOUNT-1; participants treated with tirzepatide reduced body weight from baseline by 20.9%. In addition, the percentages of participants achieving body weight reduction of ≥5% (98.2%), ≥10% (93.1%), ≥15% (78.7%), or ≥20% (57.0%) by the end of the 36-week tirzepatide lead-in period were substantial and clinically meaningful.

SURMOUNT-1 sub studies

In addition to the main study, there were 2 addenda to SURMOUNT-1:
- Dual-energy X-ray Absorptiometry (DXA) addendum
- Ambulatory Blood Pressure Monitoring addendum

The DXA addendum was conducted in a subset of study participants to evaluate changes in body composition associated with weight loss. The ABPM addendum was conducted in a subset of study participants to evaluate the impact of tirzepatide on BP and HR.

Dual-Energy X-ray Absorptiometry Addendum

The objective was to demonstrate that tirzepatide (5, 10, and 15 mg combined) QW is superior to placebo for total body fat mass. The primary endpoint was the percent change in total body fat mass from baseline.

Participants who were eligible for the main study had the option to participate in the DXA addendum. Study sites performed a baseline DXA scan between Visits 2 and 3 (Weeks -1 and 0) for participants who gave consent and met all eligibility requirements. At Visit 21 (Week 72) or early termination, study sites performed post-baseline DXA scans. 255 participants were included who received at least 1 dose of study drug. The baseline characteristics were consistent with the overall trial population. More participants randomised to tirzepatide completed the study than participants randomised to placebo. The most common reason for study discontinuation was withdrawal by subject.

Table 25 summarises the percent change in total body fat mass at Week 72. Pooled tirzepatide 5, 10, and 15 mg achieved greater mean percent change from baseline in total body fat mass compared with placebo.

Table 25. Percent Change from Baseline in Total Body Fat Mass at Week 72 mITT – Efficacy Analysis Set – DXA Addendum

Parameter	Placebo (N = 36)	TZP 5/10/15 mg (N = 124)
Baseline (kg)	49.4	46.6
Percent change from baseline at 72 weeks (%)	-8.2††	-33.9†††
Percent change difference from placebo at 72 weeks (%) (95% CI)	N/A	-25.7*** (-31.4, -20.0)

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; DXA = dual-energy X-ray absorptiometry; LOCF = last observation carried forward; mITT = modified intent-to-treat; N = number of participants with baseline and postbaseline values; N/A = not applicable; TZP = tirzepatide.

Note 1: ANCOVA, LOCF. Only the last nonmissing postbaseline observation on or prior to the last dose date + 14 days was carried forward.

Note 2: Least-squares means are shown.

††p-Value <0.01, †††p-Value <0.001 versus baseline.

***p-Value <0.001 versus placebo.

Pooled tirzepatide (5, 10, and 15 mg) also achieved (assessed as secondary endpoints, from baseline to Week 72) greater mean change in total body fat mass (mean -15.9 Kg vs -3.6 Kg with placebo), but also resulted in bigger mean percent (-10.9% with tirzepatide vs -2.6% with placebo) and actual (-5.6 kg with tirzepatide vs -1.2 kg with placebo) reduction in total lean mass. However, the total fat to lean mass loss ratio was greater in the pooled tirzepatide group compared with the placebo group.

The results of the DXA sub-study showed an average 33.9% total fat mass reduction in the tirzepatide group (compared with 8.2% in the placebo group) while lean mass loss was almost 3 times less (10.9% with tirzepatide vs 2.6% with placebo), suggesting that the observed weight loss with tirzepatide is most likely due to a reduction in fat tissue with a favourable shift in the balance of lean to fat mass. Taken together with the findings on waist circumference noted above, this indicates an overall beneficial effect on body composition.

Ambulatory Blood Pressure Monitoring Addendum

The objective was to assess the effect of tirzepatide (5, 10, and 15 mg) compared with placebo on 24-hour mean HR and 24-hour mean BP (SBP/DBP). The endpoints were:

- Mean change in 24-hour mean HR from baseline to 36 weeks
- Mean change in 24-hour mean BP from baseline to 36 weeks

This part is discussed under the Safety section below.

Overall conclusions on clinical efficacy

This variation application for the new CWM indication is primarily supported by the pivotal SURMOUNT-1 and SURMOUNT-2 trials. The first trial, conducted in non-diabetic patients, investigated the same tirzepatide doses as the ones approved for T2DM (5, 10 and 15 mg); the latter, conducted in T2DM patients, examined only the two highest doses (10 and 15 mg).

No specific dose finding studies were carried out for the CWM development program; instead, the dose selection was based on the initial T2DM studies, taking into consideration efficacy and safety/tolerability aspects, and PK/PD modelling. The CWM program comprises also non-diabetic patients with a more extreme weight/BMI range and different characteristics, which in turn means additional factors may impact dose-response; therefore, in the absence of dedicated dose response studies it is not possible to confirm that the tested dose range is the optimal one in the CWM setting. Nevertheless, it is acknowledged that different dose levels were examined in the pivotal trials, which permit evaluation of their respective efficacy and safety.

SURMOUNT-1 and -2 were both Phase 3, multicentre, randomised, double-blinded studies designed to examine superiority of once-weekly tirzepatide, as an adjunct to dietary/lifestyle measures and exercise, over placebo on weight loss in participants with obesity, or overweight with weight-related comorbidities, without or with T2DM respectively. Co-primary efficacy endpoints were mean percent change in body weight and percentage of participants with ≥5% body weight reduction at 72 weeks. The treatment duration of 72 weeks included up to 20 weeks of dose-escalation. In SURMOUNT-1 tirzepatide 5, 10, or 15 mg were tested, while in SURMOUNT-2 only the two highest doses.

In terms of the statistical aspects, SURMOUNT-1 and SURMOUNT-2 used similar design and methodology. Two different estimands were used to describe treatment effects of once weekly tirzepatide compared to placebo and the co-primary endpoints and key secondary endpoints. The treatment regimen estimands describe the treatment effects regardless of adherence to treatment (or use of rescue medication) and the efficacy estimands describe the treatment effects in patients who remained in the study (and without using rescue medication for hyperglycaemia). The analyses' methods are acceptable and aligned to the target estimands. The strategy used to control the type 1 error as a results of testing doses in parallel and key secondary endpoints is acceptable.

SURMOUNT-1, the largest of the two studies, randomised a total of 2539 participants, approximately equally distributed between the four groups. The majority of study subjects were female and middle age and had one or more co-morbidities. Most were younger than 65 years with very few participants over 75 yrs. SURMOUNT-2 randomised 938 T2DM patients, again approximately equally distributed across the treatment groups. In this trial men were better represented (49.3% *vs* 32.5% in SURMOUNT-1); patients were somewhat older (mean 54.2 years) than SURMOUNT-1 (44.9 years) and weighted slightly less (mean BMI 36.1 kg/m2 *vs* 38.0 kg/m2 in SURMOUNT-1). In both trials most subjects also had other comorbidities. Groups were generally well balanced in terms of demographics and disease characteristics. Completion rates were high; in SURMOUNT-1 almost 90% of the participants on tirzepatide completed the primary study period, and 84% to 86% of them

across the tirzepatide groups completed on study drug; these percentages were much higher than in the placebo group (77% and 73.6% respectively). Even higher completion rates were recorded in SURMOUNT-2.

Overall, the study populations appear comparable to non- and diabetic populations in previous similar studies in this field. In SURMOUNT-1 there were very few overweight patients (140; 5.5%) with BMI <30 kg/m2. In SURMOUNT-2 the relative percentage was higher but still there were only 163 patients with BMI <30 kg/m2. The Applicant provided a further analysis showing also results from 1221 overweight patients included in the previous SURPASS program in T2DM. Given that SURMOUNT and T2DM phase 3 programs share generally the same dosing regimen and that the majority of patients in the previously reviewed SURPASS trials would have met the relevant SURMOUNT weight-related inclusion criteria (with BMI ≥27 kg/m2 and the weight-related comorbidity of T2DM), the approach appears reasonable.

Overall, the data indicate consistent results in overweight patients. In most instances the weight loss appears less pronounced compared to obese patients, the data still indicate a significant and clinically relevant effect compared to placebo (and other comparators in SURPASS studies). In terms of safety no significant differences in various AEs across baseline BMI groups were noted. In conclusion there are no concerns about a considerably different benefit:risk in overweight patients compared to the obese population.

Both SURMOUNT-1 and -2 results provided clear evidence of a significant and clinically relevant effect of all examined tirzepatide doses on weight. In SURMOUNT-1 the primary analysis confirmed the superiority of tirzepatide showing that, compared to placebo, patients on active therapy had an average 11.9% to 17.8% body weight reduction across the three doses with more than 85% of participants achieving a weight loss of 5% or more (even with the lowest dose), a threshold that is considered clinically meaningful and expected to result in health benefits. Similar, although less pronounced, effects were seen in the primary analyses of SURMOUNT-2. In terms of timing, in both trials an early separation of curves was seen with significant differences compared to placebo recorded as early as 4 weeks with a persistent effect and further decreases in body weight until almost the end of the 72-week treatment period.

In both trials there were consistent results across most *key* secondary (as well as other secondary and exploratory) endpoints in favour of tirzepatide. More tirzepatide treated participants achieved considerable reductions in body weight of 10%, 15% or 20% or more and a substantial percentage (in SURMOUNT-1 almost up to 40% of those who received the highest dose; efficacy estimand) had a ≥25% body weight reduction. It is noteworthy that a large percentage of SURMOUNT-1 participants, even from higher BMI classes, achieved a normal post-baseline BMI (<25 kg/m2); up to around 40% of those with Class I obesity and up to around 17% of participants with Class II obesity. Of importance, tirzepatide treatment also showed improvements, with significant differences compared to placebo, in almost all assessed cardiovascular and metabolic parameters including systolic and diastolic blood pressure, lipids, fasting insulin as well as waist circumference. A significant effect was also seen in glycaemic parameters. Of note, in SURMOUNT-1 almost 95% of the tirzepatide treated participants initially diagnosed with prediabetes reverted to normoglycemia by the end of the trial, compared to 61.9% of those who received placebo. At the same time, only few patients progressed to (pre-) diabetes. The PRO results in both studies also demonstrated significant improvements in most measured parameters with tirzepatide.

The SURMOUNT-1 dual-energy X-ray absorptiometry (DXA) sub study in 255 participants showed a significant, on average 33.9% total fat mass, reduction in the tirzepatide group (compared with 8.2% in the placebo group) while lean mass loss was almost 3 times less, suggesting that the observed weight loss with tirzepatide is most likely due to a reduction in fat tissue with a favourable shift in the balance of lean to fat mass. Taken together with the waist circumference findings, this indicates an overall beneficial effect on body composition.

Overall, the efficacy results were consistent, clinically relevant, and clearly in favour of tirzepatide.

The subgroup analyses of the co-primary endpoints in both SURMOUNT studies were in general consistent with the main results, with efficacy confirmed across different subgroups and irrespective of age, sex, race, ethnicity, baseline BMI, baseline prediabetes status, and geographic region.

According to the regulatory guidance for this area, the predictive value of weight loss after short-term treatment with respect to long-term efficacy should be documented, in order to identify a population with expected long-term benefit and include potential "stopping rules" for non-responders in the product label. The proposed product information includes relevant advice (section 4.2 of the SmPC) that *if patients have been unable to lose at least 5% of their initial body weight 6 months after titrating to the highest tolerated dose, a decision is required on whether to continue treatment, taking into account the benefit/risk profile in the individual patient*.

It should be noted that efficacy data beyond 72 weeks are not available and in both SURMOUNT trials follow-up was very short. At present there is no information about the maintenance of the effect on weight and other parameters beyond that period or in patients who may stop therapy including any possible withdrawal effects. Ongoing studies may address this point in future but at this stage this is an important gap in the evidence.

Also there are no data on the potential long term impact on morbidity and mortality in adults with obesity. The Applicant indicated that they have initiated Phase 3 Study I8F-MC-GPIJ (SURMOUNT-MMO). SURMOUNT-MMO is a long term, double-blind, placebo-controlled event-driven study to investigate whether tirzepatide is superior to placebo in reducing obesity-related diseases and death in adults living with obesity and established CVD or CVD risk factors, excluding diabetes. The completion of SURMOUNT-MMO is expected in 2027. In addition, results from SURPASS-CVOT, in participants with T2DM, may provide further insight. Completion of SURPASS-CVOT is expected in 2024.

Overall, SURMOUNT-1 and -2 have provided convincing evidence on the efficacy of tirzepatide in CWM in both diabetic and non-diabetic patients, showing clinically relevant weight loss and beneficial effects on cardiovascular, metabolic and other parameters in the studied populations.

4. Clinical Safety

Introduction

The applicant provided two separate Safety Summaries. The first included an integrated safety summary and comprised pivotal data from the current CWM program (mainly SURMOUNT-1, as SURMOUNT-2 final report was not available) as well previous T2DM SURPASS studies.

The second and most recent Safety Summary includes only pooled data from SURMOUNT-1 and SURMOUNT-2. The Safety Section in this assessment report discusses all datasets considered as part of this submission. Although an effort has been made to consolidate the findings, some results submitted at different stages are presented and discussed separately. For the sake of clarity, the pooled SURMOUNT-1 and -2 dataset is presented here as "SURMOUNT Set". The initial safety summary examined different datasets, as discussed below and these are named accordingly.

The focus of the review is the new safety findings from the SURMOUNT -1 and -2 trials as these are the most relevant to the new proposed CWM indication.

SURMOUNT Set

As noted above, the most recently submitted safety summary includes pooled data for the two pivotal SURMOUNT-1 and -2 trials. An overview of the analysis set is shown below.

Table 26. Summary of SURMOUNT-1 + SURMOUNT-2 Analysis Set

Studies	SURMOUNT-1 SURMOUNT-2
Time Period	First dose of treatment to safety follow-up visit or date of study withdrawal
Description	Pooled data of SURMOUNT-1 and SURMOUNT-2
Treatment Groups	Placebo (N=958) TZP 5 mg (N=630); SURMOUNT-1 only TZP 10 mg (N=948) TZP 15 mg (N=941) TZP_ALL (N=2519) Total (N=3477)
Treatment Comparison	TZP 5, 10, 15 mg, TZP_ALL vs. placebo
Analyses	Full set of safety analyses[a]

Abbreviations: AESI = adverse event of special interest; DCAE = discontinuation due to adverse event; ECG = electrocardiogram; N = number of participants; SAE = serious adverse event; TEAE = treatment-emergent adverse event; TZP = tirzepatide; vs. = versus.

[a] Includes: exposure, demographics, medical history, concomitant medications, TEAEs, SAEs, DCAEs, special safety topics (including AESIs), labs, vital signs, ECGs.

The integrated safety summary comprised safety data from different studies from the current CWM as well the previous T2DM clinical development, as described below. The aim was to assess the safety profile of tirzepatide in participants with baseline BMI ≥27 kg/m2, so data from the following studies were integrated:

- Phase 3 Study I8F-MC-GPHK (SURMOUNT-1), in participants with obesity or overweight and without diabetes (primary study period; all enrolled participants)
- Phase 3 Study I8F-MC-GPHN (SURMOUNT-4), preliminary results from participants with obesity or overweight and without diabetes (open-label lead-in period; all enrolled participants)
- two Phase 2 and 7 Phase 3 SURPASS studies from the original T2DM application (only participants with BMI ≥27 kg/m2), and

- Phase 3 Study I8F-MC-GPHO (SURPASS-AP-Combo), in participants with diabetes (only participants with BMI ≥27 kg/m2). This was a Phase 3, randomised, open-label, parallel-group study that investigated the effects of treatment with tirzepatide 5, 10, and 15 mg QW compared with titrated insulin glargine in participants with T2DM who had inadequate glycaemic control on stable doses of metformin with or without a sulfonylurea.

Analysis sets

The studies considered in this safety summary comprise those that are placebo-controlled, active-comparator controlled, and uncontrolled open label, each of which provides different but relevant data informing the safety of tirzepatide in the overweight/obesity population. Moreover, the 9 completed Phase 3 studies were fixed-dose studies with the same tirzepatide maintenance doses and dose-escalation schedules that will be proposed for the prescribing information, in contrast to the Phase 2 studies that had different dose-escalation regimens and SURMOUNT-4 which is a maximum tolerated dose (MTD) study. Therefore, 4 integrated analysis sets were created that leveraged these differences among the studies to inform the safety assessment.

Results from placebo-controlled analysis sets provide an assessment of the strength of evidence for an imbalance between tirzepatide and placebo (via p-values, if available) and the magnitude of effect (via odds ratios, if available). Dose effects were examined via a separate analysis set by comparing the tirzepatide groups (5, 10, and 15 mg) per randomisation. Hence, the 2 *primary* analysis sets to detect drug and dose effects, respectively, are the Phase 3 Placebo-Controlled Analysis Set (AS1C) and the Phase 3 Dose Effect Analysis Set (AS2C). AS1C includes only Phase 3 placebo-controlled fixed-dose studies. SURMOUNT-1 participants comprise 76.5% of the total participants in AS1C. AS2C includes all Phase 3 fixed-dose studies that had tirzepatide 5, 10, and 15 mg treatment groups. SURMOUNT-1 participants comprise 30.0% of the total participants in AS2C. The Phase 2/3 Analysis Set (AS3C) includes all Phase 2 and 3 studies and all tirzepatide doses.

In this analysis set, all tirzepatide doses are pooled (TZP_ALL) and there is no comparison made to placebo or active comparator. This analysis set was created to facilitate identification of rarer events that require further scrutiny through case reviews. The Phase 2/3 Comparator-Controlled Analysis Set (AS4C) integrates data for all Phase 2 and 3 studies that included a comparator and provides an assessment of any differences between tirzepatide (all doses pooled) and comparators (placebo and active comparators pooled). A description of analysis sets is provided in Table 27.

Table 27. Analysis Sets for Integration of Tirzepatide Phase 2 and 3 Study Data

Analysis Sets	Studies	Time Period	Description	Treatment Groups (All Participants)	Treatment Groups (Participants with Overweight/Obesity)	Treatment Comparison	Analyses
Phase 3 Placebo-Controlled Analysis Set (AS1C)	SURMOUNT-1 SURPASS-1 SURPASS-5	First dose of treatment to end of safety follow-up visit or date of study withdrawal[a]	Integrated data of fixed dose Phase 3 studies compared to placebo for studies with placebo group[b] and same dose-escalation schedule proposed for the label	Placebo (N=878) TZP 5 mg (N=867) TZP 10 mg (N=876) TZP 15 mg (N=871) TZP_ALL (N=2614) Total (N=3492)	Placebo (N=827) TZP 5 mg (N=832) TZP 10 mg (N=830) TZP 15 mg (N=828) TZP_ALL (N=2490) Total (N=3317) SURMOUNT-1: 76.5% of total	TZP 5, 10, 15 mg, TZP_ALL vs. placebo	Full set of safety analyses[c]
Phase 3 Dose Effect Analysis Set (AS2C)	SURMOUNT-1 SURPASS-1 SURPASS-2 SURPASS-3 SURPASS-4 SURPASS-5 SURPASS-J Mono SURPASS-J Combo SURPASS-AP Combo	First dose of treatment to end of safety follow-up visit or date of study withdrawal[a]	Integrated data from TZP-treated participants in all Phase 3 fixed-dose studies with the same dose-escalation schedule for dose comparison	TZP 5 mg (N=2561) TZP 10 mg (N=2566) TZP 15 mg (N=2575) Total (N=7702)	TZP 5 mg (N=2109) TZP 10 mg (N=2095) TZP 15 mg (N=2122) Total (N=6326) SURMOUNT-1: 30.0% of total	Only TZP dose arms: 10 mg vs. 5 mg 15 mg vs. 5 mg 15 mg vs. 10 mg	Full set of safety analyses[c]
Phase 2/3 Analysis Set (AS3C)	SURMOUNT-1 SURMOUNT-4[d] GPGB GPGF SURPASS-1 SURPASS-2 SURPASS-3 SURPASS-4 SURPASS-5 SURPASS-J Mono SURPASS-J Combo SURPASS-AP Combo	First dose of treatment to end of safety follow-up visit or date of study withdrawal[a,d]	Integrated data from TZP-treated participants for pooled TZP doses. Includes all Phase 2 and 3 studies and all TZP doses. It is created to facilitate identification of rare events that require further scrutiny through case reviews. All TZP doses are pooled.	TZP_ALL (N=8780)	TZP_ALL (N=7354) SURMOUNT-1 and -4: 36.4% of total	Summary only, no comparison	Exposure, demographics, TEAEs, SAEs, DCAEs, special safety topics (including AESIs), labs shift to high/low, vital signs, ECG threshold
Phase 2/3 Comparator-Controlled Analysis Set (AS4C)	SURMOUNT-1 GPGB GPGF SURPASS-1 SURPASS-2 SURPASS-3 SURPASS-4 SURPASS-5 SURPASS-J Mono SURPASS-AP Combo	First dose of treatment to end of safety follow-up visit or date of study withdrawal[a]	Integrated data for all Phase 2 and 3 studies including comparator. All tirzepatide doses are pooled. All comparators (placebo and active comparators) are pooled.	Comparators (N=3217) TZP_ALL (N=7555) Total (N=10772)	Comparators (N=2711) TZP_ALL (N=6372) Total (N=9083) SURMOUNT-1: 28.0% of total	TZP_ALL vs. Comparators	Exposure, demographics, TEAEs, SAEs, DCAEs, AESIs

Abbreviations: AESI = adverse event of special interest; AP = Asia Pacific; DCAE = discontinuation due to adverse event; ECG = electrocardiogram; N = number of participants; SAE = serious adverse event; TEAE = treatment-emergent adverse event; TZP = tirzepatide; vs. = versus.

a For SURMOUNT-1, study withdrawal refers to the withdrawal during the primary treatment period. Participants with and without prediabetes are included at the 72-week primary endpoint.

b The placebo group in SURPASS-5 (Study GPGI) is comprised of placebo + titrated insulin.

c Full set of safety analyses includes exposure, demographics, medical history, concomitant medications, TEAEs, SAEs, DCAEs, special safety topics (including AESIs), labs, vital signs, ECGs.

d The data from SURMOUNT-4 are from the 36-week open-label tirzepatide treatment period including 4-week safety follow-up period for participants withdrawn during the open-label treatment period.

Although conducted in different populations, pooling together the safety data from the 2 SURMOUNT trials in the 'SURMOUNT set' is reasonable and relevant to the new proposed indication. However, it should be noted that the lower 5 mg dose was not tested in SURMOUNT-2.

In relation to the other datasets, given that SURMOUNT-1 and T2DM phase 3 programs share the same dosing regimen and that the majority of patients across the Phase 2 and 3 T2DM studies (estimated around 78% of the safety population) met the overweight/obesity criteria (with BMI ≥27 kg/m2 and the weight-related comorbidity of T2DM), the pooling approach in the additional analysis sets (AS1C etc) appears also reasonable and allows a broader evaluation, particularly important for the less common AEs.

It is important that safety information from SURMOUNT trials alone is considered separately

to identify potential new signals and possible differences between the CWM non-diabetic and the T2DM population. From those additional datasets of main interest are AS1C and AS2C and data from those two will be primarily presented in this AR.

Patient exposure

SURMOUNT Set

Overall, in the SURMOUNT-1 + SURMOUNT-2 analysis set a total of 2519 participants received at least 1 dose of tirzepatide, for a total of 3201.7 patient-years exposure, and 958 received at least 1 dose of placebo. The mean exposure to tirzepatide across the 3 tirzepatide groups was 66.3 weeks (5 mg, 66.8 weeks; 10 mg, 66.2 weeks; 15 mg, 66.2 weeks) and mean exposure to placebo was 62.9 weeks. Across the 3 tirzepatide groups, 88.8% of participants were exposed to tirzepatide for at least 52 weeks, and 76.5% were exposed for at least 72 weeks. In the placebo group, 80.3% of participants were exposed to placebo for at least 52 weeks and 68.4% were exposed for at least 72 weeks.

Table 28. Summary of Study Drug Duration

	SURMOUNT-1				SURMOUNT-2			SURMOUNT-1 + SURMOUNT-2 Analysis Set				
	Placebo (N=643)	TZP 5 mg (N=630)	TZP 10 mg (N=636)	TZP 15 mg (N=630)	Placebo (N=315)	TZP 10 mg (N=312)	TZP 15 mg (N=311)	Placebo (N=958)	TZP 5 mg (N=630)	TZP 10 mg (N=948)	TZP 15 mg (N=941)	TZP_ALL (N=2519)
Weeks of exposure, n (%)												
≥0	643 (100.0)	630 (100.0)	636 (100.0)	630 (100.0)	315 (100.0)	312 (100.0)	311 (100.0)	958 (100.0)	630 (100.0)	948 (100.0)	941 (100.0)	2519 (100.0)
≥4	637 (99.1)	624 (99.0)	628 (98.7)	626 (99.4)	312 (99.0)	309 (99.0)	309 (99.4)	949 (99.1)	624 (99.0)	937 (98.8)	935 (99.4)	2496 (99.1)
≥8	629 (97.8)	615 (97.6)	619 (97.3)	618 (98.1)	308 (97.8)	306 (98.1)	303 (97.4)	937 (97.8)	615 (97.6)	925 (97.6)	921 (97.9)	2461 (97.7)
≥12	618 (96.1)	608 (96.5)	610 (95.9)	611 (97.0)	304 (96.5)	304 (97.4)	301 (96.8)	922 (96.2)	608 (96.5)	914 (96.4)	912 (96.9)	2434 (96.6)
≥16	609 (94.7)	607 (96.3)	602 (94.7)	603 (95.7)	301 (95.6)	302 (96.8)	299 (96.1)	910 (95.0)	607 (96.3)	904 (95.4)	902 (95.9)	2413 (95.8)
≥20	602 (93.6)	602 (95.6)	593 (93.2)	598 (94.9)	298 (94.6)	296 (94.9)	295 (94.9)	900 (93.9)	602 (95.6)	889 (93.8)	893 (94.9)	2384 (94.6)
≥24	591 (91.9)	599 (95.1)	586 (92.1)	592 (94.0)	293 (93.0)	294 (94.2)	294 (94.5)	884 (92.3)	599 (95.1)	880 (92.8)	886 (94.2)	2365 (93.9)
≥36	549 (85.4)	590 (93.7)	573 (90.1)	574 (91.1)	284 (90.2)	293 (93.9)	285 (91.6)	833 (87.0)	590 (93.7)	866 (91.4)	859 (91.3)	2315 (91.9)
≥48	518 (80.6)	574 (91.1)	561 (88.2)	556 (88.3)	274 (87.0)	291 (93.3)	279 (89.7)	792 (82.7)	574 (91.1)	852 (89.9)	835 (88.7)	2261 (89.8)
≥52	500 (77.8)	562 (89.2)	556 (87.4)	554 (87.9)	269 (85.4)	286 (91.7)	278 (89.4)	769 (80.3)	562 (89.2)	842 (88.8)	832 (88.4)	2236 (88.8)
≥72	427 (66.4)	491 (77.9)	486 (76.4)	468 (74.3)	228 (72.4)	249 (79.8)	232 (74.6)	655 (68.4)	491 (77.9)	735 (77.5)	700 (74.4)	1926 (76.5)
Exposure summary												
Mean weeks	61.88	66.80	65.40	66.08	65.06	67.73	66.30	62.9	66.8	66.2	66.2	66.3
SD	19.60	15.58	17.85	16.76	17.57	14.73	16.21	19.01	15.58	16.92	16.58	16.46
Total patient-years	762.56	806.53	797.17	797.86	392.77	405.02	395.15	1155.3	806.5	1202.2	1193.0	3201.7

Abbreviations: N = number of participants in the analysis population; n = number of participants in specified category; SD = standard deviation.
Notes: Total patient-years is calculated as sum of duration of exposure in days for all patients in dosing regimen/365.25.
Duration of exposure is calculated as date of first dose of study drug to date of last dose of study drug plus 7 days.

Phase 3 Placebo-Controlled Analysis Set (AS1C)

A total of 2490 participants received at least 1 dose of tirzepatide and 827 received at least 1 dose of placebo. Of the participants receiving tirzepatide, 832 participants were assigned to 5 mg, 830 participants were assigned to 10 mg, and 828 participants were assigned to 15 mg. The mean exposure to tirzepatide across the 3 tirzepatide groups was 59.2 weeks (5 mg, 59.8 weeks; 10 mg, 58.9 weeks; 15 mg, 58.7 weeks) and mean exposure to placebo was 56.5 weeks. Across the 3 tirzepatide groups, 67.1% of participants were exposed to tirzepatide for at least 52 weeks, and 58.0% were exposed for at least 72 weeks. In the placebo group, 60.5% of participants were exposed to placebo for at least 52 weeks, and 51.6% were exposed for at least 72 weeks.

Phase 3 Dose Effect Analysis Set (AS2C)

A total of 6326 participants received at least 1 dose of tirzepatide; 2109 participants were assigned to 5 mg, 2095 were assigned to 10 mg, and 2122 were assigned to 15 mg. The mean exposure to tirzepatide was similar in the 3 tirzepatide groups (5 mg, 53.7 weeks; 10 mg, 53.4 weeks; 15 mg, 53.1 weeks). Across the 3 tirzepatide groups, the percentage of participants exposed to tirzepatide for at least 52 weeks and 72 weeks was similar: o 52 weeks (5 mg, 55.3%; 10 mg, 55.4%; 15 mg, 54.9%), and o 72 weeks (5 mg, 32.3%; 10 mg, 32.8%; 15 mg,

31.0%).

The overall safety population is adequate in terms of numbers exposed and length of exposure, and meets the relevant regulatory requirements. Baseline demographic and other characteristics were generally well balanced between the different treatment groups.
It should be noted, however, in relation to CWM very limited safety data beyond 72 weeks of therapy are currently available.

Overview

SURMOUNT Set

In the SURMOUNT-1 + SURMOUNT-2 Analysis Set, the percentage of participants reporting SAEs, discontinuations from the study due to an AE, and deaths was similar between tirzepatide groups (TZP_ALL) and placebo (Table 28). However, the percentage of participants reporting TEAEs (TZP_ALL, 79.04%; placebo, 73.28%) or discontinuing study drug due to an AE (TZP_ALL, 6.07%; placebo, 3.44%) was greater in the TZP_ALL group, compared to placebo. These comparisons between the tirzepatide and placebo groups are consistent with the findings in the Placebo-Controlled Analysis Set in the SCS.

Table 29. Overview of Adverse Events Safety Population SURMOUNT-1 + SURMOUNT-2 Analysis Set

	SURMOUNT-1 + SURMOUNT-2 Analysis Set				
Category[b]	Placebo (N=958)	TZP 5 mg (N=630)	TZP 10 mg (N=948)	TZP 15 mg (N=941)	TZP_ALL (N=2519)
Deaths[c]	4 (0.42)	4 (0.63)	4 (0.42)	1 (0.11)	9 (0.36)
SAEs	67 (6.99)	40 (6.35)	62 (6.54)	59 (6.27)	161 (6.39)
Discontinuation from study due to AE	22 (2.30)	16 (2.54)	21 (2.22)	26 (2.76)	63 (2.50)
Discontinuation from study drug due to AE	33 (3.44)	30 (4.76)	60 (6.33)	63 (6.70)	153 (6.07)
TEAEs	702 (73.28)	510 (80.95)	762 (80.38)	719 (76.41)	1991 (79.04)

Abbreviations: AE = adverse event; N = number of participants in treatment group; n = number of participants with at least 1 AE per event type; SAE = serious adverse event; SCS = Summary of Clinical Safety; TEAE = treatment-emergent adverse event; TZP = tirzepatide.
a Participants with obesity/overweight in AS1C in SCS.
b Participants may be counted in more than 1 category.
c Deaths are also included as SAEs and discontinuations due to AEs.

Phase 3 Placebo-Controlled Analysis Set (AS1C)

• The percentage of participants reporting SAEs, discontinuation from study due to AE, and deaths was similar between tirzepatide groups (TZP_ALL) and placebo in AS1C.
• The percentage of discontinuations from study treatment due to an AE was higher in the TZP_ALL (5.9%) group compared to placebo (3.1%).
• The percentage of participants reporting TEAEs was higher in the TZP_ALL group (78.1%) than placebo group (71.2%; Table 30).

The comparisons between tirzepatide and placebo groups are consistent with the findings in the placebo-controlled analysis set in the original T2DM application. The frequencies of events in all categories, except discontinuation from study treatment due to AE, were slightly higher across all treatment groups (tirzepatide and placebo) relative to the original T2DM application. Discontinuation of study treatment due to AE was lower in the tirzepatide groups while higher in placebo compared to the original T2DM application in which rates were 6.7% and 2.6% in TZP_ALL and placebo, respectively.

Table 30. Overview of Adverse Events Safety Population Participants with Overweight/Obesity in Phase 3 Placebo Controlled Analysis Set (AS1C)

Category[a]	n (%)					TZP_ALL vs. Placebo p-value[b]
	Placebo (N=827)	TZP 5 mg (N=832)	TZP 10 mg (N=830)	TZP 15 mg (N=828)	TZP_ALL (N=2490)	
Deaths[c]	4 (0.48)	4 (0.48)	2 (0.24)	1 (0.12)	7 (0.28)	0.399
SAEs	53 (6.41)	51 (6.13)	57 (6.87)	41 (4.95)	149 (5.98)	0.690
Discontinuation from study due to AE	18 (2.18)	19 (2.28)	19 (2.29)	23 (2.78)	61 (2.45)	0.621
Discontinuation from study treatment due to AE	26 (3.14)	38 (4.57)	56 (6.75)	54 (6.52)	148 (5.94)	0.002
TEAEs	589 (71.22)	654 (78.61)	648 (78.07)	643 (77.66)	1945 (78.11)	< 0.001

Abbreviations: AE = adverse event; N = number of participants in treatment group; n = number of participants with at least 1 AE per event type; SAE = serious adverse event; TEAE = treatment-emergent adverse event; TZP = tirzepatide; vs. = versus.

[a] Participants may be counted in more than 1 category.

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

[c] Deaths are also included as SAEs and discontinuations due to AEs.

Phase 3 Dose Effect Analysis Set (AS2C)

For the categories of TEAEs and discontinuation of study treatment due to an AE, there was an increase with higher dose groups (Table 31). The percentages of participants reporting SAEs and discontinuations from study due to an AE was similar across the 3 tirzepatide dose groups in AS2C. Overall, these results are consistent with the data presented in the dose effect analysis set in the original T2DM application.

Table 31. Overview of Adverse Events Safety Population Participants with Overweight/Obesity in Phase 3 Dose Effect Analysis Set (AS2C)

Category[a]	n (%)		
	TZP 5 mg (N=2109)	TZP 10 mg (N=2095)	TZP 15 mg (N=2122)
Deaths[b]	20 (0.95)	9 (0.43)	10 (0.47)
SAEs	159 (7.54)	161 (7.68)	133 (6.27)
Discontinuation from study due to AE	45 (2.13)	40 (1.91)	42 (1.98)
Discontinuation from study treatment due to AE	116 (5.50)	150 (7.16)	156 (7.35)
TEAEs	1526 (72.36)	1552 (74.08)	1615 (76.11)

Abbreviations: AE = adverse event; N = number of participants in treatment group; n = number of participants with at least 1 AE per event type; SAE = serious adverse event; TEAE = treatment-emergent adverse event; TZP = tirzepatide.

[a] Participants may be counted in more than 1 category.

[b] Deaths are also included as SAEs and discontinuations due to AEs.

Frequently reported TEAEs

SURMOUNT Set

Table 32 presents a summary of frequently reported TEAEs by decreasing frequency based on the TZP_ALL group. The majority of frequently reported TEAEs that were reported by higher percentages of participants in tirzepatide groups compared with placebo were in the Gastrointestinal disorders (GI) SOC (TZP_ALL, 55.66%; placebo, 29.65%).

Table 32. Summary and Analysis of TEAEs Occurring in ≥5% of Participants in any Treatment Group Safety Population. SURMOUNT-1 + SURMOUNT-2 Analysis Set

Preferred term	n (%)					TZP_ALL vs. Placebo p-value[b]
	Placebo (N=958)	TZP 5 mg[a] (N=630)	TZP 10 mg (N=948)	TZP 15 mg (N=941)	TZP_ALL (N=2519)	
Nausea	81 (8.46)	155 (24.60)	275 (29.01)	263 (27.95)	693 (27.51)	<0.001
Diarrhoea	75 (7.83)	118 (18.73)	197 (20.78)	212 (22.53)	527 (20.92)	<0.001
COVID-19	143 (14.93)	94 (14.92)	151 (15.93)	115 (12.22)	360 (14.29)	0.654
Constipation	50 (5.22)	106 (16.83)	134 (14.14)	102 (10.84)	342 (13.58)	<0.001
Vomiting	21 (2.19)	52 (8.25)	102 (10.76)	118 (12.54)	272 (10.80)	<0.001
Decreased appetite	28 (2.92)	59 (9.37)	103 (10.86)	85 (9.03)	247 (9.81)	<0.001
Dyspepsia	37 (3.86)	56 (8.89)	85 (8.97)	93 (9.88)	234 (9.29)	<0.001
Headache	51 (5.32)	41 (6.51)	59 (6.22)	56 (5.95)	156 (6.19)	0.444
Abdominal pain	28 (2.92)	31 (4.92)	46 (4.85)	54 (5.74)	131 (5.20)	0.004
Eructation	6 (0.63)	24 (3.81)	52 (5.49)	48 (5.10)	124 (4.92)	<0.001
Alopecia	8 (0.84)	32 (5.08)	40 (4.22)	46 (4.89)	118 (4.68)	<0.001
Dizziness	20 (2.09)	26 (4.13)	52 (5.49)	34 (3.61)	112 (4.45)	0.001
Hyperglycaemia	49 (5.11)	1 (0.16)	6 (0.63)	4 (0.43)	11 (0.44)	<0.001

Abbreviation: N = number of participants in treatment group; n = number of participants with at least 1 treatment emergent
adverse event; TZP = tirzepatide.
a The TZP 5-mg group is only from SURMOUNT-1.
b The p-values are from the Cochran-Mantel-Haenszel test of general association stratified by study.

In addition to the most frequently reported TEAEs, there were some imbalances between TZP_ALL and placebo in other less frequent TEAEs reported by at least 1% in TZP_ALL, with more events reported in tirzepatide. Most concerned AEs previously seen in the original T2DM application.

Phase 3 Placebo-Controlled Analysis Set (AS1C)

The majority of frequent TEAEs, reported by higher percentages with tirzepatide groups were in the GI SOC (TZP_ALL, 54.0%; placebo, 28.5%). Except for COVID-19, headache, and nasopharyngitis, the majority of frequently reported TEAEs were reported by a higher percentage of participants in TZP_ALL compared with placebo. Overall, this pattern of TEAEs, with the most frequent TEAEs being primarily GI-related, is consistent with the placebo-controlled analysis set in the original T2DM application.

Table 33. Summary and Analysis of Treatment-Emergent Adverse Events Occurring in ≥5% of Participants in Any Treatment Group Safety Population Participants with Overweight/Obesity in Phase 3 Placebo-Controlled Analysis Set (AS1C).

Preferred term	n (%)					TZP_ALL vs. Placebo p-value[a]
	Placebo (N=827)	TZP 5 mg (N=832)	TZP 10 mg (N=830)	TZP 15 mg (N=828)	TZP_ALL (N=2490)	
Nausea	69 (8.34)	184 (22.12)	239 (28.80)	231 (27.90)	654 (26.27)	< 0.001
Diarrhea	66 (7.98)	141 (16.95)	160 (19.28)	180 (21.74)	481 (19.32)	< 0.001
Constipation	38 (4.59)	118 (14.18)	120 (14.46)	87 (10.51)	325 (13.05)	< 0.001
COVID-19	94 (11.37)	94 (11.30)	100 (12.05)	84 (10.14)	278 (11.16)	1.00
Vomiting	15 (1.81)	64 (7.69)	75 (9.04)	94 (11.35)	233 (9.36)	< 0.001
Decreased appetite	23 (2.78)	70 (8.41)	87 (10.48)	74 (8.94)	231 (9.28)	< 0.001
Dyspepsia	32 (3.87)	72 (8.65)	76 (9.16)	82 (9.90)	230 (9.24)	< 0.001
Headache	51 (6.17)	51 (6.13)	48 (5.78)	46 (5.56)	145 (5.82)	0.744
Eructation	5 (0.60)	31 (3.73)	38 (4.58)	43 (5.19)	112 (4.50)	< 0.001
Injection site reaction	2 (0.24)	23 (2.76)	42 (5.06)	34 (4.11)	99 (3.98)	< 0.001
Nasopharyngitis	43 (5.20)	35 (4.21)	28 (3.37)	27 (3.26)	90 (3.61)	0.027

Abbreviation: N = number of participants in treatment group; n = number of participants with at least 1 treatment-emergent adverse event; TZP = tirzepatide; vs. = versus.

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

In addition to the most frequently reported TEAEs, there were some imbalances between TZP_ALL and placebo in other less frequent TEAEs reported by at least 1% in TZP_ALL, with more events reported in tirzepatide. Most concerned AEs previously seen in the original T2DM application. However, a newly identified AE was alopecia (TZP_ALL, 4.0%; placebo, 0.7%). The most commonly-reported term under alopecia was hair loss (63% in AS1C). This finding is consistent with other treatments leading to substantial and rapid weight reduction in this population, such as bariatric surgery and long-acting incretin-based therapies.

Phase 3 Dose Effect Analysis Set (AS2C)

Table 34 presents a summary of frequently reported TEAEs (≥5% in any treatment group) in AS2C by decreasing frequency. The most frequently reported TEAEs were in the Gastrointestinal disorders SOC. The most frequently reported TEAEs (≥5%) that showed an incremental increase with higher dose groups were nausea, diarrhoea, decreased appetite vomiting, and dyspepsia. These dose-related effects are generally consistent with the dose effect analysis set in the original T2DM application.

Table 34. Summary and Analysis of Treatment-Emergent Adverse Events Occurring in at Least 5% of Participants with Overweight/Obesity in Any Treatment Group Safety Population Phase 3 Dose Effect Analysis Set (AS2C)

	n (%)		
Preferred term	TZP 5 mg (N=2109)	TZP 10 mg (N=2095)	TZP 15 mg (N=2122)
Nausea	367 (17.40)	484 (23.10)	525 (24.74)
Diarrhea	343 (16.26)	394 (18.81)	423 (19.93)
Decreased appetite	176 (8.35)	225 (10.74)	230 (10.84)
Constipation	189 (8.96)	195 (9.31)	168 (7.92)
Vomiting	128 (6.07)	178 (8.50)	221 (10.41)
Dyspepsia	134 (6.35)	154 (7.35)	176 (8.29)
COVID-19	109 (5.17)	118 (5.63)	107 (5.04)

Abbreviation: N = number of participants in treatment group; n = number of participants with at least 1 treatment-emergent adverse event; TZP = tirzepatide.

The pattern of TEAEs across analysis sets was similar, with no new findings observed in AS3C or AS4C.

TEAEs severity

In the SURMOUNT-1 and -2 trials (SURMOUNT set), the majority of participants reporting at least 1 TEAE had events with a maximum severity of mild or moderate (TZP_ALL, 90.8%; placebo, 92.2%. The individual TEAE reported with the highest frequency of "severe" in TZP_ALL was nausea (0.75%). Overall, this pattern of TEAEs, with the most frequent being gastrointestinal (GI)-related and generally mild or moderate in severity is consistent with the Placebo-Controlled Analysis Set in AS1C (TZP_ALL, 91.0%; placebo, 89.3%). Most participants in the TZP_ALL group experienced TEAEs in the GI SOC and most were reported as mild or moderate in severity (TZP_ALL, 95.7%).

In AS1C the frequency of *severe* ratings of nausea, vomiting, and diarrhoea were slightly higher than those reported in the placebo-controlled analysis set in the original T2DM application, but low overall (nausea: 0.3% vs. 0%, vomiting: 0.3% vs. 0%, and diarrhoea: 0.4% vs. 0.4% for TZP_ALL vs. placebo, respectively). A similar pattern was seen in the AS2C. Similar to the original application, there was no apparent dose related effect for severe events of nausea, diarrhoea, constipation, or dyspepsia.

General information, warnings and individual GI adverse events are already included in the product information. Among the less frequent reported events alopecia (hair loss) was identified. The SURMOUNT data also showed that dizziness was reported more commonly among tirzepatide patients. Hair loss and dizziness have now been included in the updated SmPC (as common events).

Deaths and Serious adverse events

Deaths

There were 13 deaths (TZP_ALL, 9 [0.36%]; placebo, 4 [0.42%]) in the SURMOUNT-1 + SURMOUNT-2 Analysis Set (Table 35). Of these, 11 occurred in SURMOUNT-1 (TZP_ALL, 7 [0.37%]; placebo, 4 [0.62%]), and 2 occurred in SURMOUNT-2 (TZP_ALL, 2 [0.32%]; placebo, 0 [0%]). There was no pattern in the causes of death observed among tirzepatide-treated participants in SURMOUNT-1 and SURMOUNT-2. The causes leading to more than 1 death were due to COVID-19 and trauma.

In AS1C, altogether there were 72 deaths that occurred during the Phase 2 and 3 studies after participants with overweight/obesity received at least 1 dose of study drug and are included in the clinical trial database. A total of 40 participants out of 7354 participants (0.54%) receiving tirzepatide and 32 participants out of 2711 participants (1.18%) receiving placebo or active comparator comprise the total number of deaths. Over half (61.11%) of the deaths occurred in SURPASS-4, which was conducted in participants with increased CV risk.

Table 35. Overview of Adverse Events Safety Population SURMOUNT-1 + SURMOUNT-2 Analysis Set and Placebo-Controlled Analysis Set (AS1C) in the SCS

	n (%)									
	SURMOUNT-1 + SURMOUNT-2 Analysis Set					Placebo-Controlled Analysis Set (AS1C)[a]				
Category[b]	Placebo (N=958)	TZP 5 mg (N=630)	TZP 10 mg (N=948)	TZP 15 mg (N=941)	TZP_ALL (N=2519)	Placebo (N=827)	TZP 5 mg (N=832)	TZP 10 mg (N=830)	TZP 15 mg (N=828)	TZP_ALL (N=2490)
Deaths[c]	4 (0.42)	4 (0.63)	4 (0.42)	1 (0.11)	9 (0.36)	4 (0.48)	4 (0.48)	2 (0.24)	1 (0.12)	7 (0.28)
SAEs	67 (6.99)	40 (6.35)	62 (6.54)	59 (6.27)	161 (6.39)	53 (6.41)	51 (6.13)	57 (6.87)	41 (4.95)	149 (5.98)
Discontinuation from study due to AE	22 (2.30)	16 (2.54)	21 (2.22)	26 (2.76)	63 (2.50)	18 (2.18)	19 (2.28)	19 (2.29)	23 (2.78)	61 (2.45)
Discontinuation from study drug due to AE	33 (3.44)	30 (4.76)	60 (6.33)	63 (6.70)	153 (6.07)	26 (3.14)	38 (4.57)	56 (6.75)	54 (6.52)	148 (5.94)
TEAEs	702 (73.28)	510 (80.95)	762 (80.38)	719 (76.41)	1991 (79.04)	589 (71.22)	654 (78.61)	648 (78.07)	643 (77.66)	1945 (78.11)

The available data do not raise any concerns about excess mortality in the tirzepatide groups. In SURMOUNT-1 a small number of patients died during the study without any indication of higher rates among tirzepatide patients. All deaths were considered not related to study drug by the investigators, except one patient for whom however, a number of possible confounding factors were present. In SURMOUNT-2 there were 2 deaths, both in the tirzepatide groups, but both were considered not related to the study drug by the investigator.

Other Serious Adverse Events

SURMOUNT Set

The percentages of participants in the SURMOUNT-1 + SURMOUNT-2 Analysis Set who reported at least 1 SAE were similar in the TZP_ALL and placebo groups: TZP_ALL: 161 participants (6.39%), and placebo: 67 participants (6.99%) (Table 34 above). The most frequently reported SAEs were in the SOC of Infections and infestations (TZP_ALL, 2.02%; placebo, 1.98%). SAEs reported by at least 0.2% (n=5) in the TZP_ALL group were: COVID-19 pneumonia (TZP_ALL, 0.52%; placebo, 0.63%), COVID-19 (TZP_ALL, 0.36%; placebo, 0.63%), cholelithiasis (TZP_ALL, 0.48%; placebo, 0.42%), cholecystitis acute (TZP_ALL, 0.28%; placebo, 0.21%), appendicitis (TZP_ALL, 0.28%; placebo, 0.31%),

acute kidney injury (TZP_ALL, 0.24%; placebo, 0.21%), and prostate cancer (TZP_ALL, 0.22%; placebo, 0.28%). The findings are consistent with the Placebo-Controlled Analysis Set in the SCS, in which 5.98% of participants in the TZP_ALL group and 6.41% of participants in the placebo group reported at least 1 SAE and the SOC of Infections and infestations had the highest percentage of SAEs (TZP_ALL, 2.05%; placebo, 1.81%).

Phase 3 Placebo-Controlled Analysis Set (AS1C)

Table 36 presents a summary of SAEs reported by ≥0.2% of participants in the pooled tirzepatide group in AS1C. Overall, the percentage of participants reporting at least 1 SAE was similar across tirzepatide doses. The SOC with the highest percentage of SAEs in AS1C was Infections and infestations, with similar percentages of participants reporting events across tirzepatide doses, TZP_ALL, and placebo groups.

In the placebo-controlled analysis set in the original T2DM application, the Cardiac disorders SOC had the highest percentage of SAEs reported in both the TZP_ALL (1.3%) and placebo (1.7%) groups, followed closely by the Infection and infestations SOC (1.1% TZP_ALL, 0.4% placebo).

Table 36. Summary and Analysis of Serious Adverse Events Reported by ≥0.2% of Participants in TZP_ALL. MedDRA Preferred Term within System Organ Class by Decreasing Frequency Safety Population Participants with Overweight/Obesity in Phase 3 Placebo-Controlled Analysis Set (AS1C)

System Organ Class Preferred Term	n (%)					TZP_ALL vs. Placebo p-value[a]
	Placebo (N=827)	TZP 5 mg (N=832)	TZP 10 mg (N=830)	TZP 15 mg (N=828)	TZP_ALL (N=2490)	
Participants with ≥1 SAE	53 (6.41)	51 (6.13)	57 (6.87)	41 (4.95)	149 (5.98)	0.690
Infections and infestations	15 (1.81)	18 (2.16)	20 (2.41)	13 (1.57)	51 (2.05)	0.645
COVID-19 pneumonia	5 (0.60)	6 (0.72)	3 (0.36)	3 (0.36)	12 (0.48)	0.693
COVID-19	6 (0.73)	1 (0.12)	6 (0.72)	1 (0.12)	8 (0.32)	0.130
Appendicitis	3 (0.36)	4 (0.48)	0	2 (0.24)	6 (0.24)	0.580
Hepatobiliary disorders	5 (0.60)	6 (0.72)	9 (1.08)	6 (0.72)	21 (0.84)	0.473
Cholelithiasis	3 (0.36)	3 (0.36)	4 (0.48)	3 (0.36)	10 (0.40)	0.852
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	10 (1.21)	7 (0.84)	3 (0.36)	6 (0.72)	16 (0.64)	0.111
Cardiac disorders	5 (0.60)	6 (0.72)	4 (0.48)	2 (0.24)	12 (0.48)	0.647
Respiratory, thoracic, and mediastinal disorders	4 (0.48)	5 (0.60)	5 (0.60)	2 (0.24)	12 (0.48)	0.990
Renal and urinary disorders	2 (0.24)	3 (0.36)	2 (0.24)	3 (0.36)	8 (0.32)	0.721
Vascular disorders	4 (0.48)	1 (0.12)	3 (0.36)	3 (0.36)	7 (0.28)	0.375
Psychiatric disorders	0	2 (0.24)	3 (0.36)	1 (0.12)	6 (0.24)	0.153

Abbreviations: incl = including; MedDRA = Medical Dictionary for Regulatory Activities; N = number of participants in treatment group; n = number of participants with at least 1 SAE; SAE = serious adverse event; TZP = tirzepatide; vs. = versus.

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

Phase 3 Dose Effect Analysis Set (AS2C)

Overall, no important differences in SAEs were observed between participants in the 3 tirzepatide dose groups of AS2C: The SOC with the highest percentage of SAEs was 'infections and infestations', with similar percentages of participants in all 3 tirzepatide dose groups.

Overall, the lack of dose-related effect with SAEs is consistent with the dose effect analysis set in the original TD2M application. Similarly, the most frequently reported SAEs in the original application were acute myocardial infarction, COVID-19 pneumonia, and coronary artery disease. The percentage of participants with SAEs of cholelithiasis was 0.10% in the

dose effect analysis set in the original application. There were consistent findings in the AS3C and AS4C sets.

In general SAEs appear evenly distributed between groups, without notable imbalances and with no clear pattern suggesting a dose relationship; however, the numbers for individual events are small to permit firm conclusions. It is noted that SAEs related to COVID-19 were among the most commonly reported in SURMOUNT trials.

In SURMOUNT-1 alone there were 160 participants who had at least 1 SAE during the study, again similarly distributed between groups (6.8%, 6.3%, 6.9%, 5.1% in the placebo and tirzepatide, 5, 10 and 15 mg groups, respectively). The percentage of participants reporting at least 1 SAE was comparable between the tirzepatide and the placebo group. Out of 160 participants who reported SAEs, 34 (21.3%) reported COVID-19-related SAEs.

Otherwise, the most frequent SAEs were hepatobiliary disorders (with cholelithiasis and cholecystitis being the most common). For cholelithiasis there were no differences between placebo and tirzepatide groups. However, for cholecystitis (reported as 'cholecystitis acute' and 'cholecystitis') there were no events in the placebo group, compared to 7 events in the three tirzepatide groups.

In SURMOUNT-2 there were 68 participants who had at least 1 SAE during the study (7.3%, 5.8%, 8.7% in the placebo and tirzepatide 10 and 15 mg groups, respectively). For each category there was a small number of individual reports, which does not permit any conclusions about specific events.

Special Safety Topics Including Adverse Events of Interest
Gastrointestinal Adverse Events
SURMOUNT Set
Gastrointestinal (GI) TEAEs were reported by 55.66% of tirzepatide-treated and 29.65% of placebo-treated participants. The most frequently (TZP_ALL >10%) reported GI TEAEs were: nausea, diarrhoea, constipation and vomiting (Table 31 above). The frequency of GI AEs was consistent with the Placebo-Controlled Analysis Set in the SCS (see below). Severity of GI AEs Among tirzepatide-treated participants reporting GI-related TEAEs, the majority were mild or moderate in severity (TZP_ALL, 95.44%), similar to the Placebo-Controlled Analysis Set AS1C (95.69%).

A total of 78 (TZP_ALL, 67 [2.66%]; placebo, 11 [1.15%]) participants experienced at least 1 severe or serious GI adverse event. The most frequently reported severe or serious GI TEAEs were: nausea vomiting and diarrhoea.

Phase 3 Analysis Sets AS1C and AS2C
In AS1C a total of 1581 participants (TZP_ALL, 54.02%; placebo, 28.54%) experienced at least 1 TEAE in the GI SOC, with more participants in the tirzepatide-treated groups reporting events compared with placebo groups. The most frequently reported GI-related TEAEs were nausea, diarrhoea, constipation, and vomiting.

Although the PTs for GI events were similar, the overall frequency of GI AEs was higher compared to the placebo-controlled analysis set in the original T2DM application (40.1% and 20.4% for TZP_ALL and placebo, respectively). Higher frequency of GI AEs in participants with overweight or obesity is partly explained by a higher underlying risk in this population

as confirmed by the frequency in the placebo group. This finding is consistent with the selective GLP-1 receptor agonists liraglutide and semaglutide.

Among participants reporting at least 1 GI-related TEAE, the majority of GI-related TEAEs were mild or moderate in severity, similar to the original T2DM application. However, a total of 69 (TZP_ALL, 2.4%; placebo, 1.2%) participants experienced at least 1 serious or severe GI event in AS1C. The frequency for TZP_ALL was numerically higher compared to TZP_ALL (1.1%) in the placebo-controlled analysis set in the original T2DM application. The increase is related to SURMOUNT-1 which accounted for 59 (TZP_ALL, 52; placebo, 7) of the 69 participants. The most common TEAE were nausea, vomiting and diarrhoea. The percentage of participants discontinuing tirzepatide due to GI AEs (3.61%) was lower than that reported in the placebo-controlled analysis set in the original T2DM application (5.0%), whereas the percentage in the placebo groups was similar (0.48% in this application vs. 0.4% in the original application. The most frequently reported GI PTs leading to discontinuation of study drug were nausea, diarrhoea and vomiting.

Consistent findings were seen in the Phase 3 Dose Effect Analysis Set (AS2C). The frequency of GI AEs was numerically higher compared to the frequency (43.6%) in the dose effect analysis set in the original T2DM application. An overall incremental increase in higher dose groups was observed for these events. However, the incidence of severe or serious GI events was similar among all tirzepatide dose groups.

Generally, GI AEs are recognised for this class and the specific findings and patterns appear, for the most part, consistent with the known profile of tirzepatide. However, the overall frequency of GI AEs in the CWM trials was higher than what was previously reported in the T2DM dossier. It is argued that this may be explained by the underlying increased risk of GI disorders associated with obesity. It is true that there were similar findings with other selective GLP-1 RAs such as liraglutide and semaglutide. On the other hand, it is reassuring that the rates of discontinuations due to GI AEs (tirzepatide all 3.61% vs placebo 0.48%; AS1C) was not excessive compared to that reported in the placebo-controlled analysis set in the original T2DM dossier. The most frequently reported GI PTs leading to discontinuation of study drug were nausea, diarrhoea and vomiting.

In general, most GI AEs were mild or moderate; still 69 patients in AS1C (tirzepatide 2.4%; placebo, 1.2%) participants experienced at least 1 serious or severe GI event; most were reported in SURMOUNT-1. The most common TEAE were nausea, vomiting and diarrhoea. The results suggest a dose relationship (5 mg 43.76%, 10 mg 49.07% and 15-mg 52.73%; AS2C). Onset of symptoms such as nausea, vomiting, or diarrhoea appeared to be greater during the first 4 weeks and tended to stabilise over time. Such findings are consistent with the original T2DM dossier.

Among the less common AEs there were 2 reports of gastroparesis. Overall, considering the total exposure of around 2500 patients to tirzepatide in the two SURMOUNT trials (for a total of 3201.7 patient-years) it appears that severe cases of impaired gastric emptying and gastroparesis are very rare. Based on the limited information available and the history of diabetes in the two cases, it is difficult to establish a direct causal relationship with tirzepatide therapy or whether tirzepatide treatment might have exacerbated a pre-existing condition.
In the current SmPC there is a warning that “Tirzepatide has not been studied in patients with severe gastrointestinal disease, including severe gastroparesis, and should be used with caution in these patients.” and at different parts there is information that tirzepatide can delay

gastric emptying.

Dehydration events were also analysed, as GI events such as vomiting or diarrhoea may lead to dehydration and volume depletion, which can also affect renal function and may result in acute renal failure. In SURMOUNT trials a total of 16 participants (TZP_ALL, 15 [0.60%]; placebo, 1 [0.10%]) experienced at least 1 treatment-emergent dehydration event (with 3 participants reporting severe/serious events all in tirzepatide groups. In AS1C there were very few reports, driven by events in the SURMOUNT-1 study. In AS2C the percentage of tirzepatide-treated participants reporting dehydration was low (0.33%, 21 events) across nine Phase 3 clinical studies (the highest number in patients treated with 15 mg). This percentage was similar to that reported in the dose effect analysis set in the original T2DM application (0.31%). Acceptable warnings regarding this are included in the SmPC.

Renal Safety

SURMOUNT Set

A total of 19 (0.75%) tirzepatide-treated and 6 (0.63%) placebo-treated participants experienced at least 1 treatment-emergent renal event (Table 37). A total of 11 of these participants (TZP_ALL, 9 [0.36%]; placebo, 2 [0.21%]) experienced at least 1 severe or serious renal event. Six of the tirzepatide-treated participants were from SURMOUNT-1, and 4 of them reported serious renal events. The remaining 3 tirzepatide-treated participants were from SURMOUNT-2, and all three events were reported as both serious and severe.

Of the total 7 serious renal events in tirzepatide-treated participants across SURMOUNT-1 and SURMOUNT-2, 2 reported GI TEAEs of diarrhoea and/or vomiting while the other 5 had concurrent medical conditions such as septic shock and food poisoning. The frequency of severe or serious renal events was higher in both the tirzepatide and placebo groups, compared to the Placebo-Controlled Analysis Set (0.18% and 0.03% for TZP_ALL and placebo, respectively), leading to a similar relative difference between the groups.

Table 37. Summary of Treatment-Emergent Renal Events MedDRA Preferred Term by Decreasing Frequency within Event Category Safety Population Phase 3 Placebo-Controlled Analysis Set (GPHK, GPHL)

SMQ Scope Preferred Term	Placebo (N=958) n(%)	TZP 5mg (N=630) n(%)	TZP 10mg (N=948) n(%)	TZP 15mg (N=941) n(%)	TZP All (N=2519) n(%)
Participants with >=1 TEAE of Renal Events	6 (0.63)	6 (0.95)	8 (0.84)	5 (0.53)	19 (0.75)
Acute renal failure (SMQ)	3 (0.31)	4 (0.63)	8 (0.84)	4 (0.43)	16 (0.64)
Narrow	3 (0.31)	4 (0.63)	8 (0.84)	4 (0.43)	16 (0.64)
Acute kidney injury	2 (0.21)	3 (0.48)	6 (0.63)	4 (0.43)	13 (0.52)
Renal impairment	1 (0.10)	1 (0.16)	1 (0.11)	0	2 (0.08)
Renal failure	0	0	1 (0.11)	0	1 (0.04)
Chronic kidney disease (SMQ)	3 (0.31)	2 (0.32)	1 (0.11)	1 (0.11)	4 (0.16)
Narrow	3 (0.31)	2 (0.32)	1 (0.11)	1 (0.11)	4 (0.16)
Chronic kidney disease	2 (0.21)	2 (0.32)	0	1 (0.11)	3 (0.12)
Renal failure	0	0	1 (0.11)	0	1 (0.04)
Kidney fibrosis	1 (0.10)	0	0	0	0

The frequency of TEAEs within the SMQs of Acute renal failure or Chronic kidney disease was higher in participants with lower baseline eGFR in both tirzepatide and placebo groups. These results are consistent with results observed for the Placebo-Controlled Analysis Set (see below).

In terms of eGFR and UACR analyses, mean reductions from baseline in eGFR to Week 72 were small, with no clinically meaningful difference between tirzepatide groups. The percentages of participants shifting to higher eGFR categories were comparable in the

TZP_ALL (3.3%) and placebo groups (3.6%). The percent reduction in UACR from baseline at 72 Weeks was significantly greater in tirzepatide groups (range: 19.1% to 24.7%), compared to placebo: 6.6%. The percentage of participants who shifted to a higher UACR category was numerically smaller in TZP_ALL (7.0%) compared with placebo (10.3%), while the percentage of participants that shifted to a lower UACR category was numerically greater in TZP_ALL (7.5%) compared to placebo (4.7%).

Phase 3 Analysis Sets AS1C and AS2C
In the Phase 3 Placebo-Controlled Analysis Set (AS1C), a total of 21 (0.84%) participants receiving tirzepatide and 4 (0.48%) participants receiving placebo experienced at least 1 treatment-emergent renal event. Of these participants, 14 participants receiving tirzepatide and 3 participants receiving placebo were from the SURMOUNT-1 study.
A total of 7 participants in AS1C (TZP_ALL, 0.18%; placebo, 0.03%), all from the SURMOUNT-1 study (TZP_ALL, 6 participants; placebo, 1 participant), experienced at least 1 severe or serious renal event.

In the AS2C set, in a total of 79 (1.25%) participants with at least 1 treatment-emergent renal event (14 from the SURMOUNT-1) there was no incremental increase with higher dose groups in treatment-emergent renal events in AS2C. These findings were similar to those reported in the dose effect analysis set in the original T2DM application, in which the frequency of renal events for TZP_ALL was 1.27% and there was no dose-related effect. Incidence of AEs within the SMQs of Acute renal failure or chronic kidney disease were higher in tirzepatide-treated participants with baseline eGFR ≥30 to <60 mL/min/1.73 m2 compared to higher baseline eGFR categories. Results should be interpreted with caution due to the limited number of participants with low eGFR (≥30 to <60 mL/min/1.73 m2) at baseline (N=80).

In terms of eGFR and urine albumin/creatinine ratio (UACR) evaluation, the proportion of participants who maintained their eGFR category or shifted to a lower eGFR category was similar between tirzepatide groups and placebo group in AS1C and similar across the 3 tirzepatide dose groups in AS2C; the percentage of participants who shifted to a higher UACR category was lower in the tirzepatide groups compared to the placebo group in AS1C, and similar across the 3 tirzepatide dose groups in AS2C. There was a statistically significant reduction in mean percent change from baseline in UACR across all tirzepatide groups starting at Week 24 in AS2C.

It should be noted that in all Phase 3 studies, including SURMOUNT-1, patients with severe renal impairment were excluded.

In the initial T2DM dossier review no important issues about the renal safety of tirzepatide were identified. There are, however, some additional findings from SURMOUNT trials.
As noted above, in SURMOUNT trials a slightly higher percentage of tirzepatide patients than placebo reported renal events, mostly acute renal failure/acute kidney injury. In SURMOUNT-1 a total of 17 (0.7%) participants experienced at least 1 event of renal disorders. The most common was acute renal failure reported more frequently in the tirzepatide groups than in the placebo group [1 (0.2%), 4 (0.6%), 4 (0.6%), 4 (0.6%) in the placebo and the 3 tirzepatide groups respectively]. Serious events were generally rare and almost equally distributed. The numbers are small to permit firm conclusions and in many cases there were possible confounding factors and/or were associated with other AEs; also in general other renal parameters do not suggest a nephrotoxic effect of therapy. However, the

imbalances between treatment groups in the reports of acute renal failure/acute kidney injury are notable; also 'acute kidney injury' appears among the most common SAEs in post marketing reports.

The Applicant has provided further information and analysis of acute renal failure/acute kidney injury reports in SURMOUNT trials. It is agreed that, given the overall exposure to tirzepatide in the studies, the incidence of such AEs was very low and in the majority of cases there were various confounding factors, including other medical conditions, concomitant medication or relevant risk factors. It is noted, however, that in several cases, GI AEs were also reported which could have led to dehydration and in turn resulted in or contributed to renal impairment. A relevant warning is included in section 4.4 of the SmPC.
In the previous T2DM dossier review, no important issues about the renal safety of tirzepatide were identified. Also, in general other renal parameters examined in the tirzepatide studies so far do not suggest a nephrotoxic effect of therapy.

Overall, it is agreed that at present there is no sufficient evidence to confirm a causal direct relationship between the reported acute renal failure/injury events and tirzepatide treatment; no further action in terms of an update of the product information is required at this stage.

Hepatic disorders
SURMOUNT Set
Overall, the percentage of participants reporting hepatic events was similar in tirzepatide and placebo-treated participants (1.95% and 2.09%, respectively). Tirzepatide-treated participants with serum transaminases of >3×ULN and total bilirubin >2×ULN, as well as the participants with elevations of AST or ALT >10×ULN, all have potential explanations for the abnormalities, and did not meet criteria for drug-induced hepatotoxicity. The overall hepatic safety findings was consistent with those reported in the SCS.

In SURMOUNT-1, 3 tirzepatide-treated participants had serum aminotransferase and total bilirubin levels of >3×ULN and >2×ULN, respectively. Each of these participants had medical conditions to explain the elevated liver tests and did not meet Hy's Law criteria for drug-induced hepatotoxicity. In SURMOUNT-2, no participants had serum aminotransferase and total bilirubin levels of >3×ULN and >2×ULN, respectively.

Phase 3 Analysis Sets AS1C and AS2C
Overall, the percentage of participants reporting hepatic events was similar in tirzepatide and placebo-treated participants (1.81% and 2.06%, respectively) in AS1C. In AS2C, 2.39% of tirzepatide-treated participants reported a hepatic TEAE, with no difference across the 3 tirzepatide dose groups.

In terms of liver enzymes treatment with tirzepatide led to a mean decrease in ALT and AST. The percentage of participants with ALT or AST ≥3×ULN or ≥5×ULN was similar in tirzepatide- and placebo-treated participants in AS1C. The percentage of participants with ALT or AST ≥10×ULN was 0.4% (12 participants) in tirzepatide-treated participants vs. 0% in placebo-treated participants in AS1C. All of the cases had other causes associated with the elevated liver tests other than drug-induced hepatotoxicity. There was no difference across the 3 tirzepatide dose groups in AS2C for ALT or AST ≥3×ULN, ≥5×ULN, or ≥10×ULN. In AS3C, 3 participants had serum ALT and total bilirubin levels within the range of Hy's law criteria for hepatotoxicity, but each participant had a medical reason explaining the elevated liver tests and did not meet criteria for drug-induced hepatotoxicity. As the 3

participants with serum transaminases of >3×ULN and total bilirubin >2×ULN, as well as the participants with elevations of AST or ALT >10×ULN, all have causes explaining the abnormalities, and did not meet criteria for drug-induced hepatotoxicity, the overall hepatic safety findings remain consistent with those reported in the original T2DM application.

Gallbladder-Related Disorders

SURMOUNT Set

Treatment-emergent gallbladder-related disorders were reported in 1.98% of tirzepatide-treated participants and 1.67% of placebo-treated participants. The most frequently reported events were cholelithiasis, cholecystitis acute, and cholecystitis. The incidence of cholecystitis when combining terms cholecystitis and cholecystitis acute was 0.67% for tirzepatide and 0.21% for placebo.

Table 38. Summary of Treatment-Emergent Acute Gallbladder Disease MedDRA Preferred Term by Decreasing Frequency within SMQ Safety Population Phase 3 Placebo-Controlled Analysis Set (GPHK, GPHL)

SMQ Scope Preferred Term	Placebo (N=958) n (%)	TZP 5mg (N=630) n (%)	TZP 10mg (N=940) n (%)	TZP 15mg (N=941) n (%)	TZP ALL (N=2519) n (%)
Participants with >=1 TEAE of Acute Gallbladder Disease	16 (1.67)	12 (1.90)	22 (2.32)	16 (1.70)	50 (1.98)
Gallbladder related disorders (SMQ)	16 (1.67)	12 (1.90)	19 (2.00)	13 (1.38)	44 (1.75)
Narrow	16 (1.67)	12 (1.90)	19 (2.00)	13 (1.38)	44 (1.75)
Cholelithiasis	10 (1.04)	7 (1.11)	11 (1.16)	10 (1.06)	28 (1.11)
Cholecystitis acute	2 (0.21)	1 (0.16)	5 (0.53)	4 (0.43)	10 (0.40)
Cholecystitis	0	4 (0.63)	3 (0.32)	0	7 (0.28)
Cholecystitis chronic	3 (0.31)	1 (0.16)	1 (0.11)	3 (0.32)	5 (0.20)
Cholecystectomy	0	2 (0.32)	2 (0.21)	0	4 (0.16)
Biliary colic	0	0	1 (0.11)	0	1 (0.04)
Biliary dyskinesia	1 (0.10)	0	0	0	0
Gallbladder enlargement	1 (0.10)	0	0	0	0
Gallstone related disorders (SMQ)	11 (1.15)	7 (1.11)	11 (1.16)	11 (1.17)	29 (1.15)
Narrow	11 (1.15)	7 (1.11)	11 (1.16)	11 (1.17)	29 (1.15)
Cholelithiasis	10 (1.04)	7 (1.11)	11 (1.16)	10 (1.06)	28 (1.11)
Bile duct stone	0	0	0	1 (0.11)	1 (0.04)
Obstructive pancreatitis	2 (0.21)	0	0	0	0

Severe or serious gallbladder related events were reported by 28 tirzepatide-treated (1.11%) and 8 placebo-treated (0.84%) participants. Of these, 25 tirzepatide-treated participants reported serious events. The most frequently reported severe or serious events in tirzepatide-treated participants were cholelithiasis (15 participants [0.60%]), cholecystitis acute (8 participants [0.32%]), and cholecystitis (3 participants [0.12%]). The incidence of gallbladder-related events increased with higher weight reduction in tirzepatide-treated participants. Generally these results are consistent with the Placebo- Controlled Analysis Set in the SCS.

Phase 3 Analysis Sets AS1C and AS2C

In the Phase 3 Placebo-Controlled Analysis Set (AS1C) treatment-emergent gallbladder disease was reported in 40 (1.61%) participants in the TZP_ALL group and 8 (0.97%) participants in the placebo group (Table 39). All the placebo-treated participants and 37 of the 40 tirzepatide-treated participants were from SURMOUNT-1. The most frequently reported gallbladder-related event was cholelithiasis (TZP_ALL, 0.88%; placebo, 0.73%). Cholecystitis, including PTs of cholecystitis and acute cholecystitis, was more frequently reported in tirzepatide groups compared with placebo (TZP_ALL, 0.5%; placebo, 0%). All the cholecystitis-related events occurred in the SURMOUNT-1 study.

Table 39. Summary of Treatment-Emergent Gallbladder Disease Safety Population Participants with Overweight/Obesity in Phase 3 Placebo- Controlled Analysis Set (AS1C)

	n (%)				
Preferred Term	Placebo (N=827)	TZP 5 mg (N=832)	TZP 10 mg (N=830)	TZP 15 mg (N=828)	TZP_ALL (N=2490)
Participants with ≥1 TEAE	8 (0.97)	15 (1.80)	17 (2.05)	8 (0.97)	40 (1.61)
Gallbladder related disorders	8 (0.97)	15 (1.80)	15 (1.81)	5 (0.60)	35 (1.41)
Cholelithiasis	6 (0.73)	9 (1.08)	9 (1.08)	4 (0.48)	22 (0.88)
Cholecystitis	0	4 (0.48)	3 (0.36)	0	7 (0.28)
Cholecystitis acute	0	1 (0.12)	4 (0.48)	1 (0.12)	6 (0.24)
Cholecystitis chronic	3 (0.36)	1 (0.12)	1 (0.12)	3(0.36)	5 (0.20)
Cholecystectomy	0	2 (0.24)	1 (0.12)	0	3 (0.12)
Biliary colic	0	1 (0.12)	0	0	1 (0.12)
Gallstone related disorders	6 (0.73)	9 (1.08)	9 (1.08)	5 (0.60)	23 (0.92)
Cholelithiasis	6 (0.73)	9 (1.08)	9 (1.08)	4 (0.48)	22 (0.88)
Bile duct stone	0	0	0	1 (0.12)	1 (0.04)
Obstructive pancreatitis	1 (0.12)	0	0	0	0
Biliary tract disorders	1 (0.12)	1 (0.12)	2 (0.24)	4 (0.48)	7 (0.28)
Bile duct stone	0	0	0	1 (0.12)	1 (0.04)
Biliary colic	0	1 (0.12)	0	0	1 (0.04)
Biliary obstruction	0	0	0	1 (0.12)	1 (0.04)
Cholangitis acute	0	0	0	1 (0.12)	1 (0.04)
Hyperbilirubinemia	0	0	1 (0.12)	0	1 (0.04)
Jaundice	0	0	0	1 (0.12)	1 (0.04)
Post cholecystectomy syndrome	0	0	0	1 (0.12)	1 (0.04)
Sphincter of Oddi dysfunction	0	0	1 (0.12)	0	1 (0.04)
Obstructive pancreatitis	1 (0.12)	0	0	0	0

Abbreviations: N = number of participants in treatment group; n = number of participants with at least 1 treatment-emergent adverse event; TEAE = treatment-emergent adverse event; TZP = tirzepatide.

A total of 22 (0.88%) tirzepatide-treated participants and 5 (0.60%) placebo-treated participants reported serious or severe gallbladder-related events in AS1C. All 27 participants were from SURMOUNT-1. The most frequently reported serious or severe gallbladder-related events in tirzepatide-treated participants were cholelithiasis.

In the Phase 3 Dose Effect Analysis Set (AS2C) a total of 82 (1.30%) tirzepatide-treated participants reported gallbladder-related events. The percentage was similar to the original T2DM application (1.00%). Of the 82 participants, 37 participants were from SURMOUNT-1, and 45 were from Phase 3 SURPASS studies. There were comparable percentages of participants with gallbladder-related events in each tirzepatide dose group and the most frequently-reported event was cholelithiasis (5 mg, 0.85%; 10 mg, 0.81%; 15 mg, 0.57%), similar to the dose effect analysis set in the original T2DM application. There was a trend observed with increased gallbladder-related events and higher weight reduction, but the small numbers of events within each weight reduction category preclude definitive interpretation. A total of 36 (0.57%) tirzepatide-treated participants reported serious or severe gallbladder-related events in AS2C, most commonly cholelithiasis. As in the original T2DM application, there was no relationship between tirzepatide dose and incidence of serious or severe gallbladder-related events.

The increased risk of cholelithiasis with tirzepatide and other GLP-1 RAs is known and cholelithiasis is included in the SmPC.

Gallbladder related events were more frequently reported in the CWM than in previous T2DM studies, which is not unexpected for a population with more extreme obesity. Severe or serious gallbladder related events appear also more common in the CWM population. In

SURMOUNT-1 there were 45 (1.8%) participants that experienced at least 1 TEAE of gallbladder disease, most frequently cholelithiasis which was most common with tirzepatide 5 mg (n=7, 1.1%) and 10 mg (n=9, 1.4%) than placebo (n=6, 0.9%) and tirzepatide 15-mg (n=3, 0.5%). TEAEs of 'cholecystitis' and of 'cholecystitis acute' only occurred in tirzepatide participants (in total n=13).

Generally, in the SURMOUNT trials the evidence suggests that increased weight loss appears to be related with higher risk of gallbladder events, with greater rates seen in participants with maximum weight reduction ≥20%. This has been reflected in the SmPC.

The SmPC has been updated to include also 'cholecystitis'.

Exocrine Pancreas Safety

SURMOUNT Set

In the 2 SURMOUNT trials there were a total of 14 (0.56%) tirzepatide-treated participants with 20 events and 4 (0.42%) placebo-treated participants with 4 events who reported a pancreatic event.

There was no imbalance in adjudication-confirmed pancreatitis between tirzepatide- and placebo-treated participants, with 5 (0.20%) TZP_ALL and 2 (0.21%) placebo participants each confirmed to have 1 event of acute pancreatitis. There were no cases of chronic pancreatitis or unknown (unable to determine), and no cases were adjudicated as severe or critical.

Table 40. Summary of Adjudication Confirmed Pancreatic Events – AESI MedDRA Preferred Term by Decreasing Frequency within Event Category Safety Population Phase 3 Placebo-Controlled Analysis Set (GPHK, GPHL)

SMQ Scope Preferred Term	Placebo (N=958) n (%)	TZP 5mg (N=630) n (%)	TZP 10mg (N=948) n (%)	TZP 15mg (N=941) n (%)	TZP ALL (N=2519) n (%)
Participants with >=1 Adjudication Confirmed Pancreatic Events	2 (0.21)	1 (0.16)	1 (0.11)	3 (0.32)	5 (0.20)
Acute pancreatitis (SMQ)	0	1 (0.16)	1 (0.11)	3 (0.32)	5 (0.20)
Broad	0	0	1 (0.11)	0	1 (0.04)
Abdominal pain upper	0	0	1 (0.11)	0	1 (0.04)
Narrow	0	1 (0.16)	0	3 (0.32)	4 (0.16)
Pancreatitis acute	0	1 (0.16)	0	2 (0.21)	3 (0.12)
Pancreatitis	0	0	0	1 (0.11)	1 (0.04)
Obstructive pancreatitis	2 (0.21)	0	0	0	0

Tirzepatide was associated with increases in p-amylase and lipase. The percentage of participants with p-amylase and lipase >3×ULN were 1.39% and 1.55%, respectively, for tirzepatide-treated participants and 0.84% and 0.94%, respectively, for placebo treated participants. In SURMOUNT-2, of 28 participants with p-amylase >3×ULN, 3 participants had pancreatic events sent for adjudication. None of the events were positively adjudicated. Similarly, of 27 participants with lipase >3×ULN, 4 participants had pancreatic events sent for adjudication. None of the events were positively adjudicated.

Amylase and lipase levels increased during the first 12 weeks of treatment, and then plateaued for the remainder of the treatment period, followed by decreases during the 4-week safety follow-up. All mean values remained within the normal range. This pattern, and degree of elevation (>3×ULN) in pancreatic enzymes in tirzepatide-treated participants were consistent with results observed in the Placebo-Controlled Analysis Set in the SCS.

Phase 3 Analysis Sets AS1C and AS2C

In the Phase 3 Placebo-Controlled Analysis Set (AS1C) Table 41 summarises *investigator-reported events, non-investigator-reported triggered events, and adjudicated* pancreatic events. There were a total of 15 (0.60%) tirzepatide-treated participants with 24 events and 2 (0.24%) placebo-treated participants with 2 events of suspected pancreatitis sent for CEC-adjudication (SURMOUNT-1: TZP_ALL, 11 participants; placebo, 1 participant).
Of these: 12 tirzepatide-treated and 2 placebo-treated participants were reported by the investigators, and 3 participants with 7 events were non-investigator-reported triggered events identified by prespecified MedDRA PTs. All 3 participants were from the tirzepatide 15 mg-group in SURMOUNT-1. In total, 3 (0.12%) tirzepatide-treated participants and 1 (0.12%) placebo-treated participant were each confirmed by adjudication to have 1 event of acute pancreatitis.

There were no cases of chronic pancreatitis or unknown (unable to determine), and no cases were severe or critical. These cases all occurred in SURMOUNT-1.

Table 41. Summary of Adjudicated Pancreatic Events Participants with Overweight/Obesity Phase 3 Placebo-Controlled Analysis Set (AS1C)

	n (%); events				
Events	**Placebo (N=827)**	**TZP 5 mg (N=832)**	**TZP 10 mg (N=830)**	**TZP 15 mg (N=828)**	**TZP_ALL (N=2490)**
Investigator-reported events	2 (0.24); 2	5 (0.60); 7	6 (0.72); 9	1 (0.12); 1	12 (0.48); 17
Non-investigator reported triggered events	0	0	0	3 (0.36); 7	3 (0.12); 7
CEC pancreatitis assessment	2 (0.24); 2	5 (0.60); 7	6 (0.72); 9	4 (0.48); 8	15 (0.60); 24
No	1 (0.12); 1	4 (0.48); 6	6 (0.72); 8	3 (0.36); 7	13 (0.52); 21
Unknown (unable to determine)	0	0	0	0	0
Yes	1 (0.12); 1	1 (0.12); 1	1 (0.12); 1	1 (0.12); 1	3 (0.12); 3
Acute pancreatitis	1 (0.12); 1	1 (0.12); 1	1 (0.12); 1	1 (0.12); 1	3 (0.12); 3
Chronic pancreatitis	0	0	0	0	0
Diagnostic criteria used to confirm acute pancreatitis					
Symptoms and imaging	0	1 (0.12); 1	0	0	1 (0.04); 1
Symptoms and elevated enzymes	0	0	1 (0.12); 1	1 (0.12); 1	2 (0.08); 2
Imaging and asymptomatic elevated enzymes	0	0	0	0	0
Symptoms, imaging, and elevated enzymes	1 (0.12); 1	0	0	0	0

Abbreviations: CEC = clinical endpoint committee; N = total number of participants in specified treatment group; n = number of participants with at least 1 pancreatic event; TZP = tirzepatide.

In AS2C there were a total of 55 participants with 70 events of suspected pancreatitis sent for CEC-adjudication. In total, 11 (0.17%) tirzepatide-treated participants were determined to have acute pancreatitis by adjudication. Similar percentages of participants in each of the 3 tirzepatide groups had adjudication-confirmed acute pancreatitis. Of the 11 participants with acute pancreatitis, 3 were from SURMOUNT-1 (0.16% of TZP-treated participants in SURMOUNT-1), and 8 participants were from Phase 3 T2DM studies (0.18% of TZP-treated participants in the Phase 3 T2DM studies).

In terms of pancreatic enzymes in general tirzepatide was found to be associated with increases in p-amylase and lipase. More TZP_ALL participants had elevated pancreatic enzymes >3×ULN compared to placebo (0.6% vs. 0% p-amylase, and 1.4% vs. 0.4% lipase) in AS1C, but there was no treatment imbalance in participants with elevated enzymes across tirzepatide doses (AS2C). Time analysis suggested that after peaking between 12 and 40 weeks of treatment, pancreatic enzyme levels remained relatively stable through 72 weeks, and decreased during the 4-week safety follow up. There was no relationship between elevated pancreatic enzymes and adjudication confirmed pancreatitis.

Elevations in pancreatic enzymes in tirzepatide-treated participants were consistent with the profile of tirzepatide reported in the original T2DM application as well as currently marketed incretin-based therapies in this population.

Overall, pancreatitis events were rare in all treatment groups and the results appear consistent with the tirzepatide known profile as well as other GLP-1 RA. Mean lipase and amylase levels increased with tirzepatide but in the absence of other signs and symptoms, such elevations alone are not considered predictive of acute pancreatitis. Nevertheless, information about acute pancreatitis, and lipase and amylase increases is included in the product information.

Cardiovascular Safety

One known effect of GLP-1 receptor agonists is an increase in heart rate (HR), usually with either no change or a mild reduction in blood pressure (BP). Changes in HR attenuate over time and in long-term cardiovascular (CV) outcomes studies, GLP-1 RAs have been associated with reduced risk for major adverse cardiac events (MACE) in participants with T2DM. A CV meta-analysis was performed in the tirzepatide T2DM clinical program for the original T2DM application. Cumulatively, a total of 142 participants experienced the primary endpoint (adjudicated MACE-4) across all seven Phase 3 clinical studies. By comparing pooled tirzepatide vs. pooled comparators, a hazard ratio of 0.80 (95% CI, 0.57 to 1.11) was attained on the primary endpoint. The meta-analysis results demonstrated that treatment with tirzepatide was not associated with excess CV risk.

Blood Pressure

In SURMOUNT trials (SURMOUNT Set) treatment with tirzepatide was associated with decreases in systolic and diastolic blood pressure compared with placebo. Maximal mean decreases in SBP and DBP through Week 72 were:

	SBP (mmHg)	DBP (mmHg)
Placebo	-1.8	-1.1
TZP 5 mg	-7.7	-5.0
TZP 10 mg	-7.8	-4.4
TZP 15 mg	-8.3	-4.2

In AS1C reductions in mean SBP and DBP were greater with tirzepatide compared to placebo. Across dose groups in AS2C, greater reductions in SBP were observed with increasing tirzepatide dose (6.3, 7.4, and 8.0 mmHg for tirzepatide 5, 10, and 15 mg, respectively); reductions in mean DBP from baseline were similar across the tirzepatide dose groups (3.4 to 3.9 mmHg). The dose-related effects were similar to the original T2DM application but the decreases in SBP and DBP were modestly more pronounced.

In relation to reports of 'hypotension' in SURMOUNT trials more tirzepatide-treated participants (66, 2.62%) reported such events (in wider terms) than placebo (10, 1.04%). For TZP_ALL, the frequency of hypotension-related events was higher in those who were taking an antihypertensive medication (2.16%) relative to those who were not (1.23%). 7 severe or serious events were reported in the broad cluster of hypotension (TZP_ALL, 6 [0.24%]; placebo, 1 [0.10%]) and all events resolved. Of the 6 events in tirzepatide-treated participants, 4 events were reported in SURMOUNT-1, including 2 SAEs of hypotension. More hypotension-related TEAEs, were also observed with tirzepatide (62 participants, 2.49%) than placebo (6 participants, 0.73%) in A1SC. These TEAEs were infrequent and primarily mild and moderate in severity for participants in AS1C and AS2C. Hypotension-related events were reported with a greater frequency in SURMOUNT-1 than in the T2DM

studies in AS1C and AS2C.

Tirzepatide treatment is associated with decreases in blood pressure. Reports of hypotension appear more common in the CWM trials than previously seen in T2DM studies. This has been reflected in the SmPC.

Heart rate

In SURMOUNT trials (SURMOUNT Set) the mean pulse rate increased in all tirzepatide groups by Week 4 and reached maximum value during dose escalation. Maximal increases in pulse rate through Week 72 were: placebo: 0.4 bpm, tirzepatide 5 mg: 2.7 bpm, tirzepatide 10 mg: 5.0 bpm, and tirzepatide 15 mg: 4.4 bpm. Mean pulse rate then gradually decreased throughout the study from maximum values such that the difference from placebo at 72 weeks was 0.5 to 2.1 bpm across tirzepatide doses. At the safety follow-up, the mean pulse rate in the tirzepatide groups was approximately 2-3 bpm lower than placebo and baseline values.

In A1SC there were no clinically meaningful changes from baseline over time for pulse rate in the placebo group but the mean pulse rate began to increase in all tirzepatide groups by Week 4 and reached maximum value during dose escalation. The maximal increases in pulse rate were: placebo: 0.8 bpm, tirzepatide 5 mg: 2.7 bpm, tirzepatide 10 mg: 5.2 bpm, and tirzepatide 15 mg: 4.5 bpm. The maximal increases in pulse rate were similar to those reported in the placebo-controlled analysis set in the original T2DM application (3.3 to 5.2 bpm). A dose-dependent increase to maximum value of mean pulse rate (3.4 to 5.0 bpm) was also observed across tirzepatide dose groups in AS2C. Mean pulse rate then gradually decreased from maximum throughout the study treatment period wherein the difference from placebo at 72 weeks was 0.5 to 2.4 bpm across tirzepatide doses.

A further assessment of tirzepatide effect on pulse rate changes in the SURMOUNT-1 ABPM substudy confirmed that increases in pulse rate are small and consistent with the assessment of pulse rate measured by routine vital signs.

Increase in HR is a known adverse effect of therapy with GLP-1 RA, still of uncertain clinical relevance. The findings in CWM trials appear consistent with previous tirzepatide studies. Relevant information is already included in the product information.

Arrhythmias and Cardiac Conduction Disorders

Similar frequencies of participants in TZP_ALL (3.97%) and placebo (4.07%) experienced at least 1 TEAE of arrhythmia and cardiac conduction disorders in the SURMOUNT Set. 10 participants reported at least 1 severe or serious TEAE of arrhythmia or cardiac conduction disorder, and the frequency was similar between TZP_ALL (0.32%) and placebo (0.21%) groups. Also in AS1C similar frequencies of participants in TZP_ALL (88; 3.53%) and placebo (27; 3.26%) experienced at least 1 TEAE of arrhythmia and cardiac conduction disorders. A total of 7 participants experienced at least 1 serious or severe TEAE of arrhythmia and cardiac conduction disorders in AS1C, and the frequency was similar between TZP_ALL (0.20%) and placebo (0.24%). There were 6 events experienced by a total of 5 tirzepatide treated participants (3 events in 3 participants from SURMOUNT-1).

Investigator-reported and CEC-adjudicated MACE

In SURMOUNT Set, fewer tirzepatide-treated participants compared to placebo had at least 1 MACE event confirmed by CEC (TZP_ALL, 0.64%; placebo, 0.94%) (Table 42). This is

consistent with the Placebo-Controlled Analysis Set in the SCS and the overall Mounjaro CV meta-analysis in which tirzepatide was not associated with excess CV-related risk.

Table 42. Summary of Composite MACE, its Component, and All Cause Death Modified Intent-to-Treat Population – Safety Analysis Set Phase 3 Placebo-Controlled Analysis Set (GPHK, GPHL)

	Placebo N=958 n(%)	TZP 5mg N=630 n(%)	TZP 10mg N=948 n(%)	TZP 15mg N=941 n(%)	TZP ALL N=2519 n(%)
Reported by Investigator					
MACE	9 (0.94)	5 (0.79)	8 (0.84)	6 (0.64)	19 (0.75)
Death Due to CV Cause	3 (0.31)	0	1 (0.11)	0	1 (0.04)
MI	1 (0.10)	2 (0.32)	3 (0.32)	2 (0.21)	7 (0.28)
Hospitalization for Unstable Angina	0	1 (0.16)	1 (0.11)	1 (0.11)	3 (0.12)
Hospitalization for Heart Failure	3 (0.31)	0	0	1 (0.11)	1 (0.04)
Coronary Interventions	3 (0.31)	0	3 (0.32)	2 (0.21)	5 (0.20)
CABG	0	0	0	0	0
PCI	3 (0.31)	0	3 (0.32)	2 (0.21)	5 (0.20)
Cerebrovascular Events	3 (0.31)	2 (0.32)	4 (0.42)	2 (0.21)	8 (0.32)
Stroke	1 (0.10)	2 (0.32)	3 (0.32)	2 (0.21)	7 (0.28)
TIA	2 (0.21)	0	1 (0.11)	0	1 (0.04)
All Cause Death	4 (0.42)	4 (0.63)	4 (0.42)	1 (0.11)	9 (0.36)

In A1SC, a similar percentage of participants in tirzepatide groups compared to placebo had at least 1 investigator-reported potential MACE event submitted for adjudication [TZP_ALL, 0.72%; placebo, 0.85%, and had at least 1 MACE-related event confirmed by CEC [TZP_ALL, 0.68%; placebo, 0.73% (Table 43]. There were a total of 23 participants with CEC adjudicated events, of which 9 in the TZP_ALL group and 5 in the placebo group were from SURMOUNT-1.

Table 43. Summary of Composite MACE, Its Component, and All Cause Death mITT Population Participants with Overweight/Obesity in Phase 3 Placebo- Controlled Analysis Set (AS1C)

	n (%)				
MACE Confirmed by CEC	**Placebo (N= 827)**	**TZP 5 mg (N= 832)**	**TZP 10 mg (N= 830)**	**TZP 15 mg (N= 828)**	**TZP_ALL (N=2490)**
MACE	6 (0.73)	7 (0.84)	8 (0.96)	2 (0.24)	17 (0.68)
Death due to CV cause	3 (0.36)	1 (0.12)	1 (0.12)	0	2 (0.08)
MI	1 (0.12)	1 (0.12)	3 (0.36)	1 (0.12)	5 (0.20)
Hospitalization for Unstable Angina	1 (0.12)	0	0	0	0
Hospitalization for Heart Failure	0	3 (0.36)	1 (0.12)	0	4 (0.16)
Coronary Interventions	2 (0.24)	0	2 (0.24)	2 (0.24)	4 (0.16)
CABG	0	0	0	0	0
PCI	2 (0.24)	0	2 (0.24)	1 (0.12)	3 (0.12)
Cerebrovascular Events	2 (0.24)	2 (0.24)	3 (0.36)	0	5 (0.20)
Stroke	1 (0.12)	2 (0.24)	2 (0.24)	0	4 (0.16)
TIA	1 (0.12)	0	1 (0.12)	0	1 (0.04)
All Cause Death	4 (0.48)	4 (0.48)	2 (0.24)	1 (0.12)	7 (0.28)

Abbreviations: CABG = coronary artery bypass graft; CEC = clinical endpoint committee; CV = cardiovascular; MACE = major adverse cardiovascular events; MI = myocardial infarction; mITT= modified intent-to-treat population; N = number of participants in the analysis population; n = number of participants in the specified category; PCI = percutaneous coronary intervention; TIA= transient ischemic attack; TZP = tirzepatide.

The CV findings in the CWM trials, including MACE, appear consistent with the known profile of tirzepatide and its previous T2DM studies.

As noted above, so far no excess CV risk has been identified, while tirzepatide appears to have a positive effect on CV parameters such as blood pressure and lipids (see Efficacy above). The ongoing CV outcome trial in patients with T2DM (SURPASS-CVOT) and the morbidity and mortality outcomes trial in people with obesity or overweight without T2DM (SURMOUNT-MMO) are expected to provide further information on the CV effects of tirzepatide in future, including an assessment of the potential benefit.

Thyroid Safety

C-Cell Hyperplasia and Thyroid Malignancies

In SURMOUNT Set, a total of 2 TEAEs of papillary thyroid cancer (TZP_ALL, 1 [0.04%]; placebo, 1 [0.10%]) were reported. Both occurred in SURMOUNT-1 and were included in the SCS. No cases were reported in SURMOUNT-2. There were no events of MTC or C-cell hyperplasia reported in the tirzepatide or placebo treatment group.

In Phase 3 Placebo-Controlled Analysis Set (AS1C) there were a total of 2 TEAEs of papillary thyroid cancer (tirzepatide 15 mg, 1 [0.12%]; placebo, 1 [0.12%]). Both events occurred in SURMOUNT-1. No events of MTC were reported in AS1C. in Phase 3 Dose Effect Analysis Set (AS2C) a total of 4 TEAEs of papillary thyroid cancer (tirzepatide 5 mg, 1 [0.05%]; tirzepatide 10 mg, 2 [0.10%]; tirzepatide 15 mg, 1 [0.05%]) were reported. Again no events of MTC.

Calcitonin

Phase 3 Placebo-Controlled Analysis Set (AS1C)

In SURMOUNT Set, generally there was no difference in the percentage of participants who shifted to a higher calcitonin category postbaseline between tirzepatide and placebo groups. There were 9 participants (5 tirzepatide-treated) with a postbaseline increase in calcitonin of at least 50% and an absolute value of at least 35 ng/L. Of the 5 tirzepatide-treated participants meeting these criteria, 4 had elevated calcitonin levels at baseline and all but one reported improved calcitonin levels at the safety follow-up visit or last laboratory evaluation. One tirzepatide-treated participant who had normal calcitonin levels at baseline was retested 9 days later with a retest value within normal limits. Four of the above 5 tirzepatide-treated participants are from SURMOUNT-1.

In AS1C nearly all participants had baseline calcitonin values ≤20 ng/L, with 5 tirzepatide-treated participants having values >20 to ≤35 ng/L. During the study period, most participants remained in the same category as at baseline. There was no difference in the percentage of participants who shifted to a higher calcitonin category postbaseline between tirzepatide and placebo groups. No notable dose-related effect was seen in AS2C
Overall, cases of tirzepatide-treated participants with postbaseline increase in calcitonin ≥50% and an absolute value ≥35 ng/L were not clinically relevant, as all but 2 cases reported decreased calcitonin levels upon repeat evaluation, regardless of study drug continuation.

In general, the CWM trial findings appear consistent with previous T2DM studies. There is no evidence of excess risk of MTC, C-cell hyperplasia, or clinically important increases in calcitonin levels with tirzepatide treatment.

Hypoglycaemia

Because the risk of hypoglycaemia is expected to be different in patients without T2DM vs. those with T2DM, hypoglycaemia was evaluated separately. Separate evaluation of these 2 populations is also warranted because the assessment of hypoglycaemia in the CWM SURMOUNT-1 study was distinct from the T2DM studies. Compared to T2DM studies in which glucometers were provided to all participants, SURMOUNT-1 did not include the routine use of glucometers to systematically capture and report hypoglycaemia.

SURMOUNT-1

Severe hypoglycaemia: of the 1896 participants exposed to tirzepatide in SURMOUNT-1, only 1 (0.05%) participant reported 1 episode of severe hypoglycaemia. The event occurred

in a hospital setting, in a participant experiencing multiple organ failure, including acute hepatic failure, which resulted in death.

The percentages and rates of tirzepatide-treated participants reporting hypoglycaemia with BG <54 mg/dL or severe hypoglycaemia were low, but higher than placebo-treated participants in SURMOUNT-1 (Table 44). The majority (26 of 34 [76%]) of hypoglycaemic events in tirzepatide-treated participants in SURMOUNT-1 were not associated with reported symptoms.

Table 44. Summary of Hypoglycaemia Incidence and Rate with BG <54 mg/dL or Severe Hypoglycaemia in SURMOUNT-1 Primary Study Period (Week 0-72 + Visit 801)

Parameter	Placebo (N=643)	TZP 5 mg (N=630)	TZP 10 mg (N=636)	TZP 15 mg (N=630)
n (%); Episodes	1 (0.16); 1	9 (1.43); 10	10 (1.57); 13	10 (1.59); 11
Aggregated rate/year	0.001	0.011	0.015	0.013
Group mean	0.001	0.012	0.015	0.012
Relative rate[a] (95% CI)	--	9.9 (1.2, 78.4)	12.6 (1.6, >100)	10.6 (1.4, 83.4)

Abbreviations: BG = blood glucose; CI = confidence interval; N = number of participants in population with baseline and postbaseline value at specified time point; n = number of participants with hypoglycemia; TZP = tirzepatide.

[a] TZP/placebo

SURMOUNT-2

To minimise the risk for hypoglycaemia in SURMOUNT-2, participants taking insulin secretagogues (for example, sulfonylurea) were to have their dose halved (or stopped if already on the lowest dose) at randomisation.

No participants in SURMOUNT-2 reported episodes of severe hypoglycaemia. The percentages of tirzepatide-treated participants reporting clinically significant hypoglycaemia with BG <54 mg/dL were higher than placebo-treated participants in SURMOUNT-2 (TZP_ALL, 26 [4.17%]; placebo, 4 [1.27%]), but the rates (tirzepatide 10 mg: 0.04 episodes/year; tirzepatide 15 mg: 0.06 episodes/year; placebo: 0.09 episodes/year) were similar.

Table 45. Summary and Analysis of Hypoglycaemia Incidence and Rate with Blood Glucose <54 mg/dL (<3.0 mmol/L) or Severe Hypoglycaemia mITT Population – Safety Analysis Set

parameters	Placebo	TZP 10mg	TZP 15mg
Baseline			
N2	315	312	311
Incidence: n (%)	2 (0.63)	0 (0)	0 (0)
Number of events	4	0	0
Aggregated rate per year	0.32	0	0
Group mean (SE)	0.27 (0.21)	0.00 (0.00)	0.00 (0.00)
Relative rate for TZP/placebo (95% CI)	-	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)
Post Baseline (Week 0-72 + Visit 801)			
N2	315	312	311
Incidence: n (%)	6 (1.90)	11 (3.53)	15 (4.82)
Number of events	43	17	24
Aggregated rate per year	0.10	0.04	0.05
Group mean (SE)	0.07 (0.06)	0.06 (0.03)	0.07 (0.03)
Relative rate for TZP/placebo (95% CI)	-	0.86 (0.18, 4.14)	0.99 (0.24, 4.13)

A total of 688 (73.3%) participants were not on an SU at baseline (Visit 3). Of those participants, 10 in all tirzepatide groups and 1 in the placebo group had ≥1 episode of hypoglycaemia with BG <54 mg/dL (<3.0 mmol/L) at any time postbaseline when excluding hypoglycaemic events that occurred after initiation of a new antihyperglycemic therapy. The incidence of hypoglycaemia with BG <54 mg/dL (<3.0 mmol/L) was higher in the tirzepatide groups than in the placebo group. The rate of hypoglycaemia with BG <54 mg/dL (<3.0 mmol/L) was similar across the tirzepatide groups and the placebo group. For all three treatment groups, the incidence and rate of clinically significant hypoglycaemia with blood glucose <54 mg/dL (<3.0 mmol/L) was higher for participants with an SU at baseline than for those without an SU.

Overall, the CWM trial data do not suggest any higher risk of hypoglycaemia over the rates seen in the previous T2DM studies.

Hypersensitivity Reactions

SURMOUNT Set

Overall, there were higher numbers of patients reporting TEAEs of hypersensitivity reactions among those who received tirzepatide than placebo (TZP_ALL, 5.12%; placebo, 3.13%; Table 46). The percentage of participants reporting immediate (occurring within 24 hours of study drug administration) hypersensitivity reactions was higher in tirzepatide-treated compared to placebo-treated participants (TZP_ALL, 2.14%; placebo, 0.42%). The percentage of participants reporting non-immediate (more than 24 hours) hypersensitivity reactions was again numerically higher in tirzepatide-treated compared to placebo-treated participants (TZP_ALL, 3.49%; placebo, 2.71%). Both types of events were driven by cutaneous reactions, and the majority of cases were mild or moderate, with no serious events reported. Overall, three participants from SURMOUNT-1 (on tirzepatide 10 and 15 mg) reported severe hypersensitivity reactions (dermatitis and rush). One participant from

SURMOUNT-1 (on tirzepatide 10 mg) who had a severe event also reported a separate anaphylactic reaction. The event was moderate in severity and did not lead to treatment discontinuation.

Table 46. Summary of Treatment-Emergent Hypersensitivity Reactions MedDRA Preferred Term by Decreasing Frequency within Event Category Safety Population Phase 3 Placebo-Controlled Analysis Set (GPHK, GPHL)

Event Category Scope Preferred Term	Placebo (N=958) n(%)	TZP 5mg (N=630) n(%)	TZP 10mg (N=948) n(%)	TZP 15mg (N=941) n(%)	TZP All (N=2519) n(%)
Participants with >=1 TEAE of Hypersensitivity Reactions	30 (3.13)	31 (4.92)	47 (4.96)	51 (5.42)	129 (5.12)
Search on Day of Drug Administration					
Anaphylactic reaction (Narrow) *a	0	0	1 (0.11)	0	1 (0.04)
Anaphylactic reaction	0	0	1 (0.11)	0	1 (0.04)
Anaphylactic reaction (Algorithm, not Narrow) *a	0	0	0	0	0
Hypersensitivity (Narrow)	30 (3.13)	31 (4.92)	47 (4.96)	51 (5.42)	129 (5.12)
Hypersensitivity	5 (0.52)	4 (0.63)	8 (0.84)	9 (0.96)	21 (0.83)
Rash	3 (0.31)	6 (0.95)	7 (0.74)	7 (0.74)	20 (0.79)
Dermatitis contact	4 (0.42)	3 (0.48)	4 (0.42)	7 (0.74)	14 (0.56)
Urticaria	4 (0.42)	4 (0.63)	5 (0.53)	3 (0.32)	12 (0.48)
Eczema	0	2 (0.32)	4 (0.42)	7 (0.74)	13 (0.52)

Phase 3 Analysis Sets AS1C and AS2C

The percentage of participants reporting immediate hypersensitivity reactions was higher in tirzepatide-treated participants compared to placebo (TZP_ALL, 2.05%; placebo, 0.36%). This difference is more pronounced than observed in the placebo-controlled analysis set in the original T2DM application (0.6% and 0.4% for TZP_ALL and placebo, respectively). Of 51 tirzepatide-treated participants, 47 were from SURMOUNT-1. The majority of immediate events were cutaneous. No events were serious. There were no discontinuations of study drug due to immediate hypersensitivity reactions.

The percentage of participants reporting *non*-immediate (more than 24 hours) hypersensitivity reactions was higher in tirzepatide-treated participants compared to placebo (TZP_ALL, 3.49%; placebo, 1.93%). The corresponding results in the placebo-controlled analysis set in the original T2DM application for TZP_ALL and placebo were 2.6% and 1.3%, respectively.

Hypersensitivity reactions have already been identified as possible adverse reactions with tirzepatide (presented as ‘common’ in the SmPC). The rates in the tirzepatide-treated participants compared to placebo in CWM trials appear higher than those previously reported in the T2DM studies. However, there were no serious events and severe cases were very rare. The SmPC has been updated to include the new information from CWM studies.

Injection Site Reactions

SURMOUNT Set

More injection site reactions were reported by tirzepatide-treated than placebo-treated participants (TZP_ALL, 7.62%; placebo, 1.77%; Table 47). No events were serious, and all were mild or moderate in severity. These results are consistent with the Placebo-Controlled Analysis Set in the SCS. Two tirzepatide-treated participants discontinued study drug due to injection site reactions. Both of these participants were from SURMOUNT-1. The reactions most frequently (71.8% of events) occurred more than 6 hours after drug administration, with 38.5% of events occurring between 24 hours and 14 days after tirzepatide injection. The most common symptoms were erythema and pruritus.

Table 47. Summary of Treatment-Emergent Injection Site Reactions MedDRA Preferred Term by Decreasing Frequency within Event Category Safety Population Phase 3 Placebo-Controlled Analysis Set (GPHK, GPHL)

High Level Term Preferred Term	Placebo (N=958) n(%)	TZP 5mg (N=630) n(%)	TZP 10mg (N=948) n(%)	TZP 15mg (N=941) n(%)	TZP All (N=2519) n(%)
Participants with >=1 TEAE of Injection Site Reactions	17 (1.77)	36 (5.71)	79 (8.33)	77 (8.18)	192 (7.62)
Injection site reactions (HLT)	17 (1.77)	36 (5.71)	77 (8.12)	77 (8.18)	190 (7.54)
Injection site reaction	2 (0.21)	18 (2.86)	45 (4.75)	36 (3.83)	99 (3.93)
Injection site erythema	0	6 (0.95)	14 (1.48)	20 (2.13)	40 (1.59)
Injection site pruritus	0	4 (0.63)	7 (0.74)	17 (1.81)	28 (1.11)
Injection site bruising	8 (0.84)	2 (0.32)	6 (0.63)	5 (0.53)	13 (0.52)
Injection site pain	2 (0.21)	5 (0.79)	4 (0.42)	2 (0.21)	11 (0.44)
Injection site rash	0	1 (0.16)	6 (0.63)	5 (0.53)	12 (0.48)
Injection site haematoma	4 (0.42)	1 (0.16)	2 (0.21)	1 (0.11)	4 (0.16)
Injection site hypersensitivity	0	1 (0.16)	4 (0.42)	2 (0.21)	7 (0.28)
Injection site haemorrhage	1 (0.10)	0	3 (0.32)	0	3 (0.12)
Injection site irritation	0	1 (0.16)	2 (0.21)	0	3 (0.12)
Injection site paraesthesia	1 (0.10)	0	1 (0.11)	0	1 (0.04)
Injection site swelling	0	0	1 (0.11)	1 (0.11)	2 (0.08)
Injection site induration	0	0	0	1 (0.11)	1 (0.04)
Injection site inflammation	0	1 (0.16)	0	0	1 (0.04)
Injection site oedema	0	0	0	1 (0.11)	1 (0.04)

Phase 3 Analysis Sets AS1C and AS2C

In AS1C, the percentage of participants reporting at least 1 injection site reaction was higher in tirzepatide-treated participants compared to placebo (TZP_ALL, 7.19%; placebo, 1.81%). This difference is more pronounced than observed in the placebo-controlled analysis set in the original T2DM application (3.2% and 0.4% for TZP_ALL and placebo, respectively). Of 179 tirzepatide-treated participants, 159 were from SURMOUNT-1. No events were serious, and all were mild or moderate in severity. Two tirzepatide-treated participants, both in SURMOUNT-1, discontinued study drug due to injection site reactions.

In AS2C the percentage of participants reporting treatment-emergent injection site reactions was higher in the 2 higher dose groups (TZP 5 mg, 3.03%; TZP 10 mg, 5.01%; TZP 15 mg, 5.28%). The onset of the first injection site reaction occurred during dose escalation in the majority of participants in the 5-, 10-, and 15-mg treatment groups. These findings are generally consistent with the original T2DM application, although the percentage of participants with injection site reactions is higher than that reported in the dose effect analysis set of the original application (TZP 5 mg, 1.94%; TZP 10 mg, 2.70%; TZP 15 mg; 3.50%). No events were serious, and all were mild or moderate in severity. Five (0.08%) tirzepatide-treated participants discontinued study drug due to injection site reactions (2 from SURMOUNT-1, and 3 from Phase 3 T2DM studies).

The majority of injection site reactions occurred more than 6 hours and up to 14 days after tirzepatide injection and the most common symptoms were erythema and pruritus. The number of participants reporting multiple events increased in higher tirzepatide dose groups.

Injection site reactions are known AEs for this class and relevant information is already included in the SmPC (presented as ‘common’). The rates in the tirzepatide-treated participants compared to placebo in CWM trials were much higher (almost double) than those previously reported in the T2DM studies, and it appears there is association with dose level with higher rates in patients receiving the two higher doses.

The SmPC has been updated to include the new information from CWM studies.

Diabetic Retinopathy

SURMOUNT-2

Participants with a history of proliferative diabetic retinopathy, diabetic macular oedema, or no proliferative diabetic retinopathy that required acute treatment were excluded based on a dilated fundoscopic examination performed by a qualified eye care professional during screening (before randomisation) to confirm eligibility. Follow-up dilated fundoscopic examination was performed when clinically indicated by any AE suspected of worsening retinopathy. Adverse events from a customized search of diabetic retinopathy complications and cases with repeat fundoscopy during the study are summarized below.

A total of 7 (1.1%) tirzepatide- and 2 (0.6%) placebo-treated participants experienced a treatment-emergent potential diabetic retinopathy complication in SURMOUNT-2 (Table 48). Two participants reported severe TEAEs of diabetic retinopathy (1 each in the placebo group and tirzepatide 10-mg group. None of the events were serious.

Table 48. Summary of Potential Treatment-Emergent Diabetic Retinopathy Complications in SURMOUNT-2

	n (%)		
System Organ Class Preferred Term	Placebo (N=315)	TZP 10 mg (N=312)	TZP 15 mg (N=311)
Subjects with ≥1 treatment-emergent diabetic retinopathy complication	2 (0.6%)	5 (1.6%)	2 (0.6%)
Diabetic retinopathy	1 (0.3%)	3 (1.0%)	0
Vision blurred	1 (0.3%)	2 (0.6%)	1 (0.3%)
Diabetic retinal edema	0	0	1 (0.3%)
Macular edema	1 (0.3%)	0	0

The frequency of treatment-emergent potential diabetic retinopathy events reported by tirzepatide-treated participants was higher in the SURMOUNT-2 study, compared with the Placebo-Controlled Analysis Set (excluding SURMOUNT-1) in the SCS (see below) where no tirzepatide treated and 2 (1.09%) placebo-treated participants reported a TEAE of potential diabetic retinopathy complications. Worsening of fundoscopic examination results was observed for 5 (0.8%) tirzepatide- and 2 (0.6%) placebo-treated participants in SURMOUNT-2. This was consistent with the percentages of tirzepatide-treated participants (0 to 1.13%) and comparator-treated participants (0 to 0.83%) with worsening fundoscopic examination results across the Phase 3 T2DM studies, irrespective of baseline BMI.

Phase 3 T2DM studies

Across the Phase 3 T2DM clinical program, the incidence of worsening of fundoscopic examination result was low. A total of 21 (0.36%) tirzepatide-treated participants compared with 6 (0.25%) comparator-treated participants experienced worsening of fundoscopic examination result. No tirzepatide-treated participants compared with 2 (1.09%) placebo-treated participants experienced a TEAE of potential diabetic retinopathy event in placebo-controlled Phase 3 T2DM studies in AS1C.

The SmPC includes a warning that tirzepatide has not been studied in patients with non-proliferative diabetic retinopathy requiring acute therapy, proliferative diabetic retinopathy or diabetic macular oedema, and should be used with caution in these patients with appropriate monitoring. ‘Diabetic retinopathy complications’ are included as ‘Important Potential Risk’ in the RMP; also, the Applicant has indicated that a dedicated substudy of SURPASS-CVOT is ongoing to further investigate the impact of tirzepatide treatment on diabetic retinopathy

progression and this is expected to provide more information on this area.

Major Depressive Disorder/Suicidal Ideation or Behaviour

SURMOUNT Set

Study participants in SURMOUNT-1 and SURMOUNT-2 were screened at trial entry and monitored throughout the study for depression, and suicidal ideation or behaviour using the Columbia-Suicide Severity Rating Scale (C-SSRS) and Patient Health Questionnaire-9 (PHQ-9) and through AE collection. Participants with severe or unstable psychiatric illness or any history of a suicide attempt were excluded from these studies.

At baseline, 18.3% of participants reported at least 1 event in the SOC of Psychiatric disorders. The most commonly reported terms were anxiety (7.7%), depression (6.8%), and insomnia (5.9%). Additionally, based on the PHQ-9 total score, 24.0% of participants had mild depression and 8.2% had moderate depression at baseline.

The TEAEs of major depressive disorder or suicidal ideation or behaviour were identified using the MedDRA PTs from the following sub-SMQs within the Depression and suicide/self-injury SMQ: Depression (excluding suicide and self-injury) (narrow), and - Suicide/self-injury (narrow). A total of 72 (TZP_ALL, 47 [1.87%]; placebo, 25 [2.61%]) participants reported at least 1 TEAE of major depressive disorder or suicidal ideation or behaviour. Events within the Suicide/self-injury SMQ were also similar between tirzepatide-treated (TZP_ALL [0.08%]) and placebo groups (0.10%).

Two suicide attempts occurred in tirzepatide-treated participants in SURMOUNT-1 and are discussed in the SCS. These participants had prior mental health diagnoses and identifiable triggers. No participants reported suicide attempt in SURMOUNT-2. Results are consistent with those observed in the Placebo-Controlled Analysis Set in the SCS for treatment-emergent major depressive disorder or suicidal ideation or behaviour (TZP_ALL, 45 [1.81%]; placebo, 22 [2.66%]).

The percentage of participants with severe/serious events was 0.20% (5 participants) with tirzepatide and 0.10% (1 participant) with placebo. The 5 tirzepatide-treated participants with severe/serious events (4 severe, 4 serious) were in SURMOUNT-1. All severe or serious events in tirzepatide-treated participants were confounded by social stressors and/or pre-existing mental health issues, including depression, post-traumatic stress disorder, or anxiety. One participant in the placebo group in SURMOUNT-2 experienced a severe, non-serious event of depression.

Similar percentages of tirzepatide-treated participants (TZP_ALL, 14 [0.6%]) and placebo treated participants (7 [0.7%]) reported at least 1 “yes” answer, indicating suicidal ideation or behaviour, on the C-SSRS during the studies. All participants reported at least 1 “yes” answer to the suicidal ideation portion of the C-SSRS (Q1-5) and 2 tirzepatide treated participants reported at least 1 “yes” answer to the suicidal behaviour” portion of the CSSRS (Q6-10). Both participants with “yes” answers in the suicidal behaviour category were from SURMOUNT-1 (non-fatal suicide attempt and interrupted attempt).

A lower percentage of tirzepatide-treated (TZP_ALL, 439 [17.7%]) compared with placebo treated participants (203 [21.7%)] experienced a shift to new or worsening depression from baseline based on the PHQ-9 score. Conversely, more tirzepatide-treated (443 [17.9%]) compared with placebo-treated (128 [13.7%]) participants reported improved depression

during the study. Overall, results on the C-SSRS and PHQ-9 assessments were consistent with those observed in the Placebo-Controlled Analysis Set in the SCS.

In summary, depression and depressive symptoms were common at baseline with 6.8% of participants having a diagnosis of depression and nearly one-third having depressive symptoms per PHQ-9 score at baseline. The frequency of depression and suicide/self-injury TEAEs was similar in tirzepatide and placebo groups for the Depression SMQ (1.79%, 2.61%) and Suicide/self-injury SMQ (0.08%, 0.10%). Severe or serious events were numerically higher in tirzepatide groups (5 participants [0.20%] compared with placebo (1 participant [0.10%]). All events were confounded by social stressors and/or preexisting mental health issues, including depression, current depressive disorder, post-traumatic stress disorder, or anxiety. Measures of suicidal ideation or behaviour (C-SSRS) were similar for tirzepatide (14 participants [0.6%]) and placebo (7 participants [0.7%]). By PHQ-9, more tirzepatide-treated participants, compared with placebo experienced improvement of depression (17.9% and 13.7%), and fewer experienced worsening/new depression (17.7% vs 21.7%).

Phase 3 Analysis Sets AS1C and AS2C

Depression and depressive symptoms were common at baseline with 7.7% of participants in AS1C and 6.7% of participants in AS2C having a diagnosis of depression at baseline, and nearly one-third of participants in SURMOUNT-1 having at least mild depression reported at baseline by PHQ-9 total score.

The frequency of depression and suicide/self-injury TEAEs was low for both tirzepatide and placebo in AS1C. TEAEs for both the Depression SMQ and the Suicide/self-injury SMQ were numerically higher in the placebo group (2.66% and 0.12%, respectively) compared with the tirzepatide groups (TZP_ALL, 1.73% and 0.08%, respectively). Similarly, based on PHQ-9 total score in SURMOUNT-1, there were more placebo treated participants compared to tirzepatide-treated participants who experienced a shift to higher categories of depression.

Table 49. Summary of Treatment-Emergent Major Depressive Disorder/Suicidal Ideation or Behavior MedDRA Preferred Term by Decreasing Frequency within SMQ Participants with Overweight/Obesity in Phase 3 Placebo- Controlled Analysis Set (AS1C)

	n (%)				
Preferred Term	Placebo (N=827)	TZP 5 mg (N=832)	TZP 10 mg (N=830)	TZP 15 mg (N=828)	TZP_ALL (N=2490)
Participants with ≥1 TEAE	22 (2.66)	11 (1.32)	20 (2.41)	14 (1.69)	45 (1.81)
Depression (excl suicide and self-injury)	22 (2.66)	11 (1.32)	19 (2.29)	13 (1.57)	43 (1.73)
Depression	14 (1.69)	9 (1.08)	14 (1.69)	10 (1.21)	33 (1.33)
Depressed mood	5 (0.60)	0	4 (0.48)	1 (0.12)	5 (0.20)
Major depression	3 (0.36)	2 (0.24)	1 (0.12)	1 (0.12)	4 (0.16)
Adjustment disorder with mixed anxiety and depressed mood	0	0	1 (0.12)	0	1 (0.04)
Discouragement	0	0	0	1 (0.12)	1 (0.04)
Suicide/self-injury	1 (0.12)	0	1 (0.12)	1 (0.12)	2 (0.08)
Suicide attempt	0	0	1 (0.12)	1 (0.12)	2 (0.08)
Suicidal ideation	1 (0.12)	0	0	0	0

Abbreviations: excl = excluding; MedDRA = Medical Dictionary for Regulatory Activities; N = number of participants in population; n = number of participants with event; SMQ = Standardised MedDRA Query;

Severe or serious events, although low overall, were numerically higher in tirzepatide groups

(AS1C, 5 participants [0.20%]; AS4C, 8 participants [0.13%]) compared with placebo and pooled comparator groups (AS1C, 0 participants; AS4C, 1 participant [0.04%]) in AS1C and AS4C, respectively. The overall rate of severe or serious events was also low in tirzepatide-treated participants for AS2C. All events were confounded by preexisting mental health issues, including depression, current depressive disorder, post-traumatic stress disorder, or anxiety.

In contrast to the original T2DM application, in which overall frequency was <1% and similar across tirzepatide and placebo groups, depression and suicide/self-injury TEAEs were more frequent overall, and higher in placebo compared to tirzepatide groups in AS1C, consistent with the known higher background rate in the obesity population. Similar to the original T2DM application, however, the majority of serious or severe events were confounded by preexisting or current mental health issues.

The higher incidence of depression in patients with obesity than in general population is recognised and it is important to detect a potential adverse impact of therapy on the risk of worsening the condition, serious events and suicidality. Overall, the available data from the SURMOUNT trials do not suggest an increased risk with tirzepatide therapy. An imbalance was noted in the very small number of severe or serious events (tirzepatide group: 5 patients [0.20%] compared with placebo: 1 patient [0.10%]) and the two suicide attempts in tirzepatide-treated participants in SURMOUNT-1. However, in all cases there appeared to be several confounding factors and conclusions are difficult.

Laboratory findings

Laboratory measures of renal, hepatic, thyroid and pancreatic function, lipids or glucose tests are discussed in separate sections above. Other laboratory results *of interest* are presented here.

Haemoglobin and anaemia

No separate information has been included for the SURMOUNT set.

In AS1C more participants in the TZP_ALL group than the placebo group (13.8% and 7.4%, respectively) shifted from normal/high haemoglobin to low haemoglobin, with no dose effect in AS2C (5 mg, 13.02%; 10 mg, 13.38%; 15 mg, 13.15%. For tirzepatide-treated participants shifting from normal/high minimum haemoglobin levels to low in AS1C, the mean drop in haemoglobin was 1.91 g/dL and the mean and median postbaseline haemoglobin levels were 11.17 g/dL and 11.20 g/dL respectively. These results were deemed not clinically meaningful and were similar to the original T2DM application.

Anaemia (cluster) was reported by 43 (1.73%) tirzepatide-treated and 7 (0.85%) placebo-treated participants in AS1C. Of the 43 tirzepatide-treated participants reporting a TEAE of anaemia in AS1C, 33 were from SURMOUNT-1. The decrease in haemoglobin from baseline for 40 of the 43 participants ranged from -0.1 to -6.2 g/dL.

There was no dose effect of tirzepatide on anaemia-related TEAEs (AS2C), and the incidence rate was similar in tirzepatide- and comparator-treated participants (AS4C). Overall, the data do not suggest that low haemoglobin or anaemia are safety concerns with tirzepatide treatment in the CWM population. These findings remain consistent with the original T2DM application.

Although there appear to be cases with confounding factors, an imbalance is noted in the

reports of anaemia between groups. Some significant changes in haemoglobin from baseline compared to placebo were also recorded in SURMOUNT-1 and-2. Overall the available evidence, in line with the previous T2DM dossier, does not raise any major concerns and does not appear sufficient to establish a causal relationship with therapy.

Safety in subgroups

Intrinsic Factors

The frequently reported TEAEs (reported by at least 5% of participants) were analysed by subgroups of participants' demographic characteristics to evaluate possible subgroup differences in response to study drug in AS1C. The following subgroups were assessed:

- sex (female, male)
- age group: <65 and ≥65 years
- BMI: <30, ≥30 to <35, ≥35 to <40, ≥40 kg/m2
- eGFR: < 60, ≥60 mL/min/1.73m2
- ethnicity: Hispanic or Latino, Not Hispanic or Latino, Not Reported; and
- race: Asian, Black/African American, White, Other

Significant subgroup-by-treatment interactions ($p<0.10$) were observed for:

- TEAE of diarrhoea and age subgroup: a significant treatment effect ($p<0.05$) vs. placebo was observed for participants <65 years but not for participants ≥65 years.
- TEAE of diarrhoea and eGFR subgroup: a significant treatment effect ($p<0.05$) vs. placebo was observed for participants with eGFR ≥60 mL/min/1.73m2 but not for participants with eGFR <60 mL/min/1.73m2.
- TEAE of eructation and sex subgroup: a significant treatment effect ($p<0.05$) vs. placebo was seen for all 3 tirzepatide dose in females, but only for tirzepatide 10 mg and 15 mg in males.
- TEAE of eructation and ethnicity subgroup: a significant treatment effect ($p<0.05$) vs. placebo was seen for all 3 tirzepatide groups in participants reporting being Not Hispanic or Latino, but only for tirzepatide 10 mg and 15 mg in those reporting being Hispanic or Latino.
- TEAE of injection site reaction and age subgroup: a significant treatment effect ($p<0.05$) vs. placebo was observed for participants <65 years but not for participants ≥65 years.

Generally, there appears to be no clear explanation for the observed effects for diarrhoea, eructation, or injection site reaction in the subgroups noted above. In several cases, the effects were driven by more events in placebo in certain subgroups. Therefore, these differences were not considered clinically meaningful, and the ADRs observed in the overall population are considered relevant across all subgroups.

Table 50 presents a summary of AE categories by age group for the AS3C set. Across Phase 2 and 3 studies in the tirzepatide program, 5909 tirzepatide-treated participants were <65 years, 1281 were 65 through 74 years, 160 were 75 through 84 years, and 4 were ≥85 years of age. The percentage of participants reporting the following events increased with increasing age groups: SAEs, AEs leading to study drug discontinuation, Accidents and injuries (SMQ), Cardiac disorders (SOC) , Vascular disorders (SOC), Central nervous system vascular disorders (SMQ), and Hypotension, falls, and fractures.

Table 50. Overview of Adverse Events by Age Category Participants with Overweight/Obesity Phase 2/3 Analysis Set (AS3C)

	n (%)			
Event Category	<65 years (N=5909)	65-74 years (N=1281)	75-84 years (N=160)	≥85 years (N=4)
Total TEAEs	4429 (74.95)	947 (73.93)	122 (76.25)	1 (25.00)
SAEs	330 (5.58)	122 (9.52)	24 (15.00)	0
Fatal	27 (0.46)	10 (0.78)	3 (1.88)	0
Hospitalization	298 (5.04)	108 (8.43)	24 (15.00)	0
Life-threatening	38 (0.64)	14 (1.09)	2 (1.25)	0
Disability	11 (0.19)	4 (0.31)	0	0
Other	52 (0.88)	25 (1.95)	2 (1.25)	0
AEs leading to study drug discontinuation	329 (5.57)	131 (10.23)	33 (20.63)	0
Accidents and injuries (SMQ)	332 (5.62)	98 (7.65)	13 (8.13)	1 (25.00)
Cardiac disorders (SOC)	248 (4.20)	94 (7.34)	24 (15.00)	0
Infections and infestations (SOC)	1674 (28.33)	336 (26.23)	45 (28.13)	0
Nervous system disorders (SOC)	796 (13.47)	154 (12.02)	18 (11.25)	0
Psychiatric disorders (SOC)	261 (4.42)	39 (3.04)	6 (3.75)	0
Vascular disorders (SOC)	263 (4.45)	89 (6.95)	16 (10.00)	0
Central nervous system vascular disorders (SMQ)	30 (0.51)	17 (1.33)	3 (1.88)	0
Quality of life decreased (PT)	0	0	0	0
Fractures[a]	58 (0.98)	23 (1.80)	1 (0.63)	0
Hypotension, falls, fractures[b]	157 (2.66)	65 (5.07)	13 (8.13)	0

Abbreviations: AE = adverse event; HLGT = High Level Group Term; HLT = High Level Term; LCQ = Lilly customized query; N = number of participants in specified age group; n = number of participants with at least one specified event; NEC = not elsewhere classified; PT = Preferred Term; SAE = serious adverse event; SMQ = Standardised MedDRA Query; SOC = System Organ Class; TEAE = treatment emergent adverse event;.

[a] Fractures includes 6 HLTs: 'Fractures and dislocations NEC,' 'Limb fractures and dislocations,' 'Pelvic fractures and dislocations,' 'Skull fractures, facial bone fractures and dislocations,' 'Spinal fractures and dislocations,' and 'Thoracic cage fractures and dislocations.'

[b] LCQ includes the 6 HLTs for fractures, 'Decreased and nonspecific blood pressure disorders and shock' HLGT, and 'Fall' PT.

The implications of increased frequency of some adverse effects by age are uncertain. AS3C was used for this analysis to allow for better representation of the higher age categories. However, the comparisons across age subgroups may still be limited by the difference in the number of participants contributing to each group (particularly age ≥75 years). In addition, there is no comparator in AS3C to allow an assessment of whether the observations are related to tirzepatide or simply to the known higher frequency of certain events in an elderly population (for example, falls, CV disorders). Therefore, the data should be interpreted with caution.

TEAEs in patient with renal impairment are discussed in other sections above.

Extrinsic Factors

Frequently reported TEAEs (reported by at least 5% of participants) were analysed by geographic region to evaluate possible regional differences in response to study drug for AS4C.

Regions that showed more reporting of frequently reported TEAEs in tirzepatide-treated participants compared to other regions in AS4C were:

- Asia (excluding Japan) o Diarrhoea (TZP_ALL): 33.8%; range for other regions (TZP_ALL): 11.5% to 19.4%, and o Decreased appetite (TZP_ALL): 24.3%; range for other regions (TZP_ALL): 7.3% to 11.2%, and
- Japan o Nasopharyngitis (TZP_ALL): 14.7%; range for other regions (TZP_ALL): 1.9% to 5.7%.

In general, the percentages of tirzepatide-treated participants experiencing frequently reported TEAEs were comparable among regions.

Pregnancy and Lactation
No studies of tirzepatide have been conducted in pregnant or nursing women. Tirzepatide is currently not recommended during pregnancy and in women of childbearing potential not using contraception.

Twenty-six pregnancies (maternal exposure) were reported in the SURMOUNT-1 (tirzepatide, 18; placebo, 4) and SURMOUNT-2 (tirzepatide, 2; placebo, 2) studies. The total of 20 pregnancies in tirzepatide-treated female participants in SURMOUNT-1 and -2 corresponds to a rate of 2.15% in women of child-bearing potential.

Of the 20 tirzepatide-treated participants reporting maternal exposure before or during pregnancy, the pregnancy outcomes were: 7 reported full-term delivery, 4 reported preterm delivery, 4 terminated their pregnancies, 1 reported spontaneous abortion, 1 reported ectopic pregnancy, and 3 outcomes unknown/not reported.

The following maternal complications during pregnancy were reported: 1 reported pre-eclampsia, 1 reported hypertension and gestational diabetes, and 1 reported hyperglycaemia.

In addition, a total of 5 participants reported paternal exposures before or during pregnancy in SURMOUNT-1 (tirzepatide, 2; placebo, 1) and SURMOUNT-2 (tirzepatide, 1; placebo, 1). In the 3 tirzepatide-treated participants, the partner of 1 reported no maternal complications, and it was unknown if there were maternal complications in the other 2. The fetal outcome was unknown in the 3 cases. There were no reported major or minor fetal malformations among participants exposed to tirzepatide.

Immunological events
As a synthetic peptide, there is a possibility of an immunogenic response to tirzepatide. As such, participants in all tirzepatide clinical studies were tested for the presence and development of tirzepatide anti-drug antibodies (ADAs). The Applicant provided a separate 'Integrated Summary of Immunogenicity', on the entire immunogenicity investigation for the tirzepatide program, including details of immunogenicity assays, data from clinical studies across the clinical program, and the relationship of immunogenicity to exposure, efficacy, and safety of tirzepatide. The analysis includes the population of the nine Phase 3 clinical studies in Dose Effect Analysis Set (AS2C), including all participants from Study SURMOUNT-1, and participants with a baseline BMI ≥ 27 kg/m2 from 8 SURPASS studies. In addition, an 'Integrated Summary of Immunogenicity Addendum' was submitted that provides a summary of pooled SURMOUNT-1 and SURMOUNT-2 immunogenicity data, including the relationship of immunogenicity to exposure, efficacy, and safety.

In AS2C across the nine Phase 3 clinical studies, 3484 (56.1%) tirzepatide-treated participants developed treatment-emergent anti-drug antibodies (TE ADA) during the planned treatment period (Table 50). The percentage is slightly higher than the percentage (51.1%) in the dose effect analysis set in the original T2DM application. The difference is driven in part by SURMOUNT-1 in which 66.0% of participants were TE ADA+. During the planned treatment period, the percentage of TE ADA+ participants was similar in each tirzepatide group. The lack of dose-related effect is consistent with the dose effect analysis set in the original T2DM application.

Table 51. Summary of Treatment-Emergent Tirzepatide ADA Status During Planned Treatment Period Participants with Overweight/Obesity Phase 3 Dose Effect Analysis Set (AS2C)

Category	n (%)			
	TZP 5 mg (N=2109)	TZP 10 mg (N=2095)	TZP 15 mg (N=2122)	TZP_ALL (N=6326)
Participants evaluable for TE ADA	2070 (98.2)	2057 (98.2)	2079 (98.0)	6206 (98.1)
Baseline ADA present	144 (7.0)	136 (6.6)	147 (7.1)	427 (6.9)
Postbaseline TE ADA+ (during planned treatment period)	1126 (54.4)	1159 (56.3)	1199 (57.7)	3484 (56.1)
Postbaseline TE ADA inconclusive	1 (0.05)	0	0	1 (0.02)
Postbaseline TE ADA-	943 (45.6)	898 (43.7)	880 (42.3)	2721 (43.8)

Abbreviations: ADA = anti-drug antibodies; N = total number of participants in specified treatment group; n = number of participants in the specified category; TE = treatment-emergent; TZP = tirzepatide.
Note: the denominator for the percentage (%) is the number of participants who were TE ADA evaluable in each treatment group, except for the percentage evaluable, where the denominator was the number of participants from the safety population (N).

Among the TE ADA evaluable population, 2.2% and 2.4% had NAb against tirzepatide activity on the GIPR and GLP-1R, and 0.8% and 0.3% had cross-reactive NAb against nGIP and nGLP-1, respectively. Maximum ADA titers in TE ADA positive participants ranged from 1:20 to 1:81920 (median 1:160).

A higher number of TE ADA+ than TE ADA- participants reported hypersensitivity and injection site related reaction; 4.9% of TE ADA+ participants and 3.0% of TE ADA- participants experienced a hypersensitivity reaction, and 7.3% of TE ADA+ participants and 0.8% of TE ADA- participants experienced an injection site reaction. In both cases the differences are more pronounced than the findings in the original T2DM application. These differences are driven by SURMOUNT-1.

No 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. The majority of hypersensitivity and injection site reactions were mild to moderate in severity. There was no severe/serious injection site reaction, and 1 participant reported a severe event of hypersensitivity reaction (rash).

There was no obvious association between TE ADA status, ADA titer, or NAb status and percent body weight change from baseline. TE ADA status, ADA titer, and NAb status had also no apparent impact on the percentage of participants achieving ≥5% body weight reduction.

In the SURMOUNT set (SURMOUNT-1 + -2 Analysis Set) during the planned treatment period, the percentage of tirzepatide-treated participants in the that were TE ADA+ was 64.5%. The percentage of TE ADA+ participants in the TZP_ALL group is slightly higher than the percentage (56.1%) reported in the Phase 3 Dose Effect Analysis Set in the SCS (see above). A higher percentage of tirzepatide-treated TE ADA+ participants (6.2%) experienced hypersensitivity reactions compared to TE ADA- participants (3.0%) during the planned treatment period. The corresponding values in the SCS were 4.9% and 3.0% for the TE ADA+ and TE ADA- participants, respectively. The majority of events were mild or moderate. Of the 3 (0.12%) tirzepatide-treated participants who experienced severe hypersensitivity reactions, 1 participant, who reported severe rash, was TE ADA+. A higher percentage of tirzepatide-treated TE ADA+ participants (11.3%) also experienced injection site reactions compared to TE ADA- participants (1.0%) during the planned

treatment period. The corresponding values in the SCS were 7.3% and 0.8% for the TE ADA+ and TE ADA- participants, respectively. All events were mild or moderate in severity. No 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.

In general, the data suggest higher rates of detected TE ADA+ in the CWM trials than previously observed in the T2DM studies. The reasons are uncertain. Also TE ADA+ appear to be associated with higher risk of hypersensitivity and injection site reactions; it is reassuring, however, that most of these reactions were not serious or severe. Section 4.8 of the SmPC has been updated to include the updated figures and relevant information in relation to the CWM studies. It appears there is no meaningful impact on the pharmacokinetics or efficacy of tirzepatide. This is consistent with the findings and conclusions of the original T2DM dossier.

Safety related to drug-drug interactions and other interactions
See Clinical Pharmacology section above.

Discontinuation due to AEs
The presentation in this section focuses on AEs that led participants to permanently discontinuation of the administration of study drug.

SURMOUNT Set
The percentages of participants in the SURMOUNT-1 and -2 Analysis Set who prematurely discontinued study drug due to an AE was higher for tirzepatide-treated participants compared to placebo-treated participants: TZP_ALL: 153 participants (6.07%), placebo: 33 participants (3.44%). Most AEs leading to study drug discontinuation with tirzepatide were in the GI SOC (TZP_ALL, 3.29%; placebo, 0.52%) with the most frequent (≥0.2% in TZP_ALL) leading to study drug discontinuation: nausea, diarrhoea, abdominal pain, and vomiting. Approximately one-half of discontinuations of study drug due to AEs occurred during dose escalation.

These results are consistent with those presented for the Placebo-Controlled Analysis Set in the SCS.

Phase 3 Placebo-Controlled Analysis Set (AS1C)
Table 52 presents a summary and analysis of AEs that were reported as the reason for discontinuation of study drug in AS1C. The percentage of participants discontinuing study treatment due to an AE was higher in each tirzepatide group compared to placebo. The most frequently reported AEs leading to discontinuation of study drug were in the GI SOC. Approximately half of the participants discontinued study drug due to AEs that occurred during dose escalation.

These results are generally consistent with those presented in the placebo-controlled analysis set in the original T2DM application. However, the frequency of premature treatment discontinuation due to AE compared to placebo is lower than that reported in the original T2DM application in which rates were 6.7% and 2.6% for TZP_ALL and placebo, respectively. This is driven, in part, by a lower frequency of treatment discontinuation due to GI AE relative to the original application in which the frequencies were 5.0% and 0.4% for TZP_ALL and placebo, respectively.

Table 52. Summary of Adverse Events as the Primary Reason for Permanent Treatment Discontinuation Reported by ≥0.2% of Tirzepatide-Treated Participants Safety Population Participants with Overweight/Obesity in Phase 3 Placebo-Controlled Analysis Set in Participants (AS1C)

System Organ Class Preferred Term	n (%)					
	Placebo (N=827)	TZP 5 mg (N=832)	TZP 10 mg (N=830)	TZP 15 mg (N=828)	TZP_ALL (N=2490)	TZP_ALL vs. Placebo p-value[a]
Participants with ≥1 DCAE	26 (3.14)	38 (4.57)	56 (6.75)	54 (6.52)	148 (5.94)	0.002
Gastrointestinal disorders	4 (0.48)	17 (2.04)	37 (4.46)	36 (4.35)	90 (3.61)	<0.001
Nausea	3 (0.36)	7 (0.84)	11 (1.33)	15 (1.81)	33 (1.33)	0.021
Diarrhea	0	3 (0.36)	7 (0.84)	6 (0.72)	16 (0.64)	0.022
Vomiting	0	1 (0.12)	5 (0.60)	1 (0.12)	7 (0.28)	0.127
Dyspepsia	0	2 (0.24)	2 (0.24)	2 (0.24)	6 (0.24)	0.164
Gastrointestinal disorder	0	1 (0.12)	3 (0.36)	2 (0.24)	6 (0.24)	0.166
Gastroesophageal reflux disease	0	1 (0.12)	2 (0.24)	3 (0.36)	6 (0.24)	0.155
Abdominal pain	0	0	2 (0.24)	3 (0.36)	5 (0.20)	0.193
Neoplasms benign, malignant, and unspecified (incl cysts and polyps)	5 (0.60)	6 (0.72)	1 (0.12)	3 (0.36)	10 (0.40)	0.463
General disorders and administration site conditions	1 (0.12)	1 (0.12)	2 (0.24)	4 (0.48)	7 (0.28)	0.411
Investigations	3 (0.36)	2 (0.24)	3 (0.36)	2 (0.24)	7 (0.28)	0.722

Abbreviations: AE = adverse event; DCAE = discontinuation of study drug due to AE; incl = including; N = number of participants in treatment group; n = number of participants with at least 1 AE reported as the primary reason for permanent discontinuation of study drug; TZP = tirzepatide; vs. = versus.

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

Phase 3 Dose Effect Analysis Set (AS2C)

The most frequently reported TEAEs leading to discontinuation of study treatment were again in the GI SOC. The SOCs in which discontinuation rates increase with increasing dose were Gastrointestinal disorders and General disorders and administration site conditions. Within Metabolism and nutrition disorders, decreased appetite was cited as reason for treatment discontinuation with increased frequency by increasing dose. As with AS1C, the frequency of premature treatment discontinuation due to an AE was lower, and in part driven by fewer discontinuations due to GI AEs, than the original application.

Post marketing experience

A report on available post-marketing data has been included in the submitted Safety Summary Addendum.

Tirzepatide was first authorised on 13 May 2022 in the US and then in 34 countries, including the UK and EU members. The overall postmarketing safety profile is consistent with the safety observed in the completed clinical trial program. The signal evaluation for anaphylactic reaction and angioedema has resulted in a core data sheet update to include those new ADRs (see below).

Based on worldwide sales of tirzepatide following first launch cumulatively, there have been an estimated 1,461,200 patients exposed to tirzepatide (any dose) with 399,500 patient-years of exposure.

Cumulatively through 28 February 2023, there have been 18,704 AEs reported from 8966 postmarketing cases. Amongst these, 781 were SAEs reported from 509 cases based on spontaneous reports. The most frequently reported SAEs in the postmarketing setting by individual MedDRA PT were: pancreatitis (n = 69; reporting rate: 0.005%); vomiting (n = 44; reporting rate: 0.003%); diarrhoea (n = 39; reporting rate: 0.003%); nausea (n = 33;

reporting rate: 0.002%); dehydration (n = 31; reporting rate: 0.002%); and acute kidney injury (n = 23; reporting rate: 0.002%). Eleven deaths were reported and captured in the LSS from postmarketing reports. Ten cases had limited information regarding the medical history, concomitant medications, autopsy details and the cause of death for an adequate medical assessment and the remaining case was confounded by concurrent influenza B infection. There was no pattern observed in the cause of death in these cases. As far as AEs of special interest are concerned, overall, the postmarketing safety data are consistent with the safety profile observed in the tirzepatide clinical trial program.

There have been 1397 case reports of PTs of off label use, intentional product misuse, and intentional dose omission reported from the postmarketing data for tirzepatide, cumulatively. In these cases, the events co-reported with the off label use were similar to the events seen in labeled indication cases.

Anaphylactic Reaction

The review of anaphylactic reaction was performed following the identification of a safety signal from postmarketing cases of tirzepatide during the routine safety surveillance activities.

The search retrieved a total of 11 postmarketing cases, reporting 22 events (including narrow and broad algorithm PTs). Of these 11 cases, 7 cases met the definition of anaphylactic reaction or were reported as anaphylactic reaction and were further assessed based on World Health Organization-Upsala Monitoring Centre causality assessment criteria. Four of the 7 cases were assessed as probable. In all 4 cases, the events occurred within 15 minutes to 1 hour of the first dose of tirzepatide. Two of these patients had prior exposure to GLP-1 RAs. In 2 of the 7 cases, the causality was assessed as possible. Both the cases were assessed as serious (life-threatening and hospitalization) requiring treatment, indicating either an alternative aetiology apparently lacking in the case or delayed hypersensitivity reaction to tirzepatide. The remaining 1 case could not be assessed for causal association.
Of these 7 cases, 5 cases reported a positive de-challenge with tirzepatide and were temporally associated with tirzepatide. None of these cases reported a positive re-challenge, however, a re-challenge would not be expected in such cases. Based on the overall assessment of postmarketing cases, there is a potential role of tirzepatide in occurrence of anaphylactic reaction.

It was concluded that while clinical trial data have not suggested an important risk of anaphylactic reaction due to tirzepatide, the postmarketing data have demonstrated a causal association between use of tirzepatide and anaphylactic reaction and are consistent with the immunogenic properties of peptide pharmaceuticals. Based on this evaluation and the potential seriousness of the event, the applicant has updated the product information with anaphylactic reaction as an ADR.

Angioedema

A notification of safety signal for anaphylactic reaction and angioedema was received by the company. In response to this notification, spontaneously reported and clinical trial cases of angioedema were evaluated. As angioedema can be a life-threatening event if not treated properly and is a symptom of anaphylaxis, already identified as an ADR for tirzepatide, a clear statement regarding angioedema has been added to the product information with angioedema (along with anaphylactic reaction) as an ADR in the post-marketing setting.

Overall conclusions on clinical safety

The safety review is primarily based on the results of the two SURMOUNT trials (pooled data in 'SURMOUNT set'). However, additional analyses sets were also examined (submitted as part of the first stage of the application), comprising safety data from SURMOUNT-1 and different studies from the previous tirzepatide T2DM clinical development. The two main sets were: AS1C that examined only Phase 3 *placebo*-controlled fixed-dose studies, with SURMOUNT-1 representing 76.5% of the total A1SC population and AS2C which examined *all* Phase 3 fixed-dose studies that had tirzepatide 5-, 10-, and 15-mg treatment groups. SURMOUNT-1 participants represented 30.0% of AS2C. Given that CWM and T2DM phase 3 programs used the same dosing regimen and that the majority of patients in the Phase 2 and 3 T2DM studies were overweight or obese the pooling approach appears reasonable; this also facilitated comparisons between the new CWM studies and the previous T2DM clinical program.

The overall safety database is considered adequate in terms of size and length of exposure and meets the relevant regulatory requirements. It should be noted, however, that in relation to CWM, limited safety data beyond 72 weeks of therapy are currently available.
In general, the safety analyses showed that the percentage of participants reporting TEAEs was higher in the tirzepatide groups (79.04% in SURMOUNT set; 78.1% in AS1C) than in the placebo group (73.28% in SURMOUNT set; 71.2% in AS1C) without, however, any clear relationship to dose level. The majority were of mild or moderate severity. Discontinuations of study treatment due to AE, although generally relatively infrequent, were also higher with tirzepatide (6.07% in SURMOUNT set; 5.94% in AS1C) than placebo (3.14% in SURMOUNT set; 3.1% in AS1C), mainly due to GI AEs and most commonly occurring during dose escalation.

As expected with the GLP-1 RA class and in consistence with the previous tirzepatide T2DM studies, the most frequent TEAEs, reported by a greater proportion of participants in tirzepatide groups compared with placebo, were GI disorders (tirzepatide 55.66%, placebo 29.65%; SURMOUNT set) with the most common being nausea, diarrhoea, constipation, vomiting, decreased appetite, and dyspepsia; the dose analyses suggest an increase in frequency with higher doses for most of those AEs. Among the less frequent TEAEs alopecia (hair loss) was identified as a new AE for tirzepatide. Hair loss has been reported with other treatments resulting in substantial and rapid weight reduction, including other GLP-1 RAs. In SURMOUNT studies dizziness was also more frequent among tirzepatide patients. Hair loss and dizziness have now been included in section 4.8 of the updated SmPC (as common events).

<u>Deaths and serious adverse events</u>

In SURMOUNT trials only a small number of deaths were recorded (13 patients; 9 [0.36%] in the tirzepatide and 4 [0.42%] in the placebo groups). All deaths were considered not related to study drug by the investigators, except one patient (on tirzepatide 5 mg) for whom however, a number of possible confounding factors were present. In general, from the whole available database there is no indication of excess mortality in the tirzepatide groups.
Serious adverse events (SAEs) were generally evenly distributed between groups, without notable imbalances and with no clear pattern suggesting a dose relationship. SAEs related to COVID-19 were among the most commonly reported in SURMOUNT trials. In SURMOUNT-1 alone there were 160 participants who reported at least 1 SAE during the study, similarly distributed between groups (6.8%, 6.3%, 6.9%, 5.1% in the placebo and tirzepatide, 5, 10 and 15 mg groups, respectively). Thirty four (34, 21.3%) of those reported

COVID-19-related SAEs. Otherwise, the most frequent SAEs were hepatobiliary disorders (with cholelithiasis and cholecystitis being the most common). In SURMOUNT-2 there were 68 participants who reported at least 1 SAE during the study (7.3%, 5.8%, 8.7% in the placebo and tirzepatide 10 and 15 mg groups, respectively). For each category there was a small number of individual reports, which does not permit any conclusions about specific events.

Special safety topics and adverse events of interest

Separate more detailed analyses were carried out for a number of safety topics, including areas previously identified as of particular interest for tirzepatide and this class of medicines, such as gastrointestinal AEs, dehydration, renal and hepatic safety, hepatobiliary disorders, metabolic acidosis, exocrine pancreas safety, thyroid safety, hypoglycaemia, cardiovascular safety, amputation or peripheral revascularization, hypersensitivity reactions, injection site reactions, immunogenicity, diabetic retinopathy complications, malignancy and major depressive disorder/suicidal ideation or behaviour. For the most part the findings were consistent with the known safety profile of tirzepatide and other GLP-1 Ras.

In relation to GI adverse events, which as noted above are the most common, an interesting finding was the generally higher frequency observed in the SURMOUNT trials (GI TEAEs 55.66% for tirzepatide, 29.65% for placebo) compared to what was previously observed in the T2DM studies (40.1% for tirzepatide, 20.4% for placebo). It is suggested that this may be explained by the increased prevalence of GI disorders associated with obesity and it is true that there were similar observations with other GLP-1 RAs such as liraglutide and semaglutide. On the other hand, it is reassuring that the vast majority of cases were mild to moderate and rates of discontinuations due to GI AEs were relatively low (tirzepatide, 3.29%; placebo, 0.52%) and comparable to those reported in the placebo-controlled analysis set in the original T2DM dossier. The most frequently reported GI AEs leading to discontinuation of study drug were nausea, diarrhoea and vomiting.

Dehydration events were also analysed as GI AEs such as vomiting or diarrhoea may lead to dehydration and volume depletion. Although rare, in SURMOUNT trials a higher number of tirzepatide treated patients reported a dehydration event (tirzepatide 15 [0.60%]; placebo, 1 [0.10%]) with 3 patients reporting severe/serious events, all in tirzepatide groups. Dehydration also appeared among the most common SAEs in postmarketing reports. The current SmPC includes a warning in section 4.4 (as part of the GI safety information).

As noted above, renal safety was among the examined special topics. In the initial T2DM dossier review no important issues about the renal safety of tirzepatide were identified. There are, however, some additional findings from SURMOUNT trials showing a higher percentage of renal events, mostly acute renal failure/acute kidney injury among tirzepatide patients. The numbers are small and in general other renal parameters do not suggest a nephrotoxic effect of therapy but some imbalances are notable; in the SURMOUNT set acute kidney injury was reported more frequently in the tirzepatide groups than in placebo (13 [0.52%] *vs* 2 [0.21%] respectively). Acute kidney injury also appeared among the most common SAEs in postmarketing reports. Given the overall exposure to tirzepatide in the studies, the incidence of such AEs was very low and in the majority of cases there were various confounding factors, including other medical conditions, concomitant medication or relevant risk factors. It is noted, however, that in several cases, GI AEs were also reported which could have led to dehydration and in turn resulted in or contributed to renal impairment. A relevant warning is already included in section 4.4 of the SmPC.

In the previous T2DM dossier review no important issues about the renal safety of tirzepatide were identified. Also, in general other renal parameters examined in the tirzepatide studies so far do not suggest a nephrotoxic effect of therapy. Overall, it is agreed that at present there is no sufficient evidence to confirm a causal direct relationship between the reported acute renal failure/injury events and tirzepatide treatment.

Another safety topic of interest for tirzepatide and for this class are gallbladder-related disorders. An increased risk of cholelithiasis with tirzepatide and other GLP-1 RAs has previously been shown and cholelithiasis is already mentioned in Section 4.8 of the SmPC as an "uncommon" adverse reaction. Gallbladder related events were more frequently reported in the CWM than in previous T2DM studies (with cholelithiasis being the most common AE in this category), which is not unexpected for a population with more extreme obesity. Severe or serious events were rare, but they still appear more common in the CWM population. An interesting finding from the SURMOUNT trials was that increased weight loss appears to be related with higher risk of gallbladder events, with greater rates seen in patients with maximum weight reduction ≥20%. Another finding was that cholecystitis was more frequent among tirzepatide patients compared to placebo. Relevant information regarding this has been added to the SmPC.

In relation to other safety topics, such as pancreatic function and pancreatitis, thyroid safety, malignancies, immunogenicity, hypersensitivity and injection site reactions and diabetic retinopathy there were no significant/unexpected findings and the results were mostly consistent with previous studies; yet in some areas higher rates (for all groups) were observed in the SURMOUNT trials (for example for hypersensitivity and injection site reactions) than in previous T2DM studies. These are reflected in the updated SmPC.

Cardiovascular (CV) safety was also reviewed in detail. There are some known issues with the class such as an increase in heart rate, previously seen with GLP-1 RAs but still of uncertain clinical relevance. Overall, the available data do not raise any major concerns about tirzepatide CV safety in this setting. So far, no excess CV risk has been identified while tirzepatide appears to have a positive effect on CV risk factors such as blood pressure and lipids (as discussed under Efficacy above). There is an ongoing CV outcome trial in patients with T2DM (SURPASS-CVOT) and a morbidity and mortality outcomes trial in people with obesity or overweight without T2DM (SURMOUNT-MMO) which are expected to provide further information on the CV effects of tirzepatide in future.

Tirzepatide treatment is associated with a drop in blood pressure. This may seem desirable from a CV risk perspective, but hypotension related events were reported in tirzepatide treated patients more commonly than in those on placebo (higher also rates among patients already receiving antihypertensive therapy, possibly reflecting lack of adequate adjustment of antihypertensive treatment to accommodate the impact of tirzepatide). Of interest, the reporting rates in the CWM trials were higher than previously seen in T2DM studies. 'Hypotension' has been added to section 4.8 of the SmPC (as 'common').

Finally, an area that is also of interest for weight loss medications, is major depressive disorder and suicidality. Overall, the currently available data from the SURMOUNT trials do not indicate an increased risk with tirzepatide therapy. An imbalance was noted in the very small number of severe or serious events that were reported in the studies (tirzepatide group: 5 patients [0.20%] compared with placebo: 1 patient [0.10%]) and the two suicide attempts in tirzepatide-treated participants in SURMOUNT-1. However, in all cases there appeared to be

several confounding factors and conclusions are difficult. Currently psychiatric adverse drug reactions do not appear in the product information of tirzepatide or other members of GLP-1 RA class. There are ongoing regulatory reviews on this subject which will provide more information.

Other issues

Laboratory findings related to renal, hepatic, thyroid and pancreatic function, lipids or glucose tests were examined as part of the relevant safety and efficacy topics (see related sections above) and were generally consistent with the known profile of the drug. Regarding anaemia and decreases in haemoglobin reported in the SURMOUNT trials, although some small imbalances between groups were noted, overall the available evidence, in line with the previous T2DM dossier, does not raise any major concerns and does not appear sufficient to establish a causal relationship with therapy.

As part of the submitted safety report, the Applicant also provided a summary of available post-marketing data collected in different territories since tirzepatide first authorisation (for T2DM) in May 2022. The information is limited given the relatively short time on the market, and the data appear generally consistent with the known safety profile of tirzepatide and the class. However, two new signals for 'anaphylactic reaction' and 'angioedema' were identified for tirzepatide; although apparently rare both are potentially serious and life-threatening and patients and health professionals should be made aware of the risk. The Applicant has updated the product information accordingly.

Summary

The data from the CWM studies were for the most part consistent with the safety profile of tirzepatide and the GLP-1 RA class, and no major concerns are raised. There were, however, some new findings, indicating a higher incidence of certain events in this population compared to what was previously reported in the T2DM studies, including gastrointestinal and gallbladder-related AEs, hypersensitivity and injection site reactions. Also, several new adverse events have been identified (including hair loss, dizziness, cholecystitis, hypotension, anaphylactic reaction and angioedema) which have been added to the product information.

Conclusion

The currently available evidence supports the efficacy of tirzepatide in weight management without raising major safety concerns. The overall benefit:risk of tirzepatide in the proposed indication for weight management is considered positive.

The proposed changes are acceptable.

In accordance with legal requirements, the Summaries of Product Characteristics (SmPCs) and Patient Information Leaflets (PILs) for products granted Marketing Authorisations at a national level are available on the MHRA website.

Decision: Grant

Date: 08 November 2023